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Communications

Aluminum–Amine Complexes for the Conversion of Carboxylic Esters to Amides. Application to the Synthesis of LTD_4 Antagonist MK-0679

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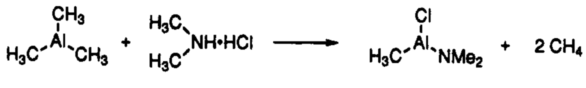
Summary: The preparation and characterization of *N,N*-dimethylammonium dialkylaluminum chloride and the use of these complexes in the synthesis of the LTD_4 antagonist MK-0679 is described.

The conversion of carboxylic esters to amides continues to be an important reaction in organic synthesis. While many old and proven methods exist for effecting this transformation, the development of newer amidation procedures allows for this chemoselective transformation in the presence of other reactive functional groups.

Weinreb has reported that organoaluminum species obtained by reaction of a trialkylaluminum with an amine[1] or amine hydrochloride[2] provide reactive aluminum complexes which are useful for the conversion of a variety of carboxylic esters and lactones to their amide counterparts. We have recently reported the use of this methodology in the preparation of a potent LTD_4 antagonist.[3] Herein, we describe the nature of the organoaluminum species and its role in the amidation of a functionalized carboxylic ester intermediate in the synthesis of MK-0679.

The addition of trimethylaluminum to dimethylamine hydrochloride was reported as a means of generating an active aluminum intermediate useful for the conversion of carboxylic esters to amides. It had been proposed[2] that the active amidating species produced in this reaction was (*N,N*-dimethylamido)chloro(methyl)aluminum, 1. The isolation and characterization of 1 was not reported.



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Trisubstituted aluminum species bearing sterically undemanding substituents are well known to exist as dimers, trimers, or polymers, possessing bridging ligands.[4] Trimethylaluminum, 2, is the quintessential example of this type of complex.[4b,c] Aluminum is formally tetravalent in these species and displays ^{27}Al NMR shifts significantly upfield (155 ppm, $W_{1/2}$ = 1.2 kHz, (lit.[5] 157 ppm)) of trivalent aluminum nuclei. The literature reports that the more sterically hindered complexes such as triisopropylaluminum and triisobutylaluminum, 3, exist as monomers.[6] The trivalent nature of $i\text{-}Bu_3Al$ is reflected by the ^{27}Al chemical shift of 253 ppm. Chemical shifts of 265 ± 10 ppm have also been reported for the sterically hindered three-coordinate $i\text{-}Pr_3Al$ and $t\text{-}Bu_3Al$ complexes.[7]

When a trialkylaluminum, such as trimethyl- or triisobutylaluminum, is added to dimethylamine hydrochlo-

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[●] Abstract published in *Advance ACS Abstracts*, February 15, 1994.

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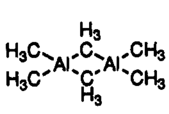

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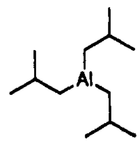


3

ride an exothermic reaction occurs accompanied by alkane evolution (eq 2). Characterization of the resultant alu-

(2)

4a: R= Me
4b: R= *i*-Bu

minum complex indicates formation of (*N,N*-dimethylammine)dialkylaluminum chlorides **4a** and **4b**.

Evidence for amine coordination in complexes **4a** and **4b** is seen in their IR spectra as NH stretching bands at 3220 and 3170 cm^{-1}, respectively. The NH proton in these complexes is also observed as a broad singlet at 1.6 ppm in their ^{1}H NMR spectra. Integration of the ^{1}H NMR spectra confirms the presence of two remaining alkyl groups on aluminum. Chlorine incorporation in complexes **4a** and **4b** has been verified by mass spectrometry.

The final support for the tetrahedral nature of these Al complexes was obtained from their ^{27}Al NMR spectra. ^{27}Al NMR spectroscopy of **4a** and **4b** shows a single resonance at 160 ppm ($W_{1/2}$ = 1.7 kHz) and 153 ppm ($W_{1/2}$ = 2.6 kHz), respectively. These chemical shifts are consistent with a tetrahedral Al nucleus.[8] Dimeric trimethylaluminum (δ 155 ppm), in which the Al is formally tetravalent, shows little change in chemical shift upon reaction with dimethylamine hydrochloride. However, in the case of the isobutyl analog a 100 ppm upfield shift is observed in going from trivalent triisobutylaluminum (δ 253 ppm) to tetravalent complex **4b**. The spectral data of **4a** and **4b** are consistent with the data reported by Krannich and Watkins for the related tetravalent aluminum species $[Me_2AlNMe_2]_2$, $^{27}Al\ \delta = 169$ ppm, and $Me_3AlNHMe_2$, $^{27}Al\ \delta = 174$ ppm.[9a,b] Complete IR and NMR spectral data for several other tetrahedral aluminum complexes of the general form $[Me_2AlNR_2]_2$ and $Me_3Al{\cdot}NHR_2$ have also been reported.[9]

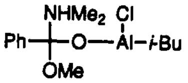
Complexes **4a** and **4b** are also readily prepared by reaction of the corresponding dialkylaluminum chloride with dimethylamine. In these cases no alkane evolution is observed (as either gas evolution or evidenced in the ^{1}H NMR spectrum).[10] Heating complexes **4a** or **4b** in toluene for 3 h at temperatures up to 100 °C results in no change in their ^{1}H, ^{13}C, or ^{27}Al NMR spectra.

While many alkylaluminum halides and chloroaluminum amine complexes exist as dimers, trimers, or polymers,[5,11] Laubengayer has isolated and characterized several alkylchloroaluminum ammine complexes and shown them to exist as monomers in benzene solution.[4a] In particular, (dimethylammine)diethylaluminum chloride was prepared from dimethylamine and diethylaluminum chloride.

