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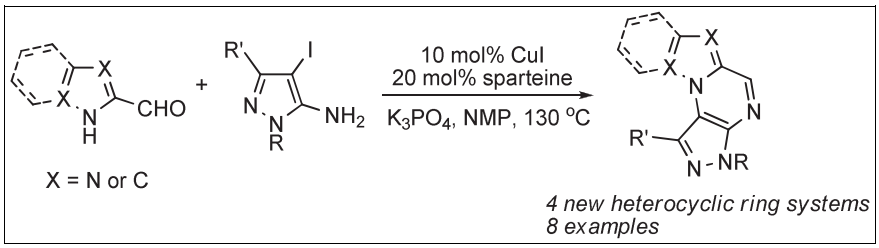

Various 2-formylazoles underwent CuI/sparteine-catalyzed annulation with 1-substituted-4-iodo-5-aminopyrazoles to produce four new heterocyclic ring systems. The reaction was demonstrated for 2-formylpyrroles, 2-formylindoles, 2-formylimidazole, and 3-methyl-5-formylpyrazole. 3-Substitution of the iodopyrazole was tolerated.

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INTRODUCTION

Recently, we reported the CuI/sparteine-catalyzed annulation of 2-formylazoles with *ortho*-aminoiodoarenes as a direct route to pyrrolo[1,2-*a*]quinoxalines and related heterocycles [1] (Scheme 1). This initial report was restricted primarily to substituted *ortho*-iodoanilines, as well as 2-amino-3-iodopyridine and 5-amino-4-iodopyrimidine as the iodide partners for the annulation. Subsequently, it was discovered that this reaction is also applicable to 1-substituted-4-iodo-5-aminopyrazoles (Scheme 1). Herein, we report our results on the scope of the reaction and the synthesis of four new heterocyclic ring systems.

RESULTS AND DISCUSSION

The required 4-iodo-5-aminopyrazoles **2a–c** were prepared in good yields by iodination of commercially available 5-aminopyrazoles **1a–c** with *N*-iodosuccinimide in CH_2Cl_2 at room temperature as shown in Scheme 2 [2]. The iodination was completely regioselective for pyrazoles **2a–b**; no 3-iodinated products were detected [3].

Initial annulation experiments used 2-formylpyrrole **3** and 1-methyl-4-iodo-5-aminopyrazole **2a**. Application of the reaction conditions developed for pyrrolo[1,2-*a*]quinoxaline synthesis (1 equiv 2-formylpyrrole, 1.5 equiv iodide, 10 mol % CuI, 20 mol% sparteine, 2.0 equiv K_3PO_4, NMP, 130 °C, 24 h) gave the desired product, 3-methyl-3*H*-pyrazolo[3,4-*e*]pyrrolo[1,2-*a*]pyrazine **4**, as a tan-colored solid in 44% yield after flash chromatographic purification on SiO_2 (Scheme 3). These standard reaction conditions were employed for all subsequent annulations described herein.

The reaction was applied to not only 2-formylpyrrole (entry 1) but also 2-formylindole (entry 2), 2-formylimidazole (entry 3), and 3-formyl-5-methylpyrazole (entry 4). In all cases, a previously unknown heterocyclic ring system was generated. Further functionalization of the formylpyrrole (entry 5) or formylindole (entry 6) moieties was tolerated. Finally, the use of *N*-phenyl iodoaminopyrazole **2b** (entry 7) or the sterically demanding 3-*tert*-butyl-4-iodo-5-aminopyrazole **2c** (entry 8) was also possible (Table 1).

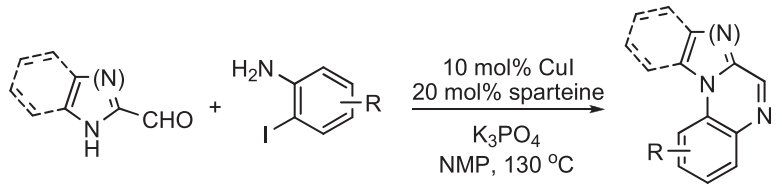
In summary, the copper/sparteine-catalyzed annulation of 2-formylazoles was applied to 4-iodo-5-aminopyrazoles. The use of either *N*-methyl or *N*-phenyl pyrazoles was possible. Substitution of the 2-formylpyrrole, 2-formylindole, and formylpyrazole moieties was tolerated, as was 3-*tert*-butyl substitution of the iodoaminopyrazole. Four previously unknown heterocyclic ring systems were generated. In addition, a simple and regioselective procedure for iodination of 5-amino-pyrazoles with N-iodosuccinimide (NIS) was developed.

