JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

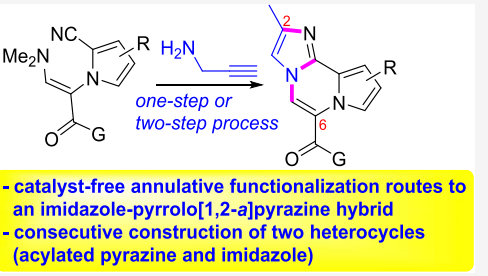
Catalyst-Free Construction of Imidazole-Pyrrolo[1,2-*a*]pyrazine Hybrid, 2,6-Disubstituted Imidazo[1,2-*a*]pyrrolo[2,1-*c*]pyrazine via Regioselective Annulative Functionalizations

Hyunjin Oh,[†] Dohui Ku,[†] Myungho Jung, Sunhee Lee, and Ikyon Kim*

Cite This: *J. Org. Chem.* 2024, 89, 17966−17990 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Highly efficient catalyst-free annulative functionalization approaches to a novel imidazole-pyrrolo[1,2-*a*]pyrazine hybrid structure were devised from the reaction of *β*-enaminone with propargylamine where regioselective conjugate substitution of *β*-enaminone with propargylamine followed by cycloisomerization proceeded smoothly in a domino fashion to construct two heterocyclic moieties (pyrazine and imidazole) via successive formation of three C−N bonds, leading to the target tricyclic skeleton.



- catalyst-free annulative functionalization routes to an imidazole-pyrrolo[1,2-*a*]pyrazine hybrid
- consecutive construction of two heterocycles (acylated pyrazine and imidazole)

INTRODUCTION

Imidazole is one of the most frequently employed heterocycles in medicinal chemistry research.[1] Moreover, as many imidazole-fused heterocycles are known to exhibit a broad range of pharmacological properties such as antianxiety, antiulcer, anthelminthic, antifungal, or antiviral activity (Figure 1),[2] design and synthesis of novel heterocyclic scaffolds fused with imidazole are highly desired.[3,4]

As part of our ongoing efforts to make novel hybrid chemical structures (Scheme 1a),[5] we recently established a catalyst-free annulative functionalization[6] route to a 1,2,4-triazole-pyrrolo-[1,2-*a*]pyrazine scaffold **3** from **1** where *β*-enaminone **2** was used as an intermediate (Scheme 1b).[7] Inspired by this work, we wondered if exposure of **2** to propargylamine[8] instead of acyl hydrazide would provide imidazole-fused pyrrolo[1,2-*a*]pyrazine **4**.[9] Mechanistically, we anticipated that intermolecular conjugate substitution of **2** with propargylamine would afford **A** where nucleophilic addition of nitrogen to the pendant nitrile followed by intramolecular hydroamination and subsequent double bond isomerization would occur to give **4** as shown in the box of Scheme 1. It should be mentioned that strategic combination of these processes has not been utilized for the successive synthesis of pyrazine and imidazole. As the expected product **4** contains unique substitution patterns around its tricyclic core which might be useful for biological studies with this class of compounds, we decided to investigate the feasibility of our hypothesis, which is described here.

RESULTS AND DISCUSSION

Based on our experience that 1,2,4-triazole-fused pyrrolo[1,2-*a*]pyrazine **3** was formed in good yield by heating a reaction mixture of **2** and acyl hydrazide in toluene at 150 °C, we expected to obtain **4** directly from **2** under the similar conditions (Table 1). When **2a** was allowed to react with propargylamine (3 equiv) in toluene at 150 °C for 20 h, however, three products (**3a**, **3a′**, and **5a**) were obtained in 15, 19, and 9% yields, respectively (entry 1). The starting material **2a** was also recovered in 53% yield. The formation of **3a′** can be rationalized as depicted in the box of Table 1. Nucleophilic addition of propargylamine to the nitrile of **2a** would give **B** where intramolecular conjugate substitution by imine would furnish **C**. Final cycloisomerization of **C** would lead to **3a′**. The reaction in EtOH at 120 °C proceeded more efficiently to give rise to **3a** and **3a′** in 72 and 17% yields, respectively (entry 2). For structural determination of **3a** and **3a′**, 2D NMR experiments (HSQC, HMBC, and NOESY) were carried out.[10] In addition, the crystal structure of **3a′** was firmly established by X-ray crystallographic analysis (Figure 2).[11] Surprisingly, we discovered that the concentration of the reaction mixture affects the product ratio; only **3a** was isolated in 98% yield when the reaction was carried out in EtOH (3 mL) at 120 °C (entries 3−6). The reaction in EtOH (0.5 mL) rather increased the formation of **3a′** (entry 7). Decreasing the amounts of propargylamine (2 or 1.5 equiv) resulted in a mixture of **3a** and **3a′** (entries 8 and 9). Lowering the reaction temperature to 100 °C also led to a mixture of **3a** and **3a′** (entry 10). These outcomes indicate that the ratio of *β*-enaminone **2a** and propargylamine, the concentration, and the

Received: June 23, 2024
Revised: October 25, 2024
Accepted: November 1, 2024
Published: November 26, 2024

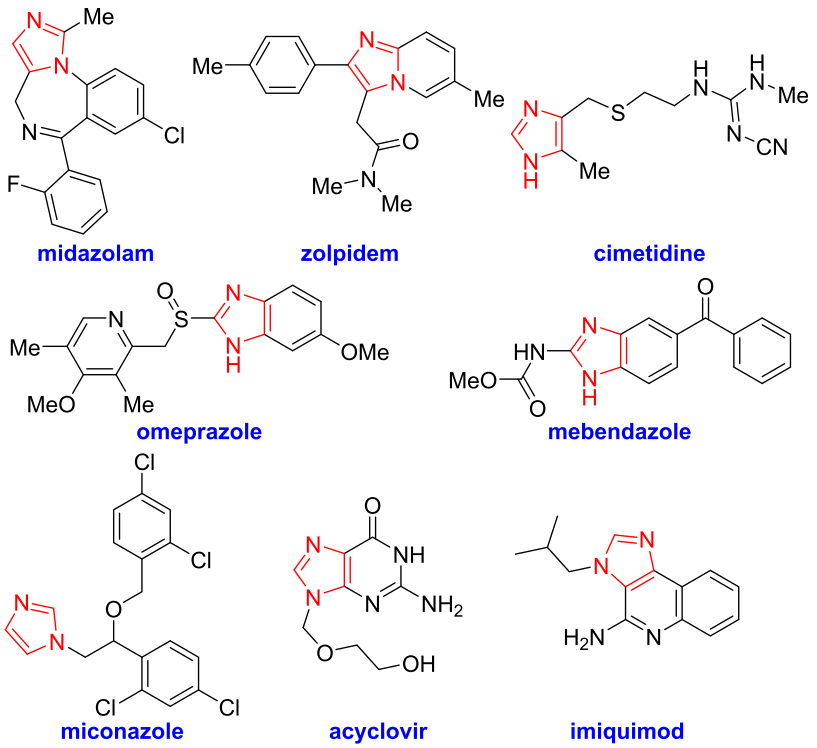
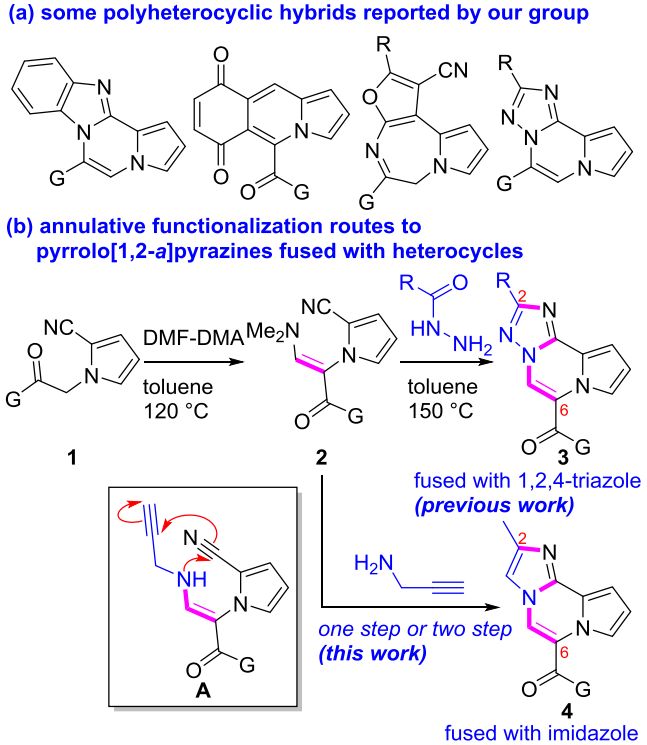


Figure 1. Bioactive Agents Containing Imidazole.

Scheme 1. Access to Hybrid Skeletons via Annulative Functionalization Strategies



reaction temperature are crucial to regioselective construction of imidazole-pyrrolo[1,2-*a*]pyrazine hybrid skeleton **3a**. The same reactions in other solvents such as CH_3CN and toluene also delivered three products (**3a**, **3a′** and **5a**) after prolonged reaction times (entries 11 and 12). Interestingly, we were able to observe the formation of **5a** in 96% yield when the reaction was carried out in toluene at 60 °C (entry 13).

Having found the optimal conditions for the synthesis of **3a**, we examined the reaction scope with diverse enaminone **2** (Table 2). Unfortunately, we were not able to observe the exclusive formation of **3b−n** with other enaminones **2b−n** under the optimized conditions except for **2a** and **2k**; The regioisomers **3′** were also detected as minor products from the reaction mixtures. Even when the scale-up reaction of **2a** (300 mg, 1.13 mmol) with propargylamine (3 equiv) was conducted in EtOH at 120 °C, a mixture of **3a** (211 mg, 68%) and **3a′** (28 mg, 9%) was obtained. The chemical structure of **3k** was unequivocally confirmed by X-ray crystallographic analysis (Figure 3).[12]

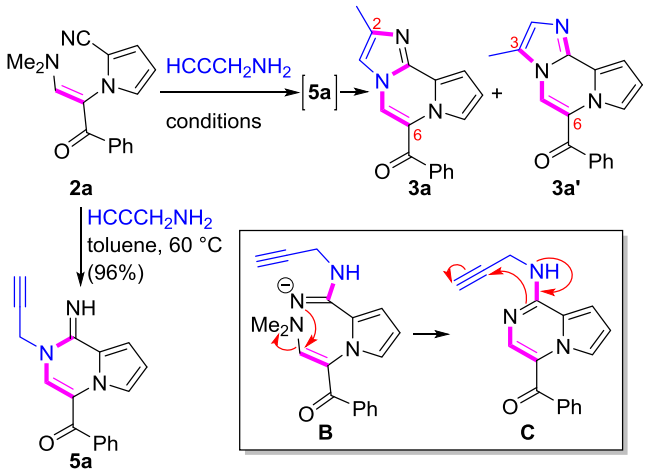
In the meantime, we also investigated the two-step sequence for the regioselective synthesis of **3** as the intermediate **5a** was isolated in 96% yield upon exposure of **2a** to propargylamine in toluene at 60 °C (Table 3). Indeed, the reactions with other enaminones **2b−n** under the same conditions delivered the corresponding intermediates **5b−n** in good to excellent yields. Heating a solution of **5a** without any catalysts[13] in EtOH at 120 °C underwent smooth cycloisomerization to form the imidazole ring,[14] cleanly furnishing the desired product **3a**. Other intermediates **5b−n** were also submitted to the same conditions to afford the corresponding products **3b−n** in excellent yields.

A scale-up reaction of **2a** (500 mg) with propargylamine in toluene at 60 °C provided **5a** in 95% yield (Scheme 2a). Subsequent cycloisomerization of **5a** (300 mg) in EtOH at 120 °C proceeded well to give **3a** in 92% yield (Scheme 2b).

When this two-step protocol was applied to **6**, a new 6-acylated diimidazo[1,2-*a*:2′,1′-*c*]pyrazine **8** was obtained by way of the intermediate **7** in good overall yield (Scheme 3a). Interestingly, exposure of *β*-enaminone **9** derived from indole-2-carbonitrile to propargylamine in toluene at 60 °C gave a

https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

Table 1. Reaction Optimization for the Synthesis of 3a[a,b]



entry	solvent (mL)	temperature (°C)	time (h)	yield (%)[b]
1	toluene (1)	150	20	15 (**3a**)/19 (**3a′**)/9 (**5a**)/53 (**2a**)
2	EtOH (1)	120	0.5	72 (**3a**)/17 (**3a′**)
3	EtOH (2)	120	0.5	81 (**3a**)/4 (**3a′**)
4	EtOH (3)	120	0.5	98 (**3a**)
5	EtOH (4)	120	1.0	96 (**3a**)/3 (**3a′**)
6	EtOH (5)	120	1.5	95 (**3a**)/3 (**3a′**)
7	EtOH (0.5)	120	0.5	69 (**3a**)/26 (**3a′**)
8[c]	EtOH (3)	120	1.0	77 (**3a**)/18 (**3a′**)
9[d]	EtOH (3)	120	2.0	80 (**3a**)/16 (**3a′**)
10	EtOH (3)	100	5	80 (**3a**)/17 (**3a′**)
11	CH_3CN (3)	120	24	36 (**3a**)/36 (**3a′**)/27 (**5a**)
12	toluene (3)	120	39	48 (**3a**)/31 (**3a′**)/20 (**5a**)
13	toluene (3)	60	16	96 (**5a**)

[a]A solution of **2a** (30 mg, 0.11 mmol) and propargylamine (3 equiv) in solvent was stirred at the indicated temperature for the indicated time. [b]Isolated yield (%). [c]Propargylamine (2 equiv) was used. [d]Propargylamine (1.5 equiv) was used.

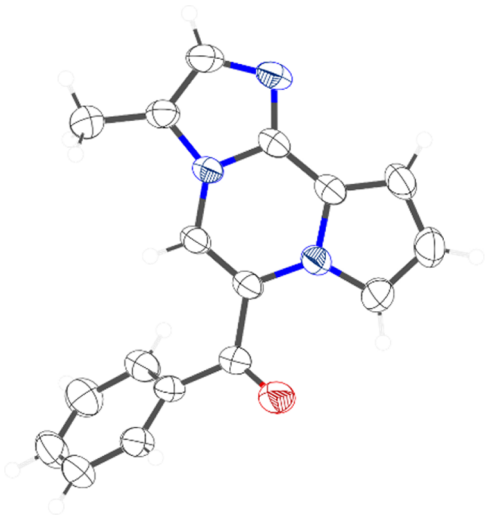


Figure 2. Thermal ellipsoid plot for 3a′ with 50% probability.

regioisomeric mixture of **10** and **11** in a ratio of 1:1.1 presumably as a result of nonselective nucleophilic addition of propargylamine (Scheme 3b). Each isomer was readily converted to the corresponding 6-acylated imidazo[2′,1′:3,4]-pyrazino[1,2-*a*]indole (**12** and **13**). Other propargylic amines such as but-3-yn-2-amine and but-2-yn-1-amine were successfully employed in the reactions with **2a** in EtOH at 120 °C to furnish **14** and **15** in good yields (Scheme 3c,3d). Pd−Cu catalyzed arylated cycloisomerization of **5a** with several aryl iodides enabled installation of an arylmethyl moiety at the C2 site of this heterocycle to afford **16**−**18** (Scheme 3e).[15]

Further expansion of the heterocyclic chemical space associated with this core scaffold was realized by simple synthetic manipulation (Scheme 4). Suzuki−Miyaura cross-coupling of **3m** with 4-methoxyphenylboronic acid provided **19** having an additional aryl group at the C9 position. Claisen−Schmidt aldol condensation[16] of **3k** with 3-chlorobenzaldehyde cleanly afforded the enone **20** which was converted to the dihydropyrazole **21** upon treatment with hydrazine in EtOH at 100 °C. In addition, exposure of **3k** to DMF-DMA led to the *β*-enaminone **22** in 88% yield. When **22** was treated with hydrazine, the pyrazole **23** was obtained, thereby permitting installation of a pyrazole motif at the C6 site. Cyclization of **22** under acidic conditions produced the polycyclic imidazole **24** in an excellent yield.[17] Finally, Friedländer reaction[18] of **3k** with 2-aminobenzaldehyde under basic conditions allowed introduction of a quinoline unit at the C6 position to give **25** in 81% yield.

