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Facile Synthesis of *N*-Dialkylaminomethyl-Substituted Heterocycles

Brian E. Love

Department of Chemistry, East Carolina University, Greenville, North Carolina 27858

loveb@ecu.edu

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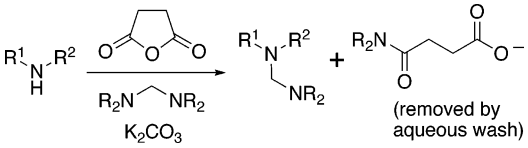


Iminium ions are generated by treatment of aminals with succinic anhydride. These iminium ions are trapped by heterocycles, giving the corresponding *N*-dialkylaminomethyl-substituted heterocycles, which are easily separated from the succinic acid monoamide byproducts by means of an aqueous base wash. The heterocyclic products are obtained in good yield and in a high state of purity without need of recrystallization or distillation.

As part of another project, a facile synthesis of usable quantities of 1-(*N*,*N*-dimethylaminomethyl)imidazole **2** was required. The standard literature preparation of this compound is the one reported by Katritzky and co-workers,[1] which is a modification of the procedure of Stocker.[2] Although this procedure provides **2** in 78% yield, the synthesis requires 48 h and gives a product contaminated with other byproducts (presumably C-aminomethylated isomers),[2] thus requiring purification by distillation.A shorter, cleaner route to **2** and related compounds was sought, and the results of that investigation are reported herein.

The concept was to allow imidazole to react with the iminium ion generated by reaction of bis(dimethylamino)methane **1** with an acylating agent[3] (Scheme 1). Acetyl chloride was initially chosen as the acylating agent, which produced the desired **2** along with an approximately equal amount of *N*,*N*-dimethylacetamide. Although the latter compound could be removed by an aqueous wash, this greatly reduced the yield of **2**, owing to its significant water solubility.

The use of cyclic anhydrides as acylating agents was then investigated because the byproducts of such reactions contain a carboxylic acid group and thus can be easily removed by base. In a typical reaction, a mixture of **1**, imidazole, and potassium carbonate in dichloromethane was treated with the solid anhydride, and after stirring at room temperature for an hour, the solution was washed with 6 M NaOH, followed by a saturated NaCl solution. Evaporation of dichloromethane from the organic phase led to isolation of good yields of **2** uncontaminated by acylation byproducts. Phthalic, maleic, and succinic anhydrides were all investigated, and although all three were successful, succinic anhydride became the anhydride of choice.[4]

SCHEME 1

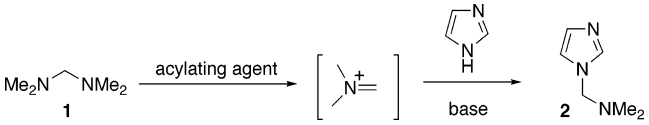
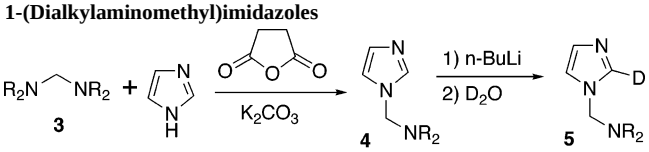
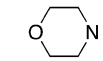
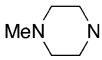


TABLE 1. Synthesis and Lithiation of 1-(Dialkylaminomethyl)imidazoles



entry	R_2N	yield of **4** (%)	%D in **5**
a	Me_2N	75	93
b		86	86
c		86	96
d		84	95
e		82	95

Extension of this methodology to the synthesis of other 1-(dialkylaminomethyl)imidazoles **4** was also investigated. The required aminals **3** were easily prepared in high yield by allowing secondary amines to react with formaldehyde.[5] Reaction of these aminals with imidazole and succinic anhydride produced the corresponding aminomethylated imidazoles **4** in good yield and in a high state of purity (Table 1).

One of the principal uses of dialkylaminomethyl groups on imidazoles is to direct lithiation at C-2, as has been demonstrated by Katritzky and co-workers.[1] Thus, the ease of lithiation of imidazoles **4** was briefly investigated. Imidazoles **4** were stirred for 30 min at 0 °C with 1.1 equiv of *n*-butyllithium, then quenched with D_2O. Percent deuterium incorporation (measured by NMR) was taken as an indication of the minimum amount of lithiation. As can be seen in Table 1, all dialkylaminomethyl groups studied were effective at directing lithiation at C-2.

Because 1-(dialkylaminomethyl)imidazoles could be prepared quickly and in a high state of purity without need of either recrystallization or distillation, application of this methodology to the synthesis of other dialkylaminomethyl heterocycles **6** was

(1) Katritzky, A. R.; Rewcastle, G. W.; Fan, W.-Q. *J. Org. Chem.* **1988**, *53*, 5685.

