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NaOH-Catalyzed Thiolysis of α,β-Epoxyketones in Water. A Key Step in the Synthesis of Target Molecules Starting from α,β-Unsaturated Ketones

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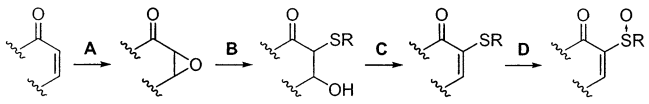
NaOH (0.02−0.3 molar equiv) is an efficient catalyst for the thiolysis reactions of α,β-epoxy ketones with alkyl and aryl thiols in water. Thiolysis of 3,4-epoxyheptan-2-one (**1**) with thiols **2a**−**d** has been accomplished in mild conditions (30 °C and pH 6 or 9) with complete C-α-regioselectivity and *anti*-stereoselectivity, and the corresponding *anti*-β-carbonyl-β-hydroxysulfides **3a**−**d** have been prepared in excellent yields (95−98%). Compounds **3a**−**d**, depending on their nature and pH conditions, have undergone dehydration, C-3 epimerization reaction, and retroaldol condensation. Dehydration of ***anti*-3a**−**d** has been chemoselectively carried out by in situ acidic treatment at 70 °C, giving stereoselectively the related (*Z*)-vinyl sulfides **4** in 89−94% overall yields. Under NaOH-catalyzed thiolysis conditions, cyclic α,β-epoxyketones **6**−**9** have shown C-α attack only and spontaneously dehydrated to furnish the corresponding vinyl sulfides in high yields (90−96%). The reactions of calchone oxide (**10**) with thiols **2b**−**d** have exclusively resulted in the formation of β-carbonylsulfides **10b**−**d** (82−93% yield), coming from the nucleophilic attack at the α-position and retroaldol condensation. To highlight the synthetic utility of this procedure, one-pot multisteps preparation of vinyl sulfides **7b** and **7c**, vinyl sulfoxides **12** and **13**, and 1,5,6,7-tetrahydro-4*H*-1,2,3-benzotriazol-4-one (**14**) starting from 2-cyclohexen-1-one (**11**) have also been reported.

Introduction

Our research is mainly devoted to the preparation of target molecules through one-pot multistep protocols.[1] Such a strategy is a very powerful tool to attain very simple workup procedures, to reduce costly labor and waste production, and to improve the chemical efficiency of a process. Water is the ideal reaction medium to succeed in this approach because it permits the manipulation of the pH of the reaction mixture allowing the reactivity of the reagents to be finely regulated. In many cases, both water and the contained inorganic catalysts can be easily recovered and reused without loss in terms of chemical efficiency.[1e,g−i,2]

In water, following a one-pot multistep approach, we have prepared a variety of target molecules. By using 1,2-epoxides as building blocks, we have recently disclosed the one-pot copper(II)-catalyzed preparation of optically active norstatines and allonorstatines[1g] and paved the route to the synthesis of 1,4-benzoxathiepinone nucleus[1h] and to the chemoselective preparation of β-hydroxysulfoxide and β-hydroxysulfones.[1i] Starting from 3-nitrocoumarins, we have accomplished an original synthesis of nitrotetrahydrobenzo[*c*]chromenones[1j] and dihydrodibenzo[*b*,*d*]furans via a one-pot five-step protocol.[1j] In all of these examples, water has been essential for the success of the syntheses.

SCHEME 1



Our current project has the aim to define a one-pot protocol for the synthesis of α-carbonyl vinyl sulfides and their sulfoxide derivatives, starting from the corresponding α,β-enones in water, via (A) epoxidation, (B) thiolysis, (C) dehydration, and (D) oxidation reactions (Scheme 1). Our intention is to employ the resulting vinylsulfoxides as Michael acceptors, dienophiles, or heterodienes in Diels−Alder reactions and as 1,3-dipolarophiles in 1,3-dipolar cycloadditions for the preparation of target molecules in aqueous medium.

As the first step within this project, we have recently reported[2f] an efficient epoxidation of α,β-unsaturated ketones by hydrogen peroxide catalyzed by NaOH or

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CTAOH in water and the preparation of α-thiophenyl-cycloxexen-2-one, in excellent yield, starting from cyclohexen-2-one by one-pot epoxidation and thiolysis/dehydration reactions. One of the trump cards of the process was the recovery of both aqueous medium and base.

