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Enantiomerically Pure *trans*-3,4-Disubstituted Tetrahydrothiophenes from Diastereoselective Thiocarbonyl Ylide Addition to Chiral α,*β*-Unsaturated Amides

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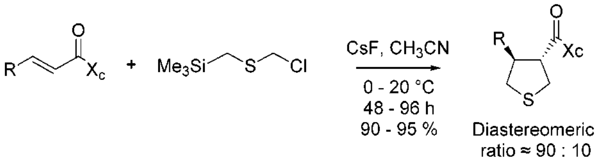
ABSTRACT



Asymmetric 1,3-dipolar cycloadditions of a sulfur-containing 1,3-dipole and α,*β*-unsaturated camphorsultam amides as dipolarophiles are described. The cycloaddition products, *trans*-3,4-disubstituted tetrahydrothiophenes, were obtained in high diastereomeric ratios (up to 90:10) and in high yields. Chromatographic removal of the minor diastereomer followed by cleavage of the chiral auxiliary furnished either the enantiomerically pure corresponding alcohol or carboxylic acid.

Ylide equivalents containing heteroatoms such as nitrogen[1] or sulfur[2] are useful intermediates for the addition to dipolarophiles such as α,*β*-unsaturated acyl derivatives. Such 1,3-dipolar cycloaddition reactions can result in the formation of five-membered rings (for example, pyrrolidine or tetrahydrothiophene derivatives) in one single step. Moreover, dipolarophiles linked to chiral auxiliaries react with nitrogen ylides to form cycloaddition products in favor of one diastereomer.[3] However, auxiliary-induced diastereoselective cycloadditions between thiocarbonyl ylides and dipolarophiles have to our knowledge not been investigated.

Recently we reported the asymmetric 1,3-dipolar cycloaddition between nitrogen-containing 1,3-dipoles and chiral dipolarophiles. Thus, α,*β*-unsaturated acyl derivatives linked

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[1] See, for example: (a) Plancquaert, M.-A.; Redon, M.; Janousek, Z.; Viehe, H. G. *Tetrahedron* **1996**, *52*, 4383−4396. (b) Bégué, J.-P.; Bonnet-Delpon, D.; Lequeux, T. *Tetrahedron Lett.* **1993**, *34*, 3279−3282. (c) Laborde, E. *Tetrahedron Lett.* **1992**, *33*, 6607−6610. (d) Padwa, A.; Dent, W. *J. Org. Chem.* **1987**, *52*, 235−244. (e) Terao, Y.; Kotaki, H.; Imai, N.; Achiwa, K. *Chem. Pharm. Bull.* **1985**, *33*, 2762−2766. (f) Padwa, A.; Chen, Y.-Y.; Dent, W.; Nimmesgern, H. *J. Org. Chem.* **1985**, *50*, 4006−4014. (g) Hosomi, A.; Sakata, Y.; Sakurai, H. *Chem. Lett.* **1984**, 1117−1120.

[2] See, for example: (a) Ye, X.-S.; Wong, H. N. C.; *J. Org. Chem.* **1997**, *62*, 1940−1954. (b) Aono, M.; Terao, Y.; Achiwa, K. *Heterocycles* **1995**, *40*, 249−260. (c) Tominaga, Y.; Takada, S.; Kohra, S. *Tetrahedron Lett.* **1994**, *35*, 3555−3558. (d) Tominaga, Y.; Ueda, H.; Ogata, K.; Kohra, S.; Hojo, M.; Ohkuma, M.; Tomita, K.; Hosomi, A.; *Tetrahedron Lett.* **1992**, *33*, 85−88. (e) Terao, Y.; Aono, M.; Achiwa, K. *Heterocycles* **1988**, *27*, 981−1008. (f) Aono, M.; Terao, Y.; Achiwa, K. *Chem. Lett.* **1987**, 1851−1852. (g) Terao, Y.; Aono, M.; Imai, N.; Achiwa, K. *Chem. Pharm. Bull.* **1987**, 35, 1734−1740. (h) Hosomi, A.; Hayashi, S.; Hoashi, K.; Kohra, S.; Tominaga, Y. *J. Org. Chem.* **1987**, *52*, 4423−4424. (i) Huisgen, R.; Mloston, G.; Langhals, E. *J. Am. Chem. Soc.* **1986**, *108*, 6401−6402. (j) Terao, Y.; Aono, M.; Takahashi, I.; Achiwa, K. *Chem. Lett.* **1986**, 2089−2092. (k) Terao, Y.; Tanaka, M.; Imai, N.; Achiwa, K. *Tetrahedron Lett.* **1985**, *26*, 3011−3014.