(2) Stocker, F. B.; Kurtz, J. L.; Gilman, B. L.; Forsyth, D. A. *J. Org. Chem.* **1970**, *35*, 883.

(3) Kinast, G.; Tietze, L.-F. *Angew. Chem., Int. Ed.* **1976**, *15*, 239.

(4) Use of maleic anhydride occasionally resulted in the formation of other byproducts, and the phthalic acid monoamides formed from some of the higher molecular weight analogues of **1** had reduced solubility in an aqueous base.

(5) Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Tetrahedron* **1997**, *53*, 2941.

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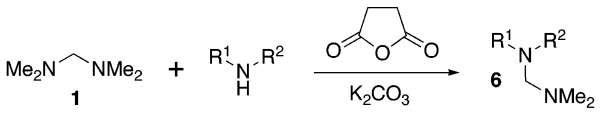
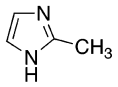
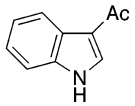
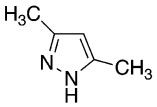
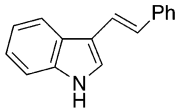
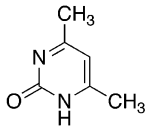
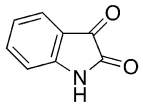
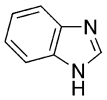
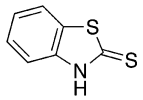
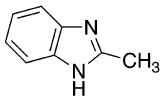
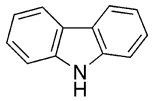
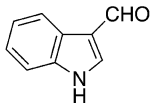
TABLE 2. Synthesis of Dimethylaminomethyl-Substituted Heterocycles



entry	heterocyclic starting material	yield of **6** (%)	workup protocol	entry	heterocyclic starting material	yield of **6** (%)	workup protocol
a		81[a]	B	**g**		78	A
b		86	A	**h**		95	A
c		0	B	**i**		0	A
d		82	A	**j**		75[c]	B
e		93	A	**k**		89	A
f		89[b]	A				

[a] Yield = 62% using workup protocol A; yield = 91% on 100 mmol scale preparation. [b] Yield = 96% on 50 mmol scale preparation. [c] Yield = 32% using workup protocol A.

investigated. The dimethylaminomethyl group has been found to be a useful lithiation directing group for the synthesis of heterocycles,[1,6−10] including compounds used as ligands for transition-metal catalysts.[11,12] Additionally, some dialkylaminomethyl heterocycles have been found to have useful pharmacological properties.[13,14]

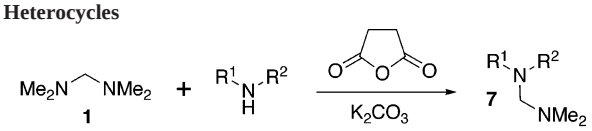
As can be seen from the data in Table 2, high yields were obtained for most substrates, though several of the amide-like heterocycles failed to give the desired products. As with the imidazole derivatives, the products were obtained in a high state of purity using the aqueous base wash as the only purification step. With these substrates, two workup protocols were employed. For most reactions, the dichloromethane solution of the crude product was washed with two 25 mL portions of 1 M NaOH, followed by 10 mL of saturated NaCl ("workup A"). For products which had comparatively high water solubility, the two 1 M NaOH washes were replaced with one wash with 10 mL of 6 M NaOH ("workup B").[15]

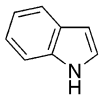
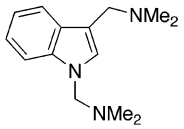
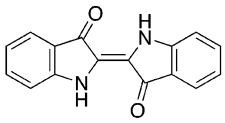
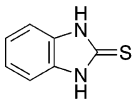
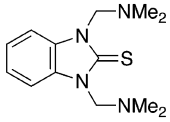
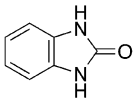
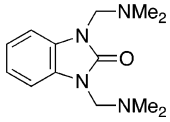
Bis(dimethylamino)methylation could also be achieved simply by combining 2 equiv each of aminal **1**, potassium carbonate, and succinic anhydride with 1 equiv of a suitable diprotic heterocycle (Table 3). Treatment of indole with just 1 equiv of the aminomethylating reaction mixture produced a mixture of gramine, isogramine, and 1,3-bis[(dimethylamino)methyl]indole **7a**, as well as some unreacted indole. Use of 2 equiv gave a 3:1 mixture of **7a**/isogramine, the crude yield of **7a** in this mixture being approximately 70%. Interestingly, benzimidazole derivatives **7c** and **7d** were obtained in good yield, even though indigo failed to give the desired product, consistent with the failure of other amide-like heterocycles to undergo this transformation. All of these reactions were worked up using workup A.

