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T3P-Mediated N−N Cyclization for the Synthesis of 1,2,4-Triazolo[1,5-*a*]pyridines

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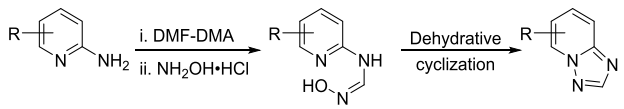
ABSTRACT: Propylphosphonic anhydride has been shown to be an effective reagent for the synthesis of substituted [1,2,4]triazolo[1,5-*a*]pyridines from the corresponding *N*′-hydroxy-*N*-formimidamides. The reactions worked under mild conditions and exhibited wide functional group tolerance, delivering the triazolopyridines in good to excellent yields and purities.

KEYWORDS: *propylphosphonic anhydride, N−N bond formation, 1,2,4-triazole, 1,2,4-triazolo[1,5-a]pyridine*

INTRODUCTION

We sought to explore the use of [1,2,4]triazolo[1,5-*a*]pyridines **1** as key building blocks in the discovery of novel medications.[1,2] We envisioned that this class of compounds could be readily accessed by the treatment of commercially available substituted 2-aminopyridines **2** with dimethylformamide−dimethylacetal (DMF−DMA) and hydroxylamine hydrochloride to afford the corresponding *N*′-hydroxy-*N*-formimidamides **3**,[3] which could then be dehydrated to form the 1,2,4-triazole ring through an intramolecular cyclization (Scheme 1). Several dehydrative conditions such as polyphosphoric acid (PPA)[4] and trifluoroacetic anhydride (TFAA)[5] have been effectively utilized for the cyclization reaction.

Scheme 1. General Synthesis of [1,2,4]Triazolo[1,5-*a*]pyridines



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RESULTS AND DISCUSSION

Our initial studies were performed using methyl-2-aminoisonicotinate **2j** as the test substrate (Table 1). The formation of the corresponding *N*′-hydroxy-*N*-formimidamide **3j** through treatment with DMF−DMA worked smoothly providing the desired product in 94% yield. However, our attempts to effect the cyclization of **3j** to form **1j** using PPA[4] or TFAA[5] based on literature precedent were met with only modest success. While the cyclization reaction afforded **1j** using either of these reagents, the product was contaminated with a significant amount of carboxylic acid **4** arising from hydrolysis of the methyl ester under the reaction conditions (entries 1 and 2, Table 1). The levels of the carboxylic acid impurity were exacerbated when Eaton's reagent[6] was used (entry 3, Table 1), prompting us to explore nonacidic conditions for the cyclization reaction.

We envisioned that the cyclization could be accomplished with a suitable nonacidic desiccant[5] and sought to examine some of the commonly used peptide coupling agents for this transformation. As anticipated, reagents such as HATU, EDCI, PyBOP, CDI, and DCC circumvented the formation of the hydrolyzed impurity **4** but, at the same time, afforded only modest conversions to the desired triazole **1j** (entries 4−8, Table 1).

In recent times, 1-propanephosphonic acid anhydride (T3P) has emerged as a mild dehydrating agent for the direct coupling of acids with amines.[7,8] We hypothesized that this reagent could be effective for the cyclization of **3j** to **1j** as well. It was gratifying to note that exposure of **3j** to T3P cleanly furnished 1,2,4-triazole **1j**, with nondetectable levels of carboxylic acid **4** (entry 9, Table 1). A quick solvent screen revealed that the reaction worked effectively in 2-MeTHF, THF, toluene, and ethyl acetate, but was much less efficient in acetonitrile and dichloromethane (entries 9−14, Table 1).

These results proved general and could be used to synthesize a range of [1,2,4]triazolo[1,5-*a*]pyridines from *N*′-hydroxy-*N*-formimidamides. Several substituted 2-aminopyridines were converted to the corresponding *N*′-hydroxy-*N*-formimidamides by treatment with DMF−DMA and then subjected to the T3P-mediated cyclization conditions; our results are summarized in Scheme 2. In most cases, the reactions proceeded to completion and the products were isolated in good to excellent yields. The reaction worked well in the case of alkoxy- (**1a**, **1k**, **1l**), phenyl- (**1b**), chloro- (**1g**, **1h**), nitro- (**1e**), cyano- (**1i**), and 5-trifluoromethyl (**1f**)-substituted analogues, demonstrating that electron-withdrawing as well as electron-donating substituents on the pyridine ring were well tolerated in the cyclization. The reactions with the 6-

