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The 9-xanthenylmethyl group: a novel photocleavable protecting group for amines

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Abstract—The 9-xanthenylmethyl group has been investigated as a photocleavable protecting group for amines. Several amines, including two amino acids, were protected in good to very good yield. Irradiation of the protected substrates in neutral solution regenerated the starting amines in good to excellent yield.

Photolabile protecting groups have led to recent advances in areas and technologies as varied as organic synthesis,[1] photolabile calcium chelators,[2] photoactive precursors of neurotransmitters[3] and time-resolved studies in disciplines ranging from cell biology[4,5] to X-ray crystallography.[6] Photoremovable protecting groups are also key to the novel techniques of light-directed synthesis, whereby the preparation of large arrays consisting of thousands of biopolymer sequences can be accomplished.[7] To advance this new technique, several photodeprotecting groups for alcohols have been developed.[8–11] However, there is still a need to develop a viable photocleavable protecting group for amines. Photoremovable protecting groups currently in use for amines employ carbamate chemistry, notably with nitrobenzyl moieties.[12] However, limitations of the *o*-nitrobenzylic system include complications due to the production of a nitrosocarbonyl byproduct, and the necessity for an acid or other scavenger in order to achieve high yields for deprotection.[13,14] More recently, dimethoxybenzoin carbamate has been developed as a photolabile protecting group for secondary amines.[15–17] It offers the advantage over nitrobenzyl carbamates of the formation of an inert byproduct, but it is not effective for primary amines or amino acids. Other substituted benzoins have also been investigated.[18]

One literature report noted that the 9-xanthenylmethyl group served as a base-sensitive protecting group for amines.[19] This group was very stable to trifluoroacetic acid and catalytic hydrogenolysis, both common thermal deprotection conditions for other protecting groups in peptide synthesis. The photochemical properties of substrates containing the 9-xanthenyl backbone have been studied previously in our research group, and we have developed the 9-phenylxanthyl (pixyl) and 9-phenylthioxanthyl (*S*-pixyl) photocleavable protecting groups for primary alcohols.[8,9] These studies suggested to us that we consider the 9-xanthenylmethyl moiety as a potential photolabile protecting group for amines.

In order to investigate the 9-xanthenylmethyl moiety as a potential photolabile protecting group for amines, five primary amines, **4a–e** (Table 1) were chosen as test substrates. Amines **4a–c** were protected by reaction with 9-xanthenylmethyl phenylcarbonate **3a** to yield carbamates **5a–c**, respectively, while substrates **4d–e** were reacted with 9-xanthenylmethyl *p*-nitrophenylcarbonate **3b** to yield **5d–e** (Scheme 1). Each of the derivatives was isolated as a pure white crystalline solid following column chromatography with an eluant of hexane:ethyl acetate. Compounds **5a–e** were characterized by melting point, ^{1}H and ^{13}C NMR and FT-IR.[20] The yields for formation of the protected amines are shown in Table 1.

Table 1. Amine protection and deprotection yields

Substrates	Protection yields[a]	Deprotection yields[b]
4a cyclohexylamine	81	90
4b benzylamine	68	72
4c phenethylamine	77	79
4d phenylalanine	62	52
4e glycine benzyl ester	84	65

[a] Isolated yield after column chromatography (hexane:ethyl acetate on silica).

[b] Photolysis conditions: 300 nm, 5°C. Deprotection yields for **5a–c** were analyzed by GC. Deprotection yields for **5d** and **5e** were analyzed by HPLC.

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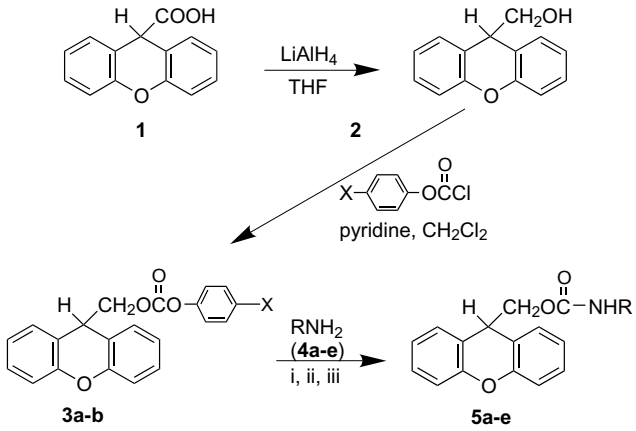

Scheme 1. **3a**: X = H, **3b**: X = NO_2. **5a–c**: i = DMF, **5d**: ii = Na_2CO_3/THF, **5e**: iii = TEA/THF.

Photochemical deprotection was accomplished by irradiation of **5a–e** in neutral aqueous acetonitrile using low pressure 300 nm mercury lamps and quartz photolysis tubes in a Rayonet photolysis chamber. Analysis of the photolysis solution by GC or HPLC showed recovery of the substrate amines. Parallel dark reactions were conducted for all experiments and demonstrated that there was no thermal reaction under the photolysis conditions.

Experiments were conducted in order to determine both the best possible solvent system and irradiation time to optimize the deprotection yield. When the solvent system was varied from 10:90 to 50:50 water:acetonitrile, an optimum deprotection yield for amine recovery was obtained using a solvent system of 40:60 water:acetonitrile for substrates **5a–c**. A solvent system of 50:50 water:acetonitrile was used for substrates **5d** and **5e**. Higher percentages of water resulted in solubility problems for some of the substrates. Reaction conditions were also optimized by varying times of irradiation. Optimum deprotection times varied from 80 to 150 min. Longer irradiation times resulted in decreased deprotection yields due to secondary photoreactions. The deprotection yields are summarized in Table 1. Very good to excellent yields were obtained for **5a–c**, demonstrating the utility of the 9-phenylxanthenyl carbamate moiety as a photolabile protecting group for primary amines. However, lower yields were obtained for **5d** and **5e**. We were unable to obtain higher yields for the deprotection due to a secondary photochemical reaction between the amines and xanthone, a byproduct of the irradiation. This secondary reaction was particularly problematic for the selected amino acid substrates. In addition, both substrates **5d** and **5e** contain γ-benzylic hydrogens, which may be abstracted by the carbonate carbonyl resulting in additional side reactions. Higher yields may be expected with other amino acid substrates.