Addition of **4b** (prepared in situ or isolated by vacuum distillation) to methyl benzoate affords quantitative conversion to *N,N*-dimethylbenzamide (eq 3). In situ

(3)

NMR studies show that the ester carbonyl carbon at 166.8 ppm disappears during the course of the reaction with a concomitant appearance of the amide carbonyl carbon at 171.6 ppm. Analysis of the reaction by IR spectroscopy shows disappearance of the ester carbonyl band at 1720 cm^{-1} accompanying formation of amide carbonyl bands at 1635 and 1605 cm^{-1}. The results support a mechanism where benzamide is formed directly under the reaction conditions. Formation of a stable tetrahedral complex, **5**,



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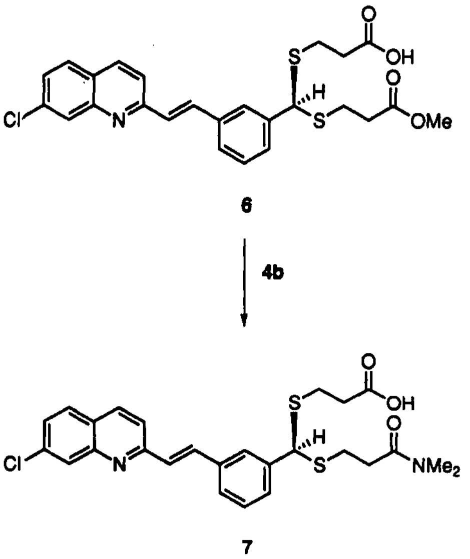
which collapses to the free amide upon hydrolytic workup has not been observed. In situ multinuclear NMR studies utilizing complexes **4a** or **4b** show no intermediates resembling Al–amide complex **1** formed during the amidation reaction.[12]

The amidation of ester–acid **6**,[3] to produce LTD$_4$ antagonist **7**, proved to be a more interesting example of the utility of this aluminum reagent. The presence of the unprotected carboxylic acid demanded a high degree of chemoselectivity in the amidation. In addition, the susceptibility of the ester to undergo a facile retro-Michael reaction required the introduction of the dimethylamine group under fairly mild conditions.



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4b

7

(4)

Multinuclear NMR and IR studies show that addition of 0.5 mol equiv of aluminum–amine complex **4b** to the ester–acid results in rapid complexation of two carboxylic

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[10] It has been reported that no gas evolution is observed upon treatment of ammonia with dimethylaluminum chloride. Blanchard, L. A.; Schneider, J. A. *J. Org. Chem.* **1986**, *51*, 1372.

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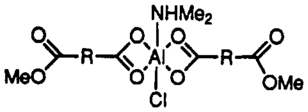
acid moieties to each aluminum, with extrusion of isobutane, affording octahedral complex 8. Analysis of the IR spectrum shows disappearance of the free carboxylic acid band at 1730 cm^{-1} with a concomitant appearance of carboxylate bands at 1600 and 1450 cm^{-1}. A shift in the ^{13}C NMR spectrum for the carboxylic acid carbon from 173.0 ppm to 180.0 ppm was also observed, consistent with carboxylate formation. No change was evident in the chemical shift of the ester carbonyl carbon (172.3 ppm). Aluminum isobutyl ligands are absent in both the ^{1}H and ^{13}C NMR spectra. Analysis of complex 8 by ^{27}Al NMR shows a single resonance at 3.0 ppm ($W_{1/2}$ = 1.0 kHz). The 150 ppm upfield shift in the ^{27}Al spectrum (from 153 ppm for the tetrahedral Al–ammine complex) is indicative of an octahedral Al species.[13] The equatorial disposition of the dicarboxylate ligands has not yet been determined.



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Addition of at least 1 mol equiv of (dimethylammine)diisobutylaluminum chloride, **4b**, to octahedral complex 8 was necessary to affect amidation of the ester moiety. Addition of less than 1 full equiv of **4b** led to incomplete conversion to amide–acid 7. Likewise, addition of less than 1 equiv of **4b** in the presence of excess dimethylamine hydrochloride afforded incomplete conversion to amide–acid. The need for at least 1 mol equiv of complex **4b** to effect the amidation indicates that the dimethylammine ligand on octahedral complex 8 is not able to act as a nucleophile and that the reaction is more complex than a simple attack of dimethylamine on Lewis acid complex 8.

To evaluate the lability of the dimethylammine ligand of octahedral complex 8 a deuterium-labeling study was performed. Complex **4b**-d_6 was prepared from iBu$_3$Al and dimethylamine hydrochloride-d_6. Addition of 0.5 mol equiv of **4b**-d_6 to ester–acid **6** led to the formation of octahedral complex **8**-d_6. Complex **8**-d_6 was then treated with 1.5 equiv of unlabeled tetrahedral complex **4b**. It was determined by ^{1}H NMR and mass spectral analysis of isolated **7** that 18% deuterium incorporation had occurred. Likewise, treatment of unlabeled **8** with 1.5 equiv of **4b**-d_6 afforded amide–acid **7** containing 83% deuterium incorporation at the amide position. These mixtures of labeled/unlabeled products indicate that the dimethylammine ligands of both the tetrahedral complex **4b** and the octahedral complex **8** are labile and undergo exchange.

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Supplementary Material Available: Experimental details of **4a**, **4b**, and **7**, including spectral data (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[13] Quadrupolar nuclei, and therefore line width, are extremely sensitive to symmetry and anisotropic effects of their environment. Chemical shift values in the region of 0.0 ppm are common for octahedral Al species. See ref 8.