10 mmol of angelicalactone in 5 mL of tetrahydrofuran (THF) was added over 5 min to a solution of 11 mmol of lithium diisopropylamide in 10 mL of THF at −78 °C. The solution was stirred at −78 °C for 15 min. The appropriate acid chloride (20 mmol) was added rapidly and the resulting suspension was stirred an additional 5 min. The reaction was worked up by the addition of ether and water. The aqueous layer was extracted twice with ether. The organic layer was dried, filtered, and concentrated. Column chromatography (1:10 ether/pentane) on silica gel afforded the acyloxyfurans as oils.

2-Acetoxy-5-methylfuran (2): colorless oil, 40% yield; IR (film) 1785, 1620, 1570, 1175 cm^{-1}; NMR ($CDCl_3$) δ 2.25 (d, J = 1 Hz, 3 H), 2.29 (s, 3 H), 5.82 (d, J = 3 Hz, 1 H), 6.02 (d of t, J = 3 Hz, 1 Hz, 1 H).

2-Hexanoyloxy-5-methylfuran (5): colorless oil, 40% yield; IR (film) 2964, 2940, 2880, 1780 cm^{-1}; NMR ($CDCl_3$) δ 0.7–1.9 (m, 9 H), 2.25 (d, 3 H), 5.75 (d, 1 H), 5.94 (d of t, 1 H).

General Procedure for the Boron Trifluoride Etherate Promoted Rearrangements. To a solution of 1.75 mmol of heterocyclic ester in 4 mL of benzene at 0 °C was added 1.75 mmol of distilled boron trifluoride etherate. The solution was allowed to warm slowly to room temperature and stirred until TLC indicated that reactant had been consumed (4–20 h). The solution was then diluted with ether, washed with sodium bicarbonate and brine, dried, and concentrated. The crude product was filtered through silica gel to afford pure product.

5-Acetyl-5-methyldihydro-2(5*H*)-furanone (2a): 65% yield; bp 65 °C (2 mm); IR (film) 1780, 1725, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.61 (s, 3 H), 2.20 (s, 3 H), 6.20 (d, J = 6 Hz, 1 H), 7.45 (d, J = 6 Hz, 1 H).

Anal. Calcd for $C_7H_8O_3$: C, 59.99; H, 5.75. Found: C, 59.88; H, 5.80.

5-Hexanoyl-5-methyldihydro-2(5*H*)-furanone (6): 40% yield; bp 77 °C (2 mm); IR (film) 2960, 2935, 2870, 1780, 1725, 1600 cm^{-1}; NMR ($CDCl_3$) δ 0.7–1.7 (m, 9 H), 1.64 (s, 3 H), 2.6 (m, 2 H), 6.23 (d, J = 6 Hz, 1 H), 7.5 (d, J = 6 Hz, 1 H).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 65.70; H, 8.20.

5-Acetylthiophen-2-ol Acetate (10): 45% yield; mp 103–105 °C; IR (mull) 1775, 1660 cm^{-1}; NMR ($CDCl_3$) δ 2.38 (s, 3 H), 2.55 (s, 3 H), 6.84 (d, J = 4 Hz, 1 H), 7.62 (d, J = 4 Hz, 1 H).

Anal. Calcd for $C_8H_8O_3S$: C, 52.16; H, 4.38. Found: C, 52.19; H, 4.41.

3-Acetyl-5-methylthiophen-2-ol (12): 40% yield, oil; IR (film) 1735, 1630 cm^{-1}; NMR ($CDCl_3$) δ 2.26 (s, 6 H), 6.26 (br s, 1 H); high-resolution mass spectrum, m/e 156.02327 ($C_7H_8O_2S$ requires 156.02451).

4-Hydroxy-4-methyl-5-oxohexanoic Acid γ-Lactone (3). (A) Platinum oxide (10 mol %) and **2a** were stirred at 23 °C in ethanol (0.5 M) under a balloon of hydrogen until TLC indicated that the reaction was complete. The mixture was filtered through Celite and concentrated in vacuo to yield **3:** 97% yield, colorless oil; IR (film) 1790, 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 3 H), 2.32 (s, 3 H), 2.6 (m, 4 H).

