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Cyclic sulfenamide: versatile template for the synthesis of 1,4-benzothiazepines

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ABSTRACT

Two efficient syntheses of 1,4-benzothiazepines, substituted in the positions 2 and 5, have been achieved either by a ring expansion reaction of cyclic sulfenamides with methylpropiolate or tosylacetylene catalyzed by pyridine, via a postulated allenolate intermediate; or by an α-sulfenylation reaction promoted by diethylamine and a subsequent acid catalyzed condensation reaction.

Among N,*S*-heterocycles, 2,3-dihydro-1,4-benzothiazepines have emerged as privileged structures with cardioprotective effect. For instance, two compounds, S107 and K201, are currently in a phase II human clinical trial for the treatment of sudden cardiac death and myocardial infarction (Scheme 1).[1]

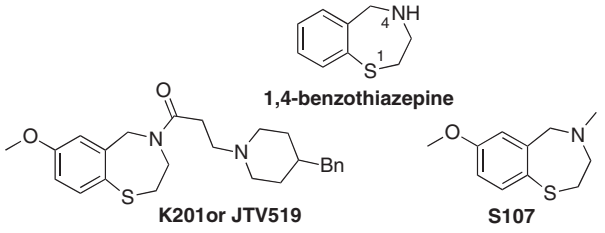
Substitutions in the positions 2, 3, or 5 in these heterocycles provide new opportunities for drug discoveries. In this context, the development of novel synthetic strategies, which fulfill the criteria of efficiency, selectivity, and atom economy, is highly desirable.

We report here two distinct but complementary approaches to synthesize 1,4-benzothiazepines[2] **2** or **3**, respectively, substituted by an ester or an alkyl group (Scheme 2). The first synthesis consists in reacting, in a single step, allenolate **A** (derived from the Michael addition of neutral organic nucleophiles to methyl propiolate) with sulfenamide[3] **1**. In the second pathway, an α-sulfenylation reaction involving the trapping of enamine **B** (derived from an amine and an aldehyde) by sulfenamide **1**, followed by an acid catalyzed condensation reaction is used.

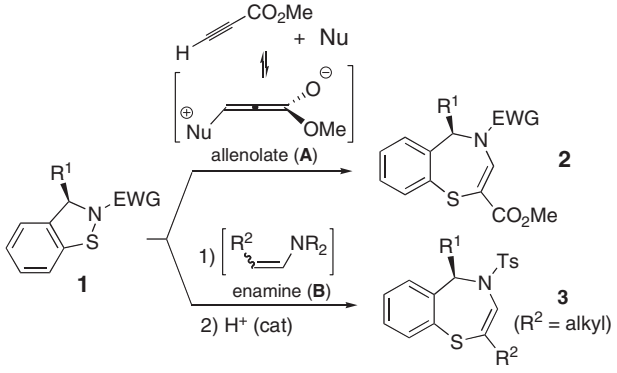
In the first approach, we initiated the project by screening for a suitable nucleophile[4] to catalyze the reaction between methylpropiolate[5] and sulfenamide **1a** (Table 1).

The main challenge in this reaction was to avoid as a side reaction, the generation of acetylide **C**[6] from the allenolate intermediate **A**, which after reaction with sulfenamide **1** led to 1,3-benzothiazines[7] **4** via a domino process[8] (Scheme 3 and Table 1,[9d] entry 1).

Our initial tests began with phosphines[9] as nucleophilic catalysts (Table 1, entries 2 and 3). Unfortunately, in acetonitrile, 1,3-benzothiazines **4a** were formed as the major products. A



Scheme 1. Structure of 1,4-benzothiazepines.



Scheme 2. Two Strategies for the Synthesis of 1,4-benzothiazepines.

