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A CONVENIENT SYNTHESIS OF THE β-LACTAM RING BY 3 + 1 CYCLIZATION

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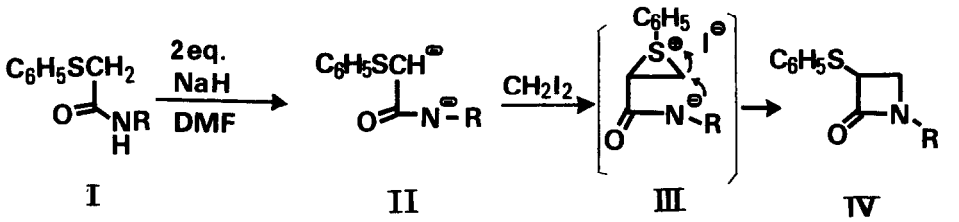
Summary: A new synthetic method for the β-lactam ring formation using the 1,3-dianion (II) of the α-phenylthioacetamide derivative (I) and methylene iodide is described. The episulfonium intermediate (III) is proposed for the reaction.

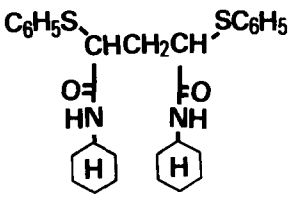
In addition to their biological activities[1] compounds which have β-lactam rings are attractive to organic chemists as a synthetic target, and great strides have been made in developing methods for formation of these four-membered rings[2]. Our continued interest in the synthesis of the β-lactam ring prompts us to report an exceptionally convenient procedure for the direct synthesis of this ring system.



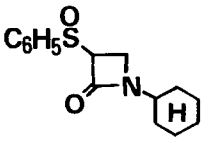
Isolated Yields of IV a: R = c-Hex., 53.5 % ; b: R = -$CH_2C_6H_5$, 26.8 % ; c: R = n-Bu., 37.9 % ; d: R = i-Bu., 28.0 %

Our approach to the synthesis of the β-lactam derivative is based on a convergent synthesis involving union of a 1-part (CH_2I_2) and a 3-part (α-thioacetamide derivative) via 1,3-dianion intermediate (II). The requisite 3-part (I) is generally prepared from the chloroacetamide derivative[3] and sodium thiophenolate in DMSO-THF solution. The 1,3-dianion (II) is generated in ab.DMF or DMF-THF (2:1) with 2.2 equivalents of NaH. Addition of CH_2I_2 (3-5 eq.) gives IV after stirring the mixture for 5-18 hr at r.t.. Although the conditions for optimization of the yield of IV have not yet been determined, the concentration of the solution is critical in suppressing the formation of the dimeric product (for example V, mp 184°), and it is necessary to perform the reaction in less than 3 % W/V solution. The structure of the β-lactam compounds (IV) were confirmed by the usual spectroscopic data and some reactions (vide infra).

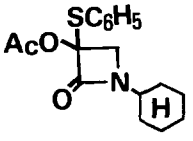
Oxidation of IVa with $NaIO_4$ in MeOH-H_2O gave two separable diastereomeric sulfoxide (VI) (IR: 1760 cm^{-1}(liq.)), both of which gave the same product (VII) on treating with Ac_2O at 80°C for 7 hr, IR: 1765, 1750 cm^{-1}(liq.). NMR (60 Mc)($CDCl_3$) δ : 0.9-2.0 (10 H), 2.09 (3H,s.), 3.3-3.8 (1H, m.), 3.55 (1H, d.) and 3.81 (1H, d.)(AB type, J=6.5 Hz). After treatment of IVa with n-BuLi at -60°in THF, addition of CH_3I, EtBr or CH_2=$CHCH_2Br$ gave the corresponding alkylated products VIII. VIIIa was identical with the β-



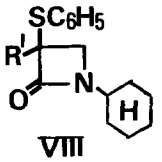
V



VI



VII



VIII

a: R' = CH_3 ; b: R' = Et

c: R' = $-CH_2CH=CH_2$

lactam derivative which was prepared from N-cyclohexyl-α-phenylthiopropyl-amide and methylene iodide by this dianion method. Furthermore the phenyl-thio part in IVa was removed by treating with Raney-Ni in MeOH at 50°C for 5-6 hr to give the known β-lactam derivative, N-cyclohexyl-2-azetidinone[2b].

The other 3-alkylthioazetidinone (β-lactam) derivatives are also obtainable from the corresponding α-alkylthioacetamide and methylene iodide, however methylene bromide is far less reactive than methylene iodide as the 1-part in this reaction.

The following is a representative procedure ----- To a solution of 550 mg of N-cyclohexyl-α-phenylthioacetamide (mp 89°) in 18 ml of DMF was added 250 mg of NaH (50% oily) at r.t.. After stirring for 20 min. 0.6 ml of CH_2I_2 was added in one portion (the temperature was observed to rise up to about 60°C). After stirring for 5 hr ethyl acetate was added and the whole mixture was washed with H_2O three times and dried over $MgSO_4$. After removal of the solvent the residual products were separated on silica gel preparative TLC (Merck) to give 280.8 mg of the desired β-lactam derivative (IVa), Rf = 0.65 (cf. Ia: Rf = 0.42, benzene : AcOEt = 5 : 1). IR : $\nu_{max.}^{liq.}$ 1755 cm^{-1}, UV: $\lambda_{max.}^{EtOH}$ 252 nm. ^{1}H-NMR ($CDCl_3$) δ : 0.85-2.0 (10 H, m.), 3.02 (1H, d.d., J = 5 and 2.5 Hz), 3.54 (1H, d.d., J = 5 and 5 Hz)[4], 3.2-3.55 (1H, m.), 4.23 (1H, d.d., J = 5 and 2.5 Hz), 7.2-7.7 (5H, m.). ^{13}C-NMR ($CDCl_3$) : 165.1, 133.2, 131.5, 129.0, 128.1, 51.1, 50.2, 44.1, 30.3, 25.1, and 24.6 ppm[4]. MS m/e : 261 (M^+), 135 (base peak). Anal. Calcd. for $C_{15}H_{19}NOS$: C, 68.93 ; H, 7.33 ; N, 5.36 ; S, 12.27. Found : C, 68.71 ; H, 7.47 ; N, 5.50 ; S, 11.74 .

At the mechanistic level, the formation of the β-lactam derivative may be attributed to first dianion (II) followed by episulfonium intermediate (III) which should be attacked by N^--anion as depicted in the first chart.

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4) For the chemical shifts and coupling constants of the monocyclic β-lactams ; see M. Hashimoto, T. Komori and T. Kamiya, J. Am. Chem. Soc. 98, 3025 (1976) and references cited therein.

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