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syn-Selective Michael Addition of Lithiated 2-Alkoxyacetates and -acetamides to α,β-Unsaturated Carbonyl Compounds

Shuji KANEMASA,* Masafumi NOMURA,† and Eiji WADA
Institute of Advanced Material Study, Kyushu University, Kasugakoen, Kasuga 816
†Department of Molecular Scienece and Technology, Interdisciplinary Graduate School
of Engineering Sciences, Kyushu University, Kasugakoen, Kasuga 816

The lithium *Z*-enolates derived from 2-alkoxyacetates and -acetamides undergo unusual syn-selective Michael addition to α,β-unsaturated carbonyl compounds, where the syn selectivity of the amide enolates is much higher than that of the ester enolates. Factors that influence the stereoselectivity are also discussed.

Michael addition is one of the most synthetically valuable methods to make a carbon-carbon bond, while the study of stereoselectivity with respect to both ends of the newly formed bond has been started recently1) and is now enthusiastically in progress. We previously reported the exclusively anti-selective Michael addition of lithiated 2-(alkylideneamino)acetates to α,β-unsaturated carbonyl compounds,2) where the frontier orbital- and chelation-controlled rigid transition state of the resulting Z-enolates was proposed to be responsible for the high anti selectivity. The fact reported later by Yamaguchi and coworkers3) that Michael addition of the lithium Z-enolates derived from α-dibenzylamino esters was very low in stereoselectivity4) would indicate the contribution of the frontier orbital interaction in our cases.

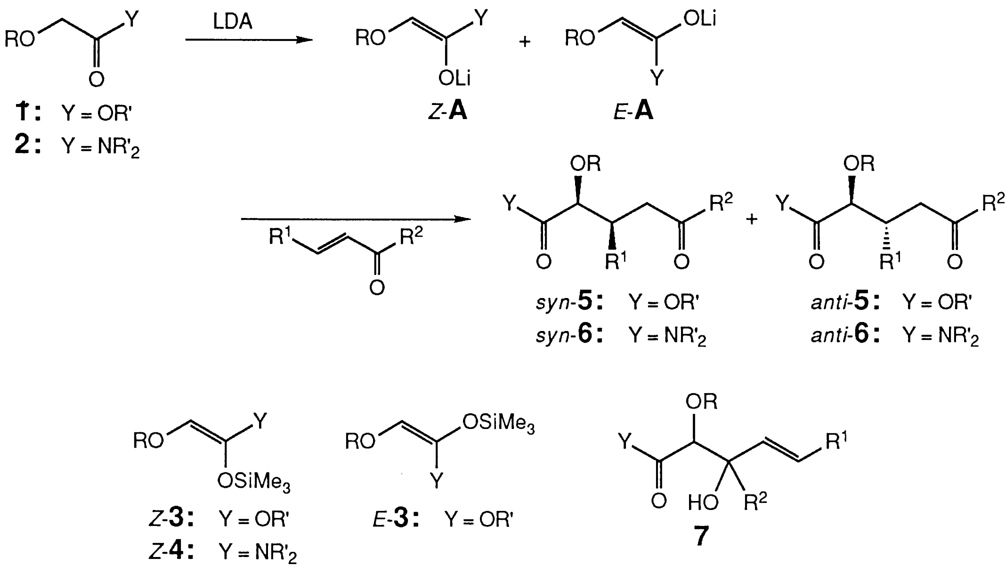
To assure the importance of such unusual attractive interaction, further examples for the stereoselectivity in the Michael addition of α-hetero-substituted enolates were surveyed. Although a lot of reaction examples are known for the Michael addition of α-alkylideneamino esters,5-7) the reaction of other α-hetero-substituted enolates is quite rare. Especially, the lithiated α-alkoxy carbonyls have never been utilized in Michael addition; they have been only employed in 3,3-sigmatropic rearrangement8) or aldol reaction.9)

We present here the unprecedented Michael reactions of 2-alkoxyacetates and -acetamides to α,β-unsaturated carbonyl compounds. The lithium enolates generated from them mostly as Z-isomers show moderate to high syn selectivities, and especially, the amide enolates undergo highly syn-selective Michael addition.

Treatment of methyl (**1a**) or isopropyl 2-methoxyacetate (**1b**) with lithium diisopropylamide (LDA) at -78 °C in tetrahydrofuran (THF) generated 97:3 mixtures of *Z*- and *E*-enolates, *Z*-**A** and *E*-**A** (both Y = OR'), whose isomer ratios were determined after silylation to *Z*-**3** and *E*-**3** with chlorotrimethylsilane (Scheme 1 and Table 1). Z-Selectivity from methyl 2-*t*-butoxyacetate (**1c**) was much lower (83:17). The geometry of lithium enolates **A** was determined on the basis of the NOE measurement between the Y and =CH groups.

