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Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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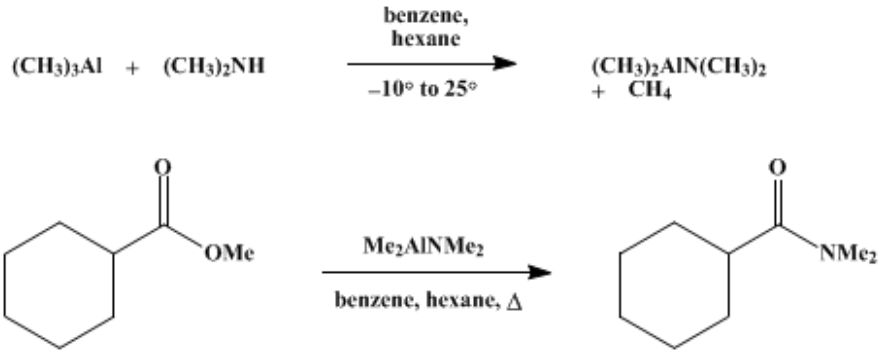
CONVERSION OF ESTERS TO AMIDES WITH DIMETHYLALUMINUM AMIDES: *N,N*-DIMETHYLCYCLOHEXANECARBOXAMIDE



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Checked by Charles W. Hutchins and Robert M. Coates.

1. Procedure

Caution! Dialkylzinc compounds, especially in undiluted form, are pyrophoric and must not be allowed to come into contact with air or moisture. These compounds should only be handled by individuals trained in their proper and safe use. [Note added January 2011]

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A dry, 300-ml., two-necked, round-bottomed flask equipped with a reflux condenser fitted with a nitrogen inlet at its top, a rubber septum, and a magnetic stirring bar is charged with 100 ml. of benzene (Note 1) and flushed briefly with nitrogen, after which 22 ml. (0.057 mole) of a 25% solution of trimethylaluminum in hexane (Note 2) is injected through the septum into the flask. The solution is stirred and cooled in an ice–salt bath at −10° to −15°, and 2.47 g. (3.64 ml., 0.0549 mole) of dimethylamine (Note 3) is added slowly with a syringe. Twenty minutes after the addition is completed, the cooling bath is removed, and the contents of the flask are allowed to stir and warm slowly to room temperature over a 45-minute period. A solution of 7.10 g. (0.0500 mole) of methyl cyclohexanecarboxylate (Note 4) in 20 ml. of benzene (Note 1) is injected through the septum. The resulting solution is heated under reflux for 22 hours, cooled to room temperature, and hydrolyzed by slow, cautious addition of 82.5 ml. (0.055 mole) of 0.67 *M* hydrochloric acid (Note 5). The mixture is stirred for 30 minutes to ensure complete hydrolysis. The upper organic layer is separated, and the aqueous layer is extracted with three 25-ml. portions of ethyl acetate. The organic extracts are combined, washed with sodium chloride solution, dried with anhydrous magnesium sulfate, and evaporated under reduced pressure. Distillation of the residual liquid under reduced pressure through a 10-cm. Vigreux column affords a 0.1–0.6 g. forerun of unreacted ester and 6.40–7.25 g. (83–93%) of *N,N*-dimethylcyclohexanecarboxamide, b.p. 100° (5.5 mm.), 57–60° (0.08 mm.) (Note 6).

2. Notes

1. The benzene was dried by distillation from calcium hydride.
2. Trimethylaluminum in hexane solution was purchased from the Alfa Division, Ventron Corporation.
3. Dimethylamine was obtained in a cylinder from the Linde Division, Union Carbide Chemical Corporation, and condensed in a dry, two-necked flask fitted with a rubber septum and cooled to −78° under nitrogen.
4. Cyclohexanecarboxylic acid is available from Aldrich Chemical Company, Inc., and conveniently

esterified by the procedure of Harrison, Haynes, Arthur, and Eisenbraun.[3] A dry, 500-ml., round-bottomed flask is charged with 225 ml. of anhydrous methanol, 1.0 ml. of concentrated sulfuric acid, and 41.0 g. (0.320 mole) of cyclohexanecarboxylic acid. The flask is fitted with a Soxhlet extractor containing 53 g. of Linde type 3A molecular sieves and a condenser bearing a calcium chloride drying tube at its top. The solution is heated at reflux for 19 hours and cooled to room temperature. The sulfuric acid is neutralized by adding 3.0 g. of sodium hydrogen carbonate, the salts are filtered, and the filtrate is evaporated under reduced pressure. The remaining liquid is distilled through a 15-cm. Vigreux column at reduced pressure, affording 35.7–36.8 g. (79–81%) of methyl cyclohexanecarboxylate, b.p. 73–76° (13 mm.).

