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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 3047–3051

Diasterodivergent synthesis of optically pure vinyl episulfides and β-hydroxy thiocyanates from a bacterial metabolite

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Received 20 December 2006; revised 22 February 2007; accepted 24 February 2007
Available online 1 March 2007

Abstract—Diasterodivergent episulfides were chemoenzymatically derived from bromobenzene by sequential toluene dioxygenase dihydroxylation, followed by chemical epoxidation and thiolysis. The epoxide ring-opening by thiocyanate ion under literature conditions rendered the corresponding hydroxy thiocyanates and not the thiiranes as usually observed. Ring closing under carefully optimized conditions allowed the preparation of optically pure thiiranes that are key precursors for the preparation of thiocondu-ritols and pseudodisaccharides.

Thiiranes, the simplest sulfur heterocycles, play an increasing pivotal role in organic synthesis as versatile building blocks in asymmetric reactions.[1] Moreover, they are used as intermediates in the pharmaceutical, polymer, pesticide, and herbicide industries.[2] Although there are many methods reported in the literature for the preparation of thiiranes,[3] the most general route is the conversion of oxiranes to thiiranes by an oxygen–sulfur exchange reaction.[4] Various sulfur introducing reagents such as inorganic thiocyanates or thiourea,[5] phosphine sulfide,[6] 3-methylbenzothiazole-2-thione,[7] dimethylthioformamide in the presence of trifluoroacetic acid,[8] silica gel supported KSCN,[9] low hydrated KSCN-liquid heterogeneous media,[10] indium halides/KSCN[11] and polymeric cosolvent/NH_4SCN[12] together with reactions performed in solvent-free conditions[13] and ionic liquids[14] have been reported. It has also been pointed out that ceric ammonium nitrate (CAN),[15] $RuCl_3$,[16] $BiCl_3$,[17] $TiO(CF_3CO_2)_2$,[18] $TiCl_3(CF_3SO_3)$,[19] as well as 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride)[20] can efficiently catalyze the conversion of epoxides to thiiranes. Even though there are various methods for the preparation of episulfides, the 'thiocyanate procedure' remains the method of choice for epoxides having reasonable S_N2 reactivity.

In continuation with our previous studies on the ring opening of vinyl oxiranes with different nucleophiles,[21] we now wish to report the resu'lts obtained by treating diasteromeric epoxides **3** with ammonium or potassium thiocyanate under several conditions. Along this study, we have developed an efficient and simple route for the preparation of the previously unknown β-hydroxy thiocyanates **4** and their corresponding thiiranes **5**. These compounds will be used in the preparation of sulfur containing analogs of cyclitols and pseudoglycosides (see Scheme 1).

The known epoxides **3a**[22] and **3b**[23] are available in two or three steps, respectively, from homochiral metabolite **1** produced by whole-cell fermentation of bromobenzene with *Pseudomonas putida* F39/D.[24] *cis*-Dienediol **1** was protected as its corresponding acetonide **2** with 2,2-dimethoxypropane and the more reactive double bond was either oxidized directly with *m*-chloroperbenzoic acid to furnish the α-oxirane or subjected to a bromination and ring-closure sequence so as to obtain the β-epoxide as previously described.[22,23,25] With both epoxides in hand, we treated them under several ring-opening conditions as shown in Table 1 in order to optimize the synthesis of deoxycyclitol precursors **4** and **5**.

The reaction of epoxides with inorganic thiocyanates is well studied and proceeds along the mechanism depicted in Scheme 2 (illustrated for the formation of **5a**).[5c,26]

The first two-steps in the sequence are fast while the last two-steps take place at a very slow rate. A literature precedent,[27] as well as our previous experience in the regiospecific ringopening of vinyl epoxides **3**,[21] indicated