(B) An acetone solution of the protected ketolactone (0.86 mmol) was added to a rapidly stirred solution of *N*-bromosuccinimide (5 mmol, 0.3 M in aqueous acetone) at 0 °C. The solution was stirred 15 min at 0 °C, then 5 min at 25 °C. It was then poured into a mixture of hexane/chloroform and saturated sodium bicarbonate. The organic layer was separated, dried, and concentrated. Chromatography on silica gel using 1:4 ether/pentane afforded 0.11 g (90%) of a colorless oil which was identical in all respects (TLC, IR, NMR) with the material prepared in A.

4-Hydroxy-4-methyl-5-oxohexanoic Acid γ-Lactone 1,3-Propylene Dithioketal. Levulinic acid (2.5 mmol) is added dropwise to a solution of 2-lithio-2-methyldithiane (5.0 mmol) at −78 °C. The solution was allowed to warm to −10 °C, then stored in the refrigerator for 20 h. The reaction mixture was then poured into ice and extracted twice with ether/chloroform. The aqueous layer was then acidified to pH 3, extracted with chloroform, dried, and concentrated: 86% yield, colorless liquid; IR (film) 1775, 750 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 3 H), 1.62 (s, 3 H), 1.8–3.6 (m, 10 H).

Anal. Calcd for $C_{10}H_{16}O_2S_2$: C, 51.66; H, 6.94. Found: C, 51.73; H, 7.02.

Acknowledgment. We wish to thank the Department of Health, Education and Welfare for generous financial assistance through Grant No. 5 S05 RR07034 administered by the Iowa State University Research Foundation.

Registry No.—**2,** 65748-93-8; **2a,** 65748-94-9; **3,** 30246-17-4; **4,** 591-12-8; **5,** 65748-95-0; **6,** 65748-96-1; **7,** 36448-58-5; **8,** 65748-97-2; **10,** 65748-98-3; **12,** 65748-99-4; acetyl chloride, 75-36-5; AmCOCl, 142-61-0; 4-hydroxy-4-methyl-5-thioxohexanoic acid γ-lactone 1,3-propylene dithioketal, 65749-00-0; levulinic acid, 123-76-2; 2-lithio-2-methyldithiane, 27969-97-7.

References and Notes

(1) W. A. Jacobs and A. B. Scott, *J. Biol. Chem.*, **87,** 601 (1930).
(2) D. Seebach and E. J. Corey, *J. Org. Chem.*, **40,** 231 (1975).
(3) E. J. Corey and B. Erickson, *J. Org. Chem.*, **36,** 3557 (1971).
(4) G. A. Kraus and B. Roth, *Tetrahedron Lett.*, 3129 (1977).
(5) A. Blatt, *Org. React.*, **1,** 342 (1942).
(6) A. B. Hornfeldt and S. Gronowitz, *Ark. Kemi.*, **21,** 250 (1963).

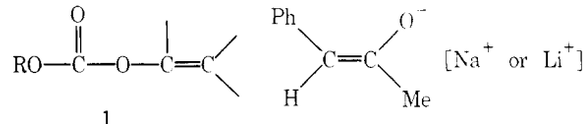
An Efficient Synthesis of Enol Carbonates

R. A. Olofson,* John Cuomo, and Bette A. Bauman

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Received October 28, 1977

Acid of Hg^{2+} catalyzed transesterification provides ready access to most carboxylic acid enol esters. Alternatively, these useful synthetic intermediates and valuable polymer precursors can be made by a second scheme involving acylation of metal enolates with carboxylic acid anhydrides.[1] Because the required starting materials are either unstable or unknown, neither of these complementary routes can be adapted to the preparation of enol carbonates (**1**). Simple enol esters have been obtained by variations of the second scheme wherein the anhydride has been replaced by the analogous acid halide. However, competitive *C*-acylation of the ambident enolate anion has generally made such processes impractical, a point forcefully demonstrated in the extensive enolate acetylation studies of House.[1] For example, *O*-acetylation of **2** was nearly quantitative with Ac_2O in dimethoxyethane.



