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ADDITION OF ELEMENTAL SULFUR TO CARBANIONS AND ITS APPLICATION FOR SYNTHESIS OF ISOPENAMS AND ISOCEPHAMS

Gholam Hosein Hakimelahi*

Department of Chemistry, McGill University
Montreal, Quebec, Canada H3A 2K6

Antonio Ugolini

Department of Chemistry, University of Montreal
Montreal, Quebec, Canada H3C 3V1

Summary - *A new synthesis of isopenams and isocephams which involves sulfur addition to carbanions followed by internal alkylation is described*

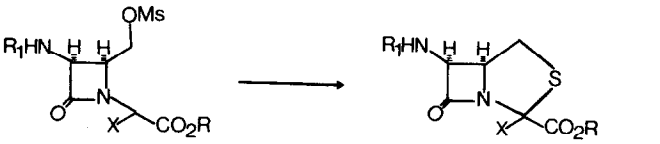
It is well known that elemental sulfur reacts with phosphonate carbanions to give α-phosphoryl thiols which upon treatment with alkylating agents are converted into α-phosphoryl sulfides[1,2]. It occurred to us that reaction of phosphonate carbanions of monocyclic β-lactam 1a with elemental sulfur may similarly afford the corresponding mercaptide salt, which as a result of an internal SN_2 displacement of the mesylate function, may give isopenam 2a. Indeed, when one equivalent of β-lactam 1a was allowed to react with 1.4 equivalents of elemental sulfur in the presence of potassium tert-butoxide, the isopenam 2a[3] was obtained in nearly quantitative yield as a mixture of two diastereomers.

In order to prove the generality and mildness of this method, an epimeric mixture of β-lactams 1b-c, 3 and 5 was reacted with S_8 and $K^+ \bar{O}CMe_3$ in THF at -20°C. After 1 h, a high yield of the corresponding bicyclic β-lactams 2b-c[4], 4[4,5], and 6[4,6] was obtained respectively.

This methodology clearly enables the use of readily accessible monocyclic β-lactams[7,8] (e.g., 1, 3 and 5), as convenient sources, for the preparation of penicillin and cephalosporin analogues.

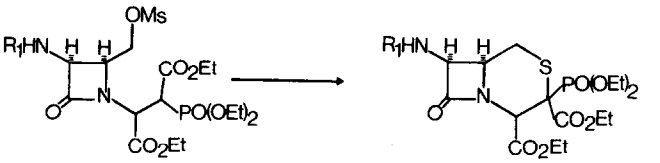
β-Lactams 2a-c, 4 and 6

To β-lactams 1a-c, 3 and 5 (1 mmol) in dry THF (15 mL) containing elemental sulfur (1.4 mmol) was added at -20°C potassium tert-butoxide (1.1 mmol) under a stream of nitrogen gas. After 15 min, the solution was stirred for 45 min at 25°C. Then water was added and the aqueous solution was extracted with ethyl acetate. The organic layer was dried, filtered and evaporated. Chromatography on silica gel using ethyl acetate as eluant gave 2a-c, 4 and 6 respectively in about 80% yield.



1 2

a) R = CMe_3, X = $PO(OEt)_2$ b) R = CH_2Ph, X = Ph c) R = Me, X =



3 4

5 6

R_1 = $COCH_2Ph$

REFERENCES AND NOTES

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2. M. Mikolajczyk, P. Balczewski and S. Grzejszczak, Synthesis, 127 (1980).
3. 2a: ν 3405, 1785, 1739, 1685 cm^{-1}; δ 1.11 (m, 15H, $2CH_3$, $C(CH_3)_3$), 2.73-3.11 (m, 2H, CH_2S), 3.61 (bs, 2H, CH_2Ph), 3.91-4.70 (m, 5H, $2CH_2O$, CH), 5.10, 5.18 (2dd, 1H, CHN, J_1 = 4.5 Hz, J_2 = 8 Hz), 6.9 (b, 1H, NH), 7.22 (s, 5H, Ph); C.I. m/e 499 (M^++1); Calcd. for $C_{22}H_{31}N_2O_7SP$: C, 53.01; H, 6.22; N, 5.62; S, 6.42. Found: C, 53.12; H, 6.32; N, 5.60; S, 6.43.
4. Pmr, ir and elemental analysis data compatible with structure proposed.
5. 4: ν 3400, 1778, 1750, 1680 cm^{-1}; C.I. m/e 557 (M^++1, S-cluster).
6. 6: ν 3405, 1780, 1740, 1685 cm^{-1}; C.I. m/e 561 (M^++1, S-cluster).
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