

Highly Stereoselective Ene Reaction of Aldimines with 2-(Alkylthio)allyl Silyl Ethers

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Summary: A stereoselective ene reaction of aldimines with 2-(alkylthio)allyl silyl ethers was developed. Under the influence of Lewis acids, *N*-acylimine or geminal biscarbamates reacted with a (*Z*)-2-(methylthio)allyl silyl ether to afford syn adducts in >94% selectivity.

Although ene reactions of aldehydes have been reported by many groups,¹ there are few examples using aldimines as enophiles² due to their poor reactivity. Recently, we introduced 2-(alkylthio)allyl silyl ethers as highly reactive enes.³ Their high reactivity led us to examine reactions with aldimines.

For the reactions of *N*-benzylimines⁴ 1a-1c with ene substrates 2a and 2b, several Lewis acids were investigated, and AlCl₃ was found to give the most satisfactory results (Table 1). The reaction of 2a with imines 1b and 1c afforded the desired products in good yield, whereas the adduct 4 was obtained in low yield from 1a.⁵ The reactivity of the ene substrate seems to be crucially dependent on the steric hindrance around the alkenyl sulfide moiety. Thus, the reaction of 2b gave the products in only moderate yield, and no desired product was obtained from trisubstituted alkenyl sulfides.

Introduction of an electron-withdrawing group on nitrogen significantly increased the reactivity of the aldimine. Under the influence of EtAlCl₂, the reaction of *N*-(methoxycarbonyl)imine 1d⁶ and ene substrate 2c proceeded smoothly even at -45 °C (Table 2, entries 1 and 2). The substrate (*Z*)-2c gave the syn adduct in 96% selectivity, while low anti selectivity was observed on the reaction of (*E*)-2c.⁷

The high lability of aliphatic *N*-(methoxycarbonyl)imines under the present reaction conditions prevented their use as enophiles, but a geminal biscarbamate readily prepared from the corresponding aldehyde and urethane⁸

Table 1. Ene Reaction of *N*-Benzylimines with 2-(Alkylthio)allyl Silyl Ethers

entry	imine	ene	product (% yield)
1	1a: R ¹ = <i>n</i> -Pr	2a: R ² = H	4 (22)
2	1b: R ¹ = <i>i</i> -Pr		5 (77)
3		2b: R ² = Me	6 (42)
4	1c: R ¹ = Ph	2a: R ² = H	7 (89)
5		2b: R ² = Me	8 (54)

Table 2. Reaction of Enophiles with 2c

entry	enophile	ene	Lewis acid	product (% yield)	syn:anti ^a
1	1d	(<i>Z</i>)-2c	EtAlCl ₂	9 (77)	96:4
2		(<i>E</i>)-2c		(47)	37:63
3	3a: R = <i>n</i> -Pr	(<i>Z</i>)-2c	BF ₃ ·OEt ₂	10 (89)	94:6
4		(<i>E</i>)-2c		(51)	20:80
5	3b: R = <i>n</i> -Hep	(<i>Z</i>)-2c		11 (84)	96:4
6		(<i>E</i>)-2c		(55)	9:91
7	3c: R = <i>i</i> -Bu	(<i>Z</i>)-2c		12 (79)	94:6
8		(<i>E</i>)-2c		(73)	6:94
9	3d: R = <i>i</i> -Pr	(<i>Z</i>)-2c		13 (88)	>99:1
10		(<i>E</i>)-2c		(21)	8:92
11	3e: R = <i>c</i> -Hex	(<i>Z</i>)-2c		14 (77) ^b	99:1
12		(<i>E</i>)-2c		(23) ^b	12:88
13	3f: R = Ph	(<i>E</i>)-2c		15 (86)	10:90

^a Each of the diastereomers is a mixture of geometrical isomers containing *Z* isomer predominantly. ^b The reaction was performed at -23 °C.

as an equivalent of *N*-(alkoxycarbonyl)imine.⁹ The reaction of biscarbamates 3a-3f and (*Z*)-2c or (*E*)-2c in the presence of BF₃·OEt₂ afforded the corresponding ene adducts as a mixture of geometrical isomers (Table 2, entries 3-13).

