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A NOVEL METHOD FOR THE GENERATION OF AN ESTER ENOLATE ANION FROM ETHOXYACETYLENE

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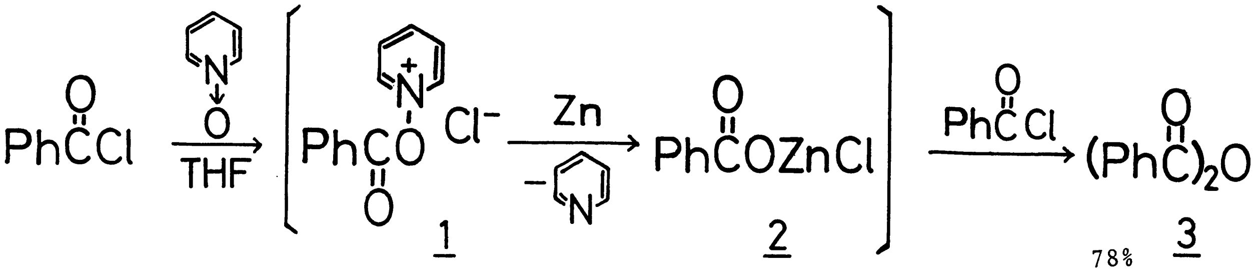
An ester enolate anion was generated in situ by the successive treatment of ethoxyacetylene with mercury(II) chloride, pyridine-1-oxide and zinc dust, and the zinc enolate thus formed further reacted with aldehydes to give α-chloro-β-hydroxyesters.

An enolate anion is one of the most important sources of carbanionic species in carbon-carbon bond-forming reactions.1) Enolate anions are generally prepared from various carbonyl compounds, and a few procedures2) have been reported for the generation of enolate anions from other sources than carbonyl compounds.

In this communication, we wish to report a novel method for the generation of the zinc enolate of an ester starting from ethoxyacetylene and the reaction of the zinc enolate with aldehydes giving α-chloro-β-hydroxyesters.

In our recent synthetic investigation, it was found that nitrogen-oxygen bond in 1-benzoyloxypyridinium salt(1) was reductively cleaved by zinc to give a carboxylate anion(2), which in turn reacted with benzoyl chloride to afford benzoic anhydride(3) in good yield (Scheme I). Further, it is known that mercuric salts catalyze the addition of carboxylic acids to methoxyacetylene.3)

Scheme I



Based on these facts, we assumed that the zinc enolate of an ester would be generated by reductive cleavage of nitrogen-oxygen bond in 1-(1-alkoxyvinyloxy)-pyridinium salt(4) with zinc. Thus, we treated ethoxyacetylene with pyridine-1-oxide in the presence of mercury(II) chloride and then successively added aldehydes and zinc dust to the mixture. After quenching, α-chloro-β-hydroxyesters(6) were isolated by usual work-up. It implies the formation of an ester enolate anion as a key intermediate in the hypothetical reaction scheme (Scheme II). The results are summarized in the Table.

