Direct Conversion of Carboxylic Esters into Ketones Using Organoaluminum Complexes

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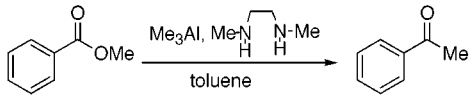
The conversion of carboxylic esters into the corresponding ketones is a fundamental organic reaction. Direct conversion of esters to ketones using nucleophiles, however, is difficult to achieve because ketones are more reactive toward nucleophiles than the starting esters, and in most cases over-reacted products such as tertiary alcohols and/or reduced products are obtained.[1] An organoaluminum reducing agent, DIBALH, is widely used for the direct conversion of esters into the corresponding aldehydes.[2] In this case, a tetrahedral alkoxyaluminum intermediate is stable under the reaction conditions and provides the mono-addition product upon hydrolyzing the reaction mixture. However, a similar process with carbon nucleophiles has been rarely reported. Therefore, indirect approaches are usually employed for the transformation. For example, the Weinreb's amide is the preferred intermediate for the delivery of nucleophiles to give ketones selectively.[3] In this case, the addition product is stabilized by a five-membered metal chelate during the reaction. We wish to report our findings that the direct conversion of esters into ketones, without the formation of the over-addition products, can be realized by organoaluminum complexes generated from a trialkylaluminum and a diamine. The system is unique in that aldehydes and ketones survive under the reaction conditions.

We have found that the reaction of methyl benzoate with an equimolar mixture of trimethylaluminum and *N*,*N*′-dimethylethylenediamine (DMEDA) in refluxing toluene followed by an aqueous workup produces only acetophenone. The conversion requires both DMEDA and Me_3Al. Variation of molar equivalents of DMEDA and Me_3Al indicates that the reaction is stoichiometric with regard to DMEDA. Although reasonable conversion (83%) was observed with two equiv of Me_3Al, near-quantitative conversion was guaranteed when three equiv was used. The results are summarized in Table 1. Other organoaluminum reagents such as Et_3Al can be equally used to give the corresponding ethyl ketones. The reaction requires the refluxing temperature of toluene and does not proceed at all at room temperature. Also, the reaction does not proceed in solvents such as THF or $CHCl_3$. Under the established conditions, various substrates have been tested and some of the results are summarized in Table 2.[4] Particularly notable is that

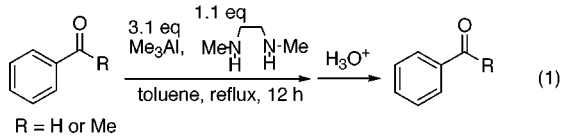
Table 1. Conversion of Methyl Benzoate to Acetophenone Using Me_3Al−Diamine Complexes

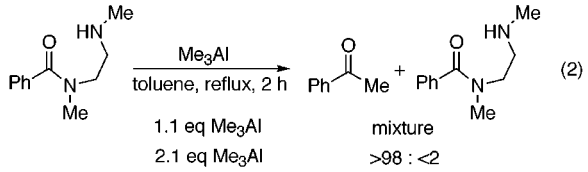


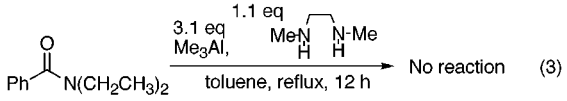
	molar equiv				
entry	diamine	Me_3Al	rxn time	temp (°C)	% conversion[a]
1	1.1	1.2	2 h	reflux	43
2	2.2	2.2	2 h	reflux	77
3	1.1	2.2	13 h	reflux	83
4	1.1	3.0	1 h	reflux	98
5	1.1	3.0	2 d	rt	0
6	0	1.2	18 h	reflux	0

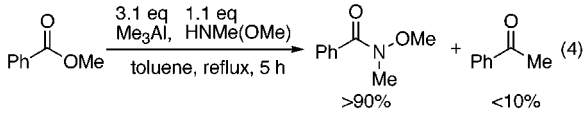
[a] Determined by GC analyses.

acetophenone and even benzaldehyde survived under the reaction conditions and recovered after aqueous workup. We have carried out several experiments depicted in eqs 1−4 to get a reasonable mechanistic picture for the transformation.[5] We observed that the conversion proceeded through transamidation and the reaction intermediate can be isolated. This is not an unexpected result since similar









transamidation using 1,2-diaminoethane− or 1,2-amino alcohol−trialkylaluminum complexes has been utilized in the literature.[6] When the intermediate amide, *N*-methyl-2-(*N*-methylamino)ethylbenzamide,[7] was treated with 1.1

(1) Kikkawa, I.; Yorifuji, T. *Synthesis* **1980**, 877−880.