1 2

However, with AcCl only 24–50% of the *O*-acetyl product was found and this was contaminated by 14–22% of the *C*-acetyl isomer and unspecified amounts of the *O,C*-diacyl species (from *C*- then *O*-acylation).[2] Even less promising product mixtures were obtained in earlier investigations of the reaction of sodium enolates with ethyl chloroformate.[3]

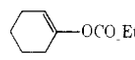
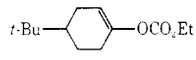
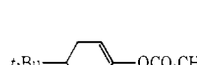
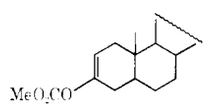
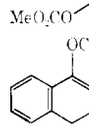
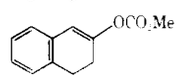
Recent communications from this laboratory have illustrated a few of the unique advantages of enol carbonates (**1**) as synthetic intermediates.[4] These and other results have encouraged us to examine further the acylation of enolates with chloroformates in the hope of developing a broadly useful synthesis of **1**.

Two potential routes to **1** readily extrapolated from the data of House et al. were not explored. These authors reported only *O* attack from treatment of α-mercuri ketones with acetyl chloride.[1] However, the costs and dangers endemic to work with organomercurials led us to discard an approach based on this observation. They also found exclusive *O*-acylation in the reaction of potassium cyclohexanone enolate with ethyl chloroformate (39% yield).[1] Generalization of this scheme was abandoned because of the expense and technical problems inherent in the preparation and use of tritylpotassium, the base required in the best applicable synthesis of potassium enolates.

However, this final result of House did provide an important lead by suggesting that selective *O*-acylation could be accomplished by coercing a lithium enolate to mimic a potassium enolate, an effect sometimes achieved by carrying out

0022-3263/78/1943-2073$01.00/0

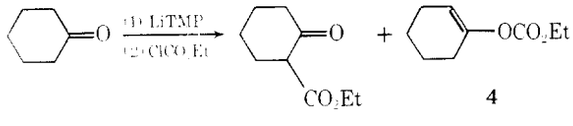
Table I. Enol Carbonates: Synthesis and Properties

Registry no.	Ketone (ROCOCl)	Product	Registry no.	No. Yield, %	BP (°C) (Torr)	MS parent *m/e* Found (Calcd)	IR stretch (CCl_4), μm C=O	IR stretch (CCl_4), μm C=C	NMR δ ($CDCl_3$) vinyl H[a]
108-94-1 541-41-3	Cyclohexanone (R = ethyl)		65496-21-1	**4** 76	112–114 (22)	*b*	5.71	5.91	5.3–5.5 (m)
98-53-3	4-*tert*-Butylcyclohexanone (R = ethyl)		65496-22-2	**5** 78	89–94 (0.1)	226.1582 (226.1568)	5.71	5.89	5.25–5.5 (m)
98-86-2	Acetophenone (R = ethyl)		65496-23-3	**6** 73	112–115 (3)	*c*	5.68	6.06	5.05 (d, *J* = 2) 5.35 (d, *J* = 2)
765-43-5 543-27-1	c-C_3H_5-COMe (R = isobutyl)		65496-24-4	**7** 60	89–96 (4)	184.1089 (184.1099)	5.67	6.01	4.55–4.65 (m) 4.68–4.78 (m)
67-64-1 1885-14-9	Acetone (R = phenyl)		65496-25-5	**8** 49[d]	68–70 (0.2)	178.0632 (178.0629)	5.64	5.96	4.71 (d, *J* = 1.5) 4.89 (d, *J* = 1.5)
5130-24-5	4-*tert*-Butylcyclohexanone (R = vinyl)		65496-26-6	**9** 47	79–83 (0.2)	224.1428 (224.1412)	5.65	5.89 6.05	4.62 (q, *J* = 2, 6) 4.97 (q, *J* = 2, 14) 5.45–5.65 (m) 7.12 (q, J = 6, 14)
566-88-1 79-22-1	5-α-Cholestan-3-one (R = methyl)		65496-27-7	**10** 74	107–108 (mp)	444.3594 (444.3603)	5.70	Too weak	5.0–5.5 (m)
529-34-0	α-Tetralone (R = isobutyl)		65496-28-8	**11** 90	126–129 (0.6)	246.1255 (246.1255)	5.66	6.02	5.80 (t, *J* = 4)
530-93-8	β-Tetralone (R = methyl)		65496-29-9	**12** 76	115–118 (0.7)	204.0777 (204.0785)	5.65	5.98	6.21 (s)

