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Unusual Stereo- and Regioselectivity Observed in Cycloadditions of the N-Titanated Azomethine Ylides Derived from t-Butyl (Benzylideneamino)acetate with α,β-Unsaturated Esters

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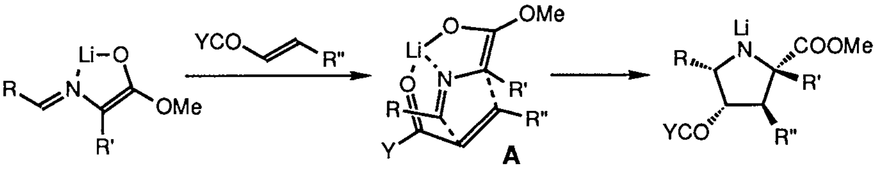
Cycloadditions of the N-titanated azomethine ylides, derived from t-butyl (benzylideneamino)acetate, with α,β-unsaturated esters afford three different types of cycloadducts, depending upon the structure of dipolarophiles and the reaction temperature. In the reactions at room temperature, exo cycloadducts are exclusively produced, while either endo cycloadducts or regioisomeric ones are obtained in the reactions at a low temperature.

The imines of α-amino esters can be transformed readily into N-metalated azomethine ylides, or the corresponding enolates, by action with metal salts and amine bases in tetrahydrofuran (THF) at room temperature.[1] The resulting ylides undergo highly stereoselective cycloadditions with α,β-unsaturated carbonyl compounds to produce 2-pyrrolidinecarboxylate derivatives, which correspond to the endo cycloadducts to E,E-ylidic forms, as shown in Eq. 1. It has been proposed that a tight chelation A would be responsible for the high stereoselection.[1,2]

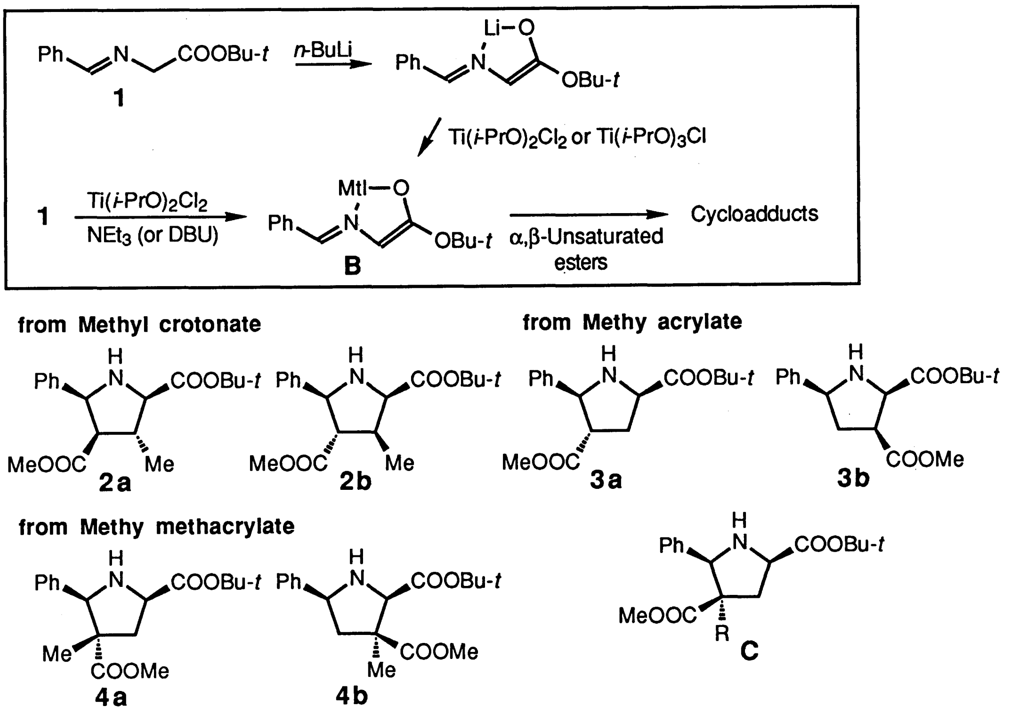


(1)