(2) (a) Zakharkin, L. I.; Khorlina, I. M. *Tetrahedron Lett.* **1962**, 619−620. (b) Winterfeldt, E. *Synthesis*, **1975**, 617−630. (c) Chandrasekhar, S.; Kumar, M. S.; Muralidhar, B. *Tetrahedron Lett.* **1998**, *39*, 909−910.

(3) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818. (b) For other examples, see: Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989; pp 695−697.

(4) A representative procedure: To a toluene (6.0 mL) solution of *N*,*N*′-dimethylethylenediamine (0.14 mL. 1.32 mmol) at 0 °C under an argon atmosphere was added dropwise trimethylaluminum (1.86 mL, 2.0 M in toluene). The reaction mixture was stirred at room temperature for 1 h before adding methyl 3-phenylpropionate (0.20 mL, 1.2 mmol). The resulting mixture was heated to reflux until the reaction was complete judged from TLC analysis (1 h). The reaction mixture was cooled to room temperature and quenched with 1 N aqueous HCl solution (or 20% aqueous solution of Rochelle salt). Extractive workup with ethyl acetate and chromatography through a short-pad of SiO_2 (eluent: 10% ether in hexanes) afforded 4-phenyl-2-butanone (135 mg, 76% yield).

(5) We have carried out ^{27}Al NMR study on the aluminum complexes. The NMR spectra of 1:1 complex of Me_3Al and DMEDA in toluene exhibited a singlet downfield (177.1 ppm) compared to that of Me_3Al (154.0 ppm) (relative to $Al(OH)_3$ in D_2O). We suspect that it may exist as dimeric or oligomeric complexes, as usually observed with many organoaluminum complexes, see: (a) Eisch, J. J. *Comprehensive Organometallic Chemistry I*; Willinson, G., Ed.; Pergamon: Oxford, 1995; Vol. 1, pp 555−682. (b) Robinson, G. H. *Coordination Chemistry of Aluminum*; VCH: New York, 1993. (c) Smith, J. D. *Organometallic Compounds of Aluminum, Gallium, Indium and Thallium*; McKillop, A., Smith, J. D., Worrall, I. J., Eds.; Chapman and Hall: New York, 1985.

(6) (a) Neef, G.; Eder, U.; Sauer, G. *J. Org. Chem.* **1981**, *46*, 2824−2826. (b) Ahn, K. H.; Cho, C.-W.; Baek, H.-H.; Park, J.; Lee, S. *J. Org. Chem.* **1996**, *61*, 4937−4943.

(7) Prepared from DMEDA by the following sequence: i) 1.0 equiv of TsCl, Py, 0 °C, CH_2Cl_2, 53%; (ii) PhCOCl, Et_3N, 0 °C, CH_2Cl_2, 96%; (iii) Na, naphthalene, 25 °C, DME, 20%.

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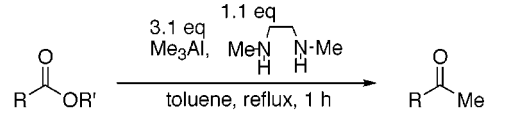
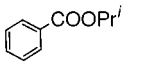
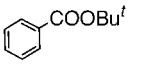
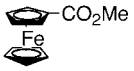
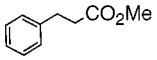
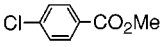
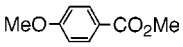
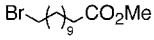
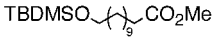
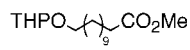
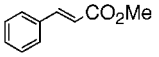
Table 2. Conversion of Various Esters to Ketones Using Me_3Al–Diamine Complexes

