Protecting Groups

1-(*o*-Nitrophenyl)-2,2,2-trifluoroethyl Ether Derivatives as Stable and Efficient Photoremovable Alcohol-Protecting Groups**

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The photochemical unmasking of chemical functional groups has been used extensively in organic synthesis.[1] Even though photochemical methods may not be suitable for larger-scale reactions, they nevertheless display remarkable selectivity during the unmasking step and are therefore orthogonal to most organic reactions. An interesting application is found in the preparation of caged compounds, which requires the chemical modification of biomolecules by photoremovable protecting groups.[2] Such protecting groups are designed first to mask the biological function and second to permit the liberation of the biomolecule by the action of light, thus triggering the biological function in a controlled way. The caged biomolecule must be stable in neutral buffered solutions, and the photochemical reaction must be efficient at wavelengths greater than 300 nm (high quantum yields) and rapid with respect to the kinetics of biological processes.

A series of photoremoveable alcohol-protecting groups have been described in the literature, including carbonates,[3] carbamates,[4] acetals,[5] and esters,[6] which each have their own photochemical properties but also represent chemical functionalities of restricted hydrolytic stability. There have been several examples of ether linkages formed with alcohol-containing biomolecules to ensure better chemical stability, including 9-phenylthioxanthyl-protected dRNAs[7] and *o*-nitrobenzyl derivatives of carbohydrates[8] and choline.[9] Alternatively, α-hydroxy-β-alkoxypivaloyl derivatives have been used for solid-phase photochemical ether cleavage to release alcohols,[10] but these reagents might not be ideal for the caging of water-soluble molecules. The synthesis of ether derivatives in the *o*-nitrobenzyl series required the design of an individual methodology for each compound. 2-*O*-(2-Nitrobenzyl)-D-glucose was synthesized by alkylating a dibutylstannylidene glucose derivative with *o*-nitrobenzyl bromide in moderate yield,[8a] whereas in two other examples a Lewis acid catalyzed reductive ring opening of a cyclic acetal[8b] or ketal[9] was used to generate 6-*O*-(2-nitrobenzyl) methylglucoside or *o*-nitrobenzyl choline ether derivatives, respectively. As for their photochemical properties, product quantum yields were 0.63 and 0.27 for the 2-*O*-(2-nitrobenzyl)-D-glucose[8a] and the *O*-[1-(2-nitrophenyl)ethyl]cho-

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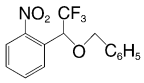
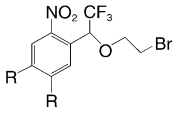
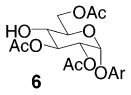
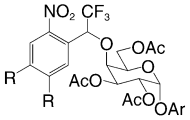
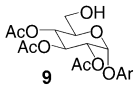
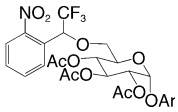
[**] The authors thank Dr. Luc Lebeau for useful discussions. This work was supported by the CNRS, the Université Louis Pasteur Strasbourg, and the Région Alsace.

  DOI: 10.1002/anie.200353247

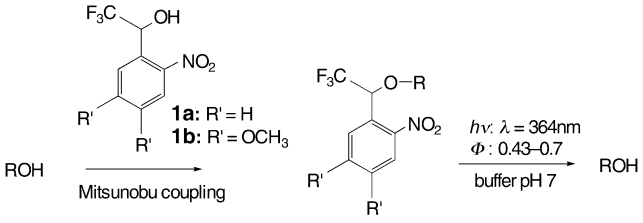
line[9] ether derivatives, respectively. The photofragmentation kinetics of *o*-nitrobenzyl ether derivatives were recently reinvestigated.[11] These studies demonstrated the decay of long-lived hemiketal intermediates to be the major fragmentation pathway, rather than the decay of the usual *aci*-nitro intermediates, thus resulting in a much slower fragmentation rate.

