Chlorine Displacement of Heterocyclic Halides by Enolate-oxygen: Synthesis of 1,3-Oxathiol-2-imines from 5-Chloro-1,2,4-thiadiazol-3(2*H*)-ones and Active Methylene Ketones and Esters

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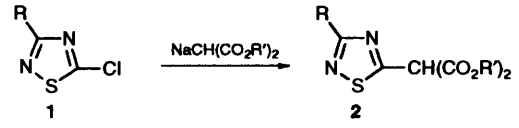
1,3-Oxathiol-2-imines **4–8** are conveniently prepared from 5-chloro-1,2,4-thiadiazol-3(2*H*)-one **3** and pentane-2,4-dione, methyl acetoacetate, dimethyl malonate and cyclohexane-1,3-diones, while the normal substitution product **9** is obtained from the thiadiazole **3** and Meldrum's acid.

Activated aryl and heteroaryl halides react with enolates to give *C*-substitution products. For instance, treatment of 5-chloro-1,2,4-thiadiazoles **1** with the sodium salt of malonic esters furnishes the 1,2,4-thiadiazole-5-malonates **2** (see Scheme 1).[1]

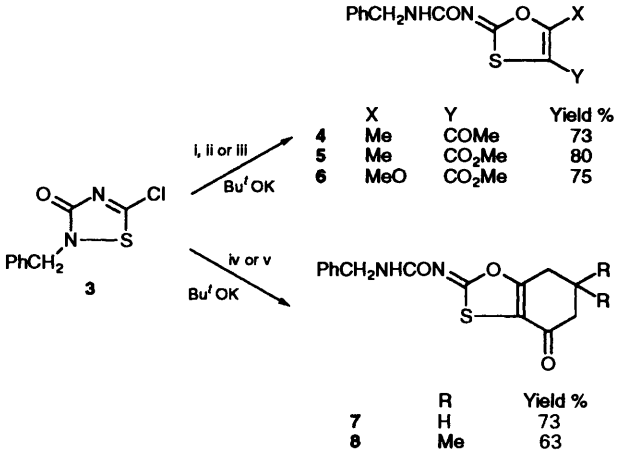


1 2

Scheme 1

We have found that the title thiadiazoles are different in this respect and yield 1,3-oxathioles[2] in most cases as a result of chlorine–oxygen substitution and ring transformation.

2-Benzyl-5-chloro-1,2,4-thiadiazol-3(2*H*)-one **3**, used in this work, was prepared by chlorination of methoxymethyl isothiocyanate in the presence of benzyl isocyanate following the procedure of Keilen and Undheim.†[3] This compound reacted with pentane-2,4-dione, methyl acetoacetate, dimethyl malonate, cyclohexane-1,3-dione and 5,5-dimethylcyclohexane-1,3-dione (dimedone) in the presence of one equiv. of potassium *tert*-butoxide in acetonitrile to give the oxathioles **4–8** as the sole reaction products (see Scheme 2). The structures were



	X	Y	Yield %
4	Me	COMe	73
5	Me	CO_2Me	80
6	MeO	CO_2Me	75

	R	Yield %
7	H	73
8	Me	63

Scheme 2 *Reagents:* i, $CH_2(COMe)_2$; ii, $MeCOCH_2CO_2Me$; iii, $CH_2(CO_2Me)_2$; iv, cyclohexane-1,3-dione; v, dimedone

established by IR, NMR, mass spectra and microanalyses. In particular, the ^1H NMR spectra show the presence of two doublets for the benzyl methylene protons, at δ 4.3 and 4.4 in a ratio of 9:1, due to restricted rotation about the amide side-chain. Although *Z*–*E* isomerization about the imine function of such compounds is fast at room temperature,[4] the stereochemistry is assumed to be *Z* (*vide infra*). The pertinent ^{13}C NMR data are listed in Table 1 and the assignments were based on the multiplicity of the coupled spectra.

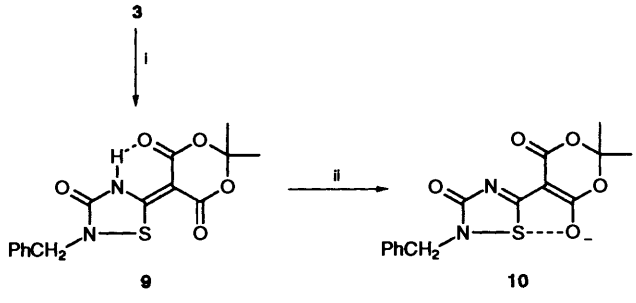
Table 1 Selected ^{13}C chemical shifts of the heterocycles[a]

Compound	Solvent	CH_2[b]	CON=	C-2	C-4	C-5
4	$(CD_3)_2SO$	43.3	160.6	171.5	118.9	153.6
5	$(CD_3)_2SO$	43.4	160.7	171.9	108.2	155.3
6	$(CD_3)_2SO$	43.3	160.6	168.1	82.5	156.0
7	$(CD_3)_2SO$	43.5	160.2	172.5	115.9[c]	163.8[c]
8	$CDCl_3$	44.6	160.4	175.0	116.6[c]	160.9[c]

[a] The chemical shifts are given in ppm downfield from TMS. [b] $^1J_{CH}$ = 137–138. [c] C-4 and C-5 refer to the oxathiole C-atoms.

