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SELECTIVE MONO O-ALKYLATION OF γ-RESORCYLIC ESTERS

by

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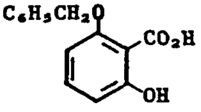
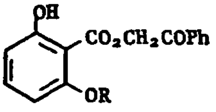
Abstract: The use of diethylazodicarboxylate/triphenylphosphine for the selective mono-O-alkylation of γ-resorcylic esters is described.

No general method has been published for the synthesis of 6-alkoxysalicylic acids. In particular, existing syntheses of 3- and 5-benzyloxysalicylic acids[1,2] were found to be unsuitable for the preparation of the corresponding 6-substituted isomer (1), a compound we required for the synthesis of zearalanone analogues.[3] We now report a method for the synthesis of (1) applicable to a wide range of 6-alkoxy derivatives.



(1)



(2) R=H, (3) $R=CH_2C_6H_5$

Diethylazodicarboxylate has been used in the synthesis of aryl alkyl ethers.[4] The mild, neutral conditions associated with this reagent lead to selective alkylation of resorcylic esters. Phenacylresorcylate[5] (2) in dry tetrahydrofuran containing triphenylphosphine (1.5eq) and benzyl alcohol (1.5eq) at 25°C under an atmosphere of nitrogen was treated with a solution of diethylazodicarboxylate (1.5eq) in dry tetrahydrofuran added dropwise over a period of 2 hours. The solvent was evaporated leaving a gum which was triturated with cold ether to remove insoluble by-products. The ether was then evaporated to give phenacyl 6-benzyloxysalicylate (3) which was recrystallised from isopropyl alcohol (70%, m.p. 119°C). Treatment of (3) with zinc in acetic acid gave the desired acid (1) in 50% overall yield (m.p. 121-2°C, from isopropyl alcohol).

To test the generality of our procedure, a range of alcohols have been employed to alkylate the simpler methyl ester (4). The results are summarised below.

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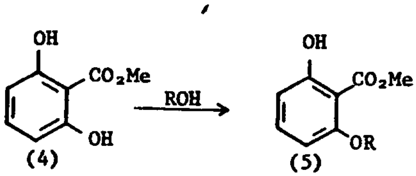
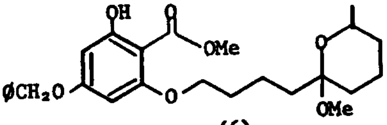


R	Me	Et	iPr	Allyl	benzyl
% yield[a,b]	76	61	55	62	73
m.p. (°C)	40-42	46	-	-	
b.p.(°C, 0.3mm Hg)	-	-	80	65	-

a. correct microanalytical data were obtained for all novel compounds.

b. products obtained as gums were purified by chromatography on Whatman S13 TLC silica followed by distillation using a ball tube oven.

The value of this new procedure was further demonstrated by the preparation in 60% yield of the key intermediate (6) used in the synthesis of a macrocyclic lactone.[3]



(6)

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2. H. Baganz and R. Krattner, Arch. Pharm., 1960, 293, 393.
3. R.J. Bass, B.J. Banks, M.R.G. Leeming and M. Snarey, submitted for publication in J. Chem. Soc., Perkin I.
4. M.S. Manhas, W.H. Hoffman, Bansi Lai, and A.K. Bose, J. Chem. Soc., Perkin I, 1975, 461; S. Bittner and Y. Assaf, Chem. and Ind., 1975, 281.
5. Prepared from phenacylbromide and γ-resorcylic acid using potassium hydrogen carbonate in dry dimethylformamide (80%, m.p. 67°C from methanol).

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