We have thereafter continued to work on the research project of N-metalated azomethine ylides, with the aim of establishing the hitherto unknown asymmetric cycloaddition of azomethine ylides. In the course of our investigation along this line, we came across a successful generation of N-titanated azomethine ylides from t-butyl (benzylideneamino)acetate by action with dichlorodiisopropoxytitanium, or chlorotriisopropoxytitanium, and triethylamine; their cycloadditions with several α,β-unsaturated esters have been briefly investigated.

It is quite recent that Grigg and coworkers reported cycloaddition reactions of the imines of α-amino esters with methyl acrylate in the presence of dichlorodiisopropoxytitanium and triethylamine, where the reversal of normal regioselectivity was observed.[3] Their report prompted us to publish our own results in this communication letter.[4)] Since our results contain some useful pieces of information which is quite different from the precedent, they would serve complementally in the field of azomethine ylide chemistry. Much contribution is expected, therefore, to the mechanistic consideration of the cycloaddition of N-metalated azomethine ylide.

t-Butyl (benzylideneamino)acetate (1) was lithiated into the N-lithiated ylide by treatment with butyllithium at -78 °C in toluene,[5)] which was then transmetalated with dichlorodiisopropoxytitanium or chlorotriisopropoxytitanium to generate the corresponding N-titanated azomethine ylides B [Mtl = $Ti(i\text{-}PrO)_2Cl$ or $Ti(i\text{-}PrO)_3$] as shown in Scheme 1. The former ylide B [Mtl = $Ti(i\text{-}PrO)_2Cl$] was also generated directly from imine 1, at -78 °C in dichloromethane, by action with dichlorodiisopropoxytitanium and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). These N-titanated azomethine ylides B underwent highly stereoselective cycloaddition with methyl crotonate to give the endo cycloadduct 2a, which has the same stereochemistry as that of the crotonate cycloadduct[1)] of the N-lithiated azomethine ylide derived from methyl (benzylideneamino)acetate (Entries 1-3 of Table 1).[6)]



Scheme 1.

A dramatic change of stereoselectivity was observed when the reaction temperature, both for the generation and cycloaddition steps, was raised up to 0 °C or higher; the exo cycloadduct 2b was obtained as a sole product (Entries 4-7). The structure of 2b was confirmed mainly on the basis of ^1H NMR spectrum: 5-H couples with 4-H ($J_{5-4} = 9.2$ Hz) which appears as a double doublet; the ester methyl (COOMe, δ 3.62) is out of the shielding cone from 5-Ph.

Similar reactions of ylide B [Mtl = $Ti(i\text{-}PrO)_2Cl$] with methyl acrylate (Entry 8) and methyl methacrylate (Entries 11 and 12) at room temperature produced the exo cycloadducts 3a and 4a, respectively, as sole products in both cases. It was of our great surprise that the identical reactions at a low temperature (-78 °C to -20 °C) produced the regioisomeric endo cycloadducts 3b (Entries 9 and 10) and 4b (Entry 14), not the endo cycloadduct C (R = H and Me) with a normal regiochemistry. It was found that the isomer ratio 4a/4b was dependent on the polarity of reaction solvent (Entries 11-13): Both dichloromethane and toluene favored for the formation of the exo isomer 4a, while THF for the regio isomer 4b.

