ORGANIC LETTERS

2010
Vol. 12, No. 19
4268−4270

Diastereoselective Conjugate Addition of Organocuprates to Chiral *N*-Enoyl Oxazolidinethiones

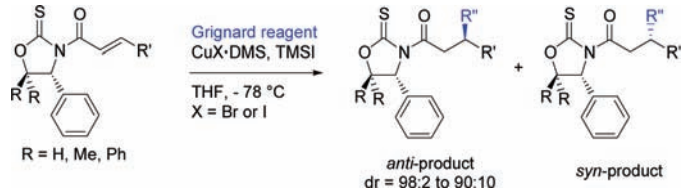
Rocío Sabala,[†] Luis Hernández-García,[‡] Aurelio Ortiz,[†] Moisés Romero,[‡] and Horacio F. Olivo*[,‡]

Facultad de Ciencias Químicas, Benemérita Universidad Autónoma de Puebla, Pue. 72570, Mexico, and Division of Medicinal and Natural Products Chemistry, The University of Iowa, Iowa City, Iowa 52242

horacio-olivo@uiowa.edu

Received July 20, 2010

ABSTRACT



Addition of organocuprates, generated in situ using an excess of a 1:2 mixture of CuI·DMS and Grignard reagent, to *N*-enoyl oxazolidinethiones in the presence of excess TMSI gave preferentially the *anti* diastereomer where the addition took place when the conformation of the substrate was *syn*-s-*cis*. The reaction was investigated with indene-based and three different phenyl glycine derived oxazolidinethiones.

Conjugate addition of active methylene compounds, the Michael reaction, is one of the most fundamental carbon−carbon bond forming reactions in organic chemistry.[1] Organocuprate additions to α,β-unsaturated carboxylic acids attached to chiral oxazolidinones have been well studied. The asymmetric 1,4-addition of organocuprates to chiral α,β-unsaturated *N*-acyl-4-phenyl-2-oxazolidinones was initially reported by Hruby in 1993.[2] Appropriate reagents and conditions have been found to achieve diastereoselective additions of organocuprates to *N*-enoyl oxazolidinones.[3] When the conformation of the *N*-enoyl oxazolidinone is *anti*-s-*cis*, the *syn* addition product is obtained, and when the conformation is *syn*-s-*cis*, the *anti* addition product is then obtained (Figure 1). The conjugate addition of organocuprates to chiral *N*-enoyl oxazolidinones has been employed in the syntheses of several natural products.[4]

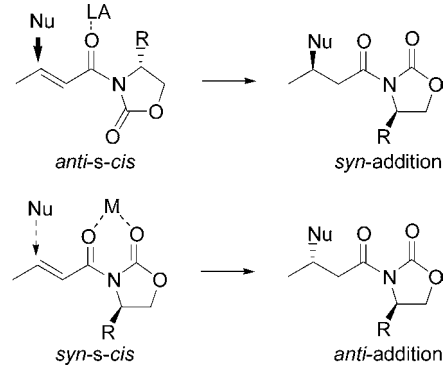


Figure 1. *anti*-s-*cis* and *syn*-s-*cis* conformations of *N*-enoyl oxazolidinones.

Thiazolidinethione and oxazolidinethione chiral auxiliaries are becoming more popular because of their highly diaste-

[†] Benemérita Universidad Autónoma de Puebla.
[‡] The University of Iowa.

(1) (a) Bergmann, E. D.; Ginsburg, D.; Pappo, R. *Org. React.* **1959**, *10*, 182–542. (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771–806. (c) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. (d) Alexakis, A.; Backvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008**, *108*, 2796–2823.

(2) Nicolas, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766–770.

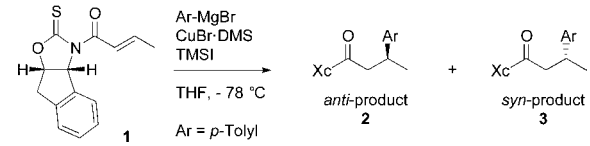
10.1021/ol101687e
Published on Web 08/31/2010

reoselective aldol reactions and particularly in the more troublesome acetate aldol reaction.[5] In addition, these auxiliaries have shown to be directly displaced by different nucleophiles. *N*-Acyl derivatives can be easily prepared from coupling of the auxiliary with a carboxylic acid or with an acyl chloride.[6]

Palomo et al. have shown that *N*-enoyl oxazolidinethiones undergo a Lewis acid-promoted intramolecular Michael addition with high diastereoselectivity to yield β-sulfanyl imides.[7,8] Kataoka et al. have shown that *N*-cinnamoyl oxazolidinethiones can react with benzaldehydes in the presence of BF_3•OEt_2 in a tandem Michael-aldol reaction.[9,10] Other rearranged products can also be obtained during the preparation of *N*-enoyl oxazolidinethiones when employing sodium hydride and the corresponding acid chloride.[11] Despite the interest in asymmetric transformations with chiral oxazolidinethione auxiliaries, no report has yet appeared of conjugate addition of organocuprate nucleophiles.[12] Herein, we describe reaction conditions to carry out this reaction.