[a] Coupling constants in Hz, multiplet = m, quartet = q, etc. [b] Known compound, lit. bp 108–110 (20 Torr). [c] Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 69.05; H, 6.22. [d] Corrected yield: see text.

a reaction in a very polar, highly ionizing solvent. Lithium enolates are most conveniently made by deprotonation of ketones with lithium amide bases. For such a process to be useful in the present work, it is crucial that the liberated amine be much less reactive toward chloroformates than the generated enolate.[5] Most amines, including diisopropylamine (the conjugate acid of the most popular amide base), fail this test. Recently lithium 2,2,6,6-tetramethylpiperidide (LiTMP) was introduced by this laboratory as the base of choice in situations with similarly stringent selectivity requirements and its success in a variety of applications[6] invited the prediction that HTMP could not effectively compete with an enolate for chloroformate.

Initial studies were performed on the deprotonation of cyclohexanone with LiTMP followed by acylation with ethyl chloroformate. As anticipated, both the *C*- and *O*-acyl products (**3** and **4**) were isolated with dimethoxyethane (10% **3**, 11% **4**) or THF (−78 °C: 16% **3**, 16% **4**; 25 °C: 16% **3**, 16% **4**) as the solvent. When the THF was diluted with DMF (1:1), the ratio of **4**:**3** improved to 2.5:1 and the yield of **4** increased to 35%.



3 **4**

With the even more polar hexamethylphosphoric triamide (HMPA) as the cosolvent, no *C*-acyl product was found and further increases in the yield of **4** were realized. The best results were obtained when cyclohexanone (1 equiv) was added to LiTMP (1.1 equiv) in THF at −78 °C. The enolate solution was then warmed to room temperature and diluted with an equal volume of HMPA. Addition of ethyl chloroformate (1.1 equiv) was followed by a reaction work-up in which the byproduct, HTMP, and the high-boiling HMPA were removed by extraction from pentane with aqueous pH 4 citrate buffer. The yield of pure, distilled 1-cyclohexenyl ethyl carbonate (**4**) was an excellent 76%.

Other enol carbonates which have been synthesized by this procedure are listed in Table I along with reaction yields, physical properties, and spectral data of structural importance. Yields are generally good to excellent, no *C*-acylation products were found, and all compounds were readily isolated pure except **8** which was contaminated by some diphenyl carbonate. Two products are possible in the reactions of cyclopropyl methyl ketone, β-tetralone, and 5-α-cholestan-3-one but in each case only one isomer was found. The structure (**7**) from the cyclopropyl ketone is in accord with expectations but the isolation of the conjugated product (**12**) from β-tetralone is somewhat surprising since the *C*-formylation, oxalylation, and carboxylation of β-tetralone are reported to give either primarily or exclusively the 3 isomer.[7] Based on analogies with other enolate and enol ester forming reactions of cholestan-3-one,[8] the product **10** should have its C=C bond in the 2

position as pictured. However, a Δ^3-ene structure has not been rigorously excluded. From the products (**8** and **9**), it is evident that in this reaction aryl and vinyl chloroformates[9] behave like simple alkyl chloroformates. To our knowledge, the cyclohexenyl vinyl carbonate (**9**) is the first known example of a mixed bis(enol) carbonate though such species would be of special interest in polymer chemistry.

Efforts to prepare an enol carbonate from cyclohexane carboxaldehyde were unsuccessful. Evidently, the use of LiTMP does not avoid the aldol condensation complications normally encountered in endeavors to make solutions of aldehyde enolates. Attempts to extend the reaction to the synthesis of enol chloroformates by enolate acylation with phosgene also failed. Unlike chloroformates, phosgene reacts rapidly with HMPA at 0 °C.[10]

The HMPA effect carries over to the reaction of LiTMP derived cyclohexanone enolate with acetyl chloride. Using THF as the solvent, the product ratio of 2-acetylcyclohexanone to cyclohexenyl acetate was 2:1. With 1:1 THF–HMPA only the latter was obtained though the yield was a mediocre 25%. Acylation with benzoyl chloride gave 2-benzoylcyclohexanone as the sole product (50% yield) with THF as the reaction solvent but this *C*-acyl product (52% yield) was joined by cyclohexenyl benzoate (13% yield) in 1:1 THF–HMPA. Little practical value of this procedure in the synthesis of simple enol esters is foreseen.

