

One-Pot Synthesis of Benzo[*e*]1,4-oxathiepin-5-ones under Solvent-Free Condition via Self-Promoted Thiolysis of 1,2-Epoxides

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Under solvent-free conditions, thiosalicylic acid (2) efficiently self-promotes the thiolysis of 1,2epoxides 1, *anti*-stereoselectively and generally totally β -regioselectively. The resulting β -hydroxysulfide products 3 have been obtained in very good yields. Benzo[e]1,4-oxathiepin-5-ones 4 have been easily prepared in a regio- and diasteroselective manner and in satisfactory yields under SFC by a one-pot protocol including nucleophilic ring opening of 1,2-epoxides 1 by thiosalicylic acid (2) and thermally induced lactonization of β -hydroxy arylsulfides 3. Solvent-free condition and the absence of any catalyst make this procedure atom-economical and environmentally friendly.

Introduction

Heterocyclic small molecules play a pivotal role in the search for new therapeutic and drug candidates¹ and are essential to elucidate the chemistry of living processes.² Recent advances in biology have provided many potentially useful targets for which new small-molecule modulators have to be found.³ Starting from the concept of "privileged structures",⁴ synthetic methodologies have been developed to synthesize natural productlike or active druglike small molecules on the basis of a target-oriented synthesis or a combinatorial approach.^{5a} Schreiber recently pointed out the urgent need to explore "new chemical spaces" by accessing new structures having unknown properties, namely, diversity-oriented synthesis,⁵ and proposed a complete revolution in the approach to pharmaceutical discovery.

Thiazepinones are a very interesting class of compounds that show a wide spectrum of biological activity;⁶ many synthetic procedures have been proposed to prepare a variety of derivatives.⁷ In contrast, the pharmacological properties of the isosterically related oxathiepinones have never been tested, supposedly because of the lack of an efficient synthetic method for their preparation. To our knowledge, only one paper has reported the synthesis of a mixture of 2- and 3-phenyl 2,3-dihydro-1,4-benzoxathiepin-5-one, via thiolysis of styrene oxide by thiosalicylic acid (**2**). The reaction was carried out in refluxing benzene, catalyzed by *p*-toulenesulfonic acid (*p*-TsOH), and the overall yield was low.⁸

As a continuation of our research devoted to the development of a green organic chemistry by using water as reaction medium or by performing organic transformations under solvent-free conditions (SFC),⁹ we are currently engaged in a project aimed at defining a versatile, environmentally friendly, and atom-economical synthesis of 1,4-oxathiepinones.

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SCHEME 1. Synthesis of Benzo[e]1,4-oxathiepin-5-one 4a in Water



Recently, we have approached the synthesis of a 1,4benzoxathiepin-5-one **4a** by performing the thiolysis of cyclohexene oxide (**1a**) under aqueous basic conditions with thiosalicylic acid (**2**) and subsequent in situ lactonization of the corresponding adduct **3a** under acidic refluxing conditions (Scheme 1).^{9h} These promising results suggested that the one-pot synthetic strategy based on the reaction of 1,2-epoxides with thiosalicylic acid (**2**) and subsequent lactonization of the resulting hydroxy carboxylic acids could be one of the most straightforward ways to synthesize 1,4-oxathiepin-5-one moiety. Therefore we decided to study these processes under different conditions: (i) in the presence of a reaction medium, (ii) under SFC, and (iii) in the presence and in the absence of a Brønsted acid catalyst.

