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4-THIOXO-2-AZETIDINONES BY CYCLOADDITION OF THIOKETENES WITH ISOCYANATES

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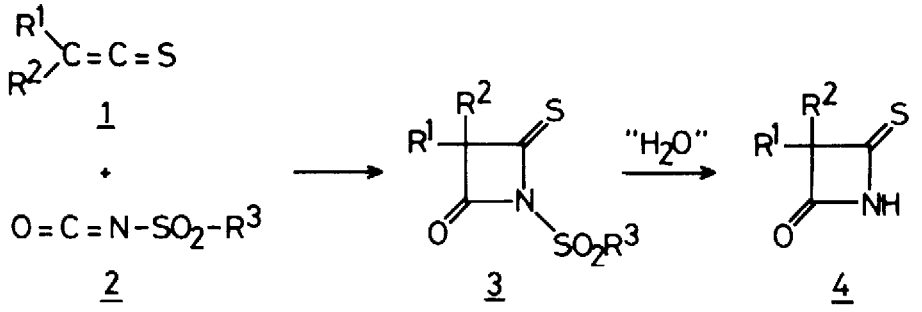
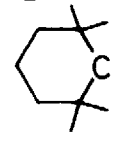
Summary - The (2+2) cycloaddition of thioketenes 1 with isocyanates 2 yields 4-thioxo-2-azetidinones 3, which can be hydrolyzed to the N-unsubstituted compounds 4 and thus used as versatile intermediates.

4-Thioxo-2-azetidinones (monothiomalonimides) represent interesting building-blocks for heterocyclic synthesis, particularly for modifications of ß-lactam antibiotics. The available methodology for the synthesis of these compounds involves multi-step procedures. [1-3] A simple approach to the four-membered ring system should be provided by the (2+2) cycloaddition of thioketenes 1 with isocyanates 2, if, as is the case in the reaction with azomethines, [4] the C=C bond of 1 is the reactive site. Furthermore, removal of the N-sulfonyl residue should afford the hitherto unknown N-unsubstituted 4-thioxo-2-azetidinones.



1a: R^1 = iPr, R^2 = tBu
b: $R^1 = R^2$ = tBu
c: R^1, R^2 = 

2a: R^3 = OPh
b: R^3 = Ph
c: R^3 = 4-MeC_6H_4
d: R^3 = Me
e: R^3 = Cl

The sterically hindered thioketenes 1a-c [5] require heating at 100 - 150°C for 12 - 48 hours for complete reaction with the isocyanates 2a-d. Chromatographic workup then yields yellow 1:1 adducts as main products. The constitution 3 can be derived from IR absorptions at high wavenumber characteristic of a carbonyl group in a four-membered ring and from UV bands in the visible range, which are readily assigned to the $n \rightarrow \pi^*$ transition of a thiocarbonyl group (Table). Moreover, ^{13}C NMR signals at δ = 198.3 and 169.7 (3c) or 205.6 and 167.9 (3e) prove the presence of thiocarbonyl and carbonyl carbons. Thus, the cycloaddition takes place between the C=C bond of 1 and the C=N bond of 2.

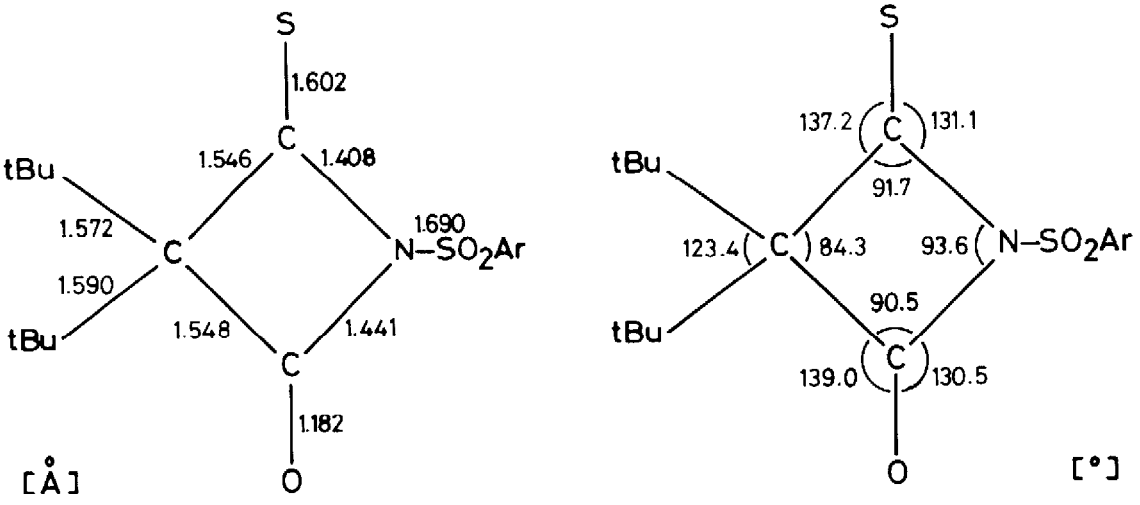


Figure. Schematic presentation of important bond distances and angles in the crystal structure of 3b