EXPERIMENTAL

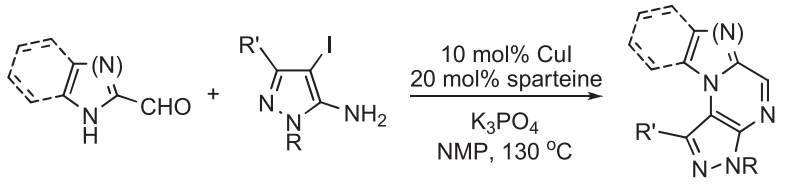
The pyrazoles **1a–c** and the formylazoles **3, 5, 7, 9, 11**, and **13** were purchased from commercial sources and used as received. Melting points were determined on a Mel-Temp 3.0 and are uncorrected. ^1H and ^{13}C NMR spectra were obtained on a Bruker 400 MHz spectrometer in d_6-DMSO or $CDCl_3$ (^1H at 400 MHz and ^{13}C at 100 MHz). Elemental analyses were obtained from Intertek-QTI, Whitehouse, NJ.

Scheme 1

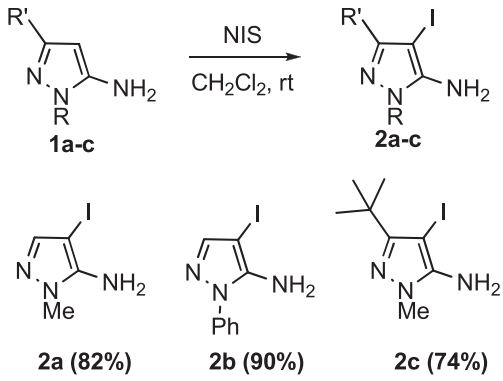
CuI/sparteine-catalyzed synthesis of pyrrolo[1,2-a]quinoxalines (ref. 1):



Extension of the reaction to 4-iodo-5-aminopyrazoles (this work):



Scheme 2



General procedure for iodination of aminopyrazoles. A solution of aminopyrazole in CH_2Cl_2 (0.5 M) was treated at room temperature with *N*-iodosuccinimide (1.0 equiv). The reaction mixture was stirred at room temperature for 1 h, transferred to a separatory funnel, and then washed with water. The organic phase was dried over $MgSO_4$, filtered through a short pad of SiO_2, and concentrated to give the iodide as a solid. The solid was further purified by recrystallization from CH_2Cl_2/hexanes.

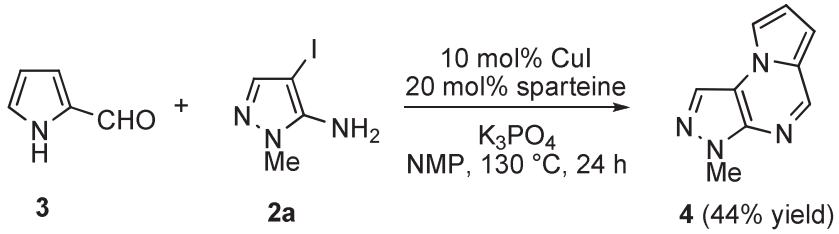
4-Iodo-1-methyl-1H-pyrazol-5-amine (2a). According to the general procedure, 1-methyl-5-aminopyrazole (5.28 g, 54.4 mmol) and *N*-iodosuccinimide (12.23 g, 54.4 mmol) yielded 4-iodo-1-methyl-1H-pyrazol-5-amine (**2a**) as a brown solid (9.93 g, 82% yield). mp 109–112 °C (CH_2Cl_2/hexanes). ^{1}H NMR (d_6-DMSO) δ 7.09 (s, 1H), 5.25 (br s, 2H), 3.53 (s, 3H); ^{13}C NMR (d_6-DMSO) δ 147.1, 140.9, 37.4, 35.3. *Anal.* Calcd. for $C_4H_6IN_3$: C, 21.54; H, 2.71; N, 18.84; Found: C, 21.80; H, 2.79; N, 18.51.