Table 1. Titanium(IV)-Induced Cycloaddition of *t*-Butyl (Benzylideneamino)acetate **1** with α,β-Unsaturated Esters[a)]

Entry	Dipolarophile	Metal halide	Base[b)]	Solvent[c)]	Temp °C	Time h	Products (yield/%)[d)] *Endo*	*Exo*	*Regio*	Recovered **1**[e)]
1	Methyl crotonate	$TiCl_2(i\text{-}PrO)_2$	*n*-BuLi[f)]	TL	–78/–30	1/17	**2a** (55)			
2		$TiCl(i\text{-}PrO)_3$	*n*-BuLi[f)]	TL	–78/–30	4/13.5	**2a** (70)			15
3		$TiCl_2(i\text{-}PrO)_2$	DBU	DCM	–78	24	**2a** (53)			38
4		$TiCl_2(i\text{-}PrO)_2$	TEA	DCM	0	2.5		**2b** (51)		22
5		$TiCl_2(i\text{-}PrO)_2$	TEA	DCM	r.t.	13		**2b** (65)		
6		$TiCl_2(i\text{-}PrO)_2$	DBU	DCM	r.t.	2		**2b** (75)		
7		$TiCl_2(i\text{-}PrO)_2$	TEA	DCM	reflux	1		**2b** (65)		
8	Methyl acrylate	$TiCl_2(i\text{-}PrO)_2$	DBU	DCM	r.t.	5		**3a** (75)		
9		$TiCl_2(i\text{-}PrO)_2$	DBU	DCM	–20	24			**3b** (75)	
10		$TiCl_2(i\text{-}PrO)_2$	DBU	DCM	–78	24			**3b** (55)	trace
11	Methyl methacrylate	$TiCl_2(i\text{-}PrO)_2$	TEA	DCM	r.t.	6		**4a** (70)		5
12		$TiCl_2(i\text{-}PrO)_2$	TEA	TL	r.t.	13		**4a** (83)		
13		$TiCl_2(i\text{-}PrO)_2$	TEA	THF	r.t.	4		**4a** (27)	**4b** (35)	
14		$TiCl_2(i\text{-}PrO)_2$	TEA	THF	–78	24			**4b** (31)	54

a) All the reactions were carried out by employing 1 equivalent of a titanium compound and 1.1 equivalent of a base. b) DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; TEA: triethylamine. c) DCM: dichloromethane; TL: toluene; THF: tetrahydrofuran. d) Yield of the isolated products. e) The recovery percentage was determined by ^1H NMR spectrum of the crude reaction mixture. f) Imine **1** was treated initially with butyllithium (1 equiv.) at –78 °C and then with a titanium compound.

The structures of exo cycloadduct 4a and regioisomeric cycloadduct 4b, each as representative examples, were assigned on the basis of ^1H NMR spectra including an NOE measurement (4a: 2-H and 5-H are observed as a double doublet and a singlet, respectively, and 4-Me is in the shielding cone from 5-Ph. 4b: 2-H and 5-H appear as a singlet and a double doublet, respectively, and notable NOEs exist between 2-H and 3-Me, 2-H and 5-H, 3-Me and 5-H).[6)]

The exclusive formation of exo cycloadduct 3a in the above case (Entry 8) makes a sharp contrast with the precedingly reported case,[3)] where regioisomeric cycloadduct, dimethyl 5-(2-naphthyl)-2,3-pyrrolidinedicarboxylate, and its transesterification product were produced in a similar reaction of the N-titanated azomethine ylide, derived from methy (2-naphthylideneamino)acetate, with methyl acrylate at room temperature.

The dramatic change of stereoselectivity and regioselectivity, thus observed in the cycloadditions of N-titanated azomethine ylides B, can not be fully explained yet. However, it is certain, based on the following observation, that the ylide structure depends upon the generation temperature of ylide: The N-titanated ylide B [Mtl = $Ti(i\text{-}PrO)_2Cl$], or its isomer, afforded the exo product 2b (45%) alone when generated at room temperature and allowed to react with methyl crotonate at -78 °C, while a mixture of 2a and 2b (65%, 3:4 by ^{1}H NMR) was obtained when the equivalent ylide was generated at -78 °C and allowed to react with the same crotonate at room temperature.7)

The ylide generated at -78 °C presumably has a chelated structure like B, since its cycloaddition with methyl crotonate led to the exclusive formation of a typical chelation-controlled cycloadduct 2a. Accordingly, the ylide generated at room temperature would be a nonchelated type, as Grigg suggested.3) A similar exo selectivity has been observed in the cycloadditions of N-sodioazomethine ylides, which are characterized more or less as metal enolates.8) The reversal of regioselectivity may be deeply related with this anionic character of the ylide intermediate involved.8,9) The size of titanium atom as well as the bulky isopropoxyl ligands would be responsible for the fragility of the titanium chelation.

