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Reaction of 1,3-dimethyl-5-acetyl-barbituric acid (DAB) with primary amines. Access to intermediates for selectively protected spermidines

Emerson T. da Silva and Edson L. S. Lima*

Universidade Federal do Rio de Janeiro, Instituto de Química, Departamento de Química Orgânica, Cidade Universitária, 21945-970 Rio de Janeiro, RJ, Brazil

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Abstract—The ability of 1,3-dimethyl-5-acetyl-barbituric acid (DAB) to react with primary amines in a chemoselective fashion was applied to the synthesis of a selectively protected spermidine.

The addition of nitrogen-containing nucleophiles to 2-acylcycloalkane-1,3-diones to give *exo*-cyclic enamino diketones is a well documented process, which has been proven useful in the synthesis of several biologically active compounds (Fig. 1).[1]

This reactivity pattern has been applied by Bycroft et al. in the development of Dde and related compounds as protective groups for primary amines.[2] While most of the applications of Dde were addressed to the solid-phase synthesis of polyamine conjugates, the solution-phase synthesis of polyamines still demands for protective groups orthogonal to those more commonly used, such as carbamates and imides.[3]

In our attempts to prepare a selectively functionalized spermidine we have observed that 1,3-dimethyl-5-acetyl-barbituric acid (DAB) reacts with a range primary amines under mild conditions to afford the corresponding enamine in good yields (Table 1).[4,5] Thus, both unbranched and α-branched primary amines react with DAB at room temperature (entries 1–3). The reaction is slowed by electron-withdrawing groups (entry 4), but is chemoselective for functionalized amines (entries 5–9).[6] Acid-sensitive functional groups are tolerated in the reaction conditions (entry 6). Substrates which may form intramolecular hydrogen bond react slowly at room temperature, but the enamines can be efficiently obtained under reflux (entries 7–9).[7,8]

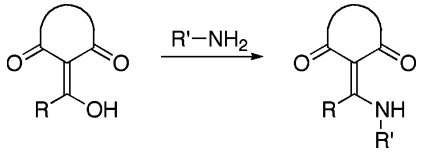

Figure 1. Reaction of amines with 2-acylcycloalkane-1,3-diones.

We next turned our attention to the removal of DAB. Given the precedent of solid-phase transamination reactions with Dde, we attempted similar protocols.[9,10] However, no reaction was observed when the DAB-benzylamine adduct (entry 4) was subjected to the treatment with either *n*-propylamine or ethanolamine in THF at room temperature overnight. Deprotection was successfully carried out with aqueous hydrazine in ethanol, leading to the recovery of the amine and the formation of the hydrazone **1** (Scheme 1).[11]

Encouraged by these results we investigated the use of this protective group in the synthesis of a selectively protected spermidine. Accordingly, (3-aminopropyl)-benzylamine was reacted with DAB to provide enamine **2** (Scheme 2, entry 7),[8] which was then subjected to *N*-alkylation with 4-bromobutylphthalimide (1 equiv.).[12] The spermidine **3** was obtained as a colorless oil in 76% yield after flash-chromatography. Since the removal of phthalimide with hydrazine requires heating in ethanol, we were able to selectively remove DAB from **3** with aqueous hydrazine in THF at 0°C during 1.5 h, to obtain the known spermidine **4** as the sole product in 79% yield.[13]

* Corresponding author. Tel.: +55-21-2562-7369; fax: +55-21-2562-7256; e-mail: edson@iq.ufrj.br