The importance of vinyl sulfides in organic synthesis is well-recognized. They have been used as acceptors in the Michael addition and Peterson olefination sequence,[3] as nucleophiles in the intramolecular attack to oxonium ions,[4] as 1,3-dipolarophiles,[5] as dienophiles,[6] and as a part of diene[7] or heterodiene[8] systems. Their reactivity becomes higher when they are converted to the corresponding vinyl sulfoxides and sulfones,[9] and in particular, α-carbonylvinyl sulfides and sulfoxides are of high interest considering the wide spectrum of reactivity they can display.[9a,d,g]

α-Carbonylvinyl sulfides are prepared by different methods[10] including Pummerer-style elimination of water of the corresponding saturated sulfoxide[10a,b] and the reaction of cycloalkanones with phenylsulfenyl chloride.[10a,e] The synthesis of these molecules based on the thiolysis α,*β*-epoxy ketones has been sporadically reported, e.g., the reaction of cyclic α,*β*-epoxycycloalkenones with sodium thiolates in organic solvents.[10c,g,h] This is perhaps due to the fact that thiolysis of α,*β*-epoxy ketones (especially in the case of acyclic substrates) is generally considered to be neither regio- or stereoselective at the C-α position.[11]

To our knowledge, there is no report dealing with the reaction of thiols with α,*β*-epoxy ketones in sole water. This is surprising considering that in water 1,2-epoxides are very reactive and that a high regio- and stereoselctivity can be achieved in the nucleophilic ring-opening of the oxirane ring. In principle, the thiolysis of α,*β*-epoxy ketones in water is therefore a very promising process for significantly improving the synthesis of α-carbonyl vinyl sulfides and sulfoxides, providing that related regio- and stereoselectivity problems be solved.

In this paper, we report the first study on the NaOH-catalyzed regio- and stereoselective thiolysis of cyclic and acyclic α,*β*-epoxyketones **1** and **6**−**10** with thiols **2a**−**d** in water and its application to the one-pot synthesis of a variety of acyclic and cyclic α-carbonyl vinyl sulfides [(**Z**)-**4a**−**d**, **6b**, **7b**−**d**, **8b**−**c**, **9c**,**d**], *β*-carbonyl sulfides (**10b**−**d**), α-carbonyl vinyl sulfoxides (**12**) and (**13**), and 1,5,6,7-tetrahydro-4*H*-1,2,3-benzotriazol-4-one (**14**).

Results and Discussion

3,4-Epoxy-heptan-2-one (**1**) and thiols **2a**−**d** were chosen to investigate the thiolysis reaction in water under basic conditions.

Butylthiol (**2a**) and phenylthiol (**2b**) were selected as representative alkyl- and arylthiols. *p*-Carboxyphenylthiol (**2c**) was considered an attractive substrate because of the carboxy functionality that will imprint to the final vinyl sulfides or sulfoxides a higher solubility in water. This parameter could be essential to efficiently catalyze a reaction in water by a Lewis-acid. (1*S*)-Camphor-10-thiol (**2d**) was chosen in view of the preparation of optically active vinyl sulfides. The results of NaOH-catalyzed thiolysis of **1** with **2a**−**d** are reported in Table 1.

The pH of the reaction medium and the molar equivalents of NaOH are crucial parameters for the success of the reaction.

Butylthiol (**2a**) (pK_a = 11.40,[12a] 10.88[12b]) gave the complete conversion of **1** to ***anti*-3a** at pH 9 in just 30 min while at pH 6 a 50% conversion only was reached after 24 h (Table 1, entries 1 and 2). Phenylthiol (**2b**) ($pK_a = 6.5$[13]) showed a very high reactivity at pH 9 giving ***anti*-3b** in 30 min while at pH 6 needed 5 h to complete the reaction (Table 1, entries 4 and 5). *p*-Carboxyphenylthiol (**2c**) ($pK_a = 6$[14]) was very reactive at pH 6 giving the complete conversion in 1 h to ***anti*-3c** (Table 1, entry 7) and optically active (1*S*)-camphorthiol (**2d**) ($pK_a = 9.39 \pm 0.2$[15]) gave the clean product ***anti*-3d** in 8 h at pH 9 (Table 1, entry 10).

