Intramolecular Wittig Reactions with Thioesters: the Synthesis of 7-Oxo-3-phenylthio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylates

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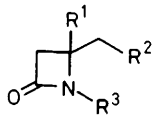
Summary 4-Carboxymethylazetidin-2-ones have been converted into phenylthioesters and then into the 7-oxo-3-phenylthio-1-azabicyclo[3.2.0]hept-2-ene ring system *via* an intramolecular Wittig reaction.

THE intramolecular reaction of a stabilised phosphorane with an aldehyde or ketone has been widely used to prepare cephalosporins,[1] oxadethiacephems,[2] the olivanic acid ring system,[3] and thienamycin analogues.[4] Interaction with the carbonyl group of 4-acylthioazetidin-2-ones derived from phenoxymethylpenicillin gives the penem ring structure.[5] We now report an internal Wittig cyclisation with thioesters which leads to the 7-oxo-1-azabicyclo-[3.2.0]hept-2-ene ring system having a phenyl sulphide substituent at the C(3) position of the nucleus.

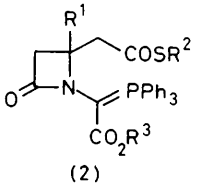
Initially we chose to use as our starting β-lactam 4-methyl-4-carboxymethylazetidin-2-one (**1b**), obtained by hydrogenolysis of the corresponding ester (**1a**).† The latter was readily prepared from benzyl 3-methylbut-3-enoate and chlorosulphonyl isocyanate by the method of Graf.[6]



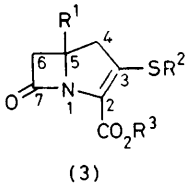
(1)

a; R^1 = Me, R^2 = CO_2CH_2Ph, R^3 = H
b; R^1 = Me, R^2 = CO_2H, R^3 = H
c; R^1 = Me, R^2 = COSPh, R^3 = H
d; R^1 = H, R^2 = $CH{=}CH_2$, R^3 = H
e; R^1 = H, R^2 = $CH{=}CH_2$, R^3 = $C(:PPh_3)CO_2$-$CH_2C_6H_4NO_2$-*p*
f; R^1 = H, R^2 = CO_2H, R^3 = $C(:PPh_3)CO_2$-$CH_2C_6H_4NO_2$-*p*

The acid (**1b**) was converted [$(EtO)_2POCl$–Et_3N–PhS-Tl][7] into the thioester (**1c**)† (70%), m.p. 103—104 °C, which with *p*-nitrobenzyl glyoxylate followed by the established procedure[1-5] gave the phosphorane (**2a**),† m.p. 184—185 °C. When (**2a**) was heated in toluene‡ under reflux for 3 days a 53% yield of the bicyclic compound (**3a**),† m.p. 142—146 °C, was isolated after chromatography on florisil. The product showed§ a u.v. absorption maximum at 318 nm (ε 17,000) and a β-lactam carbonyl i.r. absorption at 1780 cm^{-1} characteristic of the natural olivanic acid derivatives.[8]



(2)



(3)

a; R^1 = Me, R^2 = Ph, R^3 = $CH_2C_6H_4NO_2$-*p*
b; R^1 = H, R^2 = Ph, R^3 = $CH_2C_6H_4NO_2$-*p*
c; R^1 = H, R^2 = Ph, R^3 = Bu^t
d; R^1 = Me, R^2 = $C_6H_4NO_2$-*p*, R^3 = Bu^t
e; R^1 = H, R^2 = $C_6H_4NO_2$-*p*, R^3 = Bu^t
f; R^1 = Me, R^2 = $C_6H_4NO_2$-*p*, R^3 = CH_2Ph
g; R^1 = H, R^2 = $C_6H_4NO_2$-*p*, R^3 = CH_2Ph
h; R^1 = Me, R^2 = Et, R^3 = Bu^t

Subsequently, we used this procedure to prepare the corresponding 1-azabicycloheptene (**3b**) lacking the C(5) methyl group. 4-Allylazetidin-2-one (**1d**)[3] was converted into the phosphorane (**1e**),† m.p. 182—183 °C, and then subjected to ozonolysis (CH_2Cl_2–CF_3CO_2H, −70 °C) followed by oxidation with *m*-chloroperbenzoic acid (room temperature) . Chromatography on silica gave the acid¶ (**1f**)†

† Satisfactory microanalyses and/or accurate mass data were obtained.

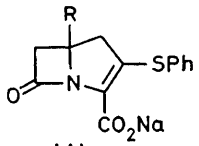
‡ Cyclisations were conducted at a concentration of 1 mg ml^{-1} under argon.

§ The other bicyclic compounds described also showed these spectral characteristics; further characterisation was by n.m.r. and mass spectrometry. For the characteristic i.r. and u.v. absorptions of natural olivanic acid derivatives see ref. 8.

¶ Residual traces of trifluoroacetic acid (TFA) which caused some protonation of the phosphorane could be removed by stirring for a brief period with basic alumina in dichloromethane.

(69%), m.p. 127—133 °C, which was readily converted *via* the mixed phosphonic anhydride into the thioester (**2b**)† (70%), m.p. 186—188 °C. This phosphorane was heated in refluxing toluene for 24 h to give an 18% yield of (**3b**),† m.p. 112—114 °C. More prolonged heating led to a greater degree of decomposition, and in general cyclisations producing products possessing the C(5) methyl group could be subjected to longer reaction times.

Other examples** showed the influence of both the thioester and phosphorane ester on the ease of cyclisation; in addition the sensitive nature of some thiol substituents to the reaction conditions was also revealed. Thus, using the phosphorane t-butyl ester (**2c**)† gave a 39% yield of the *S*-phenyl derivative (**3c**)† after only 6 h. With the highly activating *p*-nitrophenyl group the thioester (**2d**)† gave 54% of (**3d**),† m.p. 129—131 °C, after 5 h. In contrast, reaction of (**2e**)† showed extensive degradation after only 15 min, although a small yield (7%) of (**3e**) was isolated. Similarly with the benzyl ester (**2f**)† a 61% yield of (**3f**)† was obtained after 10 h, while cyclisation of (**2g**)† had to be stopped after 1·5 h giving 7% of (**3g**),† m.p. 126—131 °C. Interestingly with the ethylthioester (**2h**),† (3 days at reflux) the ethyl derivative (**3h**)† (32%) was obtained, whereas under identical conditions no product could be detected in the series lacking the methyl substituent.



(4)

a, R = Me
b; R = H

Removal of the acid protecting groups from (**3a**) and (**3b**) (H_2–Pd–C–aqueous dioxan) allowed the isolation of the corresponding sodium salts (**4a**) and (**4b**), λ_{max} (H_2O) 300 nm, ν_{max} (KBr)[8] 1750 cm^{-1}, with (**4b**) being somewhat more labile. Antibacterial *in vitro* tests revealed that (**4b**) showed considerable activity against a number of Gram positive and Gram negative organisms, while (**4a**) was only weakly active.

(*Received*, 15*th June* 1979; *Com.* 630.)

** Other examples were prepared by essentially the same methods as described for (**2a**) or (**2b**) by incorporation of the appropriate thiol and/or glyoxylate ester.

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