Hydration of the Triple Bond in some 4-(Alk-2-ynylthio)azetidin-2-ones

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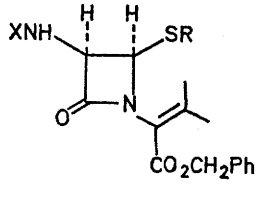
Summary Addition of secondary amines to the triple bond of some 4-(alk-2-ynylthio)azetidin-2-ones or the derived sulphoxides, followed by very ready hydrolysis of the resulting enamines, provides a convenient route to the corresponding β-keto-sulphides and -sulphoxides.

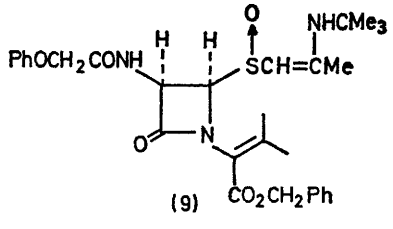
SINCE the thiazolidine ring of certain penicillanates is cleaved by methyl iodide and strong anhydrous base to give 4-methylthioazetidin-2-ones such as (**1a**),[1] it appeared that an analogue in which the *S*-substituent was a 2-oxoalkyl group might be useful in a projected conversion of the penicillin nucleus into cephalosporin analogues.[2] Attempts to introduce such groups using bromo-ketones failed, but the desired ketones were obtained by the addition of the elements of water to acetylenic intermediates. Treatment of benzyl 6β-triphenylmethylaminopenicillanate[3] with prop-2-ynyl bromide and potassium t-butoxide in tetrahydrofuran (2·5 h; room temperature) gave the acetylenic sulphide (**2a**),† m.p. 90—92° [ν(C≡CH) 3250 cm^{-1}] in 52% yield together with the isomeric allene (**3a**) (28%) [ν(C=C=C) 1940 cm^{-1}]. Similarly, 3-phenylprop-2-ynyl and but-2-ynyl bromides gave (**4a**) (78%),† m.p. 141°, and (**5a**) (57%)† respectively, no allenes being detected in these cases.

The prop-2-ynylthioazetidinone (**2b**)† was obtained by detritylation of (**2a**) with toluene-*p*-sulphonic acid in acetone followed by treatment with phenoxyacetyl chloride and triethylamine. Refluxing of (**2b**) for 1 h in methanol containing mercuric sulphate and dilute sulphuric acid then gave the ketone (**6b**) (70%),† but this procedure failed with non-terminal acetylenes and was unsuitable for compounds containing the acid-labile tritylamino-group. Reaction with mercuric chloride in piperidine[4] at room temperature for 30 min converted (**2a**) into the ketone (**6a**) (90%), while in refluxing piperidine the ketone was obtained in the absence of mercuric salts. Formation of the benzyl ketoen

a; X = Ph_3C
b; X = $PhOCH_2CO$

(**1**) R = Me
(**2**) R = $CH_2C{:}CH$
(**3**) R = $CH{:}C{:}CH_2$
(**4**) R = $CH_2C{:}CPh$
(**5**) R = $CH_2C{:}CMe$
(**6**) R = CH_2COMe
(**7**) R = CH_2COCH_2Ph
(**8**) R = CH_2COEt





(9)

† Satisfactory microanalysis or accurate mass measurement.

(**7a**) (58%)† from the phenylacetylene (**4a**) required refluxing for 90 min in piperidine irrespective of whether mercuric chloride was present. The but-2-ynyl sulphide (**5a**) failed to react even under forcing conditions, but the derived sulphoxide (obtained by treatment with *m*-chloroperbenzoic acid, major stereoisomer, m.p. 133–135°)† was converted into the keto-sulphoxide during 4 h in piperidine at room temperature, and reduction with triphenylphosphine and acetyl chloride in dimethylformamide at 5° then gave the keto-sulphide (**8a**).†

Ketone formation in the above experiments presumably resulted from very ready hydrolysis of an intermediate enamine during work-up. Pyrrolidine or morpholine could be used instead of piperidine, but diethylamine was less reactive. Heating of (**4a**) in pyrrolidine followed by evaporation gave a residue with strong i.r. absorption at 1560 cm^{-1} (enamine) and no ketonic carbonyl absorption, but chromatography on silica gel sufficed to bring about conversion into the ketone (**7a**). When the sulphoxide of (**2b**) was treated in benzene at room temperature with 5 equiv. of the relatively unreactive t-butylamine for 15 min the sulphoxide of the allene (**3b**), ν_{max} ($CHCl_3$) 3350, 1950, 1930 (allene), 1780, 1715, and 1688 cm^{-1} was obtained together with the enamine (**9**), ν_{max} ($CHCl_3$) 3400, 3300, 1770, 1715, 1685, and 1590 (enamine) cm^{-1}, but after 6 h (**9**) was the only product.

There is no proof that isomerisation of the acetylene to an allene precedes enamine formation in all cases, but such base-promoted interconversions are well known and the central carbon atom of the allene system is very susceptible to nucleophilic attack.[5] Moreover, such a mechanism would explain why, in both the sulphide and sulphoxide series, the keto-group in the end-product is invariably β to sulphur. This appears to be the first utilisation of the uncatalysed reaction of suitable acetylenes and amines as a route to β-keto-sulphides and sulphoxides. Its application in a novel conversion of penicillin derivatives into cephalosporin analogues is exemplified in the following communication.[2] All compounds showed the expected spectroscopic properties.

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[1] J. P. Clayton, J. H. C. Nayler, R. Southgate, and P. Tolliday, *Chem. Comm.*, 1971, 590; J. P. Clayton, J. H. C. Nayler, and R. Southgate, B.P., 1,269,279/1972.
[2] J. H. C. Nayler, M. J. Pearson, and R. Southgate, following communication.
[3] J. C. Sheehan and K. R. Henery-Logan, *J. Amer. Chem. Soc.*, 1962, **84**, 2983.
[4] H. Kagan, A. Marquet, and J. Jacques, *Bull. Soc. chim. France*, 1960, 1079.
[5] C. J. M. Stirling, *J. Chem. Soc.*, 1964, 5856, 5863; C. H. McMullen and C. J. M. Stirling, *J. Chem. Soc.* (*B*), 1966, 1217.