By using 0.02−0.3 molar equiv of NaOH, the thiolyses of **1** with thiols **2a**−**d** in water at 30 °C and at pH 6−9 were very fast (0.25−8 h) and completely α-regio- and *anti*-stereoselective, exclusively giving *anti*-*β*-hydroxy sulfides **3a**−**d** with excellent yields (95−98%) (Table 1, entries 2, 6, 7, and 10).[16]

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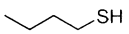
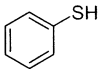
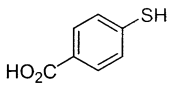
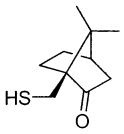
(15) The value is calculated using Advanced Chemistry Development (ACD Software Solaris V4.76). Due to its low solubility in water, the real pK_a value is expected to be higher. (1*S*)-Camphorthiol is completely soluble in water at pH ≥ 13 in 0.5 M concentration.

TABLE 1. Thiolysis of 3,4-Epoxyheptan-2-one (1) by Thiols 2a−d in Water at 30 °C

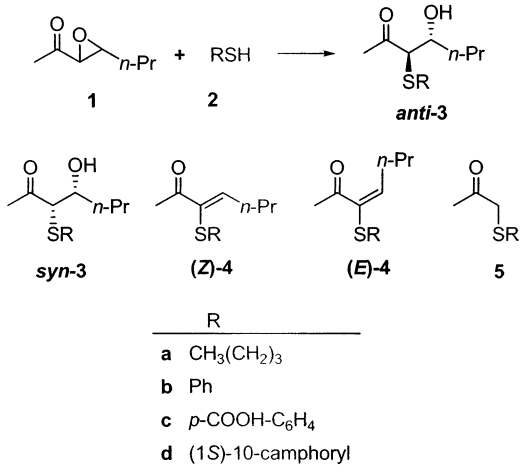
Entry	Thiol[a]	pH	NaOH[b]	Time[c]	Products[d]					Yield[e]
			(molar equiv)	(h)	*anti*-3	*syn*-3	(*Z*)-4	(*E*)-4	5	(%)
1	 **2a**	6	0.015	24[f]	100	0	0	0	0	-
2		9	0.025	0.5	100	0	0	0	0	98
3		12	0.10	0.25	80	20	0	0	0	-
4	 **2b**	6	0.025	5	100	0	0	0	0	95
5		9	0.3[g]	0.5	100	0	0	0	0	97
6		12	0.3	0.25	13	8	55	< 1	24	-
7	 **2c**	6	0.3	1	100	0	0	0	0	98
8		9	1.2	0.5			-[h]			-
9		12	2.0	0.1			-[h]			-
10	 **2d**	9	0.02	8	100	0	0	0	0	98
12		12	0.10	8	18	0	9	0	73	67[i]

[a] 1.05 molar equiv. [b] The amount of NaOH reported in the table is added at once. [c] Reaction time relative to a conversion >99%. [d] Ratios evaluated by ^{1}H NMR analysis. [e] Yield of the isolated crude product. [f] Reaction conversion: 50%. [g] NaOH was added slowly maintaining the pH around 9.0 (see the Experimental Section). [h] Mixture of ***syn***- and ***anti*-3c**, **-4c**, and **-5c** for which ratios could not be correctly measured. [i] Yield of the isolated pure product **5d** after chromatographic purification.

A catalytic amount of NaOH is sufficient to complete the reaction, because while the thiolysis is proceeding, the ring-opening of the 1,2-epoxide leads to the formation of an alkoxide ion which is responsible for further basification of the reaction medium.

Under more basic conditions (NaOH 0.10−2.0 molar equiv), the thiolyses of **1** were not selective due to the high instability of compounds ***anti*-3a−d** already at 30 °C that, to different extents, underwent to epimerization reaction at the C-3, to retroaldol condensation[17] and to dehydration reaction generally giving complex mixtures of products (***syn***- and ***anti*-3a−d**, **4a−d**, and **5a−d**) (Scheme 2). Thus, while at pH 12 ***anti*-3a** gave only a partial C-3 epimerization with the formation of a 4:1 mixture of ***anti*-3a** and ***syn*-3a** (Table 1, entry 3), the hydroxyl sulfide ***anti*-3c** quickly decomposed and already at pH 9.0 a complex mixture of products was obtained. By ^{1}H NMR analysis, ***syn***- and ***anti*-3c**, **-4c**, and **-5c** were identified but overcrowded signals due to additional decomposition products hampered the correct percentage

SCHEME 2. Products Obtained from the Reaction 3,4-Epoxyheptan-2-one (1) with Thiols 2



assignment for each compound (Table 1, entries 8 and 9, respectively). At pH 12, thiolysis of **1** with **2b** (Table 1, entry 6) predominantly gave dehydration of ***anti*-3b** to form the olefin **(*Z*)-4b** (55%), plus ***syn*-3b** (8%) and **5b** (24%) coming from the epimerization and retroaldol reactions respectively). Compound ***anti*-3d** at pH 12 evolved preferentially to give retroaldol condensation product **5d** (73%, Table 1, entry 12); the epimerization did not occur while dehydration product **(*Z*)-4d** was only 9% of the compounds' mixture.

