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Copper-Catalyzed Annulation of 2-Formylazoles with *o*-Aminoiodoarenes

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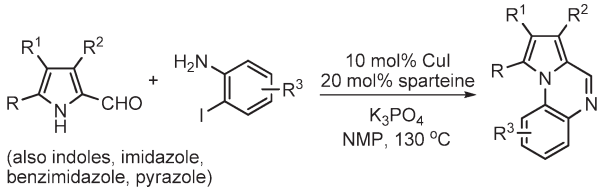
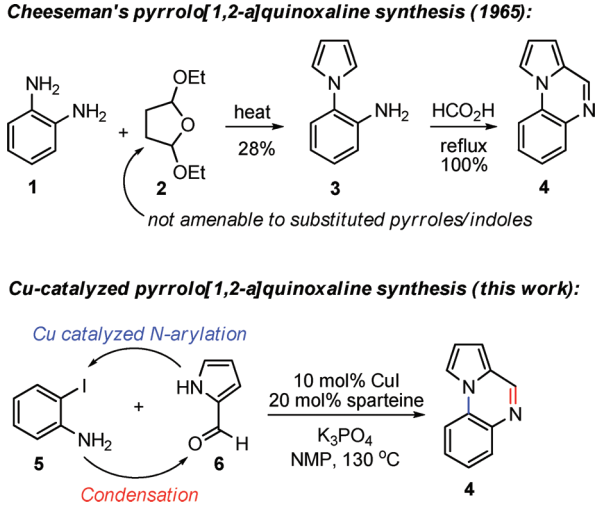


In the presence of catalytic CuI and sparteine, 2-formylpyrroles can be annulated with *o*-aminoiodoarenes to give substituted pyrrolo[1,2-*a*]quinoxalines and related heterocycles. The reaction also works for annulation of 2-formylindoles, 2-formylimidazole, 2-formylbenzimidazole, and a 3-formylpyrazole.

The pyrrolo[1,2-*a*]quinoxaline ring system is present in a small but rapidly growing number of biologically active molecules.[1] The available methods for synthesis of this heterocycle, however, are few. Cheeseman and Tuck reported the first synthesis of the parent unsubstituted pyrrolo[1,2-*a*]quinoxaline **4** in 1965 (Scheme 1).[2] This two-step procedure has limitations in the potential substitution patterns on the pyrrole nucleus. Variations of this procedure have been described in which compounds of structure type **3** are accessed by alternative chemistry, typically S_NAr of 2-fluoronitroarenes with *N*-metalated pyrroles, followed by reduction of the nitro

SCHEME 1. Cheeseman's Pyrrolo[1,2-*a*]quinoxaline Synthesis and Our Cu-Catalyzed Approach



group.[3] Kobayashi and co-workers have described the Lewis acid catalyzed cyclization of 1-(2-isocyanophenyl)pyrroles to give pyrrolo[1,2-*a*]quinoxalines in good yields, though the isocyanide substrates require a multistep synthesis.[4] Ma and Yuan have recently described the synthesis of a structurally related ring system, pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones, by CuI/L-proline catalyzed coupling of *N*-trifluoroacetyl-2-haloanilines with methyl pyrrole-2-carboxylates, followed by *in situ* hydrolysis of the *N*-trifluoroacetyl group and intramolecular amide formation.[5] Given the ready availability of substituted 2-formylpyrroles and 2-iodoanilines, a direct annulation process by copper-catalyzed pyrrole N-arylation and imine formation appeared to be an attractive one-step route to pyrrolo[1,2-*a*]quinoxalines (Scheme 1).[6] This method would allow for the regioselective incorporation of diverse substitution on the heterocyclic core. Herein we describe our results on the development of this methodology.