Although Michael adducts **5a,b,f,i** were the only products in the reaction with α,β-unsaturated esters, 1,2-adducts **7** were always produced along with **5** from α,β-unsaturated ketones (Table 1).10) Michael adducts

5 could be separated from **7** through the careful operation of column chromatography on silica gel. The Michael adducts were mixtures of *syn*-**5** and *anti*-**5**, in most cases inseparable by chromatographic operation, whose structures were assigned on the basis of spectral data[11] and their conversion to enol lactones.[12]



Scheme 1.

To be noteworthy, according to the results listed in Table 1, are (1) the lithium *Z*-enolates derived from α-alkoxy esters mostly showed syn selectivity, (2) a smaller 2-alkoxy substituent was more favored for the syn selectivity (MeO > *t*-BuO, entries 1-11 and 12-14), (3) a phenyl group at the carbonyl carbon of the acceptor molecules increased the selectivity (entries 4, 5, 8, 10, and 11), (4) the selectivity was not influenced by the E/Z ratio of acceptor molecules (entries 4-7),[13] and (5) the addition of hexamethylphosphoric triamide (HMPA) only slightly decreased selectivity (entries 1 and 2), indicating that in the transition state the stabilization by chelate formation would be still operating even in the presence of HMPA.

Lithiation of 2-methoxy-*N*,*N*-dimethylacetamide (**2a**) or -*N*,*N*-diisopropylacetamide (**2b**) with LDA in THF at -78 °C resulted in the exclusive formation of *Z*-enolates *Z*-**A** (Y = NR'_2) as confirmed by the subsequent silylation to *Z*-**4** (Scheme 1 and Table 1). In the Michael additions to α,β-unsaturated carbonyl compounds, much higher levels of syn selectivity were observed regardless of the nature of substituents of the acceptor molecules (entries 15-25) to provide *syn*-**6** as major adducts; the selectivity did not depend upon the bulkiness of the dialkylamino groups (entries 15-20 and 21-25). The structures of *syn*-**6** as major diastereomers were confirmed by their conversion to 4-substituted 3-alkoxyperhydro-2-pyrone derivatives.[14]

It is now clear that the lithium *Z*-enolates derived from α-alkoxy esters or amides show syn selectivity in their Michael additions. This makes a striking contrast with the usual anti selectivity that the lithium *Z*-enolates of simple ketones, esters, or amides exhibit,[15] while reactions of lithiated *N*-propanoylpyrrolidine with 1-aryl-1-oxo-2-butenes[16] or ethyl crotonate[17] and those of lithiated 2-phenylacetates with cinnamates[18] are among exceptions.

Table 1. Michael Addition of Lithiated α-Alkoxy Acetates **1** and Amides **2** to α,β-Unsaturated Carbonyl Compounds[a)]

Entry		RO	Y	Z/E[b)]	R^1	R^2	Time h	Product	Yield[c)] %	1,4/1,2[d)]	syn/anti[d)]
1	**1a**	MeO	MeO	**3a** 97:3	Me	MeO	1.5	**5a**	45	100:0	73:27
2		MeO	MeO		Me	MeO[e)]	1.5	**5a**	37	100:0	63:37
3		MeO	MeO		Ph	MeO	20	**5b**	17	100:0	64:36
4		MeO	MeO		Me	Ph (87:13)[f)]	14	**5c**	91	40:60	85:15
5		MeO	MeO		Me	Ph (>99:1)[f)]	1	**5c**	91	39:61	86:14
6		MeO	MeO		Me	*t*-Bu (73:27)[f)]	2.5	**5d**	39	65:35	63:37
7		MeO	MeO		Me	*t*-Bu (>99:1)[f)]	2.5	**5d**	61	72:28	69:31
8		MeO	MeO		*i*-Pr	Ph	26.5	**5e**	60	79:21	81:19
9	**1b**	MeO	*i*-PrO	**3b** 97:3	Me	MeO	1	**5f**	49	100:0	61:39
10		MeO	*i*-PrO		Me	Ph (>99:1)[f)]	1.5	**5g**	91	50:50	82:18
11		MeO	*i*-PrO		*i*-Pr	Ph	3	**5h**	67	42:58	73:27
12	**1c**	*t*-BuO	MeO	**3c** 83:17	Me	MeO	6	**5i**	68	100:0	65:35
13		*t*-BuO	MeO		Me	Ph (87:13)[f)]	13	**5j**	41	40:60	63:37
14		*t*-BuO	MeO		*i*-Pr	Ph	3	**5k**	41	38:62	52:48
15	**2a**	MeO	NMe$_2$	**4a** Z only	Me	MeO	2	**6a**	63	100:0	93:7
16		MeO	NMe$_2$		Me	MeO[e)]	1	**6a**	77	100:0	88:12
17		MeO	NMe$_2$		Ph	MeO	1	**6b**	79	100:0	97:3
18		MeO	NMe$_2$		Me	Ph	2.5	**6c**	53	59:41	95:5
19		MeO	NMe$_2$		Me	*t*-Bu	2	**6d**	65	99:1	94:6
20		MeO	NMe$_2$		*i*-Pr	Ph	1.5	**6d**	55	45:55	>99:1
21	**2b**	MeO	N(*i*-Pr)$_2$	**4b** Z only	Me	MeO	1	**6e**	94	100:0	98:2
22		MeO	N(*i*-Pr)$_2$		Me	MeO[e)]	1	**6e**	83	100:0	89:11
23		MeO	N(*i*-Pr)$_2$		Me	Ph	2	**6f**	89	58:42	82:18
24		MeO	N(*i*-Pr)$_2$		Me	*t*-Bu	2	**6g**	82	87:13	82:18
25		MeO	N(*i*-Pr)$_2$		*i*-Pr	Ph	1.5	**6h**	81	44:56	>99:1