The NaOH-adding procedure is also important. Indeed, the reactions of **1** with thiols **2a**, **2c**, and **2d**, were

(16) We have also considered the possibility of a Brønsted acid catalysis and we have performed the thiolsysis of **1** with **2a** and **2b** at pH 2.0. After 24 h at 30 °C **2a** gave complete conversion to ***anti*-3a**, while after 72 h **2b** gave 90% conversion to ***anti*-3b**. This result can be justified on the basis of the higher nucleophilicity of alkylthiol with respect to aryl ones.

(17) β-Hydroxy-α-thiophenyl cyclohexanones derivatives, upon treatment with strong bases (ethylthiolate or methoxide ions or lithium diisopropylamide) in organic solvents, give exclusive retroaldol condensation. It is also reported that C-α epimerization under strong base conditions (ethylthiolate or methoxide ions) occurs via retroaldol condensation: (a) Caine, D.; Crews, E.; Salvino, J. M. *Tetrahedron Lett.* **1983**, *24*, 2083−2086. (b) Silvermann, R. B. *J. Am. Chem. Soc.* **1981**, *103*, 3, 5939−5941.

TABLE 2. Basic Treatment of β-Hydroxy Sulfides *anti*-3a−d

entry	hydroxy sulfide	pH	*T* (°C)	products[a] (*Z*)-4	(*E*)-4	5
1	**3a**	9	70	26	14	60
2	**3a**	13	30[b]	40	9	51
3	**3b**	9	70	67	<1	33
4	**3b**	13	30	83	0	17
5	**3c**	9	70	100[c]	0	0
6	**3c**	13	30	nd[d]		
7	**3d**	9	70[b]	33	13	54
8	**3d**	13	30[b]	37	13	50

[a] Ratios evaluated by ^{1}H NMR analysis. [b] 24 h. [c] Isolated as a crude product in 92% yield. [d] Only decomposition products were formed.

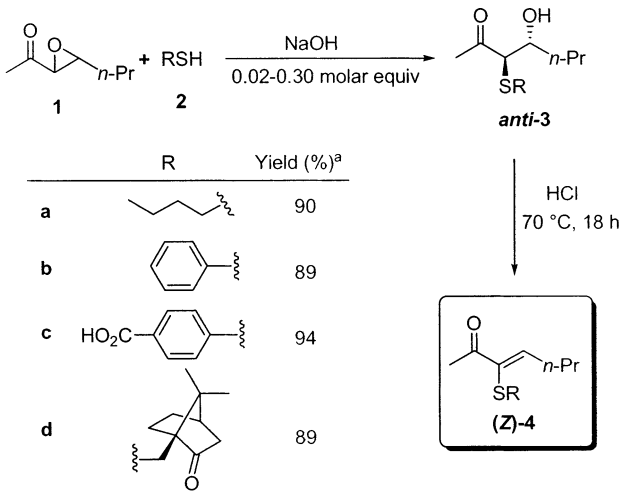
performed by adding at once the amount of NaOH (as 0.1 or 1 M aqueous solution) to the mixture of reagents and the pH remained approximately the same during all the reaction time. Differently, in the thiolysis of **1** with **2b** better results were obtained by adding dropwise the aqueous base (0.3 molar equiv) and maintaining the pH around 9 for all the reaction time (Table 1, entry. 5).

We have also checked the possibility to selectively convert the *anti*-α-carbonyl-β-hydroxy sulfides **3a**−**d**, prepared at pH 6−9 (Table 1), into vinyl sulfides **4a**−**d** and α-carbonyl sulfides **5a**−**d** by dehydration or retroaldol condensation, respectively.

Basic treatment of ***anti*-3a**−**d** at different temperatures always gave mixtures of products except in the case of substrate ***anti*-3c**, where only vinyl sulfide **(*Z*)-4c** was formed after heating at 70 °C at pH 9.0 (Table 2). E1cb dehydration was prevalent in the case of aryl thiols while a slightly preferential formation of retroaldol product was obtained for alkanethiols.

