Synthesis of α-Hydroxycarboxamides from Acetonides of α-Hydroxycarboxylic Acids and Primary Amines

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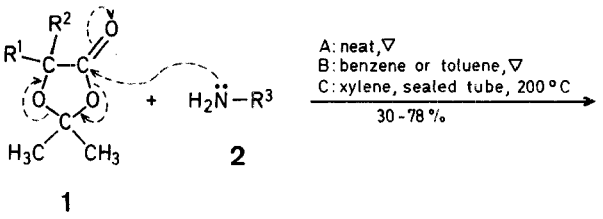
The reaction of acetonides of α-hydroxycarboxylic acids with primary amines on heating provides a useful synthetic route to *N*-substituted α-hydroxycarboxamides. In general, formation of the α-hydroxycarboxamides is favored by the presence of only small substituents on the acetonide, by sufficient nucleophilicity of the amine, and by high-boiling aprotic solvents.

Cyclic acetal-like compounds formed from *vic*-dihydroxy compounds, α-hydroxycarbonyl compounds, α-hydroxycarboxylic acids, or α-hydroxycarboxamides and acetone are defined as acetonides. These compounds are mainly used as protected forms of the above-mentioned bifunctional hydroxy compounds[1] but they have also been utilized for determining the configuration of two vicinal hydroxy groups[2] and for enhancing or retarding the biological activity of certain drugs such as ampicillin[3] and fluocinolone[4]. Despite this wide range of applicability, the preparative use of acetonides has received rather little attention.

Our search for an efficient synthesis of α-hydroxycarboxamides **(3)** lead us to study the reaction of primary amines **(2)** with the acetonides **(1)** of α-hydroxycarboxylic acids. One example of this reaction type, i.e., the reaction of the acetonide of α-hydroxyphenylacetic acid with ammonia to give α-hydroxyphenylacetamide (mandelamide), has been reported in detail[5]. We now describe further examples of this reaction type and comment its utility for the synthesis of α-hydroxycarboxylic acids and its limitations.



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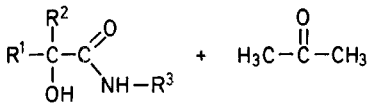
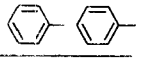
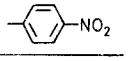


3

1	R^1	R^2
a	H	H
b	CH_3	H
c		H
d		

2	R^3
a	n-C_3H_7
b	
c	
d	

From the results listed in the Table it can be seen that a limiting factor of the formation of the α-hydroxycarboxamides **3** is steric hindrance of the acetonides **1**. The yields of products **3** also depend on the nucleophilicity of the amines **2** and, to a certain degree, on the reaction conditions. In all experiments, the ratio **2/1** used was 5/1; the yields obtained with this ratio are better than those obtained with the usual 1/1 ratio which could be deduced from the reaction scheme. As regards reaction time and temperature, their variation can exert a decisive influence on the results; thus, the simple acetonide **1b** reacts smoothly with amine **2b** in the absence of solvent or in boiling benzene whereas the bulky acetonide **1d** fails to undergo any detectable reaction under the same conditions. However, when the reaction of acetonide **1d** with 2-aminopyridine **(2b)** is performed in boiling toluene (24 h) α-hydroxy-*N*-(2-pyridinyl)-diphenylacetamide[8] **(3db)** is obtained in 41 % yield. Similarly, with less nucleophilic amines higher reaction temperatures and longer reaction times are required to achieve the formation of products **3** in acceptable yields. This is shown by the remarkable difference in reactivity between amines **2a** and **2c**. Amine **2a** reacts with acetonide **1c** at reflux to give α-hydroxy-*N*-propylphenylacetamide[9] **(3ca)** in 78 % yield whereas amine **2c** proved unreactive under identical conditions; however, when amine **2c** was allowed to react with acetonide **1c** in xylene in a sealed tube at 200 °C (24 h) α-hydroxyphenylacetanilide[10] **(3dd)** was obtained in 53 % yield. 4-Nitroaniline **(2d)** failed to give any product with the bulky acetonide **1d** under a variety of conditions.

