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N-Methyl-*N*-(*o*-nitrophenyl)carbamates as photolabile alcohol protecting groups

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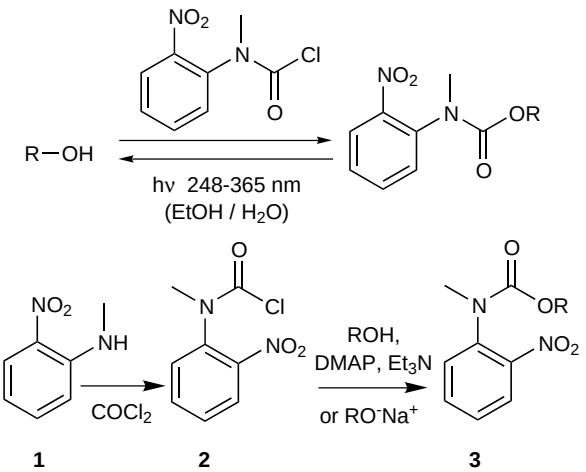
Abstract—*N*-Methyl-*N*-(*o*-nitrophenyl)carbamates represent new photoremovable alcohol protecting groups. This protecting group is easily incorporated by chemical coupling of the corresponding alcohol to *N*-methyl-*N*-(*o*-nitrophenyl)carbamoyl chloride. High yield and clean deprotection are induced by photolysis in protic solvents (water, ethanol or ethanol/water mixtures) from 254 to 365 nm. © 2001 Elsevier Science Ltd. All rights reserved.

Protecting groups represent useful tools in organic synthesis provided they fulfil a series of criteria including a convenient and efficient synthesis, chemical stability and an efficient and selective removal. Many protecting groups have been developed for alcohols, such as ester and ether derivatives, to modulate their base and acid sensitivity.[1] Orthogonality of protecting groups was also developed for alcohols[2–4] to extend their synthetic use.

Photolytic removal of protecting groups represents an interesting issue in synthetic organic chemistry, allowing a very selective unmasking of a chemical function,[5] while photolytic orthogonality was recently described for the protection of carboxylic acids.[6] The *o*-nitrobenzyl group represents the most widely used photoremovable protecting group in organic chemistry. This photolytic unmasking has also been extensively used in biology to permit a spatio-temporal release of biologically active compounds from their precursors named caged compounds.[7] Very few examples used the photochemical deprotection of alcohol groups to achieve the functional masking of a biomolecule such as the photochemical release of choline[8] and glucose[9] from *o*-nitrobenzyl ether precursors and more recently of adenosine from an anthraquinon-2-ylmethoxycarbonyl precursor.[10] Also, photochemical release of alcohols from silyl protection was described using a hydrosilylation reaction of arylethynyl acetates.[11] The description of the photorelease of carboxylic acids from 1-acyl-7-nitroindolines amides[12] prompted us to investigate the possibility of extending such a photolytic reaction to carbamates for an ultimate release of alcohols. The present article describes the use of such carbamates as photoremovable protecting groups of alcohols.

We studied first simple carbamate derivatives i.e. *N*-methyl - *N* - (2 - nitrophenyl)methyloxycarboxamide **3a** and *N*-benzyl-*N*-(2-nitrophenyl)benzyloxycarboxamide **3b**, to set up a convenient and easy synthesis of the alcohol protection step, which is described in Scheme 1.

The *N*-methyl-2-nitroaniline **1** is quantitatively converted to the *N*-methyl-*N*-(2-nitrophenyl)carbamoyl



Scheme 1. *N*-Methyl-*N*-(*o*-nitrophenyl)carbamates as photolabile protecting groups. Principle and synthesis.

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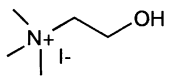
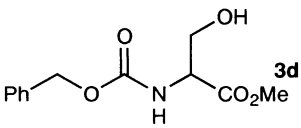
Table 1. Structure and yields of protection and photodeprotection of the different alcohols masked with **2**. (a) Those alcohols were too volatile and could not be satisfactorily detected by UV and subsequently quantified by HPLC. Their photodecomposition could be appreciated by near UV spectra evolution and followed by HPLC: disappearance of the starting material, together with the formation of *N*-methyl-2-nitrosoaniline. (b) The protected choline **3c** used the alternative synthetic pathway, starting from the corresponding chloroformate and *N*-methyl-2-nitroaniline **1** (see text).

