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# A Regio- and Stereoselective Michael Addition of Amide Dienolates to α,β-Unsaturated Esters

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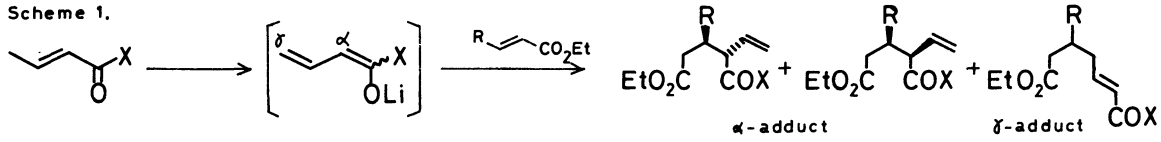
β-Alkyl-α-vinylglutaramides with threo- or erythro-configuration were synthesized stereoselectively by the Michael addition of amide dienolates to α,β-unsaturated esters.

Dienolates are generated by the treatment of unsaturated carboxylic acid derivatives with bases under appropriate reaction conditions, and the regioselectivity in the protonation, alkylation, or addition to carbonyls have been well documented.[1, 2, 3] The use of the reactive intermediate to the Michael-type reaction, however, is quite rare.[4] During our continuous investigations on the stereocontrolled construction of the adjacent tertiary carbons,[5] we found that the lithium dienolates of unsaturated tertiary amides add to α,β-unsaturated esters at α-carbon and β-alkyl-α-vinylglutaramides with threo- or erythro-configuration are synthesized stereoselectively (Scheme 1). The products contain chiral centers connected to vinyl groups, and would be useful building blocks for the synthesis of various natural products.

Scheme 1.




Dienolates of unsaturated esters,[1] carboxylic acids,[2] and secondary amides[3] were treated with unsaturated esters with little success. For example, the reaction of N-isopropyl-2-butenamide with ethyl 2-decenoate (1) gave a mixture of α- and γ-adduct (37 and 50% yield, respectively), and the stereoselectivity was low (2:1) for the former. Then, tertiary amide dienolates[3] were used. Three methods were employed to generate the dienolates: 1) α,β-Unsaturated amide was treated with LDA in THF-HMPA (4:1) (Method A). 2) β,γ-Unsaturated amide was reacted with LDA in THF (Method B). 3) α,β-Unsaturated amide was treated with LDA in THF (Method C). Because of the Michael addition of LDA,[1] the Method C is applicable only to β,β-disubstituted unsaturated amides. Several dienolates generated from butenamides by the Method A and B were added to 1, and the stereochemistry of the products was examined (Table 1). Threo-adduct was synthesized highly selectively from N-(2-butenoyl)-pyrrolidine (2) by Method A. Erythro-selectivity was enhanced by using Method B, and the best result was obtained with N-(3-butenoyl)-N-methylvalinol 3. The absence of HMPA

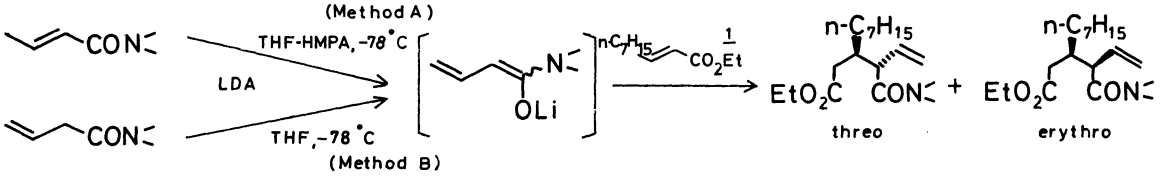
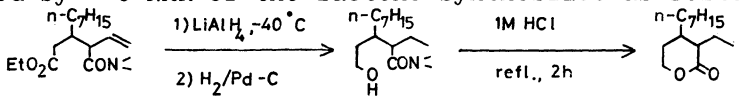


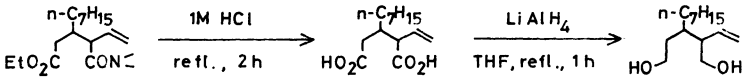

Table 1. The Stereoselectivity in the Michael Addition of Amide Dienolate

| -N< | threo : erythro[a] (Yield/%) Method A | Method B[b] |
|---|---|---|
| -N□ | >20 : 1 (65)[c] | >10 : 1 (70)[d] |
| $-NMe_2$ | >20 : 1 (68) | ——— |
| -N⬡ | 5 : 2 (82) | 1 : 2 (59) |
| $-N(i\text{-}Pr)_2$ | 1 : 1 (68) | 1 : 3 (68)[d] |
| $-N^{Me}_{MeOCH_2O}$ | 4 : 1 (77)[e] | 1 : 5 (83)[e], f)<br>5 : 1 (82)[f], g) |

a) The ratio was determined by $^{13}$C-NMR of the product, unless otherwise noted. b) Amides were prepared from 3-butenoic acid in 40-70% yields (ClCOCOCl or t-BuCOCl, amine, $Et_3N$; $CH_2Cl_2$, 0 °C, 1 h). c) γ-Adduct was isolated in 10% yield. d) A mixture of 3-butenamide and 2-butenamide (2:1) was used. e) The ratio was determined by $^{13}$C-NMR of the lactone synthesized as follows.




f) The ratio was determined by $^{13}$C-NMR of the diol synthesized as follows.




g) The reaction was carried out in THF-HMPA (4:1).

