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ADDITION REACTIONS OF THIAZOL-5(4H)-ONES—IV[1]

SYNTHESIS, TAUTOMERISM AND ADDITION REACTIONS OF 2-PHENYLTHIAZOLE-5-THIOLS

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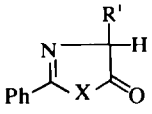
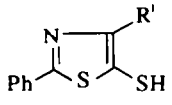
Abstract—4-Substituted 2-phenylthiazole-5-thiols **3** undergo addition reactions of a different type from those of their oxygen analogues, the oxazol- and thiazol-5(4H)-ones, since they exist in solution entirely in the thioenol tautomeric form. Their addition reactions involve only the exocyclic sulphur atom, and they behave as typical heteroaromatic thiols towards unsaturated systems, giving sulphides. A mesoionic thiazole-5-thiol, however, is shown to possess cycloaddition reactivity, undergoing cycloaddition-extrusion reactions with unsaturated systems comparable with well-established reactions of oxygen analogues.

4 - Substituted 2 - phenyl-oxazol - 5(4H) - ones (**1**) show substantial differences in addition reactivity compared with analogues in which the ring O atom is replaced with sulphur (i.e. thiazol-5(4H)-ones **2**)[1,2] due to different electronic distributions on corresponding ring atoms and on the exocyclic O atom in the two series. A shift in tautomeric equilibrium in favour of the enolic and mesoionic forms accompanies the substitution of the ring O atom of an oxazol-5-one by an S atom, and is a consequence of the greater aromatic character of thiazoles compared with correspondingly-substituted oxazoles.[cf 3]

We now report the synthesis of representative 2-phenylthiazole-5-thiols (**3**), and a study of their tautomeric behaviour and addition reactivity. In comparison with established features of the chemistry of corresponding oxazol-5(4H)-ones (**1**)[4,5] and thiazol-5(4H)-ones (**2**),[1,2] the thiols show a total shift in tautomeric equilibrium towards the thioenol form **3**, thus extinguishing the propensity of this ring system, as represented by oxazolones and thiazolones, towards Michael addition, ene reaction, and cycloaddition reactivity.[1,2] The mesoionic system (**4**) included in this study is shown to undergo cycloaddition reactions leading to products which we have also isolated from corresponding reactions of the thiazol-5-one analogue of **4**. It has been stated[5] that the mesoionic thiazol-5-thione ring system (e.g. **4**) shows a greatly diminished 1,3-dipolar cycloaddition reactivity compared with its oxygen analogues, but our results indicate that this ring system, as represented by **4**, shows substantial cycloaddition reactivity.



1: X = O
2: X = S



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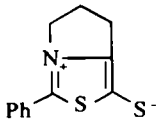

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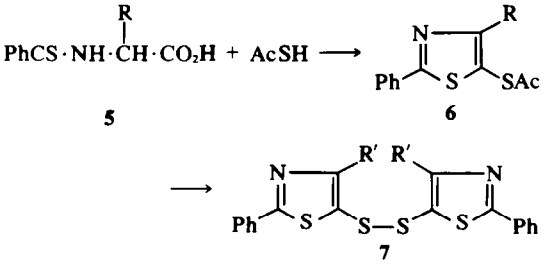
Synthesis and tautomeric behaviour of 2 - *phenylthiazole* - 5 - *thiols* (**3**). As part of a study of the reactions of amino-acids with thioacetic acid we showed[6] that α-thiobenzamido-acids (**5**) give 2 - phenyl - 5 - acetylmercaptothiazoles (**6**) by reaction with thioacetic acid at 100° during 12 hr. Aqueous alkaline hydrolysis of **6** in air gives the disulphide (**7**) from which the corresponding thiols (**3**) are obtained as fluorescent yellow-green oils, by reduction with sodium borohydride in methanol under N_2. NMR spectra of thiols prepared in this way showed that in both polar and non-polar solvents there was no tendency to isomerise into the mesoionic or thiono-tautomeric forms. This behaviour is in contrast with that of corresponding 2-phenyloxazol-5(4H)-ones, which exist as such in solvents through the whole polarity range,[3] and with that of corresponding thiazolones, which exist preferentially in the enolic form in solvents of moderate polarity, and entirely in the enolic form in the solid state.