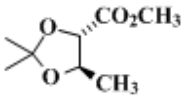
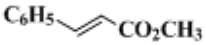
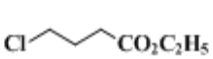
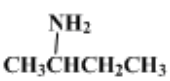
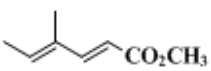
5. To avoid excessive foaming at the beginning of the hydrolysis, the checkers recommend that the hydrochloric acid solution be added 1 or 2 drops at a time. The rate of addition may be increased once the initially vigorous foaming subsides.

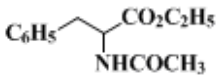
6. The spectral properties of the product are as follows: IR (neat) $cm.^{-1}$: 1640 (C=O); ^1H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 1.05–1.95 (m, 10H, $5CH_2$), 2.50 (m, 1H, CH), 2.94 (s, 3H, NCH_3), 3.06 (s, 3H, NCH_3). A boiling point of 107–108° (7 mm.) has been reported for *N,N*-dimethylcyclohexanecarboxamide.[4]

3. Discussion

This procedure,[5] based on the work of Ishii and co-workers,[6] affords a mild and general method for converting a wide variety of esters to primary, secondary, and tertiary amides (Table I). While the preparation of the tertiary amide, *N,N*-dimethylcyclohexanecarboxamide, described here is carried out in benzene, aluminum amides derived from ammonia and a variety of primary amines have been prepared by reaction with trimethylaluminum in dichloromethane and utilized for aminolysis in this solvent. Although 1 equivalent of dimethylaluminum amides, prepared from amines, was generally sufficient for high conversion within 5–48 hours, best results were obtained when 2 equivalents of the aluminum reagent, prepared from ammonia, was used. Diethylaluminum amides can also effect aminolysis, but with considerably slower rates.

TABLE I
PREPARATION OF AMIDES FROM ESTERS BY AMINOLYSIS WITH DIMETHYLALUMINUM AMIDES[5]

Ester	Amine	Reaction Time (hours)[a]	Isolated Yield of Amide (%)
	NH_3	2[b]	70
	NH_3	16	69
	NH_3	12	86
		48	76
		45	74

		40	77
$CH_3CO_2(CH_2)_3CH_3$	$C_6H_5NH_2$	40	78
$C_6H_5CO_2C_2H_5$	$C_6H_5CH_2NH_2$	25	93
	$(CH_3)_3CNH_2$	45	79

[a] The solvent was dichloromethane except as noted.

[b] Benzene was used as solvent.

Although the preparation of carboxamides by direct aminolysis is a well-known and widely studied reaction,[7] the synthetic utility of this process is limited. The reactions generally require long heating periods at relatively high temperatures, and the reagents and catalysts used are usually strong bases.[8] The present procedure has the advantages of lower temperatures and moderate reaction times. The aluminum amides are conveniently prepared *in situ* and appear to be mild, nonbasic reagents, compatible with many functional groups.[5] The isolation is simple, since hydrolysis of the aluminum reagents and products affords only methane and acid-soluble aluminum salts. Another advantage is that amides of volatile amines may be prepared without the use of sealed tubes.

N,*N*-Dimethylcyclohexanecarboxamide has been prepared by acylation of dimethylamine with cyclohexanecarbonyl chloride[9] and by double alkylation of vinylidene-bis(dimethylamine) with 1,5-diiodopentane to the cyclic amidinium salt followed by hydrolysis.[4]

References and Notes

1. This work was carried out at the Department of Chemistry, Fordham University, Bronx, New York 10458.
2. Present address: Department of Chemistry, Pennsylvania State University, University Park, Pennsylvania 16802.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

NH_3

$CH_3CO_2(CH_2)_3CH_3$

$C_6H_5NH_2$

$C_6H_5CO_2C_2H_5$

$C_6H_5CH_2NH_2$

$(CH_3)_3CNH_2$

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

aluminum (7429-90-5)

dimethylamine (124-40-3)

dichloromethane (75-09-2)

Cyclohexanecarboxylic acid (98-89-5)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

N,N-Dimethylcyclohexanecarboxamide (17566-51-7)

cyclohexanecarbonyl chloride (2719-27-9)

1,5-diiodopentane (628-77-3)

calcium hydride (7789-78-8)

trimethylaluminum (75-24-1)

methyl cyclohexanecarboxylate (4630-82-4)

vinylidene-bis(dimethylamine) (815-62-3)