A Facile Preparation of Primary Carboxamides

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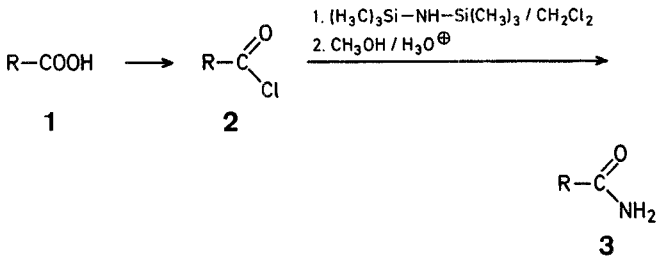
The methods reported for the conversion of carboxylic acids into primary amides[1] include the reaction of acids with ammonium carbonate or urea, the ammonolysis of the corresponding esters or anhydrides, and the reaction of acyl chlorides with gaseous or aqueous ammonia. In the case of polyfunctional or insufficiently stable educts it has to be expected that these methods afford the desired primary amides only in low yields or not at all.

Recently, two groups reported[2,3] the conversion of acyl halides into hydroxamic acids or silylamides via the corresponding silylhydroxylamines or silylamines, respectively. In view of the unusual mildness of these types of reactions, it was felt that certain modifications of the described procedures may improve their general utility.

We have now found that a variety of acyl chlorides **2** react with a 2–3 fold excess of hexamethyldisilazane (bis[trimethylsilyl]-amine) in dichloromethane to give, after hydrolysis, fair to good yields of the corresponding primary amides **3**, thus providing a mild and useful entry to this class of compounds.



The reaction can be performed in the presence of several functional groups. Thus, chloroacetamide[4,5] and dichloroacetamide[6] were obtained without significant displacement of the Cl atom and no double-bond shift was observed in the reaction of the β,γ-unsaturated acyl chloride **2k**. Further, the conversion of carboxylic acids **1f–i** (monoalkyl phthalates) into phthalamic esters **3f–i** via the acyl chlorides **2f–i** proceeded in good yields whereas the amidation of acids **1f–i** by standard methods[7,8] resulted in much lower yields of compounds **3f–i** along with the formation of large amounts of phthalimide.

However, not all investigated carboxylic acids could be converted into carboxamides via the acyl chlorides by our procedure. For example, 2-acyloxybenzoic acids **1e,p** were instead converted into imides **4e,p** via isomerisation, probably due to the mild basicity of the reaction medium[9]. Despite of this

Table. Carboxymides (**3**) from Carboxylic Acids (**1**) via Reaction of the Acyl Chlorides (**2**) with Hexamethyldisilazane

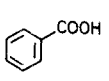
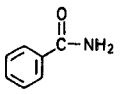
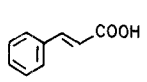
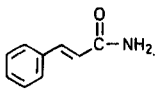
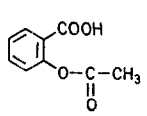
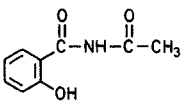
Acid **1**	Product[a]	Yield[b] [%]	m.p. [°C][c]	Molecular Formula[d] or Lit. m.p. [°C]	$[\alpha]_D^{25}$[e]
a Cl–CH_2–COOH	**3a** Cl–CH_2–CO–NH_2	87	118–120° (ethyl acetate)	121°[12]	–
b $CHCl_2$–COOH	**3b** $CHCl_2$–CO–NH_2	90	98° (water)	99°[12]	–
c 	**3c** 	87	128–130° (water)	132–133°[12]	–
d 	**3d** 	92	145–147° (toluene)	148°[12]	–
e 	**4e** 	65	142° (ethyl acetate)	141.5–143°[9]	–