a) All reactions were performed at -78 °C in THF. b) Z/E Ratio of the lithium enolate. c) Total yield for the isolated mixture of 1,4- and 1,2-adducts. d) Determined by ^{1}H NMR and/or GLC. e) THF:HMPA = 5:1 v/v. f) E/Z Ratio of the acceptor used.

References

1) D. A. Oare and C. H. Heathcock, "Topics in Stereochemistry," ed by E. L. Eliel and S. H. Wilen, John Wiley & Sons, New York (1989), pp. 227-407.

2) S. Kanemasa, A. Tatsukawa, E. Wada, and O. Tsuge, *Chem. Lett.*, **1989**, 1301; S. Kanemasa, O. Uchida, and E. Wada, *J. Org. Chem.*, **55**, 4411 (1990); S. Kanemasa, A. Tatsukawa, and E. Wada, *ibid.*, **56**, 2875 (1991); H. Yamamoto, S. Kanemasa, and E. Wada, *Bull. Chem. Soc. Jpn .*, **64**, xxxx (1991).

3) M. Yamaguchi, K. Torisu, and T. Minami, *Chem. Lett.*, **1990**, 377.

4) Contrarily, the reaction of *E*-enolates was exclusively syn-selective (See Ref. 3).

5) J. M. McIntosh, R. K. Leavitt, P. Mishra, K. C. Cassidy, J. E. Drake, and R. Chadha, *J. Org. Chem.*, **53**, 1947 (1988).

6) G. Stork, A. Y. W. Leong, and A. M. Touzin, *J. Org. Chem.*, **41**, 3491 (1976); P. Bey and J. P. Vevert, *Tetrahedron Lett.*, **1977**, 1455; J. J. Fitt and H. W. Gschwend, *J. Org. Chem.*, **42**, 2639 (1977); R. Grigg, J. Kemp, G. Sheldrick, and J. Trotter, *J. Chem. Soc., Chem. Commun.*, **1978**, 109; V.

Dryanska, K. Popandova, and C. Ivanov, *Tetrahedron Lett.*, **1979**, 443; R. Grigg, J. Kemp, J. Malone, and A. Tangthongkum, *J. Chem. Soc., Chem. Commun.*, **1980**, 648.

7) U. Schöllkopf, D. Pettig, U. Busse, E. Egert, and M. Dyrbusch, *Synthesis*, **1986**, 737; K. Tomioka, K. Yasuda, and K. Koga, *J. Chem. Soc., Chem. Commun.*, **1987**, 1345; W. Hartwig and L. Born, *J. Org. Chem.*, **52**, 4352 (1987); D. Pettig and U. Schöllkopf, *Synthesis*, **1988**, 173; U. Schöllkopf, D. Pettig, E. Schulze, M. Klinge, E. Egert, B. Benecke, M. Noltemeyer, *Angew. Chem., Int. Ed. Engl.*, **27**, 1194 (1988); A. E. Achqar, M. Boumzebra, M.- L. Roumestant, and P. Viallefont, *Tetrahedron*, **44**, 5319 (1988).

8) J. K. Cha and S. C. Lewis, *Tetrahedron Lett.*, **25**, 5263 (1984).

9) A. M. Touzin, *Tetrahedron Lett.*, **1975**, 1477; C. H. Heathcock, J. P. Hagen, E. T. Jarvi, and M. C. Pirrung, S. D. Young, *J. Am. Chem. Soc.*, **103**, 4972 (1981).

10) The 1,2-adducts **7** were also mixtures of diastereomers whose ratios are not mentioned here.

