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Stable Configuration of Ester-Stabilized Azomethine Ylides. Stabilization of anti-Form by 1,5-Dipolar Interaction and of syn-Form by Hydrogen Bonding

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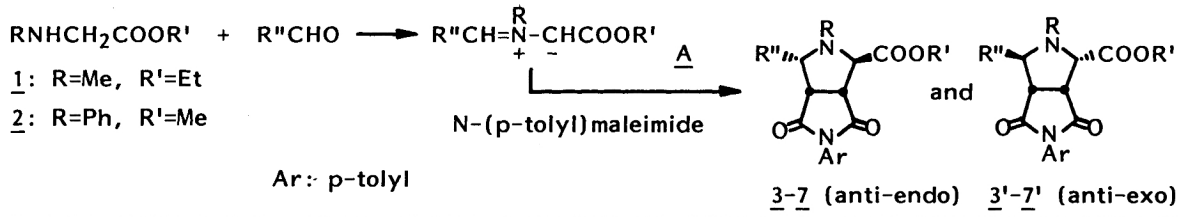
Stable configuration of ester-stabilized azomethine ylides is found to depend upon the substituent on the ylide nitrogen. Thus, N-substituted azomethine ylides derived from N-substituted 2-aminoacetates and carbonyl compounds undergo cycloaddition with olefinic dipolarophiles predominantly in anti forms, while N-protonated (or N-unsubstituted) azomethine ylides generated from 2-iminoacetates exclusively in syn forms.

Although 1,3-dipolar cycloaddition reaction utilizing azomethine ylide is now of current interest as a powerful tool in natural product synthesis,[1] stereochemical aspects of this reaction are left unsolved. Only quite recently, systematic cycloadditions of heteroaromatic N-ylides with olefinic dipolarophiles have been investigated, showing that anti forms of the ylides are stabilized by carbonyl substituents.[2] However, it is so far quite difficult to predict which form of open-chain azomethine ylides is to be concerned in its cycloaddition. The present communication refers to a factor by which the stable configuration of open-chain azomethine ylides bearing a carbonyl substituent is determined.

Reaction of ethyl N-methylglycinate 1 or methyl N-phenylglycinate 2 with benzaldehyde under reflux in toluene generated azomethine ylide A,[3] which was captured by N-(p-tolyl)maleimide to give a mixture of endo and exo cycloadducts to the anti form of ylide A, 3 + 3' or 4 + 4' (Table 1).[4,5] Only in the former reaction, a low yield formation of endo cycloadduct 8 to the syn form of A was accompanied. Use of aliphatic aldehydes under similar conditions led to competitive generation of alkyl-substituted A (R" = alkyl), alkenyl-substituted azomethine ylide B (R"' = H), and/or dienamines C (R"' = H or Me). They underwent 1,3-dipolar cycloaddition or Diels-Alder reaction with N-(p-tolyl)maleimide to give cycloadducts 5-7, 5'-7', and 9-10.

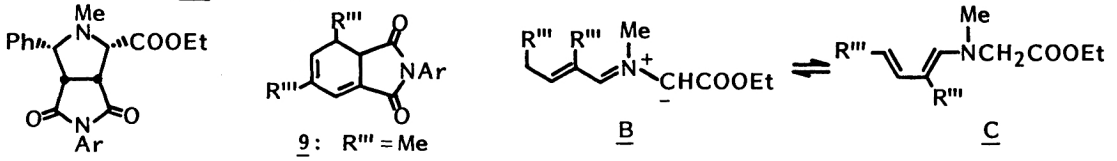
Thus, ester-stabilized azomethine ylides A and B bearing an N-substituent have been involved in the cycloadditions with N-(p-tolyl)maleimide predominantly in anti forms. The endo-exo ratio is independent upon the substituent R" on the ylide carbon; it is dependent upon the substituent R on the nitrogen. Presumably this low endo selectivity has resulted from the steric repulsion between R and the maleimide plane on an endo approach of the ylide A or B to the maleimide. Such steric repulsion was reduced when acyclic olefinic dipolarophiles were employed as dipolar-

Table 1. Cycloaddition of Ester-stabilized Azomethine Ylides Bearing an N-Substituent with Cyclic Olefinic Dipolarophile[a)]



Amine	Aldehyde	Time/h	R	R'	R"	Product	Yield/%[b)]	Isomer ratio endo:exo
1	PhCHO	24	Me	Et	Ph	3+3'	84[c)]	75:25
2	PhCHO	24	Ph	Me	Ph	4+4'	77	45:55
1	EtCHO	24	Me	Et	Et	5+5'	48[d)]	77:23
2	EtCHO	24	Ph	Me	Et	6+6'	64	47:53
1	MeCHO	1	Me	Et	MeCH=CH (t)	7+7'	76[e)]	76:24

