Unusually Stable Azetidinone Sulfenic Acids

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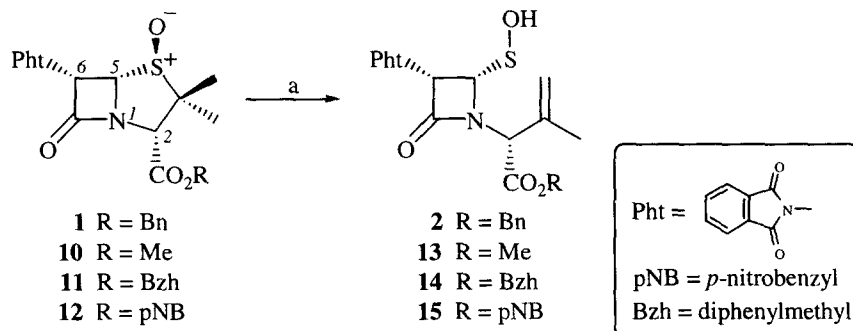
Abstract

Sulfoxides of (2S,5S,6S)-penams rearrange upon heating in benzene or toluene to form unusually stable azetidinone sulfenic acids. A reversal of the process, the annelation of the sulfenic acids, is disfavoured due to steric congestion on the *endo*-face of the corresponding penam sulfoxides. © 1998 Elsevier Science Ltd. All rights reserved.
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In the course of studies on the synthesis of unnaturally configured cephalosporins [1,2], we carried out kinetic experiments studying the rate of deuterium incorporation into sulfoxides of diastereoisomeric benzyl 6-phthalimidopenicillanates[2] according to the methodology of Cooper [3]. Somewhat surprisingly, heating sulfoxide **1** in benzene/D_2O for 150 min [cf. **Scheme 1, 1 → 2** in the presence of D_2O (100 equiv.)] resulted in formation of an unusually stable *O*-deuterated sulfenic acid **2** as the major product (~90% by ^{1}H NMR), which was characterised spectroscopically and by its further chemical transformations. In contrast, other diastereoisomers of **1** [*i.e.* (2S,4R,5R,6R), (2S,4S,5R,6S), and (2S,4S,5S,6R)] gave, as expected from the previous work [3], the parent sulfoxides (as sole products) with varied levels of deuterium incorporation into one of the geminal methyl groups [2]^2.

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1 R = Bn	**2** R = Bn	Pht =
10 R = Me	**13** R = Me	
11 R = Bzh	**14** R = Bzh	pNB = *p*-nitrobenzyl
12 R = pNB	**15** R = pNB	Bzh = diphenylmethyl

Scheme 1

Reagents and conditions: (a) PhH, reflux, 150 min, sulfenic acid:sulfoxide *ca.* 10:1.

Although sulfenic acids are frequently evoked as transient species in various chemical and biochemical processes [4-10], few stable examples are known [11-19]. Since the pioneering work of Morin *et al.* on transformation of penicillins into cephalosporins [20,21], intermediate sulfenic acids derived from

penam sulfoxides *via* a reversible thermal rearrangement have been studied and exploited [22,23]. To our knowledge, only one example **4** of a relatively stable sulfenic acid prepared (in low yield) *via* this transformation has so far been reported (**Scheme 2**) [24].
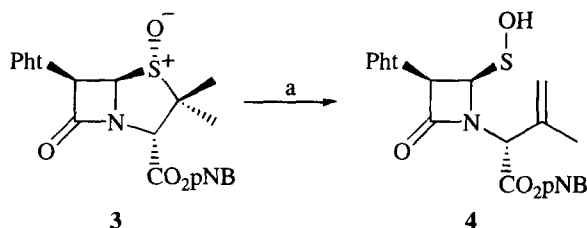
Scheme 2

Reagents and conditions: (*a*) EtOAc, reflux, 10 min, **3**:**4** *ca.* 4:1.

