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AMINOALUMINUM HYDRIDE AS NEW REDUCING AGENTS. III.[1] SELECTIVE REDUCTION OF CARBOXAMIDES TO ALDEHYDES

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Bis(4-methyl-1-piperazinyl)aluminum hydride was found to be a useful reagent for reduction of various N,N-disubstituted carboxamides, such as N-acylmorpholines and N,N-dimethylcarboxamides, to provide the corresponding aldehydes in fairly good yields.

In preceding papers,[1,2] it has been shown that diaminoaluminum hydride, especially bis(4-methyl-1-piperazinyl)aluminum hydride (BMPA), is a very useful reagent for preparation of aldehydes from corresponding carboxylic acids or their esters. We have subsequently been studying on the application of this new reagent, BMPA, for reduction of carboxamides to the corresponding aldehydes.

As synthesis of aldehydes from readily available carboxylic acid derivatives is one of the most important and highly desirable means in organic syntheses, numerous methods have been reported, among which reduction with lithium aluminum hydride has been widely studied.[3] The most successful development has involved selective reduction of N,N-disubstituted carboxamides such as 1-acylcarbazoles,[4] 1-acyl-3,5-dimethylpyrazoles,[5] 1-acylimidazoles,[6] 1-acylaziridines[7] and N-methylanilides,[8] by this reagent. Partial reduction of N,N-dimethylcarboxamides with sodium aluminum hydride,[9] lithium di- or triethoxyaluminum hydride[10] was also reported to be a useful method for preparation of aldehydes. In these reactions, carboxamides are reduced with such reagents to give generally a mixture of the corresponding amines and aldehydes. Therefore, it is generally required to select a suitable reducing reagent and reaction conditions according to the nature of the amides.

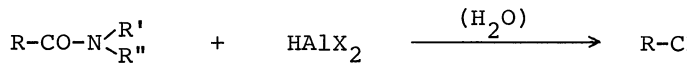
In the present experiment, attempts were made for reduction of N-benzoylmorpholine which was adopted as a model compound by the use of various diaminoaluminum hydrides prepared from aluminum hydride and secondary amines. The effect of the amine involved in the reagent on the selectivity of reduction was first examined and it was found that the effect was similar to that observed in the cases of carboxylic acids and esters.[1,2] The reagent BMPA or dimorpholinoaluminum hydride (DMA) was found also to be a suitable reagent for this purpose as compared with diethylamine or N-methylaniline hydrides similar to the results obtained in reduction of carboxylic acids or esters. Further, reduction of several kinds of carboxamides, such as N-acylmorpholines, N,N-dialkylamides, N-methylbenzanilide, and benzanilide was examined using BMPA or DMA as a reducing agent as shown in Table 1.

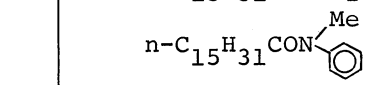
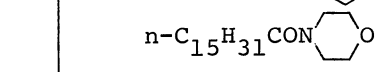
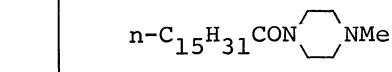
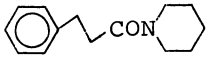
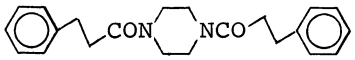
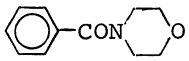
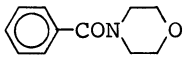
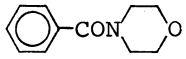
The advantage of BMPA or DMA in the reduction of various carboxamides was apparently different from the reduction with lithium aluminum hydride or its derivatives. Various carboxamides, which give only poor yields of the corresponding aldehydes by use of lithium aluminum hydride,[11] as N-acylpiperidine, and N,N-dimethylamide, were easily reduced by 2.5-3 molar amount of BMPA to afford the aldehydes in 70-80% yields. Benzanilide was reduced under the same conditions with 3.5 molar amount of BMPA to afford benzaldehyde in 42% yield, though N-monosubstituted carboxamides have so far never been employed as a precursor for preparation of aldehydes. On the contrary, reduction of N-methylbenzanilide using BMPA or DMA gave benzaldehyde in a relatively low yield (48% and 34%, respectively) along with N-benzyl-N-methylaniline (30% and 48%, respectively), whereas the reduction smoothly proceeded to give the aldehyde in 68% yield when lithium aluminum hydride was employed as described by Weygand et al.[8b] Whereas, N-methylpalmitanilide was reduced with BMPA to give palmitaldehyde in 73% yield in contrast to the result that lithium aluminum hydride[8b] afforded the aldehyde in 98% yield.

