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One-step Conversion of Esters to Acyl Azides Using Diethylaluminum Azide

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Abstract: Diethylaluminum azide, prepared from either sodium azide and diethylaluminum chloride or hydrazoic acid and triethylaluminum, reacts with esters to yield acyl azides in one step.

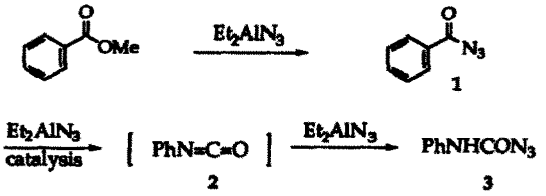
The ability of acyl azides to undergo the Curtius rearrangement makes them important precursors to isocyanates, which in turn can be converted to a variety of amine derivatives such as carbamates, ureas, and amines.[1] Several different methods have been developed for the synthesis of acyl azides. The most widely used method involves conversion of a carboxylic acid to an acid chloride or an anhydride which is then reacted with either sodium azide[2] or some other azide derivative.[3, 4] In connection with our work on indole alkaloids, we needed to convert an ester to an acyl azide, a transformation that would have taken two to three steps using the available methodology. We report here a new, one-step procedure for the conversion esters to acyl azides.

In considering different compounds for this transformation, we sought a reagent that combined the nucleophilic azide unit with a highly oxophilic species. The ideal reagent appeared to be a dialkylaluminum azide, since related organoaluminum reagents had already been shown to effect the direct conversion of esters to thiol esters,[5] selenol esters,[6] and amides.[7] Although both dimethyl and diethylaluminum azide were first prepared and studied in the 1960's,[8] there appear to be only two reports of their use as reagents.[9] We have found diethylaluminum azide, prepared in situ from either sodium azide and diethylaluminum chloride (Eq. 1, method **A**) or hydrazoic acid and triethylaluminum (Eq. 2, method **B**),[10] to be an effective reagent for the direct conversion of esters to acyl azides.

$$\mathrm{Et_2AlCl} + \mathrm{NaN_3} \xrightarrow[\text{rt, 4h}]{\substack{\text{method A} \\ \text{hexanes}}} \mathrm{Et_2AlN_3} \qquad (1)$$

$$\mathrm{Et_3Al} + \mathrm{HN_3} \xrightarrow[\text{rt, 4h}]{\substack{\text{method B} \\ \text{hexanes/PhH}}} \mathrm{Et_2AlN_3} \qquad (2)$$

During initial studies we observed that one equivalent of a hexanes/PhH solution of Et_2AlN_3 slowly converted methyl benzoate to benzoyl azide, 1 (Eq 3). After 3h, the acyl azide was obtained in 30% yield along with recovered starting material. Although the yield of the acyl azide was increased with longer reaction time, the formation of a polar, azide-containing side product was also observed. The side product was later determined to be phenylcarbamoyl azide (3) and is believed to arise from a Lewis acid catalyzed rearrangement of the acyl azide to the isocyanate followed by addition of an azide unit.[11] Indeed, azide 3 can be formed cleanly by treating benzoyl azide with Et_2AlN_3.



(3)

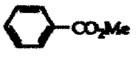
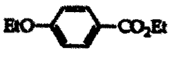
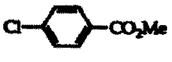
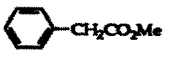
We have examined various conditions for the ester-azide interconversion, (Table 1). Generally, the reactions were carried out at room temperature using 2 equivalents of Et_2AlN_3.[12] The yield for the acyl azide formation was independent of the method of the Et_2AlN_3 generation. Attempts to speed up the reaction with heat proved unsuccessful and led to greater carbamoyl azide formation as well as decomposition. In order to see if the Lewis acid catalyzed carbamoyl azide formation could be prevented, the reaction was carried out using an excess of the ester (last entry). Under these conditions the acyl azide was the sole product, formed in good yield (based on the Et_2AlN_3).

