

A NEW SYNTHESIS OF α -HYDROXYCARBOXYLATES AND 2-HYDROXYBENZOATES

*Khalaj, Ali**

Faculty of Pharmacy, Tehran University of Medical Sciences,
P.O.Box 14155-6451, Tehran, I. R. Iran

Aboofazeli, Reza

Faculty of Pharmacy, Shahid Beheshti University of Medical Sciences,
P.O.Box 14155-6153, Tehran, I. R. Iran

ABSTRACT: *A new synthesis of α -hydroxycarboxylates and 2-hydroxybenzoates based on the reaction of acetonides of α -hydroxycarboxylic acids and 2-hydroxybenzoic acid with sodium alkoxides in the corresponding alcohols as solvent is described. In general, decreasing the steric hindrance of the reactants and increasing the boiling points of alcohols increased the yields and decreased the required time for the reactions.*

KEY WORDS: *α -Hydroxycarboxylates, 2-Hydroxybenzoates, Acetonides, Sodium alkoxides.*

The synthesis of alkyl esters of α -hydroxycarboxylic acids and 2-hydroxybenzoic acid is of interest because of their various biological effects such as antispasmodic activities of **3ba-bf** and **3da-dg** [1,2], counterirritant activity, **3ca** [3] and antiacne properties of **3ab** [3].

Although individual preparations of esters **3aa-df** by conventional methods have been described, it seems that the method with general applicability is the reaction of alcohols with acids in the presence of mineral acids [1,2,4]. However, the reaction is reversible and requires either distillation of water or ester or azeotropic removal of water. Furthermore, the reaction with tertiary alcohols usually is accompanied by elimination and results in poor

yields of the impure esters.

In continuation of our interest in the use of acetonides of α -hydroxycarboxylic acids and its successful application for the synthesis of α -hydroxycarboxamides [5], we describe further synthetic applicability of these compounds for a new, simple and general synthesis of esters **3aa-df**.

Reaction of acetonides **1** with equimolar or excess amount of alcohols **2** in the absence of solvent or in aprotic solvents like benzene or toluene were unsuccessful. However, fair to good yields of esters **3** were obtained by the reaction of acetonides **1** with three equimolar of sodium salts of alcohols **2** in the corresponding alcohols as solvent. The use of only one equimolar of alkoxides gave unsatisfactory results.

* To whom correspondence should be addressed

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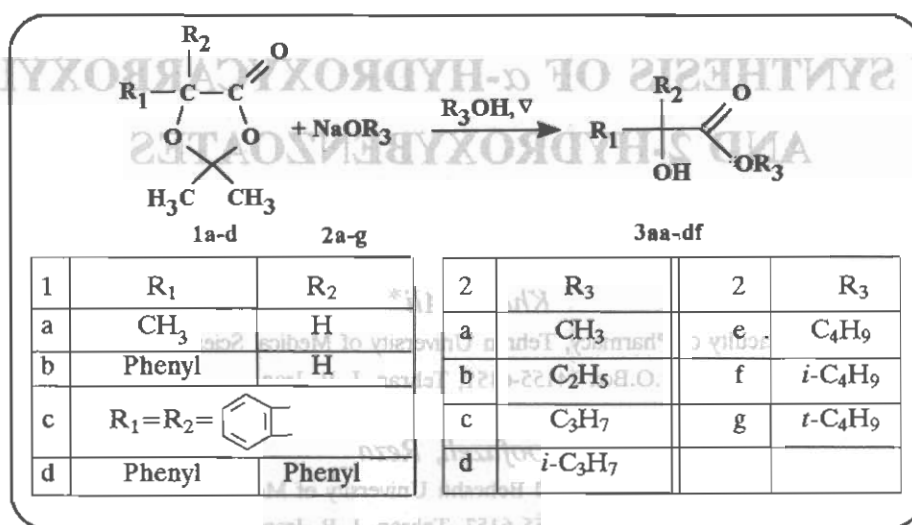


Table 1: Esters 3 prepared

3 (reference)	Reaction Time (h)	Yield (%)	3 (reference)	Reaction Time (h)	Yield (%)
*3aa ⁹	1.5	60	3ca ⁴	4.0	51
3ab ⁹	1.5	64	3cb ¹⁰	4.0	51
3ac ⁹	2.0	67	3cc ⁴	5.0	57
3ad ⁹	2.5	69	3cd ⁴	5.0	57
3ae ⁹	2.5	70	3ce ⁴	4.0	58
3af ⁹	2.5	71	3cf ⁴	5.0	58
3ag ⁹	4.0	43	3cg ¹¹	8.0	35
3ba ¹	3.0	53	3da ²	5.0	48
3bb ¹	3.0	58	3db ²	5.0	53
3bc ¹	3.0	59	3dc ²	5.0	58
3bd ¹	3.5	64	3dd ²	7.0	54
3be ¹	3.5	62	3de ²	7.0	56
3bf ¹	4.0	63	3df ²	7.5	45
3bg ¹	6.0	47			

*3aa means from 1a and 2a, etc.

From the results listed in Table 1, it can be concluded that both steric hindrance of the reactants and boiling points of alcohols 2 markedly influence the yield and the time of the reactions. Thus, the reaction of simple acetone 1a gave higher yield and required shorter times than those with bulky acetones 1b-d and the yield of esters of each acetone increased with increasing the boiling points of alcohols 2a-g. As expected, due to the steric hindrance, sodium t-butoxide failed to give any

detectable product with bulky acetone 1d even in boiling t-butyl alcohol in a sealed tube, sodium t-butoxide in comparison with alkoxides of 2a-f gave lower yields of esters on reaction with acetone 1a-c. In general, this method which provides an alternative route for the synthesis of esters of α -hydroxycarboxylic acids has the advantages of mild reaction conditions, simple workup procedure and good yield and thus compares favorably with the known methods for the preparation of esters 3aa-df.

All esters prepared in this work have been previously prepared and reported. The products were characterized by their spectral data, mp or bp which were fully in accord with the expected structures and identical to the literature values [1,2,4,9-11].

fate. The crude products after evaporation of the chloroform were distilled or crystallized to give pure esters 3.

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EXPERIMENTAL

Acetonides 1a-c were prepared by the reaction of the corresponding α -hydroxycarboxylic acids with acetone in the presence of sulfuric acid in 60%, 85% and 75% yields respectively [6,7]. Acetonide 1d was prepared through the reaction of the diazonium salt of 2-aminobenzoic acid with acetone in 70% yield [8]. α -hydroxycarboxylic acids used for the preparation of acetonides 1a-d were commercially available from Fluka.

General procedure for the preparation of α -hydroxycarboxylic acid and 2-hydroxybenzoic acid esters 3

A solution of the acetonide (0.01 mol) and sodium alkoxide (0.03 mol) in 20 mL of the corresponding alcohol was stirred and refluxed for 3 hours. After completion of the reaction (TLC control), the solution was allowed to return to the room temperature, filtered and the filtrate was rotary evaporated. The residue was dissolved in chloroform (10 mL) and the solution was washed successively with 0.05 N sodium hydrogen carbonate solution and water and was dried with anhydrous magnesium sul-

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