11) Some spectral data of **5c**: ^{1}H NMR ($CDCl_3$) syn: $\delta = 0.99$ (3H, d, $J_{Me\text{-}3} = 7.0$ Hz, 3-Me), 2.69 - 2.82 (1H, m, H-3), 2.87 (1H, dd, $J_{gem} = 16.9$ and $J_{4\text{-}3} = 7.0$ Hz, one of H-4), 3.26 (1H, dd, $J_{gem} = 16.9$ and $J_{4\text{-}3} = 6.6$ Hz, the other of H-4), 3.37 (3H, s, 2-MeO), 3.78 (3H, s, COOMe), 3.87 (1H, d, $J_{2\text{-}3} = 3.7$ Hz, H-2), 7.44 - 7.57, and 7.94 - 8.00 (5H, m, Ph). anti: $\delta = 1.06$ (3H, d, $J_{Me\text{-}3} = 7.0$ Hz, 3-Me), 3.40 (3H, s, 2-MeO), 3.74 (1H, d, $J_{2\text{-}3} = 4.8$ Hz, H-2), 3.75 (3H, s, COOMe); ^{13}C NMR ($CDCl_3$) syn: $\delta = 14.97$ (3-Me), 32.45 (C-3), 41.28 (C-4), 51.79 (COOMe), 58.72 (2-MeO), 82.62 (C-2), 128.09, 128.61, 133.13, 137.10 (each Ph), 172.36 (COOMe), and 199.23 (C-5). anti: $\delta = 16.90$ (3-Me), 32.53 (C-3), 40.49 (C-4), 51.85 (COOMe), 58.60 (2-MeO), 84.49 (C-2), 128.55, 133.00 (each Ph), 172.43 (COOMe), and 199.04 (C-5).

12) A 39:61 mixture of **5c** (86:14) and the 1,2-adduct was hydrolyzed to the corresponding carboxylic acid (quant, 85:15) by treatment with NaOH under reflux in aqueous EtOH (1.5 h), where the 1,2-adducts that remained unreacted was removed off by chromatography. Subsequent cyclization of the acid with $(COCl)_2$ in CH_2Cl_2 at room temperature (12 h) gave an inseparable 86:14 mixture of *trans*- and *cis*-3-methoxy-4-methyl-6-phenyl-3,4-dihydro-2(*H*)-pyrone (82%): ^{1}H NMR ($CDCl_3$) trans: $\delta = 1.28$ (3H, d, $J_{Me\text{-}4} = 7.0$ Hz, 4-Me), 3.62 (1H, d, $J_{3\text{-}4} = 11.0$ Hz, H-3), 3.63 (3H, s, 3-MeO), 5.55 (1H, d, $J_{5\text{-}4} = 2.9$ Hz, H-5); cis: $\delta = 1.13$ (3H, d, $J_{Me\text{-}4} = 7.0$ Hz, 4-Me), 3.59 (3H, s, 3-MeO), 4.12 (1H, d, $J_{3\text{-}4} = 6.2$ Hz, H-3), and 5.83 (1H, d, $J_{5\text{-}4} = 6.6$ Hz, H-5). Other signals are overlapping. ^{13}C NMR ($CDCl_3$) trans: $\delta = 17.72$ (4-Me), 32.48 (C-4), 59.62 (3-MeO), 79.97 (C-3); cis: $\delta = 13.79$ (4-Me), 30.93 (C-4), 58.82 (3-MeO), 77.92 (C-3).

13) This was because *Z*-enones were much less reactive than *E*-enones (S. Kanemasa, M. Kumegawa, E. Wada, and M. Nomura, *Bull. Chem. Soc. Jpn.*, **64**, xxxx (1991)).

14) As a typical example, a 93:7 mixture of **6a** was reduced with lithium aluminum hydride in THF at -40 °C to give *N,N*-dimethyl-5-hydroxy-2-methoxy-3-methylpentanamide which was then cyclized to 3-methoxy-4-methylperhydro-2-pyrone by treatment with 1 M HCl. The major isomer was assigned to be 3,4-trans somer on the basis of NOE spectrum (4-Me/H-3).

15) C. H. Heathcock and D. A. Oare, *J. Org. Chem.*, **50**, 3022 (1985); T. Mukaiyama, M. Tamura, and S. Kobayashi, *Chem. Lett.*, **1986**, 1817; K. Kpegba, P. Metzner, and R. Rakotonirina, *Tetrahedron*, **45**, 2041 (1989); B. B. Lohray and R. Zimbiniski, *Tetrahedron Lett.*, **31**, 7273 (1990).

16) D. A. Oare, M. A. Henderson, M. A. Sanner, and C. H. Heathcock, *J. Org. Chem.*, **55**, 132 (1990).

17) M. Yamaguchi, K. Hasebe, S. Tanaka, and T. Minami, *Tetrahedron Lett.*, **27**, 959 (1986).

18) L. Viteva and Y. Stefanovsky, *J. Chem. Res. (S)*, **1990**, 232.

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