We surveyed different reaction conditions and found that Grignard reagents added stereoselectively to *N*-crotonoyl indene-based oxazolidinethione **1** in THF at low temperature (Table 1). Poor diastereoselectivity was observed when the organocuprate reagent was prepared using 6 equiv of Grignard reagent and 3 equiv of CuBr•DMS (entry 1). The diastereoselectivity greatly improved when an equimolar mixture of CuBr•DMS and Grignard reagent was employed in a 6-fold excess (entry 2). Addition of TMSI as a Lewis acid improved slightly the yield of the addition without affecting the diastereoselectivity (entry 3). Increasing the amount of Grignard reagent and adding the Lewis acid was also beneficial (entry 4). Better results were obtained when

Table 1. Conjugate Addition to *N*-Crotonoyl Oxazolidinethione **1**



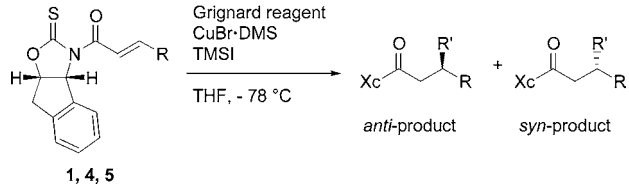
entry	CuBr	Grignard	TMSI	yield[a] (%)	**2**:**3**[b]
1	3	6	0	68	2:1
2	6	6	0	58	95:5
3	3	3	3	65	95:5
4	3	6	3	65	95:5
5	3	4.5	3	70	98:2
6	6	6	6	62	95:5

[a] Isolated total yield of two diastereomers. [b] As determined by ^{1}H NMR peak integrations with crude products.

an excess of Grignard reagent was added in the presence of TMSI (entries 5 and 6). X-ray single-crystal analysis of the major diastereomer (**2**) established unambiguously the relative stereochemistry of the newly formed stereocarbon.[13]

More reproducible results were obtained when using 3 equiv of CuBr•DMS, 6 equiv of Grignard reagent, and 3 equiv of Lewis acid.[14] These conditions were used with other Grignard reagents (Table 2). We obtained similar results

Table 2. Conjugate Addition to *N*-Crotonoyl Oxazolidinethione[a]



entry	*N*-enoyl	Grignard	yield[b] (%)	*anti*:*syn*[c]
1	**1** R = Me	R′ = Ph	76	(**2b**:**3b** = 95:5)
2	**1** R = Me	R′ = *p*-Tol	70	(**2a**:**3a** = 95:5)
3	**4** R = Ph	R′ = Me	45	(**3b**:**2b** = 1:1)
4	**5** R = *p*-Tol	R′ = Me	30	(**3a**:**2a** = 3:1)

[a] See Supporting Information for actual structures of products in the table. [b] Isolated total yield of two diastereomers. [c] As determined by ^{1}H NMR peak integrations with crude products.

when phenylmagnesium bromide was used instead of the *p*-tolyl Grignard reagent (entries 1 and 2). To our surprise, low yields and poor diastereoselectivities were obtained when methylmagnesium bromide was used as the Grignard reagent and added to the *N*-cinnamoyl and the *N*-(4-methylcinnamoyl) oxazolidinethiones (entries 3 and 4). Others have also observed lower yields and diastereoselectivities when *N*-cinnamoyl derivatives are employed.[3a]

We decided to explore other chiral oxazolidinethiones with only a phenyl group on C4 to compare the effect of having

(3) (a) Liao, S.; Han, Y.; Qiu, W.; Bruck, M.; Hruby, V. J. *Tetrahedron Lett.* **1996**, *37*, 7917–7920. (b) Williams, D. R.; Kissel, W. S.; Li, J. J. *Tetraheron Lett.* **1998**, *39*, 8593–8596. (c) Schneider, C.; Reese, O. *Synthesis* **2000**, 1689–1694. (d) Pollock, P.; Dambacher, J.; Anness, R.; Bergdahl, M. *Tetrahedron Lett.* **2002**, *43*, 3693–3697. (e) Dambacher, J.; Anness, R.; Pollock, P.; Bergdahl, M. *Tetrahedron* **2004**, *60*, 2097–2110. (f) Perez, L.; Bernès, S.; Quintero, L.; Anaya de Parrodi, C. *Tetrahedron Lett.* **2005**, *46*, 8649–8652. (g) Sprecher, H.; Pletscher, S.; Möri, M.; Marti, R.; Gaul, C.; Patora-Komisarska, K.; Otchertianova, E.; Beck, A. K.; Seebach, D. *Helv. Chim. Acta* **2010**, *93*, 90–110.