Scheme II

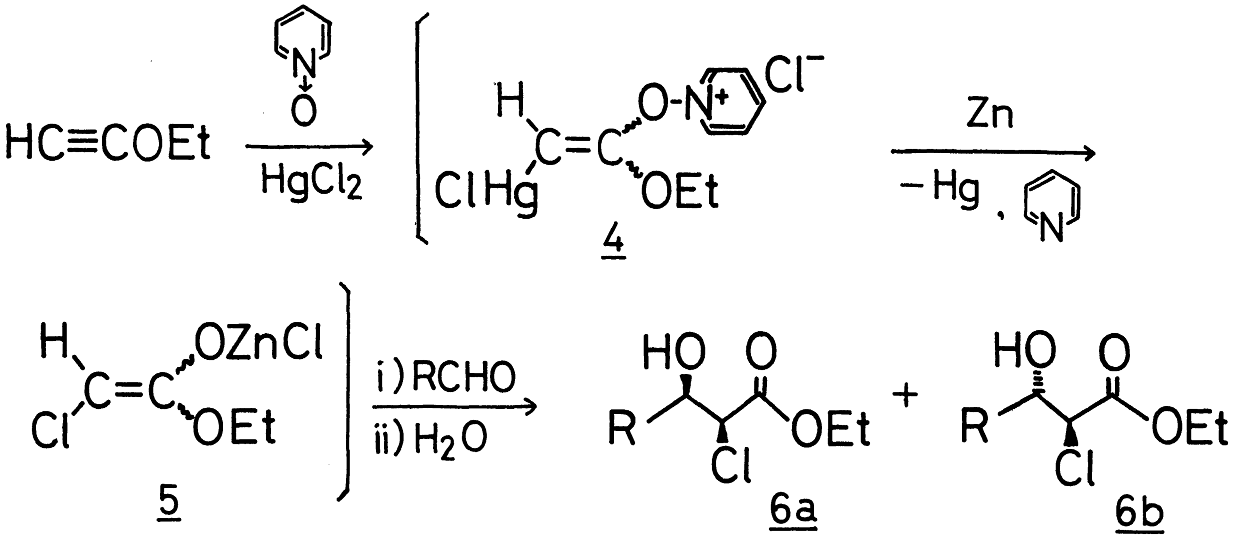


Table The synthesis of α-chloro-β-hydroxyesters

Aldehyde	Time(h)	Yield of 6(%)a)	6a:6bb)
PhCHO	3	81	67:33c)
Cl  CHO	2	80	69:31c)
n-C_7H_{15}CHO	15	67	64:36d)
PhCH_2CH_2CHO	2	77	68:32c)

a) Yields are based on aldehydes. All products gave satisfactory NMR and IR spectra.

b) The configuration was assigned by comparison of NMR spectra and HPLC analysis of the glycidic ester cyclized using sodium ethoxide with those of the glycidic ester cyclized using cesium fluoride.

c) The ratio was determined by HPLC analysis.

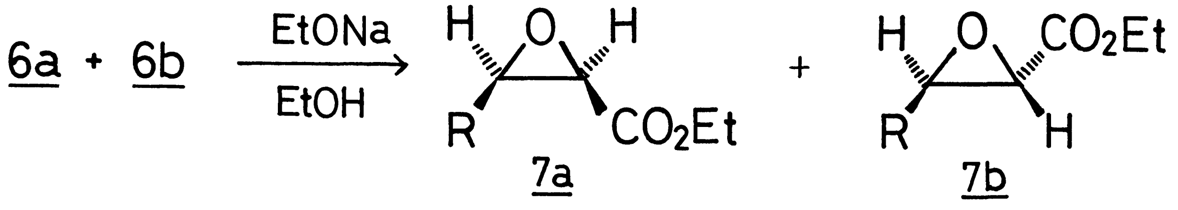
d) The ratio was determined by HPLC analysis of the phenoxyacetylated product.

Careful examination of reaction conditions revealed that small excess of ethoxyacetylene over mercury(II) chloride was necessary and that the use of absolutely dry reagents and solvent raised the yield of α-chloro-β-hydroxyester.4) The ratios of diastereoisomers (7a:7b) were almost 7:3 in all cases and independent of the temperature of oxymercuration step, the temperature of aldol reaction, and the solvent.

A typical procedure is described for the synthesis of ethyl 2-chloro-3-hydroxy-3-phenylpropionate: To a tetrahydrofuran(THF, 0.5 ml) solution of mercury(II) chloride(278 mg, 1.0 mmol) was added a THF(1.3 ml) solution of pyridine-1-oxide(215 mg, 2.3 mmol) at room temperature under an argon atmosphere and white solid precipitated during the addition. Then a THF(1.3 ml) solution of ethoxyacetylene(95 mg, 1.4 mmol) was added at 0°C and white solid disappeared. The resulting mixture was stirred at 0°C for 1 h and then the temperature was allowed to warm up to room temperature. A THF(2 ml) solution of benzaldehyde(60 mg, 0.57 mmol), and zinc dust(191 mg, 2.9 mmol) was added successively. As the reaction proceeded, a mass of mercury fell to the bottom of the flask indicating that a reductive elimination of mercury had occurred with an introduction of the chlorine atom at α-position. After stirring for 3 h the reaction was quenched with phosphate buffer solution(pH 7, 5 ml). The insoluble materials were filtered off through Celite and the filtrate was extracted with ethyl acetate. The combined extracts were dried over anhydrous magnesium sulfate. Ethyl 2-chloro-3-hydroxy-3-phenylpropionate(105 mg, 81%) was isolated by thin layer chromatography [silica gel]. Bp 145°C/0.1 mmHg (by bulb to bulb distillation); Found: C, 57.54; H, 5.75; Cl, 15.18%. Calcd for $C_{11}H_{13}ClO_3$: C, 57.78; H, 5.73; Cl, 15.50%; NMR($CDCl_3$) δ 1.06 and 1.21(3H, t, J=7Hz), 3.4-3.7(1H, m), 3.7-4.3(3H, m), 4.7-5.1(1H, m), 7.21 (5H, s); IR(neat) 3480, 1740 cm^{-1}. The ratio(6a:6b) was 67:33.