ROH	Carbamate	Protection yield	Deprotection yield
CH_3—OH	**3a**	94%	(a)
$PhCH_2$—OH	**3b**	94%	(a)
	**3c**	(b)	100%
	**3d**	88%	91%

chloride **2** by treatment with phosgene (or a phosgene substitute). This precursor, which solidifies at lower temperature, can be stored for months when protected from light. It is converted to the carbamate[13] in high yield either by treatment with an excess alcohol in the presence of DMAP and NEt_3 or with the corresponding sodium alkoxide (Table 1). The carbamates are isolated using standard purification procedures (i.e. silica gel chromatography). Alternatively, the alcohols can also be firstly converted to their chloroformate derivatives with phosgene (or an equivalent) and treated subsequently with *N*-methyl-2-nitroaniline **1**, as was the case for the protected choline derivative **3c**.[14]

The *N*-methyl-*N*-(*o*-nitrophenyl)carbamates are slightly sensitive to hydrolytic conditions especially in basic medium, therefore they cannot be used in a synthetic strategy using such reaction conditions. This protecting group is however compatible with strong non-nucleophilic basic conditions, i.e. with lithium diisopropylamide or lithium bis(trimethylsilyl)amide (THF, up to 0°C). As expected, these carbamates are also stable in non-aqueous acidic conditions such as pure TFA or TFA/CH_2Cl_2 mixtures.

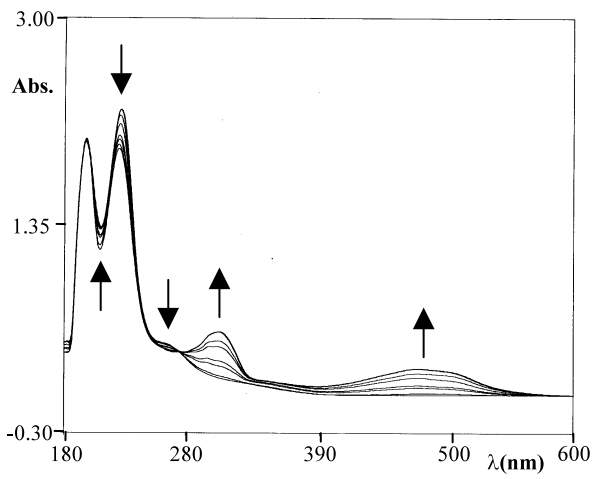
Table 2. Deprotection yield generated by irradiation of 1.4 ml 10^{-4} M and 2×10^{-4} M solutions of compound **3c** in water, at different wavelengths, for 1 h. The amount of released choline was assessed by an enzymatic test[8]

	254 nm	312 nm	365 nm
1.10^{-4} M	100%	100%	76%
2.10^{-4} M	100%	91%	52%

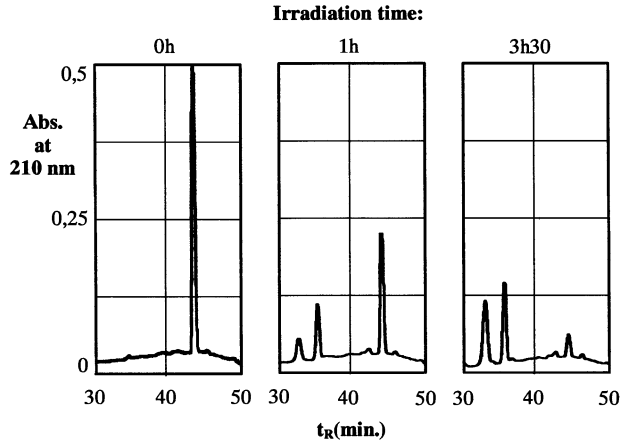
The photochemical reactivity of these derivatives was tested in different solvents and wavelengths using a 1000 W Xe-Hg lamp connected to a grating monochromator. The light intensity was measured with a thermopile coupled to a microvolmeter. These carbamates were photolabile in different solvents but the best results were obtained in protic solvents such as H_2O, EtOH or $EtOH/H_2O$ mixtures. The probes were sensitive at the different wavelengths we tested, 365, 312 and 254 nm, respectively, corresponding to maximum emission lines of the Xe-Hg lamp. They showed a faster decomposition at 254 nm (Table 2). Besides the desired alcohol, *N*-methyl-2-nitrosoaniline was identified during these photolytic reactions. The structure of this compound was assessed by NMR, MS and IR.[15] Its strong UV absorbance λ_{max} 308 nm ($\varepsilon=11000$ M^{-1} cm^{-1}), 472 nm ($\varepsilon=5900$ M^{-1} cm^{-1}) should allow an easy monitoring of the photolytic reaction by UV spectroscopy. However, the fragmentation mechanism of these carbamates remains unclear and cannot be deduced from the usual photolytic mechanism proposed either on *o*-nitrobenzyl[16] or on the 1-acyl-7-indoline derivatives.[12] Consequently, we did not take advantage of the formation of this nitroso compound to monitor the photolytic reaction.

We analyzed in more detail two photolytic reactions, the protected choline and serine derivatives **3c** and **3d**, respectively. Scheme 2 shows the UV spectra of the photodecomposition of compound **3c** in water. The formation of isobestic points (202 and 276 nm) is indicative of a clean photodecomposition process. The photolytic reaction led to a quantitative formation of choline tested by means of an enzymatic test.[8]

The photolytic deprotection of the serine derivative **3d** could be fully monitored by HPLC, allowing visualization of the disappearance of the starting compound **3d** with the concomitant formation of the unprotected serine derivative and the *N*-methyl-2-nitrosoaniline (Scheme 3).



