Heterocycle Synthesis

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Synthesis of Nitrogen Heterocycles by the Ring Opening of Pyridinium Salts**

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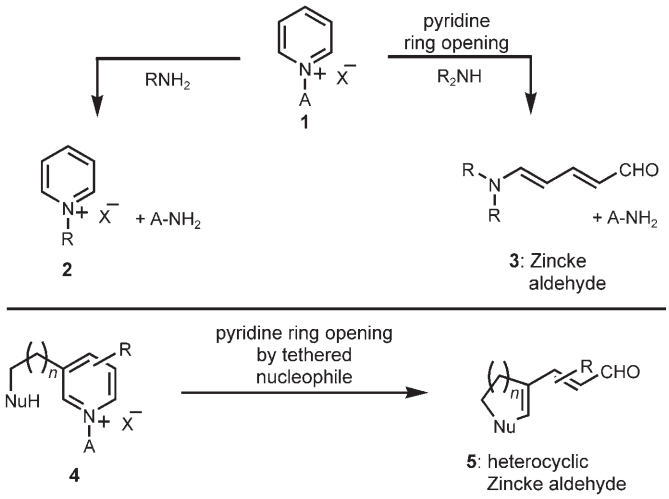
The ring-opening reaction of pyridinium salts dates back over a century to the pioneering work of Zincke and König.[1] Activation of pyridines as their pyridinium salts renders the heterocycle electrophilic at the 2- and 4-positions and enables a diverse range of productive chemistry, with or without ring opening.[2] Treatment of appropriately activated pyridinium salts, such as **1** (Scheme 1), with primary amines leads to the



Scheme 1. Proposed use of tethered nucleophiles to induce pyridinium ring opening leading to substituted heterocycles. A = generic activating group.

formation of new pyridinium salts (**2**), whereas the use of secondary amines cleanly affords the products of ring opening.[3,4] Both the ring-opening process and the product 5-amino-2,4-pentadienals (**3**),[4a] now known as Zincke alde-

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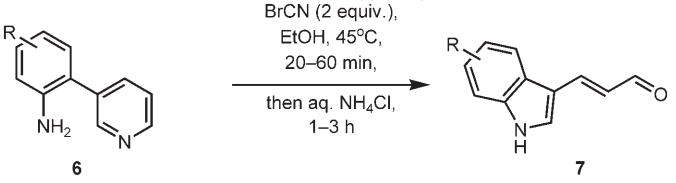
hydes, appear ideally suited for manifold applications in synthesis; to date, however, this potential has remained largely unrealized.[5]

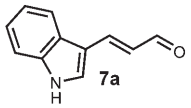
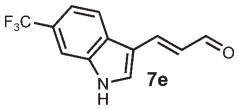
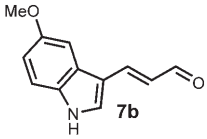
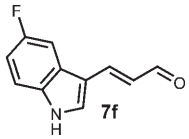
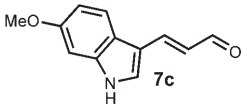
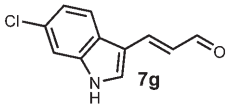
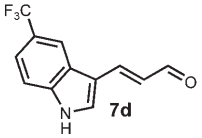
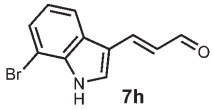
We anticipated that the ring opening of activated pyridines by nucleophiles tethered at pyridine C3 would generate a range of useful heterocycles bearing a versatile propenal side chain at C3 of the newly formed ring (**4**→**5**, Scheme 1). By rendering the initial step of this process intramolecular, we hoped to extend the range of nucleophiles beyond simple secondary amines. Thus, the appropriate selection of tether and nucleophile would provide access to a variety of different heterocycles. Our initial progress toward this goal, which entails a nonobvious route to nitrogen heterocycles from pyridines, is the subject of this communication.

The indole nucleus is ubiquitous in natural products and medicinal chemistry. As a result, numerous different approaches to this ring system exist, each offering different levels of practicality for varying applications;[6] indeed, new methods are continually being developed.[7] We expected that a convergent biaryl coupling/pyridine ring opening sequence would provide access to a family of indole derivatives of significant utility, while concurrently providing proof of principle for our general heterocycle synthesis.

Table 1: Formation of substituted indoles from pyridinyl anilines.



