

Oxidative Deprotection of Diphenylmethanimines

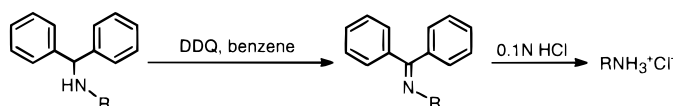
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Received August 18, 1999

ABSTRACT



The diphenylmethyl amino protecting group can be efficiently removed by initial oxidation of the amine to an imine by 2,3-dichloro-5,6-dicyanobenzoquinone. The resulting imine can then be easily hydrolyzed under mildly acidic conditions. This method is particularly well suited for the preparation of α -amino phosphinates and α -amino phosphonates.

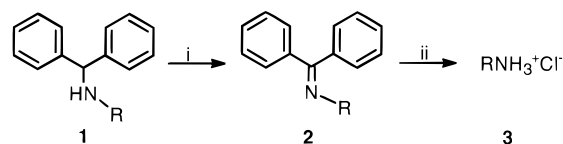
The benzhydryl or diphenylmethyl (Dpm) group has been used as a protecting group for carboxylic acids,¹ alcohols,² and amines.³ As a protecting group for the amine functionality, it offers an alternative to the trityl group by its relative stability to strong acid conditions.⁴ Traditionally, removal of the diphenylmethyl protecting group from an amine functionality has been achieved via hydrogenation,^{5a} using triethylsilane/TFA,^{5b} or under vigorous acidic conditions.^{3a} We describe an oxidative approach to release of the protecting group in which the secondary amine is oxidized to an imine, which can be hydrolyzed under mildly acidic conditions. Moreover, this method of imine formation has synthetic applications in the Schiff base mediated preparation of α -amino acids,⁶ α -amino phosphinates,⁷ and α -amino phosphonates.⁸

The high oxidation potential ($E_0 = 1000$ mV)⁹ of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) has resulted in the

extensive use of this compound as a dehydrogenating agent in organic synthesis.⁹ Despite this, examples of the quinone-mediated oxidation of amines are limited. In general, primary and secondary aliphatic amines undergo nucleophilic displacement reactions with halogen-containing quinone oxidants, whereas aliphatic tertiary amines are known to react by way of a charge transfer complex to give enamines.¹⁰ Recently, however, DDQ has been reported to effect the oxidative removal of the *p*-methoxybenzyl protecting group of an indole nitrogen¹¹ and the oxidative fragmentation of the alkaloid catharanthine.¹²

The Dpm protecting group was removed through initial oxidation of the secondary amine to an imine as outlined in Scheme 1. The Dpm-amine was dissolved in anhydrous

Scheme 1^a



^a Reagents: (i) DDQ, benzene, crushed 4A molecular sieves, 60 °C, 1 h.; (ii) 0.1 N HCl, diethyl ether, 6 h.

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benzene in the presence of crushed 4A molecular sieves at 60 °C.¹³ Addition of DDQ (1 equiv) gave quantitative

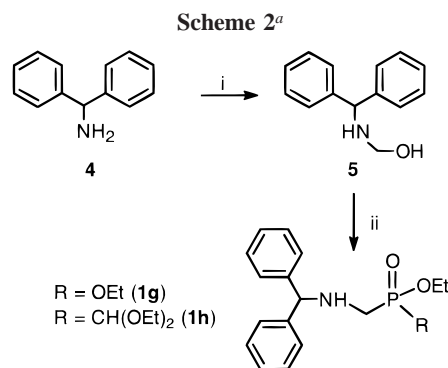
formation of the imine after 1 h. The DDQ-derived byproducts of the reaction precipitated from solution and were easily removed by filtration. Upon mild acid hydrolysis, the desired amines were obtained in good to excellent yields as the hydrochloride salts (Table 1).

