Organocatalytic Nucleophilic Ring Opening of Cyclopropanecarbaldehydes by Benzenethiols: Tandem Synthesis of Benzo[*b*]thiepines

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Received 9 January 2009

Abstract: An unprecedented nucleophilic ring opening of cyclopropanecarbaldehydes with benzenethiols proceeds regioselectively under the catalysis of 40 mol% proline to afford fair to good yields of 4-phenylthio-substituted butyraldehydes. If *o*-thiosalicylaldehydes are employed, a tandem homoconjugate addition–aldol reaction occurs, which constitutes an expedient entry to pharmaceutically valuable 2,3-dihydrobenzo[*b*]thiepine-4-carbaldehydes.

Key words: ring opening, tandem reactions, heterocycles, regioselectivity, aldol reactions

Cyclopropane-containing derivatives enjoy increasing utilities in synthetic chemistry because of two main facts.[1] One is that the rapid development of carbene chemistry has rendered cyclopropane derivatives easily accessible, and the other is that the cyclopropane ring resembles a C=C double bond in many aspects to qualify it as a functional carbon group. Especially, the ring opening has been proved to be a very useful route to the myriad of functionalized carbon skeletons.[1g,2] The ring opening mostly relies on activation with additional functional groups, and the activations can be categorized into two classes.[3] The first class includes the reactions of donor–acceptor cyclopropanes.[1f] The second class features electrophilic reaction of cyclopropanes, which are usually activated by cation-stabilizing groups or attached electron-withdrawing groups. Within the latter context, the most widely investigated substrates have been those activated by two *gem*-substituted electron-accepting groups, for example, 1,1-cyclopropane dicarboxylic acid esters.[4–6] In general, the cyclopropane ring has to be further activated to achieve a successful nucleophilic-induced ring opening. The well-established methods employ a Lewis acid such as $Ni(ClO_4)_2 \cdot 6H_2O$,[3] $BF_3 \cdot OEt_2$,[7] $SnCl_4$,[8] TMSOTf.[9]

As evidenced by an explosive growth in the number of publications in recent years, organocatalysis has become a rapidly evolving field.[10] The use of organocatalytic transformations implies a connotation of ecologically benign and green chemistry. Numerous organocatalysts have been developed to prompt a broad range of reactions, some of which are either difficult to proceed or require expensive and toxic metal previously.

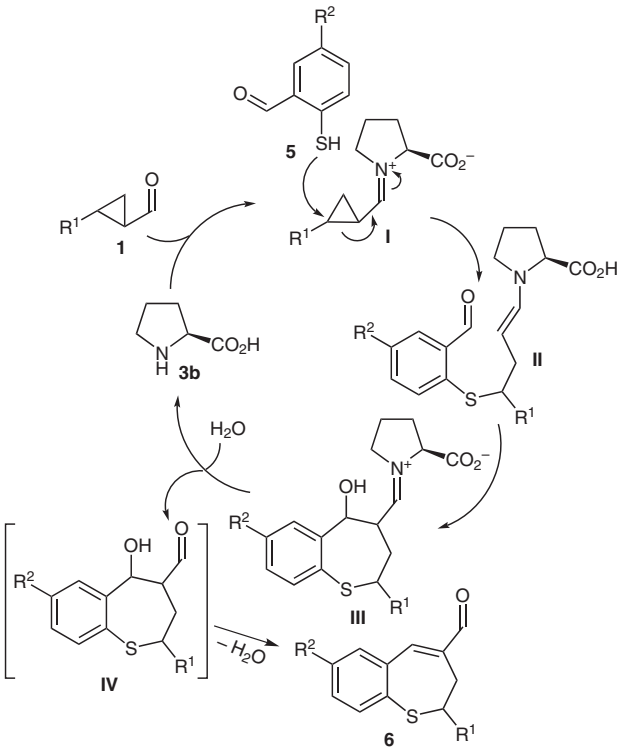
SYNLETT 2009, No. 11, pp 1830–1834
Advanced online publication: 12.06.2009
DOI: 10.1055/s-0029-1217370; Art ID: W00809ST