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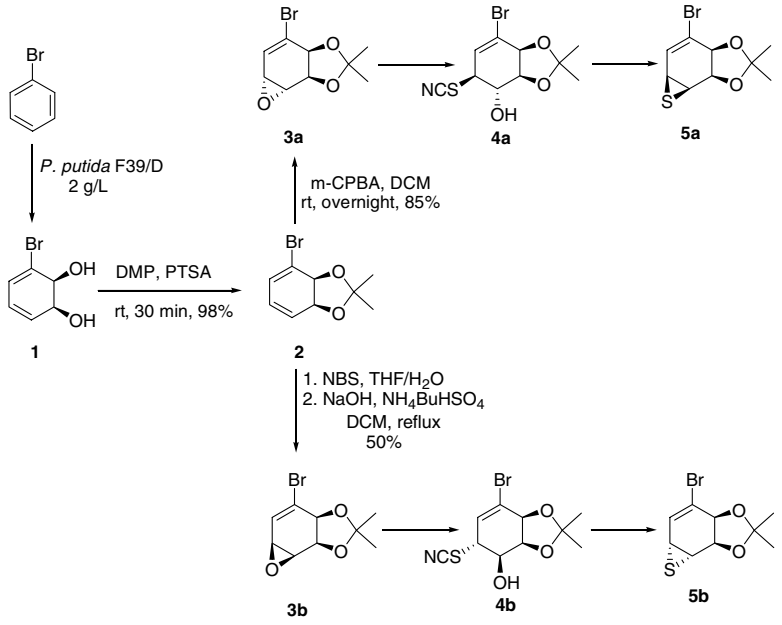
doi:10.1016/j.tetlet.2007.02.113

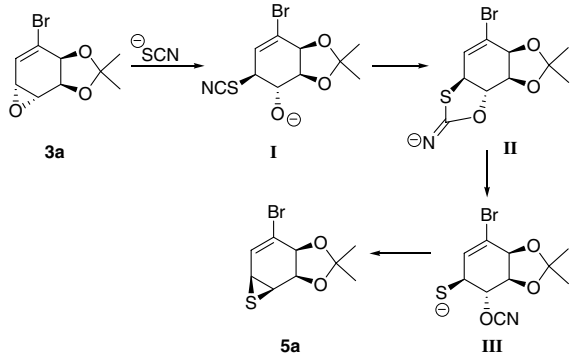


Scheme 1. Synthesis of diasteromeric β-hydroxy thiocyanates **4** and their corresponding thiiranes **5**.

Table 1. Thiocyanation of epoxide **3a** under various conditions

Entry	Catalyst	Solvent, temp, time	Yield (%) **4a**/**5a**
1	$RuCl_3$ 20%	CH_3CN, rt, 4 h	84/—
2	CAN 20%	*t*-BuOH, rt, 15 min	62/—
3	$Yb(OTf)_3$ 10%	CH_3CN, rt, 8 h	75/—
4	$Yb(OTf)_3$ 30%	CH_3CN, rt, 4 h	79/—
5	$Yb(OTf)_3$ 10%	DCM, rt	No reaction
6	$Yb(OTf)_3$ 30%	DCM, rt	No reaction
7	—	CH_3CN, rt, 4 h	85/—
8	—	*t*-BuOH, rt, 1 h	74/—
9	—	EtOH–H_2O, rt, 24 h	45/45
10	—	EtOH–H_2O, 70 °C, 1 h	45/45[a]
11	—	EtOH–H_2O, reflux, 1 h	25/50[a]
12	NaOH pH: 9	EtOH–H_2O, rt, 30 min	45/45
13	NaOH pH: 9	EtOH–H_2O, 70 °C, 30 min	45/45[a]
14	NaOH pH: 9	EtOH–H_2O, 90 °C, 30 min	—/40[a]
15	NaOH pH: 10	EtOH–H_2O, reflux, 15 min	—/60–70[a]

[a] Significant amounts of polar material were formed in these reactions.



Scheme 2. Accepted mechanism for the oxirane–thiirane conversion.

that the regiochemistry of the attack is controlled by stereoelectronic effects, directed to the allylic position as we experimentally observed. Overall, the entire reaction is accompanied by Walden inversion at both of the two C atoms of the ring.

When we tested the reaction on epoxides **3**, we initially observed that the main products isolated from the reaction medium were hydroxy thiocyanates **4** derived from an intermediate of type I (Scheme 2). This is unusual, because in most systems the anion I is rapidly converted into the corresponding thiirane.[5c,15,16,19,28] Furthermore, there are few methods reported in the literature for the synthesis of β-hydroxy thiocyanates from the corresponding epoxides.[26,29] Although the hydroxy thiocyanates themselves are of potential interest to our project, we tested different reaction conditions in order to complete the transformation and furnish the desired episulfides.

Most of the experiments were performed on α-epoxide **3a**, and the complete results are shown in Table 1. In all of the reactions conducted at room temperature and without the addition of a base, we observed that the corresponding β-hydroxy thiocyanate was formed as the main product, and the best yield was obtained in the absence of a catalyst (entries 1–9).

