THIAZOLO[3,2-*a*][1,3,5-TRIAZINES. PREPARATION OF 4-SUBSTITUTED 2-THIAZOLYL ISOTHIOCYANATES AND THEIR REACTIONS WITH ISOCYANATES, ALDIMINES AND CARBODIIMIDES

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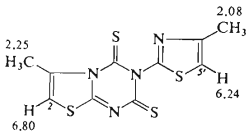
4-(Methyl- or phenyl)-2-thiazolyl isothiocyanates were synthesized from the appropriate amine hydrochlorides by the thiophosgene method. The [4 + 2] cycloaddition reaction of 4-methyl-2-thiazolyl isothiocyanate with isocyanates and aldimines afforded thiazolo[3,2-*a*]-1,3,5-triazine derivatives. 4-Phenyl-2-thiazolyl isothiocyanate on the other hand, did not react with isocyanates. Carbodiimides were found to react with 4-methyl-2-thiazolyl isothiocyanate by a [2+2] cycloaddition to yield the substituted 1,3-thiazetidines.

The 1,3-diazadiene system of 2-pyridyl isothiocyanate was employed in our preceding paper[1] for the synthesis of pyrido[1,2-*a*]-1,3,5-triazine derivatives *via* [4+2] cycloaddition reactions. This paper deals with the application of the 1,3-diazadiene grouping of 4-substituted 2-thiazolyl isothiocyanates in the preparation of thiazolo[3,2-*a*]-1,3,5-triazine derivatives. 4-Methyl-2-thiazolyl isothiocyanate (*I*) has already been prepared[2] from 2-amino-4-methylthiazole and thiophosgene in water–ether medium in the presence of sodium hydrocarbonate as a neutralization agent. Distillation gave in a low yield the oily product having a strong tendency to polymerize; this feature is, however, unfavourable for synthetic purposes. The isothiocyanate *I* prepared in a 36% yield by modification of the thiophosgene method was immediately used in the studied reactions; it was prepared from the 2-amino-4-methylthiazole hydrochloride in water–benzene in the presence of calcium carbonate and purified by chromatography. The presumed tendency to dimerization[1] was confirmed by the isolation of 6-(4-methyl-2-thiazolyl)-3-methylthiazolo[3,2-*a*]-1,3,5-triazine-5,7-dithione (*II*). The dimer *II* showed in its electron impact mass spectrum the $M^{+\cdot}/2$ ion. The extended conjugation of bonds through the condensed heterocyclic skeleton was seen by the absorption at λ_{max} 362 nm ($\log \varepsilon$ 3·83). The different nature of the two thiazole rings, dearomatized and aromatic, caused a distinct transmission of spin–spin interactions of the methyl group protons and that of the thiazole ring in the ^{1}H NMR spectrum. The same synthetic procedure was also applied for the

synthesis of 4-phenyl-2-thiazolyl isothiocyanate (*III*) stable at ambient temperature as a monomer.



$^4J_{CH_3-H^{2'}} = 2.2$

$^4J_{CH_3-H^{5'}} = 0.8$

II

Values of chemical shifts δ[ppm]

The dienophilic components in cycloaddition reactions of isothiocyanates *I* and *II* were isocyanates. The [4+2] cycloaddition involving the methyl derivative *I* was spontaneous and produced 6-R^1-3-methylthiazolo[3,2-*a*]-1,3,5-triazin-5-one--7-thiones *IV*–*VII* in good yields (Table I).

TABLE I

List of the synthesized thiazolo[3,2-*a*]-1,3,5-triazines

Compound	Formula (mol.weight)	Calculated/Found % N	Calculated/Found % S	M.p., °C (yield, %)
IV	$C_{12}H_9N_3OS_2$ (275·3)	15·26 15·13	23·29 23·38	207—209 (87)
V	$C_{12}H_8ClN_3OS_2$ (309·8)	13·56 13·32	20·70 20·41	197—199 (61)
VI	$C_{12}H_8BrN_3OS_2$ (354·3)	11·86 11·85	18·10 17·94	222—224 (54)
VII	$C_{16}H_{11}N_3OS_2$ (325·3)	12·92 12·84	19·71 19·56	165—167 (65)
VIII	$C_{13}H_{13}N_3S_2$ (275·4)	15·25 15·61	23·29 23·03	216—218 (66)
IX	$C_{14}H_{15}N_3S_2$ (289·4)	14·52 14·69	22·16 21·98	182—184 (66)
X	$C_{15}H_{18}N_4S_2$ (318·4)	17·59 17·36	20·14 20·25	195—197 (72)
XI	$C_{20}H_{19}N_3OS_2$ (381·5)	11·01 11·37	16·81 16·64	180—182 (55)