Although organocatalyzed nucleophilic addition to α,β-unsaturated carbonyl systems has been thoroughly studied,[10,11] as far as we are aware, a homoconjugate nucleophilic version to a cyclopropane ring under activation with organocatalysis remains untouched.[12] Replacing a C=C double bond with a cyclopropane ring, the reaction with nucleophiles may provide an attractive entry into homo-Michael addition products. In this letter, we wish to report that cyclopropanecarbaldehydes can be activated by (*S*)-proline to trigger an effective homoconjugate nucleophilic ring opening with benzenethiols. In the same way, using *o*-thiosalicylaldehydes as the nucleophile, the protocol constitutes an unprecedented tandem homoconjugate addition–aldol reaction affording benzo[*b*]thiepines, which are of considerable biological significances.[13]

In the domain of organocatalysis, secondary amines have been widely employed as iminium catalysts.[10b] For example, (*S*)-proline, being an inexpensive and nontoxic natural amino acid that is safe for use, has been found to perform well in a number of transformations.[10e] We envisioned that the formation of an iminium ion of the aldehyde group in cyclopropanecarbaldehydes may render the three-membered ring far more electrophilic to be attacked by a nucleophile and result in the formation of 1,4-difunctional compounds.

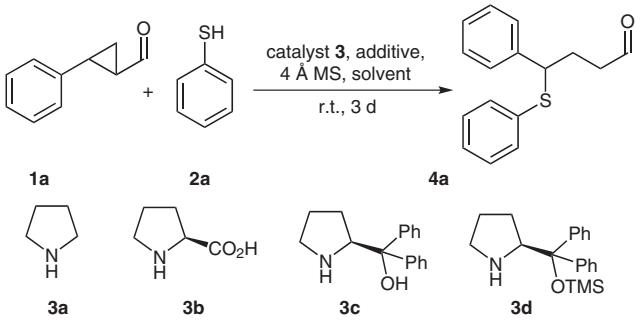
We elected initially to treat 2-phenylcyclopropane-carbaldehyde (**1a**) with benzenethiol (**2a**) along with a secondary amine as the catalyst (Scheme 1). The required starting aldehyde **1a** was easily prepared from ethyl cinnamate by cyclopropanation using DMSY ($Me_2SO^+CH_2^-$) in DMSO on the double bond followed by reduction with LAH and oxidation with PCC in CH_2Cl_2.

A set of different reaction conditions including varying solvents and acid additives was tested with emphasis on the screening of amine catalyst. Several representative results are shown in Table 1. The reactions were performed at room temperature with 1 mmol of **1a** and 1.2 equivalents of **2a** in the presence of an amine catalyst along with a small amount of 4 Å MS. To our delight, the use of 20 mol% of pyrrolidine **3a** in combination of a stoichiomeric amount of 2-nitrobenzoic acid could effectivelly promote the expected homoconjugate addition with exclusive regioselectivity. After stirring for three days in toluene, the reaction reached a maximal conversion (TLC) and the adduct 4-phenyl-4-(phenylthio)butyraldehyde (**4a**) was isolated in a low yield (Table 1, entry 1). We then turned to the use of (*S*)-proline (**3b**) as the catalyst without additive,



Scheme 1 The plausible mechanism of the tandem reaction

Table 1 Screening for the Optimal Reaction Conditions



Entry	Cat. (equiv)	Additive	Solvent	Time (d)	Yield (%)[a]
1	**3a** (0.2)	2-nitrobenzoic acid	toluene	3	25
2	**3b** (0.4)	none	CH_2Cl_2	3	27
3	**3b** (0.2)	none	THF	3	28
4	**3b** (0.4)	none	THF	2	45
5	**3b** (0.4)	none	THF	3	55
6	**3b** (0.8)	none	THF	3	50
7[b]	**3b** (0.4)	none	THF	3	0
8	**3c** (0.2)	4-chlorobenzoic acid	toluene	3	0
9	**3d** (0.2)	benzoic acid	toluene	3	n.d.[c]

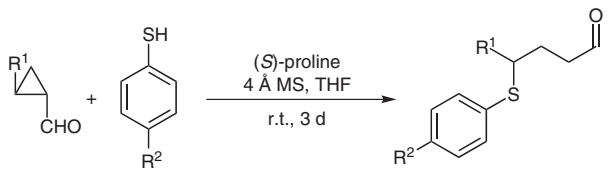
[a] Isolated by chromatography.
[b] Without addition of 4 Å MS.
[c] Not detected.