***anti*-3a**−**d** at 70 °C under acidic conditions selectively gave vinyl sulfides **(*Z*)-4a**−**d** in satisfactory yields (Scheme 3).[18] This result allowed the preparation of (*Z*)-**4a**−**d** to be carried out by a one-pot procedure starting from α,β-epoxy ketone **1** (Scheme 3). The *Z*-configuration of the compounds **(*Z*)-4a**−**d** has been confirmed by NOESY experiments, and H^1 NMR data are in agreement with the results obtained by Warren et al.[10b] It must be noticed that while under basic conditions a mixture of *E*/*Z* alkenes were obtained, under acidic conditions a complete *Z*-stereoselectivity was found. This can be justified considering that under acidic conditions the anchimeric assistance of sulfinyl group to form a thiiranium intermediate species, is very efficient giving a resulting *cis*-elimination and then a complete *Z*-stereoselectivity while, under basic conditions and in the case of alkylsulfinyl group (**3a**,**d**), presumably a competition of an E1cB and E2 mechanisms acted to give a mixture of *Z*- and *E*-alkenes.

SCHEME 3. One-Pot Synthesis of (*Z*)-4a−d by Thiolysis of 1



[a] From **1** after chromatography.

The investigation was then extended to the thiolysis of α,β-epoxycycloalkenones **6**-**8**, 2-methyl-1,4-naphthoquinone oxide (**9**) and calchone oxide (**10**) with thiols **2b**−**d**, and the results are reported in Table 2. The thiolsyses of compounds **6**−**9** proceeded, again under basic conditions, by using a catalytic amount of NaOH (0.1−0.3 molar equiv) at 30 °C with exclusive nucleophilic attack at C-α, but in these cases the thiolysis reactions were always accompanied by the dehydration of the resulting β-hydroxy sulfides to give the corresponding vinyl sulfides **6b**, **7b**−**d**, **8b**,**c**, and **9c**,**d** (Table 3, entries 1−8) in excellent yield. The only exception was the thiolysis of **8** with thiol **2b** that required reflux conditions for 1 h to have a complete dehydration.[20] 1,2-Epoxide **9** was almost totally insoluble in aqueous medium, but its high reactivity allowed the products **9c** and **9d** to be obtained in very short reaction times already at 30 °C.

Calchone oxide **(10)** showed a peculiar behavior. This substrate is very insoluble in water and poorly reactive at 30 °C. At 70 °C, thiolyses of **10** with **2b**−**d** were accomplished, but only the products **10b**−**d** deriving from the retroaldol reaction were isolated; thus, under aqueous basic conditions thiols **2b**−**d** attached the α-position of calchone oxide (**10**). According to our previous experience where CTAOH or CTABr/NaOH systems promoted the epoxidation of highly insoluble calchone,[2f] we found that using CTAOH and CTABr/NaOH (0.3 molar equiv) at 30 °C, instead of NaOH, **10b** and **10c** were isolated in almost quantitative yield after 12 h (Table 3, entries 10, 11, 13, and 14).

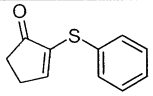
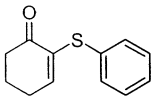
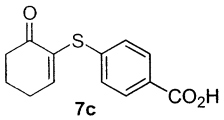
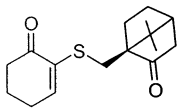
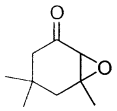
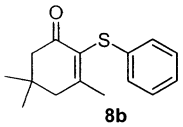
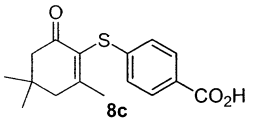
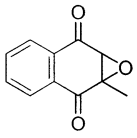
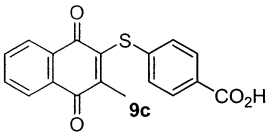
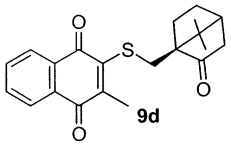
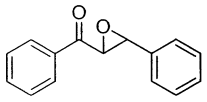
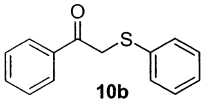
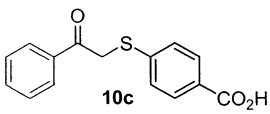
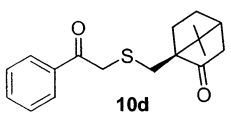
Then we moved to investigate the synthetic utility of the protocol and we focused our attention to the one-pot synthesis in water of vinyl sulfides **7b** and **7c**, vinyl sulfoxides **12** and **13,** and 1,5,6,7-tetrahydro-4*H*-1,2,3-benzotriazol-4-one (**14**) starting from cyclohex-2-en-1-one (**11**) (Scheme 4).