The use of $RuCl_3$ as catalyst allowed the formation of **4a** in higher yield than the use of CAN, however, the time was significantly longer. $Yb(OTf)_3$, a catalyst that had been successfully used by us for the reaction of epoxide **3a** with thiophenol[21a] seemed to be less efficient than Ru(III) to render thiocyanohydrin **4a** and this reaction did not proceed at all when it was carried out in DCM as solvent. The results obtained performing the reactions in the absence of a catalyst were similar or superior to the ones run in the presence of a Lewis acid (entries 7–9). This led us to conclude that a catalyst was not necessary in this reaction. Furthermore, entry 9 shows that if

the reaction is run in EtOH–H_2O at room temperature, an equimolecular amount of thiocyanohydrin and episulfide is obtained. This result encouraged us to carry out the reaction at reflux to facilitate the conversion of **3a** into **5a** in spite of the fact that it is well documented that polymerization might occur under those conditions.[5c,30]

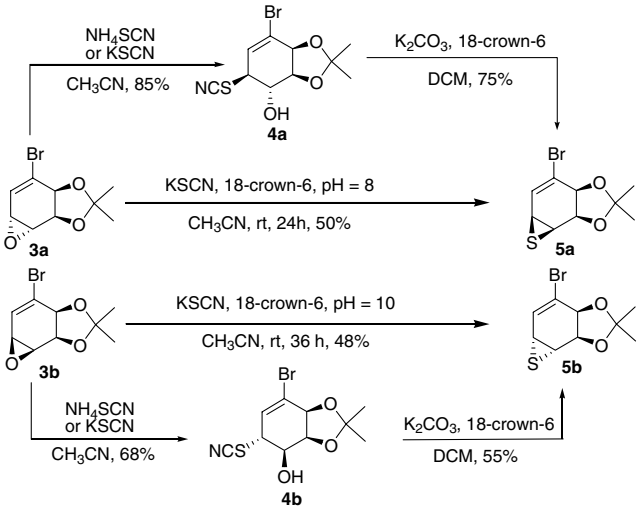
The observed result indicated that a higher reaction temperature did not increase the yield of cyclized product and the episulfide was obtained contaminated with variable amounts of polar unidentified material (entries 10 and 11). We reasoned that **4a** could be converted to **5a** using an aqueous base in order to enhance the nucleophilicity of the oxygen atom in intermediate I.[31] Therefore, we increased the pH in the reaction medium. Under moderate basic conditions (pH = 9, 10) and particularly above room temperature, the hydroxy thiocyanate was consumed and the yield of episulfide tend to increase. However, the formation of undesired products was observed particularly if the reaction was run at elevated temperature (entries 12–15). These results showed that in this aqueous medium, delicate pH control is very important so as to obtain a high yield of the desired thiirane. As a consequence, the yield shown in entry 15 exhibited low reproducibility and the amount of polymerized material varied among different runs.

In the search of more reproducible reactions, free of polar by-products, we turned our attention to a two-step procedure with isolation of the particularly stable thiocyanohydrin **4a**. Therefore, we subjected the isolated thiocyanate to different basic conditions in order to attempt its cyclization. The most interesting results are summarized in Table 2.

We initially treated the thiocyanohydrin with the same conditions that provided the best results in the direct conversion of the epoxide: moderate base and EtOH–H_2O as solvent system. Again, the cyclization did not occur in good yield at room temperature and heating the reaction mixture or increasing the amount of base used caused the destruction of the material. In addition, a new product was observed in this reaction. The compound was identified as the α-epoxide **3a**, presumably formed by reversion of the desired cyclization process with the oxyanion attacking the C-6 and the thiocyanide ion acting as the leaving group.[32] At this point, we decided to try two alternatives of phase transfer catalysis: ammonium salts and crown ether catalysis, both in a weakly polar solvent such as DCM. The tetrabutylammonium salt furnished compound **5a** in 45% yield accompanied with the usual decomposition material and 15% epoxide formation. On the other hand, the crown ether catalyzed reaction delivered the product in 10 min at room temperature, in 75% yield without signs of decomposition and with only traces of epoxide **3a** (entry 5). A parallel experiment run in the absence of 18-crown-6 just afforded recovered starting material. This result prompted us to reconsider a one-pot procedure, using the combined power of the crown ether catalysis and the unusual high yield obtained for the formation of β-hydroxy thiocyanate when the reaction is performed in a polar solvent.