but with an increased dosage (40 mol%) in CH_2Cl_2 as the solvent. Again, the reaction could also proceed to furnish a slightly higher yield of **4a** (Table 1, entry 2). Considering the poor solubility of **3b** in CH_2Cl_2, the reaction medium was switched to THF. The reaction could occur under the catalyst of 20 mol% of **3b** to afford **4a**, but still in a low yield (Table 1, entry 3). Increasing the amount of **3b** to 40 mol% could improve the yields (Table 1, entries 4 and 5). Further increase in the amount of the employed catalyst **3b** did not show beneficial efffects on improving the yield. In addition, we found that addition of 4 Å MS was also a vital point to promote this thia-homoconjugate addition (Table 1, entry 7). Unexpectedly, when (*S*)-diphenyl(pyrrolidin-2-yl)methanol (**3c**) was employed as the catalyst, the reaction did not occur at all, and with (*S*)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine (**3d**) as the catalyst, the target compound could not be detected after stirring for three days (Table 1, entries 8 and 9). Thus, the opmimized conditions were defined to be 40 mol% **3b** as catalyst in THF at room temperature with the addition of 4 Å MS.

With optimized conditions in hand, we next explored the scope and generality of the protocol (Table 2). A range of 2-phenylcyclopropanecarbaldehydes **1** and benzenethiols **2** bearing different substituent at the *para* position on both of the phenyl rings were investigated, respectively.[14] As indicated in Table 2, the reactions were applicable to a wide variety of combinations of **1** and **2** (Table 2, entries 1–12). Both electron-donating groups and electron-accepting groups can be tolerated. The results revealed that an electron-withdrawing substituent, such as fluorine atom, residing either on the phenyl ring of **1** or **2** or both could appreciably facilitate the reaction. For instance, the use of **1b** carrying a strong electron-donating group provided generally lower yields than the use of 2-(4-fluorophenyl)cyclopropanecarbaldehyde (**1c**,Table 2, entries 5–8 vs. 9–12, respectively). However, the substituent effects of benzenethiols **2** seemed to be less pronounced than that of **1**. In the pairing of **1c** with **2d**, where both substrates bear a fluorine substituent, the reaction afforded the highest yield of the homoconjugate addition product **4l** (Table 2, entry 12). We next became interested in examining the role of phenyl substituent in cyclopropanecarbaldehydes **1**. As shown in Table 2, although cyclopropanecarbaldehyde **1d** could also be employed to produce the corresponding 4-phenylthio-substituted butyraldehydes **4**, the yields were generally lower than the phenyl-substituted analogues **1a–c** (Table 2, entries 13–16). In addition, when aliphatic thiols such as ethanethiol were used as the nucleophilic reagents, the reaction only delivered the trivial dithioacetals.

To further expand the scope of the proline-catalyzed homoconjugate addition protocol, the reaction of **1** with *o*-thiosalicylaldehydes **5** were investigated (Table 3).[15] Recently, organocatalytic tandem Michael–aldol reaction has been reported by two pioneer research groups, providing catalytic asymmetric synthesis of thiochromenes.[16] Our work was directed to develop a tandem homoconju-

Table 2 Ring Opening of Cyclopropanes **1** by Nucleophilic Addition Using Benzenethiols **2**



1 **2** **4**

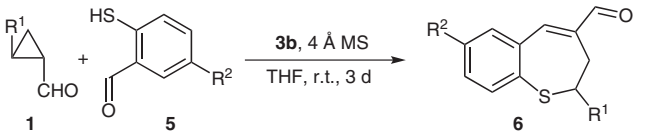
Entry	R^1	**1**	R^2	**2**	Product	Yield (%)[a]
1	Ph	**1a**	H	**2a**	**4a**	55
2	Ph	**1a**	Me	**2b**	**4b**	26
3	Ph	**1a**	Cl	**2c**	**4c**	39
4	Ph	**1a**	F	**2d**	**4d**	53
5	4-$MeOC_6H_4$	**1b**	H	**2a**	**4e**	41
6	4-$MeOC_6H_4$	**1b**	Me	**2b**	**4f**	40
7	4-$MeOC_6H_4$	**1b**	Cl	**2c**	**4g**	33
8	4-$MeOC_6H_4$	**1b**	F	**2d**	**4h**	43
9	4-FC_6H_4	**1c**	H	**2a**	**4i**	57
10	4-FC_6H_4	**1c**	Me	**2b**	**4j**	47
11	4-FC_6H_4	**1c**	Cl	**2c**	**4k**	43
12	4-FC_6H_4	**1c**	F	**2d**	**4l**	61
13	H	**1d**	H	**2a**	**4m**	43
14	H	**1d**	Me	**2b**	**4n**	15
15	H	**1d**	Cl	**2c**	**4o**	29
16	H	**1d**	F	**2d**	**4p**	35