(18) The dehydration of β-hydroxy sulfides has been generally performed under acidic conditions by using 20 mol % of *p*-toluensulfonic acid (*p*-TsOH) in organic solvent.[19] We have studied separately this step starting from the corresponding pure β-hydroxy sulfides, by using in water H_2SO_4 or HCl at 70 °C, 18 h, and in CH_2Cl_2 20 mol % of *p*-TsOH at reflux for 10 days. H_2SO_4 gave lower yields due to some carbonization, while *p*-TsOH gave excellent results in conditions apparently milder than those utilizing HCl but with a very long reaction time. In this work, we have preferred the aqueous HCl procedure that allowed the one-pot protocol to be realized, and the use of *p*-TsOH is indeed viable.

(19) Fox, D. J.; House, D.; Warren S. *Angew. Chem., Int. Ed.* **2002**, *41* 2462−2482.

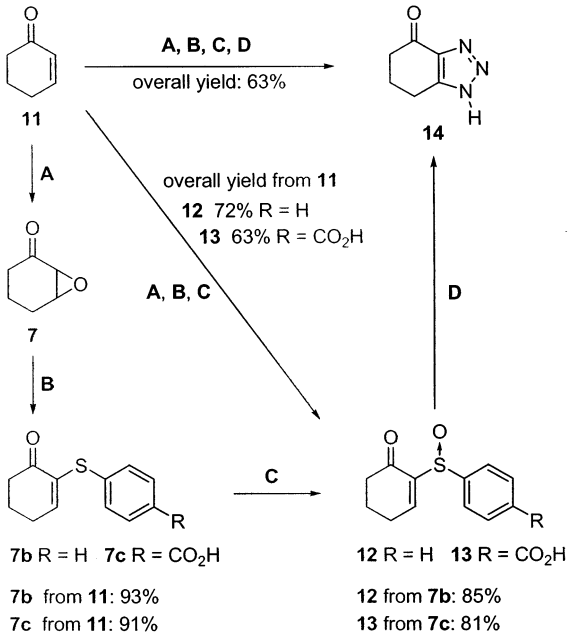
(20) At 30 °C after 1 h a 3:1 mixture of hydroxy sulfide and vinyl sulfide was isolated. After heating to reflux for an additional 1 h, only vinyl sulfide product was obtained.

TABLE 3. Thiolysis of α,β-Epoxy Ketones 6−10 in Water at 30 °C

Entry	α,β-Epoxy Ketone	Thiol[a]	pH	NaOH (molar equiv)	Time (h)	Products	Yield[b] (%)
1	 **6**	**2b**	9	0.3	0.5	 **6b**	95
2	 **7**	**2b**	9	0.3	0.5	 **7b**	96
3	**7**	**2c**	6	0.3	1	 **7c**	95
4	**7**	**2d**	9	0.1	0.25	 **7d**	93
5	 **8**	**2b**	9	0.3	2[b, 17]	 **8b**	90
6	**8**	**2c**	9	0.5	1	 **8c**	95
7	 **9**	**2c**	-[c]	0.1	4	 **9c**	95
8	**9**	**2d**	-[c]	0.025	1	 **9d**	91
9	 **10**	**2b**	-[c, d]	0.3	1[e]	 **10b**	93
10			CTAOH	0.3	12		92
11			CTABr/NaOH	0.3	12		92
12			-[c, d]	0.3	7[e]		95
13	**10**	**2c**	CTAOH	0.3	12		93
14			CTABr/NaOH	0.3	12	 **10c**	92
15	**10**	**2d**	-[c] 0.02		24[e]	 **10d**	82

[a] Yield of the isolated pure product. [b] 1 h at 30 °C and 1 h at reflux. [c] The reaction mixture is highly heterogeneous, and the pH measurement is hardly trustful. [d] After 24 h at 30 °C, no conversion at all. [e] Reaction performed at 70 °C.

