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A NEW SYNTHESIS OF CARBOXYLIC ACID HYDRAZIDES VIA ORGANOALUMINUM REAGENTS

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Summary: Ethyl esters reaction under mild reaction conditions with dimethylaluminum hydrazides to give the corresponding carboxylic acid hydrazides in moderate to good yields.

Hydrazides are conveniently prepared by the acylation reaction of hydrazines, esters being the most common acylating agents[1]. While the reaction of hydrazine with an ester is rather straightforward, complications arise when substituted hydrazines are employed. For example, 1,1-disubstituted hydrazines do not react with acetate or with benzoate[2], although they do react with formates, acid anhydrides and esters activated with electron withdrawing group[3]. 1,2-Disubstituted hydrazines react with esters with great difficulty. These complications and others restrict the preparation of hydrazides from common and readily available esters.

We wish to report an alternative procedure in which the problems described above are overcome. This method, involving the use of dimethylaluminum hydrazides in the ester to hydrazides conversion, is based upon the amide preparation of Weinreb, et. al.[5-7]. The required dimethylaluminum hydrazides were prepared in situ by the reaction of $(CH_3)_3$ Al with the corresponding hydrazines in a 1:1 ratio in $CHCl_3$-toluene under an argon atmosphere. Best results were obtained when 2.5 equivalents of the aluminum complex were used per one equivalent of ester. The conversions of esters to hydrazides were normally carried out either at room temperature or at 40-45° C when bulky hydrazides or esters were employed (Table I).

$$RCO_2Et + R_1R_2NNR_3Al(CH_3)_3 \longrightarrow R\text{-}\overset{\overset{O}{\|}}{C}\text{-}NR_3NR_1R_2$$

The following procedure for the preparation of 1-(4-methylbenzoyl)-2, 2-dimethylhydrazide is representative: To a solution of 1,1-dimethylhydrazine (1.56 mL (Aldrich), 15.9 mmol) in dry $CHCl_3$ (10 mL), was added dropwise (15 min) under Ar a solution of trimethylaluminum in toluene (7.95 mL (Aldrich), 2M sol, 15.9 mmol). The mixture was kept at r.t. with stirring for an additional 1 h. Subsequently, ethyl 4-methylbenzoate (1.04 g, 6.36 mmol) was added and the solution was warmed to 45° C and kept under Ar for 16 h. The reaction mixture was poured carefully (exothermic reaction) into 100 mL of 2N HCl and the resultant mixture was stirred at 40° C for 0.5 h. The aqueous layer was separated, washed with $CHCl_3$ and made basic with sodium hydroxide solution. The aqueous solution was then extracted with ethyl acetate and the residue remaining after concentration of the dried (Na_2SO_4) extract was crystallized from toluene, affording .72 g (80%) of the title compound, m.p. 112-113° C; IR (KBr) 3200, 3015, 1635, 1610,1330, 1300 cm^{-1}; ^1H NMR (CD_3OD), δ 7.65 (d, 2H, J=8.8 Hz), 7.25 (d, 2H, J=8.8 Hz), 2.65 (s, 6H), 2.4 (s, 3H); MS, m/z. 178.11018 (calcd. for $C_{10}H_{14}N_2O$: 178.11061). Several of the prepared hydrazides assume an acidic character. Thus, during the workup, they no longer dissolved in acid but were found in the organic phase (Table I, entries 2 and 6). The hydrazide 10 precipitated out during the workout and was crystallized from MeOH.

Table 1: Preparation of Hydrazides from Ethyl Esters with Dimethylaluminum Hydrazide

Entry Number	Ester	Hydrazine	Reaction Time (hr)	Temp.	% Yield of Hydrazides
(1)	ethyl hexanoate	$(CH_3)_2NNH_2$	16	40° C	82
(2)	ethyl hexanoate	$PhNHNH_2$	12	25° C	91
(3)	ethyl hexanoate	2-hydrazinopyridine	12	25° C	83
(4)	ethyl hexanoate	$CH_3NHNHCH_3$	16	40° C	72
(5)	ethyl 4-methyl-benzoate	$(CH_3)_2NNH_2$	16	40° C	80
(6)	ethyl 4-methyl-benzoate	$PhNHNH_2$	12	25° C	87
(7)	ethyl 4-methyl-benzoate	2-hydrazinopyridine	12	25° C	71
(8)	ethyl 4-methyl-benzoate	$CH_3NHNHCH_3$	12	45° C	72
(9)	ethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylate	$(CH_3)_2NNH_2$	18	45° C	82
(10)	ethyl β-carboline 3-carboxylate	$PhNHNH_2$	18	45° C	92

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