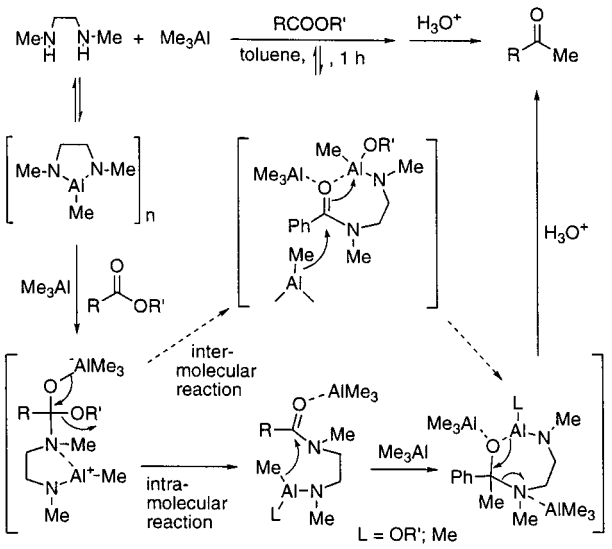


Entry	Ester	Yield (%)[a]
1		(98)
2		(98)
3		53
4		76
5		68
6		59
7		(95)
8		71
9		22[b]
10		6[c]

[a] Isolated yields after column chromatography: Those in parenthesis are conversion determined by NMR analysis. [b] The transamidation intermediate was isolated in 85% yield. [c] Polymerization was observed.

equiv of Me_3Al, a mixture of acetophenone and the starting material was obtained. When 2.1 equiv of Me_3Al was used, a complete conversion was observed. Thus, activation of the carbonyl oxygen by Lewis-acidic aluminum species seems to be required for the nucleophilic attack. No change was observed when a simple amide, *N*,*N*-diethylbenzamide, was treated with a 3:1 complex of Me_3Al and DMEDA. These results indicate that the amino group of the intermediate plays an important role for the subsequent nucleophilic attack. Based on these experiments, we could draw a possible reaction pathway as shown in Scheme 1.[8] Between the two pathways, intermolecular attack of "Me"-nucleophile vs intramolecular attack, the latter is believed to be the preferred route because *N*-methoxy-*N*-methylbenzamide, which would proceed through the intermolecular version if it were the case, gave less than 10% of acetophenone even after refluxing for 5 h (eq 4). When 2-(*N*-methylamino)-ethanol was used instead of DMEDA, the same transformation occurred but with a much slower rate.[9] The intramolecular transfer of the Me-nucleophile from the corresponding alkoxyaluminum group must be less favorable compared to the case of aluminum amide group. This result indicates that the intramolecular transfer of the nucleophile is the rate-determining step. The intramolecular transfer of the Me-nucleophile to the carbonyl group activated by Lewis-acidic Me_3Al and stabilization of the subsequent addition intermediate as the chelated aluminum species would explain the occurrence of the rather difficult transformation of the intermediate amide to the corresponding ketone. The addition intermediate, a seven-membered aminal compound, may have additional coordination of Me_3Al and thus overall 3 equiv of trialkylaluminum are necessary for the fast reaction. On the basis of this mechanism, we could explain the complete chemoselectivity observed toward aldehyde and ketone. In both cases, the addition of DMEDA to the carbonyl group would provide an aluminum-chelated tetrahedral intermediate that is inert toward the subsequent nucleophilic attack. Upon hydrolysis, the starting material is readily regenerated. Carboxylic esters of secondary and tertiary alcohols are readily converted to the ketones. The conversion was near-quantitative for the substrates that do not have multiple Lewis-basic atoms.[10] For those substrates that contain Lewis-basic atoms such as THP-ether, the transamidation intermediates remained as the major component, resulting in the lower conversion to the corresponding ketones.

Scheme 1



In summary, a direct and selective conversion of esters into ketones that is a fundamental reaction but difficult to achieve is now possible through organoaluminum–diamine complexes. Aldehydes and ketones survive under the reaction conditions. A mechanistic study established that the conversion proceeds through transamidation and subsequent intramolecular nucleophilic attack mediated by organoaluminum complexes.

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(8) The depicted structures of organoaluminum intermediates are merely based on the stoichiometry.

(9) The transamidation product, *N*-(hydroxyethyl)-*N*-methylbenzamide, was slowly, but not completely, converted to the acetophenone (40% conversion after 5 h).

(10) The moderate to good yields shown in the table is due to the loss occurred during the isolation of volatile products.