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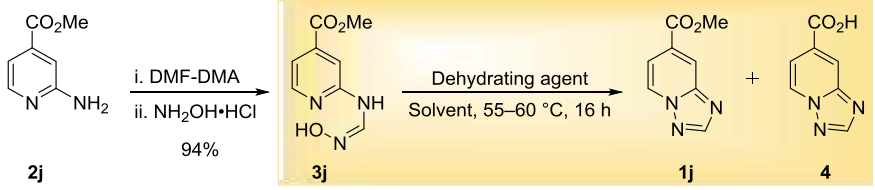
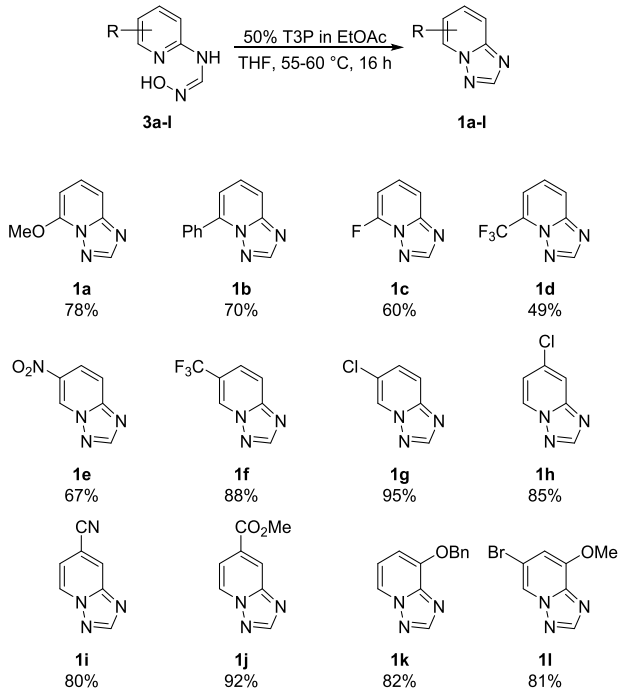
Table 1. Screening of Various Dehydrating Agents for the Cyclization of 3j[a]



entry	dehydrating agent (equiv)	solvent	1j (HPLC area %)	4 (HPLC area %)
1	TFAA (3.0)	2-MeTHF	76	24
2	polyphosphoric acid (3.0)	2-MeTHF	80	20
3	Eaton's reagent (3.0)	2-MeTHF	37	63
4	HATU (1.5)	2-MeTHF	3	<0.05
5	EDCI (1.5)	2-MeTHF	4	<0.05
6	PyBOP (1.5)	2-MeTHF	35	<0.05
7	CDI (1.5)	2-MeTHF	1	<0.05
8	DCC (1.1)	2-MeTHF	30	<0.05
9	50% T3P in EtOAc (1.5)	2-MeTHF	92	<0.05
10	50% T3P in EtOAc (1.5)	EtOAc	96	<0.05
11	50% T3P in EtOAc (1.5)	THF	99	<0.05
12	50% T3P in EtOAc (1.5)	PhMe	92	<0.05
13	50% T3P in EtOAc (1.5)	MeCN	5	<0.05
14	50% T3P in EtOAc (1.5)	CH_2Cl_2[b]	10	<0.05

[a]All reactions were conducted on a 1 g scale. [b]Carried out at 40 °C.

Scheme 2. Synthesis of Various [1,2,4]Triazolo[1,5-*a*]pyridines Using T3P



fluoro- and 6-trifluoromethyl-substituted *N*′-hydroxy-*N*-formimidamides (**1c**, **1d**) provided slightly lower yields, in line with the results reported with TFAA for formimidamines derived from 6-substituted pyridines.[5] Compounds **1g**, **1h**, and **1l** were of particular interest since the presence of the halo substituents in these compounds would allow for further elaboration via appropriate cross-coupling reactions. In general, all of these reactions worked under fairly mild conditions, and most importantly, the residues from the coupling agent (T3P) were water-soluble and could be removed via simple aqueous washes. In particular, the cyclization of **3l** to **1l** was carried out on a 1.6 kg scale (see Experimental Section), affirming the scalability of the T3P-mediated reaction.

The methodology was extended to the cyclization of *N*′-hydroxy-*N*-formimidamides derived from other *α*-aminoheteroarenes as well. The *N*′-hydroxy-*N*-formimidamides synthesized from 3-amino-6-methoxypyridazine (**5** → **6**), 2-aminopyrazine (**8** → **9**), and 3-aminoisoquinoline (**11** → **12**) underwent efficient ring closure to provide the corresponding 1,2,4-triazoles **7**, **10**, and **13** (Scheme 3).

In summary, we have developed a general methodology for the cyclization of *N*′-hydroxy-*N*-formimidamides derived from *α*-aminoheteroarenes using T3P. The reactions proceeded under mild conditions, exhibited wide functional group tolerance, and provided the corresponding heteroaryl-fused 1,2,4-triazoles in moderate to excellent yields.

EXPERIMENTAL SECTION

General Information. All reactions were performed under a nitrogen atmosphere. All compounds were purified by flash chromatography using silica gel (20−40 *μ*m) as needed. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CDCl_3$ = *δ* 7.26; $(CD_3)_2SO$ = *δ* 2.50). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$ = *δ* 77.16; $(CD_3)_2SO$ = *δ* 39.50). Melting points were obtained using a Stuart SMP10 instrument. HRMS was recorded on a Thermo Velos Orbitrap mass spectrometer (ESI and APCI source).