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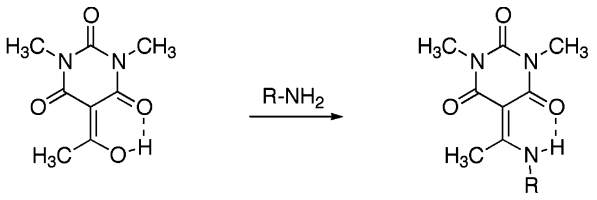
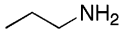
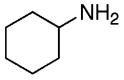
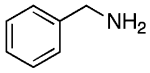
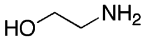
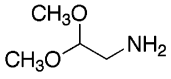
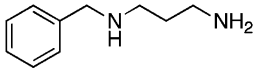
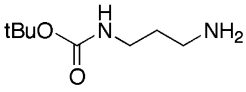
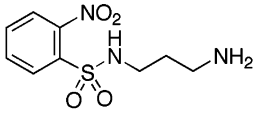
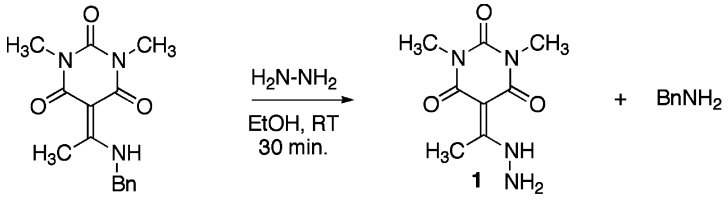
Table 1. Reaction of DAB with primary amines[a]



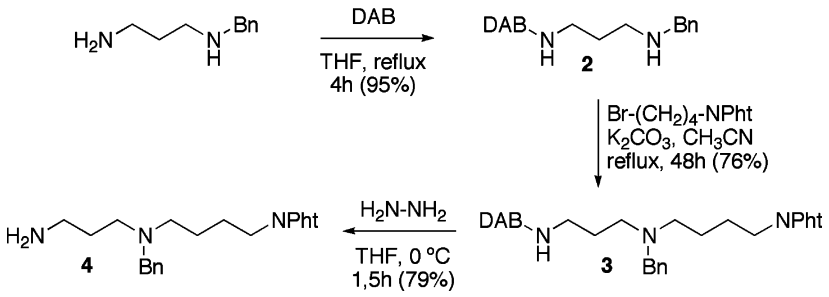
entry	Amine	Conditions	Yield (%)
1		0.5 h, R.T.	80
2		2.5 h, R.T.	70
3		3 h, R.T.	65
4		17 h, R.T.	90
5		1 min., R.T.	85
6		1 h, R.T.	90
7		4 h, Reflux	95
8		4 h, Reflux	90
9		8 h, Reflux	70

[a] General procedure: To a solution of 1,3-dimethyl-5-acetyl-barbituric acid (DAB) (0.51 mmol) in THF (10 mL) was added 1 equivalent of the amine. The mixture was stirred under the conditions indicated in Table 1, and the reaction was monitored by TLC. After the reaction was judged complete, the solvent was removed in the rotovap, and the residue was purified by flash chromatography.

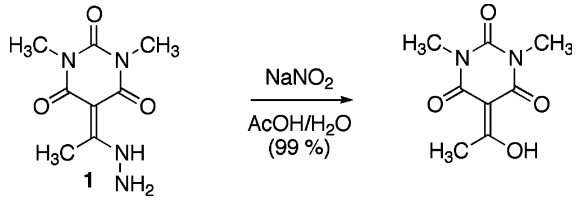


Scheme 1. Removal of DAB with hydrazine.

Other features of DAB deserve note. For instance, it provides quite simple ^{1}H and ^{13}C NMR spectra, and the imines are shelf-stable and soluble in organic solvents. Additionally, we observed that DAB can be quantitatively recovered by the nitrosation of **1** (Scheme 3).[14]



Scheme 2. Synthesis of a selectively protected spermidine.



Scheme 3. Recovery of DAB.

In conclusion, we believe that based on the smooth conditions required for introduction and removal of DAB, this protective group will find application in the synthesis of polyamines.

