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Approaches to a photocleavable protecting group for alcohols

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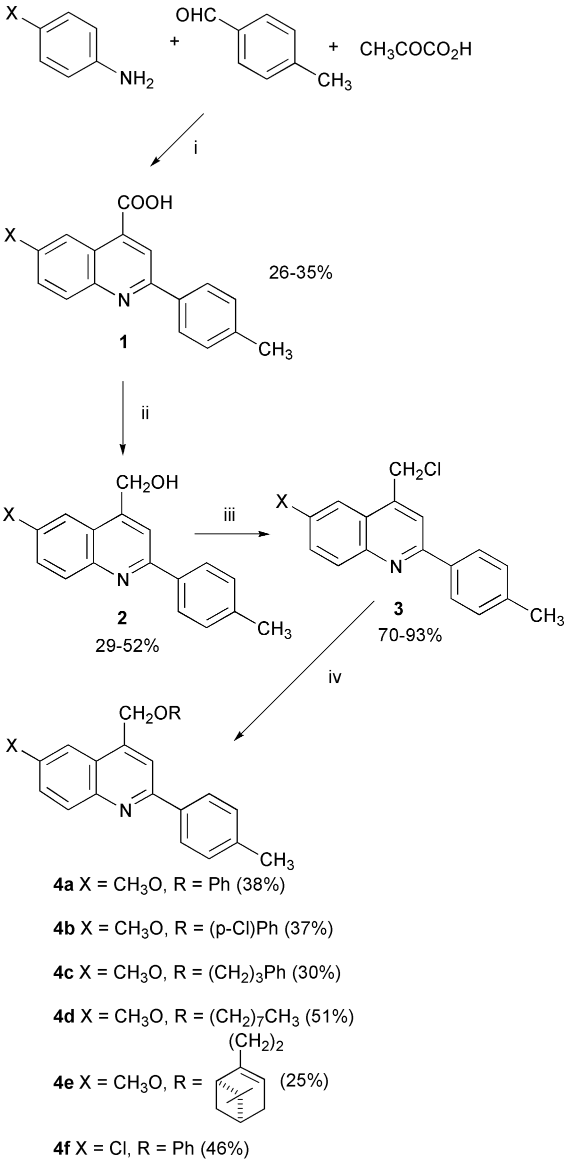
A new protecting group for the alcohol functionality was devised and shown to be removed photochemically under ultraviolet light in the presence of a radical scavenger in high yields.

A protecting group is frequently introduced into a molecule during a multistep synthesis to prevent a certain functional group from reacting while a chemical reaction is performed selectively on another site of the molecule.[1] One useful protecting group for a hydroxy group is the benzyl ether group. The benzyl ether linkage has high stability, but this stability also means that deprotection is difficult. Existing cleavage methods[2] include chemical,[3–7] electrochemical,[8,9] and photochemical[10–12] methods. Chemical methods usually involve strong reducing conditions, while photochemical methods may be slow and complicated by accompanying photodegradation of the protected fragment. A strongly absorbing aryl group might minimize undesired photoreactions, and our observation of facile photocleavage of the phenyl quinolinyl group suggested it might be easily reacted photochemically. It has a strong absorption in the near ultraviolet (*e.g.* $\varepsilon = 22\,400$ at $\lambda_{max} = 347$ nm for compound **4e**). This group was utilized as a photochemically removable protecting group for amines *via* a sulfonamide photocleavage, which sets the precedent for its use with alcohols.[13]

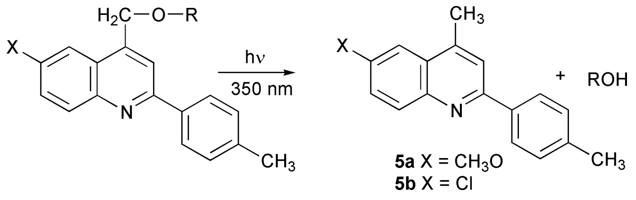
A practical three-step synthesis of candidate quinoline compounds (**4a–4f**) with electron withdrawing or electron supplying substituents utilized a Doebner condensation to give the phenyl quinolinyl carboxylic acid, which was reduced and treated with thionyl chloride. The general synthetic pathway to this protecting reagent is shown in Scheme 1. Ether formation with alcohols to be protected proceeded smoothly under the usual conditions.[14] It is noted that previous studies reported successful synthetic pathways to quinoline methanols (compound **2**, Scheme 1).[15,16]