4-Iodo-1-phenyl-1H-pyrazol-5-amine (2b). According to the general procedure, 1-phenyl-5-aminopyrazole (4.20 g, 26.4 mmol) and *N*-iodosuccinimide (5.94 g, 26.4 mmol) yielded 4-iodo-1-phenyl-1H-pyrazol-5-amine (**2b**) as a brown solid (6.74 g, 90% yield). mp 127–130 °C (CH_2Cl_2/hexanes). ^{1}H NMR ($CDCl_3$) δ 7.54–7.47 (m, 4H), 7.43 (s, 1H), 7.40–7.35 (m, 1H), 3.98 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 145.2, 143.5, 138.6, 129.6, 127.9, 123.7, 41.9. *Anal.* Calcd. for $C_9H_8IN_3$: C, 37.92; H, 2.83; N, 14.74; Found: C, 38.01; H, 2.89; N, 14.90.

***3-tert*-Butyl-4-iodo-1-methyl-1*H*-pyrazol-5-amine (2c).** According to the general procedure, 3-*tert*-butyl-1-methyl-1H-pyrazol-5-amine (4.05 g, 26.4 mmol) and *N*-iodosuccinimide (5.94 g, 26.4 mmol) yielded 3-*tert*-butyl-4-iodo-1-methyl-1H-pyrazol-5-amine (**2c**) as a brown solid (5.45 g, 74% yield). mp 96–100 °C (CH_2Cl_2/hexanes). ^{1}H NMR (d_6-DMSO) δ 5.08 (br s, 2H), 3.54 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (d_6-DMSO) δ 154.1, 148.0, 37.1, 35.1, 32.7, 28.9. *Anal.* Calcd. for $C_8H_{14}IN_3$: C, 34.42; H, 5.06; N, 15.05; Found: C, 34.59; H, 4.91; N, 15.22.

General procedure for copper-catalyzed annulation reaction. A glass pressure tube with a teflon screw cap was charged with a magnetic stir bar, the 2-formylazole (2.00 mmol,

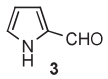
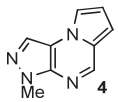
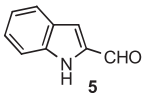
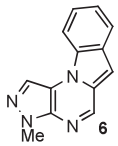
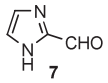
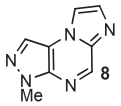
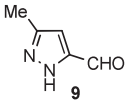
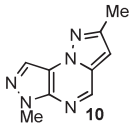
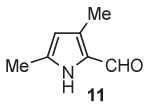
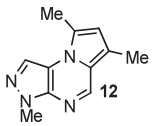
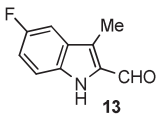
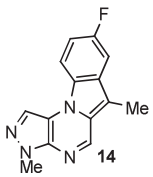
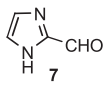
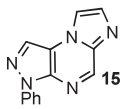
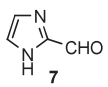
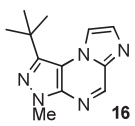
Scheme 3



3 **2a** **4** (44% yield)

Table 1

Scope of the annulation reaction with 4-iodo-5-aminopyrazoles.

Entry	Iodide	Formylazole	Product	Yield (%)[a]
1	**2a**	 **3**	 **4**	44
2	**2a**	 **5**	 **6**	54
3	**2a**	 **7**	 **8**	36
4	**2a**	 **9**	 **10**	41
5	**2a**	 **11**	 **12**	38
6	**2a**	 **13**	 **14**	62
7	**2b**	 **7**	 **15**	36
8	**2c**	 **7**	 **16**	31

[a]Isolated yields after purification by chromatography on SiO_2.

1 equiv), the aminoiodopyrazole (3.00 mmol, 1.5 equiv), K_3PO_4 (849 mg, 4.00 mmol, 2 equiv), CuI (38 mg, 0.2 mmol, 0.1 equiv), sparteine (92 μL, 0.4 mmol, 0.2 equiv), and NMP (1.0 mL). The system was sealed with a septum, evacuated, and filled with nitrogen, and the septum quickly replaced with the screw cap. The tube was heated in a 130 °C oil bath for 24 h. After cooling to RT, the reaction mixture was diluted with EtOAc and filtered through a Celite pad by using copious EtOAc to rinse the tube and the Celite pad. The filtrate was concentrated and the crude product purified by chromatography on SiO_2 by using hexanes/EtOAc as the eluant.