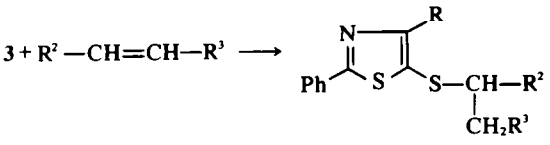


5 **6** **7**

Addition reactions of 4 - *substituted* 2 - *phenylthiazole* - 5 - *thiols* (**3**). Reactions of thiols (**3**) with representative electron-deficient alkenes led to the formation of adducts (**8**) through nucleophilic addition of the thiol to the alkene. No cycloadducts, Michael adducts, or ene reaction products, were isolated.

No reaction occurred between the thiols (**3**) and dimethyl acetylenedicarboxylate under conditions through which oxazol-5(4H)-ones and thiazol-5(4H)-ones give pyrroles in high yields through a cycloaddition-extrusion mechanism. Similarly, no adducts were formed between **3** and representative heterocumulenes (Ph·NCO, Ph·NCS), azo-compounds (diethyl azodicarboxylate, 4 - phenyl - 1,2,4 - triazolin - 3,5 - dione), or N - morpholino - 1 - cyclohexene; all these compounds are known to participate in cycloaddition reactions with oxazol-5-ones

or thiazol-5-ones, but the thiols (3), in contrast, readily undergo oxidation to the disulphide with a number of these unsaturated systems.



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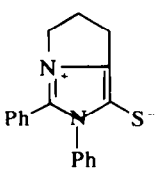
Addition reactions of the mesoionic 2-phenylthiazole-5-thiol (4). The mesoionic thiazole-5-thiol (4) reacted with excess phenyl isothiocyanate in refluxing toluene during 48 hr to give the mesoionic imidazole-5-thiol (9), through a cycloaddition-extrusion sequence already exemplified by the reaction of the thiazolone analogue of 4 with Ph·NCS and with other unsaturated systems.[1] Also, dimethyl fumarate underwent cycloaddition with the mesoionic thiazole-5-thiol (4) in refluxing toluene, to give the cycloaddition-extrusion 1:2-adduct (10), as obtained from the corresponding thiazolone and dimethyl fumarate.[1]



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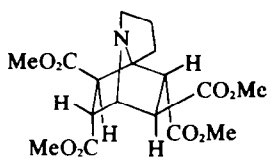

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A contrast has been drawn[5] between the mesoionic thiazol-5-one and thiazol-5-thione systems, the former being stated[5] to undergo typical 1,3-dipolar cycloaddition reactions which were not entered into by the 5-thiones; although no products were isolated from reaction mixtures containing 4 and maleic anhydride, dimethyl acetylenedicarboxylate, acrylonitrile, phenyl isocyanate, 1 - phenyl - 1,3,4 - triazolin - 2,5 - dione, diethyl azodicarboxylate or N - morpholino - 1 - cyclohexene, all of which give adducts (or in the latter case, N-thiobenzoylamino-acid morpholides) with thiazol-5-ones,[1,2] we have shown that the dipolar cycloaddition reactivity expected of 4 by virtue of its mesoionic structure is capable of being demonstrated in its reactions with phenyl isothiocyanate and with dimethyl fumarate. However, the room temperature reaction conditions under which thiazolone analogue of 4 gives cycloaddition-extrusion products[2] with dimethyl fumarate and with phenyl isothiocyanate are not sufficient to bring about corresponding reactions with 4.

EXPERIMENTAL

General. Procedures and instrumentation applied in the experimental work are as described in Part II.[2]

Preparation of 4-substituted 2 - phenylthiazole - 5 - thiols (3).

(a) A soln of 6[6] (R^1 = Ph·CH_2; 1·0 g) in piperidine (10 ml) was evaporated to dryness at room temp. *in vacuo*, and the residual yellow-green oil was stored under N_2 and used as such in reactions with unsaturated systems (*vide infra*).

(b) A soln of 7 (R^1 = Me),[6] 0·21 g, in MeOH (40 ml) was treated with 15 equiv $NaBH_4$. The mixture was purged with N_2 and subsequent operations were conducted under N_2. The yellow-green fluorescent soln was diluted with H_2O, and extracted into Et_2O and the water-washed extracts were dried ($MgSO_4$) and evaporated, giving 3 (R^1 = Me), as a yellow oil; UV (MeOH): λ_{max} 210 nm (log ϵ 4·24), 226 (4·24), 378 (4·30).