6 **7**

Entry	Product	Yield [%]	Entry	Product	Yield [%]
1	 **7a**	78[a]	5	 **7e**	78
2	 **7b**	73[b]	6	 **7f**	65
3	 **7c**	80	7	 **7g**	74
4	 **7d**	63	8	 **7h**	80

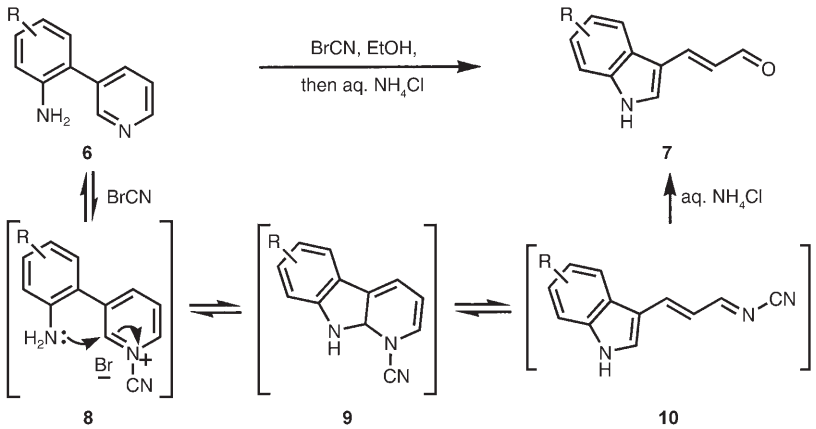
[a] In a single 110-mmol experiment, a 60% yield was obtained, affording over 10 g of **7a**. [b] Performed at 0.8 mM; the typical procedure is performed at 0.10 M.

A series of pyridinyl-aniline precursors of type **6** (Scheme 2) were synthesized efficiently by Suzuki biaryl couplings.[8] A variety of activating agents were screened,[9] and inexpensive cyanogen bromide emerged as the reagent of choice for indole formation (**6**→**7**). Thus, treatment of a variety of pyridinyl anilines with cyanogen bromide in warm ethanol rapidly afforded the desired indoles (**7**) after hydrolysis of the presumed *N*-cyanoimine intermediate (Table 1). A plausible mechanism to account for the formation of these products is provided in Scheme 2.[10]

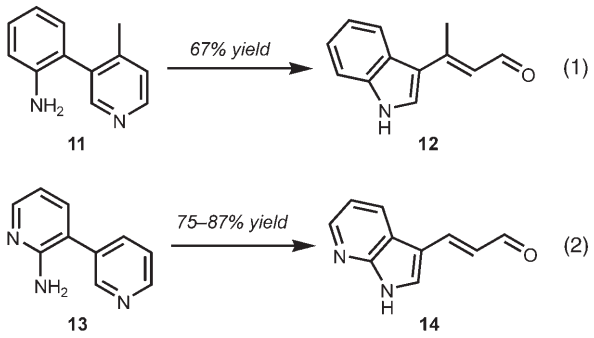
To date, this indolization procedure has proven to be general; Table 1 lists every substrate of type **6** that we have subjected to these conditions. A variety of substituents of varying electronic nature are tolerated, and good to excellent yields are observed in nearly every case. The sole outlier is entry 2 of Table 1, wherein the formation of a stable imine condensation product of the aniline and the indole product **7b** occurs under standard conditions, thus preventing completion of the reaction. This problem was easily circumvented by using more dilute reaction conditions, which served to minimize this undesired bimolecular condensation.

The strength of this strategy lies in its ability to deliver benzene-ring-substituted indoles with the propenal side chain at C3. The location of such a versatile handle at this position distinguishes this method of indole construction; one could imagine a myriad of uses for the enal function. Very useful [4+2] cycloaddition reactivity of either the enal (as dienophile) or the aminopentadienal (as diene) is anticipated for these and related products. In addition, recent work of MacMillan and co-workers suggests that a number of useful enantioselective transformations might be performed on the unsaturated aldehyde moiety of these indole products.[11,12]

Although the results in Table 1 clearly demonstrate versatility with respect to substitution on the carbocyclic ring of the indole, we anticipated that the use of functionalized pyridines would enable the introduction of substituents on the enal side chain. The preliminary experiment shown in [Eq. (1)] supports this idea as the 4-methylpyridine derivative **11** is converted into **12** in a yield comparable to those obtained with unsubstituted pyridines. In addition,



Scheme 2. Presumed reaction course for the conversion of pyridinyl anilines into indoles.



this reaction works especially well in the formation of a 7-azaindole (**14**, [Eq. (2)]) starting from the interesting bipyridine **13**. Given the importance of azaindoles in medicinal chemistry,[13] this is a significant result.

Initial efforts to expand this reactivity to pyridines bearing non-aniline nucleophiles, such as 3-(2-ethylamino)-pyridine (**15**), led, as anticipated, to exclusive *N*-cyanation of the primary amine. We considered the balance of nucleophilicity associated with anilines of type **6** and expected that, by depressing the nucleophilicity of the tethered amine in substrates such as **15**, our strategy might be amenable to the synthesis of other nitrogen heterocycles. With the *N*-benzoyl amide of 3-(2-ethylamino)-pyridine (**16**), no productive reactivity was observed upon exposure to the optimal conditions for indole formation. However, generation of the *N*-arylated pyridinium salt **17**, and subsequent treatment of this activated pyridine with excess dimethylamine with warming in an open flask, led to *N*-benzoyl dihydropyrrole **18** in 57% yield over two steps (Scheme 3). This transformation may proceed through an initial pyridinium ring opening by dimethylamine to form **19**, followed by cyclization of the amide onto the conjugated iminium ion to afford **20** with release of volatile dimethylamine; this iminium ion is hydrolyzed upon workup to afford **18**. Other mechanisms have not been ruled out.