Herein we describe new *o*-nitrobenzyl ether derivatives, substituted with a trifluoromethyl group at the benzylic position: NPT (1-(2-nitrophenyl)-2,2,2-trifluoroethyl) and DMNPT (1-(4,5-dimethoxy-2-nitrophenyl)-2,2,2-trifluoroethyl) ethers. The presence of the trifluoromethyl substituent makes general synthetic pathways for the ether derivatives from alcohols possible through a Mitsunobu coupling reaction (Scheme 1). The NPT and DMNPT ether derivatives synthesized displayed remarkable photochemical properties. They released alcohols

Table 1: Ether synthesis with 1-(*o*-nitrophenyl)-2,2,2-trifluoroethanol derivatives **1a** and **1b**: Mitsunobu reactions in benzene in the presence of **A**: DIAD/PPh_3 (1.5 equiv) or **B**: TMAD/PBu_3 (1.5 equiv).[a]

Alcohols		Ether derivative		A/B	*t* [h]	*T* [°C][b]	Yield [%] (Conv. [%])[c]
C_6H_5–OH	**1a**		**2a**	**A**	1	0	18
				A	120	RT	40
				A	24	70	70
				B	2.5	70	83 (>95)
Br–OH	**1a**		**3a**	**A**	240	RT	31 (85)
	1b		**3b**	**A**	48	70	43 (73)
 **6**	**1a**		**7a**	**B**	24	70	8 (28)
	1b		**7b**	**B**	24	70	7 (35)
 **9**	**1a**		**10a**	**B**	24	70	18 (60)

[a] DIAD = diisopropyl azodicarboxylate, TMAD = tetramethyl azodicarboxamide, Ar = *p*-MeC_6H_4. [b] RT = reaction was carried out at room temperature. [c] Conv. = conversion.

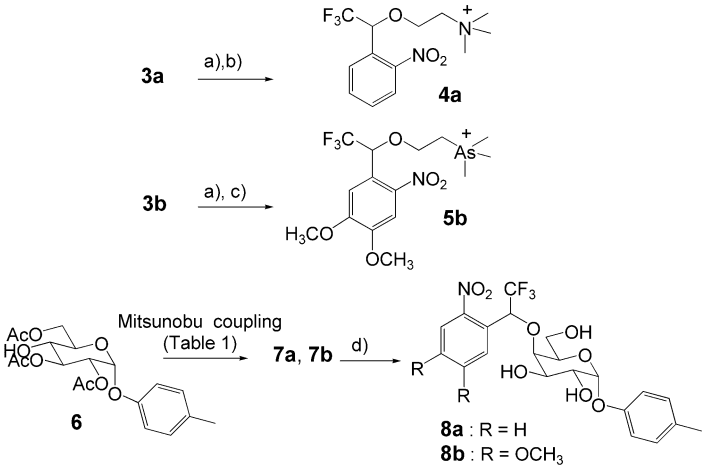


Scheme 1. 1-(*o*-Nitrophenyl)-2,2,2-trifluoroethanol derivatives as photoremovable alcohol-protecting groups.

with high quantum yields ($0.4 < \Phi < 0.7$), thus conferring to the DMNPT derivatives excellent photolytic efficiencies above 300 nm.

The strong basic reaction conditions of the ether Williamson synthesis do not accommodate the halogenated *o*-nitrobenzyl derivatives, which polymerize or decompose under such conditions.[8a,9] Therefore, we considered the possibility of using a Mitsunobu coupling reaction[12] to synthesize the NPT and DMNPT ether derivatives. The 1-(*o*-nitrophenyl)-2,2,2-trifluoroethanol derivatives **1a** and **1b** were synthesized by nitration of trifluoroacetophenone[13] or of the corresponding 3,4-dimethoxy derivative with nitric acid at 0 °C, and subsequent reduction with $NaBH_4$. The presence of the trifluoromethyl group at the benzylic position[14] does sufficiently increase the acidity of the alcohols **1a** and **1b** to permit their successful conversion into a series of ether derivatives by using a Mitsunobu coupling reaction with different alcohols (Table 1). Benzyl alcohol was used to assess experimental improvement of the coupling reaction with the derivative **1a**.[15,16] However, low yields were obtained for the coupling reaction with secondary alcohols (**7a** and **7b**), which is probably a result of steric factors (Table 1).