Initial screening experiments employed 2-iodoaniline **5** and 2-formylpyrrole **6**. Several ligands, bases, and solvents were examined. The use of NMP as solvent was preferred because of its high boiling point, although DMF and DMAC were also effective. A screen of bases (Na_2CO_3, K_2CO_3, Cs_2CO_3, and K_3PO_4) showed K_3PO_4 to be most effective. Various ligands promoted the cyclization, including *trans*-1,2-(methylamino)cyclohexane, *trans*-1,2-diaminocyclohexane, and *N*,*N*′-dimethylethylenediamine. These ligands were competitively *N*-arylated, however, and thus a larger excess of ligand and iodide proved necessary to reach full conversion of 2-formylpyrrole.[7] Sparteine was found to be an

(1) (a) Guillon, J.; Dumoulin, H.; Dallemagne, P.; Reynolds, R.; Rault, S. *Pharm. Pharmacol. Commun.* **1998**, *4*, 33–38. (b) Guillon, J.; Dallemagne, P.; Pfeiffer, B.; Renard, P.; Manechez, D.; Kervran, A.; Rault, S. *Eur. J. Med. Chem.* **1998**, *33*, 293–308. (c) Guillon, J.; Boullouard, M.; Lisowski, V.; Stiebing, S.; Lelong, V.; Dallemagne, P.; Rault, S. *J. Pharm. Pharmacol.* **2000**, *52*, 1369–1375. (d) Prunier, H.; Rault, S.; Lancelot, J. C.; Robba, M.; Renard, P.; Delagrange, P.; Pfeiffer, B.; Caignard, D. H.; Misslin, R.; Guardiola-Lemaitre, B.; Hamon, M. *J. Med. Chem.* **1997**, *40*, 1808–1819. (e) Guillon, J.; Reynolds, R. C.; Leger, J.-M.; Guie, M.-A.; Massip, S.; Dallemagne, P.; Jarry, C. *J. Enzyme Inhib. Med. Chem.* **2004**, *19*, 489–495. (f) Guillon, J.; Forfar, I.; Mamani-Matsuda, M.; Desplat, V.; Saliege, M.; Thiolat, D.; Massip, S.; Tabourier, A.; Leger, J.-M.; Dufaure, B.; Haumont, G.; Jarry, C.; Mossalayi, D. *Bioorg. Med. Chem.* **2007**, *15*, 194–210.

(2) Cheeseman, G. W. H.; Tuck, B. *Chem. Ind.* **1965**, 1382.

(3) Harrak, Y.; Weber, S.; Gomez, A. B.; Rosell, G. *Arkivoc* **2007**, *4*, 251–259.

(4) (a) Kobayashi, K.; Matoba, T.; Irisawa, S.; Matsumoto, T.; Morikawa, O.; Konishi, H. *Chem. Lett.* **1998**, 551–552. (b) Kobayashi, K.; Irisawa, S.; Matoba, T.; Matsumoto, T.; Yoneda, K.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1109–1114.

(5) Yuan, Q.; Ma, D. *J. Org. Chem.* **2008**, *73*, 5159–5162.

(6) For an approach to substituted 2-formylpyrroles, see: Reeves, J. T.; Song, J. J.; Tan, Z.; Lee, H.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2007**, *9*, 1875–1878.

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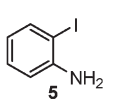
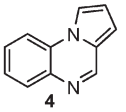
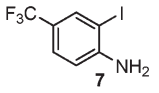
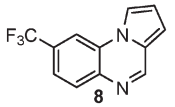
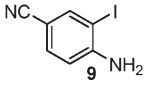
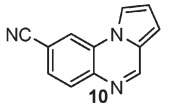
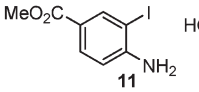
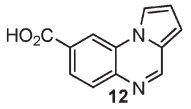
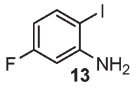
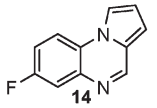
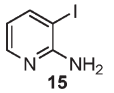
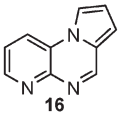
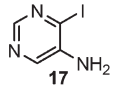
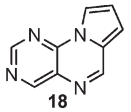
TABLE 1. Annulation of 2-Formylpyrrole with Substituted Aminoiodoarenes[a]

Entry	Iodoarene	Product	Yield (%)[b]
1	 **5**	 **4**	83
2	 **7**	 **8**	69
3	 **9**	 **10**	48
4	 **11**	 **12**	61
5	 **13**	 **14**	66
6	 **15**	 **16**	78
7	 **17**	 **18**	63

[a]Reaction conditions: 10 mol % CuI, 20 mol % sparteine, 2 equiv of K_3PO_4, 1.5 equiv of aminoiodoarene, 1.0 equiv of **6**, 130 °C, 24 h. [b]Isolated yields after chromatography on SiO_2.

