Synthesis and Photolysis of 4-Thioxoazetidin-2-ones

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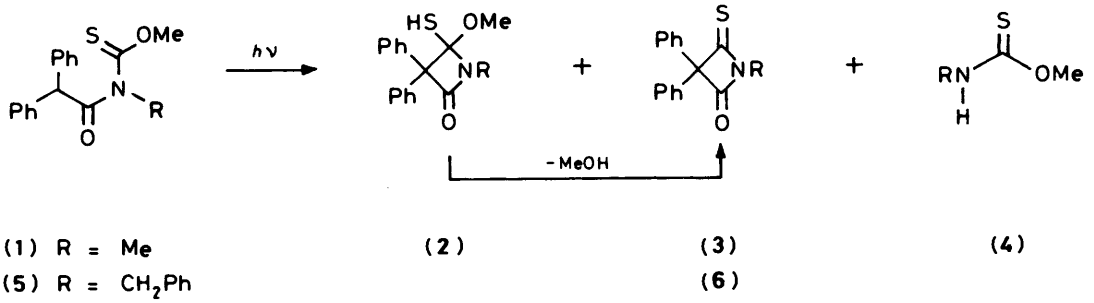
3,3-Diphenyl-4-thioxoazetidin-2-ones have been synthesized by photocyclisation of *N*-diphenylacetylthiocarbamates, and 3-phenyl-4-thioxoazetidinones have been prepared by thionation of azetidine-2,4-diones. Photolysis of the 3,3-diphenyl derivatives in methanol gave 2-methoxythiazolidin-4-ones *via* α-cleavage, whereas the 3-phenyl derivatives were photochemically unreactive.

4-Thioxoazetidin-2-ones (4-thioxo β-lactams or monothiomalonimides) were unknown until recently. They can be prepared by (*a*) cleavage of thiolsulphinates formed from β-lactam 4-sulphenic acids,[1,2] (*b*) Norrish type II cleavage of 4-acylmethylthio β-lactams,[3] and (*c*) [2 + 2]-cycloaddition of thioketenes with isocyanates.[4] Thioxoazetidinones are useful synthetic precursors for β-lactams related to antibiotics.[5,6] Furthermore, photochemical reactions of monothioimides have recently received considerable attention.[7–9] We report here novel synthesis of 4-thioxoazetidin-2-ones and their photochemical reactions.

Results and Discussion

Synthesis.—(*a*) 3,3-*Diphenyl*-4-*thioxoazetidin*-2-*ones.* Irradiation of *N*-diphenylacetyl-*N*-methylthiocarbamic acid *O*-methyl ester (**1**) in benzene gave 4-mercapto-4-methoxy-1-methyl-3,3-diphenylazetidin-2-one (**2**) (37%), 1-methyl-3,3-diphenyl-4-thioxoazetidin-2-one (**3**) (26%), and *N*-methylthiocarbamic acid *O*-methyl ester (**4**) (29%) (Scheme 1). Formation



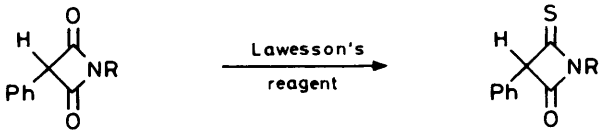
(**1**) R = Me
(**5**) R = CH_2Ph

(**2**) (**3**) (**6**) (**4**)

Scheme 1.

of (**2**) and (**4**) is explained in terms of a Norrish type II cyclisation and an elimination, respectively. Compound (**3**) is apparently formed from (**2**) by elimination of methanol.[10] In fact, when the photolysate from (**1**) was heated to 100 °C for 20 min, compound (**3**) was obtained in 65% yield. Photolysis of the *N*-benzyl derivative (**5**) followed by heating afforded the corresponding 4-thioxoazetidinone (**6**) in 48% yield. This method is useful for the synthesis of 3,3-diphenyl-4-thioxoazetidin-2-ones because the starting materials can be easily prepared from commercially available reagents, but is applicable only to the diphenylacetyl derivatives: *N*-isobutyryl and *N*-phenylacetyl derivatives did not give 4-thioxoazetidinones on irradiation.

(*b*) 3-*Phenyl*-4-*thioxoazetidin*-2-*ones.* When the 3-phenylazetidine-2,4-diones (**7**), (**8**), and (**9**) were treated with Lawesson's reagent,[11] the 3-phenyl-4-thioxoazetidin-2-ones (**10**), (**11**), and (**12**) were obtained in moderate yields (47, 43, and 50%, respectively) (Scheme 2). In these reactions, no azetidine-2,4-dithiones (dithioimides) were obtained.† Since several novel



(**7**) R = Me
(**8**) R = $CHMe_2$
(**9**) R = CH_2Ph

(**10**)
(**11**)
(**12**)

Scheme 2.

