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Facile Net Cycloaddition Approach to Optically Active 1,5-Benzothiazepines

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Supporting Information

ABSTRACT: The 1,5-benzothiazepine moiety is well-known as a versatile pharmacophore, and its derivatives are expected to have antagonism against numerous diseases. Thus, it is desirable to develop a synthetic route that enables facile enantioselective preparation of a wide range of such derivatives. Although the cycloaddition approach could be considered a possible route to these compounds, to date, there has been no precedent of such a protocol. We therefore present the first example of a highly enantioselective net [4 + 3] cycloaddition to afford 1,5-benzothiazepines by utilizing α,β-unsaturated acylammonium intermediates generated by chiral isothiourea catalysts, which undergo two sequential chemoselective nucleophilic attacks by 2-aminothiophenols. This protocol provided cycloadducts in extremely high regioselectivity, with a good-to-excellent stereoselectivity being achieved regardless of the steric and electronic properties of the substrates. This method therefore offers promising synthetic routes for the construction of a library of optically active 1,5-benzothiazepines for assay evaluation.

1,5-Benzothiazepines are well-known as representative molecules in the field of pharmaceutical science (Figure 1)

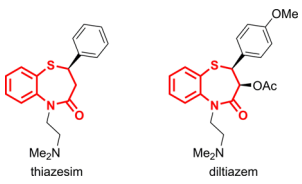
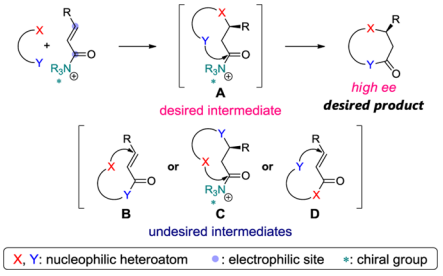


Figure 1. Representative pharmaceutical compounds containing the 1,5-benzothiazepine moiety.

and are expected to exhibit antagonism against various diseases.[1] Indeed, 1,5-benzothiazepins, such as thiazesim, originally attracted a great amount of attention as antidepressant agents. Later, thanks to a random screening program in a Japanese pharmaceutical company, calcium antagonism was unexpectedly observed, and diltiazem (Herbesser) was developed as an effective medication for the treatment of hypertension and angina and is currently used in more than 100 countries. These successful examples of the use of 1,5-benzothiazepines stress their great potential for application as pharmaceutical products. Thus, there exists a high demand for methods that allow rapid and divergent syntheses of such derivatives to support assay evaluation. To date, a few asymmetric syntheses have been reported through a multistep construction of the ring structure.[2] In this context, an asymmetric cycloaddition approach is proposed for the diversity-oriented synthesis of 1,5-benzothiazepines.

Recently, the use of α,β-unsaturated acylammonium species in organocatalyzed transformations was reported, where they were employed as components bearing two electrophilic sites to allow annulations through sequential nucleophilic attacks by carbon and heteroatom, or two carbon nucleophiles, to take place.[3] The α,β-unsaturated acylammonium species can therefore be considered a promising candidate as the intermediate of a reaction with a molecule bearing two nucleophilic heteroatoms. However, despite the clear advantages in this type of transformation, a number of alternative pathways are possible when these reactants are employed. As shown in Scheme 1, besides the

Scheme 1. Net Cycloaddition between α,β-Unsaturated Acylammonium Ion and Nucleophilic Counterpart Bearing Two Heteroatoms



desired pathway via intermediate **A**, alternative pathways through undesired intermediates **B**–**D** could also take place to lower the enantioselectivity or generate the undesired regioisomer. Therefore, to achieve a highly enantio- and regioselective net cycloaddition, pathways **B**–**D** must be suppressed.