Thus (**Scheme 2**), reflux of sulfoxide **3** in EtOAc for 10 min, followed by rapid cooling and evaporation of the solvent, furnished a mixture of sulfenic acid **4** and sulfoxide **3** in a ratio of *ca.* 1:4, which were separated by fractional crystallisation [24][3]. Although stable in the solid state, the previously reported sulfenic acid **4** is converted ($t_{1/2}$ ~3 hr, 38 °C) in chloroform solution into the parent sulfoxide **3**. In contrast, sulfenic acid **2** was stable under analogous conditions (40 hr, 40 °C, $CDCl_3$)[4]. Attempted purification of **2** by flash chromatography on silica gel led to isolation of the deconjugated isothiazolone **5** (**Scheme 3**) [20,21]. The conjugated isothiazolone **6** was formed when **2** was treated with Et_3N [20,21]. Sulfenic acid **2** could be *O*-methylated with methyl triflate according to the procedure of Koppel and Kukolja [25] to form sulfenate **7**. A conjugate addition of **2** to methyl propiolate gave (*E*)-vinylic sulfoxide **8**, as a single [>95% by ^{1}H NMR (200 MHz) analysis] epimer. Upon treatment with a catalytic amount of *p*-toluenesulfonic acid in hot DMF, sulfenic acid **2** gave cephem **9** [1,20,21].
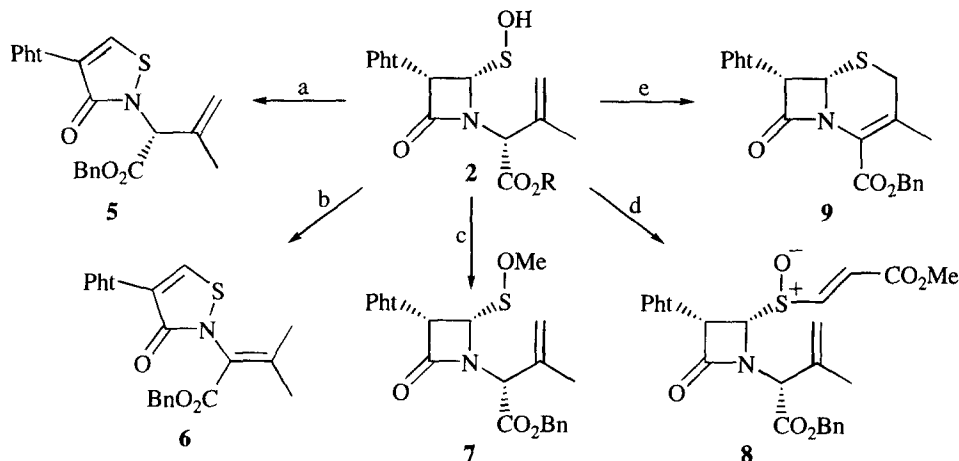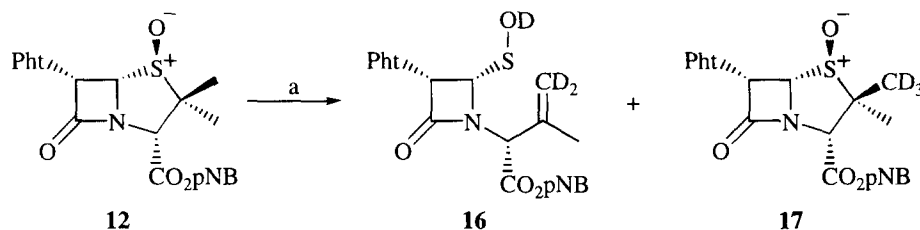

Scheme 3

Reagents and conditions: (*a*) silica gel, 56%; (*b*) Et_3N (cat.), PhH, ambient temp., 50 min, 70%; (*c*) LDA (1 equiv.), THF, – 95 °C, then CF_3SO_3Me, –95 °C → rt, 1 hr, 52%; (*d*) methyl propiolate, PhH, 50 °C, 30 min, 72%; (*e*) *p*-toluenesulfonic acid (cat.), DMF, 100 °C, 1 hr, 57%.

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[3] Prolonged heating of sulfoxide **3** in refluxing benzene for 150 min did not improve the sulfenic acid-sulfoxide ratio.

[4] The reactions reported herein were performed on sulfenic acids pre-made in a separate step (*i.e.* not generated and trapped *in situ*). The generated sulfenic acids contained ~10% of the corresponding parent sulfoxide.

Formation of stable sulfenic acids from appropriately (2*S*,5*S*,6*S*)-configured penam sulfoxides is an apparently general phenomenon. Other C-2 analogues of sulfoxide **1** (*i.e.* **10-12**) also react to form stable sulfenic acids (**13-15**, respectively) in high yield to give products only contaminated (~10%, equilibrium mixture) with the parent sulfoxides (**Scheme 1**). However, purification of the sulfenic acids by fractional crystallisation was unsuccessful. The existence of thermal equilibria between the sulfoxides and sulfenic acids was demonstrated by the prolonged (40 hr) heating of **12** in benzene in the presence of D_2O (**Scheme 4**). In this case, ^1H NMR and mass spectrometric analyses of the recovered starting material **12** (~10%) demonstrated the presence of three deuterium atoms located in the β-methyl group, *i.e.* formation of **17**.