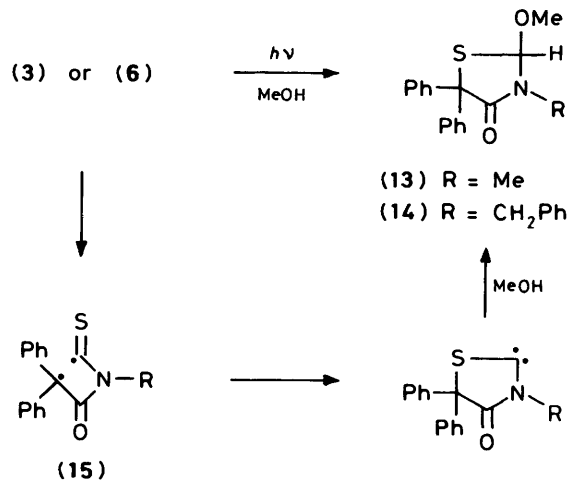
methods for the synthesis of azetidine-2,4-diones have been recently reported,[13–15] the present method may be useful for synthesis of 4-thioxoazetidin-2-ones.

Photolysis.—Irradiation of the 3,3-diphenylthioxoazetidinone (**3**) in methanol with a high-pressure mercury lamp gave 2-methoxy-3-methyl-5,5-diphenylthiazolidin-4-one (**13**) (51%). Similarly, photolysis of (**6**) afforded a thiazolidinone (**14**) (56%).

The structures of (**13**) and (**14**) were determined by elemental analysis and spectroscopy. The formation of these ring-expansion products can easily be explained in terms of a mechanism involving α-cleavage (Scheme 3). It is known that azetidine-2,4-diones undergo analogous reaction.[16]

Photolysis of the 4-phenylthioxoazetidinone (**10**) was carried out at 0 °C since compound (**10**) gradually decomposes in methanol at room temperature by methanolysis. However, the reaction did not give the corresponding thiazolidinone [as in the case of (**3**) which gave (**13**) under the same conditions], but afforded a small amount of a methanolysis product even on prolonged irradiation. The difference in the photochemical reactivity of the two monothioimides (**3**) and (**10**) can be explained in terms of the stability of the diradical intermediate (**15**) which should be strongly stabilised by the two phenyl

† Thionation of imides with P_4S_{10} gives dithioimides.[12]



Scheme 3.

groups. Steric congestion in (**3**) caused by the *gem*-diphenyl group may also enhance the α-cleavage.

It is well known that thiocarbonyl compounds undergo photochemical hydrogen abstraction or [2 + 2]-cycloaddition with alkenes as in the case of carbonyl compunds.[17] However, α-cleavage of thiocarbonyl compounds is rare because of the lower energy of the C=S reactive excited state[17a] and has been observed in the photolysis of strained compounds such as cyclobutane-1,4-dithiones.[18] The results of the present photoreaction indicate that α-cleavage of 4-thioxoazetidin-2-ones (4-membered cyclic monothioimides) is also inefficient and takes place only when the diradical intermediates are strongly stabilized by substituents.

Experimental

M.p.s were measured on a Yanagimoto Micro Melting Point apparatus and are not corrected. Yields are isolated yields. I.r. spectra were recorded for $CHCl_3$ solutions on a JASCO IRA-1 infrared spectrophotometer. N.m.r. spectra (^1H and ^{13}C) were measured for $CDCl_3$ solutions on a JEOL-100 spectrometer (100 MHz) with internal $SiMe_4$ as the standard. U.v. visible spectra were obtained on a Shimadzu UV-356 spectrophotometer.

Preparation of N-*Diphenylacetylthiocarbamates.*—To a solution of the thiocarbamate (600 mg) [prepared from the corresponding isothiocyanate and methanol] in benzene (10 ml) were added diphenylacetyl chloride (1.5 g) in benzene (10 ml) and triethylamine (1 g). The mixture was stirred at room temperature for 2 h. The reaction mixture was filtered through silica gel and the silica gel was washed with benzene. The benzene solution was evaporated and the residue was chromatographed on silica gel, eluting with benzene–ethyl acetate.