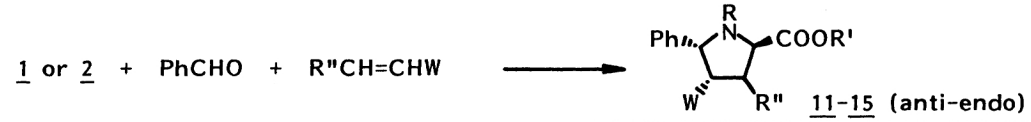
a) All reactions were carried out under reflux in toluene. The water formed was removed by the aid of Dean-Stark trap. b) Isolated yield. c~e) Accompanied by c) syn-endo cycloadduct 8 (7%), d) Diels-Alder adduct 9 (18%), and e) Diels-Alder adduct 10 (11%).



ophiles. For examples, cycloadditions of ylide A (R" = Ph) with acyclic olefins such as methyl acrylate, trans-β-nitrostyrene, and dimethyl maleate were found to be exclusively stereospecific with respect to both the ylide (anti) and the olefins (cis or trans), stereoselective (endo), and regioselective (Table 2).

Condensation of methyl glycinate 16 with carbonyl compounds leads to methyl iminoacetates, which undergo thermal tautomerization into N-protonated azomethine

Table 2. Cycloaddition of Ester-stabilized Azomethine Ylides Bearing an N-Substituent with Acyclic Olefinic Dipolarophiles[a)]



Amine	Olefin	Time/h	Product	R	R'	R"	W	Yield/%[b)]
1	CH_2=CHCOOMe	1	11	Me	Et	H	COOMe	73
2	CH_2=CHCOOMe	24	12	Ph	Me	H	COOMe	31
1	PhCH=$CHNO_2$ (t)	1	13 (3,4-trans)	Me	Et	Ph	NO_2	72
2[c)]	PhCH=$CHNO_2$ (t)	24	14 (3,4-trans)	Ph	Me	Ph	NO_2	39
1	MeOOCCH=CHCOOMe (c)	1	15 (3,4-cis)	Me	Et	COOMe	COOMe	62

a) All reactions were carried out under reflux in toluene (Dean-Stark trap).
b) Isolated yield. c) In the presence of diisopropylethylamine (1.5 equiv.).

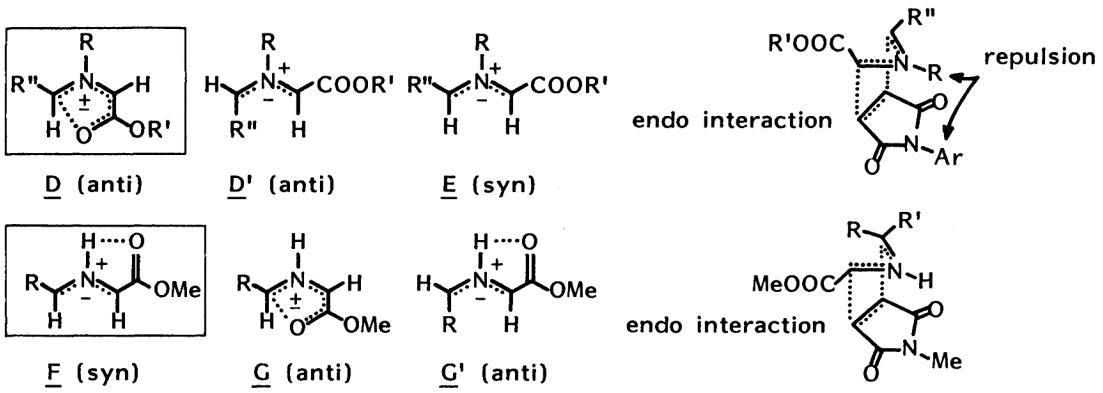
Table 3. Cycloaddition of Ester-stabilized Azomethine Ylides Bearing no N-Substituent with Cyclic Olefinic Dipolarophile

Carbonyl compound	Reaction conditions	Product[a]		R	R'	W	W'	Yield/%[b]
PhCHO[c]	toluene, ref, 24 h	17		Ph	H	COOMe	H	100
PhCHO[c]	MeCN, AcOH (10 mol%), rt, 13 h	17+18[d]	18:	Ph	H	H	COOMe	100
PhCOCHO	$CHCl_3$, ref, 16 h	19		PhCO	H	COOMe	H	100
i-PrCHO	toluene, ref, 20 h	20		i-Pr	H	COOMe	H	58
$(CH_2)_5CO$[c]	toluene, ref, 19 h	21		$(CH_2)_5$		COOMe	H	85

a) 17, 19, and 20: syn-endo; 18: anti-endo. b) Isolated yield. c) The corresponding imines were isolated and used for cycloadditions. d) 17:18=1:2 (^{1}H-NMR).