General Procedure for the Synthesis of *N*′-Hydroxy-*N*-formimidamides (3a−k, 6, 9, and 12). To an oven-dried three-neck round-bottom flask fitted with a thermocouple and reflux condenser, 2-propanol (10 mL per g of the amine) was added under a nitrogen atmosphere. Dimethyl formamide−dimethylacetal (2.6 equiv) and the amine (1.0 equiv) were

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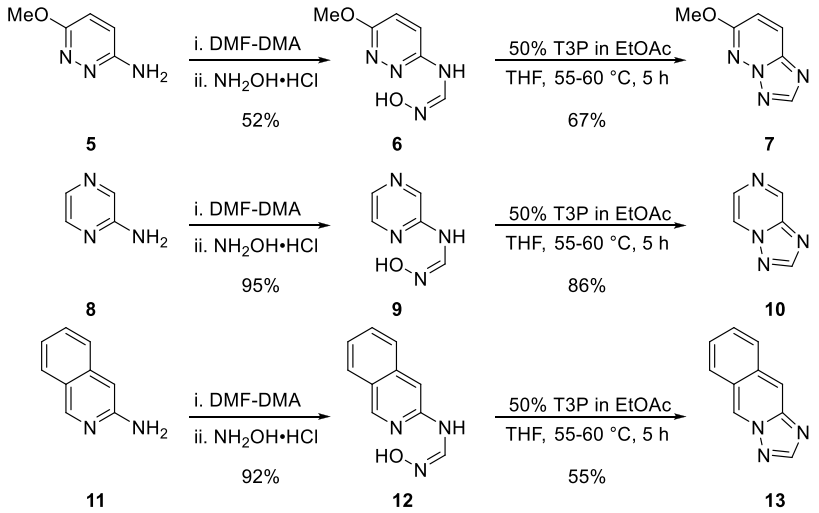
Scheme 3. Synthesis of Various [1,2,4]Triazole-Fused Heteroarenes Using T3P



added to the flask. The reaction mixture was stirred for 3 h at 80 °C. Hydroxylamine hydrochloride (1.5 equiv) was added to the reaction mass and stirred for 12 h at 50 °C. The reaction was quenched with 10% aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with 2-MeTHF (1 × 10 mL per g of the amine). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography to furnish the desired product.

*N′-Hydroxy-N-(6-methoxypyridin-2-yl)formimidamide (**3a**).* The reaction was conducted on a 5.0 g scale using the general procedure. The product was purified by column chromatography using EtOAc/*n*-heptane (1:3) as eluent to afford 2.1 g (31%) of compound **3a** as a pale brownish solid (mp 164−166 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 10.03 (s, 1H), 9.29 (d, J = 10.0 Hz, 1H), 7.86 (d, J = 10.0 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 6.59 (d, J = 8.0 Hz, 1H), 6.23 (d, J = 7.6 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 163.0, 151.5, 141.3, 136.2, 101.9, 101.4, 53.3. HRMS (ESI) (m/z): calcd for $C_7H_9N_3O_2$ 168.0768 $[M + H]^+$, found 168.0765.

*N′-Hydroxy-N-(6-phenylpyridin-2-yl)formimidamide (**3b**).* The reaction was conducted on a 4.0 g scale using the general procedure. The product was purified by column chromatography using EtOAc/*n*-heptane (1:3) as eluent to afford 2.4 g (48%) of compound **3b** as an off-white solid (mp 157−159 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 10.09 (s, 1H), 9.41 (d, J = 10.0 Hz, 1H), 8.07 (d, J = 10.0 Hz, 3H), 7.70 (t, J = 8.0 Hz, 1H), 7.39−7.49 (m, 4H), 7.02 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 154.4, 152.7, 139.5, 139.0, 136.2, 129.4, 129.1, 126.9, 112.9, 109.7. HRMS (ESI) (m/z): calcd for $C_{12}H_{11}N_3O$ 214.0975 $[M + H]^+$, found 214.0964.

*N-(6-Fluoropyridin-2-yl)-N′-hydroxyformimidamide (**3c**).* The reaction was conducted on a 5.0 g scale using the general procedure. The product was purified by column chromatography using CH_2Cl_2/CH_3OH (9:1) as eluent to afford 4.8 g (69%) of compound **3c** as an off-white solid (mp 164−166 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 10.23 (s, 1H), 9.65 (d, J = 10.0 Hz, 1H), 7.76 (dd, J = 16.4 Hz, 8.0 Hz, 1H), 7.65 (d, J = 10.0 Hz, 1H), 6.95 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.53 (dd, J = 7.6 Hz, 2.4 Hz, 1H). ^{19}F NMR (376.4 MHz, $(CD_3)_2SO$): δ 69.52. ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 162.5 (d, $J_{C\text{-}F}$ = 312.2 Hz), 152.3 (d, $J_{C\text{-}F}$ = 20.7 Hz), 143.7 (d, $J_{C\text{-}F}$ = 11.0 Hz), 135.5, 107.5 (d, $J_{C\text{-}F}$ = 5.5 Hz), 99.7 (d, $J_{C\text{-}F}$ = 47.6 Hz), HRMS (ESI) (m/z): calcd for $C_6H_6FN_3O$ 156.0568 $[M + H]^+$, found 156.0557.