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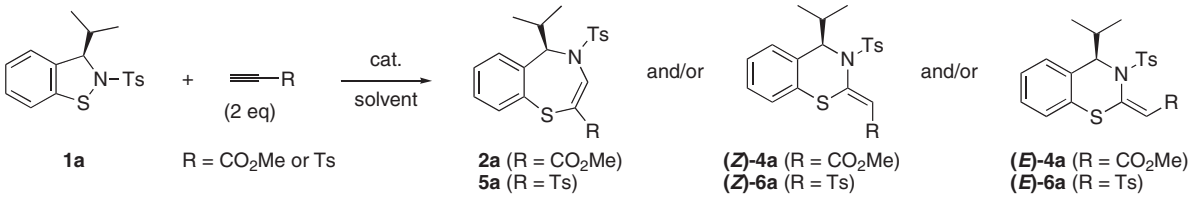
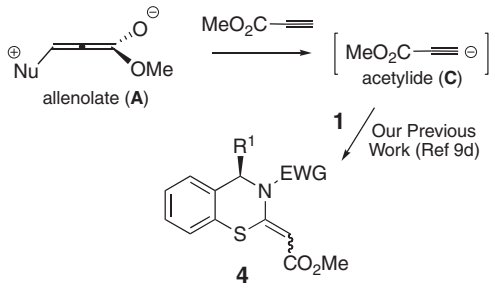
Table 1
Optimization of reaction conditions for the benzothiazepine synthesis



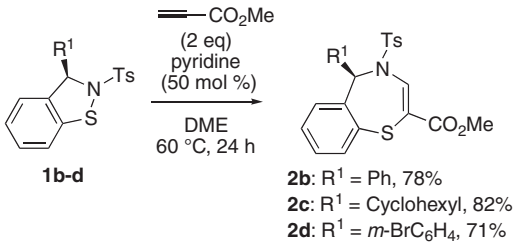
1a R = CO_2Me or Ts **2a** (R = CO_2Me), **5a** (R = Ts) (***Z***)-**4a** (R = CO_2Me), (***Z***)-**6a** (R = Ts) (***E***)-**4a** (R = CO_2Me), (***E***)-**6a** (R = Ts)

Entry	R	Catalyst (mol %)	Solvent (0.1 M)	Temp (°C)	Time (h)	% Conversion[a](% yield)[b]	Ratio[a] **2a**/***Z***-**4a**/***E***-**4a**	Ratio[a] **5a**/***Z***-**6a**/***E***-**6a**
1	CO_2Me	CsF (10)	MeCN	rt	0.5	100 (**4**, 86)	0/87/13	–
2	CO_2Me	DPPP (10)	MeCN	80	2	100	15/65/20	–
3	CO_2Me	PPh_3 (20)	MeCN	rt	0.5	100	0/84/16	–
4	CO_2Me	DABCO (20)	MeCN	rt	1	100	18/71/11	–
5	CO_2Me	DMAP (20)	MeCN	rt	0.5	100	17/72/11	–
6	CO_2Me	Pyridine (20)	MeCN	rt	24	78	22/58/20	–
7	CO_2Me	Pyridine (20)	MeCN	60	24	90	55/37/8	–
8	CO_2Me	Pyridine (20)	DMF	60	18	91	51/39/10	–
9	CO_2Me	Pyridine (30)	DME	60	24	67	100/0/0	–
10	CO_2Me[c]	Pyridine (50)	DME	60	72	24	100/0/0	–
11	CO_2Me	Pyridine (50)	DME	60	40	93 (**2a**, 69)	100/0/0	–
12	CO_2Me	Pyridine (100)	DME	60	24	100 (**2a**, 80)	100/0/0	–
13	Ts	Pyridine (50)	DME	60	2	78	–	50/0/50
14	Ts	Pyridine (50)	DME	80	1	75	–	81/0/19
15	Ts	Pyridine (25+25)	DME	80	30 + 30[d]	86 (**5a**, 61)	–	100/0/0

[a] Determined by ^1H NMR on the crude product.
[b] Isolated yields.
[c] Slow addition of methyl propiolate for 2 h.
[d] In minutes.



Scheme 3. Synthesis of 1,3-benzothiazines.