Further information about structure **4** was obtained by a single crystal X-ray analysis (Fig. 1), the results of which are in accordance with those of a recently published analogue.[5] The carbamoylimino substituent is coplanar with the oxathiole ring, with a maximum deviation from the best plane through the eight atoms 1–8 of only 0.017 Å. The configuration of the imine substituent is *Z* and the S(3)–O(8) distance is 2.63 Å. This is shorter than the sum of the corresponding van der Waals radii (3.2 Å), but slightly longer than the Huggins constant energy distance of 2.58 Å,[6] indicating no covalent bonding but rather a close interacting contact.[7] Thus, compound **4** has no real thiapentalenic properties.[8]

2,2-Dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid)[9] reacted with the thiadiazole **3** under basic conditions to give the normal substitution product **9** (see Scheme 3). This compound exhibits three carbonyl absorptions in the ^{13}C NMR spectrum ($CDCl_3$), namely at δ 152.1 (amide CO), 161.8 and 164.7 (2 × ester CO), in consonance with model compounds.[10,11] The hydrogen atom is located at the thiadiazole N-4 atom and is hydrogen bonded to the neighbouring ester carbonyl (δ_H 10.85).



Scheme 3 *Reagents:* i, Meldrum's acid–Bu'OK; ii, DABCO

† The ring carbon absorptions in the ^{13}C NMR spectrum ($CDCl_3$) of compound **3** were erroneously assigned in the original publication;[3] they should read: δ_C 162.8 (^3J 2.5, C-3) and 166.8 (C-5).

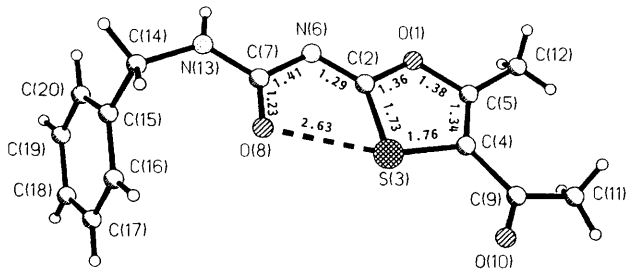
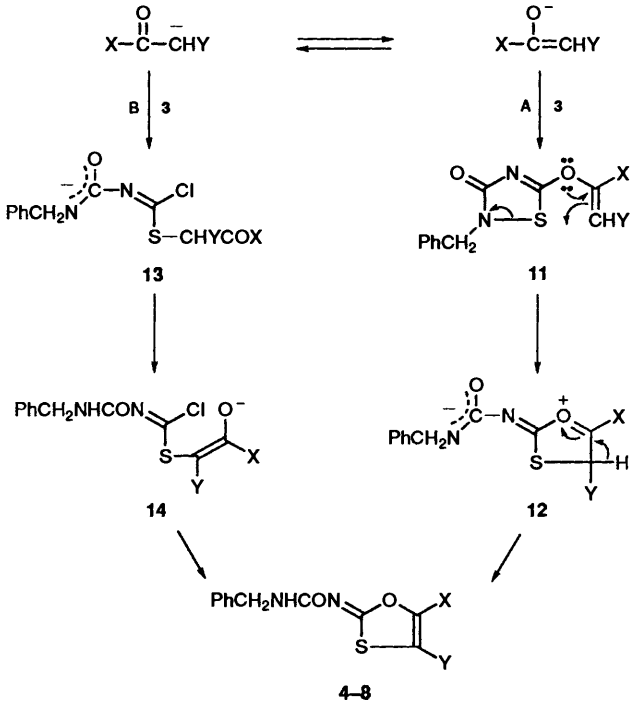


Fig. 1 Molecular structure of **4** with selected bond lengths (Å)

Removal of this hydrogen by DABCO (1,4-diazabicyclo-[2.2.2]octane) causes a downfield shift of the atoms C-3 (152.1→166.9) and C-5 (166.6→175.0), whereas the two ester carbonyls now absorb at δ 162.1 and 166.8. The magnetic non-equivalence of the ester carbonyls indicates restricted rotation around the C-5 atom, probably due to the S···O contact in structure **10** (see Scheme 3).[12]

Two pathways can be suggested for the formation of the 1,3-oxathioles **4–8** (Scheme 4). According to path A, the enolate



