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Stereoselective synthesis of enones from the reaction of aldehydes with sterically hindered dimethylaluminum enolates

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Abstract

The equimolar reaction between Me_3Al and the methyl ketones $(2,4,6\text{-}R_3\text{–}C_6H_2)C(O)CH_3$, where R = Me or ^{i}Pr, results in exclusive formation of the enolization products $[\{Me_2AlOC(2,4,6\text{-}R_3\text{–}C_6H_2){=}CH_2\}_2]$, **1** and **2**, upon heating to reflux temperature in toluene solution. The property of Me_3Al acting as a base rather than a nucleophile in these reactions is due to the sterically hindered nature of the ketones. Crystallographic analysis of **2** revealed a dimeric complex where the metal centers are bridged by the enolate anions, consistent with the previous studies of **1**. Addition of a series of aldehydes to hexane solutions of **1** and **2**, followed by heating to reflux for several hours gave enone products in generally high conversions. The presumed aluminum aldolate intermediates were not detected by in situ monitoring studies and are presumably short-lived under the reaction conditions. The enone products from the addition reactions were formed predominantly as the *E*-isomers with good to excellent stereoselectivities.

Keywords: Enolates; Aluminum; Enones; Crystal structure

1. Introduction

The reaction between triorganoaluminum compounds and ketones commonly results in four outcomes: acid-base complex formation, reduction via β-hydride elimination, direct alkylation across the carbonyl, and enolization [1]. The product distribution is influenced by all the expected factors including the nature of the organic anions, the size and electronics of the ketone, the temperature of the reaction and the solvent media used [2,3]. In general, these reactions produce a mixture of products and hence their utility in synthesis has remained limited [4,5]. We previously reported that the reaction between Me_3Al and 2,4,6-trimethylacetophenone in toluene under ambient temperature resulted in formation of the complex $[Me_3Al\cdot O{=}C(2,4,6\text{-}Me_3\text{–}C_6H_2)Me]$, which cleanly converted to the enolate $[\{Me_2AlOC(2,4,6\text{-}Me_3\text{–}C_6H_2){=}CH_2\}_2]$, **1** upon heating to reflux for several hours [6,7]. The behavior of Me_3Al as a base rather than a nucleophile to give exclusive enolization was somewhat unexpected considering the small size of the organic moiety [8,9]. The key to this selectivity was found to be dependant on the steric encumbrance of the aromatic ketone, where disubstitution at the *ortho* positions of the ring by methyl groups was required for enolization to be the dominant reaction pathway. We now report an extension to this work, investigating the reaction chemistry of two aluminum enolates derived by this direct enolization route with a series of aldehydes. In addition, the crystal structure of a new dimethylaluminum enolate intermediate has been elucidated.

2. Results and discussion

2.1. Syntheses and structural characterization

The enolate complex $[\{Me_2AlOC(2,4,6\text{-}Me_3\text{–}C_6H_2){=}CH_2\}_2]$, **1**, was prepared as previously described [6]. For

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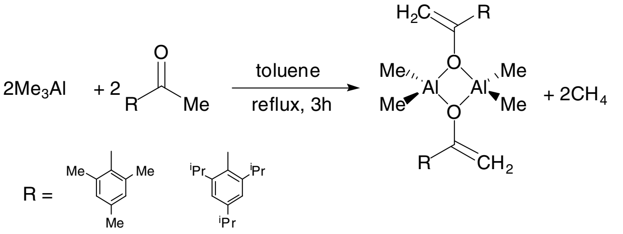
comparative purposes, the enolate [{$Me_2AlOC(2,4,6$-$^iPr_3$–$C_6H_2)$=$CH_2\}_2$], **2**, was targeted and successfully prepared as the sole product from the equimolar reaction of Me_3Al with 2,4,6-triisopropylacetophenone in toluene solution after heating to reflux for 3 h (Eq. (1)).



(1)

