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New Facile Synthesis of α-Hydroxyamides:Intermolecular and Intramolecular Catalysis in the Reaction of α-Hydroxycarboxylic Acids with N-Sulfinylamines.

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Summary: α-Hydroxycarboxylic acids (1) reacted with N-sulfinylanilines (2) to give the corresponding α-hydroxyanilides (5) in quantitative yields under mild condition: the reaction appears to involve intermolecular catalysis by the carboxylic acid moiety and intramolecular catalysis by the hydroxyl group.

Development of synthetic methods for amides has attracted considerable interest and is still explored although various efficient procedures[1-4] have been devised.

α-Hydroxyamides which are valuable not only for a noted therapeutic agent having anticonvulsant effects,[5] but also for the synthetic utility of oxazolidinediones[6] and oxindoles,[7] were prepared by the reaction of α-hydroxy esters with amines[6] or α-hydroxy acids with phosphazo compounds.[2] However yields of α-hydroxyamides are poor. We herein report a novel efficient synthesis of α-hydroxyamides and the mechanism of an interesting reaction of α-hydroxycarboxylic acids with N-sulfinylamines. Both carboxylic acids[8] and secondary alcohols[9] have been known not to react with N-sulfinylamines respectively. However, we found that α-hydroxycarboxylic acids reacted with N-sulfinylamines to give the corresponding α-hydroxyamides quantitatively at 25 °C in acetonitrile as shown in Scheme I.

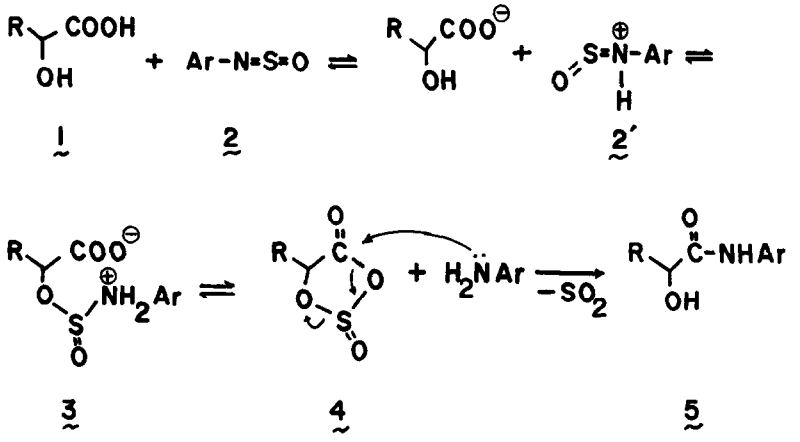
In a representative run (entry 9), N-sulfinylaniline[10] (278 mg, 2 mmol) was added slowly to DL-mandelic acid solution (304 mg, 2 mmol, CH_3CN: 10 ml) at 25 °C under nitrogen atmosphere and stirred for 3.5 h at 25 °C. The reaction was monitored by silica gel tlc. The solution was concentrated to give highly pure[11] DL-mandelanilide (454 mg, 100 %), which was further purified by recrystallization from aqueous ethanol (448 mg, 98%); mp 150-151 °C, lit[12]: 150-151 °C; ^1H NMR (60 MHz, DMSO- d_6), 9.5 (s, -NH), 7.0-7.8 (m, 10H), 6.3 (s, -OH), 5.1 (s, 1H); IR (KBr, cm^{-1}), 3350-3100, 1665, 1610, 1560 and 1500.

Results obtained are summarized in Table I, and products are confirmed by comparison of mp and spectral data with those from authentic samples or references.

Though secondary alcohols are known not to be reactive toward to N-sulfinyl aniline,[9] isopropyl alcohol reacted with N-sulfinyl-p-toluidine in the presence of trichloroacetic or

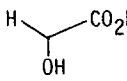
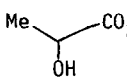
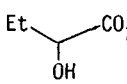
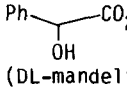
acetic acid to give the corresponding isopropyl sulfite (purified by distillation, 33%). It is clear that this reaction needs an acid catalyst. Thus, the amidation reaction seems to be initiated by intermolecular protonation to 2 by the carboxylic acid moiety of 1; This protonation enables the hydroxy group to attack 2' to form 3 that may be cyclized to 4, which is in equilibrium with 3. The released amine may attack the carbonyl carbon of intermediate, 4 to give 5 as shown in Scheme I.

