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N, N-Dibenzyl Formamide Dimethyl Acetal and N, N-Dibenzyl Chloromethylene Iminium Chloride: Two Complementary Reagents for the Protection Of Primary Amines as N, N-Dibenzyl Formamidines

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N,N-DIBENZYL FORMAMIDE DIMETHYL ACETAL AND *N,N*-DIBENZYL CHLOROMETHYLENE IMINIUM CHLORIDE : TWO COMPLEMENTARY REAGENTS FOR THE PROTECTION OF PRIMARY AMINES AS *N,N*-DIBENZYL FORMAMIDINES

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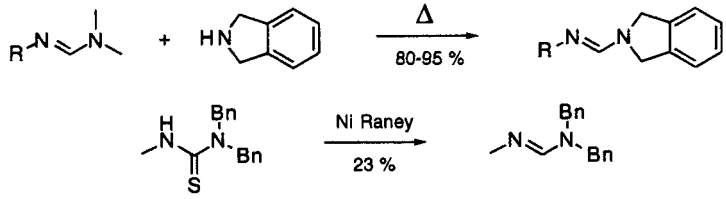
Abstract: Two complementary procedures are described for the preparation of *N,N*-dibenzyl formamidines from primary amines in high yield. The primary amine protective group can be easily introduced on polyhydroxylated molecules and is removable either by hydrolysis or hydrogenolysis.

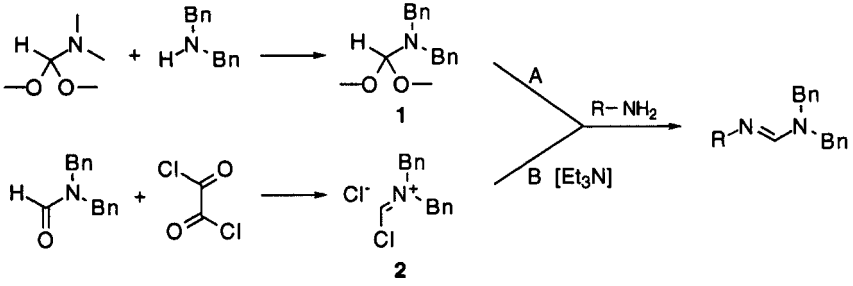
As more and more sophisticated structures are being synthesized by chemists, protective group chemistry continues to play a pivotal role in the multistep elaboration of new compounds. Recently, we have described *N,N*-dibenzyl formamidine as a new protective group for primary amines[1]. The *N,N*-dibenzyl formamidine protection can be removed either by hydrolysis or hydrogenolysis and its reactivity has been extensively compared to that of the *N,N*-dimethyl formamidine group[2].

There are only very few reports concerning the preparation of *N,N*-dibenzyl formamidines in the literature. Only two syntheses have been described that were achieved either by trans-amidination of *N,N*-dimethyl formamidines[3,4], or desulfurization of the corresponding thioureas[5] (Sch. 1).



- Scheme 1 -

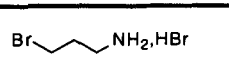
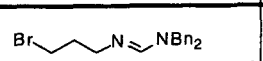
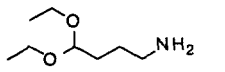
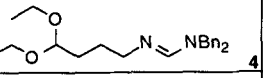
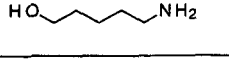
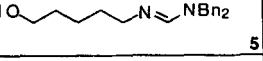
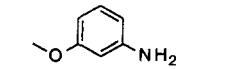
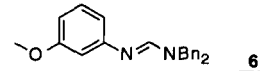
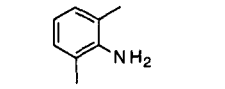
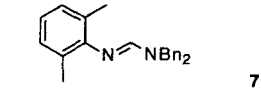
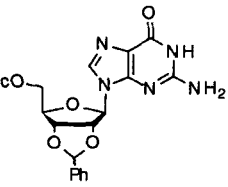
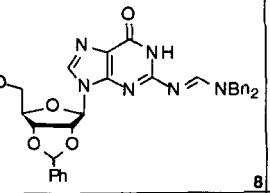
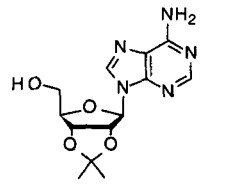
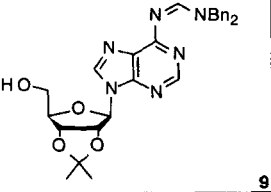
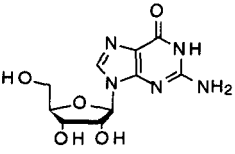
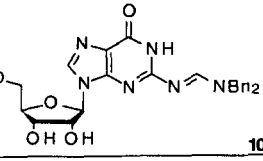
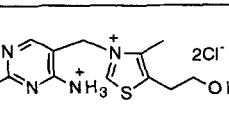
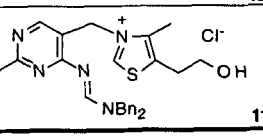
The high temperature required for the trans-amidination procedure (refluxing toluene for several hours) and the modest yield obtained by desulfurization of thioureas do not fully fit the protection-deprotection chemistry requirements. In addition, both described pathways involve two consecutive transformations on a primary amine and thus are not very convergent protecting procedures. We developed two alternative routes to *N,N*-dibenzyl formamidines using either dibenzyl formamide dimethyl acetal **1**, or *N,N*-dibenzyl chloromethylene iminium chloride **2** (Sch. 2).