No-solvent reactions are generally fast, give high selectivities and yields, and usually require easier work-up procedures and simpler equipment.¹⁰⁻¹²

Under SFC, we reported the tetrabutylammonium fluoride catalyzed 1,3-dipolar cycloaddition of nitriles with trimethylsilyl azide, ^{12a} the tetrabutylammonium bromide catalyzed *O*-trimethylsilylation of alcohols, ^{12e} the [4 + 2] cycloaddition of 3-nitrocoumarins with vinyl ethers and 1,3-dienes for the synthesis of chromenes derivatives^{12d} or dihydrobenzofurans, ^{12c} respectively, and the thiolysis of 1,2-epoxides catalyzed by Lewis or Brønsted acids and bases.^{12b} On the basis of these results, we

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Thiosalicylic Acid (2) under Various Reaction Conditions 'OH HO Ŕ ОН òн ì ΌΗ 2 3α 3β Т Entry 1,2-Epoxide Medium \mathbf{C}^{a} $C-\alpha/C-\beta$ t $(^{\circ}C)$ (%) (h) 1 DCM 30 100 99 2 Toluene Rfx 24 80 3 H₂O (pH 3.0) 30 1 20^{t} H,O (pH 9.0) 30 0.5 99° 4 5 SFC 99 30 6 6 SFC (p-TsOH) 30 5 75^d 7 DCM 48 99 95/5 50 8 Toluene Rfx 24 80 76/24 19^e 9 H₂O (pH 3.0) 78/22 30 1 10 H,O (pH 9.0) 99¹ 67/33 30 0.5 1b 11 SFC 30 4 99 85/15 60/40 12 SFC (p-TsOH) 0.5 55° 30

TABLE 1. Thiolysis of 1,2-Epoxides 1a,b with

have hypothesized that thiosalicylic acid (2) can behave, in the nucleophilic ring opening of the oxirane, both as a Brønsted acid and as a nucleophile, thereby avoiding the use of any external catalytic species in contrast to what usually happens.^{9c-e,h,12a,13} This paper reports the first general route to 1,4-oxathiepin-5-one moiety starting from 1,2-epoxides.

Results and Discussion

We have initially studied the thiolysis of two representative 1,2-epoxides, cyclohexene oxide (1a) and styrene oxide (1b), with thiosalicylic acid (2) in DCM, in toluene, in water at pH 3.0 and 9.0, and under SFC, in the presence and absence of *p*-TsOH as external Brønsted catalyst. The results obtained are summarized in Table 1.

In DCM, the thiolysis occurred with complete conversion and high regio- and stereoselectivity, but long reaction times were required to obtain β -hydroxy arylsulfides **3a** and **3b** (Table 1, entries 1 and 7). In toluene, the reaction conversion and the regioselectivity of the

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^{*a*} Conversion determined by GCL analyses. ^{*b*} trans-1,2-Cyclohexandiol was formed in 79%. ^{*c*} **3a** was isolated in 94% yield. ^{*d*} Complement to 99% were decomposition products. ^{*e*} 2-Phenyl-1,2-ethandiol was formed in 80%. ^{*f*} Products **3b** α and **3b** β were isolated in 95% overall yield.



TABLE 2. Self-Promoted Thiolysis of 1,2-Epoxides 1a-h with Thiosalycilic Acid (2) under SFC

^{*a*} Yield of the isolated products **3**.

process were significantly lower even at reflux temperature (Table 1, entries 2 and 8).

When the reagents were mixed in water, an acidic medium was generated (pH 3.0) and under these conditions the reaction conversion was low, the nucleophilic attack was poorly regioselective, and the hydrolysis reaction prevailed over the thiolysis (Table 1, entries 3 and 9). In water at pH 9.0, the thiolysis was very fast, gave high yields, but in the case of **1b**, was poorly regioselective (Table 1, entries 4 and 10).

The thiolysis of **1a** carried out under SFC was complete in 6 h at 30 °C and gave the adduct **3a** with excellent yield (Table 1, entry 5). Similarly the reaction of **1b** with **2** in the absence of solvent required 4 h to be complete and gave quantitatively the regionsomer adducts **3a** α and **3a** β in a 85/15 ratio (Table 1, entry 11). The use of *p*-TsOH (5 mol %) accelerated the reactions but gave disappointing results in terms of conversion and selectivity (Table 1, entries 6 and 12).