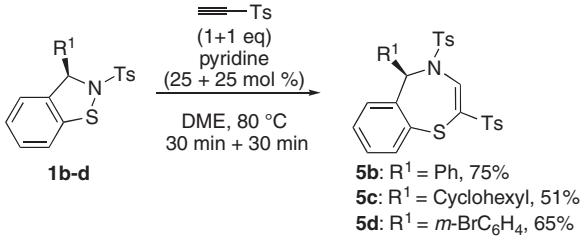
Scheme 4. Synthesis of 1,4-benzothiazepines **2b**–**d**.

similar result was obtained using DABCO[10] and DMAP[11] (entries 4 and 5) as catalysts. At room temperature, it was found that pyridine (20 mol %) catalyzed the desired ring expansion although with low efficiency (22/58/20 ratio, entry 6). The formation of 1,4-benzothiazepine **2a** was enhanced by heating at 60 °C (entries 7 and 8). Furthermore, a great improvement was observed when the reaction was performed in 1,2-dimethoxyethane (DME) instead of acetonitrile since only the expected compound **2a** was obtained (entry 9). After some non benefit experiments (entry 10: slow addition of methyl propiolate), variation of the amount of pyridine was tested. The best compromise between the yield and catalyst loading was established at 50% loading of catalyst for 69% yield (entry 11). It is however, worth mentioning that a total conversion and 80% isolated yield could be obtained with 1 equiv of pyridine (entry 12).

With these optimized conditions in hand (Table 1, entry 11), various aryl and alkylsulfenamides were tested. Using sulfenamides **1b–d**, expected 1,4-benzothiazepines **2b–d** (Scheme 4) were isolated in good yields (71-82%).[13]

We then explored the use of another electron-deficient alkyne, that is, tosylacetylene. This compound should allow further transformations and functionalization of the vinyl sulfone group.[12] Using our previous optimized conditions, an equal amount of 1,4-benzothiazepine **5a** and 1,3-benzothiazine (***E***)-**6a** was obtained (Table 1, entry 13). It is worth mentioning that the reaction was much faster as before (2 h instead of 40 h). On the other hand, when the reaction was performed at 80 °C (entry 14), the amount of the expected 1,4-benzothiazepine **5a** increased to 81% (with 75% of conversion). The best ratio in favor of **5a** was obtained by two sequential additions of 0.25 equiv of pyridine and 1 equiv of tosylacetylene, after 30 min of reaction (entry 15). Using these conditions, 1,3-benzothiazine **6a** was not detected in the crude mixture and 1,4-benzothiazepine **5a** was isolated in 61% yield.

Reactions between various sulfenamides **1b–d** and tosylacetylene were next examined (Scheme 5) and the corresponding benzothiazepines **5b–d** were obtained in each case in moderate to good yields (51–75%).[14]

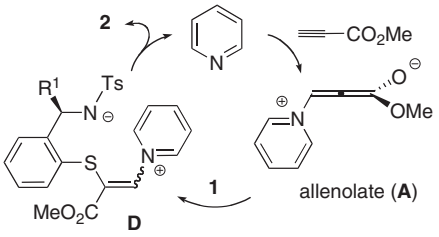


Scheme 5. Synthesis of 1,4-benzothiazepines **5b**–**d** by reaction of tosylacetylene with cyclic sulfenamides.

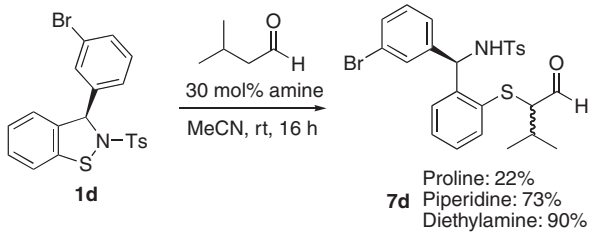
As plausible mechanism, the zwitterion **A**,[15] chelated by DME, could attack the electrophilic sulfur atom of sulfenamide **1** to lead to the corresponding zwitterion **D** which in turn cyclizes after an addition/elimination reaction (Scheme 6) into the final 1,4-benzothiazepine.