The use of the century-old pyridinium-ring-opening reaction with tethered nucleophiles has led to a convergent two-step synthesis of a series of indole-3-propenals. Preliminary experiments with tethered amides have indicated that, with the correct choice of experimental parameters, variation of nucleophile/tether combinations is also tolerated. Therefore, this reaction of pyridinium salts represents not simply a new indole synthesis, but rather the first step towards a potentially general protocol for heterocycle synthesis. We envision extension to oxygen- and sulfur-containing heterocycles, and carbocycles, as well as applications in natural-product synthesis and medicinal chemistry.

Experimental Section

General procedure for cyanogen bromide mediated pyridine ring opening: (*E*)-3-(1*H*-Indol-3-yl)-propenal (**7a**): To a 100-mL round-bottom flask equipped with a magnetic stir bar was added 2-pyridin-3-ylphenylamine (1.05 g, 6.2 mmol) and absolute ethanol (55.0 mL). The light-yellow solution was warmed to 40 °C before the addition of cyanogen bromide (1.31 g, 12.4 mmol) as a solution in EtOH (5 mL). After 20 min 10% aqueous ammonium chloride (20.0 mL) was added to the dark-red solution, which was allowed to stir at 40 °C for 3 h. The crude reaction mixture was concentrated in vacuo, and the residue was taken up in EtOAc, washed with saturated $NaHCO_3$, concentrated in vacuo, preloaded onto silica gel, and purified by flash chromatography (40% → 60% EtOAc/hexanes) to afford pure **7a** as a orange solid (695 mg, 70%): m.p. 108–110 °C (EtOAc); ^{1}H NMR (500 MHz, CD_3OD, 298 K): $\delta = 9.53$ (d, $J = 8.1$ Hz, 1H), 8.71 (d, $J = 15.7$ Hz, 1H), 7.89 (d, $J = 7.1$ Hz, 1H), 7.83 (s, 1H), 7.49 (d, $J = 7.2$ Hz, 1H), 7.30–7.23 (m, 2H), 6.75 (dd, $J = 8.1$, 15.7 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD, 298 K): $\delta = 196.8$, 150.9, 139.6, 133.9, 126.7, 124.4, 124.1, 122.9, 121.2, 114.6, 113.5; IR (KBr) 3252, 2238, 1651, 1609 cm^{-1}; TLC $R_f = 0.80$ (100% EtOAc); LRMS (ESI) *m*/*z* (relative intensity): 172 (100); HRMS (CI) *m*/*z* calcd for $C_{11}H_{10}NO$ $[M+H]^+$, 172.0762, found 172.0760.

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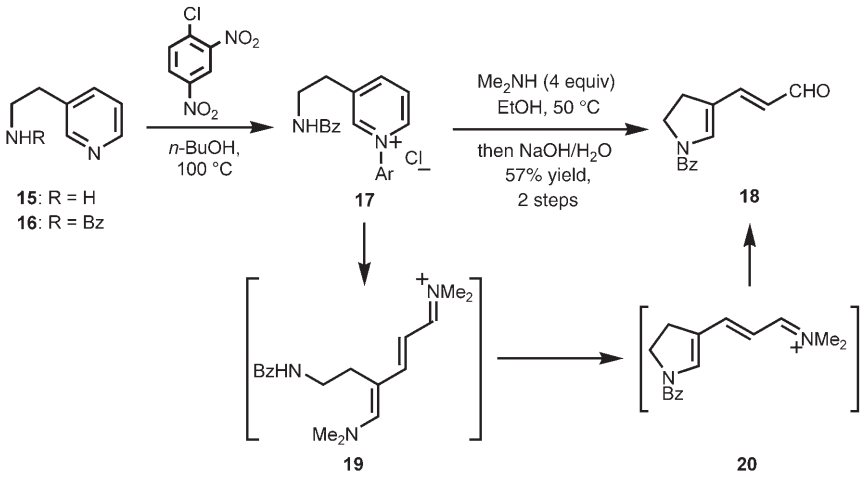

Scheme 3. The synthesis of *N*-protected dihydropyrrole **18** exemplifies alternative pyridine activation strategy for weak nucleophiles. Ar = 2,4-dinitrophenyl, Bz = benzoyl.