NMR spectra of 4-substituted 2 - phenylthiazole - 5 - thiols (3)

The spectra of 3 (R^1 = Me, Ph·CH_2) showed features in common at τ 1·9–2·8 (5H and 10H respectively, ArH) and at τ 5·9–6·6 (1H, SH, exchanged with ^2H_2O, broad s) in C^2HCl_3, acetone-$^2H_6$, dimethyl sulphoxide-$^2H_6$, or $C^2H_3O^2H$; the 4-methyl compound 3 (R^1 = Me) showed also a sharp singlet at τ 7·6–7·7, and the benzyl analogue 3 (R = Ph·CH_2) showed instead a singlet for the methylene protons at τ 5·8, with no degeneracy as should be observed if the thione tautomer is present in these solutions in amounts greater than *ca.* 2–3%.

Addition of 4 - benzyl - 2 - phenylthiazole - 5 - thiol (3; R^1 = $PhCH_2$) *to maleic anhydride*

A soln of 6 (R^1 = $PhCH_2$; 0·487 g, 1·5 mmol)[6] in excess piperidine was evaporated, and a soln of maleic anhydride (0·147 g, 1·5 mmol) in acetone (10 ml) was added to the resulting thiol under N_2. After 2 hr at room temp. the soln was evaporated, and the residual pale yellow oil was triturated with ether-petrol containing traces of piperidine to give 8 (R^1 = $PhCH_2$, R^2 or R^3 = CO·NC_5H_{10}, R^3 or R^2 = $CO_2^-NH_2^+C_5H_{10}$), m.p. 109–11° (dec), 0·40 g (49%). (Found: C, 65·0; H, 7·0; N, 7·6; S, 11·4. $C_{36}H_{37}N_3O_3S_2$ requires: C, 65·3; H, 6·75; N, 7·6; S, 11·65%).

Addition of 4 - methyl - 2 - phenylthiazole - 5 - thiol (3; R^1 = Me) *to maleic anhydride*

A soln of the thiol, prepared from 7 (1·03 g, 5 mmol), in MeOH (150 ml) was mixed with a soln of maleic anhydride (1·96 g, 20 mmol) in MeOH (10 ml). After 30 min at room temp. under N_2 the soln was evaporated to give a pale yellow oil, which on trituration with ether gave 8 (R^1 = Me, R^2 or R^3 = MeO_2C R^3 or R^2 = CO_2H), 0·72 g (43%), m.p. 153–5°. (Found: C, 53·2; H, 4·35; N, 3·9; S, 19·3. $C_{15}H_{15}NO_4S_2$ requires: C, 53·4; H, 4·5; N, 4·15; S, 19·0%); NMR (dimethyl sulphoxide-$^2H_6$): τ −2·7 (1H, CO_2H, broad s, exchanged with ^2H_2O), 1·95–2·20 (2H, ArH, m), 2·3–2·6 (3H, ArH, m), 6·1 (1H, –CH–CH_2–, t, J = 7·5 Hz), 6·35 (3H, OCH_3, s), 7·2 (2H, –CH–CH_2–, d, J = 7·5 Hz),·7·55 (3H, –CH_3, s). MS: *m/e* 103 (95%), 121 (46), 175 (19), 206 (95), 337 (M^+, 100%).

Addition of 4 - benzyl 2 - phenylthiazole - 5 - thiol (3; R^1 = Ph·CH_2) *to dimethyl fumarate*