In conclusion, a comment concerning the H$^+$arpoon base, LiTMP, seems appropriate. In the present synthetic application, unlike most others developed in our laboratory[6] and more recently in other laboratories, the success of LiTMP is not primarily a result of its proton abstracting selectivity. Instead its value derives: first, from the relative inertness of the conjugate acid, HTMP, toward chloroformates and in the longer term toward the activated ester products and, second, from the ease of removal of HTMP by a simple extraction procedure from neutral products. The first advantage is not shared by other often used amide bases and the second is a deficiency in the use of trityl anions. Though both advantages are further optimized with alkali metal hydride bases, solubility problems severely limit their utility in synthesis.

Experimental Section

Melting points were taken in a Thomas-Hoover apparatus equipped with a calibrated thermometer. Infrared spectra were obtained on a Perkin-Elmer 267 spectrophotometer, NMR spectra on a Varian A60-A spectrometer, and mass spectra on an AEI MS-902 spectrometer. Gas chromatographic analyses were performed on a Varian "Aerograph" chromatograph, Model 920, equipped with thermal conductivity detectors and fitted with a 5 ft × 0.25 in. SE-30 on Gas Chrom Q column.

The hexamethylphosphoric triamide (HMPA) was distilled from CaH_2 and the THF from LAH. The distilled chloroformates were stored over $CaCO_3$, the distilled ketones were stored under N_2, and the 2,2,6,6-tetramethylpiperidine (HTMP, Aldrich) was dried over KOH, distilled through a short Vigreaux column, and stored under N_2. The vinyl chloroformate was obtained from D. J. Wancowicz;[9] other reagents were available commercially.

1-Cyclohexenyl Ethyl Carbonate. Glassware was dried at 150 °C, assembled hot in a nitrogen stream, and set up to maintain a slight positive N_2 pressure during the reaction sequence. A three-neck flask was fitted with a stirring magnet, a pressure equalizing dropping funnel, a condenser topped with an N_2 gas inlet, and a septum cap. First, the LiTMP was prepared by dripping MeLi (0.022 mol, Ventron, ca. 1.6 M in ether) into a solution of HTMP (3.10 g, 0.022 mol) in THF (20 mL) slowly enough to accommodate the resulting methane evolution. After another 10 min, the solution was cooled in a dry ice–acetone bath[11] and cyclohexanone (2.08 g, 0.0212 mol) in THF (10 mL) was dripped in (20 min) through the dropping funnel. Stirring at ca. −70 °C was continued for another 15 min and then the clear yellow enolate solution was warmed to 25 °C and diluted with 40 mL of HMPA which caused the color to darken to an orange-brown. Next ethyl chloroformate (2.38 g, 0.022 mol) was rapidly syringed into the reaction vessel (heat generated) again changing the color to a light yellow. The mixture was then poured into 50 mL of aqueous 10% citric acid (buffered to pH 4 with 50% NaOH) and pentane (50 mL) was added.[12] After separation, the aqueous phase was extracted with pentane (2 × 25 mL) and the combined organic layers were washed with 5% $NaHCO_3$ and water and dried (anhydrous Na_2SO_4). Vacuum distillation afforded the product as a colorless liquid: 2.86 g; bp 112–114 °C (22 Torr); NMR (CCl_4) δ 1.28 (3 H, t, J = 7 Hz), 1.5–2.5 (8 H, m), 4.13 (2 H, q, J = 7 Hz), 5.3–5.5 (1 H, m); IR (CCl_4) 5.71, 7.32, 8.0 μm; mass spectrum m/e (rel intensity) 170 (p, 15), 98 (100), 83 (63), 70 (98). Analysis (GC) indicated that the product was contaminated by only a trace of cyclohexanone; 76% overall yield.[13]

The other carbonates in Table I were similarly prepared from the appropriate ketones and chloroformates except for the following minor variations. Enolate formation from cyclopropyl methyl ketone was performed at −95 °C (liquid N_2-CH_2Cl_2 bath) to give **7.** The cholestenyl carbonate **10** was isolated by recrystallization from acetone, mp 107–108 °C.