References

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2) S. Kanemasa, M. Yoshioka, and O. Tsuge, Bull. Chem. Soc. Jpn., 62, 2196 (1989).

3) D. A. Barr, R. Grigg, and V. Sridharan, Tetrahedron Lett., 30, 4727 (1989).

4) Part of the present work was presented at the 58th National Meeting of the Chemical Society of Japan, Kyoto, April 1989, Abstr., No. 1 III G28.

5) This reaction offers a convenient method for the irreversible generation of N-lithiated azomethine ylides. t-Butyl ester was employed to avoid the undesired nucleophilic attack of butyllithium to the ester moiety.

6) All new compounds cited herein were fully characterized on the basis of spectral and analytical data. ^{1}H NMR Spectral data of typical products are as follows: 2a: $\delta = 1.23$ (3H, d, $J_{\text{Me-3}} = 6.6$ Hz, 3-Me), 1.53 (9H, s, COOBu-t), 2.50 (1H, br s, NH), 2.64 (1H, ddd, $J_{3\text{-}2} = 9.2$, $J_{3\text{-}4} = 8.4$, and $J_{3\text{-Me}} = 6.6$ Hz, 3-H), 3.01 (1H, dd, $J_{4\text{-}5} = 8.8$ and $J_{4\text{-}3} = 8.4$ Hz, 4-H), 3.24 (3H, s, COOMe), 3.33 (1H, d, $J_{2\text{-}3} = 9.2$ Hz, 2-H), 4.60 (1H, d, $J_{5\text{-}4} = 8.8$ Hz, 5-H), and 7.2 - 7.3 (5H, m, Ph). 4a: 0.93 (3H, s, 4-Me), 1.49 (9H, s, COOBu-t), 2.20 (1H, dd, $J_{\text{gem}} = 13.2$ and $J_{3\text{-}2} = 8.4$ Hz, one of 3-H), 2.58 (1H, dd, $J_{\text{gem}} = 13.2$ and $J_{3\text{-}2} = 6.6$ Hz, the other of 3-H), 3.25 (1H, br s, NH), 3.71 (3H, s, COOMe), 3.94 (1H, dd, $J_{2\text{-}3} = 8.4$ and 6.6 Hz, 2-H), 4.84 (1H, s, 5-H), and 7.2 - 7.4 (5H, m, Ph). 4b: 1.46 (9H, s, COOBu-t), 1.53 (3H, s, 3-Me), 2.14 (1H, dd, $J_{\text{gem}} = 12.8$ and $J_{4\text{-}5} = 7.3$ Hz, one of 4-H), 2.41 (1H, dd $J_{\text{gem}} = 12.8$ and $J_{4\text{-}5} = 9.9$ Hz, the other of 4-H), 2.51 (1H, br s, NH), 3.61 (1H, s, 2-H), 3.68 (3H, s, COOMe), 4.28 (1H, dd, $J_{5\text{-}4} = 9.9$ and 7.3 Hz, 5-H), and 7.2 - 7.5 (5H, m, Ph).

7) In both cases, imine 1 was treated with $Ti(i\text{-}PrO)_2Cl_2$ and triethylamine in dichloromethane for 5 min at -78 °C (or at room temperature), and then the mixture was heated up to room temperature (or cooled down to -78 °C). Methyl crotonate was added and the cycloaddition was carried out at a specified temperature for 3 - 5 h.

8) S. Kanemasa, M. Yoshioka, and O. Tsuge, Bull. Chem. Soc. Jpn., 62, 869 (1989).

9) O. Tsuge, S. Kanemasa, T. Yamada, and K. Matsuda, J. Org. Chem., 52, 2523 (1987).

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