As the previous methodology cannot be applied to an acetylenic species bearing an alkyl group instead of the EWG (COOEt, Tos), a second pathway in two steps was envisioned to access benzothiazepines substituted by an alkyl group in the 2-position.[16] Instead of trapping the sulfenamide **1** by an allenolate, we chose an enamine, formed in situ by the reaction between isovaleraldehyde and an amine. This sulfenylation reaction[17] was tested with compound **1d** and various secondary amines (Scheme 7). The best yield in sulfide **7d**[18] (90%) was obtained with 30% M of diethylamine in CH_3CN at rt.

These conditions were next applied to other sulfenamides **1a–c**/**8a** (Table 2, entries 1–4) and in all cases the corresponding products were obtained in good yields. On the other hand, using propanal instead of isovaleraldehyde (entries 5–8), afforded low yields, while no reaction occurred using phenylacetaldehyde (entry 9) or acetophenone (entry 10).

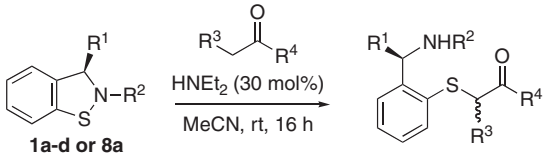


Scheme 6. Proposed mechanism for the formation of 1,4-benzothiazepines **2**.



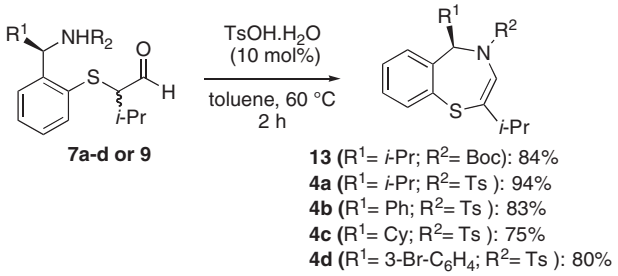
Scheme 7. Catalyst screening for the α-sulfenylation reaction of isovaleraldehyde.

Table 2
Diethylamine catalyzed α-sulfenylation reactions of carbonyl compounds[19]

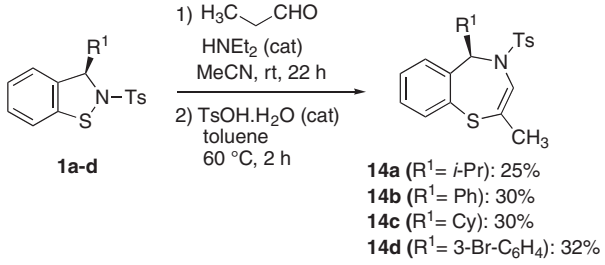


Entry	SM	R^1	R^2	R^3	R^4	Product	% Yield[a]
1	**1b**	Ph	Ts	*i*-Pr	H	**7b**	73
2[b]	**1a**	*i*-Pr	Ts	*i*-Pr	H	**7a**	77
3[b]	**1c**	Cy[c]	Ts	*i*-Pr	H	**7c**	65
4[b]	**8a**	*i*-Pr	Boc	*i*-Pr	H	**9a**	64
5	**1a**	*i*-Pr	Ts	CH_3	H	**10a**	45
6	**1c**	Cy[c]	Ts	CH_3	H	**10c**	32
7	**1b**	Ph	Ts	CH_3	H	**10b**	34
8	**1d**	3-Br-C_6H_4	Ts	CH_3	H	**10d**	37
9	**1a**	*i*-Pr	Ts	Ph	H	**11**	0
10	**1a**	*i*-Pr	Ts	H	Ph	**12**	0

[a] Isolated yields.
[b] Reaction performed at 60 °C.
[c] Cy = cyclohexyl.



Scheme 8. TsOH catalyzed condensation reactions.



Scheme 9. One-pot reactions.