CONCLUSIONS

In summary, two efficient synthetic routes to a novel imidazole-pyrrolo[1,2-*a*]pyrazine hybrid scaffold with unique substitution patterns were developed via exploitation of regioselective annulative functionalization strategies with *β*-enaminone and propargylamine where a domino intermolecular conjugate substitution-intramolecular cycloisomerization process allowed consecutive construction of pyrazine and imidazole to give the desired *N*-fused structure without any catalysts. Application of this protocol to other heterocyclic systems as well as derivatization of the resulting products permitted further expansion of the *N*-fused heterocyclic chemical space. Efforts to make some related *N*-fused heterocycles as well as biological studies with the compounds described here are currently underway and the results will be published soon.

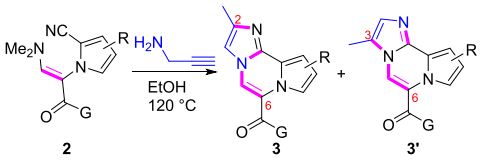
EXPERIMENTAL SECTION

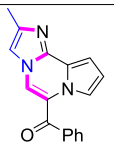
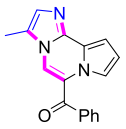
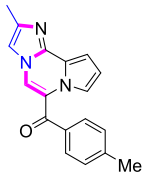
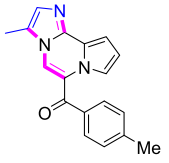
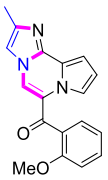
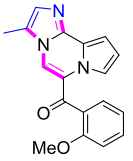
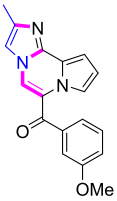
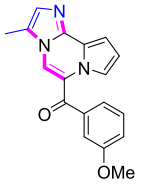
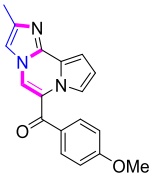
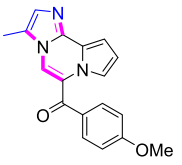
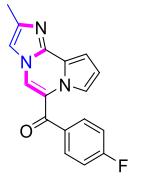
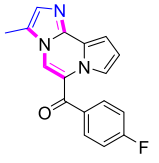
General Methods. Unless specified, all reagents and starting materials were purchased from commercial sources and used as received without purification. "Concentrated" refers to the removal of volatile solvents via distillation using a rotary evaporator. "Dried" refers to pouring onto or passing through anhydrous magnesium sulfate followed by filtration. Flash chromatography was performed using silica gel (230−400 mesh) with hexanes, ethyl acetate, and dichloromethane as the eluents. All reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (F-254) visualized with UV light. Melting points were measured by using a capillary melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer and were described as chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz (Hz), and number of protons. HSQC, HMBC, and NOESY 2D NMR spectra of **3a** and **3a′** were recorded on a 600 MHz NMR spectrometer. HRMS were measured with an electrospray ionization (ESI) and Q-TOF mass analyzer. X-ray crystal structures of **3a′** and **3k** were determined with a SuperNova, Dual, Cu at home/near, AtlasS2 diffractometer.

General Procedure for the Synthesis of **2**. A mixture of 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbonitrile (0.95 mmol, 1.0 equiv) and

https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

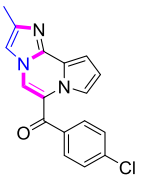
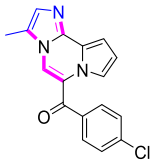
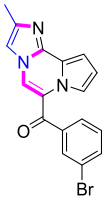
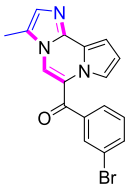
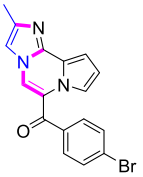
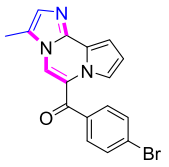
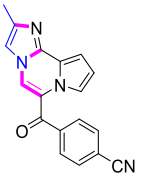
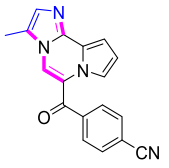
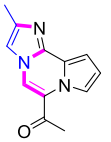
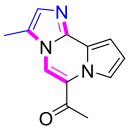
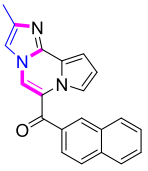
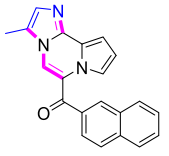
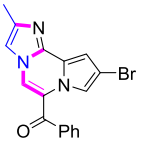
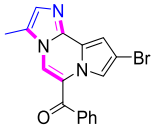
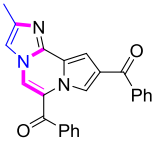
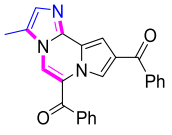
Table 2. Synthesis of 3[a,b]



entry	3	3'
1	 **3a** (98%)	 **3a'** (-)
2	 **3b** (82%)	 **3b'** (7%)
3	 **3c** (88%)	 **3c'** (5%)
4	 **3d** (76%)	 **3d'** (3%)
5	 **3e** (95%)	 **3e'** (3%)
6	 **3f** (79%)	 **3f'** (6%)

https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

Table 2. continued

entry	3	3'
7	 **3g** (77%)	 **3g'** (18%)
8	 **3h** (64%)	 **3h'** (10%)
9	 **3i** (70%)	 **3i'** (12%)
10	 **3j** (57%)	 **3j'** (30%)
11	 **3k** (83%)	 **3k'** (-)
12	 **3l** (79%)	 **3l'** (11%)
13	 **3m** (74%)	 **3m'** (6%)
14	 **3n** (70%)	 **3n'** (25%)

[a]A solution of **2** (0.11 mmol) and propargylamine (3 equiv) in EtOH (3 mL) was stirred at 120 °C. [b]Isolated yield (%).

DMF-DMA (2.0 equiv) in toluene (5.0 mL) was stirred at 120 °C for 12 h (a heating mantle was used). The reaction was carried out in a 20 mL sealed vial. The reaction mixture was concentrated *in vacuo* to yield the crude product, which was purified by silica gel column

https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

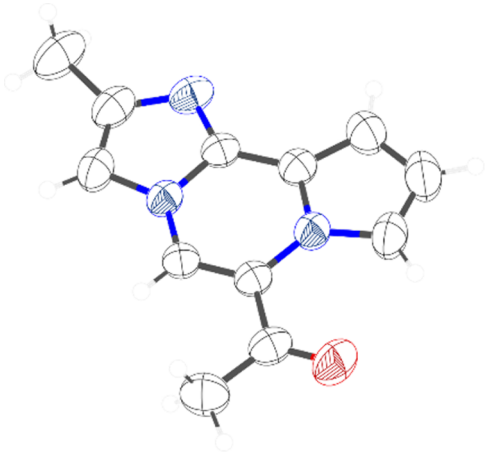
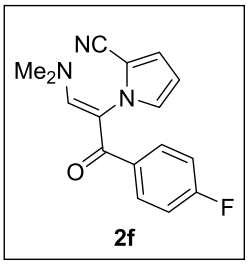


Figure 3. Thermal ellipsoid plot for 3k with 50% probability.

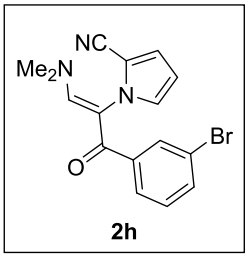
chromatography (hexane/ethyl acetate/dichloromethane = 3:1:2) to afford **2a** (247.0 mg, 98%) as a brown solid. The characterization data of **2a**−**2e**, **2g**, and **2i**−**2l** are in the ref 7.

*(Z)-1-(1-(Dimethylamino)-3-(4-fluorophenyl)-3-oxoprop-1-en-2-yl)-1H-pyrrole-2-carbonitrile (**2f**).*



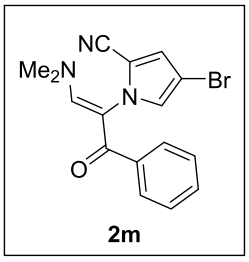
Hexane/ethyl acetate/dichloromethane (5:1:2) as the eluent; Yellow solid, mp: 103.2−103.6 °C (218.0 mg, 81%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42−7.32 (m, 3H), 6.98−6.89 (m, 2H), 6.77 (d, J = 3.6 Hz, 1H), 6.74 (d, J = 2.4 Hz, 1H), 6.16 (t, J = 3.2 Hz, 1H), 3.00 (s, 3H), 2.30 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.8, 164.8 (J = 249.0 Hz), 150.6, 135.5 (J = 4.0 Hz), 131.0, 129.9 (J = 8.0 Hz), 120.1, 115.0 (J = 22.0 Hz), 113.5, 110.2, 108.4, 108.2, 47.6, 36.0; **^{19}F NMR** (376 MHz, $CDCl_3$) δ − 109.6; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{16}H_{15}FN_3O$ 284.1194, found 284.1191.

*(Z)-1-(3-(3-Bromophenyl)-1-(dimethylamino)-3-oxoprop-1-en-2-yl)-1H-pyrrole-2-carbonitrile (**2h**).*



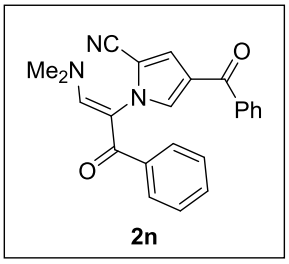
Hexane/ethyl acetate/dichloromethane (1:1:2) as the eluent; Ivory solid, mp: 81.9−82.1 °C (245.2 mg, 75%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.36 (s, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 4.0 Hz, 1H), 6.76 (d, J = 3.2 Hz, 1H), 6.19 (t, J = 3.4 Hz, 1H), 3.03 (s, 3H), 2.33 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.5, 150.9, 141.3, 132.9, 131.0, 130.4, 129.6, 125.6, 122.1, 120.3, 113.5, 110.4, 108.4, 108.3, 47.9, 36.2; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{16}H_{15}BrN_3O$ 344.0393, found 344.0390.

*(Z)-4-Bromo-1-(1-(dimethylamino)-3-oxo-3-phenylprop-1-en-2-yl)-1H-pyrrole-2-carbonitrile (**2m**).*



Hexane/ethyl acetate/dichloromethane (1:1:1) as the eluent; Yellow gum (281.2 mg, 86%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (d, J = 6.8 Hz, 2H), 7.42 (t, J = 7.2 Hz, 1H), 7.36 (t, J = 7.2 Hz, 2H), 7.30 (d, J = 6.0 Hz, 1H), 6.86 (s, 1H), 6.83 (s, 1H), 2.99 (s, 3H), 2.42 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 190.0, 151.2, 139.0, 130.4, 130.3, 128.1, 127.7, 121.1, 112.2, 109.1, 108.5, 96.6, 47.7, 36.3; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{16}H_{15}BrN_3O$ 344.0393, found 344.0393.

*(Z)-4-Benzoyl-1-(1-(dimethylamino)-3-oxo-3-phenylprop-1-en-2-yl)-1H-pyrrole-2-carbonitrile (**2n**).*

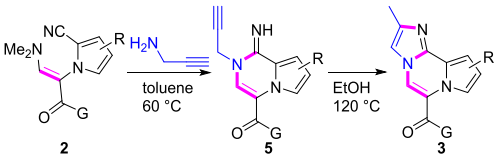


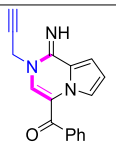
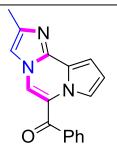
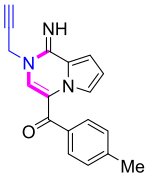
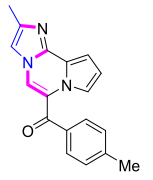
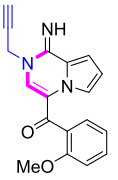
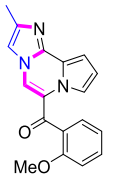
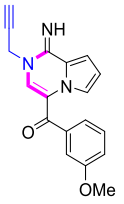
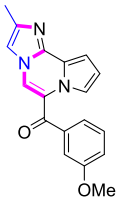
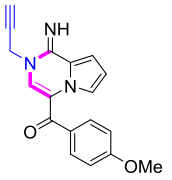
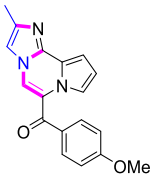
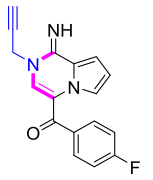
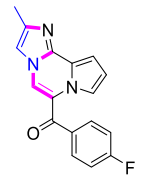
Hexane/ethyl acetate/dichloromethane (1:1:1) as the eluent; Orange gum (292.9 mg, 83%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, J = 7.2 Hz, 2H), 7.56−7.52 (m, 1H), 7.49 (d, J = 7.2 Hz, 2H), 7.45−7.42 (m, 3H), 7.40−7.35 (m, 5H), 3.06 (s, 3H), 2.49 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 190.2, 189.11, 151.0, 139.0, 138.5, 135.9, 132.4, 130.7, 129.0, 128.5, 128.4, 127.9, 125.0, 121.3, 112.5, 110.5, 108.7, 47.9, 36.9; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{23}H_{19}N_3O_2$ 370.1550, found 370.1537.

*General Procedure for the Synthesis of **3** and **3′**.* A mixture of **2** (0.11 mmol, 1.0 equiv) and propargyl amine (3.0 equiv) in ethyl alcohol (3.0 mL) was stirred at 120 °C for 30 min (a heating mantle was used). The reaction was carried out in a 7 mL sealed vial. The reaction mixture was concentrated *in vacuo* to yield the crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 4:1:2) to afford **3** and **3′** as yellow solids. X-ray crystal structure of **3k** was obtained via dissolution of the compound in a mixed solvent (dichloromethane/hexane, 1:1) and slow evaporation of the solvent at room temperature.

https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

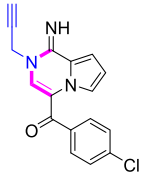
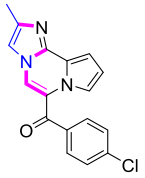
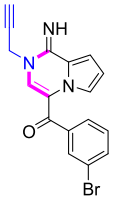
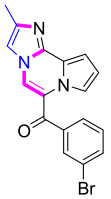
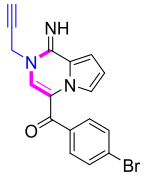
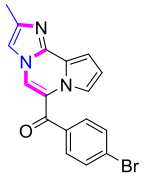
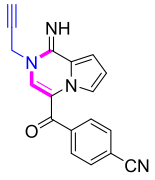
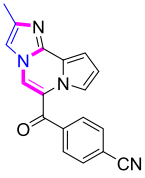
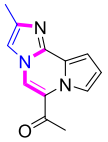
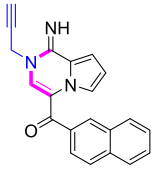
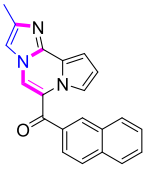
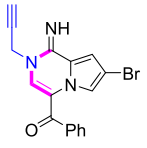
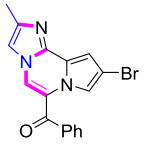
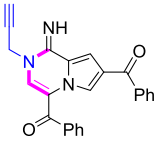
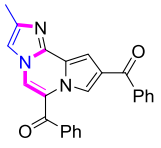
Table 3. Synthesis of 3 via 5[a,b]



entry	5	3
1	 **5a** (96%)	 **3a** (100%)
2	 **5b** (94%)	 **3b** (93%)
3	 **5c** (92%)	 **3c** (90%)
4	 **5d** (99%)	 **3d** (96%)
5	 **5e** (97%)	 **3e** (92%)
6	 **5f** (83%)	 **3f** (94%)

https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

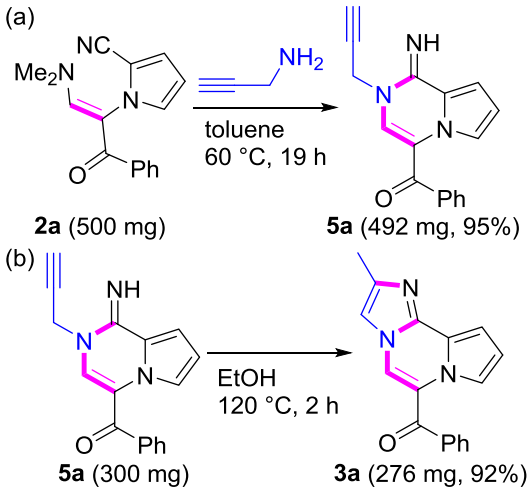
Table 3. continued

entry	5	3
7	 **5g** (90%)	 **3g** (97%)
8	 **5h** (82%)	 **3h** (89%)
9	 **5i** (95%)	 **3i** (87%)
10	 **5j** (98%)	 **3j** (87%)
11	 **5k** (75%)	 **3k** (93%)
12	 **5l** (84%)	 **3l** (100%)
13	 **5m** (83%)	 **3m** (87%)
14	 **5n** (94%)	 **3n** (90%)

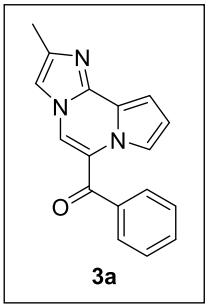
[a]A solution of **2** (0.75 mmol) and propargylamine (3 equiv) in toluene (4 mL) was stirred at 60 °C. A solution of **5** (0.18 mmol) in EtOH (2 mL) was stirred at 120 °C. [b]Isolated yield (%).

https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

Scheme 2. Scale-Up Reactions



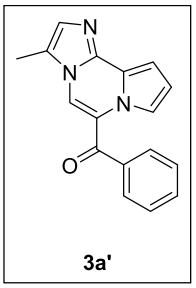
*(2-Methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)(phenyl)-methanone (**3a**).*



Hexane/ethyl acetate/dichloromethane (4:1:2) as the eluent; Yellow solid, mp: 162.7−163.1 °C (30.5 mg, 98%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.34 (d, J = 2.4 Hz, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.66 (t, J = 7.4 Hz, 1H), 7.60 (s, 1H), 7.54 (t, J = 7.6 Hz, 2H), 7.15 (d, J = 3.6 Hz, 1H), 6.97 (s, 1H), 6.76 (t, J = 3.2 Hz, 1H), 2.39 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 189.1, 142.8, 138.9, 137.7, 133.1, 129.6, 128.9, 122.09, 122.05, 121.6, 118.8, 113.4, 110.5, 103.7, 14.2; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{17}H_{14}N_3O$ 276.1131, found 276.1132.