*N′-Hydroxy-N-(6-(trifluoromethyl)pyridin-2-yl)-formimidamide (**3d**).* The reaction was conducted on a 4.0 g scale using the general procedure. The product was purified by column chromatography using CH_2Cl_2/CH_3OH (9:1) as eluent to afford 4.7 g (74%) of compound **3d** as a pale brownish solid (mp 178−180 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 10.33 (s, 1H), 9.83 (d, J = 10.0 Hz, 1H), 7.86 (t, 8.0 Hz, 1H), 7.79 (d, J = 9.6 Hz, 1H), 7.29−7.34 (m, 2H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 153.2, 144.9 (q, $J_{C\text{-}F}$ = 33.6 Hz), 139.9, 135.4, 121.7 (q, $J_{C\text{-}F}$ = 272 Hz), 114.6, 112.7. HRMS (ESI) (m/z): calcd for $C_7H_6F_3N_3O$ 206.0536 $[M + H]^+$, found 206.0528.

*N′-Hydroxy-N-(5-nitropyridin-2-yl)formimidamide (**3e**).* The reaction was conducted on a 5.0 g scale using the general procedure. At the end of the reaction, the precipitated solids were isolated by filtration. The filter cake was transferred to a clean round-bottom flask, slurried in MTBE (25 mL), filtered, and dried to afford 4.2 g (64%) of compound **3e** as a pale greenish solid (mp 186−188 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 10.62 (s, 1H), 10.35 (d, J = 9.6 Hz, 1H), 9.02 (d, J = 2.8 Hz, 1H), 8.39 (dd, J = 9.2 Hz, 2.8 Hz, 1H), 7.93 (d, J = 9.6 Hz, 1H), 7.21 (d, J = 9.2 Hz, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 156.7, 145.8, 138.5, 134.9, 134.1, 110.7. HRMS (ESI) (m/z): calcd for $C_6H_6N_4O_3$ 183.0531 $[M + H]^+$, found 183.0512.

*N′-Hydroxy-N-(5-(trifluoromethyl)pyridin-2-yl)-formimidamide (**3f**).* The reaction was conducted on a 5.0 g scale using the general procedure. The product was purified by column chromatography using CH_2Cl_2/CH_3OH (9:1) as eluent to afford 4.7 g (74%) of compound **3f** as a pale brownish solid (mp 181−183 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 10.37 (s, 1H), 9.91 (d, J = 9.6 Hz, 1H), 8.50 (s, 1H), 7.95 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.87−7.90 (m, 1H), 7.22 (d, J = 8.8 Hz, 1H). ^{19}F NMR (376.4 MHz, $(CD_3)_2SO$): δ 60.1. ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 155.4, 145.2 (q, $J_{C\text{-}F}$ = 4.3 Hz), 135.1 (q, $J_{C\text{-}F}$ = 2.8 Hz), 135.2, 124.5 (q, $J_{C\text{-}F}$ = 269 Hz), 117.6 (q, $J_{C\text{-}F}$ = 32.3 Hz), 110.5. HRMS (ESI) (m/z): calcd for $C_7H_6F_3N_3O$ 206.0536 $[M + H]^+$, found 206.0528.

*N-(5-Chloropyridin-2-yl)-N′-hydroxyformimidamide (**3g**).* The reaction was conducted on a 5.0 g scale using the general

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procedure. The product was purified by column chromatography using EtOAc/*n*-heptane (1:3) as eluent to afford 5.0 g (75%) of compound **3g** as an off-white solid (mp 189−191 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 10.17 (s, 1H), 9.54 (d, J = 10.0 Hz, 1H), 8.16 (d, J = 2.8 Hz, 1H), 7.78 (d, J = 10.0 Hz, 1H), 7.70 (dd, J = 8.8 Hz, 2.8 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 151.8, 146.0, 138.4, 135.8, 122.7, 112.2. HRMS (ESI) (m/z): calcd for $C_6H_6ClN_3O$ 172.0272 $[M + H]^+$, found 172.0261.

*N-(4-Chloropyridin-2-yl)-N′-hydroxyformimidamide (**3h**).* The reaction was conducted on a 2.0 g scale using the general procedure. The product was purified by column chromatography using EtOAc/*n*-heptane (1:3) as eluent to afford 1.4 g (52%) of compound **3h** as an off-white solid (mp 155−157 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 10.22 (s, 1H), 9.55 (t, J = 4.8 Hz, 1H), 8.11 (d, J = 5.2 Hz, 1H), 7.82 (d, J = 9.6 Hz, 1H), 7.16 (d, J = 1.6 Hz, 1H), 6.94 (dd, J= 5.6 Hz, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 153.8, 149.0, 143.6, 135.1, 116.2, 109.6. HRMS (ESI) (m/z): calcd for $C_6H_6N_3OCl$ 172.0272 $[M + H]^+$, found 172.0267.

*N-(4-Cyanopyridin-2-yl)-N′-hydroxyformimidamide (**3i**).* The reaction was conducted on a 5.0 g scale using the general procedure. The product was purified by column chromatography using EtOAc/*n*-heptane (1:3) as eluent to afford 4.2 g (62%) of compound **3i** as an off-white solid (mp 175−177 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 10.34 (s, 1H), 9.78 (d, J = 9.6 Hz, 1H), 8.36 (d, J = 5.2 Hz, 1H), 7.83 (d, J = 9.6 Hz, 1H), 7.40 (d, J = 1.2 Hz, 1H), 7.23 (dd, J = 5.2 Hz, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 153.0, 149.3, 134.7, 120.7, 117.0, 116.8, 112.7. HRMS (ESI) (m/z): calcd for $C_7H_6N_4O$ 163.0614 $[M + H]^+$, found 163.0617.