The cyclization reaction was next explored and first tested with the *N*-Boc sulfide **9a** in the presence of large excess of TFA. Compound **13** was obtained in a moderate yield (63%) due to the presence of N-deprotected product. To avoid this side reaction, 10% M of pTSA was chosen.[20] Under these conditions, the expected benzothiazepine **13** was isolated in 84% yield. This reaction was next extended to other sulfides **7a–d** (Scheme 8) to afford the corresponding 1,4-benzothiazepines **4a–d** in very good yields.[21]

As low yields were obtained in the case of aldehydes **10a–d**, the sequential one-pot reaction was investigated without the intermediate purification. 1,4-Benzothiazepines **14** were obtained in moderate overall yields (Scheme 9).[22]

In summary, we have defined conditions, which allow to trap an intermediate allenolate or enamine with a sulfenamide, respectively, using a catalytic amount of pyridine or diethylamine. This methodology provides a catalytic access to the original 2-substituted 1,4-benzothiazepines with high efficiency and atom economy.

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Supplementary data

Supplementary data (^1H and ^{13}C spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.148.

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13. *Typical procedure for the preparation of benzothiazepine **2** (**2c** as example)*: To a solution of sulfenamide **1c** (45 mg, 0.12 mmol) and pyridine (4.8 μL, 0.06 mmol, 0.5 equiv) in DME (1.0 mL) was added methyl propiolate (21.4 μL, 0.24 mmol, 2 equiv) at 60 °C and the reaction mixture was stirred at 60 °C for 24 h. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane/pentane (6/4) as the eluent to afford the corresponding benzothiazepine **2c** as a white solid (45 mg, 82%).
14. Typical procedure for the preparation of benzothiazepine **5** (**5b** as example): To a solution of sulfenamide **1b** (44 mg, 0.12 mmol) and pyridine (2.4 μL, 0.06 mmol, 0.25 equiv) in DME (1 mL) was added *p*-toluenesulfonylacetylene (21.6 μL, 0.12 mmol, 1 equiv) at 80 °C. The reaction mixture was stirred at 80 °C for 30 min, then pyridine (2.4 μL, 0.06 mmol, 0.25 equiv) and *p*-toluenesulfonyl-acetylene (21.6 μL, 0.12 mmol, 1 equiv) were added. After 30 min, the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane as the eluent to afford the corresponding benzothiazepine **5b** as a white solid (49 mg, 75%).
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18. **7d** was obtained as a 1:1 mixture of two diastereoisomers.
19. *Typical procedure for the preparation of aldehyde **7** (**7a** as example)*: A mixture of isovaleraldehyde (2 equiv) and diethylamine (0.3 equiv) in CH_3CN (1 mL for 0.10 mmol of isovaleraldehyde) was stirred for 5 min at room temperature. A solution of sulfenamide **1a** (100 mg, 0.3 mmol, 1 equiv) in CH_3CN (1 mL) was added and the mixture was stirred overnight at room temperature. After evaporation of the solvent under reduced pressure, the crude aldehyde was purified by column chromatography on silica gel using pentane/Et_2O (6/4) as the eluent to afford benzothiazepine **7a** as a yellow oil (97 mg, 77%) as a 50/50 mixture of two diastereoisomers.
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22. *Typical procedure for the preparation of benzothiazepine **14** (**14b** as example)*: A mixture of propionaldehyde (2 equiv) and diethylamine (0.3 equiv) in acetonitrile (1 mL for 0.10 mmol of propionaldehyde) was stirred for 5 min at room temperature. A solution of sulfenamide **1** (45 mg, 0.12 mmol, 1 equiv) in acetonitrile (1 mL for 0.30 mmol of sulfenamide) was added and the mixture was stirred at room temperature for 22 h. The solvent was evaporated under reduced pressure to afford the crude aldehyde **10b**, which was directly dissolved (1 equiv) in toluene (1 mL for 0.10 mmol of **10b**) and *p*-toluenesulfonic acid (0.5 equiv) was added. The mixture was stirred at 60 °C for 5 h. Water was added and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel using pentane/Et_2O (9/1) as the eluent to yield the corresponding benzothiazepine **14b** as a colorless oil (15 mg, 30%).