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N,N-Dibenzyl Formamidine as a New Protective Group for Primary Amines

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Abstract: Primary amines can be converted in high yield into *N,N*-dibenzyl formamidines under mild conditions. The *N,N*-dibenzyl formamidine group was found to be effective as a protective group for primary amines as it is stable to a variety of conditions and can be removed by catalytic hydrogenation.
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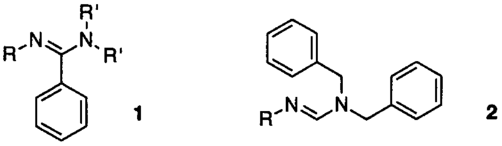
Protective group chemistry continues to play a central role in the execution of multistep organic syntheses[1]. A great variety of reagents have been developed specifically designed to protect primary amines. In the course of our work on the synthesis of nucleotide analogues, we were interested in a protective group of the exocyclic amino function of guanine and adenine that could be removed in neutral conditions. In such a case, hydrogenolysis definitely appears to be a privileged reaction. Protection of the guanosine N-2 position as a benzylimine proved to be somehow difficult and, in an unexpected manner, revealed extremely labile in the presence of the free 5'-hydroxyl function[2]. Investigation on amidines frequently used in nucleoside chemistry[3-8] led us to design benzamidine **1** as a presumably hydrogenolyzable amidine group (Fig. 1), although to our knowledge there is no example in the literature of amidine reduction by catalytic hydrogenation.



- Figure 1 -

Amidine **1** was expected to cleave in two possible ways (Fig. 2). However, all our attempts to hydrogenolyze a benzamidine-protected guanosine derivative failed, and no reaction occurred even at elevated pressure and prolonged reaction time. On the other hand we fortuitously found that *N,N*-dibenzyl formamidine **2** could be cleaved by hydrogenolysis.

Here we report a convenient procedure for the synthesis of *N,N*-dibenzyl formamidines **2** and removal of the primary amine protective group by catalytic hydrogenation.

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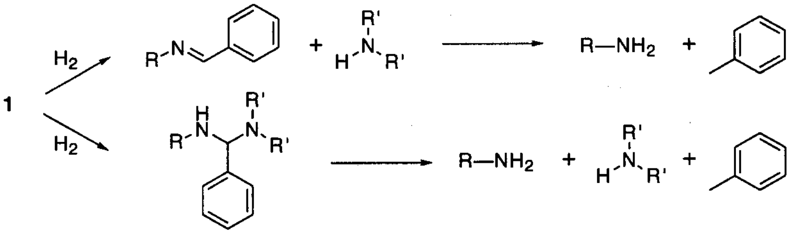
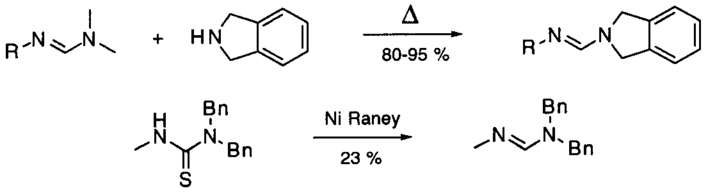


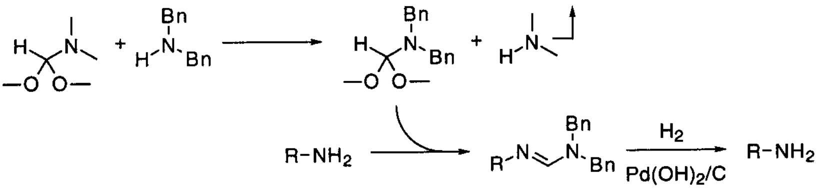
- Figure 2 -

There are only few reports concerning the synthesis of *N,N*-dibenzyl formamidines in the literature. These compounds were essentially prepared to investigate the asymmetric alkylation of formamidines, but their potential utilization as protected primary amine has not been studied yet. The syntheses were achieved either by « trans-amidination » of *N,N*-dimethyl formamidines[9,10], or desulfurization of the corresponding thioureas (Fig. 3)[11].