Scheme 4

Reagents and conditions: (*a*) PhH, D_2O (100 equiv.), reflux, 40 hr. **16:17** *ca.* 10:1.

Analogues of sulfoxide **1** containing an amido substituent at C-6 were also found to form stable sulfenic acids. For example, heating sulfoxide **18** [2] in benzene for 150 min gave a *ca.* 1.2:1 mixture of sulfenic acid **19** and the parent sulfoxide **18** (**Scheme 5**). The ratio was improved to *ca.* 10:1 when **18** was refluxed in toluene for 3 hr.
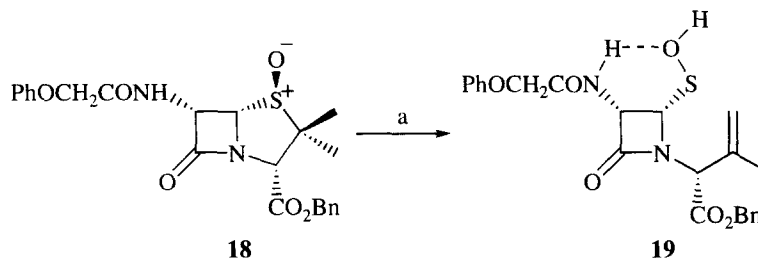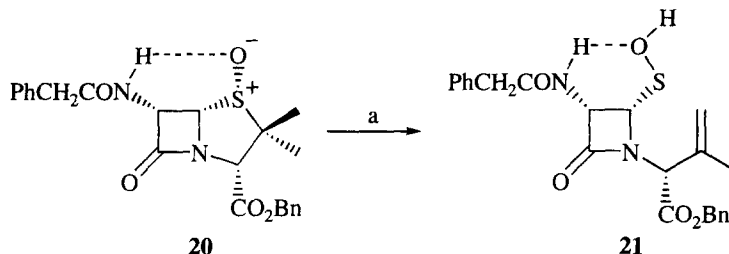

Scheme 5

Reagents and conditions: (*a*) PhH, reflux, 150 min; **19:18** *ca.* 1.2:1 or PhMe, reflux, 3 hr; **19:18** *ca.* 10:1.

The slower rate of sulfenic acid formation from **18** compared to the 6-phthalimido analogue **1** is probably the result of increased steric strain in **1**, resulting from the close proximity of the larger phthalimido group with the substituents on the thiazolidine ring, as proposed by Cooper [3].

A remarkable ease of sulfenic acid formation from (2*S*,5*S*,6*S*)-configured penam sulfoxides was demonstrated by observation that sulfoxide **20** [2] was transformed into sulfenic acid **21** (**Scheme 6**) even at room temperature (both in solution and in solid state, during storage). The low activation barrier to the thiazolidine ring opening can be attributed in this case to additional steric congestion on the *endo*-face of **20** (caused by the α-sulfoxide substituent) and the presence of an intramolecular hydrogen bond throughout the transformation **20** → **21** (cf. **18** → **19**). A low-temperature sulfoxide-sulfenic acid transformation has been previously noted by Nakamura [16] during MCPBA oxidation of 9-(*tert*-butylthio)triptycene (at 0-25 °C for 12 hr), which gave directly 9-triptycenesulfenic acid.

Scheme 6

Reagents and conditions: (*a*) storage at room temperature for 2 weeks; **21:20** *ca.* 3:1.

In summary, it has been demonstrated that (2*S*,5*S*,6*S*)-penam sulfoxides can form stable sulfenic acids. The increased stability of such species can be attributed both to the steric bulk of the modified azetidinone moiety (which prevents formation of the appropriate bimolecular complex regarded as a prerequisite for normal thiosulfinate formation [26]) and to the relative thermodynamic instability of the substrates [preventing re-cyclisation, which for sulfoxides of other diastereoisomeric penams is a favoured process (cf. **12** vs. **3**)]. In some cases (e.g. **19** and **21**), the stability of sulfenic acids might be enhanced by the presence of internal hydrogen bonding.

Acknowledgement

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