(4) (a) Williams, D. R.; Nold, A. L.; Mullins, R. J. *J. Org. Chem.* **2004**, *69*, 5374–5382. (b) Williams, D. R.; Ihle, D. C.; Brugel, T. A.; Patnaik, S. *Heterocycles* **2006**, *70*, 77–82. (c) Esumi, T.; Shimizu, H.; Kashiyama, A.; Sasaki, C.; Toyota, M. *Tetrahedron Lett.* **2008**, *49*, 6846–6849. (d) Morita, M.; Ishiyama, S.; Koshino, H.; Nakata, T. *Org. Lett.* **2008**, *10*, 1675–1678.

(5) (a) Review on thiazolidinethiones: Velazquez, F.; Olivo, H. F. *Curr. Org. Chem* **2002**, *6*, 303–340. (b) Review on oxazolidinethione: Ortiz, A.; Sansinenea, E. *J. Sulfur Chem* **2007**, *28*, 1–39.

(6) Andrade, C. K. Z.; Rocha, R. O.; Vercillo, O. E.; Silva, W. A.; Matos, R. A. F. *Synlett* **2003**, 2351–2352.

(7) Palomo, C.; Oiarbide, M.; Dias, F.; Ortiz, A.; Linden, A. *J. Am. Chem. Soc.* **2001**, *123*, 5602–5603.

(8) Ortiz, A.; Quintero, L.; Hernandez, H.; Maldonado, S.; Mendoza, G.; Bernes, S. *Tetrahedron Lett.* **2003**, *44*, 1129–1132.

(9) Kataoka, T.; Kinoshita, H.; Kinoshita, S.; Osamura, T.; Watanabe, S.-I.; Iwamura, T.; Muraloka, O.; Tanabe, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2889–2891.

(10) Kinoshita, H.; Takahashi, N.; Iwamura, T.; Watanabe, S.-I.; Kataoka, T.; Muraoka, O.; Tanabe, G. *Tetrahedron Lett.* **2005**, *46*, 7155–7158.

(11) Ortiz, A.; Quintero, L.; Mendoza, G.; Bernes, S. *Tetrahedron Lett.* **2003**, *44*, 5053–5055.

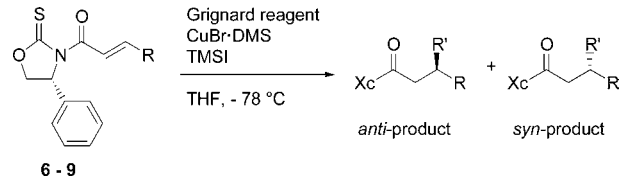
(12) Only one single case of organocuprate addition to an *N*-enoyl thiazolidinethione has appeared in the literature: Lu, C.-F.; Zhang, S.-B.; Li, Y.; Yang, G.-C.; Chen, Z.-X. *Tetrahedron: Asymmetry* **2009**, *20*, 2267–2269.

(13) See Supporting Information for CIF's.

(14) See Supporting Information for a General Procedure.

an aromatic ring locked in the indene-based oxazolidinethiones and others with free rotation or different angle of the phenyl ring. For this purpose, three other oxazolidinethiones and their *N*-enoyl derivatives were prepared (Tables 3 and 4). Addition of organocuprates to *N*-crotonoyl derivative **6** was very good when using aromatic Grignard reagents (entries 1 and 2), but lower yield and higher diastereoselectivity were observed for the ethyl Grignard (entry 3). Lower yields and diastereoselectivities were obtained with *N*-cinnamoyl derivatives **7** and **8** and small size Grignard reagent (entries 4 and 5). Very good diastereoselectivity but low yield were observed for the *N*-pentenoyl derivative and methyl Grignard (entry 6).

Table 3. Conjugate Addition to *N*-Enoyl Phenylglycine-Derived Oxazolidinethione[a]



6 - 9

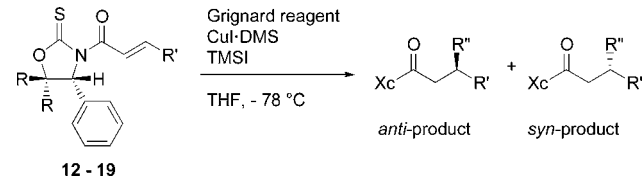
entry	*N*-enoyl	Grignard	yield[b] (%)	*anti*:*syn*[c]
1	**6** R = Me	R′ = Ph	70	(**10a**:**11a** = 90:10)
2	**6** R = Me	R′ = *p*-Tol	93	(**10b**:**11b** = 80:20)
3	**6** R = Me	R′ = Et	52	(**10c**:**11c** = 95:5)
4	**7** R = Ph	R′ = Me	40	(**11a**:**10a** = 80:20)
5	**8** R = *p*-Tol	R′ = Me	36	(**11b**:**10b** = 2:1)
6	**9** R = Et	R′ = Me	30	(**11c**:**10c** = 98:2)

[a] See Supporting Information for actual structures of products in the table. [b] Isolated total yield of two diastereomers. [c] As determined by ^{1}H NMR peak integrations with crude products.

