

THE PHENACYL PROTECTING GROUP FOR ACIDS AND PHENOLS

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Among the criteria for a useful protecting group are the ease and selectivity of its formation as well as its release on demand. The latter condition is especially met when the release reagent is one not commonly encountered in other normal synthetic operations and does not affect other functional groups. Woodward's protection of carboxylic acids as β -trichloroethyl esters, with release by zinc, is a notable example.(1) We wish to offer the phenacyl group ($C_6H_5COCH_2-$)(2) as an alternative which is removed with great facility at room temperature by zinc in glacial or dilute aqueous acetic acid. By contrast to the trichloroethyl esters, phenacyl esters can be made easily under conditions which do not involve attack on the carboxyl carbonyl, since they are formed by S_N2 attack of carboxylate anion on phenacyl bromide.(3) Similarly, phenols may also be protected as ethers by the phenacyl group with equally facile removal.

Protection of simple alcohols as phenacyl ethers was found to be unsatisfactory using *w*-diazoacetophenone/boron trifluoride with cholesterol as a model, and reactions of the alcohol with phenacyl bromide, potassium iodide and dry potassium carbonate in refluxing acetone or acetonitrile resulted mainly in recovery of the alcohol and destruction of the reagent.

Table

Acid or phenol	p-Bromophenacyl Derivative yield		Derivative m.p. (lit.)	Recovery from zinc	
	crude	recryst.		crude	recryst.
Anisic acid	97%	89%	152-3° (152°)	100%	89%
Cinnamic acid	94	a	147-8° (145°)	97	89
Succinic acid	81	a	213-4° (211°)	--	94
β -Naphthol	94	a	120-1° b	92	a
p-Hydroxybenzaldehyde	98	86	103-4° b	98	88
sym-Tribromophenol	94	a	180-3° (dec.)b	(104)	96

^a Product required no further purification

^b Previously unknown; identified by nmr and mass spectrum

The phenacylation of carboxylic acids was carried out with equimolar amounts of carboxylate anion and p-bromophenacyl bromide in water(5) or

dimethylformamide.(3) The phenols were alkylated with equimolar phenacyl bromide in refluxing acetone and dry potassium carbonate for 1-2 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 phenacyl ester (or ether) in acetic acid over a ten-minute interval, stirring for another hour, filtering and washing the zinc residues, and partitioning the filtrate in the normal fashion to isolate product acid or phenol. Some results are illustrated in the Table.

We believe the phenacyl group offers useful new latitude in protecting group choice for acids and phenols, and is unique for making available the γ -hydroxyls from γ -lactones for further reaction.(3) Presumably sulfates, sulfonic acids, phosphates and phosphonic acids can be comparably protected, although this has not been demonstrated yet. The phenacyl ethers of phenols were found stable to reflux (two hours) in 1% ethanolic alkali or 5N sulfuric acid (in ethanol-water), but β -naphthol was recovered from its derivative in 82% yield after two hours reflux in 5% ethanolic alkali.

Acknowledgement

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References

1. R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbruggen, J. Am. Chem. Soc., 88, 852 (1966). See also the β -trichloroethyl carbonates and urethans subsequently derived by T. B. Windholz and D. B. R. Johnston, Tetrahedron Letters, 1967, 2555.
2. We have used p-bromophenacyl in practice to afford higher-melting derivatives with clearer (AB) nmr patterns.
3. The special value of this procedure is exemplified in the formation of γ -hydroxy-esters from γ -lactones, which usually cannot be accomplished by trans-esterification procedures. Thus santonin yields p-bromophenacyl santonate in high yield on treatment of sodium santonate with p-bromophenacyl bromide in dimethylformamide, and the lactone (santonin) is regenerated with zinc, also in high yield.(4)
4. Dr. Peter Thieme, unpublished results in our laboratory.
5. R. L. Shriner, R. C. Fuson and D. Y. Curtin "The Systematic Identification of Organic (1) compounds," 4th ed., John Wiley, New York (1956), p. 200.