[a] Isolated yield by chromatography.

gate addition–aldol sequence to provide an attractive route to benzo[*b*]thiepines **6**, which are of considerable current biological significance.[13] To our delight, the reaction took place effectively and regioselectively to furnish the expected 2,3-dihydrobenzo[*b*]thiepine-4-carbaldehydes **6** in fair to moderate yields (Table 3). In comparison to other ways for construction of such fused heterocyclic core,[13] this organocatalyzed domino method is very straightforward, and the conditions avoid use of any expensive reagents.[17] A catalytic cycle to account for the formation of **6** is postulated in Scheme 1.

The cyclopaopanecarboxaldehyde **1** reacts with (*S*)-proline to form an iminium zwitterion **I** with loss of water, whereby the carbonyl group is suitably activated. Nucleophilic attack at the C-2 position of the cyclopropane ring results in the formation of ring-opened enamine intermediate **II** by the mercapto group of *o*-thiosalicylaldehyde. Next, the enamine **II** undergoes an intramolecular 7-*exo-trig* nucleophilic attack on the benzaldehyde moiety, leading to the initial hydroxyl iminium adduct **III**. Hydrolysis

Table 3 Tandem Reaction Leading to Benzo[*b*]thiepines



1 **5** **6**

Entry	R^1	**1**	R^2	**5**	Product	Yield (%)[a]
1	Ph	**1a**	H	**5a**	**6a**	40
2	Ph	**1a**	Me	**5b**	**6b**	35
3	Ph	**1a**	Cl	**5c**	**6c**	45
4	4-$MeOC_6H_4$	**1b**	H	**5a**	**6d**	41
5	4-$MeOC_6H_4$	**1b**	Me	**5b**	**6e**	56
6	4-$MeOC_6H_4$	**1b**	Cl	**5c**	**6f**	40
7	4-FC_6H_4	**1c**	H	**5a**	**6g**	50
8	4-FC_6H_4	**1c**	Me	**5b**	**6h**	44
9	4-FC_6H_4	**1c**	Cl	**5c**	**6i**	34
10	H	**1d**	H	**5a**	**6j**	39
11	H	**1d**	Me	**5b**	**6k**	37

[a] Isolated yield by chromatography.

of **III** produces the hydroxy aldehyde with regeneration of the catalyst **3b**. Then elimination of water occurs with assistance of the added MS, furnishing the isolated 2,3-dihydrobenzo[*b*]thiepine-4-carbaldehydes **6**. Perhaps because the chiral center in intermediate **I** is too far away from the initial reaction position of **1**, no chiral induction has been obtained in the present protocol.[18]

The structure of **6** was unambiguously confirmed by an X-ray crystal diffraction analysis for 2-(4-methoxyphenyl)-7-methyl-2,3-dihydrobenzo[*b*]thiepine-4-carbaldehyde (**6e**, Figure 1).[19]

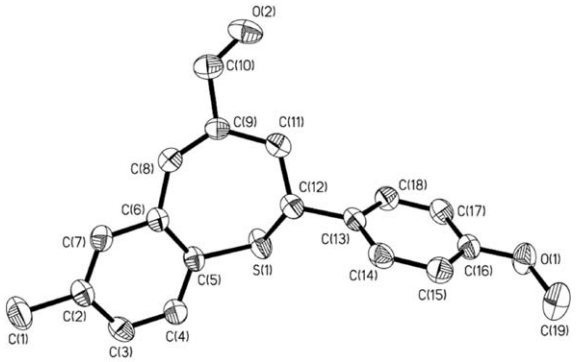
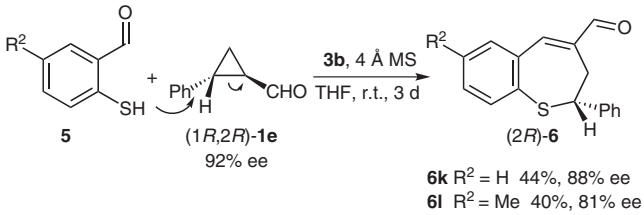