A final proof of the structure 3 was obtained by an X-ray crystallographic analysis of 3b (Figure). [6] Striking features are the comparatively long endocyclic C-N bonds and the very short C=O and C=S bond lengths. In fact, the C=S bond distance appears to be one of the shortest reported for a $C(sp^2)$-$S(sp^2)$ bond, even shorter than d(C=S) in thioformaldehyde (1.611 Å [7]). Obviously, the electron-withdrawing effect of the N-sulfonyl residue [8] and the inherent ring strain work together in 3 to suppress the usual mesomeric interaction in (thio)amide systems. In this situation the difference in the N - C=O/C=S distances indicates that the thioamide mesomerism is maintained relatively to a larger extent than the interaction within the N-CO moiety.

Thioxoazetidinones 3a-e are essentially stable toward acid hydrolysis. Action of sodium ethanolate (ethanol, 20 min reflux) on 3c-e leads to complete cleavage of the N - SO_2 bond. Usual workup affords the N-unsubstituted compound 4c as well as ethylated derivatives of type 6 and 7 as the ethyl sulfonate formed partially alkylates the anion 5.

A more convenient approach to compounds 4 is offered by the reaction of chlorosulfonyl isocyanate (2e) with thioketenes 1 (ether, 20°, 3 days). Here the expected cycloadducts 3 (R^3 = SO_2Cl) are highly labile and cannot be isolated. Chromatography (ethyl acetate/petroleum ether 1:4 for 4a, dichloromethane/petroleum ether 1:1 for 4b,c) gives 4 in fair

yields (Table).

N-Unsubstituted thioxoazetidinones 4 are readily converted into their anions (e. g. 5) by action of sodium hydride or alkanolate. The expected ambident reactivity of 5 is verified by different methylation reactions. Methyl iodide (ether, 30 min reflux) gives exclusively the S-methyl compound 6. The structure is obvious from a ^{1}H NMR signal at δ = 2.62 (CCl_4) and the absence of an $n \rightarrow \pi^*$ transition in the UV spectrum (Table). The ^{13}C NMR data may be misleading since besides δ = 180.0 for the carbonyl group a low-field resonance at δ = 213.9 might be interpreted in terms of a thiocarbonyl carbon. However, the assignment to $\delta_{C=N}$ is suggested by splitting into a quartet ($^3J_{HC}$ = 2.3 Hz) in the proton-undecoupled spectrum, and the deshielding of imino carbons on conjugation with carbonyl groups is known from similar examples. [9]