[3] See, for example: (a) Pandey, G.; Laha, J. K.; Mohanakrishnan, A. K. *Tetrahedron Lett.* **1999**, *40*, 6065−6068. (b) Ma, Z.; Wang, S.; Cooper, C. S.; Fung, A. K. L.; Lynch, J. K.; Plagge, F.; Chu, D. T. W. *Tetrahedron: Asymmetry* **1997**, *8*, 883−887. (c) Stack, J. A.; Heffner, T. A.; Geib, S. J.; Curran, D. P. *Tetrahedron* **1993**, *49*, 995−1008.

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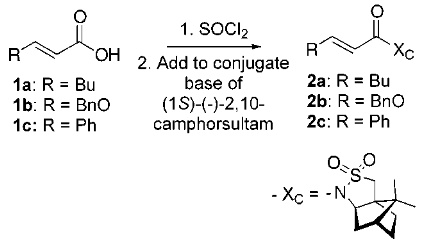
to various chiral auxiliaries were studied and we found that camphorsultam is the most efficient auxiliary among those investigated.[4]

We now wish to present a similar approach to the preparation of enantiomerically pure *trans*-3,4-disubstituted tetrahydrothiophenes.

CsF-catalyzed[5] decomposition of chloromethyl trimethylsilylmethyl sulfide **3** furnishes the thiocarbonyl ylide **3#** (Scheme 2). This adds to a variety of dipolarophiles in a stereoselective manner forming substituted tetrahydrothiophene rings.[6] Thus, when starting from dipolarophiles of the *β*-substituted (*E*)-α,*β*-unsaturated acyl type, the resulting products are *trans*-3,4-disubstituted tetrahydrothiophene derivatives.[6] We found that a number of such dipolarophiles linked to camphorsultam underwent highly diastereoselective thiocarbonyl ylide additions.

The enantiomerically pure dipolarophiles, i.e., (*E*)-α,*β*-unsaturated sultam amides **2a**−**c**, were prepared according to Scheme 1. In the presence of the CsF catalyst, the dipole precursor **3** reacted with compounds **2a**−**c** to give exclusively the two diastereomeric *trans*-3,4-disubstituted tetrahydrothiophenes **4** and **5** (Scheme 2) in excellent yields and high diastereoselectivities (Table 1).

Scheme 1. Preparation of Chiral Dipolarophiles **2a**−**c**



Scheme 2. 1,3-Dipolar Cycloaddition between **2a**−**c** and **3**

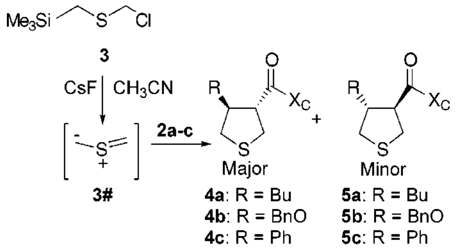


Table 1. Diastereomeric Ratio (dr) in the 1,3-Dipolar Cycloaddition between **2a**−**c** and the Dipole Precursor **3**

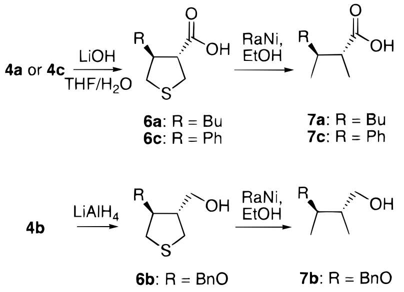
entry[a]	dipolarophile	temp (°C)	time	yield (%)[b]	product, dr **4**:**5**[c]
1[d]	**2c**	0	4 days	89	89:11
2[e]	**2c**	20	2 days	95	86:14
3[e]	**2c**	80	1 h	94	82:18
4[d]	**2a**	0	4 days	92	90:10
5[e]	**2a**	20	2 days	91	89:11
6[e]	**2a**	80	3 h	84	86:14
7[d]	**2b**	0	3 days	95	90:10
8[e]	**2b**	20	2 days	88	87:13
9[e]	**2b**	80	1 h	40	*f*

