Tetrahedron Letters No. 36, pp 3159 - 3162, 1977. Pergamon Press. Printed in Great Britain.

SOME ASPECTS OF THE CHEMISTRY OF 4-THIOXO-2-AZETIDINONE DERIVATIVES: REACTIONS WITH NUCLEOPHILIC REAGENTS

A. Brandt, L. Bassignani and L. Re*

Snamprogetti, Org. Synth. Sect., 00015 Monterotondo (Rome), Italy

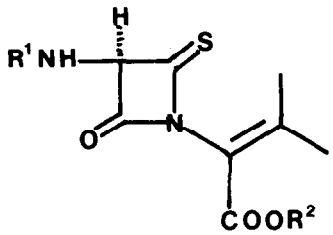
E. Mantovani, A. Robertiello and L. Settembri

Snamprogetti, Spectroscopy Sect., 00015 Monterotondo (Rome), Italy

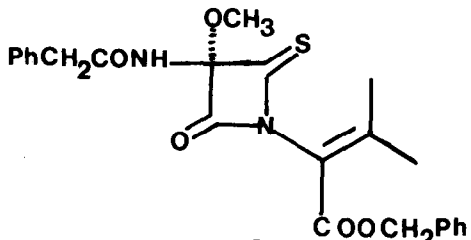
(Received in UK 1 July 1977; accepted for publication 14 July 1977)

In previous papers[1,2] we reported the synthesis and some reactions of 4-thioxo-2-azetidinones of type 1. The presence of a very labile H-3 in 1 was proved by the easy inter[1]- and intramolecular[2] alkylation of these compounds, in the presence of Et_3N, to give the corresponding S-alkylated unsaturated β-lactam derivatives. More recently, alternative methods for the synthesis of products of type 1 have been published[3,4], indicating the growing interest for these compounds. In the present communication we wish, therefore, to report some new reactions of derivatives of this general type.

Being interested in exploring the behaviour of these compounds with nucleophilic reagents without the involvement of the labile H-3, we took into account the corresponding methoxy-substituted derivative 2 [ir ($CHCl_3$):1820 (β-lactam CO), 1720 (ester CO), 1682 cm^{-1} (amide CO); nmr[5] ($CDCl_3$) δ 2.13 (3H,s) and 2.38 (3H, s) [$C=C(CH_3)$], 3.20 (3H,s, OCH_3), 3.63 (2H,s, CH_2CO), 5.20 (2H,s, $COOCH_2$), 7.30-7.50 (10 H,ss, aromatic), 7.66 (1H,s broad, NH); m/e[6] (relative intensity) 452(2) M^+, 424(5), 423(5.5), 422(10), 410(5.5), 409(17), 408(62), 406(15), 405(13), 396(15), 393(6), 361(5), 335(6), 334(5.5), 333(30), 318(6), 317(16), 315(14), 274(13), 273(100), 272(34), 271(31), 270(11), 250(17.5), 231(19.5), 205(16), 204(12), 200(18), 183(21), 182(18), 181(15), 173(16), 172(32.5), 171(19), 141(16), 140(25), 139(12), 135(55), 119(22), 118(37.5)[7]], prepared by UV irradiation of 1-(1-benzyloxycarbonyl-2-methylprop-1-enyl)-4-phenacylthio-3β-phenylacetamido-3α-methoxyazetidin-2-one[8], following the procedure given for 1[1].



1



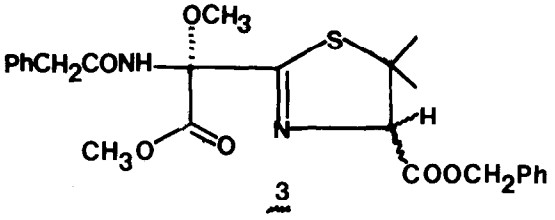
2

What stimulated our interest in compound 2 was to verify the possibility of acheiving the synthesis of the hereto unreported 5,6-disubstituted penicillins by nucleophilic attack on the C=S function, followed by intramolecular alkylation of the intermediate thiolate anion to give the thiazolidine ring moiety (compare ref. 2).