ylides.[6] These ylides were trapped by N-methylmaleimide to give single stereoisomers 17 and 19-21, but the reaction of methyl N-benzylideneaminoacetate in the presence of a catalytic amount of acetic acid afforded a mixture of two stereoisomeric cycloadducts 17 + 18 (Table 3).[7] The products 17 and 19-20 were assigned as endo cycloadducts to the syn form of the corresponding N-protonated azomethine ylides, and 18 as endo cycloadduct to the anti form of the ylide.[8]

Thus, in the cycloadditions of ester-stabilized azomethine ylides, anti form D of the ylides has been involved if the ylide nitrogen is substituted whereas syn form F has predominantly participated if the ylide nitrogen bears no substituent. Although three forms D, D', and E of N-substituted azomethine ylides are anticipated to have comparable stability from a stereochemical point of view, anti ylide D is most highly stabilized by 1,5-dipole interaction.[2] On the other hand, syn form F of N-unsubstituted azomethine ylides is more stable than the other two (G and G') since F is sterically most favored and stabilized by hydrogen bonding between the ester and NH moieties. In the presence of acid catalyst, stabilization by the hy-



drogen bonding is reduced and the anti form G gets a chance to participate in the cycloaddition.

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3) As azomethine ylide generation from N-substituted 2-amino esters and carbonyl compounds: P. N. Confalone and E. M. Huie, J. Org. Chem., 48, 2994 (1983); M. Joucla, J. Mortier, and J. Hamelin, Tetrahedron Lett., 26, 2775 (1985); O. Tsuge, S. Kanemasa, M. Ohe, and S. Takenaka, Chem. Lett., 1986, 973.

4) In the present article, the words "endo" and "exo" are used for the cycloadducts formed through endo and exo approach of a ylide to olefins, respectively.

5) All new compounds reported herein were fully characterized on the ground of spectral and analytical data. 3a: ^{1}H NMR ($CDCl_3$) δ=1.35 (3H, t, Et), 2.28, 2.32 (each 3H, s, NMe and p-Me), 3.47 (1H, dd, J=8.0 and 0.8 Hz, 3a-H), 3.75 (1H, dd, J=9.4 and 8.0 Hz, 6a-H), 4.25 (2H, q, Et), 4.40 (1H, s, 4-H), 4.49 (1H, d, J=9.4 Hz, 6-H), and 6.9-7.3 (9H, m, Ar); ^{13}C NMR ($CDCl_3$) δ=14.47, 21.18, 35.36 (each q), 48.65, 50.42 (each d), 61.00 (t), 67.53, 69.06 (each d), 171.01, 174.84, and 176.54 (each s). 3b: ^{1}H NMR ($CDCl_3$) δ=1.27 (3H, t, Et), 2.16, 2.26 (each 3H, s, NMe and p-Me), 3.41 (1H, dd, J=9.7 and 5.7 Hz, 6a-H), 3.85 (1H, dd, J=9.7 and 8.8 Hz, 3a-H), 4.17 (2H, q, Et), 4.27 (1H, d, J=8.8 Hz, 4-H), 4.37 (1H, d, J=5.7 Hz, 6-H), and 7.0-7.4 (9H, m, Ar); ^{13}C NMR ($CDCl_3$) δ=14.30, 21.24, 35.06 (each q), 46.94, 53.47 (each d), 61.29 (t), 67.48, 69.12 (each d), 170.95, 175.60, and 176.36 (each s). 8: ^{1}H NMR ($CDCl_3$) δ=1.34 (3H, t, Et), 2.25, 2.31 (each 3H, s, NMe and p-Me), 3.42 (1H, d, J=7.0 Hz, 6-H), 3.52 (1H, dd, J=8.8 and 7.5 Hz, 3a-H), 3.68 (1H, dd, J=7.5 and 7.0 Hz, 6a-H), 3.74 (1H, d, J=8.8 Hz, 4-H), 4.32 (2H, dq, Et), and 6.9-7.4 (9H, m, Ar).

6) As an imine-azomethine ylide tautomerism of 2-iminoacetates: M. Joucla and J. Hamelin, Tetrahedron Lett., 1978, 2885; R. Grigg, J. Kemp, G. Sheldrick, and J. Trotter, J. Chem. Soc., Chem. Commun., 1978, 109.

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8) ^{1}H NMR ($CDCl_3$): 17: δ=2.41 (1H, br t, NH), 3.40 (1H, dd, J=8.0 and 7.5 Hz, 6a-H), 3.66 (1H, dd, J=7.5 and 6.8 Hz, 3a-H), 4.04 (1H, dd, 8.0 and 5.5 Hz, 6-H), 4.47 (1H, dd, J=6.8 and 5.5 Hz, 4-H), and 7.30 (5H, br s, Ph). 18: δ=2.59 (1H, br, NH), 3.35 (1H, dd, J=8.5 and 7.8 Hz, 6a-H), 3.66 (1H, d, J=7.8 Hz, 3a-H), 4.38 (1H, s, 4-H), 4.59 (1H, dd, J=8.5 and 4.0 Hz, 6-H), and 7.30 (5H, br s, Ph).

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