effective ligand for the reaction that avoided this undesired side reaction due to the tertiary nature of both amino groups.[8] Optimal reaction conditions were identified as 1 equiv of 2-formylpyrrole, 1.5 equiv of 2-iodoaniline, 2 equiv of K_3PO_4, 10 mol % CuI, 20 mol % sparteine, and NMP as solvent (2 M in formylpyrrole) at 130 °C for 24 h. Using these conditions, the parent pyrrolo[1,2-*a*]quinoxaline **4** was obtained in 83% isolated yield after purification by column chromatography on SiO_2 (entry 1, Table 1). Notably, the reaction proceeded in the absence of ligand, though in this case complete conversion was not observed. In the absence of CuI, no product was detected by HPLC analysis. The use of 2-bromoaniline resulted in a much slower reaction, as after 48 h at 130 °C only ~70% conversion of 2-formylpyrrole was achieved.

The scope of the reaction was first explored with respect to structural variation of the aminoiodoarene (Table 1). Trifluoromethyl, cyano, and fluoro groups were tolerated (entries 2, 3, and 5). The methyl ester group of **11** was converted to a carboxylic acid under the reaction conditions (entry 4). This could be due to hydrolysis by the water produced from imine formation or alternatively by an iodide-mediated S_N2-type demethylation.[9]

(8) Mao, J.; Hua, Q.; Guo, J.; Shi, D. *Catal. Commun.* **2008**, *10*, 341–346.
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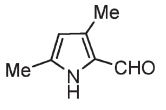
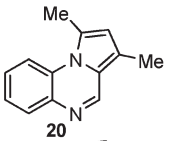
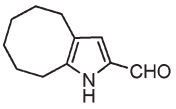
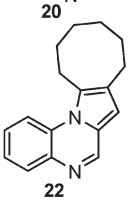
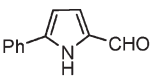
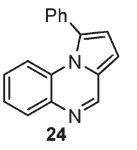
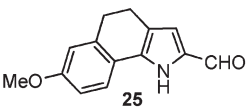
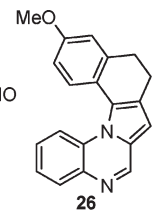
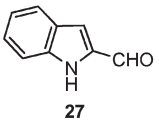
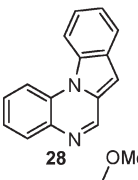
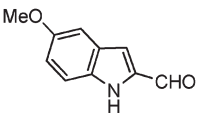
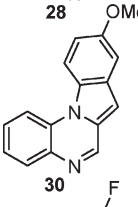
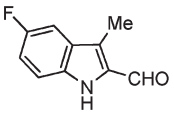
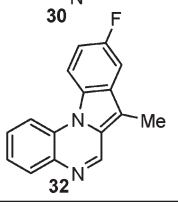
(10) Latli, B.; Jones, P.-J.; Krishnamurthy, D.; Senanayake, C. H. *J. Label. Compd. Radiopharm.* **2008**, *51*, 54–58.

TABLE 2. Annulation of Substituted 2-Formylpyrroles and 2-Formylindoles with 2-Iodoaniline[a]

Entry	Formylazole	Product	Yield (%)[b]
1	 **19**	 **20**	82[c]
2	 **21**	 **22**	74[c]
3	 **23**	 **24**	69[c]
4	 **25**	 **26**	72[d]
5	 **27**	 **28**	71
6	 **29**	 **30**	64
7	 **31**	 **32**	78

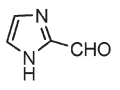
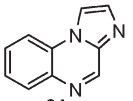
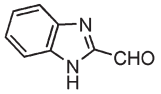
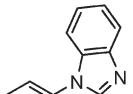
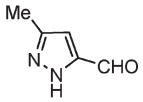
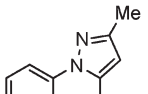
[a]Reaction conditions: 10 mol % CuI, 20 mol % sparteine, 2 equiv of K_3PO_4, 1.5 equiv of **5**, 1.0 equiv of 2-formylazole, 130 °C, 24 h. [b]Isolated yields after chromatography on SiO_2. [c]Reaction time of 36 h. [d]Reaction time of 48 h.

