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A HIGHLY STEREOSELECTIVE MICHAEL REACTION OF SIMPLE ESTER ENOLATES TO α,β-UNSATURATED ESTERS

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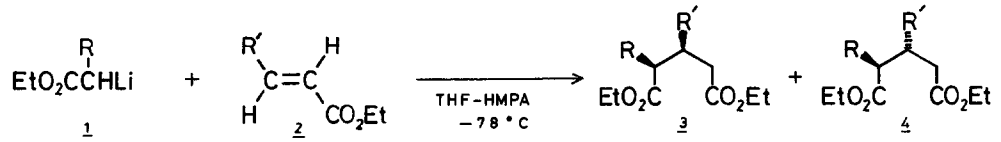
Abstract: Under a proper reaction condition, simple ester enolates add to α,β-unsaturated esters highly stereoselectively to give erythro or threo-glutarates.

Previously, we have shown that lithium enolates derived from simple monoesters react with α,β-unsaturated esters to give glutarates in high yield.[1] Under this reaction condition, however, the addition of ethyl propionate to β-monosubstituted unsaturates esters was not highly stereoselective, and a diastereomeric mixture of 2,3-disubstituted glutarates resulted. As a further synthetic investigation on this useful carbon-carbon bond formation, we wish to describe that, under a proper reaction condition, the Michael addition proceeds highly stereoselectively to give erythro- or threo-glutarates (Scheme I).



Scheme I

At first, the effect of the solvent on the reaction of lithium enolate of ethyl propionate and ethyl crotonate was examined at -78°C. And it was found that the use of THF is essential to conduct the process in synthetically acceptable manner. Other solvents such as ether, 1,2-dimethoxyethane, toluene, or hexane gave considerable amounts of by-products. Concerning the stereochemistry, it was observed that the presence of HMPA dramatically raised the diastereoselectivity. HMPA was added before and after the enolate formation step, which was claimed to give (Z)- and (E)-enolate respectively,[2] and little difference in the selectivity was observed (Table I). Thus, the change in the selectivity by the addition of HMPA is ascribed to the interaction of the polar molecule at the transition state and not to the stereochemistry of the enolate anion.

Based on these preliminary investigations, several (E)- monosubstituted

Table I. The Erythro Selective Michael Reaction.

R	R'	yield (%)[a]	purity (%)[b]	3 : 4[c]
CH_3	CH_3	82	>95	>20 : 1
		87	>95	10 : 1[d]
		96	95	3.2 : 1[e]
	$n\text{-}C_4H_9$	95	96	>20 : 1
	$n\text{-}C_7H_{15}$	86	92	>20 : 1
	Ph	85	>95	15 : 1
	$CO_2C_2H_5$	62	96	2.8 : 1
C_2H_5	CH_3	87	>95	>20 : 1
	$n\text{-}C_7H_{15}$	83	>95	>20 : 1
	Ph	90	>95	>20 : 1
	$CO_2C_2H_5$	62	>95	6.4 : 1
$n\text{-}C_8H_{17}$	CH_3	78	86	>20 : 1

[a] Isolated by distillation. All the products gave satisfactory ^1H-, ^{13}C-, and IR spectra.

[b] Determined by GLC (OV-1).

[c] Determined by ^{13}C-NMR.

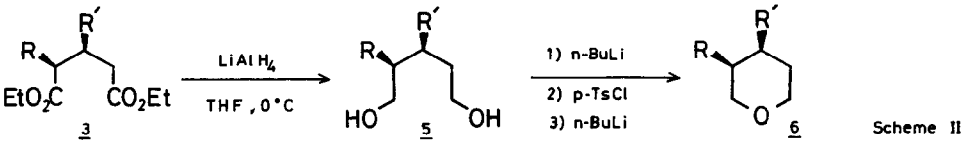
[d] HMPA was added to a solution of lithium enolate.

[e] The reaction was carried out in the absence of HMPA.

α,β-unsaturated esters were treated with the lithium enolates derived from β-monosubstituted acetates in THF-HMPA at -78°C, and the corresponding glutarates were obtained highly stereoselectively (Table I). Even the reaction of ethyl decanoate and ethyl crotonate gave a single isomer.

A typical procedure is described for the Michael reaction of ethyl propionate and ethyl crotonate: Under a nitrogen atomosphere, to a THF-hexane (2 and 1.3 ml) solution of LDA (2.0 mmol) was added HMPA (1 ml) at -78°C. After 30 min, a THF (1.5 ml) solution of ethyl propionate (208 mg, 2.0 mmol) was added and stirred for further 30 min at the temperature. Then, to the mixture was a THF (1.5 ml) solution of ethyl crotonate (168 mg, 1.5 mmol) added to react for 1h at -78°C. The reaction was quenched by adding saturated aqueous ammonium chloride. After a usual work-up, diethyl 2,3-dimethylglutarate (261 mg, 82%) was isolated by short path distillation. Bp 110°C (1 mm) (bath temperature). ^1H-NMR ($CDCl_3$) δ 0.96 (3H,d,J=6Hz), 1.12 (3H,d,J=7Hz), 1.26 (6H, t,J=7Hz), 2.0.2.7 (4H,m), 4.11 (4H,q,J=7Hz). ^{13}C-NMR ($CDCl_3$) δ 14.1, 14.3, 17.2, 33.2, 38.8, 44.1, 60.1, 60.2, 172.5, 175.2. IR (neat) 1730, 1180, 1030 cm^{-1}.