Consequently, we studied the direct room temperature oxirane–thiirane conversion of epoxides **3** exposing the compounds to potassium thiocyanate in the presence of 18-crown-6. We found that the reaction is feasible but the desired compound is obtained in slightly lower yield in one-pot than in the stepwise procedure (Scheme 3). Interestingly, β-epoxide **3b** needed longer reaction times and a higher pH to complete the reaction. This fact might be explained by the different stability of the intermediates in the mechanism conducting to the thiiranes.

The results obtained from spectroscopic data are in complete agreement with those reported for thiirane rings.[33] As a whole; the spectral features of these episulfides are similar to those of the corresponding epoxides except for the signal positions of the three-membered ring carbons. An epithio group shows larger shifts than the corresponding epoxy group, and the differences $\Delta\lambda$ between the protons on the episulfide ring are generally smaller than for the corresponding epoxides.[34]



Scheme 3. Hydroxy thiocyanate and episulfide synthesis.

Table 2. Ring-closing formation of episulfide **5a** from thiocyanohydrin **4a**

Entry	Catalyst	Solvent, temp, time	Yield (%) **3a**/**5a**
1	K_2CO_3 (1 equiv)	EtOH–H_2O, 50 °C, 10 min	7/45
2	K_2CO_3 (3 equiv)	EtOH–H_2O, reflux, 30 min	dec.
3	K_2CO_3 (1.5 equiv)	DCM, rt, 3 h	No reaction
4	NaOH/HSO_4NBu_4	DCM, reflux, 3 h	15/45/dec.
5	K_2CO_3 (1.5 equiv)/18-crown-6	DCM, rt, 10 min	5/75

These results show that the nucleophilic ring-opening of epoxide **3a** with a thiocyanate ion under standard conditions generates thiocyanohydrin **4a** as the major product instead of episulfide **5a** as it would be expected in agreement to literature procedures.[15,16,26,35] Nevertheless, the hydroxy thiocyanates can be cyclized into the corresponding thiiranes or, alternatively, the epoxides can be directly converted in episulfides if the appropriate conditions of temperature, pH, solvent and catalysts are applied as above described. Both isomers of compounds **4** and **5** are precursors of unknown deoxygenated thioconduritols and thioinositols. These compounds are currently being synthesized in our laboratory to be included in a library of cyclitols and tested as glycosidase inhibitors. The complete account of the synthesis and biological testing results for the whole library will be reported in due course.

Acknowledgements

The following organizations contributed to support this work: the International Foundation for Science (IFS Grant F/3078-2) and DINACYT (Project FCE8068). A.B. is grateful to PEDECIBA and DINACYT for a Doctoral Fellowship. The authors acknowledge Mr. Horacio Pezzaroglo for recording the NMR spectra.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.113.

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episulfide), 37.8 (C4, episulfide), 73.5 (C5), 76.2 (C6), 109.9 (C), 120.2 (C1), 132.9 (C2); Anal. found C, 41.29; H, 4.25; calcd for $C_9H_{11}BrO_2S$ C, 41.08; H, 4.21. Compound **5b**: White crystalline solid; mp 95.5–97.5 °C; $[\alpha]_D^{20}$ +93.1 (*c* 0.55, CH_2Cl_2); IR (KBr): ν_{max} 1378.3, 1228.8, 1053.3, 625.0 (C–S) cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 1.46 (s, 3H), 1.48 (s, 3H), 3.43 (t, $J_{32} = 5.34$ Hz, $J_{34} = 5.40$ Hz, 1H, H-3), 3.55 (dd, $J_{43} = 5.68$ Hz, $J_{45} = 6.94$ Hz, 1H, H-4), 4.30 (d, $J_{65} = 5.65$ Hz, 1H, H-6), 5.06 (dd, $J_{54} = 6.98$ Hz, $J_{56} = 5.75$ Hz, 1H, H-5), 6.63 (d, $J_{23} = 4.59$ Hz, 1H, H-2); ^{13}C RMN ($CDCl_3$/TMS) δ 26.9 (CH_3), 28.1 (CH_3), 30.9 (C3, episulfide), 33.3 (C4, episulfide), 73.5 (C5), 76.0 (C6), 111.5 (C), 126.2 (C1), 129.1 (C2); Anal. found C, 41.09; H, 4.54; calcd for $C_9H_{11}BrO_2S$ C, 41.08; H, 4.21.

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