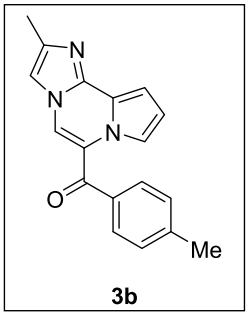
*Synthesis of **3a′**.* A mixture of **2a** (0.11 mmol, 1.0 equiv) and propargyl amine (3.0 equiv) in ethyl alcohol (0.5 mL) was stirred at 120 °C for 30 min (a heating mantle was used). The reaction was carried out in a 7 mL sealed vial. The reaction mixture was concentrated *in vacuo* to yield the crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 6:1:2) to afford **3a′** (8.1 mg, 26%) as a yellow solid along with **3a** (21.5 mg, 69%) as a yellow solid. X-ray crystal structure of **3a′** was obtained via dissolution of the compound in a mixed solvent (dichloromethane/hexane, 1:1) and slow evaporation of the solvent at room temperature.

*(3-Methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)(phenyl)-methanone (**3a′**).*



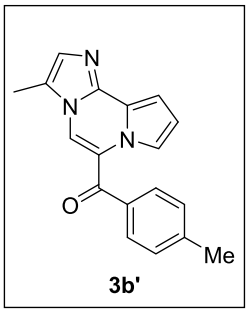
Hexane/ethyl acetate/dichloromethane (6:1:2) as the eluent; Yellow solid, mp: 191.5−192.4 °C (8.1 mg, 26%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.86 (d, J = 7.6 Hz, 2H), 7.69 (t, J = 7.6 Hz, 1H), 7.57 (t, J = 7.2 Hz, 2H), 7.48 (s, 1H), 7.15 (s, 2H), 6.77 (s, 1H), 2.32 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 189.2, 139.0, 137.6, 133.4, 130.1, 129.8, 129.0, 122.6, 122.4, 122.0, 118.8, 118.3, 113.3, 103.5, 8.9; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{17}H_{14}N_3O$ 276.1131, found 276.1148.

*(2-Methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)(p-tolyl)-methanone (**3b**).*



Hexane/ethyl acetate/dichloromethane (5:1:2) as the eluent; Yellow solid, mp: 162.6−163.0 °C (26.1 mg, 82%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (d, J = 3.2 Hz, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.59 (s, 1H), 7.34 (d, J = 7.6 Hz, 2H), 7.15 (d, J = 4.0 Hz, 1H), 6.96 (s, 1H), 6.75 (t, J = 3.6 Hz, 1H), 2.47 (s, 3H), 2.39 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.8, 144.2, 142.6, 138.9, 134.9, 129.9, 129.6, 122.2, 122.1, 120.9, 118.7, 113.3, 110.5, 103.6, 21.9, 14.2; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{16}N_3O$ 290.1288, found 290.1292.

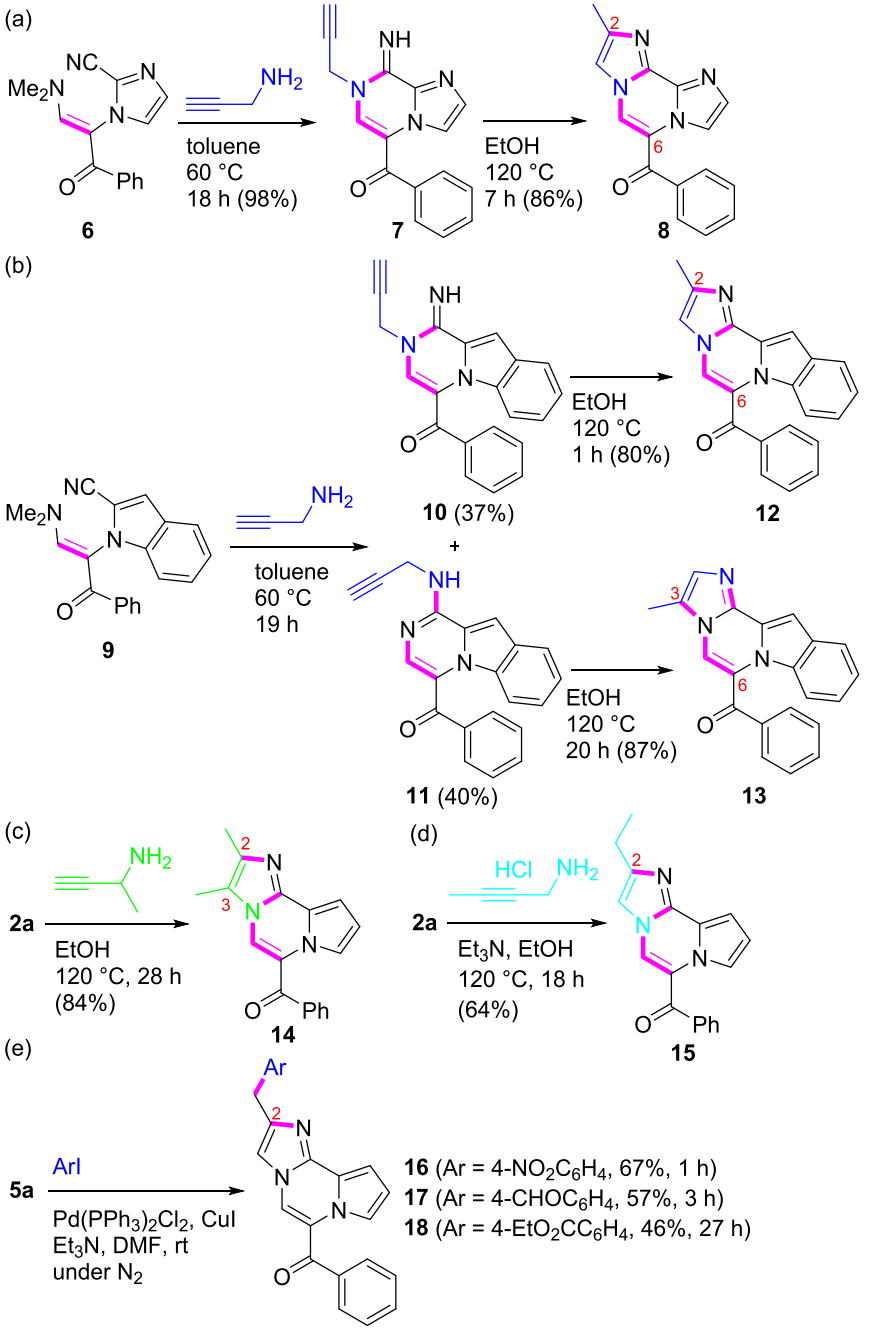
*(3-Methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)(p-tolyl)-methanone (**3b′**).*



Hexane/ethyl acetate/dichloromethane (5:1:2) as the eluent; Yellow solid, mp: 249.6−250.1 °C (2.3 mg, 7%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19−8.16 (m, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.46 (s, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 4.0 Hz, 2H), 6.75 (t, J = 2.8 Hz, 1H), 2.49 (s, 3H), 2.33 (s, 3H);

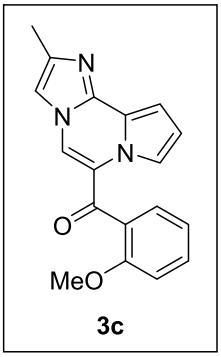
https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

Scheme 3. Applications



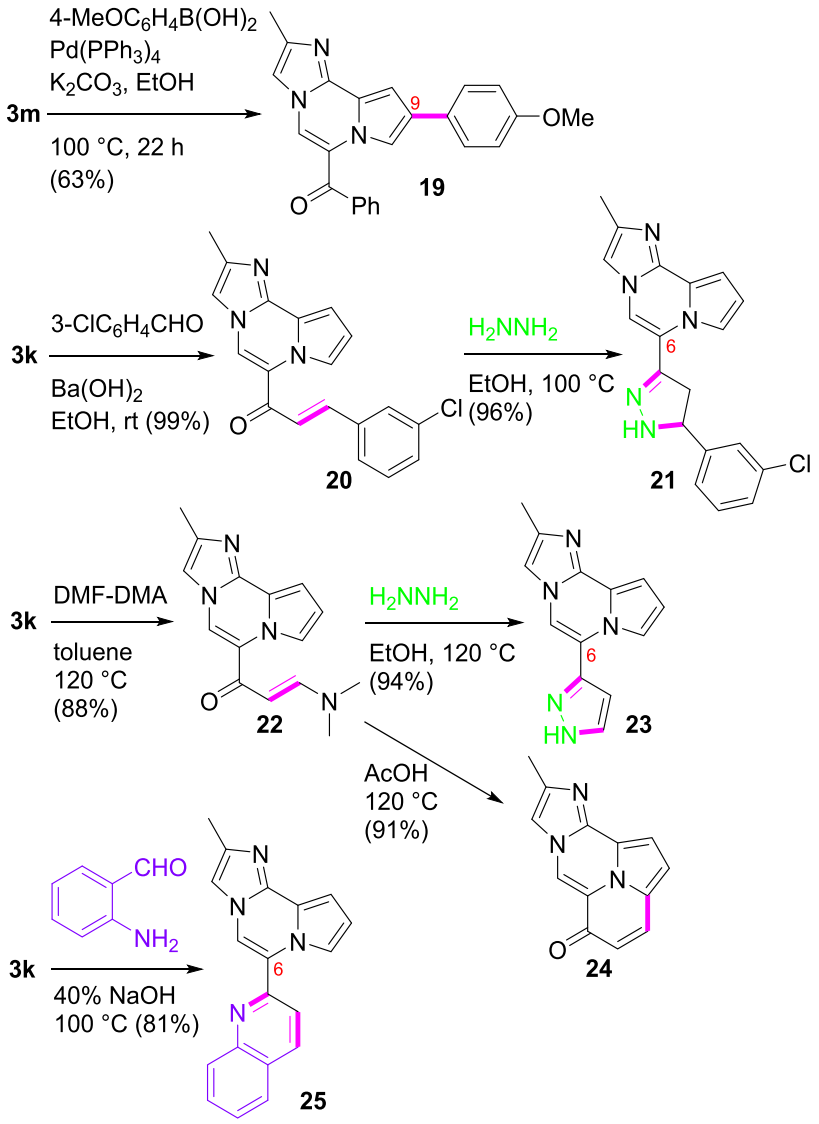
$^{13}C\{^1H\}$ **NMR** (100 MHz, $CDCl_3$) δ 188.8, 144.5, 139.0, 134.8, 130.0, 129.9, 129.7, 122.60, 122.57, 122.0, 118.2, 118.1, 113.2, 103.3, 21.9, 8.9; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{16}N_3O$ 290.1288, found 290.1293.

*(2-Methoxyphenyl)(2-methylimidazo[1,2-a]pyrrolo[2,1-c]-pyrazin-6-yl)methanone (**3c**).*



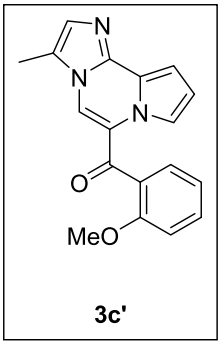
https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

Scheme 4. Derivatization



Hexane/ethyl acetate/dichloromethane (4:1:2) as the eluent; Yellow solid, mp: 215.5−215.9 °C (29.6 mg, 88%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.66 (d, J = 3.2 Hz, 1H), 7.56 (s, 1H), 7.52 (t, J = 8.2 Hz, 1H), 7.39 (d, J = 7.2 Hz, 1H), 7.16 (d, J = 3.6 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.93 (s, 1H), 6.77 (t, J = 3.2 Hz, 1H), 3.77 (s, 3H), 2.37 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.8, 157.3, 142.8, 139.2, 132.6, 129.6, 127.5, 122.9, 122.8, 122.0, 120.8, 119.3, 113.3, 111.7, 110.4, 103.8, 55.9, 14.2; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{16}N_3O_2$ 306.1237, found 306.1236.

*(2-Methoxyphenyl)(3-methylimidazo[1,2-a]pyrrolo[2,1-c]-pyrazin-6-yl)methanone (**3c'**).*

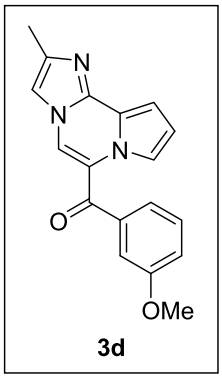


Hexane/ethyl acetate/dichloromethane (4:1:2) as the eluent; Yellow solid, mp: 238.2−239.1 °C (1.7 mg, 5%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.45 (d, J = 7.5 Hz, 2H), 7.15−7.08 (m, 3H), 7.05 (d, J = 8.4 Hz, 1H), 6.77 (s, 1H), 3.78 (s, 3H), 2.27 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.8, 157.5, 132.9, 130.1, 129.9, 127.4, 123.4, 122.5, 121.8, 120.8, 120.0, 118.8, 113.2, 111.8,

https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

103.3, 77.4, 55.9, 8.9; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{16}N_3O_2$ 306.1237, found 306.1247.

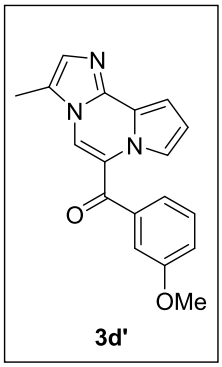
*(3-Methoxyphenyl)(2-methylimidazo[1,2-a]pyrrolo[2,1-c]-pyrazin-6-yl)methanone (**3d**).*



3d

Hexane/ethyl acetate/dichloromethane (4:1:2) as the eluent; Yellow solid, mp: 136.1−136.5 °C (25.5 mg, 76%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.34−8.30 (m, 1H), 7.64 (s, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.36−7.30 (m, 2H), 7.18 (d, J = 8.4 Hz, 1H), 7.14 (d, J = 3.6 Hz, 1H), 6.97 (s, 1H), 6.75 (t, J = 3.4 Hz, 1H), 3.87 (s, 3H), 2.38 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.9, 159.9, 142.8, 138.9, 129.8, 122.1, 122.04, 121.98, 121.6, 119.2, 118.8, 114.2, 113.3, 110.5, 103.6, 55.7, 14.2; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{16}N_3O_2$ 306.1237, found 306.1236.