Figure 1 ORTEP picture of compound **6e**

Finally, the enantiomerically enriched cyclopropanealdehyde **1e** was prepared according to a known procedure in 92% ee.[20] The reaction of **1e** with **5a** as well as **5b** was performed under the similar conditions (Scheme 2). To our delight, the reaction proceeded well to provide the op-

tically active benzo[*b*]thiepines (2*R*)-**6k** (88% ee) and, respectively, (2*R*)-**6l** (81% ee).[16,20] Mechanistically, the ring opening step may be viewed as an S_N2-type attack of the mercapto group on the electrophilic 2*R*-carbon in **1e**. Thus, the chiral carbon is assumed to undergo inversion of configuration, leading to the formation of 2*R*-configured products **6**.



Scheme 2 Tandem reaction using (1*R*,2*R*)-2-phenylcyclopropanecarbaldehyde **1e** as substrate

In summary, we have presented the first proline-catalyzed ring opening of cyclopropanecarbaldehydes by nucleophilic attack of benzenethiols. Using *o*-thiosalicylaldehydes as the nucleophiles, the protocol constitutes a novel organocatalyzed homoconjugate addition–aldol domino reaction. The reaction proceeds with complete regioselectivity to furnish the biologically intetresting benzo[*b*]thiepines in moderate yields.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We thank Dr. Yue Zou for helpful discussions, and Mr. Peng Li for performing the X-ray crystal structure analysis.

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(14) **General Procedure for the Ring Opening of Cyclopropanecarbaldehydes 1 by Nucleophilic Attack with Benzenethiols 2**

A mixture of cyclopropanecarbaldehyde **1** (1 mmol), benzenethiol **2** (1.2 mmol), (*S*)-proline (46 mg, 0.4 mmol), and 4 Å MS (500 mg) in THF (2 mL) was stirred at r.t. for 3 d, then H_2O (5 mL) was added to quench the reaction. The aqueous phase was extracted with Et_2O (100 mL), and the organic phase was dried over Na_2SO_4, filtrated, and concentrated. The residue was purified by column

chromatography (silica gel, PE–EtOAc) to afford **4a**–**p** as pale yellow oil. All new compounds have been isolated in pure form and characterized by spectral data (^{1}H NMR, ^{13}C NMR, and MS).

Selected Data for Compounds 4

Compound **4a**: yield 55%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.66 (1 H, s, CHO), 7.30–7.18 (10 H, m, ArH), 4.16 (1 H, dd, *J* = 6.9, 8.3 Hz, SCH), 2.48 (2 H, t, *J* = 7.3 Hz, $COCH_2$), 2.30–2.15 (2 H, m, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 201.1, 141.0, 134.3, 132.4, 128.7, 128.5, 127.7, 127.4, 127.2, 52.6, 41.7, 28.5. GC-MS (EI): *m/z* = 256.1 $[M]^+$.

(15) Typical procedure for the tandem synthesis of benzo[*b*]-thiepines **6** was operated as described in ref. 14, except for replacing benzenethiols **2** with *o*-salicylaldehydes **5**. The reaction gave **6** as off-white crystal solids. All new compounds have been isolated in pure form and characterized by spectral data (^{1}H NMR, ^{13}C NMR, and MS).

Selected Data for Compounds 6

Compound **6e**: yield 56%; mp 120–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.62 (1 H, s, CHO), 7.40–6.84 (8 H, m, ArH, and CH=C), 4.26 (1 H, dd, *J* = 3.2, 11.4 Hz, SCH), 3.79 (3 H, s, OCH_3), 3.26–3.02 (2 H, m, CH_2), 2.37 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.9, 159.0, 150.4, 141.8, 137.5, 136.0, 135.2, 134.7, 134.5, 132.9, 130.9, 128.0, 114.2, 55.4, 52.6, 37.3, 21.0. ESI-HRMS: *m/z* calcd for $C_{19}H_{18}O_2S$: 310.1028; found: 310.1031.

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(18) Enantiomeric excess was determined chromatographically as follows: Diacel CHIRALPAK AS-H, hexane–2-PrOH (80:20), flow rate 0.6 mL/min, λ = 254 nm.

(19) A single crystal of **6e** suitable for X-ray diffraction analysis was obtained by recrystallization from CH_2Cl_2–*n*-hexane. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 726088.

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