Removal of the solvent in vacuo and replacement by hexane followed by cooling the solution to −45 °C resulted in the precipitation of high quality crystals of **2**. In turn, this allowed the characterization of **2** by ^1H and ^{13}C NMR spectroscopy, and also by single-crystal X-ray diffraction. The ^1H NMR spectrum of **2** in C_6D_6 shows a single set of signals for the aromatic *meta*-Hs and also for the methyl groups attached to the aluminum, consistent with the expected composition. A pair of doublets due to the olefinic protons are present and two independent sets of ^iPr groups in a 2:1 ratio arising from the *ortho*- and *para*-units, respectively, complete the spectrum. A somewhat different pattern is found in the ^{13}C NMR spectrum of **2**. Three independent methyl resonances at δ 23.35, 24.48 and 27.07 are found, along with two methine signals at δ 31.23 and 35.15. This pattern suggests that the methyl carbons of the *ortho*-isopropyl groups are inequivalent. Indeed, the recent characterization by Kunicki of the closely related complex [$Ph_2AlOC(2,4,6$-$^iPr_3$–$C_6H_2)$=$CH_2\}_2$], **3**, displays a very similar ^{13}C NMR spectrum [10]. This pattern of signals can be explained by restricted rotation of the aromatic groups locking the isopropyl units into asymmetrical environments [11]. Interestingly, the ^1H NMR spectrum of **3** also displays this behavior whereas that of **2** shows only a single set of resonances for the *ortho*-units. This suggests greater flexibility in **2** due to smaller methyl groups being attached to the metal compared with phenyl groups in **3**. These studies are also consistent with the expected dimeric aggregation remaining intact in solution.

X-ray crystallographic studies of **2** revealed the expected dimeric arrangement, with a central Al_2O_2 ring (Fig. 1). This structure is in accord with those previously reported for **1** and **3** [6,10]. Two almost identical but independent dimers are formed within the unit cell of **2** and their key bond lengths and angles are given in Table 1. In general, the geometric parameters in **2** are similar to those reported for related Al_2O_2 ring systems [12]. For example, the mean Al–O distance of 1.870 Å (range 1.863–1.878 Å), and the mean Al–C distance of 1.950 Å (range 1.949–1.952 Å) are within the ranges of those found in **1** and **3**. Also the mean Al–O–Al and O–Al–O angles of 100.75° and 79.25° in **2** are within 1.5° of those in **1** and **3**. In all three complexes **1**–**3** the enolate group sits approximately in the same plane as the Al_2O_2 ring, with Al–O–C=CH_2 dihedral angles of 23.3 and 22.0° in **1** and **3**, whereas the two independent dimers of **2** have these angles at 28.1° and 31.8°. The overall similarity of **1**–**3** indicates that the increase in steric hindrance at the *ortho*-positions of the aromatic ring in **2** and **3** compared to **1**, or the increased size of the organic anion of **3** compared to that in **1** and **2** has little notable effect on the structures adopted. Nevertheless, the structural characterization of **2** represents an addition to the small handful of crystal structures that have been successfully completed for aluminum enolates derived from simple ketones [13].

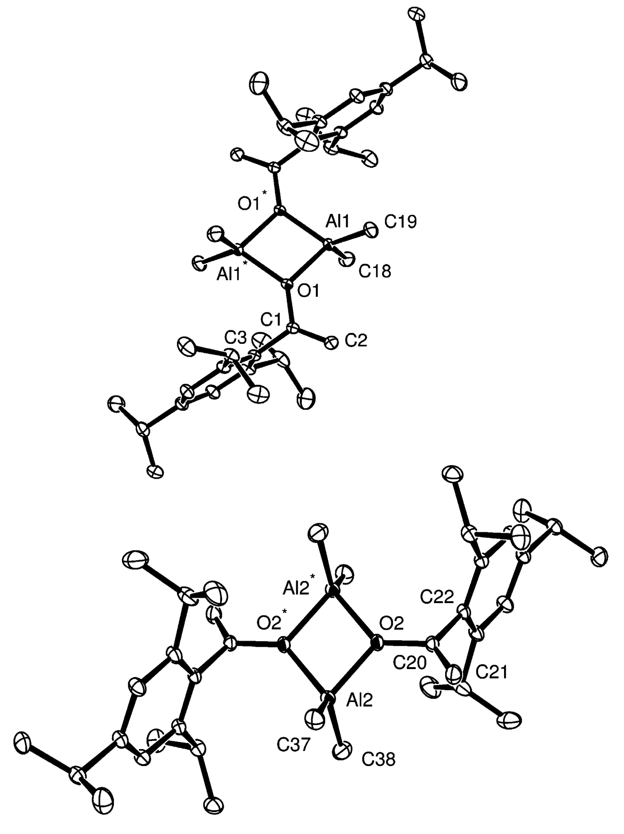


Fig. 1. Crystal structure of the two independent molecules of **2**, showing two alternative views of the dimers. Hydrogen atoms are removed for clarity.

2.2. Reaction of enolates 1 and 2 with aldehydes

We were interested in determining the reactivity of the aluminum enolates **1** and **2** with aldehydes. From our perspective the most desirable reaction was aldol addition, due to the importance of this transformation in the stereoselective formation of new carbon–carbon