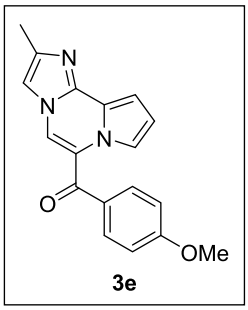
*(3-Methoxyphenyl)(3-methylimidazo[1,2-a]pyrrolo[2,1-c]-pyrazin-6-yl)methanone (**3d′**).*



3d'

Hexane/ethyl acetate/dichloromethane (4:1:2) as the eluent; Yellow solid, mp: 184.1−184.5 °C (1.0 mg, 3%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.25−8.24 (m, 1H), 7.51−7.49 (m, 1H), 7.44 (t, J = 7.4 Hz, 1H), 7.38 (d, J = 6.5 Hz, 2H), 7.20 (d, J = 8.4 Hz, 1H), 7.13 (s, 2H), 6.75 (s, 1H), 3.88 (s, 3H), 2.32 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.8, 160.0, 138.8, 130.0, 129.8, 122.6, 122.3, 122.2, 122.0, 119.7, 118.9, 118.3, 114.2, 113.2, 103.4, 77.4, 55.7, 8.9; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{16}N_3O_2$ 306.1237, found 306.1242.

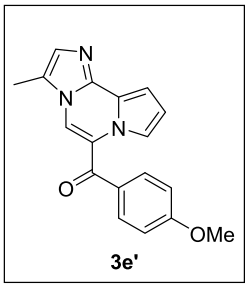
*(4-Methoxyphenyl)(2-methylimidazo[1,2-a]pyrrolo[2,1-c]-pyrazin-6-yl)methanone (**3e**).*



3e

Hexane/ethyl acetate/dichloromethane (4:1:2) as the eluent; Orange solid, mp: 174.3−174.7 °C (31.9 mg, 95%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (d, J = 2.8 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.55 (s, 1H), 7.12 (d, J = 3.2 Hz, 1H), 7.00 (d, J = 8.4 Hz, 2H), 6.97 (s, 1H), 6.72 (t, J = 3.6 Hz, 1H), 3.90 (s, 3H), 2.38 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.7, 163.9, 142.4, 138.8, 132.2, 129.9, 122.3, 122.1, 119.7, 118.5, 114.2, 113.2, 110.5, 103.4, 55.8, 14.2; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{16}N_3O_2$ 306.1237, found 306.1240.

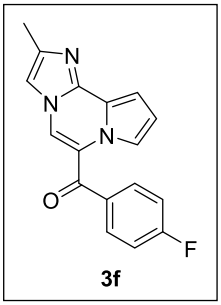
*(4-Methoxyphenyl)(3-methylimidazo[1,2-a]pyrrolo[2,1-c]-pyrazin-6-yl)methanone (**3e′**).*



3e'

Hexane/ethyl acetate/dichloromethane (4:1:2) as the eluent; Yellow solid, mp: 193.0−193.5 °C (1.0 mg, 3%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (dd, J = 2.8, 1.2 Hz, 1H), 7.86 (d, J = 8.8 Hz, 2H), 7.40 (s, 1H), 7.12−7.09 (m, 2H), 7.01 (d, J = 8.8 Hz, 2H), 6.72−6.70 (m, 1H), 3.90 (s, 3H), 2.32 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.7, 164.1, 138.9, 132.3, 129.8, 129.7, 122.7, 122.6, 122.0, 117.9, 117.0, 114.2, 113.1, 103.2, 55.8, 9.0; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{16}N_3O_2$ 306.1237, found 306.1241.

*(4-Fluorophenyl)(2-methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)methanone (**3f**).*



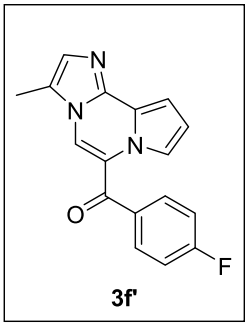
3f

Hexane/ethyl acetate/dichloromethane (4:1:2) as the eluent; Yellow solid, mp: 199.6−200.0 °C (25.5 mg, 79%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 (d, J = 2.8 Hz, 1H), 7.87−7.79 (m, 2H), 7.56 (s, 1H), 7.20 (t, J = 8.4 Hz, 2H), 7.12 (d, J = 4.0 Hz, 1H), 6.96 (s, 1H), 6.73 (t, J = 3.2 Hz, 1H), 2.36 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.5, 167.0 (J = 249.0

https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

Hz), 142.8, 138.8, 133.8 (J = 4.0 Hz), 132.2 (J = 8.0 Hz), 122.1, 121.9, 121.0, 118.6, 116.2 (J = 22.0 Hz), 113.4, 110.5, 103.6, 14.2; **^{19}F NMR** (376 MHz, $CDCl_3$) δ − 104.5**; HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}FN_3O$ 294.1037, found 294.1040.

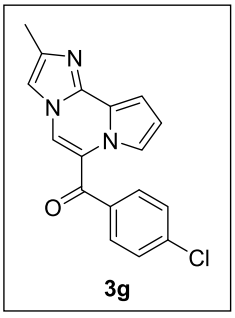
*(4-Fluorophenyl)(3-methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)methanone (**3f′**).*



3f'

Hexane/ethyl acetate/dichloromethane (4:1:2) as the eluent; Yellow solid, mp: 242.3−242.8 °C (1.9 mg, 6%); **^{1}H NMR** (400 MHz, Acetone-d_6) δ 8.18 (dd, J = 2.8, 1.2 Hz, 1H), 8.13 (dd, J = 8.8, 5.6 Hz, 2H), 7.92 (s, 1H), 7.39 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 1.0 Hz, 1H), 6.97 (dd, J = 4.0, 1.6 Hz, 1H), 6.74−6.71 (m, 1H), 2.38 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.6, 165.9 (J = 254.0 Hz), 139.0, 133.7 (J = 6.0 Hz), 132.4 (J = 9.0 Hz), 130.1, 122.6, 122.4, 122.0, 118.3, 118.2, 116.3 (J = 22.0 Hz), 113.4, 103.5, 8.9; **^{19}F NMR** (376 MHz, $CDCl_3$) δ − 104.1**; HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}FN_3O$ 294.1037, found 294.1044.

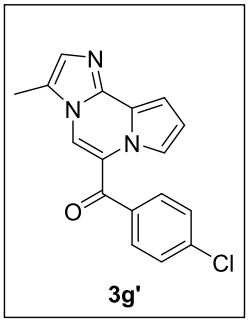
*(4-Chlorophenyl)(2-methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)methanone (**3g**).*



3g

Hexane/ethyl acetate/dichloromethane (3:1:2) as the eluent; Yellow solid, mp: 198.2−198.6 °C (26.2 mg, 77%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (d, J = 3.2 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.57 (s, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 3.2 Hz, 1H), 6.96 (s, 1H), 6.73 (t, J = 3.6 Hz, 1H), 2.36 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.8, 142.9, 139.5, 138.8, 135.9, 131.0, 129.2, 122.0, 121.8, 121.4, 118.7, 113.4, 110.5, 103.7, 14.2; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}ClN_3O$ 310.0742, found 310.0744.

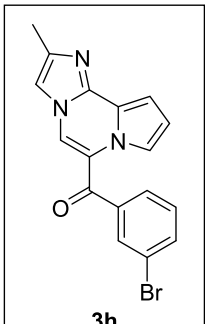
*(4-Chlorophenyl)(3-methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)methanone (**3g′**).*



3g'

Hexane/ethyl acetate/dichloromethane (3:1:2) as the eluent; Yellow solid, mp: 230.1−230.5 °C (6.1 mg, 18%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22−8.20 (m, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.43 (s, 1H), 7.14 (d, J = 3.6 Hz, 2H), 6.76 (t, J = 3.6 Hz, 1H), 2.33 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.9, 139.9, 139.0, 135.9, 131.1, 130.2, 129.3, 122.6, 122.2, 122.0, 118.7, 118.2, 113.4, 103.6, 8.9; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}ClN_3O$ 310.0742, found 310.0746.

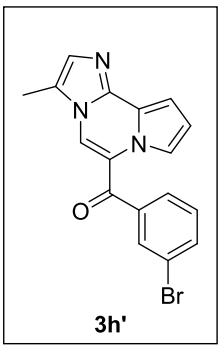
*(3-Bromophenyl)(2-methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)methanone (**3h**).*



3h

Hexane/ethyl acetate/dichloromethane (4:1:2) as the eluent; Yellow solid, mp: 211.0−211.4 °C (24.9 mg, 64%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 (d, J = 3.2 Hz, 1H), 7.93 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.60 (s, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.15 (d, J = 3.6 Hz, 1H), 6.99 (s, 1H), 6.76 (t, J = 3.4 Hz, 1H), 2.39 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.5, 143.0, 139.5, 138.9, 135.9, 132.3, 130.4, 128.0, 123.1, 122.1, 122.0, 121.7, 118.9, 113.5, 110.6, 103.8, 14.3; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}BrN_3O$ 354.0237, found 354.0234.

*(3-Bromophenyl)(3-methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)methanone (**3h′**).*

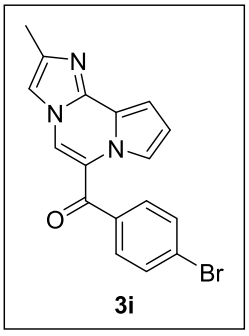


3h'

https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

Hexane/ethyl acetate/dichloromethane (4:1:2) as the eluent; Yellow solid, mp: 233.5−233.9 °C (3.9 mg, 10%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.00 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.46−7.42 (m, 2H), 7.16 (s, 2H), 6.78−6.67 (m, 1H), 2.34 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.6, 139.4, 139.0, 136.2, 132.6, 130.4, 130.3, 128.2, 123.3, 122.6, 122.0, 119.3, 118.3, 113.5, 103.7, 77.4, 9.0; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{17}H_{13}BrN_3O$ 354.0237, found 354.0238.

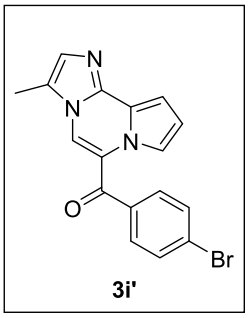
*(4-Bromophenyl)(2-methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)methanone (**3i**).*



3i

Hexane/ethyl acetate/dichloromethane (5:1:2) as the eluent; Yellow solid, mp: 179.3−179.7 °C (27.3 mg, 70%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33−8.29 (m, 1H), 7.73−7.66 (m, 4H), 7.58 (s, 1H), 7.17 (d, J = 4.0 Hz, 1H), 6.99 (s, 1H), 6.77 (t, J = 3.4 Hz, 1H), 2.40 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.0, 143.0, 138.9, 136.4, 132.2, 131.1, 128.2, 122.1, 121.8, 121.5, 118.8, 113.5, 110.5, 103.8, 14.3; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{17}H_{13}BrN_3O$ 354.0237, found 354.0233.

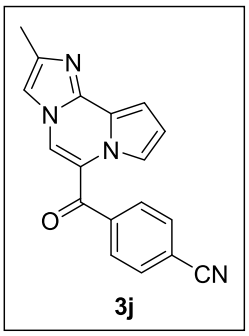
*(4-Bromophenyl)(3-methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)methanone (**3i'**).*



3i'

Hexane/ethyl acetate/dichloromethane (5:1:2) as the eluent; Yellow solid, mp: 253.4−253.8 °C (4.7 mg, 12%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.23−8.22 (m, 1H), 7.75−7.70 (m, 4H), 7.44 (s, 1H), 7.15 (d, J = 4.0 Hz, 2H), 6.79−6.75 (m, 1H), 2.34 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.0, 136.3, 132.3, 131.2, 130.2, 128.5, 122.6, 122.2, 122.0, 118.8, 118.3, 113.4, 103.6, 77.4, 9.0; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{17}H_{13}BrN_3O$ 354.0237, found 354.0239.

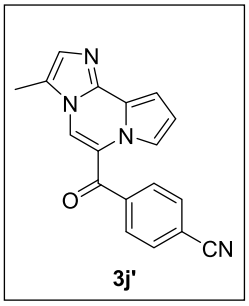
*4-(2-Methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazine-6-carbonyl)-benzonitrile (**3j**).*



3j

Hexane/ethyl acetate/dichloromethane (2:1:2) as the eluent; Orange solid, mp: 285.4−285.8 °C (18.8 mg, 57%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.41 (d, J = 3.6 Hz, 1H), 7.91−7.84 (m, 4H), 7.57 (s, 1H), 7.19 (d, J = 3.2 Hz, 1H), 6.99 (s, 1H), 6.80 (t, J = 3.4 Hz, 1H), 2.40 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.5, 143.4, 141.5, 139.0, 132.7, 129.9, 122.6, 122.1, 121.5, 119.0, 117.8, 116.3, 113.8, 110.5, 104.2, 14.3; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{18}H_{13}N_4O$ 301.1084, found 301.1086.

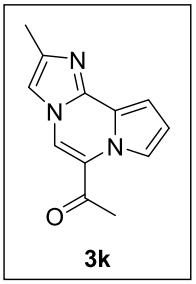
*4-(3-Methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazine-6-carbonyl)-benzonitrile (**3j'**).*



3j'

Hexane/ethyl acetate/dichloromethane (2:1:2) as the eluent; Yellow solid, mp: 242.7−243.1 °C (9.9 mg, 30%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.34−8.32 (m, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.0 Hz, 2H), 7.42 (s, 1H), 7.18 (d, J = 2.0 Hz, 2H), 6.81−6.79 (m, 1H), 2.33 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.5, 141.3, 132.8, 130.6, 130.0, 122.0, 121.9, 119.9, 118.5, 117.8, 116.6, 113.7, 104.0, 77.4, 14.3, 8.9; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{18}H_{13}N_4O$ 301.1084, found 301.1091.

*1-(2-Methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)ethan-1-one (**3k**).*



3k

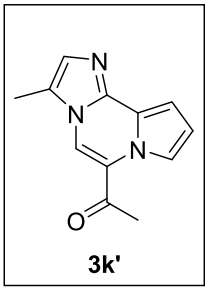
Hexane/ethyl acetate/dichloromethane (4:1:2) as the eluent; Yellow solid, mp: 199.4−199.8 °C (19.5 mg, 83%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.54 (d, J = 3.2 Hz, 1H), 7.82 (s, 1H), 7.05 (d, J = 3.2 Hz, 1H), 6.89 (s, 1H), 6.67 (t, J = 3.2 Hz, 1H), 2.52 (s, 3H), 2.34 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$)

https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

δ 190.2, 142.7, 138.8, 121.9, 121.6, 119.6, 119.4, 113.2, 110.3, 103.2, 26.6, 14.2; **HRMS** (ESI-QTOF) *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}N_3O$ 214.0975, found 214.0976. The crystal **3k** for X-ray crystallographic analysis was obtained via dissolution of the compound in a mixed solvent (dichloromethane/ethyl acetate/EtOH, 1:1:1) and slow evaporation of the solvent at room temperature.

Synthesis of 3k′. A mixture of **2k** (0.64 mmol, 1.0 equiv) and propargyl amine (3.0 equiv) in ethyl alcohol (2.8 mL) was stirred at 120 °C for 1 h (a heating mantle was used). The reaction was carried out in a 7 mL sealed vial. The reaction mixture was concentrated *in vacuo* to yield the crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 1:1:1) to afford **3k′** (19.0 mg, 14%) as a yellow solid along with **3k** (95.1 mg, 70%) as a yellow solid.

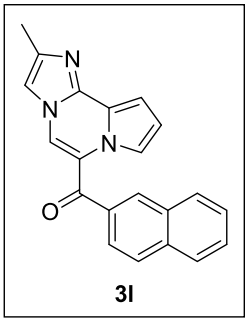
*1-(3-Methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)ethan-1-one (**3k′**).*



3k'

Hexane/ethyl acetate/dichloromethane (1:1:1) as the eluent; Yellow solid, mp: 183.7−184.2 °C (19.0 mg, 14%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.79 (d, *J* = 2.8 Hz, 1H), 7.14 (d, *J* = 2.4 Hz, 1H), 7.10 (s, 1H), 6.72 (d, *J* = 2.8 Hz, 1H), 2.66 (s, 3H), 2.45 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 190.5, 139.1, 130.2, 122.5, 122.3, 121.7, 119.2, 117.1, 113.3, 103.3, 26.8, 9.0; **HRMS** (ESI-QTOF) *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}N_3O$ 214.0975, found 214.0977.