SCHEME 4. Single-Step and One-Pot Synthesis of 7b, 7c, and 12−14[a]



[a] Key: (A) H_2O_2/H_2O, 1−3 °C, 30 min, startiong pH 12;[21] (B) (i) thiol **2b** (R = H), 30 °C, pH 9.0, 0.5 h, (ii) thiol **2c** (R = CO_2H), 30 C, pH 6.0, 1 h (see Table 2); (C) Na_5IO_6, 30 °C, (i) 3 h (R = H), (ii) 1 h (R = CO_2H); (D) $NaNH_3$, pH 7.0, 30 °C, 3 h, 91%.

First, the oxidation of vinyl sulfoxides and 1,3-dipolar cycloaddition of **12** in sole water (Scheme 4, steps C and D) were investigated. Step A was previously reported,[2f] and step B has been just defined.

Vinyl sulfides **7b** and **7c**, treated with sodium periodate in water at 30 °C, gave the corresponding vinyl sulfoxides **12** and **13** in 85 and 81% yields, after 3 and 1 h respectively (step C, Scheme 4). Vinyl sulfoxide **12** showed a very high reactivity when treated with sodium azide at 30 °C in water, giving the 1,3-dipolar cycloaddition in 3 h only and affording, after elimination of phenylsulfenyl acid, the corresponding 1,5,6,7-tetrahydro-4*H*-1,2,3-benzotriazol-4-one (**14**) in 91% yield (step D, Scheme 4).

Vinyl sulfides **7b** and **7c** were then prepared starting from the α,*β*-enone **11** via consecutive one-pot epoxidation and thiolysis/dehydration in 93% and 91% overall yields (Scheme 4). By submitting to sodium periodate oxidation the reactions mixtures coming from **11** and containing **7b** or **7c**, vinyl sulfoxides **12** or **13** were prepared in 72% and 63% overall yield, respectively, by a one-pot procedure. When the one-pot protocol was continued, triazole **14** was obtained directly starting from cyclohex-2-en-1-one (**11**) in a very good 63% overall yield (Scheme 4).

All new compounds have been fully characterized and their structures confirmed by standard analytical and spectroscopic methods (see the Experimental Section and the Supporting Information).

Currently, studies on the extension of this reaction and on the applications of α-aryl- and alkylsulfenylalkenones are ongoing in our laboratory.

In conclusion, we have reported a study on the influence of the pH on the thiolysis of α,*β*-epoxyketones in water and we have found that NaOH can be used in catalytic amount (0.02−0.30 molar equiv) to efficiently promote the thiolysis of cyclic and acyclic α,*β*-epoxy ketones with a variety of alkyl- and arylthiols. The use of a catalytic amount of base avoids side reactions to be triggered and allows a complete regio- and stereoselectivity to be attained. These results make possible the use of the thiolysis of α,*β*-epoxy ketones for an efficient synthesis of α-carbonyl vinyl sulfides.

While thiolysis of cyclic α,*β*-epoxy ketones **6**−**9** gave the corresponding vinyl sulfides directly, the hydroxyl sulfides **3a**−**d** coming from 3,4-epoxyheptan-2-one (**1**) required an additional acidic treatment to obtain an efficient dehydration process.

One-pot multistep protocols in water to prepare α-carbonyl sulfoxides and triazole **14** starting from cyclohex-2-en-1-one (**11**) in very good yields have also been reported. Water has confirmed its efficiency as reaction medium and that its unique properties can give a very good contribution for improving the ecocompatibility of organic synthesis.

Experimental Section

Typical Thiolysis Procedure: Preparation of *rel*-(3*R*,4*R*)-3-Butylthio-4-hydroxyheptan-2-one (3a). A 189 mg (2.1 mmol) portion of butylthiol (**2a**) was added to 3.75 mL of water and 0.25 mL of NaOH 0.1 M aqueous solution to obtain a resulting pH = 9.0. Then after 5 min, 256 mg (2.0 mmol) of 3,4-epoxyheptan-2-one (**1**) was added, and after an additional 0.5 h under vigorous magnetic stirring at 30 °C, the reaction mixture was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under vacuum to give the crude hydroxysulfide. **3a** was isolated as an oil in ≥98% purity by silica gel column chromatography (Etp/AcOEt: 8:2 (gradient), silica/sample: 30:1) in 94% yield.