The stereochemical features⁷ exhibited in the reactions of aliphatic biscarbamates 3a-3f are similar to those of aromatic *N*-(methoxycarbonyl)imine 1d. The reaction with (*Z*)-2c preferentially produced syn adducts in good yield, whereas anti product with lower selectivity was obtained from (*E*)-2c in moderate to low yield. This result may be rationalized by assuming the six-membered chairlike transition states^{3c} TS-1 and TS-2 shown in Figure 1. In the reaction of biscarbamates, these transition states

(9) Geminal biscarbamate as a precursor of *N*-acyliminium intermediate in hetero Diels-Alder reactions: Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987; Chapter 2, p 34 and references cited therein.

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 (7) Treatment of the products with ozone followed by periodic acid gave β-(methoxycarbonyl)amino acids, which were methylated to afford corresponding esters. The stereochemistry was confirmed by comparing the ¹H NMR spectra with those of authentic materials prepared from *cis*- and *trans*-β-lactams (supplementary material).
 (8) (a) Kraft, W. M.; Herbst, R. M. *J. Org. Chem.* 1945, 10, 483. (b) Krow, G.; Rodebaugh, R.; Carosin, R.; Figures, W.; Pannella, H.; DeVicaris, G.; Grippi, M. *J. Am. Chem. Soc.* 1973, 95, 5273.

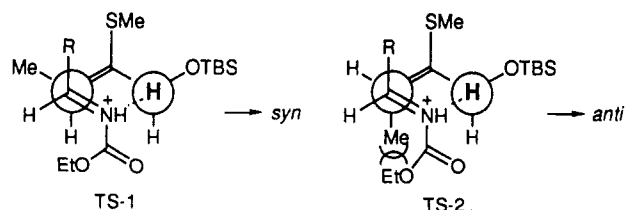
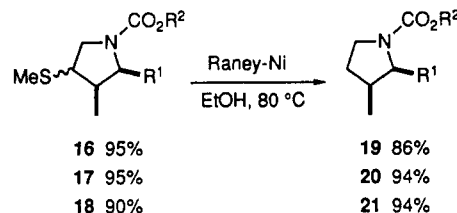
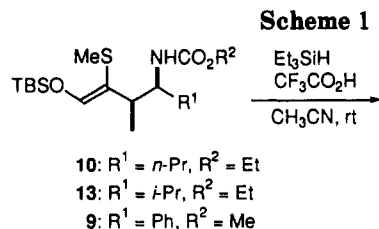


Figure 1.

involve an *N*-acyliminium intermediate with the *E* configuration¹⁰ and contain both *R* and *N*-acyl groups on axial positions. Therefore, the reaction of (*Z*)-**2c** proceeds through TS-1 to give syn product, and (*E*)-**2c** leads to anti adduct via TS-2. In TS-1, a larger *R* group may lower selectivity due to steric interaction with the allylic methyl group, but nonetheless high selectivity was exhibited as shown in entry 11. On the other hand, TS-2 is considerably disfavored by severe steric repulsion between the allylic methyl group and the *N*-acyl group, which leads to a decrease of product yield as well as diastereoselectivity. Analogous six-membered chairlike transition states could also be involved in the reaction of *N*-(methoxycarbonyl)imine **1d**.

The ene adducts containing the enol silyl ether moiety as well as the protected amino group show promise for synthetic utility in the construction of heterocycles. For example, treatment of adducts **9**, **10**, and **13** with trieth-



ylsilane and trifluoroacetic acid followed by desulfurization afforded pyrrolidine derivatives in good yield (Scheme 1). We are currently investigating an application to the stereoselective synthesis of natural products.

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Supplementary Material Available: Experimental procedures and spectral data for **2a–2c** and **4–21** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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