N-*Diphenylacetyl*-N-*methylthiocarbamic acid* O-*methyl ester* (**1**). M.p. 66—67 °C (Found: C, 68.15; H, 5.7; N, 4.6. $C_{17}H_{17}NO_2S$ requires C, 68.2; H, 5.7; N, 4.65%); $\nu_{max.}$ 1 690 cm^{-1}; $\lambda_{max.}$(cyclohexane) 270 (ε 18 300) and 331 nm (ε 100); δ_H 3.48 (3 H, s, NMe), 3.89 (3 H, s, OMe), 5.75 (1 H, s, methine), and 7.0—7.4 (10 H, m, Ph); δ_C 38.5 (q), 58.8 (q), 59.9 (d), 127.1 (d), 128.5 (d), 128.6 (d), 139.1 (s), 175.1 (s), and 192.4 (s).

N-*Benzyl*-N-*diphenylacetylthiocarbamic acid* O-*methyl ester* (**5**). M.p. 113—114 °C (Found: C, 73.5; H, 5.7; N, 3.7. $C_{23}H_{21}NO_2S$ requires C, 73.55; H, 5.65; N, 3.75%); $\nu_{max.}$ 1 705 cm^{-1}; δ_H 3.92 (3 H, s, Me), 5.27 (2 H, s, CH_2), 5.71 (1 H, s, methine), and 7.0—7.4 (15 H, m, Ph); δ_C 53.9 (t), 59.0 (q), 59.8 (d), 127.1—128.7, 136.6 (s), 139.0 (s), 175.1 (s), and 192.7 (s).

Synthesis of 3,3-*Diphenyl*-4-*thioxoazetidin*-2-*ones by Photolysis of* N-*Diphenylacetylthiocarbamates.*—A solution of the *N*-acylthiocarbamate (600 mg) in benzene (100 ml) in a Pyrex tube was deaerated by bubbling argon through it, and was irradiated with a 1000-W high-pressure mercury lamp for 4—8 h. After the solvent had been removed the residue was chromatographed on silica gel, eluting with benzene. The yields of thioxoazetidinones increased when the residue was heated to 100 °C for 20 min before chromatography.

4-*Mercapto*-4-*methoxy*-1-*methyl*-3,3-*diphenylazetidin*-2-*one* (**2**). M.p. 138—140 °C (Found: C, 68.0; H, 5.65; N, 4.65. $C_{17}H_{17}NO_2S$ requires C, 68.2; H, 5.7; N, 4.65%); $\nu_{max.}$ 1 750 cm^{-1}; δ_H 3.21 (3 H, s, NMe), 3.28 (3 H, s, OMe), 3.70 (1 H, s, SH), and 7.3—7.6 (10 H, m, Ph); δ_C 26.8 (q), 49.1 (q), 95.7 (s), 126.7 (d), 128.0 (d), 128.5 (d), 135.6 (s), and 171.3 (s); *m/z* (c.i.) 300 ($M^+ + 1$).

1-*Methyl*-3,3-*diphenyl*-4-*thioxoazetidin*-2-*one* (**3**) (65%). M.p. 109—110 °C (Found: C, 71.8; H, 4.9; N, 5.2. $C_{16}H_{13}NOS$ requires C, 71.9; H, 4.9; N, 5.25%); $\nu_{max.}$ 1 810 cm^{-1}; $\lambda_{max.}$(MeOH) 263 (ε 15 300) and 388 nm (ε 90); δ_H 3.16 (3 H, s, Me) and 7.2—7.7 (10 H, m, Ph); δ_C 26.7 (q), 79.2 (s), 126.9 (d), 128.2 (d), 128.6 (d), 135.9 (s), 171.9 (s), and 209.0 (s).

1-*Benzyl*-3,3-*diphenyl*-4-*thioxoazetidin*-2-*one* (**5**) (48%). M.p. 77—78 °C (Found: 76.9; H, 5.05; N, 4.05. $C_{22}H_{17}NOS$ requires C, 76.95; H, 5.0; N, 4.05%); $\nu_{max.}$ 1 800 cm^{-1}; δ_H 4.79 (2 H, s, CH_2) and 7.2—7.6 (10 H, m, Ph); δ_C 44.8 (t), 79.6 (s), 127.0 (d), 128.2 (d), 128.3 (d), 128.6 (d), 128.8 (d), 133.8 (s), 135.8 (s), 171.6 (s), and 208.2 (s).

General Procedure for the Synthesis of 3-*Phenyl*-4-*thioxoazetidin*-2-*ones.*—To a toluene (or xylene) solution (30 ml) of a 3-phenylazetidine-2,4-dione (400 mg) was added Lawesson's reagent (1 g) and the resulting mixture was refluxed for 6—8 h. After the solvent had been removed, the residue was chromatographed on silica gel, eluting with benzene.