Phenyl derivative *III* did not react with isocyanates at room temperature and so did after a 5 h reflux in toluene, too. A similar situation was *e.g.* with 4-substituted 2-aminothiazoles, where the fusion of a heterocycle *via* addition-cyclization reaction did not take place, if the bulky substituent was located in position 4 (ref.[3]).

Thiazolo[3,2-*a*]-1,3,5-triazines *IV*–*VII* displayed in the electron spectrum a characteristic absorption band at λ_{max} 355 nm (log ε 3·86–4·28). The IR spectra of these derivatives revealed strong absorption bands at 1 538–1 547 cm^{-1} and less intense ones at 1 589–1 600 cm^{-1}, attributable to stretching vibrations of C=C bonds. The endocyclic C=N and C=O absorptions at the 1,3,5-triazine backbone were observed at 1 656–1 680 and 1 744–1 750 cm^{-1}, respectively. The ^1H NMR spectra of compounds *IV*–*VII* exhibited an approximately 0·2 ppm downfield shift of the methyl group resonance, when compared with that of the dimer *II*. The value of the coupling constant due to protons of the methyl group and that in position 2 of the thiazolo[3,2-*a*]-1,3,5-triazine ring, $^4J_{CH_3,H^2}$ = 2·5 Hz, was in a good agreement with the value reported for dearomatized thiazole ring in the dimer *II*. Mass spectra of compounds *IV*, *VI* and *VII* displayed peaks of molecular ions of low intensity (3·13, 0·77 and 0·78%, respectively). The principal direction of the molecular ion fragmentation was the retro Diels–Alder cleavage.

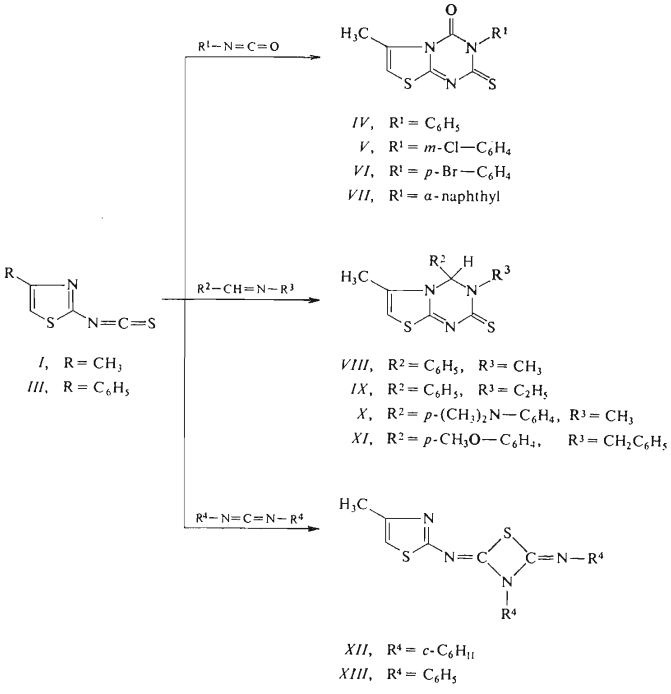
Reaction ability of the 1,3-diazadiene structure of 4-methyl-2-thiazolyl isothiocyanate towards the C=N double bond was also utilized in a [4+2] cycloaddition with some aldimines in which 5,6-disubstituted 5*H*-3-methylthiazolo-[3,2-*a*]-1,3,5-triazine-7-thiones *VIII*–*XI* (Table I) were prepared.

The UV spectra of compounds *VIII*–*XI* exhibited a characteristic absorption band at λ_{max} 348–354 nm (log ε 4·06–4·46); the IR spectra displayed noticeable absorption bands at 1 508–1 534 cm^{-1} associated with C=C stretching vibrations; absorption bands of the C=N bond (1 593–1 613 cm^{-1}) were less intense. Peaks of ions in the mass spectra were ascribable to species coming from the retro Diels–Alder fragmentation; only compound *VIII* showed the peak of molecular ion (0·13% relative intensity). Low solubility of the compounds made it impossible to take their ^1H NMR spectra.