Scheme 2. UV spectra of **3c** photolysis (1.4 ml, 10^{-4} M in water at 254 nm) as a function of time (0, 10, 20, 30, 45, 60 min).



Scheme 3. HPLC profiles at $\lambda = 210$ nm of photodeprotection of the serine derivative **3d**: **3d** ($t_R = 45$ min); unprotected serine ($t_R = 36$ min), *N*-methyl-2-nitrosoaniline ($t_R = 33$ min). 1.4 ml of a 1.5 M **3d** solution in ethanol/water (1/1) was irradiated for 3 h 30 at 254 nm. 100 µl samples were injected on a C_{18} hypersil column with 1 ml/min flow rate using a (H_2O, 0.1% TFA):(CH_3CN, 0.1% TFA) gradient from (100:0) to (0:100) in 55 min. The slower photodecomposition process observed for **3d** compared to **3c** (Table 2) is due to lower light intensity used during this experiment (about 75% energy weakening of the 1000 W lamp).

We used the serine derivative **3d** for a larger scale photodecomposition reaction (27 mg in 400 ml EtOH) using a quartz reactor. The irradiation was stopped after 90 min photolysis. Evaporation of the solvent followed by a rapid filtration over silica gel provided 15 mg (91%) of the desired serine compound.

In summary, the *N*-methyl-*N*-(*o*-nitrophenyl)carbamates represent a new class of photolabile alcohol protecting groups, which are easily synthesized and can be used at organic synthetic scale.

Acknowledgements

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13. The NMR spectra of these carbamates and the starting carbamoyl chloride **2** show the presence of rotamers which collapse at higher temperature (DMSO-d_6 at 80°C). *N*-Methyl-*N*-(2-nitrophenyl)carbamoyl chloride **2** could not be heated in DMSO due to its instability in this solvent.
14. Protected methanol **3a**. Methyl alcohol (0.2 M) with metallic sodium (1.3 equiv.) and carbamoyl chloride **2** (1 equiv.) were stirred for 15 min at rt yielding 94% of **3a** after chromatography (CH_2Cl_2 as eluent).
Protected benzyl alcohol **3b**. Benzyl alcohol (3 equiv.), DMAP (0.5 equiv.), Et_3N (1.1 equiv.) and carbamoyl chloride **2** (1 equiv.) in CH_2Cl_2 (0.2 M) were mixed for 1 night at rt and 94% of compound **3b** was obtained, after flash chromatography.
Protected choline **3c**. The precursor of this derivative was synthesized by condensing 2-nitro-*N*-methylaniline (1 equiv.) and 2-chloro-*N*,*N*-dimethylethylamine (1.25 equiv.) by reflux in xylene (0.2 M) for 1 night. After a rapid filtration on silica gel, the isolated chloride product was converted into its iodide derivative with NaI (10 equiv.) by 1 night reflux in acetone (0.2 M), followed by silica gel flash chromatography. Finally, the quaternary ammonium salt could be precipitated in toluene (0.05 M) saturated with methyliodide and isolated by centrifugation. The obtained powder was rinsed with pentane (58% overall yield).
Protected serine **3d**. *N*-Benzoyloxyserine carboxylate (1 equiv.) was transformed to its methyl ester by 1 night stirring in methanol (0.2 M) with trimethylsilyl chloride (4 equiv.) and isolated in 95% yield by flash chromatography (TLC detection was ensured by spraying with a solution of 1% $Ce_2(SO_4)_3$, 38% $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ in 10% H_2SO_4 and then heating the plate). The protected serine (1.5 equiv.), DMAP (0.5 equiv.), Et_3N (1.2 equiv.) and carbamoyl chloride **2** (1 equiv.) were stirred for 1 night at rt in CH_2Cl_2 (0.2 M) yielding 88% of compound **3d**, after flash chromatography.
15. *N*-Methyl-2-nitrosoaniline. ^1H NMR ($CDCl_3$, δ ppm) 11.01 (s, 1H, NH); 8.70 (d, 1H, H3); 7.46 (ddd, 1H, H5); 6.96 (dd, 1H, H4); 6.84 (d, 1H, H6); 2.95 (d, 3H, N-CH_3 coupled with NH as seen by COSY). ^{13}C NMR ($CDCl_3$, δ ppm) 157 (C1); 142 (C3, very weak); 139 (C4); 117 (C5); 114 (C6); 29 (N-CH_3); (C2-NO could not be seen). MS calcd for $C_7H_8N_2O$: 136.16; found: 159.06 (M+ 22.99). IR (cm^{-1}) 1620+1360 (N=O st.), 1520 (C-NO arom. st.), 1420–1450 (N=NO st. from dimer), 1120 (C-N st.).
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