By using these coupling reactions a variety of alcohol-containing molecules with a potential biological function were converted into their corresponding NPT or DMNPT ether derivatives. Caged choline and[9] arsenocholine[17] were selected for the potential photochemical regulation of cholinesterases[18] and α-tolylgalactosides[19] for that of lactose permease transporter.[20] Neither processes require fast time resolution, with the cholinesterases investigated under cryophotolytic conditions and subsequent controlled temperature increase,[21] whereas the turnover rate of the transporter is about 15 s^{-1}. The synthesis of the NPT and DMNPT ether derivatives required for the photochemical study is outlined in Scheme 2. The direct synthesis of the galactosides through selective opening of cyclic 4,6-acetals, previously described for the modification of glycosides at C4 by an *o*-nitrobenzyl group,[8b] failed in our hands in this series. The synthesis of the 4-substituted galactoside derivative required the use of a



Scheme 2. Synthesis of caged choline, arsenocholine, and 4-substituted α-tolylgalactosides: a) NaI, acetone, reflux, 22 h, 90%; b) NMe_3, toluene, 25 °C, 40 h, 75%; c) $AsMe_3$, acetonitrile, reflux, 20 h, 74%; d) MeONa (cat.), MeOH, 0 °C, 20 h, 92%.

glucoside[22] corresponding to the epimer of **8** at C4 to take into account the inversion of configuration that occurs during Mitsunobu coupling.

Figure 1 shows the photolytic reactions of compounds **4a** and **5b** in terms of their UV difference spectra ($h\nu$: $\lambda =$ 364 nm, in a phosphate buffer at pH 7.2). A clean photolytic

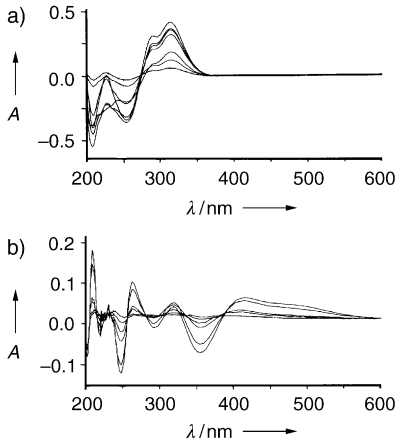


Figure 1. Difference UV spectra showing the reaction progress during photolysis at 364 nm of a) NPT choline (**4a**) and b) DMNPT arsenocholine (**5b**) at 25 °C in a phosphate buffer (0.1 M, pH 7.2).

reaction (Figure 1a) is depicted for the NPT derivative **4a**, which leads to the quantitative formation of choline, as demonstrated by NMR spectroscopic analysis (not shown), together with, presumably, (*o*-nitroso)trifluoroacetophenone hydrate. The structure of the proposed nitroso compound is in agreement with spectroscopic data (UV: $\lambda_{max} = 313$ nm; IR: $\tilde{\nu}(NO) = 1510\ cm^{-1}$). Its formation was demonstrated by HPLC to be concomitant with the disappearance of the starting compound (not shown). The photolytic reaction in the DMNPT series was more complex as a result of the photolytic instability of the corresponding nitroso derivative during the time course of the photolysis. The absorbance of the nitroso derivative ($\lambda_{max} = 311$ and 378 nm) is observed initially, but this compound is subsequently converted into two unidentified compounds that absorb at wavelengths above 380 nm. The quantitative photolytic release of arsenocholine was established by using an enzymatic assay[9] (not shown). The main point of interest of the dimethoxy-substituted derivatives is their absorbance above 300 nm ($\lambda_{max} = 340$ nm; $\varepsilon = 3650$). Independent of the DMNPT ether derivative tested, favorable photolytic evolution of the reaction was observed between 320 and 380 nm, as depicted for **5b** (Figure 1b).