[a] To one of the dipolarophiles **2a**, **2b** or **2c** (1 molar equiv) in CH_3CN (8 mL/mmol dipolarophile) were added the dipole precursor **3** (1.3 molar equiv) and CsF (2−3 molar equiv) under an atmosphere of argon. Quenching with H_2O (20−40 mL/mmol dipolarophile), extractions with EtOAc (3 × 20−40 mL/mmol dipolarophile), and drying ($MgSO_4$) gives the two diastereomers **4** and **5** after chromatography. [b] Isolated total yield of **4** and **5** after liquid chromatography. [c] Calculated on the crude products by ^1H NMR. [d] Performed on a 3 mmol scale. [e] Performed on a 0.1 mmol scale. [f] Not measured.

(1*S*)-(−)-2,10-Camphorsultam was found to be very efficient as a chiral inducer for this type of cycloaddition sequence. High diastereoselectivities were observed for all three dipolarophiles **2a**−**c**. When the reaction temperature was increased, a small decrease in selectivity was observed while the yields remained practically constant. However, at elevated temperature, the dipolarophile **2b** gave the cycloaddition products in very low yield and the reaction became very sluggish (entry 9). When the temperature was kept at 0 °C, all three dipolarophiles reacted cleanly during 4 days to give the products **4** and **5** in high isolated yields (up to 95%) and high diastereomeric ratios (up to 90:10), see entries 1, 4, and 7. In all cases, the diastereomers **4** and **5** were easily separated by liquid chromatography. For example, diastereomerically pure **4a** was obtained in 84% overall yield.

Nondestructive removal of the chiral auxiliary to give the corresponding enantiomerically pure carboxylic acid or alcohol along with recovered camphorsultam was accomplished using LiOH in refluxing THF:H_2O or $LiAlH_4$, respectively (Scheme 3). To confirm the configurations at positions 3 and 4 of the tetrahydrothiophene ring, **6a**−**c** were transformed to their corresponding desulfurized, known compounds **7a**−**c** using Ra−Ni in refluxing EtOH (Scheme 3). The $[\alpha]_D$ values of these compounds were used for the

Scheme 3. Cleavage of the Camphorsultam Auxiliary and Subsequent Reductive Desulfurization



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(6) Hosomi, A.; Matsuyama, Y.; Sakurai, H. *J. Chem. Soc., Chem. Commun* **1986**, 1073−1074.

confirmation of the absolute configurations at C-3 and C-4: **7a** $[\alpha]^{25}_{D} = -38.1$ (lit.[7] for ent-**7a** $[\alpha]^{23}_{D} = +40.65$); **7b** $[\alpha]^{25}_{D} = -55.9$ (lit.[8] $[\alpha]^{20}_{D} = -41.7$); **7c** $[\alpha]^{25}_{D} = -63.1$ (lit.[7] for ent-**7c** $[\alpha]^{21.5}_{D} = +53.1$).

We also prepared the enantiomerically pure oxazolidinone dipolarophiles of type **2**, where X_C in the amides were derived from 4(*S*)-*tert*-butyl- and 4(*R*)-phenyl-2-oxazolidinone. The CsF-catalyzed cycloaddition reactions of these dipolarophiles with compound **3** were not successful. Although the yields were high, the diastereomeric ratios obtained were unsatisfactory: 55:45.

In conclusion, enantiomerically pure *trans*-3,4-disubstituted tetrahydrothiophenes **6** were obtained via asymmetric cycloaddition reactions between a sulfur-containing 1,3-dipole (**3**#) and α,*β*-unsaturated (1*S*)-(−)-camphorsultam amides as chiral dipolarophiles. We have also demonstrated that a dipolarophile containing a vinyl ether moiety (i.e. **2b**) can be used as the reactive partner in the cycloaddition sequence resulting in the enantioselective introduction of a 4-hydroxy equivalent in the tetrahydrothiophene ring.

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Supporting Information Available: Text giving experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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