- Scheme 2 -

Dibenzyl formamide dimethyl acetal **1** is obtained *via* a trans-amidation reaction of DMF dimethyl acetal[6-8] with dibenzylamine. Alternatively, the iminium salt **2** is obtained through the reaction of *N,N*-dibenzyl formamide with oxalyl chloride[9]. That procedure proved to be efficient and definitely safer than that described by Arnold for the obtaining of such salts and requiring phosgene[10].

- Table 1[11] -

Entry	Reactant	Product	Method A Yield (%)	Method B Yield (%)
1		 3	50 (93*)	99
2		 4	75	99
3		 5	78	59
4		 6	88	91
5		 7	93	85
6		 8	99	82
7		 9	87	41
8		 10	70	8**
9		 11	0 (66*)	-

* That yield was obtained using the alternative procedure described in note 23 for the preparation of **1**.
** That yield was obtained with an excess of reagent **2** (6.0 eq.) and Et_3N (12.5 eq.).

Both reagents **1** (method A) and **2** (in the presence of triethylamine, method B) react smoothly with primary amines at room temperature or 0 °C to yield the corresponding dibenzyl formamidines (see experimental procedures below). Results obtained with a series of differently functionalized primary amines are summarized in Table 1.

In all cases, the chloro-iminium compound **2** (method B) appeared more reactive than the formamide dimethyl acetal **1** (method A), and *N,N*-dibenzyl formamidines were generally obtained at 0 °C within less than 2 hours. Thus, in the case of monofunctional alkylamines, method B revealed more attractive and higher yields were obtained (entries 1 and 2). The especially low yield obtained with method A at entry 1 resulted from partial displacement of bromide by dibenzylamine. That side-reaction could be avoided by modifying the procedure for the preparation of **1**[23]. In the case of anilines both methods afforded comparable high yields, even with hindered substrates (entries 4 and 5). When working with hydroxylated compounds, method A definitely appeared more efficient than method B (entries 3, and 6 to 9). The more striking example observed is concerned with guanosine that was protected at its exocyclic amino function following method A without prior protection of the sugar moiety (entry 8). In the course of the reaction, the 2',3'-*O*-dibenzylaminomethylene compound[12] could not be detected indicating that the trans-acetalisation reaction between the nucleoside and *N,N*-dibenzylformamide dimethyl acetal does not take place in our experimental conditions. The use of the Arnold's salt for the straightforward protection of guanosine as its formamidine failed, and whatever the excess of reagent **2** (1 to 6 eq.) and triethylamine (2.1 to 12.5 eq.) used, yield never exceeded 8 %. This is presumably due to the transient activation of the hydroxyl groups in guanosine as alkoxy-iminium functions $[R\text{-}O\text{-}CH{=}NBn_2]^+Cl^-$. These activated species are subject to chlorination reactions (through displacement of alkoxy-iminium moieties by chloride anions)[13-16], intramolecular cyclization (through displacement of the nucleogugal 5'-substituent, alkoxy-iminium or chloride, by N^3)[17-20], as well as formylation reactions (resulting from hydrolysis of remaining

alkoxy-iminiums during aqueous work-up). The protection of thiamine (vitamin B1) could not be either achieved following method B as the vitamin is not stable in basic media[21,22] and was completely decomposed in our experimental conditions (entry 9). The corresponding formamidine could be prepared however from *N,N*-dibenzyl formamide dimethyl acetal and thiamine hydrochloride in a satisfactory yield using a slight modification of the procedure for the preparation of **1** in order to avoid the presence of unreacted dibenzylamine[23].

Experimental procedures[24].

Method A : Dimethyl formamide dimethyl acetal (2.5 mmol), and dibenzylamine (7.5 mmol) are refluxed in dry acetonitrile for 20 hours. The reaction mixture is reduced *in vacuo* and traces of remaining DMF dimethyl acetal are removed by two successive evaporations with toluene. The crude residue is dissolved in anhydrous CH_3CN and added to the primary amine (1.0 mmol) in CH_3CN[25]. 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.