The photochemical properties of compounds **4a**, **5b**, **8a**, and **8b** are summarized in Table 2. The quantum yields for the photoconversion of these compounds were very high: up to 0.7 for the NPT-substituted derivatives, and also above 0.4 for the DMNPT derivatives. The *o*-nitroveratryl group has been tested as a photoremovable protecting group on numerous biomolecules as a chromophoric substitute for the weakly absorbing *o*-nitrobenzyl derivatives at $\lambda > 300$ nm. In most cases this modification led to a dramatic decrease in the photolytic quantum yield. To our knowledge the highest value

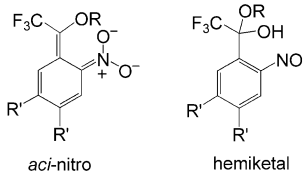
Table 2: Photofragmentation parameters of NPT (**4a**, **8a**) and DMNPT (**5b**, **8b**) ether derivatives.[a]

Compound	k [s^{-1}] (*aci*-nitro decay)	ϕ
4a	$k_1 = 3.2\times10^5$, $k_2 = 1.4\times10^4$	0.70
5b		0.43
8a		0.62
8b		0.52

[a] All details for the determination of the *aci*-nitro decay can be found in reference [9]. The determination of the quantum yield for the photoconversion of compounds **4a**, **5b**, **8a**, and **8b** is described in the Experimental Section.

was described for a DMNPE–NAD (1-(4,5-dimethoxy-2-nitrophenyl)diazoethyl β-nicotinamide adenine dinucleotide) analogue[23] ($\Phi = 0.19$), whereas 4,5-dimethoxy-2-nitrobenzyl ether derivatives displayed values as low as 0.006.[24] We have no explanation for these discrepancies, but with the observed high quantum yields together with the favorable evolution of the photolytic reaction above 320 nm, the DMNPT caging group demonstrated unprecedented photolytic efficiencies at these wavelengths. With such photolytic properties, DMNPT ethers should find application in biphoton excitation processes.

The rate-limiting step of the photolytic reaction is presumably the fragmentation of the nitroso hemiketal intermediate,[11] rather than the decay of the *aci*-nitro intermediate (Scheme 3). Rate constants of $3.2\times10^5\ s^{-1}$ and



Scheme 3. Postulated intermediates in the photofragmentation reaction of NPT (R′ = H) and DMNPT (R′ = OCH_3) ether derivatives.

$1.4\times10^4\ s^{-1}$ at pH 7.2 were determined for the decay of the *aci*-nitro intermediate derived from compound **4a** (Table 2). Preliminary results indicate that the formation of the nitroso hemiketal intermediate (Scheme 3) is fast (sub-millisecond time range), which suggests that the final release of the alcohol together with the formation of the trifluoromethyl ketone derivative is rate-limiting. Partial deprotonation of the hemiketal intermediate at neutral pH (a value of 9.1[25] has been reported for the pK_a of related hemiketals) could accelerate such a decomposition process. The details of the kinetics of the photochemical decomposition of such *o*-nitrobenzyl ether derivatives are currently under investigation.[26]

NPT and DMNPT ether derivatives are stable and efficient photoremovable alcohol-protecting groups. As in the case of related nitrobenzyl alcohol-protecting groups, the NPT or DMNPT caging groups are not suitable for the investigation of fast biological processes. Nevertheless, the use of NPT and DMNPT caging groups might be extended to the masking of other chemical functional groups, such as

carboxylic and phosphoric acids, for which a faster release is expected.[11b] The caging of relevant neurotransmitters and second messengers is presently under investigation.