In our previous study, we reported an organocascade reaction via two nucleophilic attacks by different heteroatoms to α,β-unsaturated acylammonium species.[4] In the course of this study, we noted the high chemoselectivity of the described intermediates, which exclusively captures a sulfur-centered nucleophile at the β-position via a sulfa-Michael addition. Thus, we proposed a net cycloaddition reaction of an α,β-unsaturated acylammonium salt, with a reagent containing both

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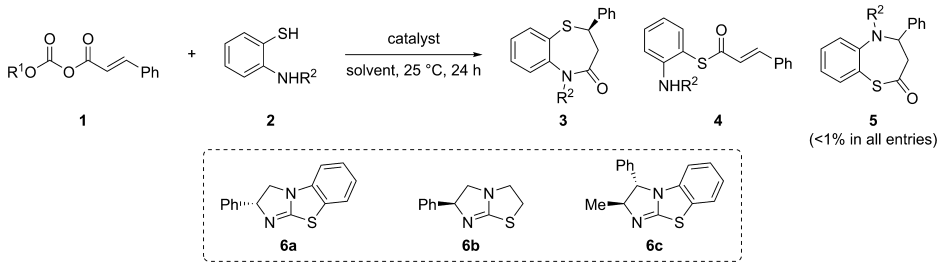
Table 1. Optimization of Conditions[a]



entry	catalyst (mol %)	R^1, R^2	solvent	yield of **3** (%)[b]	yield of **4** (%)[b]	*ee* of **3a** (%)
1	**6a** (10)	*i*-Pr (**1a**), Ts (**2a**)	toluene	86	<1	95
2	**6b** (10)	*i*-Pr (**1a**), Ts (**2a**)	toluene	38	<1	−78
3	**6c** (10)	*i*-Pr (**1a**), Ts (**2a**)	toluene	51	<1	−90
4	**6a** (10)	*i*-Pr (**1a**), Ts (**2a**)	benzene	84	<1	94
5	**6a** (10)	*i*-Pr (**1a**), Ts (**2a**)	EtOAc	74	<1	93
6	**6a** (10)	*i*-Pr (**1a**), Ts (**2a**)	THF	<1	41	
7	**6a** (10)	*i*-Pr (**1a**), Ts (**2a**)	CH_2Cl_2	87	<1	96
8	**6a** (10)	*i*-Pr (**1a**), Ts (**2a**)	$CHCl_3$	84	<1	97
9	**6a** (10)	Et (**1b**), Ts (**2a**)	$CHCl_3$	76	<1	97
10	**6a** (10)	Bn (**1c**), Ts (**2a**)	$CHCl_3$	35	<1	96
11[c]	**6a** (10)	*i*-Pr (**1a**), Ts (**2a**)	$CHCl_3$	98	<1	97
12[c]	**6a** (10)	*i*-Pr (**1a**), Boc (**2b**)	$CHCl_3$	<1	73	
13[c]	**6a** (5)	*i*-Pr (**1a**), Ts (**2a**)	$CHCl_3$	95	<1	97
14[c,d]	**6a** (0.5)	*i*-Pr (**1a**), Ts (**2a**)	toluene	87	<1	94

[a]Reactions were run using **1** (0.15 mmol), **2** (0.15 mmol), the catalyst, and the solvent (0.3 mL). [b]Isolated yields. [c]Reactions were run using 75 mg of 4 Å molecular sieves. [d]Reaction was run using 0.17 mmol of **2a** at 40 °C for 48 h.

sulfur and nitrogen atoms, in hope that the reaction could proceed through the desired intermediate corresponding to intermediate **A** in Scheme 1. In addition, we expected that the stereoselectivity could also be attained by the use of a chiral nucleophilic organocatalyst.