Method B : Oxalyl chloride (1.5 mmol) is added dropwise to *N,N*-dibenzyl-formamide (1.1 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture is stirred for 3 hours at room temperature. Anhydrous toluene is added and volatile materials are removed *in vacuo*. The hygroscopic residue is dissolved in CH_2Cl_2 and added to a mixture of the primary amine (1.0 mmol) and triethylamine (2.1 mmol) in CH_2Cl_2 at 0 °C. The solution is stirred for 2 hours at room temperature before it is extracted twice with aqueous $NaHCO_3$. The organic layer is dried over anhydrous $MgSO_4$, reduced *in vacuo* and the residue is purified by chromatography on silica gel.

In conclusion, two complementary methods for the protection of polyfunctional primary amines as *N,N*-dibenzyl formamidines are described and

compared. The reactions are performed under very mild experimental conditions and yields obtained are high to excellent.

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(10) Arnold, Z. *Coll. Czech. Chem. Commun.* **1959**, *24*, 4048.

(11) Selected spectral data. (**3**) : ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.86 (s, 1H); 7.36-7.10 (m, 10H); 4.37 (s, 4H); 3.48 (t, J = 6.4 Hz, 2H); 3.43 (t, J = 6.4 Hz, 2H); 2.11 (q, J = 6.4 Hz, 2H). (**4**) : ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.62 (s, 1H); 7.33-7.12 (m, 10H); 4.53 (t, J = 5.1 Hz, 1H); 4.31 (s, 4H); 3.85-3.40 (m, 4H); 3.34 (t, J = 5.9 Hz, 2H); 1.70-1.62 (m, 4H); 1.25 (t, J = 6.9 Hz, 6H). (**5**) : ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.72 (s, 1H); 7.42-7.20 (m, 10H); 4.38 (s, 4H); 3.65 (t, J = 6.4 Hz, 2H); 3.38 (t, J = 6.6 Hz, 2H); 1.67-1.62 (m, 4H); 1.25 (q, J = 7.0 Hz, 2H). (**6**) : ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.98 (s, 1H); 7.82-7.20 (m, 14H); 6.80-6.62 (m, 3H); 4.74 (s, 2H); 4.35 (s, 2H); 3.67 (s, 3H). (**7**) : ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.60 (s, 1H); 7.46-7.30 (m, 10H); 7.10 (d, J = 7.3 Hz, 2H); 6.92 (t,

J = 7.3 Hz, 1H); 4.54 (s, 4H); 2.32 (s, 6H). (**8**, 2 diastereomers) : ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 8.94 and 8.93 (2s, 1H); 7.73 (s, 1H), 7.60-7.15 (m, 15H); 6.24 and 6.16 (2d, J = 2.5 Hz, 1H); 6.23 and 6.02 (2s, 1H); 5.37 (dd, J = 2.5, 6.6 Hz, 1H); 5.03 (m, 1H); 4.75-4.39 (m, 5H); 3.91 (m, 1H). (**9**) : ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 9.37 (s, 1H); 8.55 (s, 1H); 7.96 (s, 1H); 7.42-7.10 (m, 10H); 5.89 (d, J = 5.0 Hz, 1H); 5.22 (dd, J = 5.0, 5.6 Hz, 1H); 5.10 (d, J = 5.6 Hz, 1H); 4.87 (s, 2H); 4.53 (s, 1H); 4.43 (s, 2H); 4.10-3.70 (m, 2H); 1.63 (s, 3H); 1.36 (s, 3H). (**10**) : ^{1}H-NMR (CD_3OD, 200 MHz) δ 9.05 (s, 1H); 8.10 (s, 1H); 7.40-7.20 (m, 10H); 5.99 (d, J = 5.9 Hz, 1H); 4.73 (dd, J = 5.5, 5.9 Hz, 1H);4.68 (s, 2H), 4.53 (s, 2H); 4.37 (dd, J = 3.3, 5.5 Hz, 1H); 4.14 (m, 1H); 3.82 (AB part of ABX syst., J_{AB} = 12.2 Hz, J_{AX}=2.7 Hz, J_{BX} = 2.7 Hz, Δν = 13.0 Hz, 2H). (**11**) : ^{1}H-NMR (CD_3OD, 200 MHz) δ 9.25 (s, 1H); 8.49 (s, 1H); 7.41-7.23 (m, 8H); 7.11-7.06 (m, 2H); 5.51 (s, 2H); 4.60 (s, 4H); 3.69 (t, J = 5.7 Hz, 2H); 2.93 (t, J = 5.7 Hz); 2.62 (s, 3H); 2.43 (s, 3H).

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(23) Dimethyl formamide dimethyl acetal (5 eq.) and dibenzyl amine (3 eq.) are refluxed without solvent until the amine has completely disappeared when checked by TLC. Excess DMF dimethyl acetal is removed by two successive evaporations with xylene. Reaction with thiamine hydrochoride (1 eq.) is run in anhydrous methanol so as to solubilize the vitamin.

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(25) 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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