The behavior of thiosalicylic acid (2) deserves a comment. The thiolysis of 1,2-epoxides with thiophenol did not occur in DCM or SFC unless Brønsted or Lewis acids were used.^{12b,13b} The thiol group of thiosalicylic acid (2) is expected to be less nucleophilic than that of thiophenol. Nevertheless, in DCM and SFC the thiolysis of 2 with 1a and 1b did not need to be catalyzed, and when a Brønsted acid was used, disappointing results were obtained.

To better understand these results, we also carried out thiolysis of **1a** and **1b** with *o*-carboxymethyl-thiophenol and *p*-carboxy-thiophenol under the same reaction condi-

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tions illustrated in Table 1. The reactions worked only in water at pH 9.0, whereas in DCM, PhMe, H₂O (pH 3.0), and SFC in the absence and presence of *p*-TsOH, no β -hydroxy arylsulfides were detected or disappointing results were obtained. The reaction is only successful when a carboxylic functionality is at the ortho position to the mercapto group. This self-promoted thiolysis could be the consequence of a favorable hydrogen bond between the oxirane ring and the thiosalicylic acid (**2**), which favors catalytically and geometrically the approach of the reagents, particularly in aprotic solvents and under SFC.

Summarizing the results in Table 1, the simplest, most convenient, and atom-economical protocol for the thiolysis of 1a and 1b with 2 is that carried out under SFC without catalyst. With the aim of developing a simple and fast route to benzo[e]1,4-oxathiepin-5-ones, thiolysis under SFC was extended to a variety of substituted 1,2-epoxides 1. The results obtained are reported in Table 2. All reactions proceeded satisfactorily in short times, and the resulting β -hydroxy arylsulfide products **3** were isolated in 85-95% yields. All new products were fully characterized (see Supporting Information). In the case of alkyl-1,2-epoxides, thiol **2** attacked almost exclusively at $C-\beta$ except in the case of **1e** where the C- α regioisomer was formed in an appreciable amount (15%, Table 2). The thiolysis of 1b proceeded with the prevalent formation of the **3ba** regioisomer (85%) as expected (Table 1, entry 11 and Table 2).

The second step in our synthetic approach to the benzo-[e]1,4-oxathiepin-5-one ring was the lactonization of hydroxy-thio carboxylic acids 3. Lactonization and esterification reactions are important processes and have been largely investigated to find mild catalysts and efficient procedures for 100% conversion of equimolecular amounts of carboxylic acids and alcohols.¹⁴ The activation of the carboxylic function in various solvents and/or high temperatures is generally required.¹⁴ One of the most efficient protocols has been realized by Yamamoto H. et al. who have demonstrated that under dehydrating conditions, hafnium(IV) chloride and alkoxide are very efficient catalysts for this process.^{14a} Sc(OTf)₃,^{14c} Ti(Oi-Pr)₄^{14a} and diphenylammonium triflate^{14b} also efficiently promoted esterification and lactonization reactions. In our case the transformation can be more complicated than usual because of the presence of a sulfide functionality. In fact it is known that acids promote the formation of thiiranium ion, which can evolve to give [1,2] sulfanyl migration by elimination or substitution reactions.¹⁵

Taking adduct **3a** as a typical substrate, we studied the lactonization process under various reaction conditions. The results obtained are illustrated in Table 3. This transformation required 24 h in refluxing water under acidic conditions to furnish **4a** in 70% yield (Scheme 1 and Table 3, entry 1).^{9h} Ti(IV) and Hf(IV) chlorides (in stoichiometric or catalytic amounts) in DCE at 50 °C were not effective catalysts; their use resulted in the formation of a 4/1 mixture of *cis* and *trans-* β -chloro sulfides **5**. The first one was derived from the direct hydroxyl substitu-