Aminoiodopyridine **15** and aminoiodopyrimidine **17**[10] worked well in the annulation and provided convenient access to the unusual pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (**16**) and pyrrolo[2,1-*h*]pteridine (**18**) ring systems.

The reaction was next explored with respect to substitution of the formylpyrrole component (Table 2). Substitution at positions 3−5 of the pyrrole ring was well tolerated (entries 1−4) and allowed access to unique pyrrolo[1,2-*a*]quinoxalines. In addition, the methodology could be extended to 2-formylindoles to provide indolo[1,2-*a*]quinoxalines in good yields (entries 5−7).[11]

(11) Joseph, M. S.; Basanagoudar, L. D. *Synth. Commun.* **2003**, *33*, 851–862.

TABLE 3. Annulation of Formyldiazoles with 2-Iodoaniline[a]

Entry	Formyldiazole	Product	Yield (%)[b]
1	 **33**	 **34**	51
2	 **35**	 **36**	50
3	 **37**	 **38**	83

[a]Reaction conditions: 10 mol % CuI, 20 mol % sparteine, 2 equiv of K_3PO_4, 1.5 equiv of **5**, 1.0 equiv of formyldiazole, 130 °C, 24 h. [b]Isolated yields after chromatography on SiO_2.

The further extension of the reaction to 2-formyldiazole compounds was briefly explored (Table 3). Both 2-formylimidazole and 2-formylbenzimidazole underwent the reaction to give imidazo[1,2-*a*]quinoxaline (**34**) and benzimidazo[1,2-*a*]-quinoxaline (**36**) in moderate yields. The reaction also worked well for annulation of a formylpyrazole (entry 3) to provide 2-methylpyrazolo[1,5-*a*]quinoxaline (**38**) in 83% yield. These results suggest the methodology may be applicable to an even broader range of 1-aza-2-formylheterocycles.

In conclusion, a simple one-step copper-catalyzed synthesis of pyrrolo[1,2-*a*]quinoxalines from *o*-aminoiodoarenes and 2-formylpyrroles has been developed. The method is amenable to structural variation of both reaction partners and consequently serves as a useful alternative to existing routes to pyrrolo[1,2-*a*]quinoxalines. Indolo[1,2-*a*]quinoxalines can be prepared under the same reaction conditions by starting with 2-formylindoles. In addition, the reaction can be extended to 2-formylimidazole, 2-formylbenzimidazole, and a 3-formylpyrazole to generate a range of unique tricyclic heterocycles.

Experimental Section

General Procedure. Pyrrolo[1,2-*a*]quinoxaline (4). A flask equipped with a magnetic stir bar and reflux condensor was charged with 2-formylpyrrole (951 mg, 10.0 mmol, 1.0 equiv), 2-iodoaniline (3.29 g, 15.0 mmol, 1.5 equiv), K_3PO_4 (4.25 g, 20.0 mmol, 2.0 equiv), and CuI (190 mg, 1.00 mmol, 0.10 equiv). The flask was evacuated and filled with nitrogen, and then NMP (5.0 mL) was charged via syringe followed by sparteine (0.46 mL, 2.00 mmol, 0.20 equiv). The flask was heated in a 130 °C oil bath for 24 h, at which time HPLC analysis indicated complete consumption of 2-formylpyrrole. The reaction mixture was cooled to room temperature, diluted with EtOAc, and filtered through a pad of Celite, using EtOAc to rinse the flask and Celite pad. The filtrate was concentrated, and the residue was purified by column chromatography on SiO_2 (hexanes/EtOAc, 70:30 to 50:50) to give **4** (1.40 g, 83% yield) as a tan solid: mp 131−133 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (s, 1 H), 7.94 (d, J = 7.95 Hz, 1 H), 7.89 (s, 1 H), 7.82 (d, J = 8.15 Hz, 1 H), 7.51−7.48 (m, 1 H), 7.44−7.41 (m, 1 H), 6.88−6.86 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 135.8, 130.1, 128.0, 127.8, 126.5, 125.1, 114.2, 114.0, 113.8, 107.3; HRMS calcd for $C_{11}H_9N_2$ [M + H] 169.0760. found 169.0769.

Supporting Information Available: Analytical data and copies of ^{1}H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.