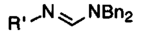
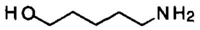
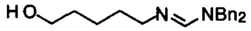
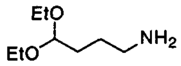
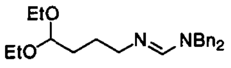
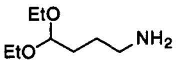
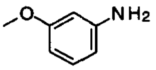
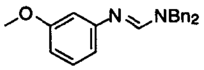
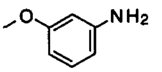
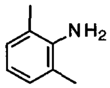
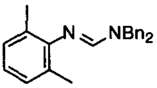
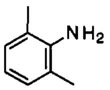
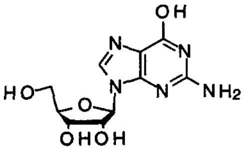
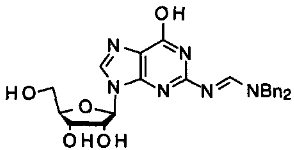
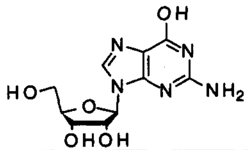
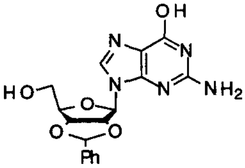
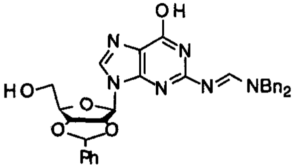
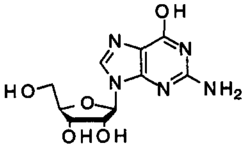
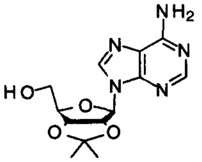
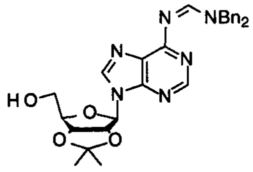
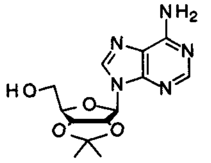
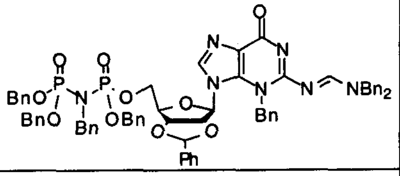
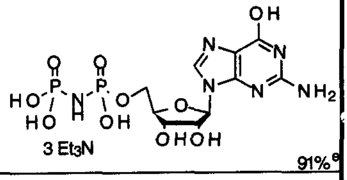
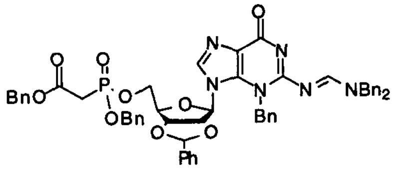
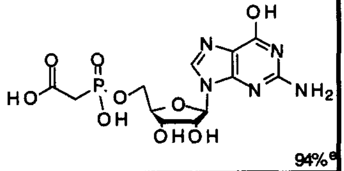


- Figure 3 -

The high temperature required for the trans-amidination procedure (refluxing toluene for several hours) and the modest yield obtained by desulfurization of thioureas do not fully fit the protection-deprotection chemistry requirements. Thus we developed an alternative route starting from dimethyl formamide dimethyl acetal (Fig. 4). A trans-amidation reaction of DMF dimethyl acetal[12] with dibenzylamine affords the intermediate *N,N*-dibenzyl formamide dimethyl acetal. That compound reacts smoothly with a primary amine at room temperature to give the corresponding amidine in a high yield (Tab. 1). Removal of the *N,N*-dibenzyl formamidine protection by catalytic hydrogenation is accomplished using the Pearlman catalyst[13]. The reaction practically do not occur if Pd/C is used instead of $Pd(OH)_2/C$[14].



- Figure 4 -

$R{-}NH_2$ ⟶		⟶ $R''{-}NH_2$
	 78%	 52%[a]
	 49%	 60%[a]
	 89%	 90%[b]
	 94%	 83%[c]
	 71%[d]	 95%[b]
	 99%	 99%[b]
	 87%	 99%[b]
—		 91%[e]
—		 94%[e]

- Table 1 -

[a]Pd(OH)$_2$/C, H$_2$ (70 psi), MeOH/H$_2$O 1/1, RT. [b]Pd(OH)$_2$/C, H$_2$ (70 psi), *t*-BuOH/H$_2$O 1/1, RT. [c]Pd/C-Pd(OH)$_2$/C 1/2, H$_2$ (70 psi), MeOH/H$_2$O 95/5, RT. [d]Intact guanosine (28%) was recovered. [e]Pd/C-Pd(OH)$_2$/C 1/1, H$_2$ (70 psi), *t*-BuOH/H$_2$O 1/1, RT.