A family of compounds was prepared to test whether photocleavage of this group would proceed with ultraviolet light (350 nm) in good yields. The alcohols examined included one compound (**4e**), which would likely be destroyed under strong oxidizing or reducing conditions. Scheme 2 and Table 1 summarize the results from photocleavage of the quinolinyl methyl ethers. The only quinoline product detected after the photocleavage of the protected alcohol was **5a** (or **5b**), while the yields of deprotected alcohols were excellent.

Photoreactions of substrates **4a–4f** in quantities of 50 mg or 500 mg were studied. All irradiations were performed in a 100 ml pyrex tube, under nitrogen gas, and the required reaction time was observed to range from 15 minutes (for a 50 mg photoreaction) to 24 h (for a 500 mg photoreaction). A Rayonet preparative photoreactor (model # RPR-208) was used as the light source. The solvent used for all photoreactions was propan-2-ol. We observed that the reactions were reasonably fast and 100% conversion was achieved in short irradiation times, in small-scale reactions. In some cases we observed that the product might be partially destroyed, particularly in the



Scheme 1 *Reagents and conditions*: i, absolute ethanol, reflux, 36 h; ii, LAH, THF, 20 h; iii, SOCl$_2$, 2 h; iv, ROH, NaOH, DMF, 3 h.



Scheme 2 Photocleavage of the protected alcohol under UV light (350 nm).

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† Deceased (September 9, 2001). This paper is dedicated to his memory.

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Table 1 Photocleavage of protected alcohols under UV light (350nm)[a]

Entry	Substrate	Concentration/mmol	*t*/min[b]	Scavenger[c]	Conversion (%)	Yield (%)
1	**4a**	0.141	30	None	65	60
2	**4a**	0.141	30	Dodecanethiol	100	42
3	**4a**	0.141	60	None	100	83
4	**4a**	0.141	20	Dodecanethiol	100	85
5	**4a**	0.141	15	Dodecanethiol	98	92
6	**4a**	1.410	600	D-Sorbitol	100	92
7	**4b**	0.128	40	None	33	25
8	**4b**	0.128	90	None	100	78
9	**4b**	0.128	40	D-Sorbitol	100	93
10	**4c**	0.126	180	D-Sorbitol	99	85
11	**4d**	0.127	180	D-Sorbitol	97	82
12	**4e**	1.170	1440	D-Sorbitol	100	88
13	**4f**	0.139	50	None	65	57
14	**4f**	0.139	90	None	100	79

[a] All reactions were carried out under nitrogen gas, in a 100 ml pyrex tube and propan-2-ol as a solvent. [b] Irradiation time in minutes. [c] 0.50% w/v dodecanethiol, 0.18% w/v D-Sorbitol.

latter stages of the photochemical reaction, which suggested the addition of a radical scavenger might improve the overall yield. Dodecanethiol and sorbitol were effective in achieving improved yields, as shown by entries 5 and 9 of Table 1. The larger scale reactions of **4a** and **4e** gave excellent yields when 0.18% w/v D-sorbitol was present. Chloro-substituted phenyl quinoline **4f** reacted more slowly than **4a**, where an electron-supplying methoxy group seemed to promote a faster cleavage. This consideration led to the initial design of a phenyl quinoline system bearing electron-supplying substituents. Table 1 summarizes the results obtained after irradiation of various protected alcohols under different reaction conditions.

In conclusion, ultraviolet photochemical cleavage of quinolinyl methyl ethers in the presence of a radical scavenger gave promising results.

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