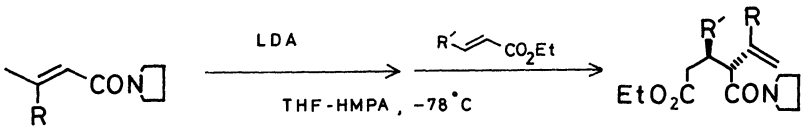



Table 2. The Threo-Selective Michael Addition of Dienolates

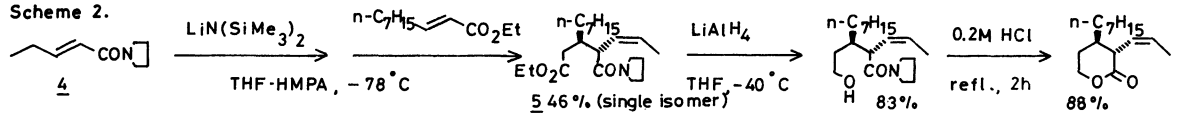
| R | R' | Yield/% | threo : erythro[a] |
|---|---|---|---|
| H | $CH_3$ | 62[b] | >20 : 1 |
| | $n\text{-}C_4H_9$ | 59[b] | >20 : 1 |
| | $n\text{-}C_7H_{15}$ | 65[b] | >20 : 1 |
| $CH_3$ | $CH_3$ | 81 | >20 : 1 |
| | $n\text{-}C_4H_9$ | 84 | >20 : 1 |
| | $n\text{-}C_7H_{15}$ | 91<br>95 | >20 : 1<br>>20 : 1[c] |
| | Ph | 87 | >20 : 1 |

a) Determined by $^{13}$C-NMR of the product. b) A small amount (about 10%) of γ-adduct was detected. c) Method C was used.

seems to play an important role in the formation of the erythro-adduct, as the reaction of 3 in THF-HMPA gave threo-adduct predominantly.

The threo-selective Michael addition was conducted using several pyrrolidine amide dienolates generated by Method A. N-(3-Methyl-2-butenoyl)pyrrolidine gives the threo-α-(2-propenyl)glutaramides exclusively in THF-HMPA (Table 2). The reaction could be performed also in THF (Method C). (Z)-Threo-adduct 5 was obtained from N-(2-pentenoyl)pyrrolidine (4) (Scheme 2).[6] The use of $LiN(SiMe_3)_2$,

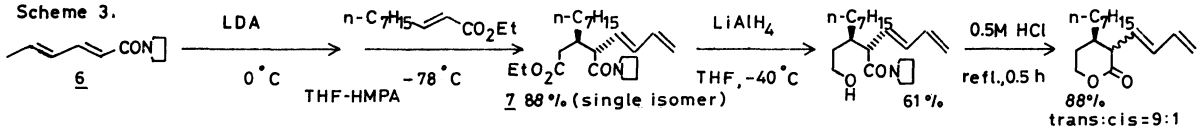
Scheme 2.




4 5 46% (single isomer) 83% 88%

instead of LDA, gave a higher yield of 5. Lithium trienolate,[7] generated from N-(2,4-hexadienoyl)pyrrolidine (6), reacted with an unsaturated ester regio- and stereoselectively, and α-adduct 7 with (E)-threo-configuration was obtained in high yield (Scheme 3). The construction of a new quarternary carbon was performed

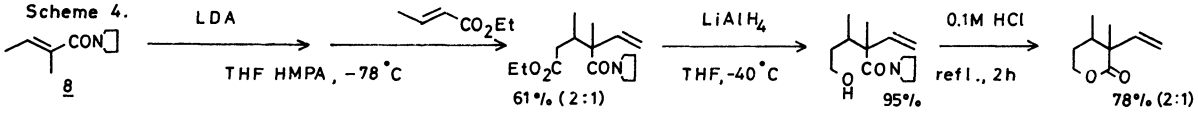
Scheme 3.




6 7 88% (single isomer) 61% 88% trans:cis=9:1

using the dienolate of 2-methyl-2-butenamide 8. The process, however, was not stereoselective under the present reaction conditions (Scheme 4).

Scheme 4.