Scheme I



In the reaction of 1 (R=Me) and 2 (Ar=Ph), sulfur dioxide was isolated (ca. 90%) and confirmed.[13] In order to trap aniline and intermediate 4, the reaction was carried out, and column chromatographed at 4 °C in a cold room. The aniline[14] peak was detected by UV detector and isolated (4 %) actually by a low pressure liquid column chromatography though 4 was neither isolated nor detected. The formation of 4 was indirectly proved by the reaction of mandelic acid with thionyl chloride in the presence of two equimolar triethylamine by following addition of aniline *in situ* to give 5. This reaction can be best explained to proceed *via* formation of an intermediate, 4. When an equivalent amount of aniline was added to the reaction mixture of 1 (R = Ph) and 2 (Ar = tolyl), 5 mixtures (R=Ph, Ar=tolyl, 70%, R=Ph, Ar=Ph[15], 30%) were isolated. N-Phenylamide is apparently attributed to the nucleophilic attack of aniline to the carbonyl carbon of 4.[15] The α-carboxylic acid moiety has an important role because, for instance, DL-mandelic acid ethyl ester does not react with 2: starting material is recovered quantitatively under the same reaction conditions. When an equimolar amount of triethyamine or strong acid such as trichloroacetic or trifuluoroacetic acid was added to the reaction mixture of 1 and 2, formation of 5 was not detected.[16] It is assumed that intermediate 3 is forced to return to 1 and 2 in the presence of base or acid because it inhibits formation of intramolecular zwitterion, 3, required for the cyclization to 4.[16] The work described herein may be of efficient synthetic use of α-hydroxyanilides though the mechanism is not completed. The scope and study of a new heterocyclic intermediate, 4 are under investigation,

Table I. Synthesis of α-Hydroxyamides

entry	1	2, Ar	reactn. time(h)	reactn. temp.(°C)	5 Yield(%)[a,b]	mp, ref.
1	 (glycolic acid)	Ph	8	25	100[a](98)[b]	92-94°C
2	glycolic acid	P-Cl-C_6H_4	6	25	100 (96)	168-170°C[6]
3	glycolic acid	P-Me-C_6H_4	6	25	98 (96)	143-144°C[6]
4	 (DL-lactic acid)	Ph	5	25	98 (95)	56- 57°C[6]
5	DL-lactic acid	P-Cl-C_6H_4	5	25	97 (95)	98-100°C[6]
6	DL-lactic acid	P-Me-C_6H_4	5	25	96	101-103°C[6]
7	 (D,L-α-hydroxybutyric acid)	Ph	6	25	98	88-89°C[17]
8	D,L-α-hydroxybutyric acid	P-Me-C_6H_4	6	25	99	110-112°C[18]
9	 (DL-mandelic acid)	Ph	3.5	25	100 (98)	150-151°C[12]
10	DL-mandelic acid	P-Cl-C_6H_4	3	25	100	163-164°C[6]
11	DL-mandelic acid	P-Me-C_6H_4	3	25	98	170-172°C[19]
12	D-tartaric acid	Ph (1 eq)[c]	1	50[e]	99[c]	178-180°C[20]
13	D-tartaric acid	Ph (2 eq)[d]	3	50[e]	97[d]	255-256°C[20]
14	D-tartaric acid	P-Cl-C_6H_4(2 eq)[d]	3	50[e]	99[d]	276-277°C[21]
15	D-tartaric acid	P-Me-C_6H_4(2 eq)[d]	3	50[e]	99[d]	264-267°C[22]

a. Isolated yields. b. Yields purified by recyrstallization.

c. Monoamide was obtained from an equivalent amount of 2.

d. Diamide was obtained from two equivalent amounts of 2.

e. The solubility of tartaric acid was poor. Thus, the heterogeneous reaction was carried out at 50°C.

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11. The purity was confirmed by HPLC: only one peak of 5 was observed.
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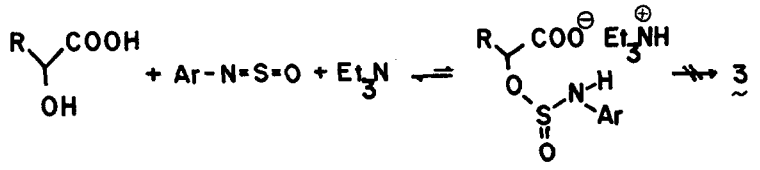
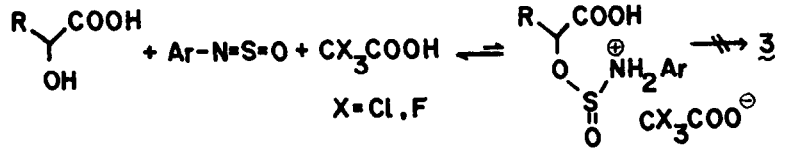
13. In several reactions of 1 and 2, SO_2 was trapped at -78 °C and confirmed by a gas mass (m/e = 64) and by a gas IR spectrum (gas cell, SO_2; 1350, 1200-1050 cm^{-1})
14. An aliquot was withdrawn from the reaction mixture from time to time, and injected into a column (silica gel; 200 mesh, solvent; CH_2Cl_2:Et_2O = 9:1) at 4°C to monitor the aniline peak by low pressure column chromatography. When aniline peak appeared, it was collected and purified to give pure aniline in 4% yield.
15. N-phenylamide may result from the direct reaction of alniline with 4 because 2 (Ar: tolyl) did not react with aniline to form N-sulfinylaniline. However, N-sulfinylaniline reacted with p-toludine to form 2 (Ar: tolyl) because of the stronger nucleophilicity of p-toludine.
16. A stronger base than the sulfinylaniline moiety in 3, such as triethylamine, and a stronger acid than the carboxylic acid moeity in 3, such as trihaloacetic acid, appear to be the driving force to regenerate 1 and 2 as shown below.





This fact also supports one intermolecular catalysis of -COOH and one intramolecular catalysis of -OH moiety in 1 for the formation of 3 and 4 in Scheme I.

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