N,N-Dibenzyl formamidines show similar chemical properties as those described for *N,N*-dialkyl formamidines[15] towards acidic, basic, and nucleophilic reaction conditions although it has not been extensively investigated. Nevertheless *N,N*-dibenzyl formamidines proved to be more resistant to neutral and basic hydrolytic conditions than *N,N*-dimethyl compounds.

It is interesting to note that hydrogenolysis of *N'*-alkyl *N,N*-dibenzyl formamidines is not as efficient as that of *N'*-aryl *N,N*-dibenzyl formamidines. The reason why is not clear now and the exact course of the reaction still remains unknown. We were not able to detect and identify any intermediate species such as *N'*-monosubstituted formamidine (bis-debenzylation of **2**), *N,N',N'*-trisubstituted aminal (saturation of the amidine double bond in **2**), or *N'*-monosubstituted aminal (both). We did not identify any formamide species neither. Additional work currently in progress is necessary to gain more insight into the reaction course.

Typical procedure for the preparation of N,N-dibenzyl formamidines:

Dimethyl formamide dimethyl acetal (1 mmol), and dibenzylamine (3 mmol) are refluxed in dry acetonitrile for 20 hours. The reaction mixture is evaporated to dryness and traces of remaining DMF dimethyl acetal are removed by two successive addition/evaporation with toluene. The crude residue is dissolved in anhydrous CH_3CN and added to the primary amine (0.4 mmol) in CH_3CN[16]. The resulting solution is stirred at room temperature until the primary amine has completely disappeared when checked by TLC. The solvent is removed *in vacuo* and the amino-protected compound is purified by chromatography on silica gel.

Typical procedure for the hydrogenolysis of N,N-dibenzyl formamidines:

A *N,N*-dibenzyl formamidine protected primary amine (1 mmol) and $Pd(OH)_2/C$ (20% Pd, moisture ca. 50%, 0.5-5 eq. w/w) in *t*-BuOH/H_2O (1/1) are stirred under a hydrogen atmosphere (70 psi) for 5 to 24 h. The catalyst is filtered off and the solvent is removed *in vacuo*. The primary amine is purified by chromatography on silica gel.

References

1. Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991.
2. Mons, S.; Lebeau, L.; Mioskowski, C. *Unpublished results* .
3. Toste, D.; McNulty, J.; Still, I.W.J. *Synth. Commun.* **1994,** *24,* 1617-1624.
4. Vu, H.; McCollum, C.; Jacobson, K.; Theisen, P.; Vinayak, R.; Spiess, E.; Andrus, A. *Tetrahedron Lett.* **1990,** *31,* 7269-7272.
5. Zemlicka, J.; Chladek, S.; Holy, A.; Smrt, J. *Coll. Czech. Chem. Commun.* **1966,** *31,* 3198-3211.
6. Theisen, P.; McCollum, C.; Andrus, A. *Nucleosides Nucleotides* **1993,** *12,* 1033-1046.
7. Seela, F.; Mertens, R.; Kazimierczuk, Z. *Helv. Chim. Acta* **1992,** *75,* 2298-2306.
8. Beaucage, S.L.; Iyer, R.P. *Tetrahedron* **1992,** *48,* 2223-2311.
9. Meyers, A.I.; Santiago, B. *Tetrahedron Lett.* **1995,** *36,* 5877-5880.
10. Beeley, L.J.; Rockwell, C.J.M. *Tetrahedron Lett.* **1990,** *31,* 417-420.
11. Kashima, C.; Shimizu, M.; Eto, T.; Omote, Y. *Bull. Chem. Soc. Jpn* **1986,** *59,* 3317-3319.
12. Abdulla, R.F.; Brinkmeyer, R.S. *Tetrahedron* **1979,** *35,* 1675-1735.
13. Pearlman, W.M. *Tetrahedron Lett.* **1967,** 1663-1664.
14. Catalysts used in that work were of commercial origin (Acros).
15. a) Gauthier, J.A.; Miocque, M.; Combet-Farnoux, C. Preparation and synthetic uses of amidines. In *The chemistry of functional groups: the chemistry of amidines and imidates;* Patai, S. Ed.; Wiley: London, 1975; Vol. 1; pp. 1-84. b) Boyd, G.V. Recent advances in the synthesis of amidines. In *The chemistry of functional groups: the chemistry of amidines and imidates;* Patai, S. and Rappoport, Z. Eds.; Wiley: Chichester, 1991; Vol. 2; pp. 339-366.
16. The reaction can be run in anhydrous DMF with a comparable yield and without any formation of *N,N*-dimethyl formamidine.

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