Next, in order to confirm the stereochemistry of the 2,3-disubstituted glutarates, we examined the conversion to tetrahydropyranes. Glutarates (3) were reduced with lithium aluminum hydride in THF at 0°C for 1h to give the corresponding 1,5-diols (5). Then, 5 were tried to cyclize to the desired tetrahydropyrans utilizing the reported one-pot methods (for example, Ph_3P-CCl_4, [3] Ph_3P-$EtO_2CN{=}NCO_2Et$ [4]). The pyrans, however, were obtained in quite low yield. So, we applied a synthesis of oxetanes from 1,3-diols[5] to the present pyran formation. Thus, 1,5-diols (5) were treated with an equimolar amount of n-butyllithium followed by p-toluenesulfonyl chloride in THF at 0°C to give monotosylates, which, without isolation, were cyclized to tetrahydropyrans (6) utilizing n-butyllithium as the base at reflux for 30 min. By this process, 6 were synthesized in high yield starting from 1,5-diols (5) (Scheme II, Table II).[6]



Scheme II

Table II. A Synthesis of Cis-3,4-disubstitutedtetrahydropyrans.

R	R'	yield (%)[a] 5	yield (%)[a] 6	cis : trans[b]
CH_3	Ph	95	70	>20 : 1
	$n\text{-}C_4H_9$	90	77	>20 : 1
	$n\text{-}C_7H_{15}$	92	84	>20 : 1
$n\text{-}C_8H_{17}$	CH_3	87	83	>20 : 1

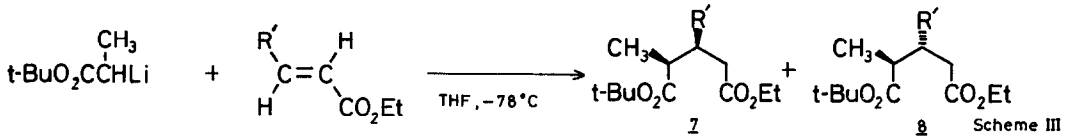
[a] All the products were isolated by silica gel chromatography and gave satisfactory ^{1}H-NMR, IR and/or ^{13}C-NMR spectra.

[b] The ratio were determined by ^{13}C-NMR.

As for the stereochemistry, the methyl group of 6 were determined, in every case, to be axial based on the following observations, indicating that the configuration of the tetrahydropyrans were cis: i) Benzylic proton of 3-methyl-4-phenyltetrahydro-2H-pyran appeared at δ 3.04 (dt,J=12,4Hz). ii) The ^{13}C-NMR chemical shift of the methyl group of the present isomers were observed at higher field (3.4-5.4 ppm),[7] compared with that of the other isomers which were synthesized by the non-stereoselective Michael reaction in the absence of HMPA. Thus, in the presence of HMPA, lithium enolates derived from monosubstituted ethyl acetatas react with (E)-α,β-unsaturated esters to give erythro-2,3-disubstituted glutarates in highly stereoselectively.

Erythro-isomers in hand, we then turned to the synthesis of the threo-2,3-

disubstituted glutarates. Though the Michael addition of ethyl propionate to (Z)-α,β-unsaturated esters was examined in THF-HMPA at -78°C, erythro-isomers were formed predominantly by the ratio of about 2:1. Notably the threo-synthesis was achieved by the use of t-butyl esters in the absence of HMPA (Scheme III, Table III). The configuration was confirmed by the con-



Scheme III

Table III. The Threo Selective Michael Reaction.

R'	yield (%)[a]	purity (%)[b]	7 : 8
CH_3	84	81	< 1 : 20
$n\text{-}C_4H_9$	61	82	< 1 : 20
$n\text{-}C_7H_{15}$	67	80	< 1 : 20

[a] All the products were isolated by distillation, and gave satisfactory ^1H-, ^{13}C-NMR, and IR spectra.

[b] Determined by GLC (OV-1).

[c] Determined by ^{13}C-NMR.

version to the tetrahydropyrans. In this case also, the presence of HMPA resulted in the exclusive erythro-formation.

It should be noted that the present methods are useful synthetic tools for the diastereoselective formation of vicinally arranged tertially carbon.[8)]

References

1) M. Yamaguchi, M. Tsukamoto, and I. Hirao, Chem. Lett., 1984, 375. 2) R. E. Ireland, R. H. Mueller, and A. K. Willard, J. Am. Chem. Soc., 98, 2868 (1976). 3) C. N. Barry and S. A. Evans, Jr., J. Org. Chem., 46, 3361 (1981). 4) J. T. Carlock and M. P. Mack, Tetrahedron Lett., 1978, 5153. 5) P. Picard, D. Leclercq, J.-P. Bats, and J. Moulines, Synthesis, 1981, 550. 6) A two-steps procedure of pyran synthesis was reported: P. Picard, D. Leclercq, and J. Moulines, Tetrahedron Lett., 1975, 2731. 7) D. K. Dalling and D. M. Grant, J. Am. Chem. Soc., 94, 5318 (1972). 8) The diastereoselective Michael reaction of enamines and nitroolefines is known: D. Seebach and J. Golinski, Helv. Chim. Acta, 64, 1413 (1980). S. J. Blarer, W. B. Schweizer, and D. Seebach, ibid, 65, 1637 (1981). And references cited therein.

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