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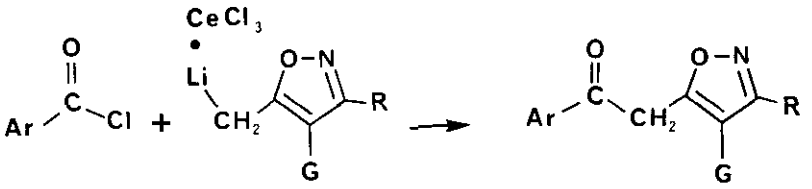
Abstract — Lithio-alkyl-isoxazoles react with acid chlorides in the presence of cerium trichloride to give β-keto-isoxazoles.

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.

The authors thank the M. J. Murdock Charitable Trust of Research Corporation, the Donors of the Petroleum Research Fund as Administered by the American Chemical Society, and the National Institutes of Health for BRSG SO7 RR 07170 for support of this work. We are also grateful to the National Science Foundation for a departmental instrument grant CHE-8504253 (GC-MS).

REFERENCES

1. For recent reviews, see: (a) T. Imamoto, Y. Tawarayama, T. Kusumoto, and M. Yokoyama, J. Synth. Org. Chem. Jpn., 1984, 42, 143.
(b) H. B. Kagan and J. L. Namy, "Handbook on the Physics and Chemistry of Rare Earths," North-Holland Publishing Company, Amsterdam, 1984, Vol. 6.
(c) H. Schumann, ibid., 1984, Vol. 7.
(d) J. R. Long, ibid., Vol. 8.
(e) H. Schumann, Angew. Chem. Int. Ed. Engl., 1984, 23, 474.
(f) N. R. Natale, Org. Prep. Proced., Int., 1983, 15, 387.
2. J.-L. Luche, J. Am. Chem. Soc., 1978, 100, 2226.
3. (a) P. Girard, J. L. Namy, and H. B. Kagan, J. Am. Chem. Soc., 1980, 102, 2693.
(b) J. Souppe, L. Danon, J. L. Namy, and H. B. Kagan, J. Organomet. Chem., 1983, 250, 227.
(c) P. Girard, R. Couffignal and H. B. Kagan, Tetrahedron Lett., 1981, 3959.
4. G. Molander and J. Etter, Tetrahedron Lett., 1984, 25, 3281.
5. (a) M. Bednarski and S. Danishefsky, J. Am. Chem. Soc., 1983, 105, 6968.
(b) Idem, ibid., 1983, 105, 3716.
6. (a) T. Imamoto, T. Kusumoto, Y. Tawarayama, Y. Sugiura, T. Mita, Y. Hatanaka, and M. Yokoyama, J. Org. Chem., 1984, 49, 3904; this reference contains citations to the considerable efforts of this group.
(b) T. Imamoto, N. Takiyama, and K. Nakamara, Tetrahedron Lett., 1985, 26, 4763.
(c) Other groups have utilized this methodology successfully: M. Kawasaki, F. Matsuda, and S. Terashima, Tetrahedron Lett., 1985, 26, 2693.
(d) T. Fukagawa, Y. Fujiwara, and H. Taniguchi, Chem. Lett., 1982, 601.
(e) M. Suzuki, Y. Kimura, and S. Terashima, Chem. Lett., 1984, 1543.
7. (a) N. R. Natale, Tetrahedron Lett., 1982, 23, 5009.
(b) N. R. Natale and D. A. Quincy, Synth. Commun., 1983, 13, 817.
(c) N. R. Natale and C. S. Niou, Tetrahedron Lett., 1984, 25, 3943.
(d) N. R. Natale, J. I. McKenna, C. S. Niou, M. Borth, and H. Hope, J. Org. Chem., 1985, 50, 5660.

(e) K. D. Bowles, D. A. Quincy, B. M. Mallet, J. I. McKenna, and N. R. Natale, J. Chem. Ed., 1985, 62, 1118.

(f) C. S. Niou and N. R. Natale, Heterocycles 1986, 24, 401.

8. Unpublished work with M. Borth.

9. A. B. Smith, II and P. A. Levenberg, Synthesis, 1981, 567.

10. In control reactions with benzoyl chloride and butyllithium, valerophenone was obtained in less than 40% yield in the absence of cerium trichloride, and 77% in the presence of cerium trichloride. Unpublished work with S. G. Yocklovich. We suggest that the moderation in reactivity is due to the oxaphilicity[12] of the lanthanide,[13] which in turn stabilizes the tetrahedral intermediate at low temperature.

11. Recent methods for the synthesis of ketones from acid chlorides and organometallics are surveyed in: S. Inaba and R. D. Rieke, J. Org. Chem., 1985, 50, 1373.

12. Based on the metal-oxygen bond length, i.e., W. J. Evans, J. W. Grate, I. Bloom, W. E. Hunter and J. L. Atwood, J. Am. Chem. Soc. 1985, 107, 405.

13. Although the organolanthanide species has been proposed to be a σ-alkyl,[6e] (i.e., $RCeCl_2$) the alternative ate complex should also be considered as a possibility, as in: G. Jeske, H. Lauke, H. Mauermann, P. N. Swepston, H. Schumann, and T. J. Marks, J. Am. Chem. Soc. 1985, 107, 8091, 8103, and 8111.

Received, 28th April, 1986