Preparation of some thiazolo[3,2-*a*]-1,3,5-triazine derivatives has already been reported[3–7], the disadvantage of them being the use of 2-aminothiazole as starting material. Its semicyclic amidiene system leads in an addition-cyclization reaction with *e.g.* ethoxycarbonyl isothiocyanate exclusively to a mixture of products[6]. The [4+2] cycloaddition reactions of 4-methyl-2-thiazolyl isothiocyanate (*I*) with isocyanates and aldimines consituted a suitable one-step method furnishing selectively a single reaction product.

Reaction of *I* with dicyclohexyl- or diphenylcarbodiimide proceeded periselectively through C=S bond of the isothiocyanate group by a [2+2] manner to afford 1,3-thiazetidine derivatives *XII*, *XIII* (Scheme 1). The possible [4+2] cycloaddition product[1] has not been isolated. The two non-equivalent C=N bonds absorbed

in the IR spectra of *XII* and *XIII* at 1 640, 1 749 and 1 632, 1 747 cm^{-1}, respectively. The respective values 0·9 Hz (*XII*) and 0·8 Hz (*XIII*) of the coupling constants $^4J_{CH_3,H^5}$ in the ^1H NMR spectra show an aromatic character of the thiazole ring. The mass spectra revealed fragments arising from degradation of the four-membered heterocycle; only derivative *XIII* showed the peak of molecular ion. The absence of a C=S group in compounds *XII* and *XIII* was indicated by a negative Feigl test[1].



I, R = CH_3
III, R = C_6H_5

IV, $R^1 = C_6H_5$
V, $R^1 = m$-Cl—C_6H_4
VI, $R^1 = p$-Br—C_6H_4
VII, $R^1 = \alpha$-naphthyl

VIII, $R^2 = C_6H_5$, $R^3 = CH_3$
IX, $R^2 = C_6H_5$, $R^3 = C_2H_5$
X, $R^2 = p$-$(CH_3)_2N$—C_6H_4, $R^3 = CH_3$
XI, $R^2 = p$-CH_3O—C_6H_4, $R^3 = CH_2C_6H_5$

XII, $R^4 = c$-C_6H_{11}
XIII, $R^4 = C_6H_5$

EXPERIMENTAL

Melting points were measured with a Kofler micro hot-stage, IR spectra in KBr discs with a UR 20 (Zeiss, Jena), UV spectra in methanol with a UV VIS Specord (Zeiss, Jena), and electron impact mass spectra with an MS 902 S (AEI, Manchester) apparatures. The electron energy in the latter

was 70 eV, trap current 100 μA, ion-source temperature 110—150°C, according to volatility of the measured compound. The ^{1}H NMR spectra (ppm, δ scale) were recorded in $CDCl_3$ and hexadeuteriodimethyl sulfoxide with a Tesla BS 427 C instrument operating at 80 MHz. Aldimines and carbodiimides employed in this paper were prepared according to reference in[1].

4-Methyl-2-thiazolyl Isothiocyanate (*I*)

Solution of 2-amino-4-methylthiazole hydrochloride (15·0 g; 0·1 mol) in water (200 ml) was added during 1 h to a stirred mixture of thiophosgene (17·1 g; 0·15 mol), benzene (200 ml), water (50 ml) and calcium carbonate (17·5 g; 0·175 mol) at 5°C. After a 3 h stirring at room temperature the solid was suction-filtered and the benzene layer from the filtrate dried with sodium sulfate. The solvent was distilled off under reduced pressure and the residue chromatographed on a silica gel column, $CHCl_3$ being the eluent. The work-up of the second fraction afforded the oily *I* (5·6 g, 36%). For $C_5H_4N_2S_2$ (156·2) calculated: 17·93% N, 41·05% S; found: 17·64% N, 42·92% S. IR spectrum cm^{-1} ($CHCl_3$): 2 002 (N=C=S). ^{1}H NMR spectrum: 2·37 (d, 3 H, CH_3), 6·48 (q, 1 H, H^5). The work-up of the third fraction by crystallization from acetone gave 6-(4-methyl-2-thiazolyl)-3-methylthiazolo[3,2-*a*]-1,3,5-triazine-5,7-dithione (*II*) (1·8 g), m.p. 143—144°C. For $C_{10}H_8N_4S_4$ (312·4) calculated: 17·93% N, 41·05% S; found: 17·62% N, 41·13% S. UV spectrum (dioxane), λ_{max}, nm (log ε): 217 (4·60), 332 (4·24), 362 (3·83). IR spectrum, cm^{-1}: 1 549 (C=C), 1 606 (C=N).