Scheme 4

oxygen displaces chlorine from the thiadiazole **3** to give the intermediate **11** which undergoes ring transformation and proton shift to yield the products **4–8**. The alternative pathway B comprises carbanion attack of the enolate at the sulfur atom of the thiadiazole **3** with concurrent ring-opening to give the substituted imidoyl chloride **13**, which then cyclizes *via* intermediate **14** to the products. Path B is favoured over path A by literature evidence that carbanions can attack heterocycles at sulfur with ring scission.[13] The overall reaction is in agreement with the HSAB (hard and soft acid and base) theory of Pearson (C-5 of **3** is hard and S-1 is soft).[14]

Experimental

Typical Procedure: 4-Acetyl-2-benzylcarbamoylimino-5-methyl-1,3-oxathiole **4**.—To a solution of pentane-2,4-dione (460 mg, 4.6 mmol) and potassium *tert*-butoxide (520 mg, 4.6 mmol) in dry acetontrile (30 cm^3) was added thiadiazole **3** (1.0 g, 4.4 mmol) dissolved in dry acetonitrile (20 cm^3), and the mixture was stirred overnight at room temperature. After removal of the solvent, the residue was washed successively with water (5 × 50 cm^3), ethanol (2 × 10 cm^3) and diethyl ether (2 × 10 cm^3), and dried *in vacuo* to give the pure oxathiole **4** (930 mg, 73%), m.p. 196–197 °C (Found: C, 57.8; H, 4.9. $C_{14}H_{14}N_2O_3S$ requires C, 57.92; H, 4.86%); ν_{max}(KBr)/cm^{-1} 3273s (NH) and 1652s, br (CO); δ_H[$(CD_3)_2SO$, 250 MHz] 2.45 and 2.55 (6 H, 2s, 2 Me), 4.3 and 4.4 (2 H, 2d in ratio 9:1, ^3J 6, CH_2), 7.15–7.35 (5 H, m, Ph), 8.4 and 7.85 (1 H, 2t in ratio 9:1, NH); δ_C[$(CD_3)_2SO$] 14.4 and 29.4 (2 Me), 43.3 (CH_2), 118.9 (C-4, $^3J_{CH}$ 4 and 2), 126.7, 127.1, 128.2 and 139.4 (Ph), 153.6 (C-5), 160.6 (CONH), 171.5 (C-2) and 190.5 (ketone CO); *m/z* 290 ($M^{\cdot+}$, 7%), 272 ($M^{\cdot+}$ − H_2O, 15), 160 (14.5), 91 ($C_7H_7^+$, 100), 65 (13) and 43 ($MeCO^+$, 81).

Note: The oxathioles **5** (80%, m.p. 159–160 °C), **6** (75%, m.p. 168.5–169.9 °C), **7** (73%, m.p. 185–186 °C) and **8** (63%, m.p. 192–193 °C), and the thiadiazole **9** (64%, m.p. 214–216 °C) were similarly prepared from the thiadiazole **3** and methyl acetoacetate, dimethyl malonate, cyclohexane-1,3-dione, dimedone (5,5-dimethylcyclohexane-1,3-dione) and Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) respectively.

Crystal Structure of Compound **4**.—*Crystal data:* $C_{14}H_{14}N_2O_3S$, M = 290.33. Triclinic, a = 7.724(1), b = 8.585(1), c = 10.927(1) Å, α = 74.951(6), β = 85.747(7), γ = 87.647(7)°, V = 697.57(9) $Å^3$ (by least-squares refinement on diffractometer angles for 20 automatically centred reflections, λ = 1.54178 Å), space group $P\bar{1}$, Z = 2, D_x = 1.382 g cm^{-3}. Yellow needles from ethanol. Crystal dimensions 0.35 × 0.10 × 0.10 mm^3, μ(Cu-Kα) = 21.49 cm^{-1}.

Data collection and processing. Siemens P4-PC diffractometer, ω–2θ mode with ω scan width 0.60 deg, ω scan speed 2–60 deg min^{-1}, graphite-monochromatized Cu-Kα radiation; 1867 reflections measured ($2.0 \leqslant 2\theta \leqslant 100.9$, $+h$, $\pm k$, $\pm l$), 1451 unique (merging R = 0.0413). Three check reflections measured every 100 reflections showed no significant decrease in intensity.

Structure analysis and refinement. Direct methods. Full matrix least-squares on F^2 with all non-hydrogen atoms anisotropic using SHELXL-93. Final R_1 and ωR_2 values of 0.0394 and 0.1158, respectively for 1271 $F > 4\sigma$(F). Siemens SHELXTL PLUS (PC version)[15] program used for other calculations and drawings.

Supplementary data. Lists of atomic coordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre.†

Acknowledgements

Financial support from the NFWO, the FKFO and the Ministerie voor Wetenschapsbeleid is gratefully acknowledged. This work has been accomplished with fellowships from the IWONL (for J. B.) and the NFWO (for W. D. and L. V. M.).

† For details of the CCDC deposition scheme, see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1994, issue 1.

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Paper 4/01142B
Received 24*th February* 1994
Accepted 18*th March* 1994