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Catalytic Generation of Cesium Acetylide by CsF: Synthesis of 1,3-Benzothiazines from Cyclic Sulfenamides

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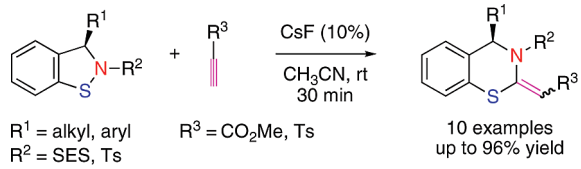
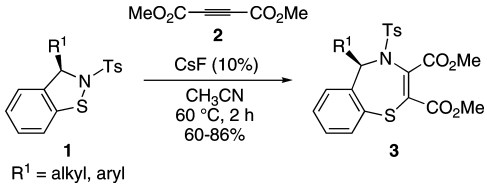
ABSTRACT



An efficient synthesis of enantiopure 1,3-benzothiazines has been achieved by reaction of cyclic sulfenamides and alkylpropiolate or tosylacetylene catalyzed by cesium fluoride.

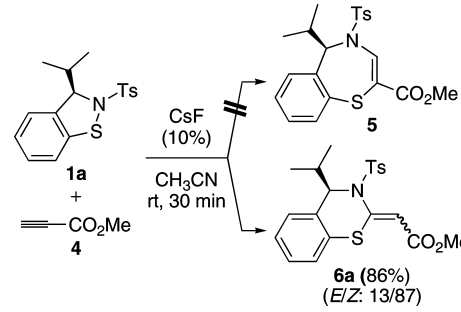
Recent studies in our laboratory have shown that enantiopure 1,4-benzothiazepines **3** can be prepared, with high efficiency and atom economy, from the cyclic sulfenamides **1** and dimethyl acetylenedicarboxylate **2**, using fluoride ion as a nucleophilic catalyst (Scheme 1).[1]

Scheme 1. Synthesis of 1,4-Benzothiazepines **3**



Surprisingly, when methyl propiolate **4** was used in the presence of CsF as catalyst, the expected 1,4-benzothiazepine **5** was not obtained (Scheme 2). Instead, 1,3-benzothiazine **6a** was isolated as a mixture of two separable isomers *E*/*Z* in 86% yield.

Scheme 2. Synthesis of 1,3-Benzothiazine **6a**



In this communication, we disclose the efficient domino process to synthesize these heterocycles, based on *in situ* catalytic generation of conjugated acetylides. Traditionally, acetylides were used for the alkynylation of carbonyl compounds, leading to the corresponding propargylic alcohols.[2]

(1) Spitz, C.; Lohier, J.-F.; Sopkova-de Oliveira Santos, J.; Reboul, V.; Metzner, P. *J. Org. Chem.* **2009**, 3936–3939.

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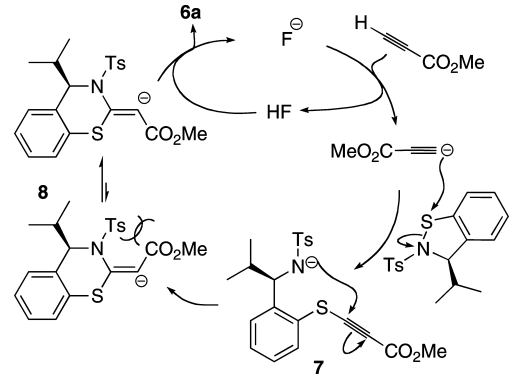
However, most studies have focused on the use of arylacetylene or alkylacetylene[3] whereas alkyl propiolates are generally problematic substrates, requiring specific reaction conditions. Indeed, due to the presence of ester function, catalytic systems such as potassium *tert*-butoxide[4] or cesium hydroxide[5] cannot be employed. Other methods, involving the *in situ* generation of zinc acetylide[6] in the presence of tertiary amine led to the aminoacrylic ester[7] instead of the acetylenic alcohol. Ammonium acetylide promoted the reaction in moderate to low yield[8] but also domino processes can take place to generate enol-protected propargylic alcohols or 1,3-dioxolane compounds.[9] Moreover, no reaction was observed with rhodium[10] or copper acetylide.[11] Consequently, two steps procedures, involving the preparation of metal acetylide in a separate step are still competitive and allowed efficient preparation of alkyl 4-hydroxy-2-alkynoates. Among alkali metal derivatives, lithium acetylide is the most efficient but required very low temperature reactions (−78 °C and −100 °C for ethyl and methyl propiolate, respectively) and careful addition of *n*-BuLi.[12] Silver acetylide is more convenient and in the presence of Cp_2ZrCl_2 (1.2 equiv) and AgOTf (0.2 equiv) promoted coupling with carbonyl compounds at room temperature.[13]

In our process, we proposed the unprecedented generation of terminal acetylide by fluoride anion (Scheme 3). Instead of generating the sulfenyl fluoride by the ring-opening reaction as expected,[1] fluorine anion is able to deprotonate[14]