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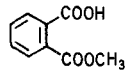
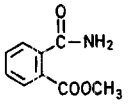
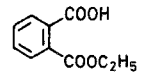
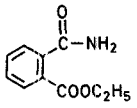
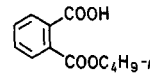
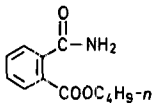
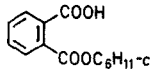
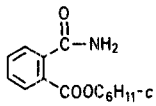
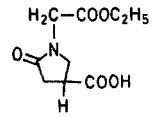
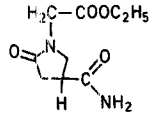
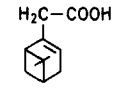
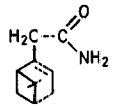
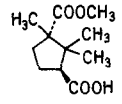
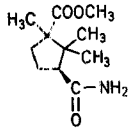
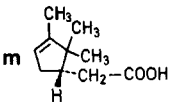
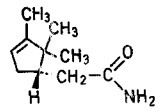
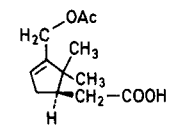
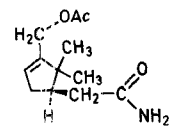
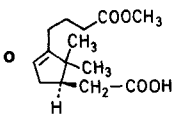
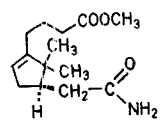
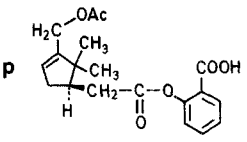
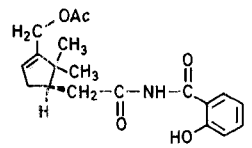
Table. (Continued)

Acid **1**	Product[a]	Yield[b] [%]	m.p. [°C][c]	Molecular Formula[d] or Lit. m.p. [°C]	$[\alpha]_D^{25}$[e]
f 	**3f** 	83	98–100° (diisopropyl ether)	98–102°[7]	–
g 	**3g** 	85	123–125° (diisopropyl ether)	$C_{10}H_{11}NO_3$ (193.2)	–
h 	**3h** 	80	64–65° (diisopropyl ether)	$C_{12}H_{15}NO_3$ (221.3)	–
i 	**3i** 	78	94–96° (diisopropyl ether)	96°[8]	–
j 	**3j** 	54	119–121° (ethyl acetate)	$C_9H_{14}N_2O_4$ (214.2)	–
k 	**3k** 	60	50–52° (hexane	$C_{11}H_{17}NO$ (179.3)	−63.5° (*c* 1.05, $CHCl_3$)
l 	**3l** 	70	125–126° (diisopropyl ether)	127–128°[13]	−54.9°[f] (*c* 10.1, ethanol)
m 	**3m** 	78	127–129° (diisopropyl ether)	$C_{10}H_{17}NO$ (167.2)	−12.8° (*c* 1.0, $CHCl_3$)
n 	**3n** 	65	90–92° (diisopropyl ether)	$C_{12}H_{19}NO_3$ (225.3)	+21.9° (*c* 1.0, $CHCl_3$)
o 	**3o** 	62	87–89° (diisopropyl ether)	$C_{14}H_{23}NO_3$ (253.3)	+12.8° (*c* 1.0, $CHCl_3$)
p 	**4p** 	50	86–89° (diisopropyl ether)	$C_{19}H_{23}NO_5$ (345.4)	+48.6 (*c* 1.0, $CHCl_3$)

[a] The I.R. and ^{1}H-N.M.R. spectra of all compounds **3** and **4** were consistent with the assigned structures.

[b] Yields of isolated pure products; not optimised; based on **2**.

[c] Uncorrected.

[d] The microanalyses were in satisfactory agreement with the calculated values: C ± 0.30, H ± 0.25, N ± 0.30.

[e] Determined with a Perkin-Elmer 241 polarimeter.

[f] Ref.[13], $[\alpha]_D^{25}$: −55.4° (*c* 10.5, ethanol).

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limitation, the present method appears to be a good alternative to the known methods for the preparation of primary carboxamides.

The acyl chlorides **2a–j, l–p** were prepared by reaction of the corresponding carboxylic acids **1** with oxalyl chloride in dichloromethane in the presence of catalytic amounts of dimethylformamide[10]. Acyl chloride **2k** was prepared via the *t*-butyldimethylsilyl ester of **1k**[11].

Carboxamides (3); General Procedure:

To a stirred, ice-cold solution of hexamethyldisilazane (4.823 g, 30 mmol) in dry dichloromethane (75 ml), a solution of the acyl chloride **2** (10 mmol) in dichloromethane (25 ml) is rapidly added and stirring at room temperature is continued overnight. Then, methanol (2 ml) is added, the mixture washed with 5% aqueous sulfuric acid (2 × 20 ml) and with saturated aqueous ammonium sulfate (2 × 20 ml) dried with magnesium sulfate, and evaporated to dryness. The residue is recrystallised from an appropriate solvent.

In the case of water soluble compounds (e.g., **3j**), the reaction mixture, after addition of methanol, is evaporated in vacuo and the residue taken up in acetone, any solid material being rejected. Evaporation of the solvent affords the crude product **3**.

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