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LETTERS

Rate enhancement in the reduction of (2,3)-α- and (2,3)-β-methylenepenam β-sulfoxides

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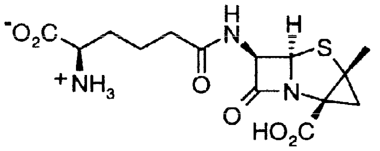
Abstract

The ease of reduction of (2,3)-α-methylenepenam β-sulfoxides, (2,3)-β-methylenepenam β-sulfoxides and bicyclic penam β-sulfoxides to the corresponding sulfides, using potassium iodide and trifluoroacetic anhydride in acetone or *N,N*-dimethylformamide, was measured. The results indicate that in general the rate of reduction of both (2,3)-α- and (2,3)-β-methylenepenam β-sulfoxides is several orders of magnitude greater than the rate of reduction of bicyclic penam β-sulfoxides. A mechanistic explanation to account for this observation is advanced.

Keywords: Penams; Reduction; Sulfoxides.

During studies directed toward the synthesis of 6β-[(5*R*)-5-amino-5-carboxypentanamido]-(2,3)-α-methylenepenicillanic acid **1** [1], an analogue of penicillin N designed as a probe for radical intermediates in the enzyme-catalysed ring expansion of penicillin N to deacetoxycephalosporin C, an efficient method for the reduction of the (2,3)-α-methylenepenam β-sulfoxide **2** (Scheme 1) [2] to the corresponding sulfide **3** was required.



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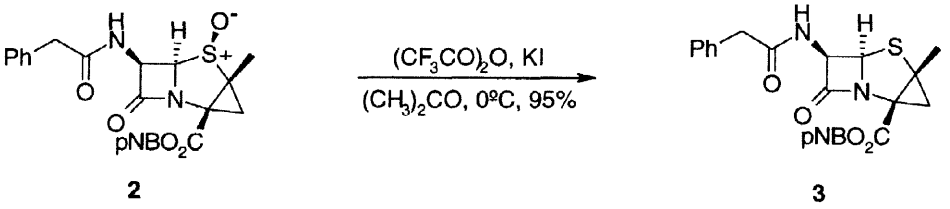
Reduction of **2** with either PBr_3 in DMF[§] [3] or potassium iodide and acetyl chloride in DMF [4] gave multiple products. Treatment of a solution of **2** in acetone with potassium iodide (3 equivalents) and TFAA (2 equivalents) however, caused the solution to rapidly darken and effected complete reduction of **2** to **3** in less than 30 minutes at 0°C. The sulfide **3** was isolated in 95% yield from this reaction after thiosulfate reductive work-up (Scheme 1).



Scheme 1

As, to our knowledge, the use of this reagent combination for the reduction of sulfoxides has not been described in the literature, it was decided to investigate the scope of this reaction for the reduction of penam β-sulfoxides further. The results of this investigation are summarised in table 1.

Table 1

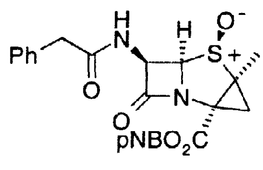
Reduction of penam β-sulfoxides using TFAA and KI in acetone.

Sulfoxide	Temperature / °C	Reaction time / hours	Conversion[a] / %	Isolated yield / %
2	0	0.5	100	95
4	0	0.5	100	65
5	0	0.5	100	65
7	25	36	65	not isolated

a: measured by integration of the 6-H resonance for the sulfoxide and the sulfide in the ^1H NMR spectrum of the crude product.

Reduction of the (2,3)-β-methylenepenam β-sulfoxides **4** and **5** [1] both proceeded to completion in less than 30 minutes under the same conditions for the reduction of **2**, and the corresponding sulfides were both isolated in 65% yield after chromatography to remove residual trifluoroacetic acid. The reduction of the (2,3)-α-methylenepenam β-sulfoxide **6** [1] could not be effected due to its insolubility in acetone. In contrast to the results obtained for **2**, **4** and **5**, no reduction of the bicyclic penam β-sulfoxide **7** had occurred after 30 minutes at 0°C and after 36 hours at 25°C the reaction had gone only 65% to completion! Other bicyclic penam β-sulfoxides were reduced equally slowly under these conditions and competing decomposition over extended reaction times was also often observed.

[§] Abbreviations: DMF: *N,N*-dimethylformamide; pNB: 4-nitrobenzyl; TFAA: trifluoroacetic anhydride.



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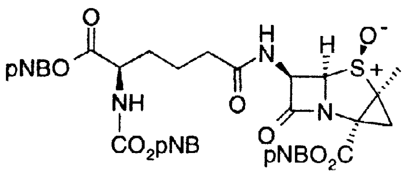

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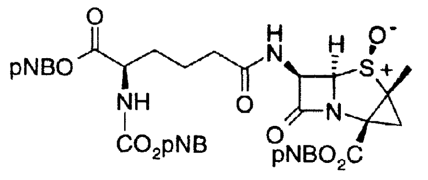

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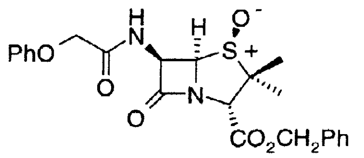

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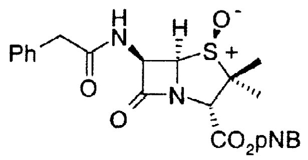

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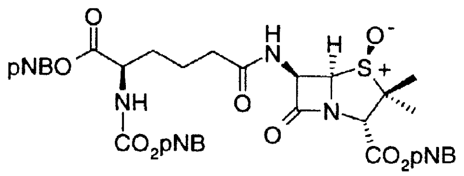