In summary, the 9-xanthenylmethyl moiety is a useful photoremovable protecting group for selected primary amines.

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20. The following synthesis is representative for **5a–c**: 9-Xanthylmethyl phenylcarbonate **3a**[19] (0.32 mmol, 0.11 g) was dissolved in 1.5 mL DMF at 50°C. Cyclohexylamine (0.35 mmol, 0.040 mL) was dissolved in 0.5 mL DMF, and added to the 9-xanthylmethyl phenylcarbonate solution. The reaction mixture was stirred overnight at 50°C. Ethyl ether (10 mL) and water (10 mL) were added to the reaction mixture. The aqueous layer was washed with ether (2×10 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo to give a white solid. Recrystallization from hexane:ethyl acetate (95:5) gave 0.078 g (72%). Mp 135–

137°C IR: 3328 cm^{-1} (N-H), 1689 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ 1.10–1.90 (m, 10H), 3.85 (m, 1H), 4.16 (d, 2H), 4.25 (t, 1H), 4.55 (d, 1H), 7.05–7.30 (m, 8H). ^{13}C NMR δ 24.80, 25.44, 33.34, 49.81, 39.08, 69.55, 116.45, 121.67, 123.13, 128.25, 129.27, 152.19, 155.29. **5b**: mp 81–83°C. IR: 1712 cm^{-1} (C=O), 3334 cm^{-1} (-NH-). ^1H NMR ($CDCl_3$) δ 4.30 (m, 5H), 5.0 (s, 1H), 7.08–7.30 (m, 13H). ^{13}C NMR δ 39.07, 45.02, 69.97, 116.51, 121.53, 123.17, 127.31, 127.36, 127.49, 128.31, 128.65, 129.23, 138.20, 152.23, 156.16. **5c**: mp 87–89°C. IR: 1710 cm^{-1} (C=O), 3328 cm^{-1} (-NH-). ^1H NMR ($CDCl_3$) δ 2.78 (t, 2H), 3.40 (q, 2H), 4.22 (m, 3H), 4.72 (s, 1H), 7.08–7.30 (m, 13H). ^{13}C NMR δ 39.045 (CH), 69.737 (CH_2), 36.132, 42.117 (CH_2CH_2), 116.48, 121.56, 123.14, 126.49, 128.29, 128.60, 128.77, 129.28, 138.71, 152.17, 156.02).

9-Xanthenylmethoxycarbonyl-L-phenylalanine **5d**. L-Phenylalanine (0.08 g, 0.49 mmol) was dissolved in 4.0 mL aqueous Na_2CO_3, and stirred at room temperature for 10 min. 9-Xanthylmethyl *p*-nitrophenylcarbonate **3b** (0.21 g, 0.55 mmol) was dissolved in 6.0 mL freshly distilled THF, and was added dropwise into the L-phenylalanine solution. The reaction mixture was stirred at room temperature for 5.5 h when TLC indicated no more 9-xanthylmethyl *p*-nitrophenylcarbonate remained. The THF was removed in vacuo. The reaction mixture was poured into 20 mL H_2O, and extracted with ether (2×20 mL). The aqueous layer was acidified with 6 M HCl to pH 2, and kept in the refrigerator overnight followed by extraction with ethyl acetate (3×20 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The remaining mixture was chromatographed on silica gel to give 0.11 g (56%) white solid. Mp 141–143°C (lit. mp 143–145°C).[19] IR: 1716 cm^{-1} (C=O), 3328 cm^{-1} (OH), 3405 cm^{-1} (NH). ^1H NMR ($CDCl_3$) δ 3.04–3.18 (m, 2H), 4.08–4.24 (m, 3H), 4.64 (dd, 1H), 5.10 (d, 1H), 7.01–7.32 (m, 13H). ^{13}C NMR δ 837.75, 38.95, 54.45, 70.08, 116.55, 121.28, 121.35, 123.22, 127.27, 128.40, 128.68, 129.29, 135.45, 152.17, 155.56, 175.77.

9-Xanthenylmethoxycarbonyl glycine benzyl ester **5e**. Glycine benzyl ester *p*-toluenesulfonate salt (0.21 g, 0.61 mmol) was dissolved in 6.0 mL THF, 400 μl triethyl amine was added, and stirred until the solution turned to clear. 9-Xanthylmethyl *p*-nitrophenylcarbonate **3b** (0.23 g, 0.60 mmol) was dissolved in 6.0 mL freshly distilled THF, and was added dropwise into the above solution. The reaction mixture was stirred at room temperature overnight, when TLC indicated no more 9-xanthylmethyl *p*-nitrophenylcarbonate remained. The THF was evaporated in vacuo, the remaining mixture was chromatographed on silica gel with 3:1 hexane:ethyl acetate to give 0.20 g (85%) of a white solid. Mp 82.5–84.5°C. ^1H NMR δ 3.94 (d, 2H), 4.16 (d, 2H), 4.26 (t, 1H), 5.16 (s, 1H), 5.25 (s, 1H), 7.00–7.34 (m, 13H). ^{13}C NMR δ 38.89, 42.70, 67.14, 70.13, 116.46, 121.38, 123.16, 128.31, 128.32, 128.49, 128.58, 129.29, 135.08, 152.10, 155.99, 169.76.