Tetrahedron Letters No.5, pp. 345-348, 1970. Pergamon Press. Printed in Great Britain.

THE PROTECTION AND MONOALKYLATION OF AMINES

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(Received in USA 15 December 1969; received in UK for publication 29 December 1969)

Two fundamental problems commonly occur in synthetic work with complex amines: (a) the need for a protecting group to vitiate the nucleophilicity of the amino nitrogen; and (b) the need for a reliable method to monoalkylate ammonia and primary amines. The protecting group should be attached in high yield, be resistant to acidic or basic hydrolysis and to oxidation and be easily removed, preferably by special reaction conditions unlikely to be utilized for other synthetic reactions performed on the protected molecule. The sulfonamide group normally fulfills all these conditions except that of easy removal. Furthermore, sulfonamides of primary amines confer sufficient acidity on the remaining amino hydrogen to allow for facile alkylation that cannot proceed past monoalkylation. To couple these two synthetic problems, then, we needed to devise a sulfonamide which is readily desulfonated.

The reductive removal of hetero-substituents α- to ketones (1) seemed likely to succeed also with α-sulfonyl groups since the stable sulfinate anion would be the leaving group in question. Accordingly, we required for amino protection a sulfonamide α- to a ketone which on reduction would yield an N-sulfinate which would in turn readily yield SO_2 and the free amine.

The following scheme embodies the double utility of the idea for protection and monoalkylation of amines.

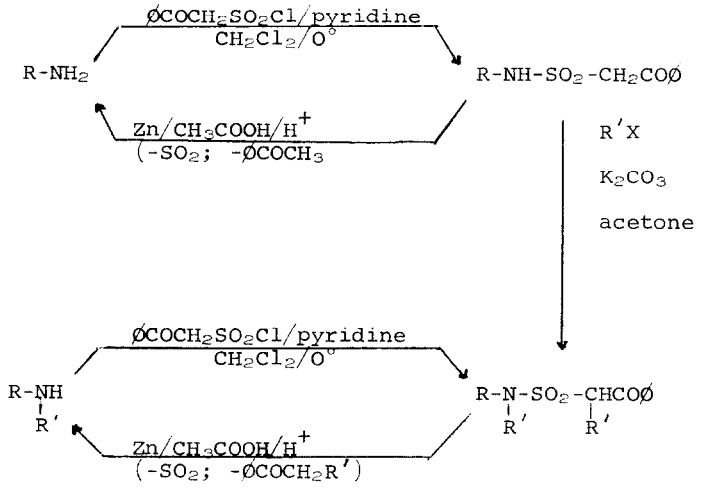

Table (3)

Amine	Aniline		Cyclohexylamine	n-Butylamine
$RNHSO_2CH_2COC_6H_5$ m.p.	110-111° C		139-140° C	97-99° C
yield	94%		91%	92%
Zinc regeneration [a] yield	72%		67%	66%
Alkylation [b] by R'	CH_3	$C_6H_5CH_2$	CH_3	CH_3
m.p.	101-102	151-153° C	106-107	Oil
yield	93%	94%	80%	78%
Zinc regeneration of amine [a]; yield	N-methylaniline 78%		N-methyl-cyclohexyl-amine --	N-methyl-n-butylamine 75%
	N-benzylaniline 98%			

a) amine isolated as hydrochloride from ether

b) agents = CH_3I, $C_6H_5CH_2Br$

In detail, the scheme works very well, as exemplified by the results shown in the Table. No effort was made to find conditions optimizing yields so that these may possibly be improved. Phenacylsulfonyl chloride (2) behaves as an ordinary sulfonyl chloride, sulfonating amines readily at ice temperature in methylene chloride containing pyridine (commonly left for several hours after slow addition of sulfonyl chloride to the amines). Like other sulfonamides, the N-phenacylsulfonyl derivatives are high-melting and generally crystallize well. Their alkylation proceeds normally with dry potassium carbonate in acetone at room temperature for 18-24 hours.

A typical procedure for removal of the phenacyl group consists in adding a several-fold molar excess of zinc dust to a room-temperature stirred solution of phenacylsulfonamide in acetic acid with a catalytic amount of concentrated HCl over a ten-minute interval, stirring for another hour, filtering and washing the zinc residues, and partitioning the filtrate.

Monoalkylation of the methylene always occurred in our examples, apparently even faster than N-alkylation. With simple alkylating agents this offers no problem in the scheme as used; with more complex alkylating agents this waste of reagent may presumably be stopped by the use of propiophenone-α-sulfonyl chloride, currently under study. The scheme suggests a new variant of the Gabriel synthesis of primary amines by alkylating phenacylsulfonamide itself, as well as C-alkylation α- to ketones, and studies of these reactions are underway.

The use of phenacylsulfonyl for protection of other groups such as phenols, enols, alcohols and mercaptans has not yet been explored but seems a reasonable extention, although likely of little value in most cases for alcohols and superfluous for phenols in view of the ease of phenacyl protection in such cases.(1)

Acknowledgement

We wish to thank the National Science Foundation (grant GP-5525) for support of this work.

References

1. For a similar use of this well-known reduction: J. B. Hendrickson and Carol Kandall, preceding communication.

2. William E. Truce and Calvin W. Vriesen, J. Am. Chem. Soc., 75, 2525 (1953). The solid chloride (m.p. 88°) is apparently indefinitely stable on the shelf and, contrary to this previous report, affords acceptable analyses.

3. All derivatives afforded the expected IR, NMR and mass spectra.