OH	S S	$H \longrightarrow \mathcal{O}_{s}$		+ (ÇI S	CO ₂ H
3	la	4a			5	
entry	medium	catalyst	Т (°С)	t (h)	product	yield ^a (%)
1	H_2O	$ m pH\sim 0$	rfx	24	4a	70
2	DCE	$TiCl_4$ (1.0 equiv)	50	8	5	59^{b}
3	DCE	$TiCl_4$ (THF) ₂ (1.0 equiv)	50	8	5	58^b
4	DCE	$HfCl_4$ (0.3 equiv)	50	8	5	58^b
5	SFC	none	50	5	4a	30
6	SFC	In(OTf)3 (0.05 equiv) 5Å MS	50	5	4a	30
7	SFC	none	200	1	4a	95

^{*a*} Isolated yield of **4a** and **5** respectively. ^{*b*} 4/1 mixture of *cis*and *trans*-2-[(2'-carboxy)thiophenyl]-1-chloro cyclohexane **5**.

tion by chloride, and the second was supposedly formed by chloride nucleophilic attack on the 2,3-cyclohexane-1-(2'-carboxyphenyl)thiiranium formed from 3a (Table 3, entries 2-4).

The best result was obtained under SFC without using any Lewis acid catalyst or dehydrating agent. The lactonization of **3a**, induced by simply heating at 200 °C in an open vial to facilitate the elimination of water, resulted in a very good yield of product 4a (Table 3, entry 7). Only 30% conversion was reached when the temperature was lowered to 50 °C (Table 3, entry 5) and when the reaction was carried out in the presence of molecular sieves and In(OTf)₃ at 50 °C (Table 3, entry 6). Longer reaction times did not change the final conversion percentage. In any case, the cyclization temperature used under SFC (Table 3, entry 7) is quite low considering that a temperature of 150 °C is usually required after anhydride activation of the carboxylic functionality and in many other esterification protocols. To the best of our knowledge, this is the first example of the preparation of a seven-membered thiolactone by simple thermal cyclization of the corresponding hydroxy-thio carboxylic acids. This result paves the way to a very simple onepot synthesis of a benzo[e]1,4-oxathiepin-5-one moiety starting from 1,2-epoxides, which does not need a reaction medium, a catalyst, dehydrating conditions, or activating steps.

Equimolar amounts of 1,2-epoxides 1a-h and thiosalicylic acid 2 were initially heated at 30-65 °C for 2-8 h in a closed vial, and then heating was continued at 100-200 °C for 1-8 h in the open vial. The corresponding 1,2-benzoxathiepin-5-ones 4a-h were produced in good to excellent yields with the exception of 4f (Table 4, entry 6).¹⁶ The results obtained are reported in Table 4.

In the cases of 1c and 1g, the conversions to 4c and 4g were only 20% and 45%, respectively, after 8 h. No improvements were observed by raising the lactonization temperature or prolonging the reaction time. These results were not completely unsatisfactory because 60%

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⁽¹⁶⁾ Preparation of **4** can be performed directly by treating the 1,2epoxides **1** with thiol **2** at the temperature and for the time reported for the lactonization process (Table 4), but sometimes slightly lower yields were obtained apparently as a result of some decomposition of **1**.

ť 1,4-benzoxathiepin-5-one Entry 1,2-Epoxide \mathbf{T}^{a} C-a/C-B Yield (° C) (h) (%)1 50-200 90 1a 6-1 4a 88/12 2 1b 50-150 4-1 85 4bα **4b**β 3 1c 30-100 43^d 8-8 4c 4 1d 60-200 2-2 1/99 85 4d $H_{13}C_{6}$ 5 1e 65-150 2 - 115/85 87 $H_{13}C_{6}$ 'n 4eβ 4eα 6 1f ÓН 4f 73^d 7 65-200 4-8 1/99 1g 4g 8 1/99 1h 65-200 89 2 - 14h

 TABLE 4. One-Pot Synthesis of 1,4-Benzoxathiepin-5-ones 4 from 1,2-Epoxides 1a-h and Thiosalicylic Acid (2) under SFC