Scheme 3. Proposed Mechanism for the Synthesis of **6a**

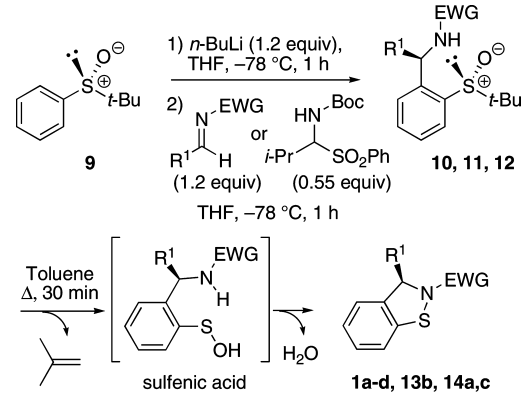


the starting alkynoate in the terminal position, probably due to the low pK_a value of this proton (p$K_a \approx 18.8$).[15] This acetylide anion reacts with the electrophilic sulfur atom[16,1] of sulfenamide to lead to intermediate **7**. The cyclization by intramolecular Michael addition forms enolate **8**, protonation[17] of which affords less hindered 1,3-benzothiazine (*Z*)-**6a** as major product and regenerates the fluoride anion.

To probe this mechanism, the lithium acetylide of methyl propiolate[11] (*n*-BuLi, THF, −100 °C) was prepared in a separate flask and then added to sulfenamide **1a**. Benzothiazine **6a** was the sole isolated compound, in 85% yield (*E*/*Z* mixture 35:65).

The scope of the reaction was next explored with a range of aryl- and alkylsulfenamides bearing different protecting groups on the nitrogen atom (EWG = Ts, SES or Boc). The required isothiazolines **1a**−**d**, **13b** and **14a,c** were prepared according to our described procedure (Scheme 4):[18] *ortho*-

Scheme 4. Synthesis of Isothiazolines **1a-d, 13b** and **14a,c**



metalation of enantiopure sulfoxide **9** followed by addition of imine or sulfone (Table 1).[19] New aminosulfoxides **10**−**12** were obtained with complete diastereocontrol when R^1 is

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Table 1. Synthesis of Isothiazolines from Aminosulfoxides

	aminosulfoxides				isothiazolines
entry	R^1	EWG	% yield[a] (compd)	dr[b]	% yield[a] (compd)
1	*i*-Pr	Ts	80 (**10a**)	>98/2	96 (**1a**)
2	Cy	Ts	74 (**10b**)	>98/2	99 (**1b**)
3	Ph	Ts	64 (**10c**)	80/20	97 (**1c**)
4	*m*-BrC_6H_4	Ts	63 (**10d**)	77/23	97 (**1d**)
5	Cy	SES	60 (**11b**)	>98/2	98 (**13b**)
6	*i*-Pr	Boc	46 (**12a**)	>98/2	99 (**14a**)
7	Ph	Boc	54 (**12c**)	80/20	98 (**14c**)

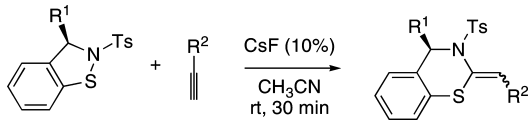
[a] Isolated yields. [b] Determined by ^{1}H NMR on the crude product.

an alkyl group (entries 1, 2, 5, 6). These observations are in agreement with the proposed stereochemical course of the reaction: four-membered transition state involving coordination of the lithium atom with the oxygen atom of the protecting group.[17] A lower asymmetric induction was observed (dr 80:20) with an aryl group (entries 3, 4, 7) but the two diastereoisomers can be easily separated by column chromatography.

By heating in toluene, aminosulfoxides undergo a [2,3]-sigmatropic process leading to isobutene and the corresponding sulfenic acid. After elimination of H_2O, the isothiazolines **1**, **13**, **14** were isolated in quantitative yields (Table 1) and in enantiopure forms.

Having the expected isothiazolines in hand, the synthesis of 1,3-benzothiazines was next generalized. We used previously optimized conditions: CsF (10 mol %) in CH_3CN at rt. With alkyl propiolate, we were able to prepare in good yields a variety of *N*-tosyl-1,3-benzothiazines **6**−**15** bearing aliphatic or aromatic groups in R^1 (Table 2, entries 1−5).

Table 2. Synthesis of 1,3-Benzothiazines **6**, **15**, **16**



entry	R^1	R^2	% yield[a] (compd)	*E*/*Z*[b]
1	*i*-Pr (**1a**)	CO_2Me	86 (**6a**)	13/87
2	Cy (**1b**)	CO_2Me	84 (**6b**)	14/86
3	Ph (**1c**)	CO_2Me	73 (**6c**)	13/87
4	*m*-BrC_6H_4 (**1d**)	CO_2Me	57 (**6d**)	17/83
5	*i*-Pr (**1a**)	CO_2Et	85 (**15a**)	13/87
6	*i*-Pr (**1a**)	Ts	96 (**16a**)	92/8
7	Cy (**1b**)	Ts	93 (**16b**)	92/8
8	Ph (**1c**)	Ts	92 (**16c**)	>98/2
9	*m*-BrC_6H_4 (**1d**)	Ts	74 (**16d**)	>98/2
10	*i*-Pr (**1a**)	Ph	0	−

[a] Isolated yields. [b] Determined by ^{1}H NMR on the crude product.

