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LETTERS

The *N*-(2-acetoxyethyl) group as a new photolabile protecting group

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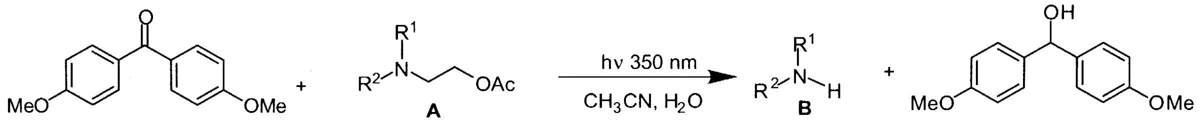
Abstract

The *N*-(2-acetoxyethyl) group can be cleaved by a photoinduced single electron transfer to 4,4′-dimethoxybenzophenone. © 2000 Published by Elsevier Science Ltd. All rights reserved.

Keywords: *N*-(2-acetoxyethyl); protection; deprotection; 4,4′-dimethoxybenzophenone; photo-induced electron transfer.

Numerous protecting groups for basic nitrogen can be found in the literature attesting to the importance of this aspect of amine chemistry.[1] The most frequently used amino protecting groups are Bn,[2] Boc,[3] Cbz,[4] and Fmoc.[5] Since removal of these groups can be problematic with highly functionalized and sensitive substrates, new protecting groups are still needed.

In this letter, we disclose that the *N*-(2-acetoxyethyl) group can be used as an efficient protecting group for the amino function. It has the advantage of being cleaved easily on irradiation of amines of type **A** in the presence of 4,4′-dimethoxybenzophenone at 350 nm in wet acetonitrile.



The *N*-(2-acetoxyethyl) derivatives of type **A** are easily obtained by treating amines of type **B** in acetonitrile with 2-bromoethyl acetate.[6] After heating the mixture under reflux for 5 h, followed by standard aqueous extractive work-up and chromatography, protected amines of type **A** were obtained in good yields. Several examples are shown in Table 1. Amines of type **A** (1 mmol) were deprotected when irradiated in the presence of 4,4′-dimethoxybenzophenone (1 mmol) and water (0.1 mL) in acetonitrile (2×10^{-2} M) at 350 nm.[7] After 3 h, the corresponding amines **B** were isolated in good yields. This photochemical process was very regioselective as cleavage of the alkyl group R^1 or R^2 was not observed. Furthermore, when an optically active amine of type **A** was irradiated, no epimerization was observed (entry 5). This process was also very chemoselective as secondary amines were recovered

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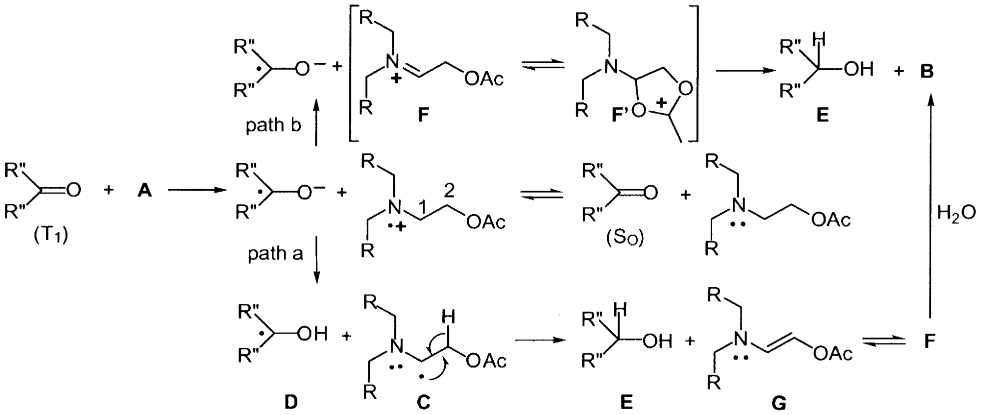
Table 1
Irradiation of amine of type **A** at 350 nm in the presence of 4,4′-dimethoxybenzophenone

Entry	Starting material **A**	Yield in **B** %
1	$R^1 = R^2 = CH_2Ph$	60
2	$R^1 = (CH_2)_2\text{-}Ph$; $R_2 = Et$	73
3	$R^1 = R^2 =$ *c*-Hex	80
4	$R^1, R^2 = \text{-}CH_2\text{-}CH_2\text{-}C($*p*-fluorophenyl$)=CH\text{-}CH_2\text{-}$	69
5	$R^1 =$ (*R*)-CH(Me)Ph ; $R^2 = Et$ [(a)]	71 [(b)]
6	$R^1 = CH_2Ph$; $R^2 = H$	0

[(a)] $[\alpha]_D = +16$ (*c* 1.0, $CHCl_3$); [(b)] $[\alpha]_D = +54$ (*c* 1.0, $CHCl_3$), similar to the $[\alpha]_D$ of the starting material.

unchanged (entry 6). The deprotection of amines of type **A** was accompanied by the reduction of 4,4′-dimethoxybenzophenone into the corresponding alcohol. The formation of **B** from **A** can be explained by a photoinduced single electron transfer (SET) (cf. Scheme 1). Extensive investigations of the photoreduction of aromatic ketones by amines have been carried out,[8] and it has been shown that an initial electron transfer to generate a radical ion pair is followed by a proton transfer to give a ketyl radical and an α-aminoalkyl radical (tertiary amine). This radical pair can undergo disproportionation to regenerate starting materials in competition with reaction of the α-aminoalkyl radical. It seems that the acetyl group enhances the acidity of the proton at C-1 and, consequently, the transfer of one proton to the ketyl radical-anion can produce radicals **C** and **D** which can be converted into alcohol **E** and intermediates **G** and **F**. After hydrolysis, these intermediates can be transformed to **B** (Scheme 1, path a). A second possibility is the abstraction of a hydrogen by the ketyl radical anion[9] that will lead to the iminium ion **F**, which can be stabilized by the acetyl group to form intermediate **F′**. These intermediates can produce the deprotected amines after hydrolysis (Scheme 1, path b).



Scheme 1. Mechanism for the transformation of amines of type **A** to amines of type **B**

In summary, a photolabile protecting group for basic nitrogen has been developed. Applications of the *N*-(2-acetoxyethyl) group as a protecting group to other synthetic situations are under study and will be reported in due course.

Acknowledgements

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6. Preparation of *N*-(acetoxyethyl)amines (general procedure): A mixture of amine (10 mmol), K_2CO_3 (2.7 g, 19.53 mmol), NaI (0.15 g, 1 mmol) and 2-bromoethyl acetate (1.2 mL, 10.88 mmol) in acetonitrile (20 mL) was heated at 60°C for 5–6 h. After cooling to rt, ethyl acetate (30 mL) and water (20 mL) were added. The organic layer was separated, dried over $MgSO_4$, filtered and the solvent was removed in vacuo. The *N*-(acetoxyethyl)amine was isolated after flash chromatography on silica gel.
7. The irradiations were performed in a Rayonet RPR-200 equipped with six low-pressure mercury lamps (RPR-3500A, 350 nm, 24 W). The solutions were introduced into 1 cm inside diameter quartz tubes.
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