In many instances, yields using the present method are superior to those obtained by "traditional" Mannich conditions

(6) Katritzky, A. R.; Rewcastle, G. W.; Vazquez de Miguel, L. M. *J. Org. Chem.* **1988**, *53*, 794.
(7) Katritzky, A. R.; Lue, P.; Chen, Y. X. *J. Org. Chem.* **1990**, *55*, 3688.
(8) Tarnchompoo, B.; Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron Lett.* **1990**, *31*, 5779.
(9) Granier, T.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 1738.
(10) Huang, L.-F.; Bauer, L. *J. Heterocycl. Chem.* **1997**, *34*, 1123.
(11) Berens, U.; Brown, J. M.; Long, J.; Selke, R. *Tetrahedron: Asymmetry* **1996**, *7*, 285.
(12) Yu, J. O.; Lam, E.; Sereda, J. L.; Rampersad, N. C.; Lough, A. J.; Browning, C. S.; Farrar, D. H. *Organometallics* **2005**, *24*, 37.
(13) Harmenberg, J.; Wahren, B.; Bergman, J.; Aakerfeldt, S.; Lundblad, L. *Antimicrob. Agents Chemother.* **1988**, *32*, 1720.
(14) Fadda, A. A.; Etman, H. A.; Ali, M. M. *Pharmazie* **1991**, *46*, 52.
(15) "Workup B" was used for all reactions shown in Table 1. When "Workup A" was applied to the synthesis of imidazole **4a**, the yield dropped from 75% to 60%.
(16) Zinner, H.; Spangenberg, B. *Chem. Ber.* **1958**, *91*, 1432.
(17) The reaction is exothermic but requires no external cooling when run on this scale.

TABLE 3. Synthesis of Bis(dimethylaminomethyl)-Substituted Heterocycles



entry	heterocyclic starting material	product	yield of **7** (%)
a			70[a]
b		—	0
c			79
d			86

[a] Impure (see text).

(direct reaction of the heterocycle with aqueous amine and aqueous formaldehyde). For example, the literature[6] synthesis of **6k** requires 12 h of heating at reflux and gives **6k** in 51% yield (compared to 89% yield under these conditions). Similarly, the literature[16] synthesis of **7d** requires 3 days of stirring at room temperature and gives **7d** in 28% yield after distillation, whereas the present method allows isolation of this compound in 86% yield.

In summary, an operationally simple procedure has been developed that allows the preparation of a wide variety of heterocycles substituted with dialkylaminomethyl groups. Advantages of this method include short reaction times and the ability to obtain products of high purity without need of recrystallization or distillation.

Experimental Section

Typical Small-Scale Synthesis. The starting heterocycle (ca. 2−3 mmol)[17] was combined with 1.1 equiv of the aminal and 1.1 equiv of K_2CO_3 in 15 mL of CH_2Cl_2 and stirred while 1.1 equiv of succinic anhydride was added in one portion. The flask was lightly stoppered, and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with 50 mL of CH_2Cl_2 and washed with either two 25 mL portions of 1 M NaOH (workup A) or one 10 mL portion of 6 M NaOH (workup B) followed by 10 mL of saturated NaCl solution. The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure, affording the product in a high state of purity.

Example of a Larger-Scale Synthesis. An 8.21 g (100 mmol) sample of 2-methylimidazole was combined with 11.40 g (111.8 mmol) of bis(dimethylamino)methane **1** and 15.21 g (110.2 mmol) of K_2CO_3 and taken up in 50 mL of CH_2Cl_2. The mixture was cooled in an ice bath and stirred as 11.04 g (110.4 mmol) of succinic anhydride was added. The temperature of the reaction mixture rose to 25 °C, and when it had dropped to 20 °C, the flask was removed from the ice bath and allowed to come to room temperature over 1 h. The reaction mixture was diluted with 150 mL of CH_2Cl_2 and washed with 100 mL of 3 M NaOH, 50 mL of 6 M NaOH, and 25 mL of saturated NaCl solution. The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure, affording 12.58 g (91%) of 1-(dimethylamino)methyl-2-methylimidazole **6a** in a high state of purity. (Note: when a 50 mmol scale preparation of **6f** was carried out under similar conditions, only a 5 °C increase in reaction mixture temperature was observed upon addition of the succinic anhydride.)

Typical Lithiation Procedure. The starting heterocycle (ca. 2 mmol) was dissolved in 10 mL of freshly distilled THF and cooled in an ice bath under nitrogen. A portion of 1.1 equiv of 1.9 M *n*-BuLi in hexane was added, and the solution was stirred in the bath for 30 min. Then the reaction was quenched by addition of 0.5 mL of D_2O. The solution was removed from the bath and allowed to come to room temperature and then diluted with 50 mL of ether and washed with 10 mL of 6 M NaOH followed by 10 mL of saturated NaCl solution. The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure.

Supporting Information Available: ^1H and ^{13}C NMR spectra and characterization data for compounds **4**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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