A NEW PHOTOCHEMICALLY REMOVABLE PROTECTING GROUP FOR AMINES

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Summary A new arylmethylsulfonyl chloride reacts with secondary or primary amines to give sulfonamides which can be photochemically cleaved, making it suitable for use as a photoremovable protecting group

The nucleophilicity of an amine frequently requires it to be "protected" during a multistep synthesis. Several protecting groups have been explored, including carbamates, amides, and N-benzyl derivatives.¹ Electrochemical² or photochemical³ cleavage offers a potential advantage in allowing other protecting groups to remain untouched during deprotection. Pincock³ generally observed good yields with aliphatic amines, but amines bearing a chromophore, such as aniline, could not be deprotected in high yield, apparently because of secondary photochemical reactions.

Our observation⁴ of facile fragmentation of 2-aryl-4-quinoline compounds suggested replacement of this chromophore for phenyl, since such compounds would have a long wavelength of absorption (λ_{max} ca 360 nm, with an ε of about 50,000) and also be capable of fragmenting efficiently, despite the low energy of the excited state. We have found that sulfonyl chloride 1 produces sulfonamides in reasonable yields, and that photochemical deprotection generally proceeds in high yields even when the amine is complex. The use of this reagent is particularly advantageous for protection of biologically important amines such as guanine, adenine, and cytosine ⁵

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Typically, the sulfonamides (2) were prepared by reacting an equimolar amount of 1 with an amine in 2-propanol at 60° for 1-5 hr. Upon cooling the sulfonamides would crystallize, in yields of about 70%

Photochemical deprotection was accomplished by irradiation of a 2-propanol solution of the purified sulfonamide in a Rayonet chamber reactor equipped with 350 nm lamps. Solutions were purged with nitrogen 20 min prior to and during irradiation. Irradiation was continued until tlc analysis showed the sulfonamide to be completely reacted (15 to 150 min for the amines studied). Table 1 gives isolated yields. The isolation procedure varied from case to case, but generally involved extraction and/or crystallization of the product amine. Products were characterized by nmr, ir, uv, and/or melting point.



1,6-Hexanedıamıne	H ₂ N (CH ₂) ₆ NH ₂	32 %
Anılıne	- NH2	58
Dıphenylamıne	(C ₆ H ₅) ₂ NH	43
n-Octylamıne	CH ₃ (CH ₂), NH ₂	91
Dı-n-hexylamıne	$\left[CH_{3}(CH_{2})_{5}\right]_{2}NH$	96
Guanine		9 5
Adenine		96
Cytosine		94

Table 1 Yields of Amines from Photochemical Deprotection of Sulfonamides

The key sulfonyl chloride, 1, was prepared in two ways The preferred route is outlined below A Doebner condensation of p-tolualdehyde, p-anisidine, and pyruvic acid in refluxing ethanol for 60 hr gave acid 5, mp 243-243 5°, in 26% yield Reduction of 5 with LiAlH₄ in dry THF at room temperature gave alcohol 6, mp 121-122, in 49% yield Alcohol 6 gave an nmr absorption at δ 4 9 (CDCl₃/dmso-d₆) for the Ar-CH₂ signal Reaction of 6 in excess thionyl chloride for 2 hr, followed by quenching with 99% formic acid gave chloride 7, mp 217-9° in 95% yield, which gave a proton absorption at δ 5 35 for the Ar-CH₂ A solution of 7 and thiourea in ethanol at reflux for 2 hr gave amidine 8, mp 249-250° in 72% yield Chlorinolysis⁶ of the amidine by treatment of an aqueous solution at 10° with chlorine gas for 30-40 min led to precipitation of the sulfonyl chloride, mp 164° (d) in 75% yield Mmr (CDCl₃/dmso-d₆) δ 5 1 (2H, sing), 3 9 (3H, sing), and aromatic absorption at 6 9-3 0 (8H, mult)



ACKNOVLEDGMENT We are grateful to the National Institutes of Health (AI12200) for financial support of this work

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(Received in USA 13 May 1982)