o-Nitrobenzyl Alcohol, a Simple and Efficient Reagent for the Photoreversible Protection of Aldehydes and Ketones

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Two independent procedures are described for the preparation of bis-*o*-nitrobenzyl acetal derivatives of aldehydes and ketones which are shown to be photoremovable in high yield by simple irradiation at 350 nm in an aprotic solvent.

The protection and deprotection of the carbonyl group[1] in organic synthesis has long stimulated interest mainly because of the importance of this group in carbon–carbon bond forming reactions, and new reagents or new conditions continue to be reported.[2] Photochemical deprotection methods can be advantageous because they may provide greater specificity and often be carried out under aprotic conditions.[3,4]

The use of the photolabile glycol reagent (**1**), which we reported earlier[3] (Scheme 1), is based on the photoredox rearrangement of *o*-nitrobenzyl systems, a long established general reaction.[5] Although reagent (**1**) is efficient and is now commercially available, it has the disadvantage of producing diastereoisomeric mixtures of the acetals (**2**) with non-symmetrical carbonyl compounds (**3**) because of its dissymmetric structure (Scheme 1).

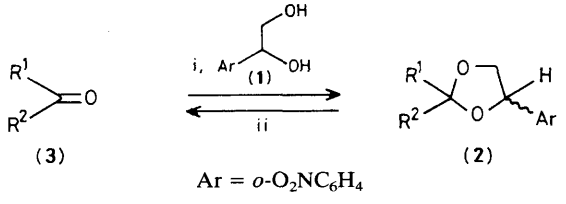
We therefore wished to devise a symmetrical reagent including the *o*-nitrobenzyloxy moiety with at least one benzylic hydrogen, necessary for photodeprotection. The simplest solution was to generate the bis-*o*-nitrobenzyl acetals (**4**) from *o*-nitrobenzyl alcohol (**5**), but such acetals are not commonly available by the usual procedures.[1] We now report the preparation of the acetals (**4**) by two independent methods and their efficient photodeprotection at 350 nm in benzene or chloroform (Scheme 2).

In the acetalization procedure (A), involving an exchange reaction using 2,2-dimethoxypropane,[6] typically, a solution (protected from light) of the carbonyl compound (**3**) (6 mmol), *o*-nitrobenzyl alcohol (**5**) (16 mmol), a catalytic amount of β-naphthalenesulphonic acid, and 2,2-dimethoxypropane (6 mmol) in benzene (20 ml) was gently heated at 80 °C for 1—4 h, the benzene distilling over being replaced. The product was isolated by flash chromatography on silica gel in the absence of light.

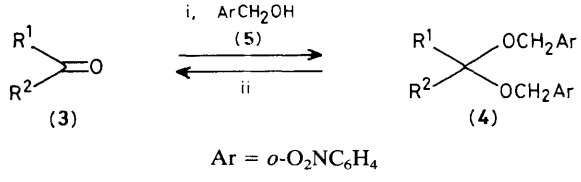
Procedure (B) involved an exchange reaction using *o*-nitrobenzyloxytrimethylsilane.[7] In a typical experiment, a solution (protected from light) of the carbonyl compound (10.2 mmol), *o*-nitrobenzyloxytrimethylsilane (20.4 mmol), and, a catalytic amount of trimethylsilyl trifluoromethanesulphonate (1—4 mmol %) in dichloromethane (≥1.5 ml) was stirred at −78 °C under argon for 48 h, and the reaction then quenched (at −78 °C) by addition of dry pyridine, isolation being as for procedure (A).

In a typical deprotection, the acetal (**4**) (10^{-2} M) in benzene was irradiated in a Pyrex vessel using a Rayonet apparatus with 350 nm lamps, until t.l.c. showed disappearance of the starting material. Solvent was evaporated off, and the product isolated by flash chromatography.

The results in Table 1 show the potential usefulness of *o*-nitrobenzyl alcohol (**5**) as a simple and efficient photoremovable protective reagent for aldehydes and ketones. It can be introduced in yields that are good by procedure (A) and better by procedure (B); yields for photodeprotection are very good. The reagent has the advantage that it gives non-dissymmetric acetals but we have not been able to introduce it in sterically congested positions such as positions 17 and 20 of steroids; reagent (**1**) will still be required for such positions.[3] We are extending our synthetic investigations, and studying the mechanism[8] of this photoredox rearrangement.



Scheme 1. *Reagents and conditions:* i, reagent (**1**), H^+ ($-H_2O$); ii, *hν* (350 nm), C_6H_6.



Scheme 2. *Reagents and conditions:* i, reagent (**5**), procedure (A) or (B); ii, *hν* (350 nm), C_6H_6.

Table 1. Protection of carbonyl compounds as the bis-*o*-nitrobenzyl acetals (**4**) and deprotection by photolysis at 350 nm.[a]

Carbonyl compound (**3**)	Procedure	Time/h	% Yield of acetal (**4**)	Irradiation time/h	% Yield of liberated (**3**)
4-Ethylcyclohexanone	A	2	88[b]	1.5	85[i]
p-Nitrobenzaldehyde	A	2	78[c]	8	91[j]
n-Nonanal	A	1	85[b]	2	95[i]
1-Naphthaldehyde	A	2	80[d]	3.5	84[j]
Acetone	A	1	95[b,e]	0.75	95[i]
Cyclododecanone	A	4	70[e,f]	2	95[i]
Androstanolone acetate	B	48	92[g]	3	93[j]
Cyclohexanone	B	48	90[h]	2	95[i]

[a] All acetals were fully characterized by spectroscopic methods. [b] Oil. [c] M.p. 131—132 °C. [d] M.p. 138—139 °C. [e] *Via* dimethoxy acetal. [f] M.p. 125—126 °C. [g] M.p. 153—154 °C. [h] M.p. 77—78 °C. [i] By n.m.r. [j] Isolated.

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