Typical One-Pot Synthesis of an Acyclic Vinyl Sulfide: Synthesis of (*Z*)-3-(Butylthio)hepten-2-one ((*Z*)-4a). A 189 mg (2.1 mmol) portion of butylthiol (**2a**) was added to 3.75 mL of water and 0.25 mL of NaOH 0.1 M aqueous solution to obtain a resulting pH = 9.0. Then after 5 min, 256 mg (2.0 mmol) of 3,4-epoxyheptan-2-one (**1**) was added, and after an additional 0.5 h under vigorous stirring at 30 °C, 0.4 mL of concd HCl was added and the reaction mixture warmed to 70 °C. After 18 h, the reaction mixture was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (1 × 5 mL), dried over Na_2SO_4, and evaporated under vacuum to give the title vinyl sulfide. **(*Z*)-4a** was isolated as an oil in ≥98% purity by silca-gel column chromatography (Etp/AcOEt: 9:1 (gradient), silica/sample: 20:1) in 90% yield: oil; R_f = 0.33 (Etp/AcOEt 9:1); IR ($CHCl_3$, cm^{-1}) 1213 (s), 1358 (w), 1461 (w), 1593 (w), 1675 (s), 2873 (w), 2933 (m), 2965 (s), 3019 (w); ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, 3H, J = 7.2 Hz), 0.95 (t, 3H, J = 7.4 Hz), 1.30−1.55 (m, 6H), 2.39 (s, 3H), 2.47 (q, 2H, J = 7.4 Hz), 2.61 (t, 2H, J = 7.4 Hz), 6.98 (t, 1H, J = 7.4 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.5, 13.921.7, 21.8, 27.0, 31.9, 32.8, 33.2, 137.2, 150.0, 197.3; GC−MS (EI, 70 eV) *m*/*z* 200 (M^+, 100), 157 (25), 143 (28), 115 (33), 95 (29), 67 (30), 43 (69). Anal. Calcd for $C_{11}H_{20}OS$ = C, 65.95; H, 10.06. Found: C, 65.98; H, 10.15.

One-Pot Synthesis of 1,5,6,7-Tetrahydro-4*H*-1,2,3-benzotriazol-4-one (14). A 0.196 g (2.0 mmol) portion of cyclohex-2-en-1-one (**11**) and 0.25 mL (0.5 molar equiv) of 2 M NaOH aqueous solution were added to 1.62 mL of water at 0−2 °C. After the mixture was stirred at this temperature for 10 min, 0.13 mL (1.1 molar equiv) of 35 wt % aqueous hydrogen peroxide was added (pH ∼11). After 0.5 h, 0.215 mL (1.15 molar equiv) of thiophenol was added at 30 °C (pH ∼9), and the stirring was continued for 30 min. At this stage, 928 mg of powdered $NaIO_4$ (2.0 molar equiv) was added and the

reaction mixture left under stirring at 30 °C. After 3 h, NaN_3 (200 mg, 1.1 molar equiv) was added and the pH of the reaction mixture adjusted to 7.0 by adding some drops of H_2SO_4 1 M aqueous solution. After 3 h at 30 °C, the reaction mixture was acidified to pH 2.0 and extracted with three 10 mL portions of ethyl acetate. The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to give the title product in 63% overall yield. The product was recrystallizated from acetone: white crystals; mp = 226−227 °C; R_f = 0.25 (absolute AcOEt); IR (Nujol, cm^{-1}) 3205 (m broad), 2944 (m), 2889 (m), 1666 (s), 1477 (m), 1077 (w), 992 (w), 846 (w); ^{1}H NMR (400 MHz, DMSO-d_6, 303 K) δ 2.04 (quintet, 2H, J = 6.2 Hz, H-6), 2.48 (*t*, 2H, J = 6.2 Hz, H-7), 2.89 (*t*, 2H, J = 6.2 Hz, H-5); ^{13}C NMR ((400 MHz, DMSO-d_6, 330 K) δ 19.8, 22.7, 38.4, 139.4, 148.1, 190.2; GC−MS (EI, 70 eV) *m*/*z* 137 (76), 109 (100), 108 (43), 80 (33), 53 (62), 52 (55). Anal. Calcd for $C_6H_7N_3O$: C, 52.55; H, 5.14; N, 30.64. Found: C, 52.59; H, 5.32; N, 30.80.

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Supporting Information Available: Full characterization charts (^{1}H NMR, ^{13}C NMR, IR, GC−MS, R_f) for compounds ***anti*-3a−d**, **(*Z*)-4a−d**, **7c**,**d**, **8b**,**c**, **9c**,**d**, **10c**,**d**, **13**, and **14** and significant spectral ^{1}H and ^{13}C NMR signals for compounds **5a**,**d** and ***syn*-3a**,**b**,**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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