Acknowledgements

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3. (a) Kuksa, V.; Buchan, R.; Lin, P. K. T. *Synthesis* **2000**, 1189–1207; (b) Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. *Tetrahedron* **1992**, *48*, 4475–4515; (c) Bergeron, R. J. *Acc. Chem. Res.* **1986**, *19*, 105–113.
4. DAB can be prepared by the reaction between acid 1,3-dimethyl-barbituric, acetic anhydride (two equivalents), and cat. DMAP in CH_2Cl_2 at room temperature for 5 h. Flash-chromatography affords DAB in 90% yield (mp: 84–86°C).
5. DAB has been previously used to protect aminosugars: A. Alchemia Pty. Ltd., Toth, I.; Dekany, G.; Kellam, B. (1999). Protecting and Linking Groups for Organic Synthesis. WO 99/15510 PCT/AU98/00808. For a related work see: Dekany, G.; Bornaghi, L.; Papageorgiou, J.; Taylor, S. *Tetrahedron Lett.* **2001**, *42*, 3129–3132.
6. (a) For the preparation of (3-aminopropyl)benzylamine (entry 7) see: Almeida, M. V.; César, E. T.; Felício, E. C. A.; Fontes, A. P. S.; Robert-Gero, M. *J. Braz. Chem. Soc.* **2000**, *11*, 154–158; (b) Preparation of (3-aminopropyl)-(2-nitro)-benzenesulfonamide (entry 9) from 1,3-diaminopropane was adapted from: Amssoms, K.; Augustyns, K.; Yamani, A.; Zhang, M.; Haemers, A. *Synth. Commun.* **2002**, *32*, 319–328.
7. The reaction of DAB with anilines and α-aminoacids afforded negligible yields of the corresponding enamine, even after 24 h of reflux in THF.
8. Data for 5-[1-(3-Benzylaminopropylamino)ethylidene]-1,3-dimethylhexahydro-2,4,6-pyrimidinetrione (entry 7): $R_f = 0.50$ ($MeOH/CH_2Cl_2$ 10%) ^1H NMR ($CDCl_3$, 200 MHz): δ 12.54 (1H, br s, -N**H**) 7.16–7.25 (5H, m, ArC-**H**), 3.72 (2H, s, -C**H**$_2$Ph), 3.48 (2H, m, C=C-N-C**H**$_2$), 3.23 (6H, s, N-C**H**$_3$) 2.70 (2H, t, $J = 6.28$ Hz, -C**H**$_2$NHBn), 2.62 (3H, s, C-C**H**$_3$), 1.78 (2H, quintet, $J = 6.28$ Hz, -CH_2C**H**$_2$$CH_2$-); ^{13}C NMR ($CDCl_3$, 50 MHz): 17.76, 27.62, 29.42, 41.79, 45.90, 53.81, 90.22, 126.98, 128.02, 128.82, 139.99, 151.32, 163.10, 166.45, 174.03; IR (film): 3339, 3086, 2954, 1699, 1655, 1608, 1591, 1472, 1363, 1222, 869, 755, 422 cm^{-1}; LRMS m/z (relative intensity): 344 (M^+ 2%), 224 (18%), 134 (14%), 106 (47%), 91 (100%), 57 (11%). HRMS for $C_{18}H_{24}N_4O_3$: 344.1848. Found: 344.1797.
9. See Refs. 2b and 2c.
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11. Typical experimental: To a solution of 5-(1-benzylaminoethylidene) - 1,3 - dimethylhexahydro - 2,4,6 - pyrimidinetrione (100 mg, 0.24 mmol) in EtOH (20 mL) was

added 2 equivalents of aqueous hydrazine. The resulting homogeneous solution was stirred at room temperature for 30 min, after which time the reaction was judged complete by TLC. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, 230–400 mesh, AcOEt/hexane 50%) to afford the free amine (28 mg, 75%) and the corresponding hydrazone (74 mg, 99%). Data for 5-(1-hydrazineethylidene)-1,3-dimethylhexahydro-2,4,6-pyrimidinetrione: mp 155–157°C. $R_f = 0.34$ (AcOEt/Hex 50%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 13.40 (1H, s br, -N**H**), 4.08 (2H, s br, N**H**$_2$), 3.31 (6H, s, N-C**H**$_3$), 2.86 (3H, s, C-C**H**$_3$); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 175.71, 151.62, 89.18, 27.94, 16.19; IR (KBr): 3329, 3240, 3195, 2998, 1697, 1632, 1462, 1361, 1019, 817, 754, 510 cm^{-1}.

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