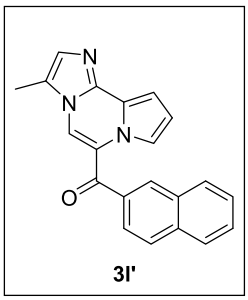
*(2-Methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)(naphthalen-2-yl)methanone (**3l**).*



3l

Hexane/ethyl acetate/dichloromethane (4:1:2) as the eluent; Yellow solid, mp: 99.2−99.6 °C (28.3 mg, 79%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.37−8.26 (m, 2H), 8.04−7.93 (m, 3H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.71−7.57 (m, 3H), 7.18 (d, *J* = 3.2 Hz, 1H), 6.95 (s, 1H), 6.77 (t, *J* = 3.4 Hz, 1H), 2.39 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 189.1, 142.7, 138.9, 135.5, 134.9, 132.3, 131.1, 129.4, 129.1, 128.9, 128.1, 127.4, 125.4, 122.3, 122.1, 121.4, 118.8, 113.4, 110.6, 103.7, 14.3; **HRMS** (ESI-QTOF) *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}N_3O$ 326.1288, found 326.1285.

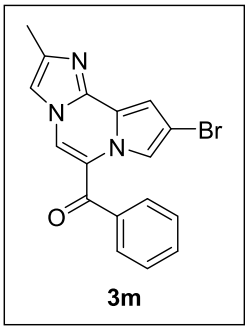
*(3-Methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)(naphthalen-2-yl)methanone (**3l′**).*



3l'

Hexane/ethyl acetate/dichloromethane (4:1:2) as the eluent; Yellow solid, mp: 231.8−232.3 °C (3.9 mg, 11%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.24 (dd, *J* = 2.6, 1.2 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.98−7.93 (m, 3H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.53 (s, 1H), 7.18−7.14 (m, 2H), 6.78 (t, *J* = 3.2 Hz, 1H), 2.29 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 189.1, 139.0, 135.7, 134.8, 132.4, 131.4, 130.0, 129.5, 129.1, 129.0, 128.1, 127.5, 125.4, 122.7, 122.6, 122.1, 118.6, 118.2, 113.3, 103.5, 9.0; **HRMS** (ESI-QTOF) *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}N_3O$ 326.1288, found 326.1294.

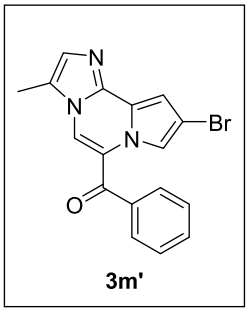
*(9-Bromo-2-methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)-(phenyl)methanone (**3m**).*



3m

Hexane/ethyl acetate/dichloromethane (3:1:2) as the eluent; Yellow solid, mp: 193.3−193.7 °C (28.8 mg, 74%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.78 (d, *J* = 7.6 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.63 (s, 1H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.13 (s, 1H), 7.00 (s, 1H), 2.39 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.8, 143.2, 137.4, 137.3, 133.2, 129.6, 129.0, 122.6, 121.8, 121.2, 118.4, 110.9, 105.8, 102.7, 14.3; **HRMS** (ESI-QTOF) *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}BrN_3O$ 354.0237, found 354.0233.

*(9-Bromo-3-methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)-(phenyl)methanone (**3m′**).*



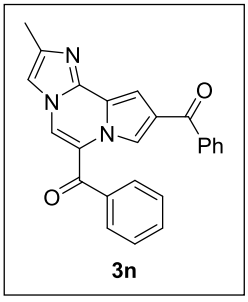
3m'

Hexane/ethyl acetate/dichloromethane (3:1:2) as the eluent; Yellow solid, mp: 190.7−191.2 °C (2.3 mg, 6%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 1.2 Hz, 1H), 7.84 (d, *J* = 7.2 Hz, 2H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 2H), 7.49

https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

(s, 1H), 7.16 (s, 1H), 7.13 (d, J = 1.2 Hz, 1H), 2.32 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.8, 137.4, 137.3, 133.5, 130.5, 129.7, 129.0, 123.0, 122.4, 121.6, 119.1, 117.9, 105.6, 102.6, 8.9; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}BrN_3O$ 354.0237, found 354.0243.

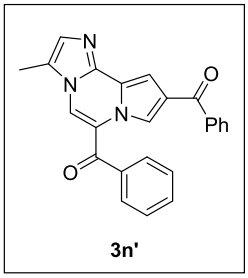
*(2-Methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazine-6,9-diyl)bis-(phenylmethanone) (**3n**).*



3n

Hexane/ethyl acetate/dichloromethane (1:1:1) as the eluent; Yellow solid, mp: 207.5−208.2 °C (29.9 mg, 70%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.85 (d, J = 1.6 Hz, 1H), 7.95−7.91 (m, 2H), 7.82−7.79 (m, 2H), 7.72 (s, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.59−7.53 (m, 4H), 7.48 (t, J = 7.6 Hz, 2H), 7.02 (s, 1H), 2.38 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 190.8, 188.6, 143.3, 139.0, 138.2, 137.1, 133.4, 132.2, 129.6, 129.4, 129.0, 128.5, 127.3, 123.9, 123.3, 122.9, 121.5, 111.4, 104.9, 14.2; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{24}H_{17}N_3O_2$ 380.1394, found 380.1402.

*(3-Methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazine-6,9-diyl)bis-(phenylmethanone) (**3n′**).*



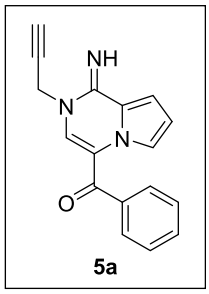
3n'

Hexane/ethyl acetate/dichloromethane (1:1:1) as the eluent; Yellow solid, mp: 165.8−166.6 °C (10.6 mg, 25%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.78 (d, J = 1.6 Hz, 1H), 7.96−7.93 (m, 2H), 7.89−7.85 (m, 2H), 7.71 (t, J = 7.6 Hz, 1H), 7.60−7.56 (m, 5H), 7.50 (t, J = 7.6 Hz, 2H), 7.19 (d, J = 1.2 Hz, 1H), 2.35 (d, J = 0.8 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 190.9, 188.6, 139.1, 138.3, 137.1, 133.7, 132.3, 130.6, 129.8, 129.4, 129.1, 128.5, 127.3, 123.6, 123.5, 123.0, 121.9, 120.7, 104.7, 8.9; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{24}H_{17}N_3O_2$ 380.1394, found 380.1392.

General Procedure for the Synthesis of 5. A mixture of **2a** (0.75 mmol, 1.0 equiv) and propargyl amine (3.0 equiv) in toluene (4.0 mL) was stirred at 60 °C for 17 h (a heating mantle was used). The reaction was carried out in a 20 mL sealed vial. The reaction mixture was concentrated *in vacuo* to yield the crude product, which was triturated with mixed solvent (hexane/dichloromethane = 5:1) to afford **5a**. Additional purification of the filtrate by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 3:1:2) furnished **5a**. Overall, **5a** was obtained in 96% yield (198.2 mg) as a brown solid.

Scale-Up Experiment. A mixture of **2a** (1.88 mmol, 1.0 equiv) and propargyl amine (3.0 equiv) in toluene (8.0 mL) was stirred at 60 °C for 19 h (a heating mantle was used). The reaction mixture was concentrated *in vacuo* to yield the crude product, which was triturated with mixed solvent (hexane/dichloromethane = 5:1) to afford **5a**. Additional purification of the filtrate by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 3:1:2) furnished **5a**. Overall, **5a** was obtained in 95% yield (491.7 mg) as a brown solid.

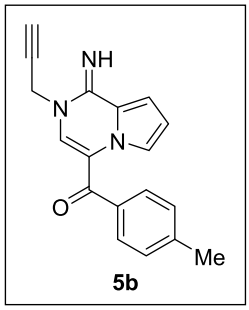
*(1-Imino-2-(prop-2-yn-1-yl)-1,2-dihydropyrrolo[1,2-a]pyrazin-4-yl)(phenyl)methanone (**5a**).*



5a

Hexane/ethyl acetate/dichloromethane (3:1:2) as the eluent; Brown solid, mp: 165.8−166.2 °C (198.2 mg, 96%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.45−8.42 (m, 1H), 7.71 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.46 (s, 1H), 6.89 (d, J = 4.0 Hz, 1H), 6.57 (t, J = 3.4 Hz, 1H), 4.76 (d, J = 2.4 Hz, 2H), 2.40 (t, J = 2.4 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.1, 151.0, 138.5, 133.2, 132.0, 129.2, 128.6, 121.9, 121.6, 116.6, 112.4, 108.7, 76.9, 75.6, 38.0; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{17}H_{14}N_3O$ 276.1131, found 276.1135.

*(1-Imino-2-(prop-2-yn-1-yl)-1,2-dihydropyrrolo[1,2-a]pyrazin-4-yl)(p-tolyl)methanone (**5b**).*

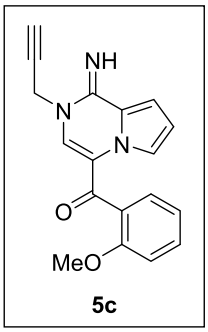


5b

Hexane/ethyl acetate/dichloromethane (3:1:2) as the eluent; Ivory solid, mp: 166.1−166.5 °C (204.0 mg, 94%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.38 (d, J = 3.6 Hz, 1H), 7.63 (d, J = 7.2 Hz, 2H), 7.43 (s, 1H), 7.29 (d, J = 7.6 Hz, 2H), 6.87 (d, J = 3.6 Hz, 1H), 6.55 (t, J = 3.2 Hz, 1H), 4.76 (d, J = 2.4 Hz, 2H), 2.45 (s, 3H), 2.42 (t, J = 2.4 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.9, 151.0, 142.8, 135.6, 132.6, 129.4, 129.3, 121.9, 121.5, 116.7, 112.3, 108.6, 77.1, 75.3, 37.9, 21.7; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{16}N_3O$ 290.1288, found 290.1290.

https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

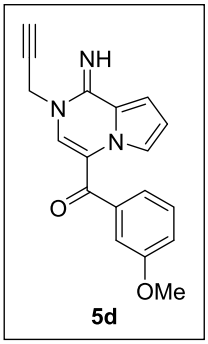
*(1-Imino-2-(prop-2-yn-1-yl)-1,2-dihydropyrrolo[1,2-a]pyrazin-4-yl)(2-methoxyphenyl)methanone (**5c**).*



5c

Hexane/ethyl acetate/dichloromethane (3:1:2) as the eluent; Ivory solid, mp: 164.8−165.2 °C (210.7 mg, 92%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.66−8.63 (m, 1H), 7.46 (t, J = 7.8 Hz, 1H), 7.35 (s, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 4.0 Hz, 1H), 6.56 (t, J = 3.4 Hz, 1H), 4.70 (d, J = 2.4 Hz, 2H), 3.82 (s, 3H), 2.33 (t, J = 2.6 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.1, 156.9, 151.1, 134.0, 131.8, 129.4, 127.9, 122.0, 121.8, 120.6, 117.5, 112.2, 111.5, 108.4, 76.9, 75.4, 55.8, 38.0; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{16}N_3O_2$ 306.1237, found 306.1234.

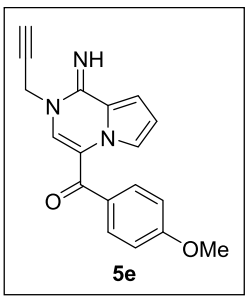
*(1-Imino-2-(prop-2-yn-1-yl)-1,2-dihydropyrrolo[1,2-a]pyrazin-4-yl)(3-methoxyphenyl)methanone (**5d**).*



5d

Hexane/ethyl acetate/dichloromethane (2:1:2) as the eluent; Yellow solid, mp: 121.1−121.5 °C (226.7 mg, 99%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44−8.41 (m, 1H), 7.51 (s, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.28 (s, 1H), 7.25−7.23 (m, 1H), 7.14−7.10 (m, 1H), 6.89 (d, J = 4.0 Hz, 1H), 6.59−6.55 (m, 1H), 4.77 (d, J = 2.8 Hz, 2H), 3.87 (s, 3H), 2.42 (t, J = 2.6 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.7, 159.8, 150.9, 139.7, 133.3, 129.6, 121.9, 121.63, 121.57, 118.4, 116.5, 113.8, 112.4, 108.7, 77.0, 75.6, 55.6, 38.0; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{16}N_3O_2$ 306.1237, found 306.1238.

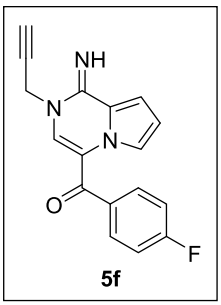
*(1-Imino-2-(prop-2-yn-1-yl)-1,2-dihydropyrrolo[1,2-a]pyrazin-4-yl)(4-methoxyphenyl)methanone (**5e**).*



5e

Hexane/ethyl acetate/dichloromethane (2:1:2) as the eluent; Yellow solid, mp: 144.9−145.3 °C (222.1 mg, 97%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32−8.29 (m, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.42 (s, 1H), 6.99 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 4.0 Hz, 1H), 6.55 (t, J = 3.4 Hz, 1H), 4.77 (d, J = 2.8 Hz, 2H), 3.90 (s, 3H), 2.43 (t, J = 2.4 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.0, 163.0, 151.0, 131.8, 131.5, 130.8, 122.0, 121.4, 116.6, 113.9, 112.3, 108.5, 75.3, 55.7, 37.8; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{16}N_3O_2$ 306.1237, found 306.1237.

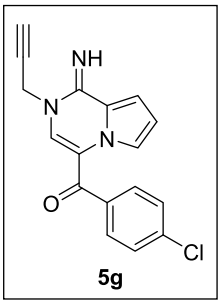
*(4-Fluorophenyl)(1-Imino-2-(prop-2-yn-1-yl)-1,2-dihydropyrrolo-[1,2-a]pyrazin-4-yl)methanone (**5f**).*



5f

Hexane/ethyl acetate/dichloromethane (3:1:2) as the eluent; Ivory solid, mp: 176.4−176.8 °C (182.6 mg, 83%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39−8.35 (m, 1H), 7.78−7.72 (m, 2H), 7.45 (s, 1H), 7.23−7.15 (m, 2H), 6.89 (d, J = 4.0 Hz, 1H), 6.57 (t, J = 3.4 Hz, 1H), 4.78 (d, J = 2.8 Hz, 2H), 2.44 (t, J = 2.6 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 186.6, 166.3 (J = 252.0 Hz), 150.9, 134.7 (J = 3.0 Hz), 132.8, 131.7 (J = 9.0 Hz), 121.9, 121.5, 116.5, 116.0 (J = 22.0 Hz), 112.4, 108.8, 76.9, 75.8, 37.9; **^{19}F NMR** (376 MHz, $CDCl_3$) δ −106.7; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}FN_3O$ 294.1037, found 294.1041.