The following experiment provides a typical procedure of the reduction of carboxamides to aldehydes: To a solution of BMPA,[2] prepared from N-methylpiperazine (1.5 g, 15 mmol) and aluminum hydride in THF (0.65 M, 11.5 ml), was added N-palmitoylmorpholine (0.98 g, 3.0 mmol) in THF (8 ml) with cooling in an ice-bath under argon stream and the solution was refluxed for 6 hr. The resulted solution was treated in a manner similar to that described in the preceding paper[1] to give a crude oil 1.0 g. This was purified by silica-gel column chromatography to give palmitaldehyde, 575 mg (80%), mp 34°C.

Experimental data obtained in the reduction of various carboxamides with BMPA or DMA are summarized in Table 1.

Table 1 Yields of Aldehydes in the Reduction of Amides by BMPA or DMA



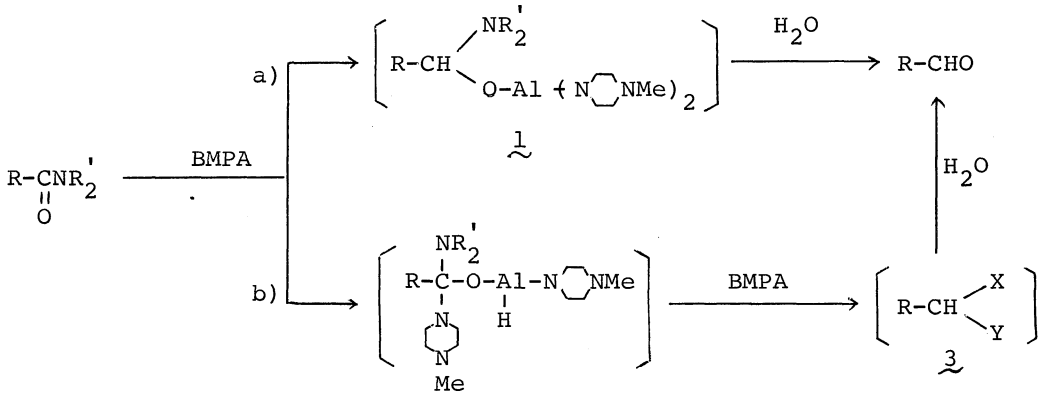
Carboxamides	Reagents	Ratio of Reagent/Amide	Conditions	Isolated[a] Aldehydes (%)
$n\text{-}C_{15}H_{31}CONMe_2$	DMA	2.5	refl. 6 hr	71
$n\text{-}C_{15}H_{31}CONMe_2$	BMPA	2.5	refl. 6 hr	70
$n\text{-}C_{15}H_{31}CONPr^i_2$	BMPA	2.5	refl. 4 hr	65
	BMPA	2.5	refl. 4 hr	73
	BMPA	2.5	refl. 6 hr	80
	BMPA	2.5	refl. 5 hr	76
	BMPA	2.5	refl. 4 hr	72
	BMPA	6.0	refl. 5 hr	72
	DMA	2.0	refl. 6 hr	(52)[b]
	BMPA	2.0	r.t. 1 hr	(56)[c]
	BMPA	2.5	refl. 5 hr	(71)
	BMPA	3.0	refl. 24 hr	(42)[d]

a) Yields by analysis with 2,4-dinitrophenylhydrazine are shown in parentheses.
b) Starting material was recovered in 25 % yield.
c) N-Benzoyl-N'-methylpiperazine was obtained in 8 % yield.
d) Starting material was recovered in 22 % yield.

Thus, BMPA is a unique selective reducing agent and provides a new preparative method of aldehydes from any of carboxylic acid, ester and amide derivatives.

The two possible reduction pathways are outlined in Scheme 1. Path (a) includes direct formation of a geminal aminoalcoholate 1, a general intermediate in the reduction of the amides to the aldehyde with metal hydrides.[3] Path (b) includes formation of an initial intermediate 2 by nucleophilic attack of of BMPA and subsequent conversion of 2 into 3, a precursor of aldehyde, with another

BMPA. The path (b) seems to be more reasonable from the fact that N-benzoyl-N'-methylpiperazine was isolated in 8% yield with the aldehyde (56%) when the reaction mixture was quenched by addition of water before the completion of the reduction of N-benzoylmorpholine with BMPA.



Scheme 1

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