The various control and comparison experiments outlined in the text involving **3, 4,** cyclohexane carboxaldehyde, phosgene, and acetyl and benzoyl chloride were also carried out by the general procedure above with the modifications discussed in the text. When product mixtures were obtained, these were often analyzed by GC prior to final purification. After 18 h the NMR spectrum of a mixture of ethyl chloroformate and HMPA was still the sum of the spectra of both compounds. In contrast, phosgene rapidly reacted with ethereal HMPA at 0 °C to evolve a gas and precipitate a white solid.

In preliminary tests, **4** was obtained in 20% yield when sodium cyclohexanone enolate was made with $NaNH_2$ in ether, diluted with HMPA, and heated to drive off the NH_3. The main product was the dehydrated aldol condensation dimer of cyclohexanone. With cyclohexanone, NaH (55% in mineral oil), and HMPA, the product mixture was even more complex, and an attempt to use lithium HMPA radical anion[14] in HMPA as the enolate generating base and solvent also failed.

Acknowledgment. We are grateful to the National Institutes of Health for the grant which supported this research.

References and Notes

(1) H. O. House, R. A. Auerbach, M. Gall, and N. P. Peet, *J. Org. Chem.*, **38,** 514 (1973).
(2) The *C*-acyl product is rapidly deprotonated by enolate. For an example of this and a use of *C*-acylation involving chloroformates see: R. G. Salomon and M. F. Salomon, *J. Org. Chem.*, **40,** 1488 (1975).
(3) A. Haller and E. Bauer, *Ann. Chim. (Paris)*, **1,** 275 (1924); for additional studies see the Experimental Section.
(4) R. A. Olofson and R. C. Schnur, *Tetrahedron Lett.*, 1571 (1977); R. A. Olofson, R. C. Schnur, L. Bunes, and J. P. Pepe, *ibid.*, 1567 (1977); R. A. Olofson, Y. S. Yamamoto, and D. J. Wancowicz, *ibid.*, 1563 (1977); R. A. Olofson and J. P. Pepe, *ibid.*, 1575 (1977).
(5) Removal of the amine (even NH_3) prior to chloroformate addition cannot be accomplished completely.
(6) R. A. Olofson and C. M. Dougherty, *J. Am. Chem. Soc.*, **95,** 581, 582 (1973); R. A. Olofson, K. D. Lotts, and G. N. Barber, *Tetrahedron Lett.*, 3381, 3779 (1976); G. N. Barber and R. A. Olofson, *ibid.*, 3783 (1976).
(7) S. W. Pelletier, R. L. Chappell, P. C. Parthasarathy, and N. Lewin, *J. Org. Chem.*, **31,** 1747 (1966), and references therein; K. Wiedhaup, A. J. H. Nollet, J. G. Korsloot, and H. O. Huisman, *Tetrahedron Lett.*, 1599 (1965); P. Grafen and R. B. Turner, *ibid.*, 3935 (1964).
(8) W. G. Dauben, R. A. Micheli, and J. F. Eastham, *J. Am. Chem. Soc.*, **74,** 3852 (1952), and references therein.
(9) Vinyl chloroformate is the only readily available enol chloroformate; made by pyrolysis of $ClCO_2CH_2CH_2OCOCl$.[4] Also see; R. A. Olofson, B. A. Bauman, and D. J. Wancowic/, *J. Org. Chem.*, **43,** 752 (1978).
(10) H. Normant, *Angew. Chem., Int. Ed. Engl.*, **6,** 1046 (1967).
(11) Reaction of HTMP with ethereal MeLi at −70 °C is too slow to be preparatively useful. However, LiTMP rapidly reacts with ketones at this temperature.
(12) If desired, HTMP can be recovered easily from the aqueous phase by basification followed by extraction. For the economical synthesis of large quantities of HTMP, the two-step process from acetone, NH_3, and $CaCl_2$ is recommended: F. Francis, *J. Chem. Soc.*, 2897 (1927); H. K. Hall, *J. Am. Chem. Soc.*, **79,** 5444 (1957).
(13) With lithium diisopropylamide instead of LiTMP as the base, the yield of **4** dropped to ca. 25–30% (even with excess $ClCO_2Et$) and the product distillation fraction contained about an equal amount of $-Pr_2NCO_2Et$ (IR, NMR, GC analysis; plus other unidentified impurities).
(14) H. Normant, T. Cuvigny, J. Normant, and B. Angelo, *Bull. Soc. Chim. Fr.*, 3441, 3446 (1965).