*(4-Chlorophenyl)(1-Imino-2-(prop-2-yn-1-yl)-1,2-dihydropyrrolo-[1,2-a]pyrazin-4-yl)methanone (**5g**).*

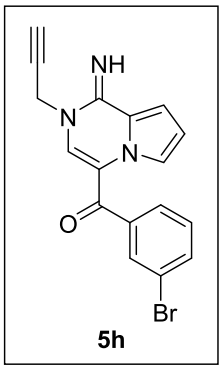


5g

Hexane/ethyl acetate/dichloromethane (3:1:2) as the eluent; Ivory solid, mp: 159.6−160.0 °C (209.1 mg, 90%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.40−8.36 (m, 1H), 7.66 (d, J = 7.6 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.44 (s, 1H), 6.88 (d, J = 4.0 Hz, 1H), 6.56 (t, J = 3.4 Hz, 1H), 4.77 (d, J = 2.4 Hz, 2H), 2.45 (t, J = 3.0 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 186.6, 150.8, 138.3, 136.8, 133.0, 130.6, 128.9, 121.9, 121.6, 116.4, 112.4, 108.8, 75.8, 37.9; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}ClN_3O$ 310.0742, found 310.0747.

https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

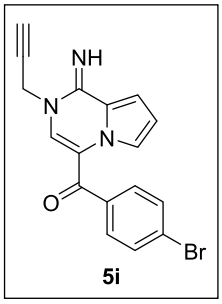
*(3-Bromophenyl)(1-Imino-2-(prop-2-yn-1-yl)-1,2-dihydropyrrolo-[1,2-a]pyrazin-4-yl)methanone (**5h**).*



5h

Hexane/ethyl acetate/dichloromethane (3:1:2) as the eluent; Ivory solid, mp: 159.2−159.6 °C (217.8 mg, 82%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.45−8.40 (m, 1H), 7.85 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.53 (s, 1H), 7.39 (t, J = 8.0 Hz, 1H), 6.89 (d, J = 4.0 Hz, 1H), 6.57 (t, J = 3.4 Hz, 1H), 4.79 (d, J = 2.4 Hz, 2H), 2.50 (t, J = 2.6 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 186.1, 150.8, 140.3, 134.8, 133.5, 132.1, 130.3, 127.7, 122.7, 121.8, 121.6, 116.2, 112.5, 108.8, 76.8, 76.3, 37.9; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{17}H_{13}BrN_3O$ 354.0237, found 354.0234.

*(4-Bromophenyl)(1-Imino-2-(prop-2-yn-1-yl)-1,2-dihydropyrrolo-[1,2-a]pyrazin-4-yl)methanone (**5i**).*

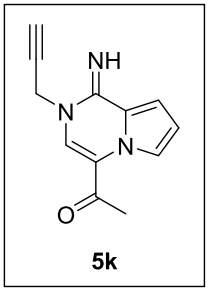


5i

Hexane/ethyl acetate/dichloromethane (3:1:2) as the eluent; Brown solid, mp: 158.7−159.1 °C (252.4 mg, 95%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (d, J = 2.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.44 (s, 1H), 6.89 (d, J = 4.0 Hz, 1H), 6.57 (t, J = 3.2 Hz, 1H), 4.78 (d, J = 2.4 Hz, 2H), 2.45 (t, J = 2.4 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 186.8, 150.8, 137.2, 133.1, 131.9, 130.7, 126.8, 121.9, 121.6, 116.4, 112.5, 108.8, 75.8, 38.0; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{17}H_{13}BrN_3O$ 354.0237, found 354.0242.

*4-(1-Imino-2-(prop-2-yn-1-yl)-1,2-dihydropyrrolo[1,2-a]-pyrazine-4-carbonyl)benzonitrile (**5j**).* Hexane/ethyl acetate/dichloromethane (2:1:2) as the eluent; Yellow solid, mp: 269.3−269.7 °C (220.7 mg, 98%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44 (d, J = 2.8 Hz, 1H), 7.83−7.77 (m, 4H), 7.43 (s, 1H), 6.90 (d, J = 4.0 Hz, 1H), 6.59 (t, J = 3.4 Hz, 1H), 4.78 (d, J = 2.4 Hz, 2H), 2.45 (t, J = 2.2 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 185.9, 150.7, 142.4, 133.9, 132.5, 129.5, 121.73, 121.71, 118.0, 116.2, 115.3, 112.7, 109.1, 76.6, 76.3, 38.1; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{18}H_{13}N_4O$ 301.1084, found 301.1084.

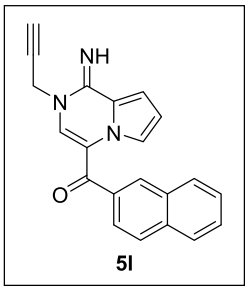
*1-(1-Imino-2-(prop-2-yn-1-yl)-1,2-dihydropyrrolo[1,2-a]pyrazin-4-yl)ethan-1-one (**5k**).*



5k

Hexane/ethyl acetate/dichloromethane (1:1:1) as the eluent; Ivory solid, mp: 139.5−139.9 °C (120.4 mg, 75%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.51 (d, J = 2.8 Hz, 1H), 7.76 (s, 1H), 6.82 (d, J = 4.0 Hz, 1H), 6.49 (t, J = 3.2 Hz, 1H), 4.83 (d, J = 2.0 Hz, 2H), 2.57 (t, J = 2.4 Hz, 1H), 2.48 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.8, 151.0, 129.5, 122.1, 121.9, 116.9, 112.2, 108.4, 75.8, 37.9, 25.8; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{12}H_{12}N_3O$ 214.0975, found 214.0976.

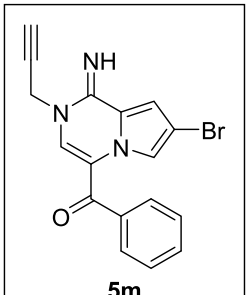
*(1-Imino-2-(prop-2-yn-1-yl)-1,2-dihydropyrrolo[1,2-a]pyrazin-4-yl)(naphthalen-2-yl)methanone (**5l**).*



5l

Hexane/ethyl acetate/dichloromethane (3:1:2) as the eluent; Ivory solid, mp: 158.4−158.8 °C (205.0 mg, 84%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.47−8.44 (m, 1H), 8.22 (s, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.94 (d, J = 7.6 Hz, 2H), 7.83 (d, J = 8.4 Hz, 1H), 7.66−7.58 (m, 2H), 7.57 (s, 1H), 6.91 (d, J = 4.0 Hz, 1H), 6.59 (t, J = 3.4 Hz, 1H), 4.76 (d, J = 2.4 Hz, 2H), 2.33 (t, J = 2.6 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.9, 151.0, 135.6, 135.0, 133.2, 132.4, 130.1, 129.1, 128.8, 128.3, 128.0, 127.2, 125.6, 122.0, 121.6, 116.8, 112.4, 108.7, 77.0, 75.6, 37.9; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{21}H_{16}N_3O$ 326.1288, found 326.1286.

*(7-Bromo-1-imino-2-(prop-2-yn-1-yl)-1,2-dihydropyrrolo[1,2-a]-pyrazin-4-yl)(phenyl)methanone (**5m**).*



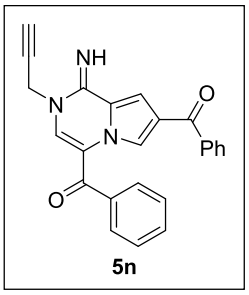
5m

Hexane/ethyl acetate/dichloromethane (3:1:2) as the eluent; Ivory solid, mp: 137.8−138.2 °C (220.5 mg, 83%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.68 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.53−7.45 (m, 3H), 6.87 (s, 1H), 4.74 (d, J = 2.0 Hz, 2H), 2.43 (t, J = 2.4 Hz, 1H); **^{13}C{^{1}H} NMR**

https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

(100 MHz, $CDCl_3$) δ 187.7, 149.6, 138.1, 133.2, 132.1, 129.1, 128.7, 122.4, 121.2, 115.9, 110.5, 100.9, 76.6, 76.1, 38.2; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}BrN_3O$ 354.0237, found 354.0234.

*(1-Imino-2-(prop-2-yn-1-yl)-1,2-dihydropyrrolo[1,2-a]pyrazine-4,7-diyl)bis(phenylmethanone) (**5n**).*



5n

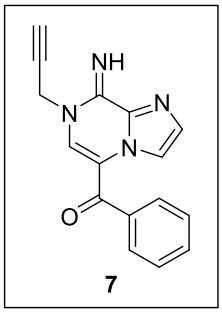
Hexane/ethyl acetate/dichloromethane (1:1:1) as the eluent; Yellow solid, mp: 145.7−146.3 °C (266.8 mg, 94%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.92 (d, J = 0.8 Hz, 1H), 7.89 (d, J = 7.6 Hz, 2H), 7.70 (d, J = 7.2 Hz, 2H), 7.62 (s, 1H), 7.60−7.55 (m, 2H), 7.50 (td, J = 7.6, 2.8 Hz, 5H), 7.43 (d, J = 0.8 Hz, 1H), 4.77 (d, J = 2.4 Hz, 2H), 2.45 (t, J = 2.4 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 190.4, 187.8, 150.4, 139.0, 137.9, 134.7, 132.28, 132.26, 129.2, 129.1, 128.7, 128.6, 126.52, 126.46, 123.1, 115.7, 110.3, 76.4, 76.2, 38.2; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{24}H_{17}N_3O_2$ 380.1394, found 380.1399.

General Procedure for the Synthesis of 3 from 5. A mixture of **5a** (0.18 mmol, 1.0 equiv) in ethyl alcohol (2.0 mL) was stirred at 120 °C for 1 h (a heating mantle was used). The reaction was carried out in a 7 mL sealed vial. The reaction mixture was concentrated *in vacuo* to yield the crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 3:1:2) to afford **3a** (49.8 mg, 100%) as a yellow solid.

Scale-Up Experiment. A mixture of **5a** (1.09 mmol, 1.0 equiv) in ethyl alcohol (6.0 mL) was stirred at 120 °C for 2 h (a heating mantle was used). The reaction was carried out in a 20 mL sealed vial. The reaction mixture was concentrated *in vacuo* to yield the crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 3:1:2) to afford **3a** (276.1 mg, 92%) as a yellow solid.

Synthesis of 7. A mixture of **6** (0.75 mmol, 1.0 equiv) and propargyl amine (3.0 equiv) in toluene (4.0 mL) was stirred at 60 °C for 18 h (a heating mantle was used). The reaction was carried out in a 20 mL sealed vial. The reaction mixture was concentrated *in vacuo* to yield the crude product, which was suspended in dichloromethane (1.5 mL) and filtered to afford **7** (203.1 mg, 98%) as an ivory solid.

*(8-Imino-7-(prop-2-yn-1-yl)-7,8-dihydroimidazo[1,2-a]pyrazin-5-yl)(phenyl)methanone (**7**).*

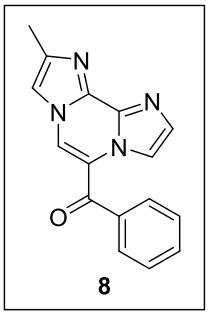


7

Ivory solid, mp: 150.5−150.9 °C (203.1 mg, 98%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.54 (s, 1H), 7.73 (s, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.45 (s, 1H), 4.81 (d, J = 2.4 Hz, 2H), 2.48 (t, J = 2.6 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.3, 149.3, 137.7, 135.6, 133.8, 132.44, 132.37, 129.1, 128.8, 119.0, 115.4, 76.7, 76.1, 38.4; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{16}H_{13}N_4O$ 277.1084, found 277.1085.

Synthesis of 8. A mixture of 7 (0.18 mmol, 1.0 equiv) in ethyl alcohol (2.0 mL) was stirred at 120 °C for 7 h (a heating mantle was used). The reaction was carried out in a 7 mL sealed vial. The reaction mixture was concentrated *in vacuo* to yield the crude product, which was purified by silica gel column chromatography (ethyl acetate/dichloromethane = 1:1) to afford **8** (42.8 mg, 86%) as an ivory solid.

*(9-Methyldiimidazo[1,2-a:2′,1′-c]pyrazin-5-yl)(phenyl)-methanone (**8**).*

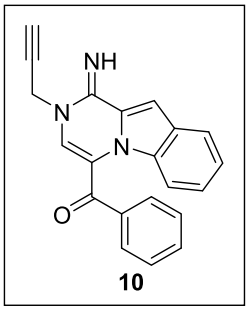


8

Ivory solid, mp: 257.4−257.8 °C (42.8 mg, 86%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.94 (s, 1H), 7.83 (d, J = 6.8 Hz, 2H), 7.69 (t, J = 7.2 Hz, 1H), 7.62 (s, 1H), 7.57 (t, J = 7.4 Hz, 2H), 7.18 (s, 1H), 2.43 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.4, 144.7, 137.0, 133.4, 133.0, 129.8, 129.6, 129.2, 129.1, 122.6, 121.4, 116.5, 112.0, 14.4; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{16}H_{13}N_4O$ 277.1084, found 277.1085.

General Procedure for the Synthesis of 10 and 11. A mixture of **9** (0.55 mmol 1.0 equiv) and propargyl amine (3.0 equiv) in toluene (4.0 mL) was stirred at 60 °C for 19 h (a heating mantle was used). The reaction was carried out in a 20 mL sealed vial. The reaction mixture was concentrated *in vacuo* to yield the crude product, which was triturated with mixed solvent (hexane/dichloromethane = 5:1) to afford **10** and **11**. Additional purification of the filtrate by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 3:1:2) furnished **10** (65.4 mg, 37%) as a yellow solid and **11** (71.5 mg, 40%) as a yellow solid.

*(1-Imino-2-(prop-2-yn-1-yl)-1,2-dihydropyrazino[1,2-a]indol-4-yl)(phenyl)methanone (**10**).*



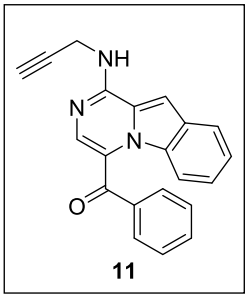
10

Yellow solid, mp: 170.8−171.2 °C (65.4 mg, 37%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, J = 7.6 Hz, 2H), 7.79 (s, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 7.2 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.43 (d, J = 8.0 Hz, 1H), 7.25−7.20 (m, 2H), 7.19 (s, 1H), 7.14 (s, 1H), 4.71 (d, J = 2.0 Hz, 2H), 2.35 (t, J = 2.8 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 185.9, 151.7, 137.2, 133.8, 133.3, 130.1, 129.2, 128.8, 128.6, 126.9, 124.1, 122.3, 121.7, 118.7, 115.9, 103.2, 77.1, 75.1, 37.9;

https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

HRMS (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{21}H_{16}N_3O$ 326.1288, found 326.1291.

*Phenyl(1-(prop-2-yn-1-ylamino)-1,2-dihydropyrazino[1,2-a]-indol-4-yl)methanone (**11**).*

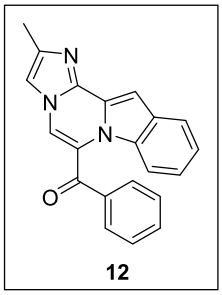


11

Yellow solid, mp: 170.7−171.3 °C (71.5 mg, 40%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.5 Hz, 2H), 7.80 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.65 (t, J = 7.5 Hz, 1H), 7.59 (s, 1H), 7.53 (t, J = 7.2 Hz, 2H), 7.36−7.28 (m, 2H), 6.99 (s, 1H), 5.79 (s, 1H), 4.43 (dd, J = 5.2, 2.4 Hz, 2H), 2.32 (t, J = 2.4 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.8, 152.6, 137.5, 137.3, 133.1, 132.1, 130.3, 128.5, 128.3, 123.4, 123.0, 122.9, 121.8, 116.2, 95.5, 92.2, 79.6, 72.0, 30.8; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{21}H_{16}N_3O$ 326.1288, found 326.1295.

General Procedure for the Synthesis of 12 and 13. A mixture of **10** (0.15 mmol, 1.0 equiv) in ethyl alcohol (2.0 mL) was stirred at 120 °C for 1 h (a heating mantle was used). The reaction was carried out in a 7 mL sealed vial. The reaction mixture was concentrated *in vacuo* to yield the crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 5:1:2) to afford **12** (39.0 mg, 80%) as a yellow solid.

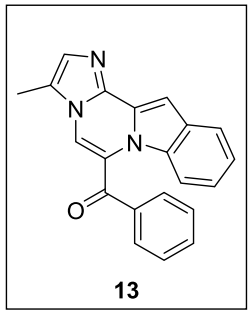
*(2-Methylimidazo[2′,1′:3,4]pyrazino[1,2-a]indol-6-yl)(phenyl)-methanone (**12**).*



12

Hexane/ethyl acetate/dichloromethane (5:1:2) as the eluent; Yellow solid, mp: 259.7−261.1 °C (39.0 mg, 80%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.8 Hz, 2H), 7.45 (s, 1H), 7.35−7.26 (m, 3H), 7.18 (t, J = 7.8 Hz, 1H), 7.04 (s, 1H), 2.44 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.6, 142.5, 138.2, 136.2, 134.6, 132.2, 130.5, 129.7, 129.2, 126.6, 124.9, 122.8, 122.6, 121.8, 115.2, 114.2, 111.9, 98.0, 14.3; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{21}H_{16}N_3O$ 326.1288, found 326.1285.