Table 1. Optimization of Conditions for Benzoyl Azide Formation.

Et_2AlN_3 method	equiv of Et_2AlN_3	solvent	conc.	time (h)	Isolated Yield (%) 1	$PhCO_2Me$	3
A	2	hexanes	1.0 M	14	62		27
B	2	hexanes	1.0 M	48	59	7	17
A	2	hexanes/PhH	0.5 M	40	68	2	18
A	2	hexanes	0.05 M	48	17	30	26
A	0.1	hexanes	0.5 M	40	77	excess	

The Et_2AlN_3 mediated conversion of esters to acyl azides is quite general and some of the examples that we have studied are summarized in Table 2.[13] The reactions were carried out at room temperature for 2 days using two equivalents of the reagent. Methyl esters were found to be more reactive than ethyl esters. Whereas esters of electron-rich aromatics were converted to the corresponding acyl azides under these conditions, electron deficient substrates (methyl 4-nitrobenzoate and methyl nicotinate) were completely unreactive. Aliphatic esters were much more reactive than aromatic esters and their transformations were carried out at 0 - 5 °C. At higher temperature and with an excess of Et_2AlN_3, alkyl esters were converted to the carbamoyl azide in good yield (entry 14).[14] A general procedure for these reaction is given below.

Table 2. Et_2AlN_3 Mediated Conversion of Esters to Acyl Azides.

Entry	Substrates	Method	Yields (%) $RCON_3$(yld)[a]	RCO_2R[b]	$RNHCON_3$
1		A	68 (69)	2	18
2		B	59 (63)	7	17
3		A	37 (55)	33	13
4		B	32 (49)	44	
5		A	39 (65)	40	8
6		B	43 (62)	31	17
7		A	28 (78)	64	2
8		B	22 (42)	47	
9		A	40 (59)	32	
10		B	34 (41)	18	15
11		A	56 (68)	18	
12		B	67 (76)	12	
13		A[c]	50 (56)	10	
14		A[d]	-		80
15	n-$C_9H_{19}CO_2Me$	B[e]	47 (60)	22	

[a] Yield based on recovered starting material. [b] Recovered starting material. [c] 0 °C, 16h.
[d] Et_2AlN_3 (3 equiv), rt, 24h. [e] 5 °C, 24h.

General Procedures[15]— Method A: Granular NaN_3 was added to a solution of Et_2AlCl (1M in hexane) and the mixture was stirred at room temperature for 4 hours, during which time NaCl was formed as a fine powder. A hexanes solution of the ester was then added and the mixture was allowed to stir. Progress of the reaction was monitored by tlc. After 2 days, the reaction was quenched carefully with 2N HCl. Extractive work up followed by chromatographic purification afforded the acyl azides. Method B: A solution of HN_3 (1.27 M in benzene)[10] dropwise to an ice bath cooled solution of Et_3Al (1.0 M in hexane). After stirring the solution at 0°C for 2 hours, a hexanes solution of the ester was added and the reaction was continued for up to 2 days. The usual work up afforded the acyl azide. Note: We have kept solutions of diethylaluminum azide under an argon at room temperature atmosphere for up to one week.[15]

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12. Less satisfactory results were generally obtained with dimethylaluminum azide and ethylaluminum azido chloride (prepared from the reaction of Et_2AlCl and HN_3).
13. All new compounds are homogeneous (TLC, NMR) and exhibited spectroscopic data (200, 250 MHz ^1H NMR, IR, HRMS) consistent with the assigned structure.
14. Phenyl acetyl azide was found to be quite unstable at room temperature. An NMR sample of this substance ($CDCl_3$) rearranged to the corespounding isocyanate with in a few hours.
15. **Caution:** Although we have not experienced any problems with aluminum azide solutions, azides are potentially unstable and should be handled with great care.

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