Experimental Section

General procedure for Mitsunobu coupling: A mixture of triphenylphosphane/diisopropyl azodicarboxylate (DIAD) or tributylphosphane/tetramethyl azodicarboxamide (TMAD) (1:1, 1.5 equiv) was added as a solution in benzene to a solution in benzene of **1a** or **1b** (1 equiv) and benzyl alcohol or 2-bromoethanol (1.2–2 equiv). The resulting mixture was stirred under an argon atmosphere (see Table 1 for reaction conditions). The solvent was removed after the time indicated, and the crude product was purified by flash chromatography or reversed-phase HPLC.

1a: ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 4.51$ (br s, 1H), 6.16 (q, $^3J(H,F) = 6.0$ Hz, 1H), 7.57–7.62 (m, 1H), 7.68–7.77 (m, 1H), 7.98 (d, $^3J(H,H) = 7.9$ Hz, 1H), 8.01 ppm (dd, $^3J(H,H) = 9.0$ Hz, $^4J(H,H) = 1.1$ Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 67.0$ (q, $^2J(C,F) = 33$ Hz), 124.3 (q, $^1J(C,F) = 283$ Hz), 125.3, 129.6, 129.9, 130.5, 133.9, 148.9 ppm.

1b: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 3.99$ (s, 3H), 4.03 (s, 3H), 6.32–6.38 (m, 1H), 7.36 (s, 1H), 7.66 ppm (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 56.7$, 56.9, 66.7 (q, $^2J(C,F) = 32$ Hz), 108.4, 110.9, 122.8 (q, $^1J(C,F) = 210$ Hz), 127.4, 141.3, 149.4, 153.7 ppm.

2a: ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 4.67$ (d, $^3J(H,H) = 11.4$ Hz, 1H), 4.72 (d, $^3J(H,H) = 11.4$ Hz, 1H), 5.94 (q, $^3J(H,F) = 3.0$ Hz, 1H), 7.30–7.42 (m, 5H), 7.56–7.63 (m, 1H), 7.74 (dd, $^3J(H,H) = 7.9$ Hz, $^3J(H,H) = 7.5$ Hz, 1H), 7.99 (d, $^3J(H,H) = 7.9$ Hz, 1H), 8.03 ppm (d, $^3J(H,H) = 8.3$ Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 73.4$ (q, $^2J(C,F) = 32$ Hz), 73.5, 123.9 (q, $^1J(C,F) = 281$ Hz), 125.3, 128.5, 128.9, 129.0, 130.4, 130.7, 133.9, 136.3, 149.7 ppm.

4a: ^{1}H NMR (300 MHz, CD_3CN, 25 °C, TMS): $\delta = 3.16$ (s, 9H), 3.55–3.67 (m, 2H), 4.00–4.14 (m, 2H), 5.99 (q, $^3J(H,F) = 9.6$ Hz, 1H), 7.78 (m, 1H), 7.86–7.95 (m, 2H), 8.18 ppm (d, $^3J(H,H) = 9.0$ Hz, 1H).

5b: ^{1}H NMR (300 MHz, CD_3CN, 25 °C, TMS): $\delta = 2.30$ (s, 9H), 2.71–2.79 (m, 2H), 3.88–4.01 (m, 2H), 3.93 (s, 3H), 3.98 (s, 3H), 6.03 (q, $^3J(H,F) = 6.1$ Hz, 1H), 7.18 (s, 1H), 7.72 ppm (s, 1H); ^{13}C NMR (300 MHz, CD_3CN, 25 °C, TMS): $\delta = 8.4$, 26.3, 56.6, 56.9, 65.1, 74.2 (q, $^2J(C,F) = 31$ Hz), 109.9, 110.4, 124.9 (q, $^1J(C,F) = 281$ Hz), 142.1, 150.2, 154.2 ppm.

