ORGANIC LETTERS

2002
Vol. 4, No. 18
3119−3121

Anionic Inverse Electron-Demand 1,3-Dipolar Cycloaddition of Nitrones with Ynolates. Facile Stereoselective Synthesis of 5-Isoxazolidinones Leading to β-Amino Acids

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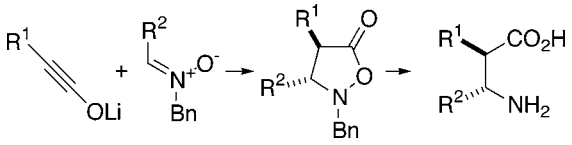
Received July 1, 2002

ABSTRACT



The inverse electron-demand 1,3-dipolar cycloaddition of nitrones with ynolates, followed by quenching with *t*-BuOH, produced substituted 5-isoxazolidinones with good *trans*-selectivity. These products were easily converted into β-amino acids.

The 1,3-dipolar cycloaddition of nitrones with alkenes[1] is an important method for preparing isoxazolidines, which can be converted into numerous building blocks for organic synthesis. Commonly, these cycloadditions involve the reaction of an electron-deficient alkene dipolarphile (LUMO) with a nitrone (HOMO). In inverse electron-demand 1,3-dipolar cycloadditions, alkenyl ethers or ketene acetals are used as electron-rich dipolarphiles (HOMO); nitrone (LUMO) activation by Lewis acids and/or with electron-withdrawing substituents or high reaction temperature are required.[2] However, uncatalyzed anionic 1,3-dipolar cycloadditions of nonactivated nitrones have not yet been reported, as far as we know.

Since developing a new synthetic method for ynolates,[3] we have continued our investigation of ynolate chemistry,[4] including [2 + 2] cycloadditions.[3,5] Although ynolates can be potentially dipolarophilic, there have been no reports on 1,3-dipolar [3 + 2] cycloadditions of ynolates. Herein, we describe the first anionic inverse electron-demand 1,3-dipolar cycloaddition of ynolates with nitrones to provide synthetically useful 5-isoxazolidinones[6] leading to β-amino acids (Scheme 1).

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(1) For reviews, see: (a) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 1069. (b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990. (c) Kobayashi, S., Jorgensen, K. A., Eds. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 2002. (d) Frederickson, M. *Tetrahedron* **1997**, *53*, 403−425. (e) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−909. (f) Gothelf, K. V.; Jorgensen, K. A. *Chem. Commun.* **2000**, 1449−1458. (g) Padwa, A., Pearson, W. H., Eds.; *Chemistry of Heterocyclic Compounds*; Wiley: New York, 2002; Vol. 58.

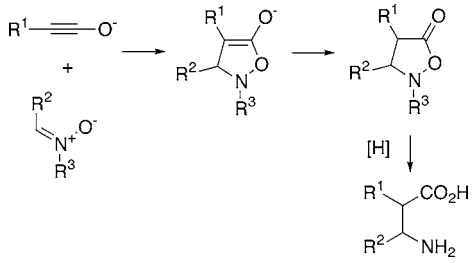
(2) For recent examples, see: (a) Kanemasa, S.; Tsuruoka, T.; Wada, E *Tetrahedron Lett.* **1993**, *34*, 87−90. (b) Seerden, J.-P. G.; Scholte op Reimer, A. W. A.; Scheeren, H. W. *Tetrahedron Lett.* **1994**, *35*, 4419−4422. (c) Simonsen, K. B.; Bayon, P.; Hazell, R. G.; Gothelf, K. V.; Jorgensen, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 3845−3853. (d) Tamura, O.; Gotanda, K.; Yoshino, J.; Morita, Y.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Mita, N.; Yamashita, M.; Ishibashi, H.; Sakamoto, M. *J. Org. Chem.* **2000**, *65*, 8544−8551.

(3) (a) Shindo, M. *Tetrahedron Lett.* **1997**, *38*, 4433−4436. (b) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, *54*, 2411−2422. (c) Shindo, M.; Koretsune, R.; Yokota, W.; Itoh, K.; Shishido, K. *Tetrahedron Lett.* **2001**, *42*, 8357−8360.

(4) For reviews, see: (a) Shindo, M. *Chem. Soc. Rev.* **1998**, *27*, 367−374. (b) Shindo, M. *J. Synth. Org. Chem. Jpn.* **2000**, *58*, 1155−1166. (c) Shindo, M. *Yakugaku Zasshi* **2000**, *120*, 1233−1246. See, also: (d) Shindo, M.; Sato, Y.; Shishido, K. *J. Org. Chem.* **2000,** *65*, 5443−5445. (e) Shindo, M.; Matsumoto, K. Mori, S.; Shishido, K. *J. Am. Chem. Soc.* **2002**, *124*, 6840−6841.