Table 1. Removal of the Dpm Protecting Group by Reaction with DDQ Followed by Acid Hydrolysis¹⁴

Amine 1	R	Product 3	Yield
a	CH ₃ CH ₂ CH ₂ -		71%
b	(CH ₃) ₂ CHCH ₂ -		84%
c	(CH ₃) ₂ CHCH ₂ CH ₂ -		80%
d	CH ₃ (CH ₂) ₅ -		78%
e			75%
f			76%
g			95%
h			41%

The oxidation occurs extremely rapidly due to the activating effect of the adjacent phenyl substituents. It has been reported that electron-donating substituents serve to accelerate quinone-mediated oxidations.⁹ In this case, the diphenyl substitution offers suitable activation for the dehydration to occur, which appears to be crucial given the fact that *N*-benzylamines were not oxidized under similar conditions.

The organophosphorus compounds **1g** and **1h** serve as precursors in the synthesis of α -amino phosphinates and phosphonates.^{7,8} The preparation of **1g** and **1h** is outlined in Scheme 2. Formalin was reacted with diphenylmethanamine (**4**) in benzene to give hemiaminal (**5**) in 85% yield as a white crystalline product. Addition of diethyl phosphite at

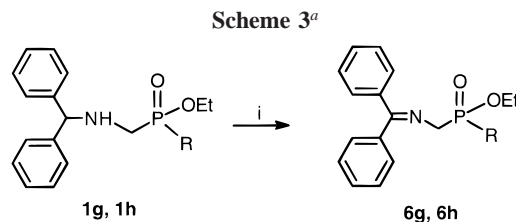


^a Reagents: (i) formalin, benzene, Dean–Stark trap, reflux, 16 h, 85%; (ii) R = OEt, diethyl phosphite, 5 h, 100 °C, 96%; R = CH(OEt)₂, ethyl diethoxymethylphosphinate, 48 h, 50 °C, 48%.

100 °C resulted in in situ dehydration of the hemiaminal which, followed by addition of the phosphite, gave 1-[diethyl-(diphenylmethyl)]methyl phosphonate (**1g**)⁸ in 96% yield.

The phosphinate (**1h**)⁷ was obtained in 48% yield using ethyl diethoxymethylphosphinate¹⁵ as the nucleophilic reagent.

DDQ oxidation of **1g** and **1h** gave an alternate synthetic route to the Schiff base synthons (**6g**, **6h**) as outlined in Scheme 3. These synthons offer a suitable template for the



^a Reagents: (i) DDQ, benzene, crushed 4A molecular sieves, 60 °C, 80–99%.

preparation of numerous α -aminophosphinates and phosphonates given the ease of deprotonation and alkylation of these compounds. Previous syntheses of the Schiff base intermediates have involved the preparation of a glycine

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(13) *N*-Diphenylmethanamines **1a–1e** were prepared by reductive amination of diphenylmethanamine and an aldehyde in the presence of sodium cyanoborohydride. The norleucine analogue **1f** was prepared by transamination of norleucine methyl ester with benzophenone imine followed by reduction with sodium cyanoborohydride.

(14) To an anhydrous solution of benzene (3 mL) and crushed 4A molecular sieves under an argon atmosphere were added the Dpm-amine (1 mmol) and DDQ (1 mmol). The reaction mixture was heated to 60 °C for 1 h in the absence of light. The deep red solution became light orange over the course of the reaction with concomitant production of a purple precipitate. The solution was cooled to room temperature and quickly filtered through a small column charged with Brockmann 1 basic alumina and washed with toluene. The solvents were removed in vacuo. The resulting yellow oils were dissolved into diethyl ether (10 mL) and 0.1 N HCl (10 mL). The two-phase mixture was vigorously stirred for 4–6 h. The phases were separated, and the ether layer was washed with 0.1 N HCl (2 × 5 mL). The aqueous layers were combined and washed with diethyl ether (2 × 5 mL). Concentration of the aqueous fraction gave the hydrochloride salts of the desired amines.

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analogue which was then transaminated with benzophenone⁷ or benzophenone imine.⁸ The current method offers a more direct synthetic route to these synthons using DDQ-mediated imine formation.

Acknowledgment. This work was supported by an Ontario Graduate Scholarship (P.B.S.) and a grant from

NSERC (J.F.H.). The authors thank Dr. G. Lajoie and Mr. W. Ding for access to ESMS facilities.

Supporting Information Available: Full experimental procedures and characterization for **1a–f**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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