[1] a) T. Zincke, *Justus Liebigs Ann. Chem.* **1903**, *330*, 361–374; b) T. Zincke, *Justus Liebigs Ann. Chem.* **1904**, *333*, 296–345; c) T. Zincke, W. Wurker, *Justus Liebigs Ann. Chem.* **1905**, *338*, 107–141; d) W. König, *J. Prakt. Chem.* **1904**, *69*, 105–137.

[2] For selected examples of reactions that occur without ring opening, see the following leading references: a) D. L. Comins, J. J. Sahn, *Org. Lett.* **2005**, *7*, 5227–5228; b) E. J. Corey, Y. Tian, *Org. Lett.* **2005**, *7*, 5535–5537; c) T. Focken, A. B. Charette, *Org. Lett.* **2006**, *8*, 2985–2988.

[3] Please see the Supporting Information for plausible mechanisms for these transformations.

[4] For reviews, please see: a) J. Becher, *Synthesis* **1980**, 589–613; b) W.-C.

Cheng, M. J. Kurth, *Org. Prep. Proced. Int.* **2002**, *34*, 587 – 608; c) C. M. Rojas in *Name Reactions in Heterocyclic Chemistry* (Ed.: J. J. Li), Wiley, Hoboken, **2005**, pp. 355 – 374. Also, see J. Becher, L. Finsen, I. Winckelmann, *Tetrahedron* **1981**, *37*, 2375 – 2378.

[5] a) For applications of these compounds in the dye industry, see: A. Mishra, R. K. Behera, P. K. Behera, B. K. Mishra, G. B. Behera, *Chem. Rev.* **2000**, *100*, 1973 – 2011; b) For a two-step azulene synthesis featuring 5-amino-2,4-pentadienals, see: K. Hafner, K.-D. Asmus, *Justus Liebigs Ann. Chem.* **1964**, *671*, 31 – 40; c) For one application in natural product synthesis, see: K. Jakubowicz, K. B. Abdeljelil, M. Herdemann, M.-T. Martin, A. Gateau-Olesker, A. A. Mourabit, C. Marazano, B. C. Das, *J. Org. Chem.* **1999**, *64*, 7381 – 7387.

[6] For a comprehensive review of methods for indole synthesis, see: J. A. Joule, *Sci. Synth.* **2001**, *10*, 361 – 652.

[7] Selected recent indole syntheses: a) T. J. Greshock, R. L. Funk, *J. Am. Chem. Soc.* **2006**, *128*, 4946 – 4947; b) D. F. Taber, W. Tian, *J. Am. Chem. Soc.* **2006**, *128*, 1058 – 1059, and references therein.

[8] For a review, see: A. Suzuki in *Modern Arene Chemistry* (Ed.: D. Astruc), Wiley-VCH, Weinheim, **2002**, pp. 53 – 106. Please see the Supporting Information for experimental details.

[9] Typical activating agents include 2,4-dinitrochlorobenzene, cyanogen halides, and sulfur trioxide. See references [1] and [4a].

[10] The conversion of **9** into **10** could conceivably occur through an electrocyclic pathway or a simple ionic mechanism; either would be followed by simple alkene geometrical isomerizations.

[11] Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051 – 15053, and references therein. Although we suspect that the reactivity of products of type **7** will almost certainly be different from regular α,β-unsaturated aldehydes owing to the conjugation of the indole nitrogen, the incorporation of an electron-withdrawing *N*-protecting group might result in reasonable reactivity in iminium-based asymmetric organocatalysis. For a relevant example, please see reference [12].

[12] An indole-3-propenal was used in an asymmetric organocatalytic Diels–Alder reaction in a synthesis of hapalindole Q: A. C. Kinsman, M. A. Kerr, *J. Am. Chem. Soc.* **2003**, *125*, 14120 – 14125.

[13] For a few select examples, see: Neurological therapy: a) N. R. Curtis, J. J. Kulagowski, P. D. Leeson, M. P. Ridgill, F. Emms, S. B. Freedman, S. Patel, S. Patel, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 585 – 588; b) G. A. Showell, F. Emms, R. Marwood, D. O'Connor, S. Patel, P. D. Leeson, *Bioorg. Med. Chem.* **1998**, *6*, 1 – 8; Antiviral therapy: c) T. Wang, Z. Zhang, O. B. Wallace, M. Deshpande, H. Fang, Z. Yang, L. M. Zadjura, D. L. Tweedie, S. Huang, F. Zhao, S. Ranadive, B. S. Robinson, Y.-F. Gong, K. Ricarrdi, T. P. Spicer, C. Deminie, R. Rose, H.-G. H. Wang, W. S. Blair, P.-Y. Shi, P.-f. Lin, R. J. Colonno, N. A. Meanwell, *J. Med. Chem.* **2003**, *46*, 4236 – 4239.

