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ALKYL AND ARYLLANTHANUM TRIFLATES: NEW REAGENTS FOR THE CONVERSION OF TERTIARY AMIDES TO KETONES

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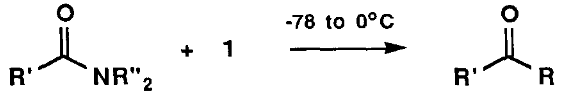
Abstract: Alkyl and aryllanthanum triflates **1** generated *in situ* from alkyl or aryllithium compounds and anhydrous lanthanum(III) triflate react with tertiary amides to provide, in excellent yield, the corresponding alkyl or aryl ketones.

There is much current interest in the use of lanthanide reagents in organic synthesis since these compounds exhibit modified reactivity by comparison with traditional reagents allowing their use for chemoselective transformations.[1] In particular, alkyllanthanide halides have been shown to function as mild nucleophiles in their addition to carbonyl compounds and related systems.[2] We have been recently studying the reactivity of analogous species derived from anhydrous lanthanum triflates[3] and alkyl or aryllithium compounds (eqn. 1).[4] We now report that these reagents react rapidly and cleanly with aromatic or aliphatic tertiary amides to provide ketones(eqn. 2). Conversion of tertiary, unhindered aryl or alkylamides(esp. N,N-dimethylamides) to ketones is traditionally effected using Grignard reagents or alkyllithiums.[5] An excess of these reagents is often required and further reaction of the initially formed ketone with the alkylmetal compound is often observed. In the case of hindered aliphatic or aromatic amides enolization or metalation can be a competing

$$\mathbf{RLi} \; + \; \mathbf{La(OTf)_3} \xrightarrow[-78^{\circ}\mathrm{C}]{\mathrm{Et_2O\ or\ THF}} \underset{\mathbf{1}}{\mathbf{RLa(OTf)_2}} \qquad \text{eqn. 1}$$

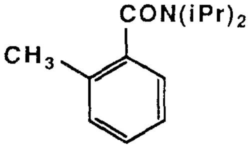
$$\mathrm{R = Me,\ Bu,\ Ph} \qquad \mathrm{OTf = {}^{-}OSO_2CF_3}$$



eqn. 2

and sometimes desirable side reaction.[6]

The results of this new addition reaction (eqn. 2) are summarized in the Table. A few points are worth noting. Both alkyl and aryllanthanum triflates react cleanly (entries 1-3 and 13). Arylamides with σ electron-withdrawing substituents or donor atoms (methoxy) require an excess of the reagent for complete reaction (entries 6-8). Even in these cases negligible formation of alcohols was observed. Halogen-metal exchange does not occur under the reaction conditions (entry 6) in line with previous results.[2a] Although ortho substituted N,N-diethylbenzamides and N,N-diisopropylbenzamides can be transformed in good yield to the corresponding ketones (entries 8 and 9), N,N-diisopropyl -ortho-toluamide (**3**) and the highly hindered N,N-diethylbiphenylamide **4** failed to react under quite vigorous conditions(entries 10 and 11).



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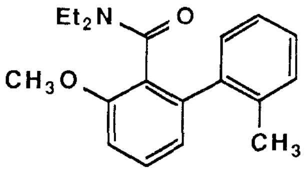

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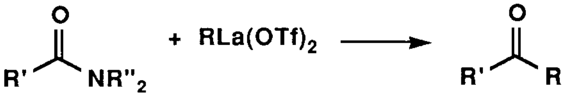
This addition process succeeds with aliphatic amides including those that could be easily enolized by more conventional reagents(e.g. entry 12). In these cases (entries 12 and 13), significant amounts of the corresponding alcohols were also formed.

The following procedure is typical: To a suspension of $La(OSO_2CF_3)_3$(1.2 mmol) in THF (5 mL) at -78°C under argon was added a solution of MeLi-LiBr in Et_2O (O.60 mL, 2.0 M) *via* syringe. After 5-10 min the amide(1.0 mmol) dissolved in THF (2 mL) was added to the homogeneous solution. After the reaction was complete, as judged by TLC, the solution was quenched with saturated NH_4Cl and warmed to room temperature. The mixture was diluted with Et_2O and the organic phase washed with 2N HCl, saturated $NaHCO_3$, brine and then dried($MgSO_4$). Concentration *in vacuo* followed by flash chromatography[7] on silica gel provided pure ketone.

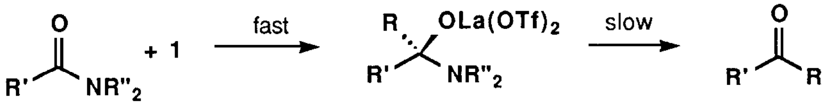
The mechanism of this reaction presumably involves initial addition of the alkyllanthanum triflate to the amide to give a tetrahedral intermediate(eqn. 3). Under the conditions of the reaction formation of this intermediate is apparently much faster

Table[a]



Entry	R'	R"	R(equiv.)	Solvent	Temp(°C)	Time(min)	Yield[b]
1	Ph	Et	Me(1.2)	THF	-78	30	95
2	Ph	Et	Ph(2.0)	THF	-78	30	98
3	Ph	Et	*n*Bu(1.2)	Et$_2$O	-30	30	94
4	*m*-tolyl	Et	Me(1.2)	Et$_2$O	0	30	92
5	*p*-tolyl	Et	Me(2.0)	THF	-78	20	98
6	*m*-ClPh	Et	Me(2.0)	THF	-78	20	95
7	*m*-MeOPh	Et	Me(3.0)	THF	-78	20	96
8	*o*-MeOPh	Et	Me(3.0)	Et$_2$O	25	20	91
9	Ph	*i*Pr	Me(1.0)	Et$_2$O	-78	30	80[c]
10	*o*-tolyl(**3**)	*i*Pr	Me(1.0)	Et$_2$O	reflux	30	N.R.
11	**4**	Et	Me(3.0)	THF	reflux	30	N.R.
12	*p*-MeOC$_6$H$_4$CH$_2$	Et	Me(3.0)	THF	-78	20	82[d]
13	2-ethylpropyl	Et	Ph(2.0)	Et$_2$O	-30	30	81[d]

a. All compounds were identified by their IR and ^{1}H-NMR spectra. b. Isolated yield following chromatography. c. The dimethyl alcohol was isolated in 10% yield. d. The corresponding dimethyl or diphenyl alcohol was formed in 16% yield.



eqn. 3

than subsequent liberation of the free ketone. A competition experiment indicated that preferential consumption of a ketone occurs under these conditions.[8]

Finally, we note that this reaction is clearly superior to classical methodology: treatment of N,N-diethylbenzamide at -78°C for 2 h with methyllithium (1.2 equiv.) led to the formation of acetophenone and 2-phenyl-2-propanol in 26 and 15% yield, respectively in addition to unreacted starting material (54%).[9]

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8. N,N-diethyl-para-toluamide (1 equiv.) and acetophenone (1 equiv.) were added to 1 equiv. of methyllanthanum triflate in THF at -78°C. Standard work up provided recovered amide (98%), acetophenone (33%) and 2-phenyl-2-propanol (65%) after column chromatography.
9. We also note that $MeCeCl_2$, prepared according to reference 2a, was not reactive towards amides under the same conditions as those observed for complete conversion using compounds **1** (R = Me).

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