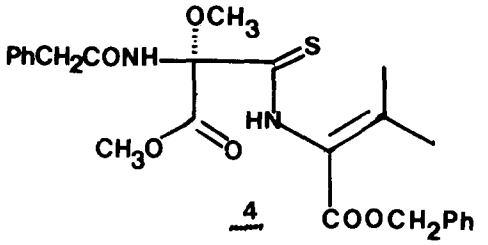
Reaction of 2 with 1 eq. of $LiOCH_3$ at -40°C in THF for 4 hr, followed by neutralization (AcOH, diluted with THF) and concentration under vacuum, gave, after preparative silica gel t.l.c. (C_6H_6 : EtOAc, 4 : 1), 3 as white foam (61% yield): ir ($CHCl_3$) 1760, 1740 (esters CO), 1688 (amide CO), 1610 cm^{-1} (C=N); nmr[5] ($CDCl_3$) δ 1.32 (3H,s), and 1.70 (3H,s) $[C(CH_3)_2]$, 3.20 (3H,s, OCH_3), 3.61 (2H,s, CH_2CO), 3.82 (3H,s, $COOCH_3$), 4.68 (1H,s, 3-H), 5.22 (2H,s, $COOCH_2$), 7.28-7.50 (10H, ss, aromatic), 7.62 (1H,s broad, NH); m/e[6] (relative intensity) 484(0.3) M^+, 454(20), 453(48.5), 451(6), 426(5), 425(29), 396(10), 394(13), 393 (19), 363(9), 349(5), 336(28), 335(26.5), 334(32.4), 319(19), 317(6), 308(16), 307(100), 287(8.5), 269(7.5), 251(7), 217(8), 215(7), 214(33), 201(9), 200(27), 199(51.5), 185(10), 172(19), 171(9), 167(15), 166(13), 157(41), 155(22), 140(31), 139(32.5), 127(34), 125(33), 119(9), 118(97)[7].

From the same t.l.c., derivative 4 was isolated as byproduct (white foam, 13% yield): ir ($CHCl_3$) 1760 (saturated ester CO), 1720 (unsaturated ester CO), 1680 cm^{-1} (amide CO); nmr[5] ($CDCl_3$) δ 1.78 (3H,s) and 2.25 (3H,s) $[C=C(CH_3)_2]$, 3.02 (3H,s, OCH_3), 3.62 (3H,s, $COOCH_3$), 3.68 (2H,s, CH_2CO), 5.15 (2H,s, $COOCH_2$), 7.32-7.46 (10H,ss, aromatic), 7.99 (1H, s broad, CONH), 9.34 (1H, s broad, CSNH)[7,9].

Preliminary experiments showed that also the reaction of 2 with CH_3Li or n-BuLi results in β-lactam cleavage.

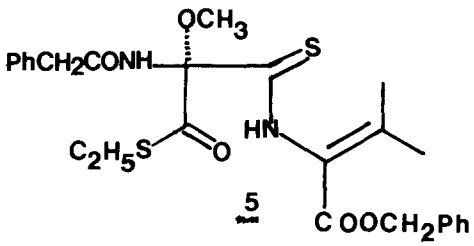


3

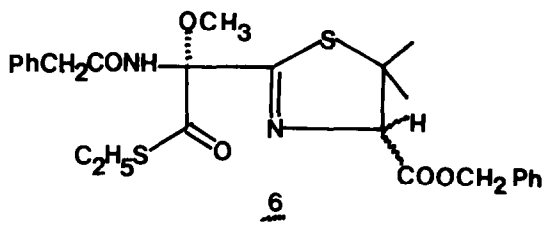


4

Finally, taking into account that C_2H_5SH reacts easily with thioketones to give mainly the corresponding dithiohemiketals[10], we investigated also the reaction of 2 with C_2H_5SH in the presence of Et_3N. In this case too, attack occurred on the β-lactam CO giving compounds 5 and 6.