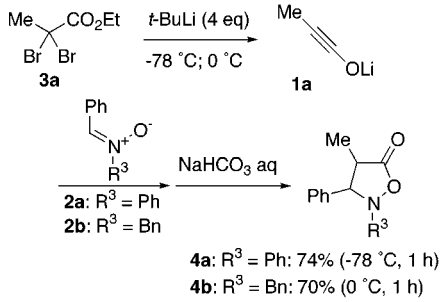
10.1021/ol0264455 CCC: $22.00
Published on Web 08/08/2002

Scheme 1



First, we examined the reaction of the ynolate (**1a**) with the nitrone (**2a**) bearing a *N*-phenyl substituent (Scheme 2).

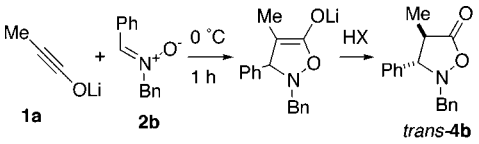
Scheme 2



To a −78 °C THF solution of the ynolate (**1a**), generated from the α,α-dibromoester (**3a**) with *t*-BuLi, was added *N*-phenyl nitrone (**2a**). After 1 h, no starting nitrone remained and the reaction was quenched with saturated aqueous $NaHCO_3$. After workup and purification, we isolated the desired 5-isoxazolidinone (**4a**) in 74% yield. Since no 4-oxazolidinone was detected, the regioselectivity was excellent, probably as a result of the FMO interaction. Next, the cycloaddition with the *N*-benzyl nitrone (**2b**) was carried out at −78 °C but did not take place. The reaction proceeded at 0 °C to afford the desired 5-isoxazolidinone (**4b**) in 70% yield. Despite the lower reactivity of the *N*-benzyl nitrones, we used them in further reactions because of the facile removal of the *N*-substituent from the products.

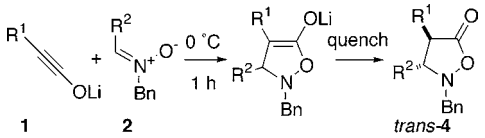
The ratio of the *cis* and *trans* diastereomers of the 5-isoxazolidinones should be dependent on the method used to quench the reaction. We then attempted to control the ratio by using several proton sources and quenching conditions, as shown in Table 1. When the reaction was protonated with an aqueous $NaHCO_3$ solution at −78 °C, **4b** was obtained in the *trans/cis* ratio of 93:7 (entry 1). The *trans* product was formed predominantly under the kinetic conditions presumably as a result of the steric interaction between the methyl and phenyl substituents in the late transition state of the protonation.[7] Quenching with more sterically hindered (entries 2 and 3) and more acidic (entries 4 and 5) proton sources gave poorer ratios. However, when the reaction was quenched with ethanol at −78 °C and warmed to 0 °C to effect isomerization to the thermodynamically stable products, complete *trans* selectivity was achieved (entry 6).

Table 1. Protonation of the 5-Isoxazolidinone Enolates



entry	HX	conditions	yield (%)	*trans*:*cis*
1	aq $NaHCO_3$	−78 °C	70	93:7
2	phenol	−78 °C	70	79:21
3	2,6-dimethylphenol	−78 °C	79	58:42
4	AcOH	−78 °C	70	68:32
5	TFA	−78 °C	58	60:40
6	EtOH	−78 °C; 0 °C	57	>99:1
7	*t*-BuOH	−78 °C; 0 °C	77	>99:1

Table 2. 1,3-Dipolar Cycloaddition of Ynolates with Nitrones To Afford 5-Isoxazolidinones



entry	R^1	R^2	quench[a]	**4**	yield (%)	*trans*:*cis*
1	Me	Me	A	**4c**	42	83:12
2	Me	Me	B	**4c**	53	>99:1
3	Me	Et	A	**4d**	85	86:14
4	Me	Et	B	**4d**	85	89:11
5	Me	*i*Pr	A	**4e**	77	9:91
6	Me	*i*Pr	B	**4e**	35	>99:1
7	Me	*t*Bu	A	**4f**	17	10:90
8	Me	*t*Bu	B	**4f**	56	>99:1
9	Bu	Me	A	**4g**	37	78:22
10	Bu	Me	B	**4g**	59	>99:1
11	Bu	Et	A	**4h**	80	86:14
12	Bu	*i*Pr	A	**4i**	72	18:82
13	Bu	*i*Pr	B	**4i**	67	91:9
14	*i*Pr	Ph	A	**4j**	75	96:4
15[b]	Me	CO_2Et	A	**4k**	76	70:30

[a] Method A: quenching with aqueous $NaHCO_3$ at −78 °C. Method B: quenching with *t*-BuOH at −78 °C, then warming to 0 °C. [b] The cycloaddition was carried out at −78 °C.

(5) For pioneering work on cycloaddition of aldehydes and ketones, see: (a) Schöllkopf, U.; Hoppe, I. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 765. (b) Hoppe, I.; Schöllkopf, U. *Liebigs Ann. Chem.* **1979**, 219−226. (c) Kowalski C. J.; Fields, K. W. *J. Am. Chem. Soc.* **1982**, *104*, 321−323. Cycloaddition of aldimines: (d) Shindo, M.; Oya, S.; Sato, Y.; Shishido, K. *Heterocycles* **1998**, *49*, 113−116. (e) Shindo, M.; Oya, S, Murakami, R. Sato, Y.; Shishido, K. *Tetrahedron Lett.* **2000**, *41*, 5943−5946. (f) Shindo, M.; Oya, S.; Murakami, R.; Sato, Y.; Shishido, K. *Tetrahedron Lett.* **2000,** *41*, 5947−5950.