^{*a*} Thiolysis and lactonization temperatures, respectively. ^{*b*} Thiolysis and lactonization reaction times, respectively. ^{*c*} Yield of isolated products. ^{*d*} See text. ^{*e*} Various reaction conditions.

of 3c and 40% of 3g could be recovered after silica gel column chromatography resulting in a 43% and 73%effective yield, respectively. Glycidol (1f) did not undergo any reaction at 100 °C, and at higher temperatures a very complex reaction mixture was obtained. This unfavorable result is supposedly due to the presence of the free hydroxyl functionality that causes side reactions in the lactonization step. *O*-Allyl and the *O*-phenyl analogues 1g and 1h were satisfactorily converted to the corresponding benzo[*e*]1,4-oxathiepin-5-ones 4g and 4h.

In addition, we also explored the use of β -mercaptopropionic acid (6). Under SFC, at 50 °C and in the absence of any catalyst, the reaction proceeded in 8 h, and the β -hydroxysulfide product **7** was obtained in 65% yield. After heating **7** in situ at 150 °C for 20 h, **8** was isolated in 61% overall yield from **1a** (Scheme 2). This result shows that the one-pot SFC protocol can also be conveniently applied to the thiolysis of 1,2-epoxides with aliphatic thiols.

In conclusion, by reacting 1,2-epoxides 1 with thiosalycilic acid (2) under SFC, in a one-pot procedure, benzo[e]1,4-oxathiepin-5-ones 4 were prepared in a completely diasteroselective and generally C- β -regioselective manner and with satisfactory yields. Starting materials are cheap, and only heating is needed to complete the whole synthesis. Because the procedure does not require





the use of solvent or additional catalyst, drying of glassware, or activating steps, this process is atomeconomical and particularly adequate for large-scale production. Further studies are underway to extend this synthetic strategy to polymer-supported mercapto carboxylic acids, with the intention of including this protocol in a process aimed at the construction of more architecturally complex molecules.

Experimental Section

Typical Thiolysis Procedure. Preparation of 3-[2'-(Carboxy)phenylthio]-1-phenoxy-propan-2-ol (3h). A screw-capped vial equipped with a magnetic stirrer was charged with thiosalicylic acid (2) (1.05 mmol, 0.165 g) and 2,3-epoxypropyl-phenyl ether (1h) (1.0 mmol, 0.137 mL). The resulting mixture was left under magnetic stirring at 65 °C for 2 h. After silica gel chromatography of the final mixture (3.8:6:0.2 EtOAc/Etp/AcOH) β -hydroxy sulfide 3h was isolated in 94% yield (0.286 g).

Typical Lactonization Procedure. Preparation of 3-(Phenoxymethyl)-2,3-dihydro-5*H*-benzo[*e*]1,4-oxathiepin-5-one (4h). The β -hydroxy sulfide 3h (1.0 mmol, 0.304 g) was heated in an open flask at 200 °C for 1 h. After direct silica gel chromatography of the crude solid (3:7 EtOAc/Etp), product 4h was isolated in 96% yield (0.274 g).

Typical One-Pot Synthesis of 1,4-Benzoxathiepin-5ones. Preparation of 3-(Phenoxymethyl)-2,3-dihydro-5*H*benzo[*e*]1,4-oxathiepin-5-one (4h). A screw-capped vial equipped with a magnetic stirrer was charged with thiosalicylic acid (2) (1.05 mmol, 0.165 g) and 2,3-epoxypropyl-phenyl ether (1h) (1.0 mmol, 0.137 mL). The resulting mixture was left under magnetic stirring at 65 °C for 2 h. The vial was then opened, and the reaction mixture was heated to 200 °C for 1 h. By silica gel chromatography of the final mixture (3:7 EtOAc/Etp), 4h was isolated in 89% yield (0.254 g).

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Supporting Information Available: Full characterization data (¹H NMR, ¹³C NMR, IR, GC-MS, R_f) for compounds **3b-h**, **4b-h**, **5**, **7**, and **8** coming from the reactions of **1a** with **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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