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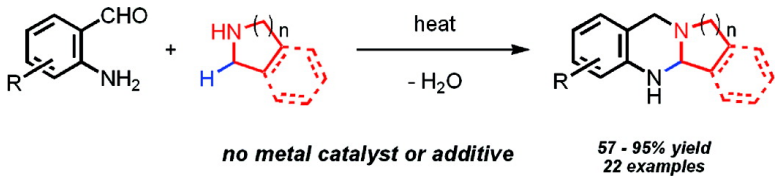

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α-Amination of Nitrogen Heterocycles: Ring-Fused Aminals

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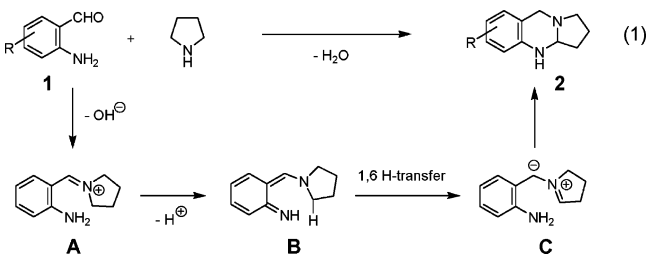
The direct functionalization of nitrogen heterocycles offers an attractive entry to important molecular targets that might otherwise require lengthy synthetic procedures.[1] Here we report a new α-functionalization reaction of cyclic amines that proceeds without the involvement of transition metals or other additives (eq 1). In this redox-neutral condensation reaction, a C−H bond α to a ring nitrogen is replaced by a C−N bond, concomitant with the formation of a new ring system.[2,3] This thermally promoted reaction between an aminobenzaldehyde (e.g., **1**) and a cyclic amine results in the formation of a ring-fused aminal (e.g., **2**) and thus provides convenient access to this structural motif.[4] The reaction conditions resemble those used in Friedländer reactions of aminobenzaldehydes and ketones to form quinolines, in which pyrrolidine is frequently used as a base promoter.[5,6] To our knowledge, aminals have not previously been reported as side products of these reactions.



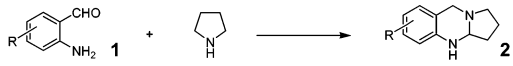
(1)

A mechanistic hypothesis for aminal formation involves proton loss from an intermediate iminium ion **A** upon rearrangement of the adjacent π-system. The resulting quinoidal intermediate **B** is envisioned to undergo a 1,6-hydrogen transfer to form dipolar intermediate **C**, which ultimately goes on to final product **2**.[7,8] Alternatively, intermediate **A** could be deprotonated by excess pyrrolidine resulting in the direct formation of intermediate **C**.[9,10]

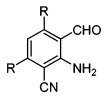
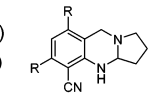
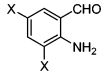
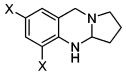
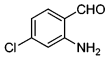
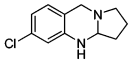
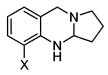
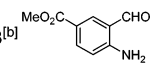
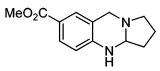
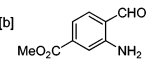
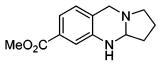
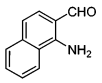
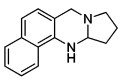
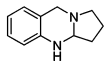
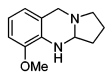
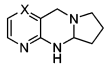
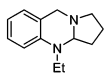
Tables 1 and 2 summarize the scope of this reaction. A range of aminobenzaldehydes was allowed to react with pyrrolidine (3 equiv) in ethanol solution at reflux (Table 1). Aminobenzaldehydes with differing substitution patterns and electronic properties proved to be suitable substrates, providing products in good yields. Electron-poor aminobenzaldehydes are particularly reactive, whereas more electron-rich substrates (Table 1, entries 11 and 12) give products in good yields after somewhat prolonged reaction times. Heterocyclic aminoaldehydes (Table 1, entries 13 and 14) give ring-fused aminals in excellent yields. A substituent on the nitrogen atom of the aminobenzaldehyde is well-tolerated (Table 1, entry 15).