*Methyl 2-(N′-Hydroxyformimidamido)isonicotinate (**3j**).* The reaction was conducted on a 25.0 g scale using the general procedure. The product was purified by column chromatography using EtOAc/*n*-heptane (1:3) as eluent to afford 21.3 g (66%) of compound **3j** as an off-white solid (mp 185−187 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 10.4 (s, 1H), 9.90 (d, J = 9.6 Hz, 1H), 8.68 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 9.6 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 165.7, 155.9, 150.3, 139.1, 135.3, 118.4, 110.4, 52.3. HRMS (ESI) (m/z): calcd for $C_8H_9N_3O_3$ 196.0717 $[M + H]^+$, found 196.0710.

*N-(3-(Benzyloxy) Pyridin-2-yl)-N′-hydroxyformimidamide (**3k**).* The reaction was conducted on a 5.0 g scale using the general procedure. The product was purified by column chromatography using EtOAc/*n*-heptane (1:3) as eluent to afford 4.7 g (77%) of compound **3k** as an off-white solid. (mp 175−177 °C.) ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 10.39 (s, 1H), 8.02 (d, J = 10.0 Hz, 1H), 7.93 (d, J = 10.0 Hz, 1H), 7.78 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 7.36−7.49 (m, 6H), 6.89 (dd, J = 8.0 Hz, 5.2 Hz, 1H), 5.23 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d6): δ 142.7, 141.2, 139.0, 136.7, 135.6, 129.1, 128.7, 128.2, 119.3, 117.1, 70.3. HRMS (ESI) (m/z): calcd for $C_{13}H_{13}N_3O_2$ 244.1081 $[M + H]^+$, found 244.1076.

*N′-Hydroxy-N-(6-methoxypyridazin-3-yl)formimidamide (**6**).* The reaction was conducted on a 4.0 g scale using the general procedure. The product was purified by column chromatography using EtOAc/*n*-heptane (1:3) as eluent to afford 2.8 g (52%) of compound **6** as an off-white solid (mp 169−171 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 10.19 (s, 1H), 9.36 (d, J = 10.0 Hz, 1H), 7.86 (d, J = 10.0 Hz, 1H), 7.38 (d, J = 9.6 Hz, 1H), 7.12 (d, J = 9.6 Hz, 1H), 3.22 (s, 3H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 161.7, 151.8, 135.6, 121.6, 120.4, 54.4. HRMS (ESI) (m/z): calcd for $C_6H_8N_4O_2$ 169.0720 $[M + H]^+$, found 169.0710.

*N′-Hydroxy-N-(pyrazin-2-yl)formimidamide (**9**).* The reaction was conducted on a 4.0 g scale using the general procedure. The product was purified by column chromatography using CH_2Cl_2/CH_3OH (9:1) as eluent to afford 5.5 g (95%) of compound **9** as an off-white solid (mp 201−203 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 10.34 (s, 1H), 9.79 (d, J = 10.0 Hz, 1H), 8.45 (d, J = 1.6 Hz, 1H), 8.14 (d, J = 1.2, 1H), 8.06 (d, J = 2.8 Hz, 1H), 7.79 (d, J = 10.0 Hz, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ149.5, 141.9, 136.7, 135.2, 134.9. HRMS (ESI) (m/z): calcd for $C_5H_6N_4O$, 139.0614 $[M + H]^+$ found, 139.0611.

*N′-Hydroxy-N-(isoquinolin-3-yl)formimidamide (**12**).* The reaction was conducted on a 5.0 g scale using the general procedure. The product was purified by column chromatography using EtOAc/*n*-heptane (1:3) as eluent to afford 6.0 g (92%) of compound **12** as an off-white solid (mp 146−148 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 10.05 (br s, 1H), 9.31 (d, J = 10.0 Hz, 1H), 9.01 (d, J = 12.8 Hz, 1H), 7.94−7.99 (m, 2H), 7.67 (d, J = 8.0 Hz, 1H), 7.58−7.61 (m, 1H), 7.35 (dd, J = 15.2 Hz, 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 156.5, 153.7, 143.1, 141.6, 136.1, 133.1, 130.5, 129.8, 129.3, 106.6. HRMS (ESI) (m/z): calcd for $C_{10}H_9N_3O$ 188.0818 $[M + H]^+$, found 188.0816.

*N-(5-Bromo-3-methoxypyridine-2-yl)-N′-hydroxyformimidamide (**3l**).* To a clean 60 L glass reactor, 2-propanol (21 L) and 5-bromo-3-methoxypyridin-2-amine (3.0 kg, 14.8 mol, 1.0 equiv) were sequentially added at 20−35 °C under a nitrogen atmosphere. DMF−DMA (4.3 kg, 34.5 mol, 2.4 equiv) was added at 20−35 °C, and the mixture was stirred for 2 h at 70−80 °C. After reaction completion, the reaction mass was cooled to 20−35 °C. Hydroxylamine hydrochloride (1.5 kg, 19.2 mol, 1.3 equiv) was charged, and the mixture was stirred for 16 h at 50−55 °C. After reaction completion, the contents of the reactor were cooled to 20−35 °C, and 10% aqueous $NaHCO_3$ (30 L) was charged and stirred for 15 min. The mass was then cooled to 0−10 °C and allowed to granulate for 1 h. The resulting slurry was filtered through a Nutsche filter, and the filter cake was washed with water (30 L). The wet solid was dried under vacuum at 45−50 °C to afford compound **3l** as a pale brown solid (3.5 kg, 99.98% purity by HPLC, 94.30% assay by HPLC, 95% yield, mp 193−195 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 10.53 (s, 1H), 7.94 (d, J = 10.0 Hz, 1H), 7.85 (d, J = 9.6 Hz, 2H) 7.55 (br s, 1H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 142.9, 141.6, 138.7, 135.2, 120.5, 110.7, 56.9. HRMS (ESI) (m/z): calcd for $C_7H_8BrN_3O_2$ 245.9873 $[M + H]^+$, found 245.9874.