4-Phenyl-2-thiazolyl Isothiocyanate (*III*)

A mixture of 4-phenyl-2-aminothiazole hydrochloride (21·2 g; 0·1 mol), water (200 ml), thiophosgene (17·1 g; 0·15 mol), dichloromethane (200 ml) and calcium carbonate (17·5 g; 0·175 mol) was stirred at room temperature for 5 h. The solid was suction-filtered and the dichloromethane layer from the filtrate was dried over calcium chloride. The solvent was distilled off under diminished pressure and the residue chromatographed on a silica gel column with $CHCl_3$ as an eluent. The work-up of the second fraction by crystallization from ether yielded *III* (8·4 g; 40%), m.p. 73—75°C. For $C_{10}H_6N_2S_2$ (218·3) calculated: 12·83% N, 29·37% S; found: 12·69% N, 29·21% S. UV spectrum (dioxane), λ_{max}, nm (log ε): 230 (4·56), 260 (4·30), 317 (3·95). IR spectrum, cm^{-1}: 2 010 (N=C=S). Mass spectrum, *m/z*: 218 ($M^{+\cdot}$).

Reaction of *I* with Isocyanates and Aldimines

A solution of isocyanate or aldimine (5 mmol) in benzene (5 ml) was added to *I* (0·78 g; 5 mmol) in benzene (10 ml) and the mixture was left to stand at an ambient temperature for 24 h. The separated crystals were filtered off, washed with benzene and crystallized from chloroform–acetone (derivatives *IV*—*VII*), or dimethylformamide (*VIII*—*XI*), (Table I).

Reaction of *I* with Carbodiimides

The solution of *I* (0·78g, 5 mmol) and carbodiimide (5 mmol) in benzene (30 ml) was refluxed for 1 h and allowed to stand at room temperature for 24 h. The solvent was distilled off *in vacuo* and the residue chromatographed on a silica gel column (eluent $CHCl_3$).

From the second fraction 3-cyclohexyl-4-cyclohexylimino-2-(4-methyl-2-thiazolylimino)-1,3-thiazetidine (*XII*), 0·85 g (47%) was separated as an oil, when dicyclohexylcarbodiimide was the starting product. For $C_{18}H_{26}N_4S_2$ (362·5) calculated: 15·45% N, 17·69% S; found: 15·44% N, 17·54% S. UV spectrum λ_{max}, nm (log ε): 209 (4·42), 245 (3·95), 320 (4·31). ^{1}H NMR

spectrum ($CDCl_3$): 1·26—2·15 (m, 20 H, 2 × C_6H_{10}), 2·33 (d, 3 H, CH_3), 2·89 (m, 1 H, $H_{cyclohexyl}$), 3·85 (m, 1 H, $H_{cyclohexyl}$), 6·52 (q, 1 H, H^5).

With diphenyl carbodiimide as the starting compound, the work-up of the first fraction by crystallization from acetone gave 3-phenyl-4-phenylimino-2-(4-methyl-2-thiazolylimino)--1,3-thiazetidine (*XIII*); yield 0·43 g, (25%), m.p. 137—138°C. For $C_{18}H_{14}N_4S_2$ (350·5) calculated: 15·54% N, 17·79% S; found: 15·76% N, 18·02% S. UV spectrum λ_{max}, nm (log ε): 207 (4·63), 220 (4·43), 262 (4·26), 328 (4·25). ^{1}H NMR spectrum: 2·32 (d, 3 H, CH_3), 6·61 (q, 1 H, $^5H_{thiazole}$), 7·11—7·52 (m, 10 H, 2 × C_6H_5). Mass spectrum, *m/z*: 350 ($M^{+\cdot}$).

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