3-Methyl-3H-pyrazolo[3,4-e]pyrrolo[1,2-a]pyrazine (4). According to the general procedure, **3** (190 mg, 2.00 mmol) and **2a** (669 mg, 3.00 mmol) yielded 3-methyl-3H-pyrazolo[3,4-e]

pyrrolo[1,2-a]pyrazine (**4**) as a brown solid (152 mg, 44% yield). mp 99–100 °C (hexanes/EtOAc). ^{1}H NMR ($CDCl_3$) δ 8.57 (s, 1H), 7.91 (s, 1H), 7.63–7.62 (m, 1H), 6.97–6.95 (m, 1H), 6.85–6.83 (m, 1H), 4.14 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 143.2, 139.3, 126.5, 122.3, 115.2, 113.9, 107.3, 94.0, 34.9. *Anal*. Calcd. for $C_9H_8N_4$: C, 62.78; H, 4.68; N, 32.54; Found: C, 62.99; H, 4.82; N, 32.18.

3-Methyl-3H-pyrazolo[3,4-e]indolo[1,2-a]pyrazine (6). According to the general procedure, **5** (290 mg, 2.00 mmol) and **2a** (669 mg, 3.00 mmol) yielded 3-methyl-3H-pyrazolo[3,4-e] indolo[1,2-a]pyrazine (**6**) as a yellow solid (242 mg, 54% yield). mp 135–138 °C (hexanes/EtOAc). ^{1}H NMR ($CDCl_3$) δ 8.73 (s, 1H), 8.14 (s, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.93 (d, J = 8.3 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.17 (s, 1H), 4.17 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.2, 139.0, 130.6, 128.8, 127.7, 124.0, 122.6, 122.5, 122.4, 113.3, 112.5, 99.6, 35.1. *Anal*. Calcd. for $C_{13}H_{10}N_4$: C, 70.26; H, 4.54; N, 25.21; Found: C, 70.10; H, 4.74; N, 25.16.

3-Methyl-3H-imidazo[1,2-a]pyrazolo[3,4-e]pyrazine (8). According to the general procedure, **7** (192 mg, 2.00 mmol) and **2a** (669 mg, 3.00 mmol) yielded 3-methyl-3H-imidazo[1,2-a] pyrazolo[3,4-e]pyrazine (**8**) as a tan solid (126 mg, 36% yield). mp 174–176 °C (hexanes/EtOAc). ^{1}H NMR ($CDCl_3$) δ 8.88 (s, 1H), 8.01 (s, 1H), 7.91 (s, 1H), 7.84 (s, 1H), 4.21 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 141.3, 140.1, 139.2, 135.1, 122.7, 115.0, 113.2, 35.2. *Anal*. Calcd. for $C_8H_7N_5$: C, 55.48; H, 4.07; N, 40.44; Found: C, 55.63; H, 4.30; N, 40.06.

2,6-Dimethyl-6H-dipyrazolo[1,5-a:3′,4′-e]pyrazine (10). According to the general procedure, **9** (220 mg, 2.00 mmol) and **2a** (669 mg, 3.00 mmol) yielded 2,6-dimethyl-6H-dipyrazolo [1,5-a:3′,4′-e]pyrazine (**10**) as a tan solid (126 mg, 41% yield). mp 158–160 °C (hexanes/EtOAc). ^{1}H NMR ($CDCl_3$) δ 8.71 (s, 1H), 8.22 (s, 1H), 6.71 (s, 1H), 4.20 (s, 3H), 2.58 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 151.0, 141.0, 139.3, 134.0, 122.7, 100.4, 94.1, 35.1, 13.9. *Anal*. Calcd. for $C_9H_9N_5$: C, 57.74; H, 4.85; N, 37.41; Found: C, 57.90; H, 4.68; N, 37.42.