General Procedure for the Synthesis of Heteroaryl-Fused 1,2,4-Triazoles (1a−k, 7, 10, and 13). To an oven-dried three-neck round-bottom flask fitted with a thermocouple and reflux condenser, THF (10 mL per g of the *N′*-hydroxy-*N*-formimidamide) was added under a nitrogen atmosphere, followed by the appropriate *N′*-hydroxy-*N*-formimidamide (1.0 equiv). The resultant mixture was stirred for 10 min at 25−30 °C. Once complete dissolution was achieved, T3P (50% solution in EtOAc, 1.5 equiv) was added slowly into the reaction vessel and stirred for 2−16 h at 55−60 °C. Then, the reaction mass was quenched with 10% aqueous $NaHCO_3$ and extracted with EtOAc (2 × 10 mL per g of the *N′*-hydroxy-*N*-formimidamide). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue

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was purified by column chromatography to furnish the desired product.

*5-Methoxy-[1,2,4]triazolo[1,5-a]pyridine (**1a**).* The reaction was conducted on a 1.0 g scale using the general procedure and was complete within 16 h. The product was purified by column chromatography using EtOAc/*n*-heptane (1:3) as eluent to afford 700 mg (78%) of compound **1a** as an off-white solid (mp 113−115 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 8.44 (s, 1H), 7.67 (dd, J = 8.8 Hz, 8.0 Hz, 1H), 7.42 (dd, J = 8.8 Hz, 0.8 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 4.14 (s, 3H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ 154.1, 151.9, 151.5, 132.1, 107.9, 92.4, 57.8. HRMS (ESI) (m/z): calcd for $C_7H_7N_3O$, 150.0662 $[M + H]^+$, found 150.0662.

*5-Phenyl-[1,2,4]triazolo[1,5-a]pyridine (**1b**).* The reaction was conducted on a 1.0 g scale using the general procedure and was complete within 5 h. The product was purified by column chromatography using EtOAc/*n*-heptane (1:3) as eluent to afford 640 mg (70%) of compound **1b** as an off-white solid (mp 103−105 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 8.54 (s, 1H), 7.99−8.01 (m, 2H), 7.88 (dd, J = 8.8 Hz, 1.2 Hz, 1H), 7.77 (dd, J = 8.8 Hz, 7.2 Hz, 1H), 7.39−7.60 (m, 3H), 7.37 (d, J = 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 153.9, 151.3, 140.6, 132.5, 130.8, 130.4, 129.6, 129.0, 115.7, 114.8. HRMS (ESI) (m/z): calcd for $C_{12}H_9N_3$, 196.0869 $[M + H]^+$, found 196.0871.

*5-Fluoro-[1,2,4]triazolo[1,5-a]pyridine (**1c**).* The reaction was conducted on a 0.5 g scale using the general procedure and was complete within 5 h. The product was purified by column chromatography using EtOAc/*n*-heptane (1:1) as eluent to afford 265 mg (60%) of compound **1c** as an off-white solid (mp 152−154 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 8.64 (s, 1H), 7.76−7.83 (m, 2H), 7.18−7.21 (m, 1H). ^{19}F NMR (376.4 MHz, $(CD_3)_2SO$): δ 107.7. ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 154.4 (d, $J_{C\text{-}F}$ =1.1 Hz), 152.1 (d, $J_{C\text{-}F}$ = 6.4 Hz), 149.5 (d, $J_{C\text{-}F}$ = 268.7 Hz), 131.7 (d, $J_{C\text{-}F}$ = 6.5 Hz), 112.2 (d, $J_{C\text{-}F}$ = 5.1 Hz), 96.0 (d, $J_{C\text{-}F}$ = 15.0 Hz). HRMS (ESI) (m/z): calcd for $C_6H_4FN_3$ 138.0462 $[M + H]^+$, found 138.0468.

*5-(Trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine (**1d**).* The reaction was conducted on a 1.0 g scale using the general procedure, and was complete within 16 h. The product was purified by column chromatography using EtOAc/*n*-heptane (1:3) as eluent to afford 450 mg (49%) of compound **1d** as an off-white solid (mp 117−119 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 8.73 (s, 1H), 8.22−8.24 (m, 1H), 7.84−7.86 (m, 2H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 154.4, 150.7, 129.4, 126.8 (q, $J_{C\text{-}F}$ = 36.7 Hz), 119.7 (q, $J_{C\text{-}F}$ = 270.5 Hz), 114.6 (q, $J_{C\text{-}F}$ = 4.3 Hz), 113.2. HRMS (ESI) (m/z): calcd for $C_7H_4F_3N_3$ 188.0430 $[M + H]^+$, found 188.0420.