We began our investigation into the net cycloaddition reaction using *α,β*-unsaturated substrate **1a** and aminothiophenol **2a** with 10 mol % of benzotetramisole catalyst **6a** in toluene at 25 °C (Table 1).[5] As expected, 1,5-benzothiazepine **3a** was obtained in high enantioselectivity, with no generation of the regioisomer being observed (Table 1, entry 1). Catalyst screening revealed that **6a** was the most effective catalyst for achieving the highest enantioselectivity (Table 1, entries 1−3).[6] Optimization of the reaction solvents was also investigated, with $CHCl_3$ being identified as the most effective solvent for yielding high stereoselectivity (Table 1, entries 4−8), whereas in THF, *α,β*-unsaturated thioester **4a** (R^2 = Ts) was obtained instead of the desired product (Table 1, entry 6). The choice of the substituent (OR^1) on the carbonic anhydride was also important for the reaction yield, with alkyl substituents giving better yields than an aryl-containing substituent (Table 1, entries 9 and 10).[7] The use of 4 Å molecular sieves as an additive further improved the yield of the reaction (Table 1, entry 11). The R^2 substituent on the nitrogen atom of aminothiophenol **2** was found to have an effect on the reaction pathway and thus influenced the identity of major product obtained from the reaction. Replacement of the tosyl group on the nitrogen atom of **2a** with a *t*-butoxycarbonyl group resulted in the formation of thioester **4b** (R^2 = Boc) (Table 1, entry 12). To evaluate the effect of catalyst loading on the reaction, one reaction was run with a reduced catalyst loading of 5 mol % (Table 1, entry 13). Even with this reduced catalyst loading, the desired product was obtained in similar yield and enantioselectivity. In addition, it was found that the catalyst loading could be reduced further to 0.5 mol % (Table 1, entry 14), although a higher temperature, longer reaction time, and a slight excess of **2a** were required. Under these conditions, the use of halogenated solvents could also be avoided while keeping the enantioselectivity high (Table 1, entry 14).

We then moved on to explore the substrate scope of the reaction with the use of 5 mol % **6a** as catalyst. Overall, good to excellent yields and enantioselectivities were obtained with a range of substrates. Electron-rich aminothiophenols gave slightly higher enantioselectivities than electron-poor ones (Table 2, **3a**−**3e**), which implies the possibility of cation-*π* interactions existing in the transition state of the enantiodetermining step. The electronic and steric characteristics of the substituents on the *α,β*-unsaturated carbonyl substrates did not have a large influence on the enantioselectivity of the reaction (Table 2, **3f**−**3m**). In addition, various combinations of aminothiophenol and *α,β*-unsaturated carbonyl substrates yielded the corresponding products in high yields and enantioselectivities (Table 2, **3n**−**3r**). These results indicate the high efficiency and generality of this net cycloaddition method by demonstrating that this protocol can provide access to a wide range of optically active 1,5-benzothiazepines. The absolute configuration of **3a** was determined by X-ray analysis (see the Supporting Information for details), and the configurations of all other examples were assigned analogously.

By using the obtained cycloadduct **3a**, we also accomplished the asymmetric synthesis of thiazesim (**8**), a heterocyclic antidepressant (Scheme 2). Deprotection of **3a** with samarium iodide afforded the corresponding secondary amine 1,5-benzothiazepine **7** (not shown in Sheme 2) without a reduction in enantiomeric excess, with its optical rotation ($[\alpha]_D^{18}$ −448.4 (*c* 0.63, $CHCl_3$)) being consistent with the literature value of the (*R*)-isomer (see the Supporting Information for details).[2b] Subsequent alkylation of **7** gave optically active thiazesim **8** in good yield.