5



6

Namely, when the reaction was carried out at r.t. for 2 hr in C_2H_5SH in the presence of stoichiometric Et_3N (with respect to 2), there was obtained 5[11] (white foam, 82% yield): ir ($CHCl_3$) 1720 (sh, unsaturated ester CO), 1690 cm^{-1} (broad, thiolester CO, amide CO); nmr[5] ($CDCl_3$) δ 1.17 (3H, t, J=8Hz, $SCH_2\underline{CH_3}$), 1.77 (3H, s) and 2.21 (3H,s) $[C=C(CH_3)_2]$, 2.80 (2H, q, J=8Hz, SCH_2), 3.00 (3H,s, OCH_3), 3.66 (2H,s, CH_2CO), 5.13 (2H,s, $COOCH_2$), 7.30-7.46 (10H, ss, aromatic), 8.03 (1H, s broad, CONH), 9.36 (1H, s broad, CSNH)[7,9].

On the other hand, when the reaction was carried out under the same conditions but for a longer time (24 hr), or at higher temperature (80°C for 2 hr), 6, formed only in traces under the reaction conditions leading to 5, was isolated[11] as the main product (white foam, 80% yield): ir ($CHCl_3$) 1743 (ester CO), 1685 (thiolester CO, amide CO), 1608 cm^{-1} (C=N); nmr[5] ($CDCl_3$) δ 1.23 (3H, t, J=8Hz, $SCH_2\underline{CH_3}$), 1.33 (3H,s) and 1.55 (3H,s) $[C(CH_3)_2]$, 2.80 (2H, q, J=8Hz, SCH_2), 3.20 (3H, s, OCH_3), 3.61 (2H,s, CH_2CO), 4,68 (1H,s, 3-H), 5.20

(2H,s, $COOCH_2$), 7.28-7.52 (10 H, ss, aromatic), 7.65 (1H, s, NH); m/e[6] (relative intensity) 514(0.1) M^+, 453(5.5), 452(7), 426(6), 425(8), 424(45), 422(5), 421 (10), 419(6), 408(7), 407(11), 334(11), 333(12), 317(7), 309(15), 308(34), 307 (100), 275(9), 272(5), 217(6), 201(6), 200(5), 199(18), 183(11), 174(8), 173(10), 172(34), 171(23), 157(44), 151(6), 141(15), 139(28.5), 126(13), 125(36), 119(17), 118(23)[7].

In conclusion, the experimental results show that nucleophilic reagents attack 2 at the C=O β-lactam to give at first type 4 and 5 derivatives which cyclize to 3 and 6 under more forcing conditions. The preferential attack on the C=O, rather than on the C=S β-lactam, indicates that in the latter the amide resonance stabilization, lacking for the C=O, as suggested by the its ir stretching vibration (1820 cm^{-1}), is still effective for the C=S group.

REFERENCES AND NOTES

(1) A. Brandt, L. Bassignani, and L. Re, Tetrahedron Lett., 3975 (1976).

(2) A. Brandt, L. Bassignani, and L. Re, Tetrahedron Lett., 3979 (1976).

(3) M.D. Bachi and J. Vaya, J. Am. Chem. Soc., 98, 7825 (1976).

(4) T.S. Chou, G.A. Koppel, D.E. Dorman, and J.W. Paschal, J. Am. Chem. Soc., 98, 7864 (1976).

(5) The 60-MHz nmr spectra were recorded on a Varian T-60 spectrometer using TMS as internal standard.

(6) The mass spectra were obtained using a Varian MAT 112 double focusing mass spectrometer, with electron impact at 70 eV. Samples were introduced via direct insertion probe.

(7) Elemental analysis gave proper values.

(8) Prepared from the corresponding substituted 4-thia-2,6-diazabicyclo [3.2.0] hept-2-en-7-one following the procedure of R. Lattrell, Justus Liebigs, Ann. Chem., 1361 (1974).

(9) The mass spectra are similar to those of the corresponding cyclic derivatives (3,6) except for the relative intensity of some peaks. In fact, the temperature conditions under which the mass spectrum was carried out, lead to extensive cyclization of 4 and 5.

(10) W.J. Middleton and W.H. Sarkey, J. Org. Chem., 30, 1384 (1965).

(11) Isolation was as for 3 and 4.