6: ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 2.07$ (s, 3H), 2.13 (s, 3H), 2.15 (s, 3H), 2.31 (s, 3H), 3.05 (d, $^3J(H,H) = 5.4$ Hz, 1H), 3.63 (td, $^3J(H,H) = 5.4$ Hz, $^3J(H,H) = 9.3$ Hz, 1H), 3.98 (m, 1H), 4.19–4.54 (m, 2H), 4.98 (dd, $^3J(H,H) = 3.7$ Hz, $^3J(H,H) = 10.3$ Hz, 1H), 5.54 (t, $^3J(H,H) = 9.0$ Hz, 1H), 5.65 (d, $^3J(H,H) = 3.4$ Hz, 1H), 6.97 (d, $^3J(H,H) = 8.8$ Hz, 2H), 7.10 ppm (d, $^3J(H,H) = 8.8$ Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 21.1$, 21.2, 21.3, 21.4, 69.6, 70.7, 70.8, 73.1, 86.9, 95.1, 117.0, 130.4, 132.8, 154.1, 170.8 ppm.

8a: ^{1}H NMR (300 MHz, CD_3OD, 25 °C, TMS): $\delta = 2.27$ (s, 3H), 3.01–4.07 (m, 6H), 5.26 (d, $^3J(H,H) = 3.4$ Hz, 0.5H), 5.40 (d, $^3J(H,H) = 3.4$ Hz, 0.5H), 5.83 (q, $^3J(H,F) = 6.0$ Hz, 0.5H), 6.02 (q, $^3J(H,F) = 6.1$ Hz, 0.5H), 6.96–7.10 (m, 4H), 7.67 (m, 1H), 7.76 (dd, $^3J(H,H) = 6.6$ Hz, $^3J(H,H) = 7.0$ Hz, 1H), 7.86 (m, 1H), 8.05 ppm (d, $^3J(H,H) = 8.3$ Hz, 1H).

8b: ^{1}H NMR (300 MHz, CD_3OD, 25 °C, TMS): $\delta = 2.30$ (s, 3H), 3.15–4.53 (m, 6H), 3.95 (s, 3H), 3.99 (s, 3H), 5.49 (d, $^3J(H,H) = 3.6$ Hz, 1H), 6.20 (d, $^3J(H,F) = 6.4$ Hz, 1H), 7.04–7.12 (m, 4H), 7.47 (s, 1H), 7.70 ppm (s, 1H).

The quantum yields for the photoconversion of compounds **4a**, **5b**, **8a**, and **8b** were determined by comparison with the photolysis of 1-(2-nitrophenyl)ethyl choline[9] ($\phi = 0.27$) or 1-(2-nitrophenyl)ethyl arsenocholine[16] ($\phi = 0.26$), which were taken as references in a phosphate buffer (0.1 M, pH 7.2) at 25 °C. Identical absorbances for the reference and the compound tested were used during the photolyses. For the NPT derivatives concentrations of 1 mM were used for both **4a** or **8a** and the 1-(2-nitrophenyl)ethyl (NPE) ether reference (identical extinction coefficients at 364 nm), whereas for the DMNPT ether derivatives a mixture of 0.1 mM of **5b** or **8b** and 1 mM of the NPE ether reference was used. The mixtures of substrate and reference were photolyzed by continuous irradiation at 364 nm, and aliquots were subjected to reversed-phase HPLC to determine the extent of the photolytic conversions. HPLC analysis was carried out on a Zorbax C18 column (4.6 × 250 nm); elution was performed at a flow rate of 1 mL min^{-1} with a linear gradient of acetonitrile in an aqueous solution of TFA (0.1 %) from 0 to 100 % (v/v) over 30 min. The retention times for **4a**, **5b**, **8a**, **8b**, (*o*-nitroso)trifluoroacetophenone, and (4,5-dimethoxy-1-nitroso)trifluoroacetophenone were 20.7, 22.4, 25.7, 24.9, 22.5, and 21.2 min, respectively. Quantum yields were estimated by considering the conversions at ≤ 30 % to limit errors due to undesired light absorption during photolysis as much as possible.

Received: November 4, 2003 [Z53247]

Keywords: caging groups · Mitsunobu reaction · photochemistry · photolysis · protecting groups

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