Although in some cases, in particular with liquid amines, the reactions can be performed without solvent, the use of a suitable aprotic, high-boiling solvent is advantageous, the yields of products **3** increasing with the following order of solvents: chloroform < acetonitrile < benzene < toluene < xylene. The dipolar aprotic solvents dimethyl sulfoxide and dimethylformamide may also be used but solvent purification and product isolation are difficult.

Table. *N*-Substituted α-Hydroxycarboxamides (**3**) from Acetonides (**1**) of α-Hydroxycarboxylic Acids (**1**) and Primary Amines (**2**)

3[a]	Solvent	Reaction Conditions	Yield[b] of 3 GQH	Recovered 1 [%]	m.p. [°C] or b.p. [°C]/torr	
					found	reported
3ab	benzene	reflux, 12 h	77	12	m.p. 133–135° (benzene)	m.p. 132–134°[12] (ethyl acetate/benzene)
3ac	toluene	reflux, 18 h	65	16	m.p. 93–94° (ethanol)	m.p. 91–92°[12] (ethanol/water)
3ad	toluene	reflux, 24 h	53	25	m.p. 192–193° (ethyl acetate)	m.p. 192°[13] (ethyl acetate)
3bb	toluene	reflux, 12 h	65	14	b.p. 140–142°/1	b.p. 140–143°/1[8]
3bc	toluene	reflux, 18 h	54	24	m.p. 58–60° (ethyl acetate)	m.p. 57–58°[11] (ether)
3bd	xylene	sealed tube, 200°C, 18 h	41	38	m.p. 142° (ethyl acetate/ethanol)	m.p. 138–139°[12] (water)
3ca	–	reflux, 12 h	78	9	m.p. 66° (methanol)	m.p. 64°[9]
3cb	toluene	reflux, 18 h	53	29	m.p. 120–121° (methanol)	m.p. 118–121°[8] (ethanol/water)
3cc	xylene	sealed tube, 200°C, 18 h	53	26	m.p. 150–151° (methanol)	m.p. 151–152°[10] (benzene/pet ether)
3cd	xylene	sealed tube, 200°C, 18 h	30	49	m.p. 151° (ethyl acetate)	m.p. 149°[14]
3da	–	reflux, 12 h	65	13	m.p. 75–77°	$C_{17}H_{19}NO_2$ (269.3)
3db	toluene	reflux, 18 h	41	41	m.p. 216° (ethyl acetate)	m.p. 215–216°[8] (isopropanol)
3dc	xylene	sealed tube, 140°C, 12 h	42	36	m.p. 178–179° (methanol)	m.p. 177–178°[15] (benzene/pet ether)

[a] **3ab** means: from **1a** and **2b**, etc.

[b] Isolated pure product.

The acetonides **1** used in this work are stable under a variety of conditions as confirmed by T.L.C. analyses of the crude reaction mixtures; in various solvents, only the spots of starting materials **1** and **2** and of products **3** were found.

From the reaction mixtures, excess amine is either removed by evaporation (**2a**) or by extraction of the chloroform solution of the crude reaction products with 5% hydrochloric acid (**82b, c**). After evaporation of chloroform, the mixture of unchanged acetonide **1** and product **3** is separated by crystallization from a suitable solvent and/or by distillation. The homogeneity of the products **3** thus obtained was established by T.L.C. analysis.

Melting ponts were determined with a Reichert hot plate melting point apparatus, and are uncorrected. T.L.C. analyses were performed on 250-μ Eastman 13181 Silica gel sheets. Spots were visualized under ordinary fluorescent light or 254-nm U.V. light or by iodine stanning. Mass spectra were recorded with a Varian Mat 311 A instrument. I.R. spectra were recorded with a Perkin-Elmer IR-267 spectrophotometer and ^{1}H-N.M.R. spectra with a Varian A-60 spectrometer.

Acetonides **1a–d** are prepared according to known procedures[5, 6, 7].