Aminobenzaldehydes were allowed to react with various cyclic amines (Table 2).[11] Piperidine shows diminished reactivity compared with pyrrolidine and provided only 6% yield of product **3** when the reaction was carried out under the original conditions. Significant improvement was achieved by conducting the reaction in a sealed tube at 140 °C, leading to the formation of **3** in 67% yield. The analogous seven- and eight-membered aza-cycles gave aminals **4** and **5** in 77 and 60% yield, respectively. Amines possessing benzylic hydrogen atoms α to the ring nitrogen are particularly good substrates (Table 2, entries 4−6). Reaction of

Table 1. Variation of the Aminoaldehyde Component[a]



(2)

entry	aminoaldehyde		product		time (h)	yield(%)
1		**1a** (R=Me)		**2a**	18	95
2		**1b** (R=Ph)		**2b**	12	92
3		**1c** (X=Br)		**2c**	23	92
4		**1d** (X=Cl)		**2d**	12	84
5		**1e**		**2e**	72	57
6		**1f** (X=Br)		**2f**	36	83
7		**1g** (X=Cl)		**2g**	18	76
8[b]		**1h**		**2h**	24	76
9[b]		**1i**		**2i**	24	60
10		**1j**		**2j**	48	58
11		**1k**		**2k**	72	73
12[c]		**1l**		**2l**	48	81
13		**1m** (X=CH)		**2m**	36	94
14		**1n** (X=N)		**2n**	13	91
15		**1o**		**2o**	80	84

[a] Reactions were run on a 1 mmol scale using 3 equiv of pyrrolidine in ethanol solution (0.25 M) at reflux. [b] As partial transesterification occurred in ethanol solution, the reaction was run in a sealed tube in methanol solution at 100 °C. [c] The reaction was run in a sealed tube in ethanol solution at 140 °C.

2-methylpyrrolidine with aminobenzaldehyde **1c** gave a mixture of regioisomers. The more substituted regioisomer **9a** was the major product of this reaction, while the minor regioisomer **9b** was obtained as a 2:1 mixture of diastereomers. This latter observation combined with the notably increased reactivity of benzylic amines suggests that a 1,6-hydride shift may be operating.[8] Further mechanistic insight is provided by the observation that the reaction of aminobenzaldehyde **1c** with proline gave the same product as the corresponding reaction with pyrrolidine under identical conditions (Table 2, entry 8). It is well-established that reactions of aldehydes with proline and other N-alkylated aminoacids form 1,3-dipolar intermediates upon decarboxylation.[12] This finding is

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Table 2. Variation of the Amine Component[a]

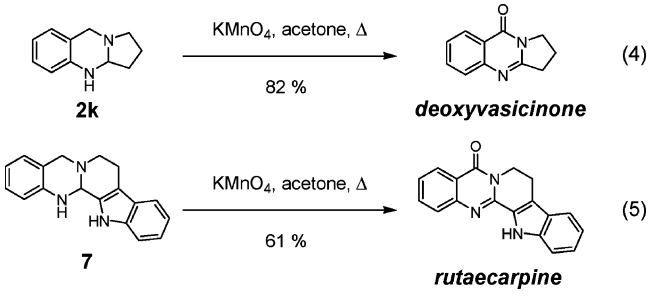
(3)

entry	amino-aldehyde	amine (equiv)	product	time (h)	yield (%)
1[b]	**1c**	(3)	**3**	48	67
2[c]	**1c**	(3)	**4**	24	77
3	**1a**	(3)	**5**	48	60
4	**1k**	(3)	**6**	48	95
5	**1k**	(2.1)	**7**	72	66
6	**1h**	(2)	**8**	48	80
7	**1c**	(2.1)	**9a**	24	60
			9b (dr=2:1)		25
8	**1c**	(2.1)	**2c**	24	50

[a] Reactions were run on a 1 mmol scale in ethanol solution (0.25 M) at reflux. [b] The reaction was run in a sealed tube in isopropanol solution at 140 °C. [c] The reaction was run in a sealed tube in ethanol solution at 140 °C.

consistent with the notion that 1,3-dipoles are likely intermediates in this reaction.

Aminals are found in a number of natural products.[13] In addition, aminals with the general structure **2** represent reduced versions of quinazolinone alkaloids, compounds that have attracted significant attention in the synthetic community due to their diverse array of biological activities.[14,15] Selective oxidation of ring-fused aminals provides rapid access to this structural motif (eqs 4 and 5). In one additional step, two steps from commercially available materials, deoxyvasicinone[16] and rutaecarpine[17] were obtained in 82 and 61% yield, respectively.



In summary, we have introduced a simple and efficient method for the synthesis of ring-fused aminals by a mild functionalization of nitrogen heterocycles. While some aminals are direct precursors of natural products, others should prove useful for preparing analogues of these biologically active materials. Ongoing studies are aimed at developing a more detailed mechanistic understanding of this reaction as well as expanding the scope and exploring related processes.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds including X-ray structures of **2c** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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