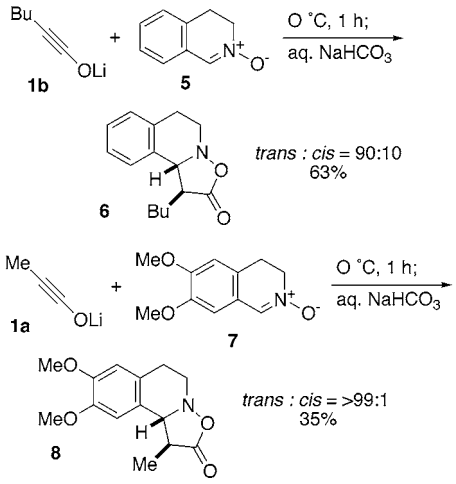
(6) For examples of syntheses of 5-isoxazolidinones, see: (a) Sibi, M. P.; Liu, M. *Org. Lett.* **2001**, *3*, 4181−4184. (b) Ishikawa, T.; Nagai, K.; Senzaki, M.; Tatsukawa, A. Saito, S. *Tetrahedron* **1998**, *54*, 2433−2448. (c) Panfil, I.; Maciejewski, S.; Belzecki, C.; Chielewski, M. *Tetrahedron Lett.* **1989**, *30*, 1527−1528. (d) Baldwin, J. E.; Harwood: L. M.; Lombard, M. J. *Tetrahedron* **1984**, *40*, 4363−4370.

Finally, quenching with *tert*-butyl alcohol afforded the best result (entry 7). Thus, the *trans*-5-isoxazolidinones (**4**) were produced in good yield with excellent stereoselectivity via the thermodynamically controlled protonation method.

To test the generality of this cycloaddition, we examined reactions using several kinds of nitrones and ynolates. As shown in Table 2, the 5-isoxazolidinones were obtained regiospecifically in good to moderate yields. In the reactions of sterically hindered nitrones, the *cis*-products were predominantly produced via kinetic protonation (quenching method A), probably as a result of the steric interaction between R^1 and the proton source in the early transition states (entries 5 and 7). The thermodynamically controlled protonation (quenching method B) provided the desired 5-isoxazolidinones with high *trans*-selectivity (entries 2, 4, 6, 8, 10, and 13). The nitrone bearing an ester ($R^2 = CO_2Et$) showed higher reactivity and gave the product (**4k**) at −78 °C (entry 15).

The 3,4-dihydroisoquinoline *N*-oxides (**5**, **7**) also afforded the desired cycloadducts (**6**, **8**) (Scheme 3).

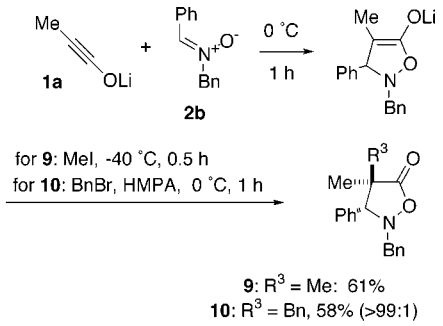
Scheme 3



The cycloadducts, nucleophilic 5-isoxazolidinone enolates, can react with electrophiles. As shown in Scheme 4, one-pot alkylation reactions provided the 3,4,4-trisubstituted isoxazolidinones (**9**, **10**) in good yields, and **10** was obtained as a single isomer.

The 5-isoxazolidinones (**4**) thus prepared can be converted into 2,3-disubstitutred β-amino acids (**11**) via hydrogenation[6d] in excellent yields without isomerization (Scheme 5).

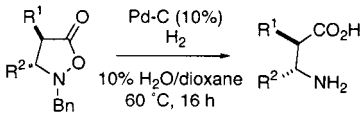
Scheme 4



9: R^3 = Me: 61%
10: R^3 = Bn, 58% (>99:1)

In conclusion, we have developed a 1,3-dipolar cycloaddition of ynolates with nitrones to afford 5-isoxazolidinones having good *trans*-selectivity and excellent regioselectivity. This is the first example of a [3 + 2] cycloaddition of an anionic dipolarophile with nonactivated nitrones not using Lewis acids. Since the cycloadducts are enolates, this reaction can be used in tandem reactions. This is a short, stereoselective access to β-amino acids, since the resulting 5-isoxazolidinones can be easily reduced in high yield.

Scheme 5



11c: R^1 = Me, R^2 = Me: >99%
11d: R^1 = Me, R^2 = Et: >99%
11b: R^1 = Me, R^2 = Ph: 89%

Acknowledgment. This research was partially supported by a Grant in Aid for Scientific Research on Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedure and spectral data of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0264455

(7) Danheiser, R. L.; Nowick, J. S. *J. Org. Chem.* **1991**, *56*, 1176−1185.