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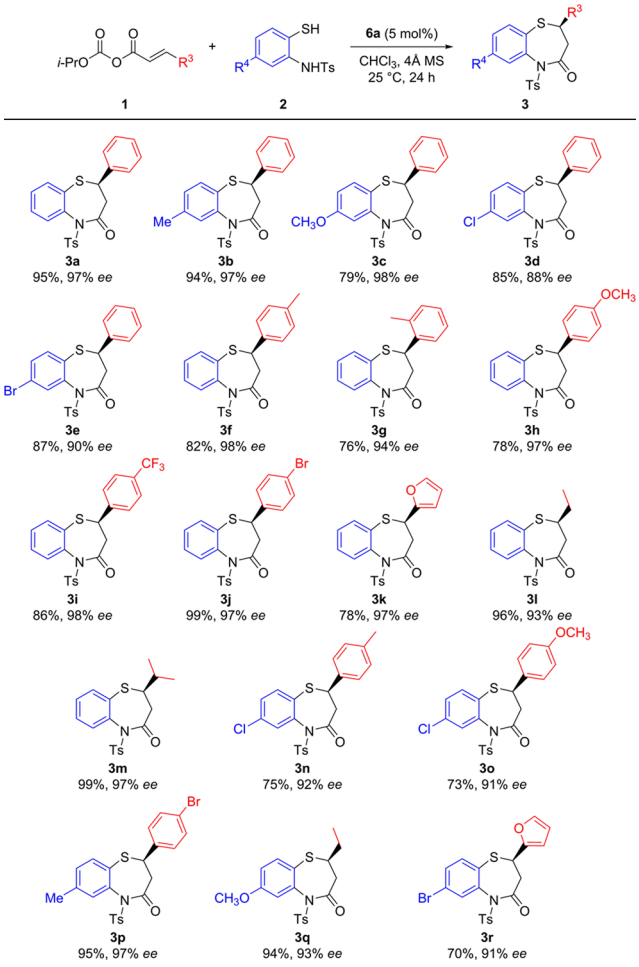
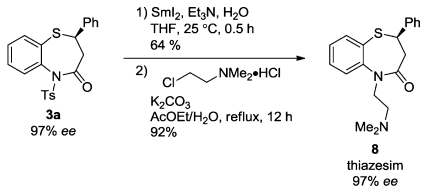
Table 2. Substrate Scope[a]



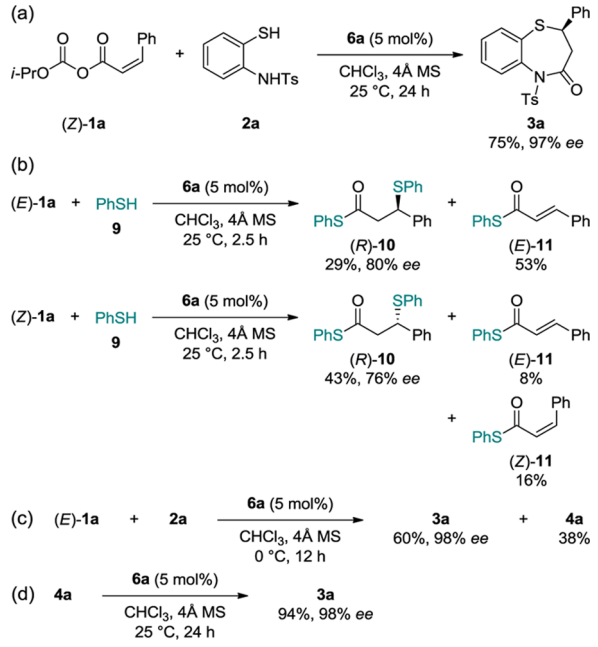
[a]Reactions were run using **1** (0.15 mmol), **2** (0.15 mmol), **6a** (0.0075 mmol), and 4 Å molecular sieves (75 mg) in $CHCl_3$ (0.3 mL). Yields represent material isolated after silica gel column chromatography.