*6-Nitro-[1,2,4]triazolo[1,5-a]pyridine (**1e**).* The reaction was conducted on a 1.0 g scale using the general procedure and was complete within 16 h. The product was purified by column chromatography using EtOAc/*n*-heptane (1:1) as eluent to afford 600 mg (67%) of compound **1e** as a yellow solid (mp 211−213 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 10.17 (t, J = 1.6 Hz, 1H), 8.83 (s, 1H), 8.39 (dd, J = 9.6 Hz, 2.4 Hz, 1H), 8.05 (dd, J = 9.6 Hz, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 157.7, 152.0, 138.5, 130.0, 125.2, 116.3. HRMS (ESI) (m/z): calcd for $C_6H_4N_4O_2$, 165.0407 $[M + H]^+$, found 165.0411.

*6-(Trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyridine (**1f**).* The reaction was conducted on a 1.0 g scale using the general procedure and was complete within 2 h. The product was purified by column chromatography using EtOAc/*n*-heptane (1:3) as eluent to afford 820 mg (88%) of compound **1f** as an off-white solid (mp 100−102 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 9.69 (s, 1H), 8.72 (s, 1H), 8.07 (d, J = 9.2 Hz, 1H), 7.96 (dd, J = 9.6 Hz, 2 Hz, 1H). ^{19}F NMR (376.4 MHz, $(CD_3)_2SO$): δ 60.1. ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 155.7, 150.7, 129.0 (q, $J_{C\text{-}F}$ =5.5 Hz), 126.1 (q, $J_{C\text{-}F}$ =2.7 Hz), 123.2 (q, $J_{C\text{-}F}$ =269.6 Hz), 117.4, 116.8 (q, $J_{C\text{-}F}$ = 34.1 Hz). HRMS (ESI) (m/z): calcd for $C_7H_4F_3N_3$, 188.0430 $[M + H]^+$, found 188.0435.

*6-Chloro-[1,2,4]triazolo[1,5-a]pyridine (**1g**).* The reaction was conducted on a 1.0 g scale using the general procedure and was complete within 5 h. The product was purified by column chromatography using EtOAc/*n*-heptane (1:3) as eluent to afford 850 mg (95%) of compound **1g** as an off-white solid (mp 114−116 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 9.35 (q, J = 0.8 Hz, 1H), 8.56 (s, 1H), 7.91 (dd, J = 9.6 Hz, 0.8 Hz, 1H), 7.76 (dd, J = 9.6 Hz, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 155.0, 149.3, 131.8, 128.2, 121.5, 117.3 HRMS (ESI) (m/z): calcd for $C_6H_4ClN_3$, 154.0167 $[M + H]^+$, found 154.0172.

*7-Chloro-[1,2,4]triazolo[1,5-a]pyridine (**1h**).* The reaction was conducted on a 1.0 g scale using the general procedure and was complete within 5 h. The product was purified by column chromatography using EtOAc/*n*-heptane (1:1) as eluent to afford 760 mg (85%) of compound **1h** as an off-white solid (mp 111−113 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 9.03 (dd, J = 10.0 Hz, 0.8 Hz, 1H), 8.56 (s, 1H) 8.1 (dd, J = 2.8 Hz, 0.8 Hz, 1H), 7.31 (dd, J = 10.0 Hz, 3.2 Hz, 1H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ 155.3, 150.7, 135.8, 130.6, 115.8, 115.8. HRMS (ESI) (m/z): calcd for $C_6H_4ClN_3$, 154.0167 $[M + H]^+$, found 154.0171.

*[1,2,4]Triazolo[1,5-a]pyridine-7-carbonitrile (**1i**).* The reaction was conducted on a 1.0 g scale using the general procedure and was complete within 16 h. The product was purified by column chromatography using EtOAc/*n*-heptane (3:1) as eluent to afford 710 mg (80%) of compound **1i** as an off-white solid (mp 174−176 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 9.23 (dd, J = 7.2 Hz, 0.8 Hz, 1H), 8.77 (s, 1H), 8.68 (dd, J = 1.6 Hz, 0.8 Hz, 1H), 7.6 (dd, J = 7.2 Hz, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 156.0, 149.3, 131.1, 123.3, 117.4, 115.3, 113.0. HRMS (ESI) (m/z): calcd for $C_7H_4N_4$, 145.0509 $[M + H]^+$, found 145.0513.

*Methyl [1,2,4]Triazolo[1,5-a]pyridine-7-carboxylate (**1j**).* The reaction was conducted on a 1.5 g scale using the general procedure and was complete within 16 h. The product was purified by column chromatography using EtOAc/*n*-heptane (3:1) as eluent to afford 1.25 g (92%) of compound **1j** as an off-white solid (mp 124−126 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 9.10 (d, J = 9.6 Hz, 1H), 8.70 (s, 1H), 8.39 (s, 1H), 7.59 (dd, J = 9.6 Hz, 2.4 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 164.7, 156.3, 151.7, 132.7, 129.8, 118.1, 116.5, 53.2. HRMS (ESI) (m/z): calcd for $C_8H_7N_3O_2$, 178.0611 $[M + H]^+$, found 178.0602.