N-Substituted α-Hydroxycarboxamides (3); Typical Procedures:

Method A, without Solvent (for Products **3ca** and **3da**):

α-Hydroxy-N-propyldiphenylacetamide (**3da**): A 25 ml round-bottom flask fitted with stirrer, reflux condenser, and calcium chloride drying tube is charged with 2,2-dimethyl-5-oxo-4,4-diphenyl-1,3-dioxolane (**1d**; 0.268 g, 1 mmol) and propanamine (**2a**; 0.35 ml, 4 mmol). The mixture is stirred and heated to boiling on a water bath for 12 h. Volatile material is then rotary-evaporated and the residue is dissolved in chloroform (10 ml). This solution is washed successively with 5% hydrochloric acid, saturated sodium hydrogen carbonate solution, and water and is dried with magnesium sulfate. The solvent is evaporated and the remaining oily product crystallized from ethyl acetate; yield of **3da**: 0.18 g (65%); colorless crystals, m.p. 75–77°C.

M.S.: $m/e = 269$ (M^+).

I.R. (KBr): $\nu = 3400, 2950, 1650, 1460, 770, 700\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 0.9$ (t, 3H, $J = 6$ Hz); 1.4 (m, 2H); 3.2 (m, 2H); 4.0 (s, 1H); 7.4 ppm (d, 10H, $J = 1$ Hz).

The mother liquors of crystallization of products **3** are evaporated and the remaining product is recrystallized from a suitable solvent to give the unreacted acetonide **1**.

Method B, in boiling Benzene or Toluene (for Products **3ab, 3ac, 3ad, 3bb, 3bc, 3cb, 3db**):

2-Hydroxy-N-Phenylpropanamide (**3bc**): A solution of 2,2,4-trimethyl-5-oxo-1,3-dioxolane (**1b**; 0.13 g, 1 mmol) and aniline (**2c**; 0.5 ml, 5 mmol) in toluene (30 ml) is stirred and refluxed for 12 h. The solvent is then evaporated and the residue worked up as in Method A; yield of **3bc**: 90 mg (54%); m.p. 58–60°C (ethyl acetate) [Ref.[11], m.p. 57–58°C (ether)].

I.R. (KBr): $\nu = 2920, 2830, 1380, 1660, 690, 750\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.3$ (t, 3H, $J = 8$ Hz); 4.5 (m, 1H); 6.8 (s, 1H); 7.4 ppm (t, 5H, $J = 8$ Hz).

In the preparation of **3bb**, the residue left after evaporation of chloroform is fractionally distilled to afford unreacted acetonide **1b** and amine **2b**. The residues of evaporation of the mother liquors of recrystallization of the other products **3** are either crystallized from suitable solvents or distilled in vacuo[6, 7] to afford the corresponding unreacted acetonides **1**.

Method C, in Xylene in a Sealed Tube at 200°C (for Products **3bd, 3cc, 3cd, 3dc**):

α-Hydroxyphenylacetanilide (**3cc**): A solution of 2,2-dimethyl-5-oxo-4-phenyl-1,3-dioxolane (**1c**; 0.2 g, 1 mmol) and aniline (**2c**; 0.5 ml, 5 mmol) in xylene (20 ml) is heated in a sealed glass tube at

200° C for 24 h. The tube is then chilled and opened and the contents are quantitatively transferred into a round-bottom flask. The solvent is evaporated and work-up performed as in Method A; yield of **3cc**: 0.12 g (53%); m.p. 150–151° C (methanol) [Ref.[10], m.p. 151° C (benzene/pet ether)].

I.R. (KBr): ν = 3550, 1650, 1550, 1600, 700, 760 cm^{-1}.

^{1}H-N.M.R. (acetone-d_6/TMS_{int}): δ = 6.6 (m, 10 H); 4.5 ppm (s, 1 H).

The residues from evaporation of the mother liquors from crystallization of products **3bd, 3cc, 3cd**, and **3dc** are either distilled in vacuo or crystallized from suitable solvents[6,7] to afford the corresponding unchanged acetonides **1**.

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