Scheme 2. Synthesis of Thiazesim (8)



To gain insight into the reaction mechanism, the net cycloaddition reaction was also carried out using α,β-unsaturated substrate **1a** in the (Z)-olefin configuration (Scheme 3a). The resulting cycloadduct was obtained in high enantioselectivity, and the absolute configuration was revealed to be (R)-configuration, which is consistent with the product obtained using the (E)-substrate. The reaction was then carried out in the presence of benzenethiol (**9**), instead of aminothiophenol **2a**, again using both the (E)- and (Z)-substrates of **1a** (Scheme 3b). In both cases, thioester products **10** and **11** were obtained, although different enantiomers of β-mercaptothioester **10** were obtained depending on the geometry of the starting materials. The α,β-unsaturated thioester (E)-**11** was also obtained for both substrates, whereas isomer (Z)-**11** was only obtained from the reaction from (Z)-**1a**. These results imply that the (Z)-substrate

Scheme 3. Mechanistic Studies



is capable of isomerizing to the (E)-form via a sulfa-Michael addition/C−C bond rotation/retro-sulfa-Michael addition process. In addition, when the reaction of **1a** with **2a** in $CHCl_3$ was carried out at 0 °C, α,β-unsaturated thioester **4a** was obtained as a side product (Scheme 3c), which implies that α,β-unsaturated thioesters (**4**) may be temporarily generated in situ under optimal conditions. Thus, we tested the reaction starting from **4a** under the optimal conditions, and the desired product **3a** was obtained in high yield and comparable enantioselectivity (Scheme 3d). These results suggest that the formation of **4** is also reversible, and thus it does not have an effect on the final outcome of the net cycloaddition. Furthermore, the formation of the α,β-unsaturated acylammonium intermediate was strongly supported by HRMS and NMR analyses of a solution of **1a** and a stoichiometric amount of **6a** in $CDCl_3$, which then afforded **3a** after the subsequent addition of **2a** with enantioselectivity comparable to the catalytic reaction (see the Supporting Information for details).

On the basis of the experimental results described above, we propose the reaction mechanism for this transformation as outlined in Scheme 4. Starting from α,β-unsaturated (E)-**1**, it is expected that the acylammonium intermediate **I** forms and that the carbonyl group is fixed in position through an n_o to σ^*_{C-S} interaction.[8] The 2-aminothiophenol can then approach from the opposite side of the phenyl group on the catalyst for steric reasons, with this process possibly aided by the presence of a cation-π interaction.[9] Subsequently, a sulfa-Michael addition followed by *N*-acylation affords the desired cycloadduct (R)-**3**. Alternatively, starting from substrate (Z)-**1**, acylammonium intermediate **V** is generated and subsequently undergoes the first sulfa-Michael addition according to the results in Scheme 3, panel b. However, it is expected that the following cyclization may be inhibited by a favorable conformational change driven by the release of repulsion energy that exists in intermediate **VI**. Thus, from intermediate **IV**, bearing a more stable conformation, thiophenol **2a** eliminates to generate (E)-intermediate **III**, which again affords 1,5-benzothiazepine (R)-**3** via intermediates **I** and **II** (see also Scheme 3a). The enantioselectivity of this reaction

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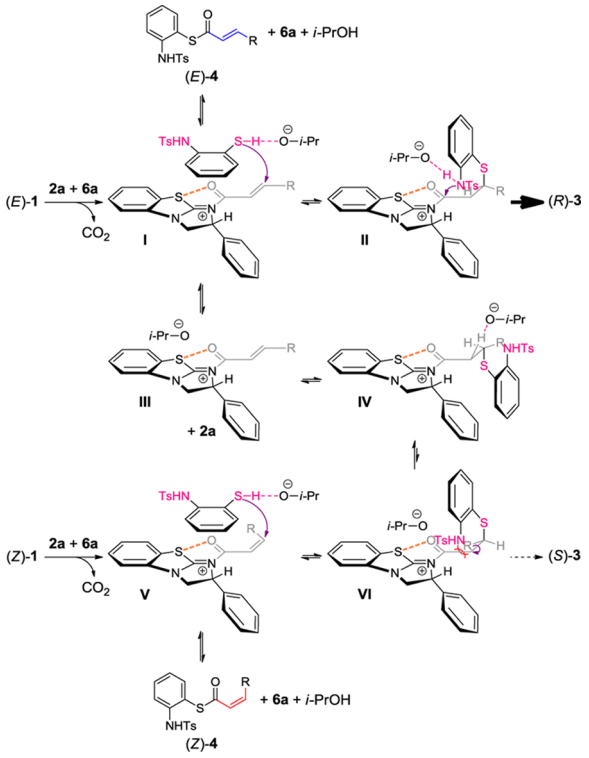
Scheme 4. Proposed Reaction Pathways for the Transformation