3,6,8-Trimethyl-3H-pyrazolo[3,4-e]pyrrolo[1,2-a]pyrazine (12). According to the general procedure, **11** (246 mg, 2.00 mmol) and **2a** (669 mg, 3.00 mmol) yielded 3,6,8-trimethyl-3H-pyrazolo [3,4-e]pyrrolo[1,2-a]pyrazine (**12**) as a tan solid (151 mg, 38% yield). mp 104–110 °C (hexanes/EtOAc). ^{1}H NMR ($CDCl_3$) δ 8.45 (s, 1H), 7.92 (s, 1H), 6.40 (s, 1H), 4.12 (s, 3H), 2.68 (s, 3H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 141.5, 140.7, 139.3, 125.8, 124.1, 122.8, 118.6, 114.3, 34.8, 13.4, 10.7. *Anal*. Calcd. for $C_{11}H_{12}N_4$: C, 65.98; H, 6.04; N, 27.98; Found: C, 66.20; H, 6.06; N, 27.73.

3,6-Dimethyl-8-fluoro-3H-pyrazolo[3,4-e]indolo[1,2-a] pyrazine (14). According to the general procedure, **13** (354 mg, 2.00 mmol) and **2a** (669 mg, 3.00 mmol) yielded 3,6-dimethyl-8-fluoro-3H-pyrazolo[3,4-e]indolo[1,2-a]pyrazine (**14**) as an orange solid (316 mg, 62% yield). mp 221–224 °C (hexanes/EtOAc). ^{1}H NMR ($CDCl_3$) δ 8.68 (s, 1H), 8.03 (s, 1H), 7.83 (dd, J = 6.3, 4.6 Hz, 1H), 7.45 (dd, J = 9.3, 2.3 Hz, 1H), 7.27–7.23 (m, 1H), 4.17 (s, 3H), 2.62 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.9, 157.5, 143.4, 139.1, 128.0, 127.9, 127.3, 126.6, 121.9, 113.7, 113.5, 113.43, 113.39, 108.8, 104.7, 104.5, 35.1, 8.5. *Anal*. Calcd. for $C_{14}H_{11}FN_4$: C, 66.13; H, 4.36; N, 22.04; Found: C, 66.19; H, 4.48; N, 22.20.

3-Phenyl-3H-imidazo[1,2-a]pyrazolo[3,4-e]pyrazine (15). According to the general procedure, **7** (192 mg, 2.00 mmol) and **2b** (855 mg, 3.00 mmol) yielded 3-phenyl-3H-imidazo[1,2-a] pyrazolo[3,4-e]pyrazine (**15**) as a brown solid (171 mg, 36% yield). mp 155–158 °C (hexanes/EtOAc). ^{1}H NMR ($CDCl_3$) δ 8.98 (s, 1H), 8.23 (s, 1H), 8.19–8.16 (m, 2H), 7.98–7.97 (m, 1H), 7.89–7.88 (m, 1H), 7.59–7.54 (m, 2H), 7.43–7.38 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 141.7, 139.8, 139.2, 138.9, 135.5, 129.9, 129.3, 127.4, 124.7, 122.1, 113.3. *Anal*. Calcd. for $C_{13}H_9N_5$: C, 66.37; H, 3.86; N, 29.77; Found: C, 66.50; H, 3.99; N, 29.50.

***1-tert*-Butyl-3-methyl-3*H*-imidazo[1,2-a]pyrazolo[3,4-e] pyrazine (16)**. According to the general procedure, **7** (192 mg, 2.00 mmol) and **2c** (837 mg, 3.00 mmol) yielded 1-*tert*-butyl-3-methyl-3H-imidazo[1,2-a]pyrazolo[3,4-e]pyrazine (**16**) as a brown solid (144 mg, 31% yield). mp 142–145 °C (hexanes/EtOAc). ^{1}H NMR ($CDCl_3$) δ 8.87 (s, 1H), 8.18 (s, 1H), 7.84 (m, 1H), 4.13 (t, 3H), 1.58 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 144.5, 141.4, 141.0, 139.6, 134.6, 115.5, 110.8, 34.6, 32.6, 29.5. *Anal*. Calcd. for $C_{12}H_{15}N_5$: C, 62.86; H, 6.59; N, 30.54; Found: C, 63.01; H, 6.54; N, 30.44.

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