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THE REACTION OF LITHIO-ALKYL-ISOXAZOLES WITH ACID CHLORIDES IN THE PRESENCE OF CERIUM TRICHLORIDE. DIRECT PREPARATION OF β-KETO-ISOXAZOLYL COMPOUNDS

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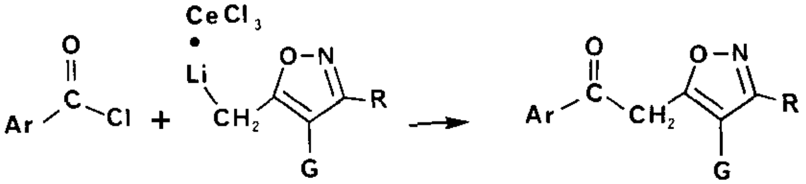
Abstract — Lithio-alkyl-isoxazoles react with acid chlorides in the presence of cerium trichloride to give β-keto-isoxazoles.

The use of the lanthanide elements to mediate organic reactions has recently gained broad application.[1] The 1,2-reduction of unsaturated ketones with sodium borohydride-cerium trichloride has become the method of choice for allylic alcohol preparation from unsaturated ketones.[2] Kagan has developed methodology for the formation of carbon-carbon bonds using samarium diiodide in a lanthanide Barbier reaction,[3] and very recently Molander has applied the lanthanide Barbier reaction to elegant intramolecular cyclizations which proceed with a high degree of stereocontrol.[4] Danishefsky has reported that lanthanide shift reagents are efficient catalysts of hetero-Diels-Alder reactions.[5] Imamoto has found that alkyl-lithium[6a] or Grignard[6b] reagents in the presence of cerium trichloride are less basic, and more selective for 1,2-addition with unsaturated ketones. Lanthanide(II) reagents have been reported to react with acid chlorides to give ketones,[6d] however, lanthanide(II) reagents are also known to ring open isoxazoles.[7a]

In a program directed towards the study of the utility of isoxazoles in synthesis,[7] we required β-keto-isoxazoles with a carboxyl functional group in the C-4 position of the isoxazolyl moiety. Oxidation of β-hydroxy isoxazoles was found to result in retro aldol fragmentation and elimination,[8] an observation consistent with the chemistry of related β-hydroxy ketones.[9] We now report that cerium trichloride moderates[10] the reactivity of lithio-alkyl-isoxazoles with acid chlorides, and that the β-keto-isoxazolyl products can be obtained in useful yields in direct fashion.[11]

The lowest yields were obtained in the case of the carboxamide (entry 3), where the limitation is probably due to the insolubility of the lithio-anion at -78°C, and the corresponding inefficiency of trans-metalation. Careful examination of the reaction mixtures and purified products by CI-MS indicate only traces of tertiary alcohol, except in one case (entry 2). The tertiary alcohol by-product in this case (entry 2) was observed as a minor product, and was readily characterized by a molecular ion in the mass spectrum [CI-MS: m/z 483 (8.2 % rel. intensity) M+1; 465 (18), M-17.]



The general experimental procedure is convenient and straightforward. The lithio-isoxazolyl-anion is prepared as previously described, by the dropwise addition of n-Butyl lithium to a cold (-78°C) solution of isoxazolyl substrate. One equivalent of anhydrous cerium trichloride was added via an airless storage tube, and the resulting slurry stirred for 1 h. A solution of the acid chloride in THF was then added via syringe, and after 2 h at -78°C, the reaction mixture was quenched. The products were purified by radial chromatography on the Harrison Associates Chromatotron. Representative results are shown in the Table.

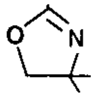
Table. Reaction of lithio-alkyl-isoxazoles with acid chlorides in the presence of cerium trichloride.

Entry	G	R	Ar	%[a,b]	MS(M^+% rel. intensity)
1	Ox[c]	CH_3	Ph	70	298 (6.9)
2	Ox	CH_3	2-furyl-	65	289 (100)
3	CON(iPr)$_2$	CH_3	Ph	50	328 (2)
4	Ox	CH_3	3,5-dimethyl-isoxazol-4-yl-	53	317 (1.7)
5	Ox	Ph	3-phenyl-5-methyl-isoxazol-4-yl	61	441 (1.6)
6	Ox	Ph	Ph	67	360 (38)
7	Ox	Ph	p-CNPh	60	385 (19.7)

[a] Products were purified by column or radial chromatography.

[b] Products gave NMR and IR data consistent with the assigned structures.

[c] Ox =



[d] CI

Further studies on the chemistry of isoxazoles and lanthanide mediated methodology are in progress.

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