When the phenyl ring on the oxazolidinethiones was flanked by the *gem*-dimethyl or a *gem*-diphenyl substituent, we observed in general very good diastereoselectivities and reaction yields (Table 4). Kanemasa and Onimura have reported the effect of 4-chiral 2,2-dialkyloxazolidines on the shielding of the diastereotopic acryloyl face.[15] Only when the *p*-tolylmagnesium bromide was employed in the addition to *N*-crotonoyl oxazolidinethione **12**, a low diastereoselectivity was always observed (entry 3). X-ray crystallographic analysis of addition product **20d** confirms the relative stereochemistry on the newly created carbon. The ortep drawing of **20d** shows the C-4 phenyl ring perpendicular to the oxazolidinethione ring. We conclude this conformation of the phenyl ring is important to achieve high diastereoselectivities.

In summary, we have found reaction conditions for the diastereoselective addition of organocuprates to *N*-enoyl oxazolidinethiones and studied the impact of the phenyl substituent on C4 on the yield and diastereoselectivity. In general, better diastereoselectivities were obtained with the C4-phenyl oxazolidinethione chiral auxiliaries. We found that by addition of the organocuprate, prepared using a 1:2 mixture of CuI·DMS or CuBr·DMS and Grignard reagent, in the presence of excess TMSI, the *N*-enoyl oxazolidinethione adopts a *syn*-s-*cis* conformation during the transition state, and the addition takes place on the less hindered side of the unsaturation, delivering preferentially the *anti*-addition product. This reaction should be valuable in the synthesis of many natural products.

Table 4. Conjugate Addition to *N*-Enoyl Phenylglycine-Derived Oxazolidinethione[a]



12 - 19

entry	*N*-enoyl oxazolidinone	Grignard	yield[b] (%) *anti*:*syn*[c]
1	**12** R = Me, R′ = Me	R″ = Et	85 (**20a**:**22a** = 98:2)
2	**12** R = Me, R′ = Me	R″ = Ph	70 (**20b**:**22b** = 90:10)
3	**12** R = Me, R′ = Me	R″ = *p*-Tol	70 (**20c**:**22c** = 60:40)
4	**13** R = Me, R′ = Et	R″ = Ph	72 (**20d**:**22d** = 98:2)
5	**13** R = Me, R′ = Et	R″ = Me	70 (**22a**:**20a** =92:8)
6	**14** R = Me, R′ = Ph	R″ = Me	80 (**22b**:**20b** = 98:2)
7	**15** R= Me, R′ = *p*-Tol	R″ = Me	80 (**22c**:**20c** = 98:2)
8	**14** R = Me, R′ = Ph	R″ = Et	80 (**22d**:**20d** = 98:2)
9	**16** R = Ph, R′ = Me	R″ = Et	75 (**21a**:**23a** = 93:7)
10	**16** R = Ph, R′ = Me	R″ = Ph	80 (**21b**:**23b** = 98:2)
11	**16** R = Ph, R′ = Me	R″ = *p*-Tol	80 (**21c**:**23c** = 98:2)
12	**17** R = Ph, R′ = Et	R″ = Ph	75 (**21d**:**23d** = 92:8)
13	**17** R = Ph, R′ = Et	R″ = Me	75 (**23a**:**21a** = 96:4)
14	**18** R = Ph, R′ = Ph	R″ = Me	80 (**23b**:**21b** = 98:2)
15	**19** R = Ph, R′ = *p*-Tol	R″ = Me	85 (**23c**:**21c** = 90:10)
16	**18** R = Ph, R′ = Ph	R″ = Et	80 (**23d**:**21d** = 98:2)

[a] See Supporting Information for actual structures of products in the table. [b] Isolated total yield of two diastereomers. [c] As determined by ^{1}H NMR peak integrations with crude products.

Acknowledgment. We thank Dr. Dale Swenson (University of Iowa) for obtaining the X-ray analysis of compound **2a** and Dr. Sylvain Bernès (Universidad Autónoma de Nuevo León) for analysis of compound **20d**. This project was funded by an ACS-GCI-PRF grant (HO). We thank CONACyT for a postdoctoral fellowship (LH) and grant Project 80915 (AO).

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds (**1**−**23**) and copies of ^{1}H and ^{13}C NMR spectra. CIF's for compounds **2a** and **20d**. Actual structures for Tables 2−4. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101687E

(15) Kanemasa, S.; Onimura, K. *Tetrahedron* **1992**, *48*, 8631–8644.