*8-(Benzyloxy)-[1,2,4]triazolo[1,5-a]pyridine (**1k**).* The reaction was conducted on a 1.0 g scale using the general procedure and was complete within 16 h. The product was purified by column chromatography using EtOAc/*n*-heptane (3:1) as eluent to afford 755 mg (82%) of compound **1k** as an off-white solid (mp 151−153 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 8.57 (dd, J = 8.8 Hz, 1.2 Hz, 1H), 8.44 (s, 1H), 7.51−7.54 (m, 1H), 7.43−7.46 (m, 1H), 7.37−7.41 (m, 3H), 7.17−7.2 (m, 1H), 7.08−7.13 (m, 1H), 5.36 (s, 2H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 153.3, 147.5, 145.1, 136.5,

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129.0, 128.7, 128.5, 122.3, 114.6, 109.1, 70.9. HRMS (ESI) (m/z) calcd for $C_{13}H_{11}N_3O$, 226.0975 $[M + H]^+$, found 226.0976.

*6-Methoxy-[1,2,4]triazolo [1,5-b] pyridazine (**7**).* The reaction was conducted on a 1.0 g scale using the general procedure and was complete within 16 h. The product was purified by column chromatography using EtOAc/*n*-heptane (1:3) as eluent to afford 600 mg (67%) of compound **7** as a pale yellow solid (mp 179−181 °C).^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 8.48 (s, 1H), 8.31 (d, J = 9.6 Hz, 1H), 7.32 (d, J = 9.6 Hz, 1H), 4.01 (s, 3H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 160.8, 151.8, 142.0, 127.8, 117.8, 55.6. HRMS (ESI) (m/z): calcd for $C_6H_6N_4O$, 151.0614 $[M + H]^+$, found 151.0619.

*[1,2,4]Triazolo[1,5-a]pyrazine (**10**).* The reaction was conducted on a 1.0 g scale using the general procedure and was complete within 5 h. The product was purified by column chromatography using EtOAc/*n*-heptane (1:3) as eluent to afford 750 mg (86%) of compound **10** as an off-white solid (mp 139−141 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 9.45 (d, J = 0.8 Hz, 1H), 9.13 (dd, J = 4.8 Hz, 1.6 Hz, 1H), 8.77 (s, 1H), 8.29 (d, J = 4.4 Hz, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 155.0, 153.6, 143.4, 132.2, 123.3. HRMS (ESI) (m/z): calcd for $C_5H_4N_4$, 121.0509 $[M + H]^+$, found 121.0512.

*[1,2,4]Triazolo[1,5-b]isoquinoline (**13**).* The reaction was conducted on a 1.0 g scale using the general procedure and was complete within 5 h. The product was purified by column chromatography using EtOAc/*n*-heptane (1:3) as eluent to afford 510 mg (55%) of compound **13** as a pale brownish solid (mp 97−99 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 10.00 (s, 1H), 8.72 (s, 1H), 8.46 (s, 1H), 8.07 (d, J = 8.8 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.56−7.60 (m, 1H), 7.46−7.50 (m, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 156.6, 149.1, 133.7, 129.1, 128.5, 127.2, 126.8, 126.2, 122.4, 111.0. HRMS (ESI) (m/z): calcd for $C_{10}H_7N_3$, 170.0713 $[M + H]^+$ found, 170.0698.

*6-Bromo-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (**1l**).* To a clean 60 L glass reactor, THF (16 L) and compound **3l** (1.6 kg, 6.5 mol, 1.0 equiv) were sequentially added at 20−35 °C under a nitrogen atmosphere. T3P (50% w/w in EtOAc, 4.4 kg, 6.5 mol, 1.0 equiv) was added at the same temperature, and the mixture was stirred for 5 h at 50−55 °C. After reaction completion, the contents of the reactor were cooled to 20−35 °C, and EtOAc (16 L) and purified water (8 L) were charged and stirred for 15 min. The organic layer was separated and the aqueous layer was backextracted with EtOAc (8 L). The combined organic layers were sequentially washed with 10% aqueous $NaHCO_3$ solution (16 L), purified water (8 L), and brine (8 L). The organic layer was concentrated under vacuum at 45 °C to ∼4 L and then *n*-heptane (24 L) was added. The mass was then cooled to 20−35 °C and allowed to granulate for 30 min. The resulting slurry was filtered through a Nutsche filter, and the filter cake was washed with *n*-heptane (8 L). The wet solid was dried under vacuum at 45−50 °C to afford compound **1l** as a pale brown solid (1.2 kg, HPLC purity 99.0%, Assay by HPLC 97.80%, 81% yield, mp 150−151 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 8.95 (d, J = 1.2 Hz, 1H), 8.46 (s, 1H), 7.26 (d, J = 1.6 Hz, 1H), 4.02 (s, 3H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 153.6, 148.4, 144.2, 122.3, 111.3, 108.3, 57.4 HRMS (ESI) (m/z): calcd for $C_7H_6BrN_3O$, 227.9767 $[M + H]^+$, found 227.9768.

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Notes

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