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To overcome the problem caused by the insolubility of **6** in acetone, use of the same reagent combination with DMF as the solvent was also examined (Table 2). Both the (2,3)-β-methylenepenam β-sulfoxide **5** [1] and the (2,3)-α-methylenepenam β-sulfoxide **6** [1] underwent rapid reduction at 0°C in DMF. Whilst the sulfide from the reduction of **5** was isolated in 90% yield after reductive workup and chromatographic purification, the crude product from the reduction of **6** contained the sulfide and another non-β-lactam product (*ca.* 1:1). Attempted chromatographic purification of this mixture led to almost total degradation of the sulfide. Although bicyclic β-lactam β-sulfoxides were reduced more quickly in DMF than in acetone, they were still reduced much more slowly than the (2,3)-α- or (2,3)-β-methylenepenam β-sulfoxides. Thus reduction of **7** was 50% complete after 2 hours at 25°C in DMF (*cf.* 65% conversion after 36 hours in acetone). After 2 hours at 25°C the reduction of **8** was 90% complete, whilst after 8 hours at this temperature the reduction of **9** had gone to completion.

Table 2

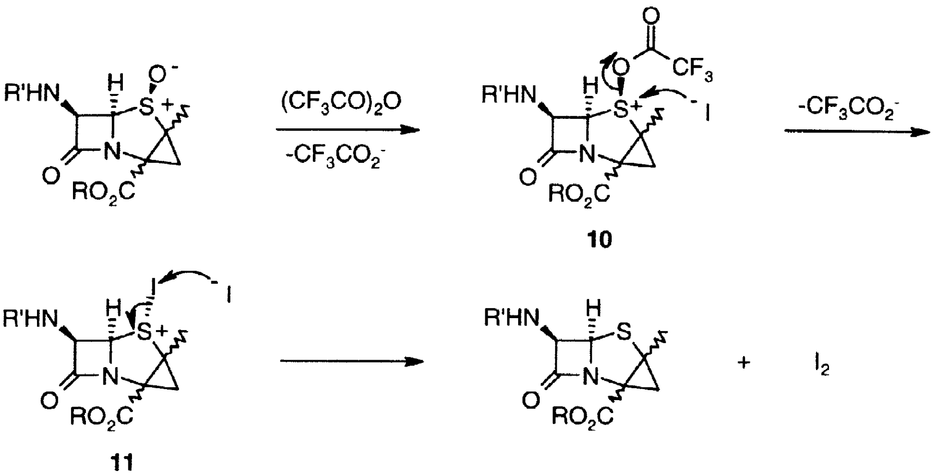
Reduction of penam β-sulfoxides with TFAA and KI in DMF

Sulfoxide	Temperature / °C	Reaction time / hours	Conversion[a] / %	Isolated yield / %
5	0	0.5	100	90
6	0	0.5	100	trace
7	25	2	50	not isolated
8	25	2	90	not isolated
9	25	8	100	60

a: measured by integration of the 6-H resonances due to the sulfoxide and the sulfide in the ^1H NMR spectrum of the crude product.

Taken together these results indicate that there is a substantial rate enhancement in the reduction of both (2,3)-α- and (2,3)-β-methylenepenam β-sulfoxides compared with the reduction of bicyclic β-lactam β-sulfoxides using TFAA and KI in either acetone or DMF. A reaction mechanism consistent with these observations involves rapid initial nucleophilic attack of the sulfoxide oxygen on TFAA [5] to yield the sulfoxonium intermediate **10**, followed by rate limiting nucleophilic displacement of trifluoroacetate by iodide to give the iodosulfonium intermediate **11**.

Subsequent nucleophilic attack of iodide on the iodine atom of **11** would then yield the sulfide and iodine (Scheme 2). The observed rate enhancement for the reduction of (2,3)-α- and (2,3)-β-methylenepenam β-sulfoxides could thus be explained by stabilisation of the transition state leading to **11** *via* interaction of the p-like orbital on sulfur with the adjacent cyclopropane σ* orbital (Figure 1).



R = 4-nitrobenzyl; R' = $PhCH_2C(O)$- or $pNBO_2CCH(NHCO_2pNB)CH_2CH_2CH_2C(O)$-

Scheme 2

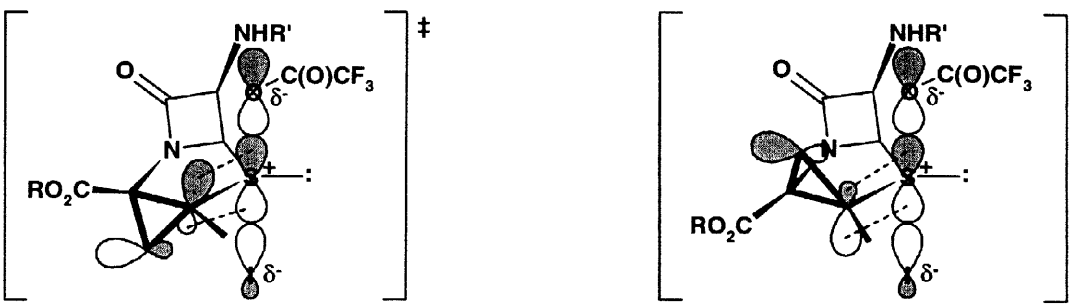


Figure 1

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References and notes:

[1] Challis GL. D.Phil. Thesis. University of Oxford, 1998.

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[5] The reaction of dimethyl sulfoxide with TFAA is very rapid. See: Sharma AK, Swern D. Tetrahedron Lett. 1974; 16: 1503-1507.