8 61% (2:1) 95% 78% (2:1)

The glutarates, thus obtained, were converted to δ-lactones by a two-steps procedures (Schemes 2, 3, 4, and Table 3). Ester group was reduced with $LiAlH_4$ at -40 °C for 30 min, and the resulted δ-hydroxyamides were treated with dilute HCl to give the cyclization product with a little to no epimerization. The vicinal coupling constants (J=8–10 Hz) between protons attached to the carbons bearing

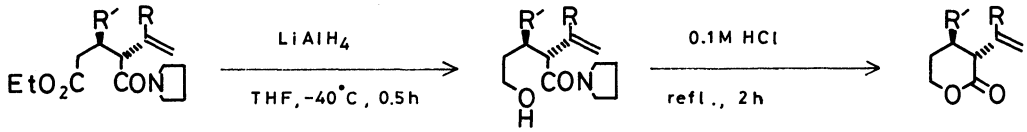



Table 3. The Synthesis of δ-Lactones

| R | R' | Yield/% Hydroxy amide | Lactone | trans : cis[a)] |
|---|---|---|---|---|
| H | $CH_3$ | 89 | 69 | 10 : 1 |
| | $n\text{-}C_7H_{15}$ | 89 | 86 | >20 : 1 |
| $CH_3$ | $CH_3$ | 82 | 67 | >20 : 1 |
| | $n\text{-}C_4H_9$ | 71 | 76 | >20 : 1 |
| | $n\text{-}C_7H_{15}$ | 89 | 68 | >20 : 1 |
| | Ph | 59 | 57 | >20 : 1 |

a) The ratio was determined by the $^{13}C$-NMR of lactone.

alkyl and vinyl groups revealed the trans arrangement of the side chains.

Erythro-selective Michael addition of dienolates was carried out using several dienolates of N-methylvalinol (Method B) in THF. The results are summarized in Table 4.

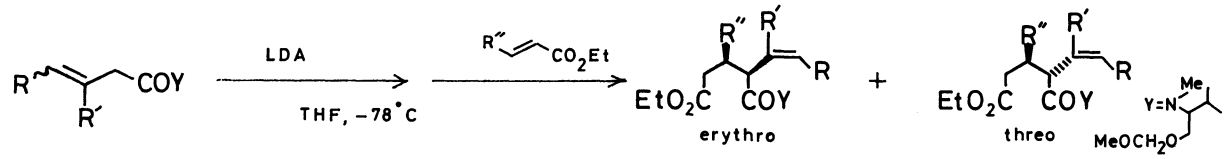
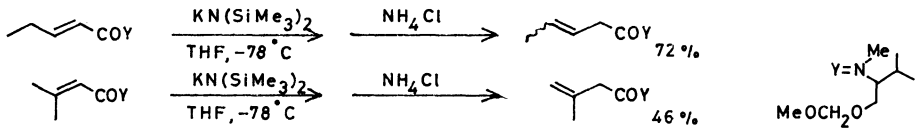



Table 4. The Erythro-Selective Michael Addition of Dienolates

| R | R' | R'' | Yield/% | erythro : threo[a)] |
|---|---|---|---|---|
| H | H | $CH_3$ | 78 | 4 : 1 |
| | | $n\text{-}C_7H_{15}$ | 82 | 5 : 1 |
| H | $CH_3$[b)] | $n\text{-}C_7H_{15}$ | 86 | 3 : 1 |
| | | | 67 | 3 : 1[c)] |
| $CH_3$ | H[b)] | $n\text{-}C_7H_{15}$ | 91 | 8 : 1 |

a) The ratio was determined by converting to diol (see Table 1 footnote f)). b) The β,γ-unsaturated amide was synthesized from α,β-unsaturated amide according to the following procedures.




c) Method C was used.

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References

1) For example; M. W. Rathke and D. Sullivan, Tetrahedron Lett., 1972, 4249; J. L. Herrmann, G. R. Kieczykowsky, and R. H. Schlessinger, ibid., 1973, 2433.
2) For example; P. E. Pfeffer and L. S. Silbert, J. Org. Chem., 36, 3290 (1971): P. E. Pfeffer, L. S. Silbert, and E. Kinsel, Tetrahedron Lett., 1973, 1163.
3) M. Majewski, G. B. Mpango, M. T. Thomas, A. Wu, and V. Snieckus, J. Org. Chem., 46, 2029 (1981); and references cited therein.
4) W. Oppolzer, R. Pitteloud, G. Bernardinelli, and K. Baettig, Tetrahedron Lett., 24, 4975 (1983).
5) M. Yamaguchi, M. Tsukamoto, S. Tanaka, and I. Hirao, Tetrahedron Lett., 25, 5661 (1984); M. Yamaguchi, M. Tsukamoto, and I. Hirao, ibid., 26, 1723 (1985); M. Yamaguchi, K. Hasebe, S. Tanaka, and T. Minami, ibid., 27, 959 (1986).
6) For example; A. S. Kende and B. H. Toder, J. Org. Chem., 47, 163 (1982).
7) For example; R. V. Stevens, R. E. Cherpeck, B. L. Harrison, J. Lai, and R. Lapalme, J. Am. Chem. Soc., 98, 6317 (1976); R. K. Boeckman, Jr. and D. M. Demko, J. Org. Chem., 47, 1789 (1982).

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