The two isomers can be separated by column chromatography.

The stereochemistry of the C=C double bond of the major diastereoisomer of benzothiazine **6c** was assigned as (*Z*) by X-ray analysis (Figure 1) which is in agreement with the proposed mechanism. It was generalized to the other compounds **6** according to ^{1}H NMR.[20]

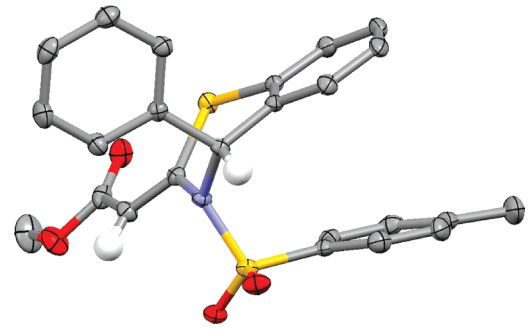


Figure 1. X-ray crystal structure of major diastereoisomer (50% thermal ellipsoids) of **6c**. Hydrogen atoms are omitted for clarity except for C*H and C=CH.

We next conducted a survey of a range of terminal acetylenes. Tosyl acetylene[21] reacted in very good yields (Table 2, entries 6−9) to afford 1,3-benzothiazines **16**. Surprisingly, the stereochemistry of the C=C double bond of the major diastereoisomer of benzothiazine **16a** was assigned as (*E*) according to X-ray analysis (Figure 2).[22] With aromatic sulfenamides **1c,d** (entries 8,9), only the isomer (*E*) was formed. On the other hand, no reaction occurred with phenyl acetylene (entry 10).

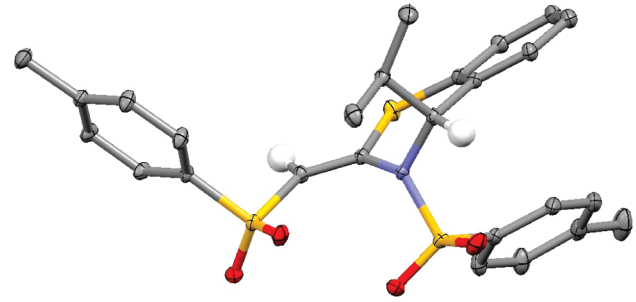


Figure 2. X-ray crystal structure of major diastereoisomer (50% thermal ellipsoids) of **16a**. Hydrogen atoms are omitted for clarity except for C*H and C=CH.

The reaction was also conducted with sulfenamide **13b** as starting material (Scheme 5). As expected, benzothiazine

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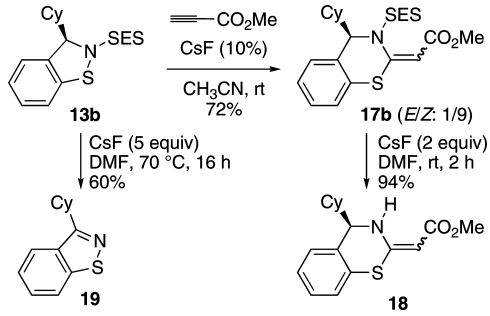
Scheme 5. Deprotection of SES Group by CsF

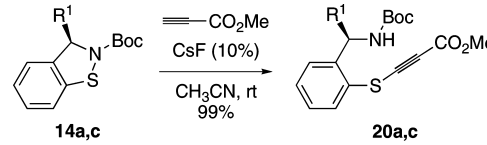


17b was obtained (72% yield). Moreover, the deprotection of 2-(trimethylsilyl)ethanesulfonyl (or SES) group by fluoride anion[23] in both compounds was not observed in CH_3CN. On the other hand, benzothiazine (*Z*)-**17b** could be deprotected when the reaction was performed in DMF. Also, in the presence of a large excess of CsF (5 equiv), deprotection of sulfenamide **13b** occurred but with aromatization to afford the corresponding aromatic compound **19** in 60% yield (Scheme 5).

On the other hand, when we next studied the reactivity of isothiazolines **14** (bearing a Boc group on the nitrogen atom) with methyl propiolate, benzothiazines were not obtained. Instead, the corresponding opened compounds **20a,c** were isolated in quantitative yields (Scheme 6) confirming the proposed mechanism.

In conclusion, we achieved the synthesis of 1,3-benzothiazines[24] with high efficiency and atom economy, via a catalytically generated cesium acetylide. Further studies with other electrophiles, in particular aldehydes and ketones, are currently underway and will be reported in the due course.

Scheme 6. Reactivity with *N*-Boc Isothiazolines **14a−c**



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Supporting Information Available: Experimental procedures and characterization for all new compounds described in this work, crystallographic data for the reported structures (CIF format). This material is available free of charge via the Internet at http://pubs.acs.org.

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