Further, it was found that trans glycidic esters(7b), useful synthetic intermediates, were stereoselectively obtained on treatment of the mixture of α-chloro-β-hydroxyesters(6a and 6b) with sodium ethoxide (Scheme III).$^{5)}$ Probably 6a isomerized to thermodynamically stable 6b before cyclization under the present conditions.$^{6)}$

Scheme III



~7 : 3

65~83%

7a:7b=15:85~1:99 $^{7)}$

It should be noted that the present reaction provides a convenient method for the synthesis of α-chloro-β-hydroxyesters in good yields from ethoxyacetylene and aldehydes by a one-pot procedure.

References

1) For review of the reactions of enolate anions see: H. O. House, "Modern Synthetic Reactions", 2nd ed., W. A. Benjamin, Inc., Monlo Park, Calif., 1972, pp. 492-765.

2) For example a) M. E. Jung and R. B. Blum, Tetrahedron Lett., 1977, 3791.
   b) I. Kuwajima, M. Kato, and A. Mori, Tetrahedron Lett., 1980, 2745.
   c) Enol esters, which are converted to the corresponding lithium enolates on treatment with methyl lithium, are synthesized from alkynes: P. F. Hudrlik and A. M. Hudrlik, J. Org. Chem., 38, 4254 (1973).

3) H. H. Wasserman and P. S. Wharton, Tetrahedron, 3, 321 (1958).

4) Reagents were handled under an argon atmosphere.

5) A typical procedure is described for the synthesis of ethyl 3-(4-chlorophenyl)-2,3-epoxypropionate: To an ethanol(0.5 ml) solution of ethyl 2-chloro-3-hydroxy-3-(4-chlorophenyl)propionate(53 mg, 0.20 mmol, a mixture of diastereoisomers) was added an ethanol(1.4 ml) solution of sodium ethoxide(0.21 mmol) at 0°C under an argon atmosphere. After stirring at 0°C for 90 min and at room temperature for 10 min, phosphate buffer solution(pH 7, 10 ml) was added. The mixture was concentrated under reduced pressure to remove most of ethanol and then extracted with ether. The combined extracts were dried over anhydrous magnesium sulfate. Ethyl 3-(4-chlorophenyl)-2,3-epoxypropionate(32 mg, 70%) was isolated by thin layer chromatography [silica gel]. Bp 150°C/0.15 mmHg (by bulb to bulb distillation); Found: C, 58.32; H, 4.83; Cl, 15.44%. Calcd for $C_{11}H_{11}ClO_3$: C, 58.29; H, 4.89; Cl, 15.64%; NMR(CCl_4) δ 1.29(3H, t, J=7Hz), 3.23(1H, d, J=2Hz), 3.92(1H, d, J=2Hz), 4.17(2H, q, J=7Hz), 7.18(4H, s); IR (neat), 1745, 1095, 900 cm^{-1}. The ratio (**7a**:**7b**) was 99:1.

6) On the other hand, the mixture of α-chloro-β-hydroxyesters (**6a** and **6b**) was converted to the mixture of cis and trans glycidic esters (**7a** and **7b**) without a serious isomerization on treatment with cesium fluoride in dimethylformamide.

7) The ratio was determined by HPLC analysis or NMR spectra and the configuration assignment was based on the coupling constant across the epoxide.

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