*(3-Methylimidazo[2′,1′:3,4]pyrazino[1,2-a]indol-6-yl)(phenyl)-methanone (**13**).*

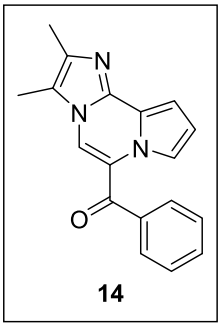


13

Hexane/ethyl acetate/dichloromethane (3:1:2) as the eluent; Yellow solid, mp: 174.4−174.9 °C (42.5 mg, 87%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.2 Hz, 2H), 7.79 (d, J = 8.0 Hz, 1H), 7.69 (t, J = 7.2 Hz, 1H), 7.54 (t, J = 7.6 Hz, 2H), 7.42 (s, 1H), 7.28−7.26 (m, 2H), 7.20−7.12 (m, 3H), 2.38 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.9, 138.2, 136.2, 134.8, 132.0, 130.4, 130.0, 129.8, 129.3, 127.1, 125.3, 123.6, 122.8, 122.6, 121.7, 114.0, 112.0, 97.8, 9.0; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{21}H_{16}N_3O$ 326.1288, found 326.1291.

Synthesis of 14. A mixture of **2a** (0.11 mmol, 1.0 equiv) and 1-methyl-prop-2-ynylamine (3.0 equiv) in ethyl alcohol (3.0 mL) was stirred at 120 °C for 28 h (a heating mantle was used). The reaction was carried out in a 7 mL sealed vial. The reaction mixture was concentrated *in vacuo* to yield the crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 4:1:2) to afford **14** (27.5 mg, 84%) as a yellow solid.

*(2,3-Dimethylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)(phenyl)-methanone (**14**).*



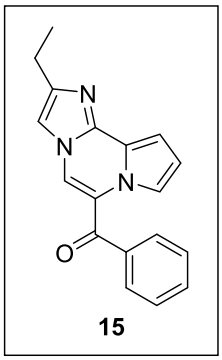
14

Yellow solid, mp: 198.0−198.4 °C (27.5 mg, 84%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 (d, J = 3.2 Hz, 1H), 7.83 (d, J = 7.6 Hz, 2H), 7.67 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.6 Hz, 2H), 7.43 (s, 1H), 7.13 (d, J = 3.6 Hz, 1H), 6.75 (t, J = 3.2 Hz, 1H), 2.33 (s, 3H), 2.23 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 189.2, 138.2, 137.8, 137.7, 133.1, 129.7, 128.9, 122.3, 121.8, 119.5, 118.2, 116.9, 113.2, 103.0, 13.2, 8.2; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{16}N_3O$ 290.1288, found 290.1290.

Synthesis of 15. A mixture of **2a** (0.04 mmol, 1.0 equiv), but-2-yn-1-amine hydrochloride (3.0 equiv), and triethylamine (3.0 equiv) in ethyl alcohol (1.0 mL) was stirred at 120 °C for 18 h (a heating mantle was used). The reaction was carried out in a 7 mL sealed vial. The reaction mixture was concentrated *in vacuo* to yield the crude product, which was purified by silica gel column chromatography (hexane:ethyl acetate:dichloromethane = 3:1:2) to afford **15** (7.0 mg, 64%) as a yellow solid.

https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

*(2-Ethylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)(phenyl)-methanone (**15**).*

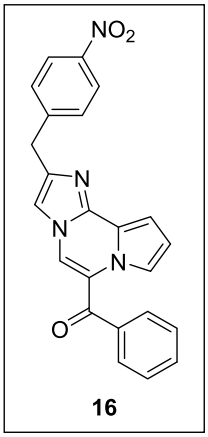


15

Yellow solid, mp: 166.7−167.0 °C (7.0 mg, 64%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.88 (dd, J = 2.4, 1.2 Hz, 1H), 7.89 (s, 1H), 7.72 (d, J = 7.0 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.4 Hz, 2H), 6.82−6.79 (m, 2H), 5.58 (s, 1H), 4.40 (dd, J = 5.0, 2.4 Hz, 2H), 1.84 (t, J = 2.4 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 189.8, 152.1, 143.1, 139.1, 131.6, 129.4, 128.4, 120.7, 120.5, 118.9, 113.6, 102.5, 80.2, 74.9, 31.3, 3.8; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{15}N_3O$ 290.1288, found 290.1292.

General Procedure for the Synthesis of 16−18. A mixture of **5a** (0.11 mmol, 1.0 equiv), 1-iodo-4-nitrobenzene (1.3 equiv), $Pd(PPh_3)_2Cl_2$ (0.1 equiv), CuI (0.1 equiv), and Et_3N (10.0 equiv) in DMF (1.0 mL) was stirred at rt for 1 h under N_2. The reaction was carried out in a 7 mL sealed vial. The reaction mixture diluted with dichloromethane (3.0 mL), and washed with water (10.0 mL). The water layer was extracted with dichloromethane (3.0 mL) one more time. The organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 3:1:2) to afford **16** (29.2 mg, 67%) as a brown solid.

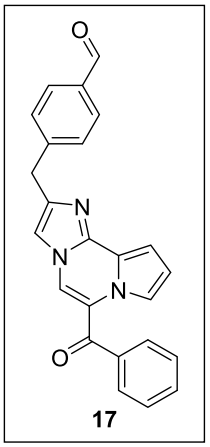
*(2-(4-Nitrobenzyl)imidazo[1,2-a]pyrrolo[2,1-c]pyrazin-6-yl)-(phenyl)methanone (**16**).*



16

Hexane/ethyl acetate/dichloromethane (3:1:2) as the eluent; Brown solid, mp: 196.7−197.1 °C (29.2 mg, 67%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (d, J = 3.2 Hz, 1H), 8.12 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 7.2 Hz, 2H), 7.64 (t, J = 7.2 Hz, 1H), 7.59 (s, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 4.0 Hz, 1H), 6.91 (s, 1H), 6.76 (t, J = 3.4 Hz, 1H), 4.17 (s, 2H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 189.0, 146.9, 146.7, 144.5, 139.4, 137.4, 133.2, 129.9, 129.6, 128.9, 123.8, 122.4, 121.8, 121.2, 119.1, 113.5, 111.5, 104.3, 35.0; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{23}H_{17}N_4O_3$ 397.1295, found 397.1300.

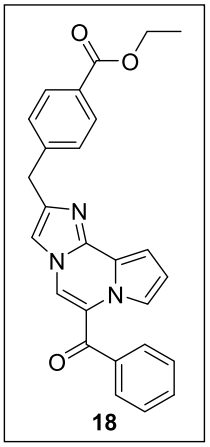
*4-((6-Benzoylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-2-yl)methyl)-benzaldehyde (**17**).*



17

Hexane/ethyl acetate/dichloromethane (3:1:2) as the eluent; Brown gum (23.8 mg, 57%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.33 (d, J = 2.8 Hz, 1H), 7.83−7.77 (m, 4H), 7.64 (t, J = 7.6 Hz, 1H), 7.57 (s, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.47 (d, J = 7.6 Hz, 2H), 7.20 (d, J = 3.6 Hz, 1H), 6.85 (s, 1H), 6.77 (t, J = 3.4 Hz, 1H), 4.17 (s, 2H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 192.1, 189.0, 146.4, 145.3, 139.3, 137.5, 135.0, 133.2, 130.2, 129.8, 129.6, 128.9, 122.4, 121.9, 121.3, 119.1, 113.5, 111.4, 104.3, 35.5; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{24}H_{18}N_3O_2$ 380.1394, found 380.1393.

*Ethyl 4-((6-Benzoylimidazo[1,2-a]pyrrolo[2,1-c]pyrazin-2-yl)-methyl)benzoate (**18**).*



18

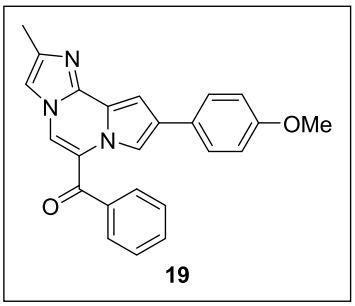
Hexane/ethyl acetate/dichloromethane (3:1:2) as the eluent; Brown gum (21.4 mg, 46%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.34 (d, J = 3.2 Hz, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 7.6 Hz, 2H), 7.64 (t, J = 7.4 Hz, 1H), 7.56 (s, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 2.8 Hz, 1H), 6.79−6.76 (m, 2H), 4.36 (q, J = 7. Two Hz, 2H), 4.14 (s, 2H), 1.38 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 189.1, 166.7, 146.0, 144.4, 139.3, 137.5, 133.2, 130.0, 129.6, 129.1, 128.9, 122.3, 122.0, 121.5, 119.1, 113.5, 111.3, 104.1, 61.0, 35.4, 14.5; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{26}H_{22}N_3O_3$ 424.1656, found 424.1659.

Synthesis of 19. A mixture of **3m** (0.08 mmol, 1.0 equiv), 4-methoxyphenylboronic acid (2.0 equiv), $Pd(PPh_3)_4$ (0.1 equiv), and K_2CO_3 (1.5 equiv) in ethyl alcohol (1.5 mL) was stirred at 100 °C for 22 h (a heating mantle was used). The reaction was carried out in a 7 mL sealed vial. The reaction mixture was concentrated *in vacuo* to yield the crude product, diluted with ethyl acetate (1.0 mL), and washed with water (1.0 mL). The water layer was extracted with ethyl

https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

acetate (1.0 mL) one more time. The organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 3:1:2) to afford **19** (20.1 mg, 63%) as an orange solid.

*(9-(4-Methoxyphenyl)-2-methylimidazo[1,2-a]pyrrolo[2,1-c]-pyrazin-6-yl)(phenyl)methanone (**19**).*

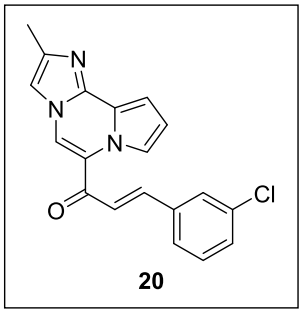


19

Orange solid, mp: 165.7−166.6 °C (20.1 mg, 63%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.59 (d, J = 1.5 Hz, 1H), 7.82 (d, J = 6.8 Hz, 2H), 7.67 (t, J = 7.6 Hz, 1H), 7.61 (d, J = 9.6 Hz, 3H), 7.55 (t, J = 7.6 Hz, 2H), 7.40 (d, J = 1.5 Hz, 1H), 6.97 (d, J = 3.2 Hz, 2H), 6.95 (s, 1H), 3.84 (s, 3H), 2.40 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 189.2, 158.8, 143.0, 138.6, 137.7, 133.1, 129.7, 129.0, 128.9, 127.3, 127.2, 122.9, 121.9, 121.5, 114.7, 114.4, 110.7, 101.2, 55.5, 14.3; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{24}H_{20}N_3O_2$ 382.1550, found 382.1559.

Synthesis of 20. A solution of **3k** (0.09 mmol, 1.0 equiv), 3-chlorobenzaldehyde (1.5 equiv), and barium hydroxide (2.0 equiv) in ethyl alcohol (1.0 mL) was stirred at rt for 10 min. The reaction was carried out in a 7 mL sealed vial. A sudden color change indicated progress of the reaction. The reaction mixture was diluted with ice-cold water (1.0 mL) and the resulting solid was filtered off *in vacuo* and washed with water (1.0 mL) to afford **20** (30.0 mg, 99%) as an orange solid.

*(E)-3-(3-Chlorophenyl)-1-(2-methylimidazo[1,2-a]pyrrolo[2,1-c]-pyrazin-6-yl)prop-2-en-1-one (**20**).*

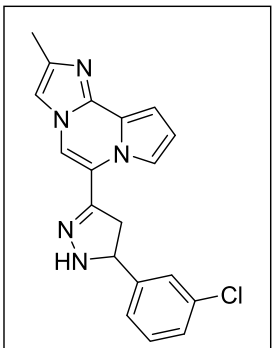


20

Orange solid, mp: 251.3−251.7 °C (30.0 mg, 99%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.56 (dd, J = 2.8, 1.2 Hz, 1H), 8.10 (s, 1H), 7.81 (d, J = 15.5 Hz, 1H), 7.66 (s, 1H), 7.51 (d, J = 7.2 Hz, 1H), 7.44−7.37 (m, 2H), 7.33 (d, J = 15.5 Hz, 1H), 7.16 (dd, J = 3.6, 1.2 Hz, 1H), 7.11 (s, 1H), 6.78−6.74 (m, 1H), 2.42 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 182.6, 144.0, 143.0, 139.2, 136.2, 135.3, 130.9, 130.5, 127.9, 127.2, 123.1, 122.3, 122.1, 119.5, 118.8, 113.5, 110.4, 103.8, 14.3; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{19}H_{15}ClN_3O$ 336.0898, found 336.0904.

Synthesis of 21. A solution of **20** (0.03 mmol, 1.0 equiv) and hydrazine monohydrate (2.0 equiv) in ethyl alcohol (1.0 mL) was stirred at 100 °C for 30 min (a heating mantle was used). The reaction was carried out in a 7 mL sealed vial. The reaction mixture was concentrated *in vacuo* to yield the crude product, which was triturated with mixed solvent (hexane/dichloromethane = 5:1) to afford **21** (10.1 mg, 96%) as a yellow solid.

*6-(5-(3-Chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)-2-methylimidazo[1,2-a]pyrrolo[2,1-c]pyrazine (**21**).*

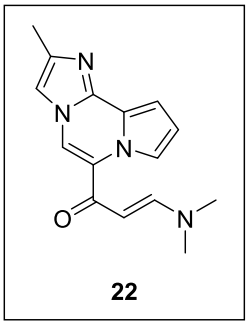


21

Yellow solid, mp: 216.2−217.1 °C (10.1 mg, 96%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.68 (dd, J = 2.8, 1.4 Hz, 1H), 7.37 (s, 1H), 7.30−7.27 (m, 2H), 7.25−7.23 (m, 1H), 7.14−7.13 (m, 2H), 6.94 (s, 1H), 6.73−6.70 (m, 1H), 6.32 (s, 1H), 4.92 (t, J = 10.0 Hz, 1H), 3.48 (dd, J = 15.6, 10.8 Hz, 1H), 3.04 (dd, J = 15.6, 9.2 Hz, 1H), 2.38 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 143.9, 143.7, 141.3, 138.1, 134.9, 130.4, 128.4, 126.7, 124.6, 122.3, 120.1, 119.0, 112.6, 111.7, 109.9, 103.1, 63.2, 41.9, 14.2; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{19}H_{17}ClN_5$ 350.1167, found 350.1176.

Synthesis of 22. A solution of **3k** (0.14 mmol, 1.0 equiv) and DMF-DMA (2.0 equiv) in toluene (1.3 mL) was stirred at 120 °C for 27 h (a heating mantle was used). The reaction was carried out in a 7 mL sealed vial. The reaction mixture was concentrated *in vacuo* to yield the crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 1:4:2) to afford **22** (33.4 mg, 88%) as a yellow solid.

*(E)-3-(Dimethylamino)-1-(2-methylimidazo[1,2-a]pyrrolo[2,1-c]-pyrazin-6-yl)prop-2-en-1-one (**22**).*



22

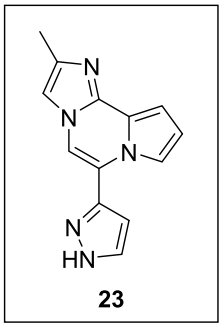
Yellow solid, mp: 167.5−167.7 °C (33.4 mg, 88%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16−8.12 (m, 1H), 7.79 (d, J = 12.0 Hz, 1H), 7.61 (s, 1H), 7.05 (d, J = 4.0 Hz, 1H), 6.99 (s, 1H), 6.66 (t, J = 3.2 Hz, 1H), 5.42 (d, J = 12.2 Hz, 1H), 3.16 (s, 3H), 2.91 (s, 3H), 2.38 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 182.0, 154.9, 141.2, 138.6, 125.1, 122.1, 118.5, 113.1, 112.5, 110.2, 102.5, 92.6, 45.4, 37.5, 14.1; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{15}H_{17}N_4O$ 269.1397, found 269.1405.