therefore seems to be mainly controlled by the defference of cyclization rate between the intermediates **II** and **VI** and is also reinforced by the face-selective sulfa-Michael addition, where the selection system supported by the reversibility of sulfa-Michael addition may impart the overall excellent enantioselectivity.[10] In addition, in the event where (*E*)-**4** and (*Z*)-**4** are generated during the course of the reaction, they could be incorporated back into the main catalytic process and ultimately lead to the formation of the desired products in high enantioselectivities.

In summary, we have demonstrated the first net cycloaddition approach to 1,5-benzothiazepines, realizing a facile synthetic route to a number of benzothiazepine derivatives. The net cycloaddition procedure resulted in excellent regioselectivity and good stereoselectivity regardless of the steric and electronic characteristics of the substrates. Mechanistic studies suggested that the reversibility of the nucleophilic attack by sulfur-centered nucleophiles to α,β-unsaturated acylammonium intermediates imparts the high regio- and enantioselectivity of the transformation. This method is potentially useful for the construction of a library of optically active 1,5-benzothiazepines. Further studies regarding both expansion of the substrate scope and application of this methodology to the preparation of derivatives for drug discovery are currently ongoing in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(6) Results of further catalyst screening are described in the Supporting Information.

(7) Although the corresponding acid chloride could be used as a substrate, the enantioselectivity was slightly lower in a preliminary study (91% yield, 88% *ee*, see the Supporting Information for details). In addition, the generation of the anhydride in situ from the corresponding carboxylic acid was also investigated, but the yield was much lower despite the comparable enantioselectivity (19% yield, 97% *ee*, see the Supporting Information for details). Further investigations for optimization of these methods are currently ongoing.

(8) The presence of intramolecular nonbonded S···O interaction has been recognized, see: (a) Minkin, V. I.; Minyaev, R. M. *Chem. Rev.* **2001**, *101*, 1247. (b) Nagao, Y.; Hirata, T.; Goto, S.; Sano, S.; Kakehi, A.; Iizuka, K.; Shiro, M. *J. Am. Chem. Soc.* **1998**, *120*, 3104. (c) Brameld, K. A.; Kuhn, B.; Reuter, D. C.; Stahl, M. *J. Chem. Inf. Model.* **2008**, *48*, 1. For discussions on attractive n_o to σ^*_{C-S} interaction between the acylammonium oxygen and the sulfur atom of isothiourea catalysts, see refs 3b, d, e, and the following: (d) Birman, V. B.; Li, X.; Han, Z. *Org. Lett.* **2007**, *9*, 37. (e) Leverett, C. A.; Purohit, V. C.; Romo, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 9479. (f) Liu, P.; Yang, X.; Birman, V. B.; Houk, K. N. *Org. Lett.* **2012**, *14*, 3288.

(9) The presence of cation-π interaction between the acylammonium cation generated by isothiourea catalysts and an aryl group in substrates was suggested in literature on the basis of computational and experimental studies, see ref 8f and the following: Belmessieri, D.; Joannesse, C.; Woods, P. A.; MacGregor, C.; Jones, C.; Campbell, C. D.; Johnston, C. P.; Duguet, N.; Concellón, C.; Bragg, R. A.; Smith, A. D. *Org. Biomol. Chem.* **2011**, *9*, 559.

(10) Since the reaction rate was not affected by the concentration (see the Supporting Information for details), the intramolecular cyclization step is considered to be the rate-determining step.

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