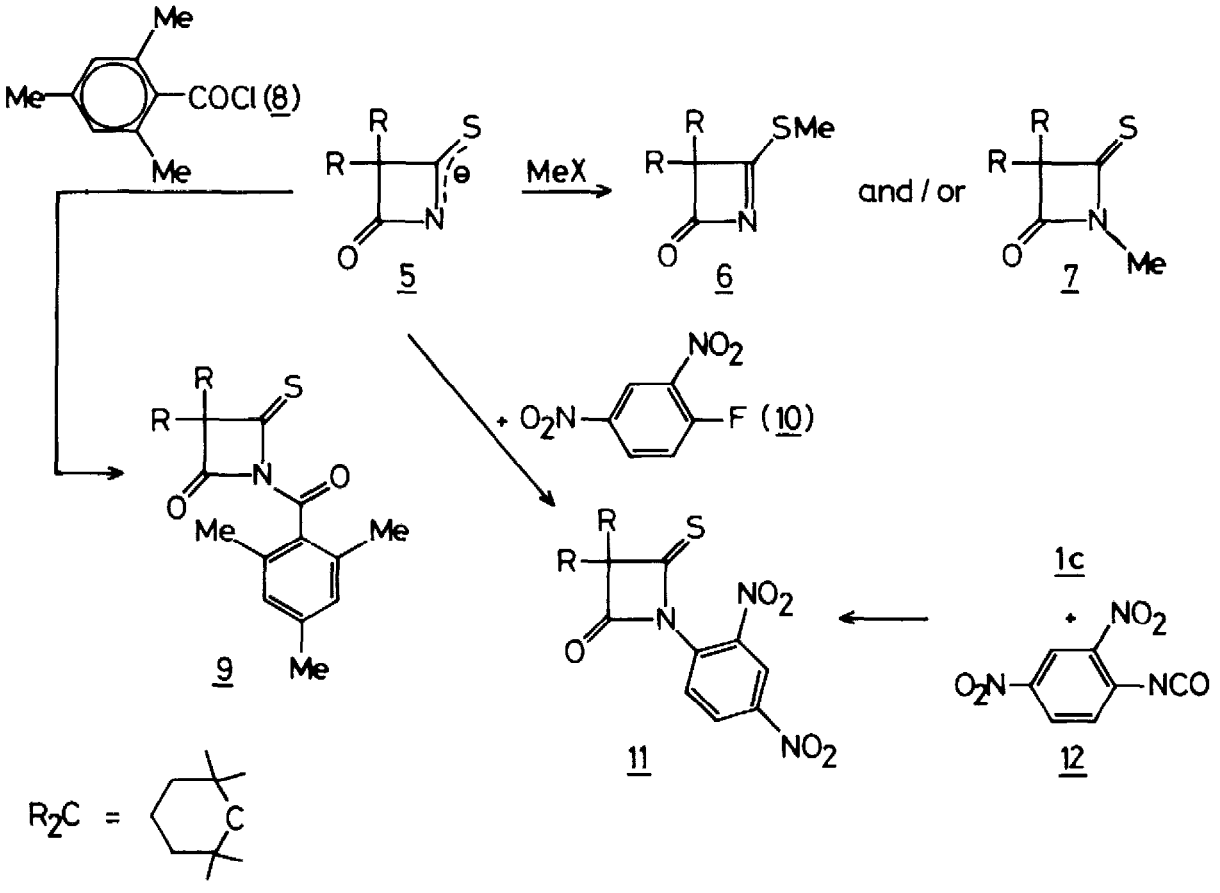
Table. Yields, melting-points, and important spectroscopic data of the new compounds [11]

Compd	Reactants	Yield [%]	m. p. [°C]	IR (KBr) $\tilde{\nu}_{NH}$	IR (KBr) $\tilde{\nu}_{CO}$ [cm^{-1}]	UV (Isooctane) λ [nm] (lg ε)
3a	1a + 2a	83	28-31	-	1835	- a)
3b	1b + 2c	29	132-134	-	1825	234(4.3), 261(4.2), 430(1.3)
3c	1c + 2a	76	81-82	-	1830	258(4.1), 434(1.3)
3d	1c + 2b	59	137-138	-	1815	235(4.2), 258(4.2), 431(1.3)
3e	1c + 2d	69	92-94	-	1830	252(4.1), 425(1.3)
4a	1a + 2e	43	98-111(dec.)	3250	1810(sh),1775	- a)
4b	1b + 2e	35	145-151(dec.)	3260	1805	- a)
4c	1c + 2e	47	172-175(dec.)	3240	1805, 1785	257(4.1), 405(1.2)
6	4c + MeI	56	96-101(dec.)	-	1780	252(4.1), 320(1.9)
	4c + TsOMe	50				
7	4c + TsOMe	33	118-132(dec.)	-	1795	265(4.2), 396(1.4)
9	4c + 8	77	93-105	-	1835,1815,1725	263(4.2), 325(sh), 460(1.5)
11	4c + 10	85	163-165	-	1820	315(sh), 430(sh),
	1c + 12	4				258(4.4), 297(4.1)

a) Not measured.

In agreement with experiences from enolate alkylations, [10] the more pronounced polarity control in the alkylation of 4 with methyl tosylate (NaOMe, MeOH, 20°C, 12 h) leads to a mixture of S- and N-methyl products 6 and 7, in which 6 still predominates in spite of the apparent ring strain of this azetine (Table). The constitution 7 is substantiated by the UV data (Table) and by NMR signals at δ = 213.1 and 175.6 for the thiocarbonyl and carbonyl carbons.

Acylation of 5 with mesitoyl chloride proceeds readily at 20°C to afford the N-acyl derivative 9. No S-acyl compound could be detected. The presence of the thiocarbonyl group in 9 is deduced from the UV spectrum (Table) and from a ^{13}C NMR signal at δ = 207.3 ($\delta_{C=O}$ = 171.5, 165.2). Also the fluoride 10 is attacked by 5 only via nitrogen to furnish the β-lactam 11. Besides the spectroscopic evidence (Table) structure 11 could be proven by an independent synthesis by way of a (2+2) cycloaddition of thioketene 1c with 2,4-dinitrophenyl isocyanate (12).



The use of thioxoazetidinones 4 for the synthesis of penam and cepham derivatives is currently under investigation.

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References and Notes

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