Synthesis of 23. A solution of **22** (0.04 mmol, 1.0 equiv) and hydrazine monohydrate (4.0 equiv) in ethyl alcohol (1.0 mL) was stirred at 120 °C for 25 min (a heating mantle was used). The reaction was carried out in a 7 mL sealed vial. The reaction mixture was concentrated *in vacuo* to yield the crude product, which was

https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990

triturated with mixed solvent (hexane/dichloromethane = 5:1) to afford **23** (8.3 mg, 94%) as a yellow solid.

*2-Methyl-6-(1H-pyrazol-3-yl)imidazo[1,2-a]pyrrolo[2,1-c]-pyrazine (**23**).*

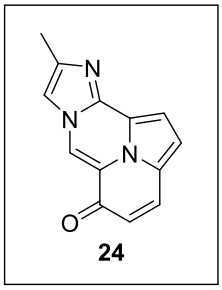


23

Yellow solid, mp: 249.3−249.9 °C (8.3 mg, 94%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.37 (s, 1H), 8.27−8.25 (m, 1H), 8.08 (s, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.39−7.38 (m, 1H), 6.87 (dd, J = 3.6, 1.5 Hz, 1H), 6.81 (d, J = 2.0 Hz, 1H), 6.68 (dd, J = 3.6, 2.8 Hz, 1H), 2.28 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 143.4, 139.4, 136.7, 130.0, 122.1, 118.9, 117.3, 111.9, 110.8, 109.7, 104.1, 101.7, 14.0; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{13}H_{12}N_5$ 238.1087, found 238.1100.

Synthesis of 24. A solution of **22** (0.11 mmol, 1.0 equiv) in acetic acid (1.0 mL) was stirred at 120 °C for 4 h (a heating mantle was used). The reaction mixture was diluted with dichloromethane (3.0 mL) and washed with aqueous sodium bicarbonate solution (3.0 mL). The aqueous layer was extracted with dichloromethane (3.0 mL) one more time. The organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloro-methane = 1:6:2) to afford **24** (22.8 mg, 91%) as a red solid.

*9-Methyl-5H-imidazo[2′,1′:3,4]pyrazino[2,1,6-cd]indolizin-5-one (**24**).*

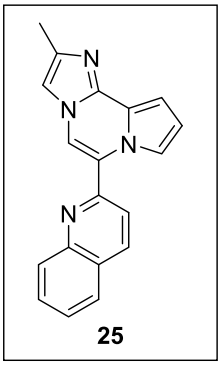


24

Red solid, mp: 271.5−271.9 °C (22.8 mg, 91%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.93 (d, J = 10.0 Hz, 1H), 7.60 (s, 1H), 7.48 (d, J = 4.0 Hz, 1H), 7.25 (s, 1H), 6.71 (d, J = 10.0 Hz, 1H), 2.58 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 177.6, 145.5, 137.0, 132.8, 125.1, 122.3, 121.9, 121.5, 117.8, 116.5, 111.6, 107.2, 14.8; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{13}H_{10}N_3O$ 224.0818, found 224.0817.

Synthesis of 25. A solution of **3k** (0.05 mmol, 1.0 equiv) and 2-aminobenzaldehyde (1.5 equiv) in ethanol (0.5 mL), containing 40% aqueous NaOH solution (0.5 mL) was stirred at 60 °C for 1 h (a heating mantle was used). The reaction was carried out in a 7 mL sealed vial. The reaction mixture was concentrated *in vacuo*, diluted with ethyl acetate (1.0 mL), and washed with water (1.0 mL). The water layer was extracted with ethyl acetate (1.0 mL) one more time. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 1:1:2) to afford **25** (11.3 mg, 81%) as a yellow solid.

*2-Methyl-6-(quinolin-2-yl)imidazo[1,2-a]pyrrolo[2,1-c]pyrazine (**25**).*



25

Yellow solid, mp: 102.9−103.4 °C (11.3 mg, 81%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.92−7.89 (m, 2H), 7.83−7.79 (m, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.66−7.61 (m, 1H), 7.49 (s, 1H), 7.15 (dd, J = 4.0, 1.2 Hz, 1H), 7.07−7.05 (m, 1H), 6.72−6.68 (m, 1H), 2.42 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 151.1, 148.0, 141.0, 138.3, 137.6, 130.6, 129.7, 127.79, 127.76, 127.7, 125.3, 122.8, 120.6, 116.6, 112.7, 111.6, 110.4, 103.0, 14.3; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{19}H_{15}N_4$ 299.1291, found 299.1307.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c01576.

^{1}H and ^{13}C NMR spectra of synthesized compounds and CIF files for **3a′** and **3k** (PDF)

Accession Codes

Deposition Numbers 2364757−2364758 contain the supporting crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

■ AUTHOR INFORMATION

Corresponding Author

Ikyon Kim − *College of Pharmacy and Yonsei Institute of Pharmaceutical Sciences, Yonsei University, Incheon 21983, Republic of Korea;* orcid.org/0000-0002-0849-5517; Phone: +82327494515; Email: ikyonkim@yonsei.ac.kr; Fax: +82327494105

Authors

Hyunjin Oh − *College of Pharmacy and Yonsei Institute of Pharmaceutical Sciences, Yonsei University, Incheon 21983, Republic of Korea*

Dohui Ku − *College of Pharmacy and Yonsei Institute of Pharmaceutical Sciences, Yonsei University, Incheon 21983, Republic of Korea*

Myungho Jung − *College of Pharmacy and Yonsei Institute of Pharmaceutical Sciences, Yonsei University, Incheon 21983, Republic of Korea*

Sunhee Lee − *College of Pharmacy and Yonsei Institute of Pharmaceutical Sciences, Yonsei University, Incheon 21983, Republic of Korea*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.4c01576

Author Contributions

†H.O. and D.K. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Research Foundation of Korea (NRF-2018R1A6A1A03023718 and NRF-2020R1A2C2005961) for generous financial support.

■ REFERENCES

(1) (a) Zhang, L.; Peng, X.-M.; Damu, G. L. V.; Geng, R.-X.; Zhou, C.-H. Comprehensive Review in Current Developments of Imidazole-Based Medicinal Chemistry. *Med. Res. Rev.* **2014**, *34*, 340−437. (b) Sharma, P.; LaRosa, C.; Antwi, J.; Govindarajan, R.; Werbovetz, K. A. Imidazoles as Potential Anticancer Agents: An Update on Recent Studies. *Molecules* **2021**, *26*, No. 4213.

(2) (a) Rani, N.; Singh, R.; Kumar, P. Imidazole and Derivatives Drugs Synthesis: A Review. *Curr. Org. Synth.* **2023**, *20*, 630−662. (b) Sharmin, D.; Divović, B.; Ping, X.; Cerne, R.; Smith, J. L.; Rezvanian, S.; Mondal, P.; Meyer, M. J.; Kiley, M. E.; Arnold, L. A.; Mian, M. Y.; Pandey, K. P.; Jin, X.; Mitrović, J. R.; Djorović, D.; Lippa, A.; Cook, J. M.; Golani, L. K.; Scholze, P.; Savić, M. M.; Witkin, J. M. New Imidazodiazepine Analogue, 5-(8-Bromo-6-(pyridin-2-yl)-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepin-3-yl)oxazole, Provides a Simplified Synthetic Scheme, High Oral Plasma and Brain Exposures, and Produces Antiseizure Efficacy in Mice, and Antiepileptogenic Activity in Neural Networks in Brain Slices from a Patient with Mesial Temporal Lobe Epilepsy. *ACS Chem. Neurosci.* **2024**, *15*, 517−526. (c) Zhang, Y.; Li, X.; Liu, F.; Bai, X.; Liu, X.; Sun, H.; Gao, C.; Lin, Y.; Xing, P.; Zhu, J.; Liu, R.; Wang, Z.; Dai, J.; Shi, D. Design of Selective PARP-1 Inhibitors and Antitumor Studies. *J. Med. Chem.* **2024**, *67*, 8877−8901.

(3) (a) Shabalin, D. A.; Camp, J. E. Recent advances in the synthesis of imidazoles. *Org. Biomol. Chem.* **2020**, *18*, 3950−3964. (b) Tolomeu, H. V.; Fraga, C. A. M. Imidazole: Synthesis, Functionalization and Physicochemical Properties of a Privileged Structure in Medicinal Chemistry. *Molecules* **2023**, *28*, No. 838.

(4) (a) Vessally, E.; Soleimani-Amiri, S.; Hosseinian, A.; Edjlali, L.; Bekhradnia, A. New protocols to access imidazoles and their ring fused analogues: synthesis from *N*-propargylamines. *RSC Adv.* **2017**, *7*, 7079−7091. (b) Wang, Y.; Jiang, M.; Liu, B.; Xianzhang, W.; Yumeng, Z.; Yao, L. Synthesis of Fused Imidazoles and Pyrimidinones from 2-Aminoazines. *Asian J. Org. Chem.* **2024**, *13*, No. e202300626. (c) Meena, N.; Nipate, D. S.; Swami, P. N.; Rangan, K.; Kumar, A. Ru(II)-Catalyzed [4 + 2]-Annulation of 2-Alkenyl/Arylimidazoles with *N*-Substituted Maleimides and 1,4-Naphthoquinones: Access to Imidazo-Fused Polyheterocycles. *J. Org. Chem.* **2024**, *89*, 2272−2282.

(5) (a) Bae, G. H.; Kim, S.; Lee, N. K.; Dagar, A.; Lee, J. H.; Lee, J.; Kim, I. Facile approach to benzo[*d*]imidazole-pyrrolo[1,2-*a*]pyrazine hybrid structures through double cyclodehydration and aromatization and their unique optical properties with blue emission. *RSC Adv.* **2020**, *10*, 7265−7288. (b) Joshi, D. R.; Seo, Y.; Heo, Y.; Park, S-h.; Lee, Y.; Namkung, W.; Kim, I. Domino [4 + 2] Annulation Access to Quinone−Indolizine Hybrids: Anticancer *N*-Fused Polycycles. *J. Org. Chem.* **2020**, *85*, 10994−11005. (c) Yoon, S. H.; Kim, S. J.; Kim, I. One-Pot Four-Component Coupling Approach to Polyheterocycles: 6*H*-Furo[3,2-*f*]pyrrolo[1,2-*d*][1,4]diazepine. *J. Org. Chem.* **2020**, *85*, 15082−15091. (d) Oh, H.; Kim, H.; Kim, I. Regioselective Access to 1,2,4-Triazole-Fused *N*-Heterocycle, Pyrrolo[1,2-*a*][1,2,4]triazolo-[5,1-*c*]pyrazine, via Double Dehydrative Cyclizations. *J. Org. Chem.* **2023**, *88*, 11748−11761.

(6) Joshi, D. R.; Kim, I. Recent advances in the synthesis of *N*-fused heterocycles from *N*-aroylmethylpyrrole-2-carboxaldehyde derivatives via annulative functionalization strategies. *Tetrahedron* **2024**, *151*, No. 133787.

(7) Oh, H.; Kim, I. Catalyst-free assembly of a polyfunctionalized 1,2,4-triazole-fused *N*-heterocycle, 6-acylated pyrrolo[1,2-*a*][1,2,4]-triazolo[5,1-*c*]pyrazine. *Org. Biomol. Chem.* **2024**, *22*, 320−336.

(8) Lauder, K.; Toscani, A.; Scalacci, N.; Castagnolo, D. Synthesis and Reactivity of Propargylamines in Organic Chemistry. *Chem. Rev.* **2017**, *117*, 14091−14200.

(9) For some polycyclic structures bearing this tricyclic core, see: (a) Mínguez, J. M.; Castellote, M. I.; Vaquero, J. J.; García-Navio, J.; Alvarez-Builla, J.; Castaño, O.; Andrés, J. Pyrrolodiazines. 2. Structure and Chemistry of Pyrrolo[1,2-*a*]pyrazine and 1,3-Dipolar Cycloaddition of Its Azomethine Ylides. *J. Org. Chem.* **1996**, *61*, 4655−4665. (b) Bae, G. H.; Kim, S.; Lee, N. K.; Dagar, A.; Lee, J. H.; Lee, J.; Kim, I. Facile approach to benzo[*d*]imidazole-pyrrolo[1,2-*a*]pyrazine hybrid structures through double cyclodehydration and aromatization and their unique optical properties with blue emission. *RSC Adv.* **2020**, *10*, 7265−7288. (c) Bakholdina, A.; Lukin, A.; Bakulina, O.; Guranova, N.; Krasavin, M. Dual use of propargylamine building blocks in the construction of polyheterocyclic scaffolds. *Tetrahedron Lett.* **2020**, *61*, No. 151970. (d) Reddy, D. S.; Novitskiy, I. M.; Beloglazkina, A. A.; Kutateladze, A. G. Oxidative Control of Photoinduced Cascade Electrocyclizations in Aromatic Azido Imines to Access Complex Fused Imidazoles or Pyrazoles. *Org. Lett.* **2024**, *26*, 2558−2563.

(10) For structural determination of **3a** and **3a′**, see HSQC, HMBC, and NOESY of them in the SI.

(11) CCDC 2364757 contains the supplementary crystallographic data for **3a′**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(12) CCDC 2364758 contains the supplementary crystallographic data for **3k**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(13) Kim, I.; Choi, J.; Lee, S.; Lee, G. H. A Highly Efficient Catalyst-Free Cycloisomerization Approach to Indolizinones. *Synlett* **2008**, *2008*, 2334−2338.

(14) For the synthesis of imidazoles from *N*-propargylamidines under other conditions, see: (a) Husinec, S.; Markovic, R.; Petkovic, M.; Nasufovic, V.; Savic, V. A Base Promoted Cyclization of *N*-Propargylaminopyridines. Synthesis of Imidazo[1,2-*a*]pyridine Derivatives. *Org. Lett.* **2011**, *13*, 2286−2289. (b) Sucunza, D.; Samadi, A.; Chioua, M.; Silva, D. B.; Yunta, C.; Infantes, L.; Carreiras, M. C.; Soriano, E.; Marco-Contelles, J. A practical two-step synthesis of imidazo[1,2-*a*]pyridines from *N*-(prop-2-yn-1-yl)pyridin-2-amines. *Chem. Commun.* **2011**, *47*, 5043−5045. (c) Li, R.-L.; Liang, L.; Xie, M.-S.; Qu, G.-R.; Niu, H.-Y.; Guo, H.-M. Copper-Catalyzed Intramolecular Cyclization of *N*-Propargyl-Adenine: Synthesis of Purine-Fused Tricyclics. *J. Org. Chem.* **2014**, *79*, 3665−3670. (d) Zhang, L.; Xiao, K.; Qiao, Y.; Li, X.; Song, C.; Chang, J. Base-Promoted Cycloisomerization for the Synthesis of Oxazoles and Imidazoles. *Eur. J. Org. Chem.* **2018**, *2018*, 6913−6918. (e) Chapman, M. R.; Kwan, M. H. T.; King, G. E.; Kyffin, B. A.; Blacker, A. J.; Willans, C. E.; Nguyen, B. N. Rapid, metal-free and aqueous synthesis of imidazo[1,2-*a*]pyridine under ambient conditions. *Green Chem.* **2016**, *18*, 4623−4627.

(15) Abbiati, G.; Arcadi, A.; Canevari, V.; Rossi, E. Palladium catalyzed synthesis of 4-substituted-2-phenylimidazoles from *N*-propargyl-benzamidine. *Tetrahedron Lett.* **2007**, *48*, 8491−8495.

(16) Kumar, D.; Sharma, K. K. Green Approach for the Synthesis of 3-(3-Arylprop-2-enoyl)-2-hydroxycyclohepta-2,4,6-trien-1-ones. *Russ. J. Org. Chem.* **2023**, *59*, 1231−1236.

(17) Kim, S.; Lee, J. H.; Yoon, S. H.; Kim, I. A regioselective [4 + 2] annulation approach to 5-acylindolizine-7-carbonitriles: generation of poly-substituted pyridines. *Org. Biomol. Chem.* **2021**, *19*, 5806−5817.
(18) Zhang, Z.; Wang, Y.; Chen, X.; Song, X.; Tu, Z.; Chen, Y.; Zhang, Z.; Ding, K. Characterization of an aromatic trifluoromethyl ketone as a new warhead for covalently reversible kinase inhibitor design. *Bioorg. Med. Chem.* **2021**, *50*, No. 116457.

https://doi.org/10.1021/acs.joc.4c01576
J. Org. Chem. 2024, 89, 17966−17990