1-*Methyl*-3-*phenyl*-4-*thioxoazetidin*-2-*one* (**10**) [41% (toluene); 47% (xylene)]. B.p. 40—55 °/10^{-3} Torr (bath temp.) (Found: C, 62.8; H, 4.75; N, 7.35. $C_{10}H_9NOS$ requires C, 62.8; H, 4.75; N, 7.3%); $\nu_{max.}$ 1 810 cm^{-1}; δ_H 3.17 (3 H, d, *J* 1.5 Hz, Me), 4.91 (1 H, q, *J* 1.5 Hz, methine), and 7.2—7.5 (5 H, m, Ph); δ_C 26.8 (q), 70.3 (d), 127.3 (d), 128.5 (d), 128.9 (d), 130.4 (s), 170.2 (s), and 206.0 (s).

1-*Isopropyl*-3-*phenyl*-4-*thioxoazetidin*-2-*one* (**11**) [43% (toluene); 32% (xylene)]. B.p. 50—75 °C/10^{-3} Torr (bath temp.) (Found: C, 65.65; H, 5.95; N, 6.35. $C_{12}H_{13}NOS$ requires C, 65.7; H, 5.95; N, 6.4%); $\nu_{max.}$ 1 800 cm^{-1}; δ_H 1.47 (6 H, d, *J* 7 Hz, Me), 4.30 (1 H, septet, *J* 7 Hz, $CHMe_2$), 4.83 (1 H, s, 3-H), and 7.1—7.4 (5 H, m, Ph); δ_C 19.6 (q), 19.8 (q), 46.9 (d), 70.7 (d), 127.2 (d), 128.4 (d), 128.9 (d), 130.6 (s), 169.7 (s), and 205.0 (s).

1-*Benzyl*-3-*phenyl*-4-*thioxoazetidin*-2-*one* (**12**). This was not completely purified [50% (xylene)]; $\nu_{max.}$ 1 810 cm^{-1}; δ_H 4.77 (2 H, s, CH_2), 4.89 (1 H, s, methine), and 6.8—7.6 (10 H, m, Ph); δ_C 45.0 (t), 70.5 (d), 127.3—128.9, 130.3 (s), 134.0 (s), 169.8 (s), and 205.0 (s).

General Procedure for the Photolysis of 4-*Thioxoazetidin*-2-*ones.*—A solution of a 4-thioxoazetidinone (400 mg) in methanol (40 ml) containing benzene (10%) was deaerated by bubbling argon throught it and was irradiated with a 1000-W high-pressure mercury lamp for 2—6 h. After the solvent had been removed, the residue was chromatographed on silica gel, eluting with benzene–ethyl acetate. Photolysis at 0 °C was carried out by use of a partially transparent Dewar.

2-*Methoxy*-5,5-*diphenyl*-3-*methylthiazolidin*-4-*one* (**13**) (51%). M.p. 57—58 °C (Found: C, 68.4; H, 5.95; N, 4.55. $C_{17}H_{17}NO_2S$ requires C, 68.2; H, 5.7; N, 4.65%); $\nu_{max.}$ 1 680 cm^{-1}; δ_H 2.98 (3 H, s, NMe), 3.13 (3 H, s, OMe), 6.08 (1 H, s, methine), and 7.1—7.7 (10 H, m, Ph); δ_C 30.6 (q), 51.1 (q), 65.5 (s), 91.6 (d), 127.4 (d),

127.5 (d), 128.1 (d), 128.4 (d), 141.9 (s), 142.9 (s), and 172.5 (s).

3-*Benzyl*-2-*methoxy*-5,5-*diphenylthiazolidin*-4-*one* (**14**) (56%). M.p. 102—103 °C (Found: C, 73.6; H, 5.7; N, 3.7. $C_{23}H_{21}NO_2S$ requires C, 73.55; H, 5.65; N, 3.75%); $\nu_{max.}$ 1 675 cm^{-1}; δ_H 3.13 (3 H, s, OMe), 4.09 and 5.14 (2 H, AB system, *J* 15 Hz, CH_2), 5.93 (1 H, s, methine), and 7.1—7.7 (15 H, m, Ph); δ_C 46.9 (t), 51.7 (q), 65.9 (s), 89.7 (d), 127.3—128.8, 135.5 (s), 141.6 (s), 143.2 (s), and 172.7 (s).

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Received 13*th July* 1987; *Paper* 7/1248