A soln of the thiol, from the S-acetyl derivative[6] 6 (R^1 = Me; 0·325 g, 1 mmol) in excess piperidine was evaporated, and the residue was dissolved in toluene (10 ml) containing dimethyl fumarate (0·432 g, 3 mmol). The soln was heated under reflux under N_2 during 2 hr, then evaporated *in vacuo*; the residual oil on trituration with Et_2O gave 8 (R^1 = $PhCH_2$, R^2 = R^3 = CO_2Me), 0·21 g, (49%), m.p. 83–5° from petrol (b.p. 80–100°). (Found: C, 61·7; H, 5·05; N, 3·15; S, 15·0. $C_{22}H_{21}NO_4S_2$ requires: C, 61·8; H, 4·95; N, 3·25; S, 14·95%); UV (MeOH): λ_{max} 216 nm (log ϵ 3·22), 310 (3·22); NMR (C^2HCl_3): τ 1·95–2·15 (2H, ArH, m), 2·4–2·8 (8H, ArH, m), 5·75 (2H, –CH_2Ph, s), 6·1 (1H, –CH–CH_2–, t, J = 6·0 Hz), 6·30 (3H, OCH_3, s), 6·33 (3H, OCH_3, s), 7·15 (2H, –CH–CH_2–, d, J = 6·0 Hz); MS: *m/e* 103 (38), 121 (28), 179 (42), 250 (100), 281 (75), 427 (M^+, 57%).

Addition of 4 - methyl 2 - phenylthiazole - 5 - thiol (3; R = Me) *to dimethyl fumarate*

A soln of 3 (R^1 = Me), prepared from the corresponding disulphide[6] (0·206 g, 1 mmol), in MeOH (40 ml) containing dimethyl fumarate (0·72 g, 5 mmol) was set aside at room temp. during 2 hr. Evaporation gave a pale yellow solid (0·14 g), m.p. 60–5° which on recrystallisation from ether-petrol gave (8; R^1 = Me; R^2 = R^3 = CO_2Me), m.p. 73–5°, 0·09 g (25%). (Found: C, 54·8; H, 4·75; N, 3·95; S, 18·3. $C_{16}H_{17}NO_4S_2$ requires: C, 54·65; H, 4·9; N, 4·0; S, 18·25%); UV (MeOH): λ_{max} 216 nm (log ϵ 4·06), 310 (4·24); NMR (C^2HCl_3): τ 1·9–2·2 (2H, ArH, m), 2·4–2·7 (3H, ArH, m), 6·10 (1H, –CH–CH_2–, t, J = 6·0 Hz), 6·25 (3H, OCH_3, s), 6·30 (3H, OCH_3, s), 7·10 (2H, –CH–CH_2–, d, J = 6·0 Hz), 7·50 (3H, CH_3, s); MS: *m/e* 103 (98), 121 (43), 174 (68), 206(92), 351(M^+, 100%).

Reaction of anhydro - 2 - phenyl - 3,4 - trimethylenethiazol - 5 - thiolium hydroxide (**4**) *with dimethyl fumarate*

The mesoionic thiazol-5-thione[1] **4** (0·233 g, 1 mmol) and dimethyl fumarate (0·576 g, 4 mmol) were mixed with toluene (10 ml); on warming, a deep red soln was obtained which became pale orange in colour during 18 hr under reflux. Evaporation *in vacuo* gave an orange oil which on trituration with MeOH gave **10** (0·20 g, 45%), m.p. 164–6°, identical with the reaction product from dimethyl fumarate and the thiazolone analogue of **4**.[1]

Attempted reaction of 4 - substituted 2 - phenylthiazole - 5 - thiols (3; R^1 = Me, $PhCH_2$) *with other unsaturated systems*

Although the fluorescence of the thiols was generally discharged within a short time after mixing solns of the thiols with dimethyl acetylenedicarboxylate, phenyl isocyanate, phenyl isothiocyanate, 4-phenyltriazolin-3,5-dione, and N-morpholino-1-cyclohexene, the only product which could be isolated in all cases (except the alkyne, which gave a black intractable tar) was **7** corresponding to the starting thiol.

Reaction of anhydro - 2 - phenyl - 3,4 - trimethylenethiazol - 5 - thiolium hydroxide (**4**) *with phenyl isothiocyanate*

(a) After 48 hr at room temp., a soln of the mesoionic thiazole-5-thione (0·233 g, 1 mmol) in phenyl isothiocyanate (2 ml) gave back the starting material on evaporation *in vacuo*.

(b) A soln of the mesoionic thiazol-5-thione (0·233 g, 1 mmol) and phenyl isothiocyanate (0·81 g, 6 mmol) in toluene (10 ml) was heated under reflux during 48 hr. The resulting soln was evaporated *in vacuo* giving **9** (0·16 g; 55%), m.p. 209° (dec), identical with the product of reaction of phenyl isothiocyanate with the thiazolone analogue of **4**.[1]

Attempted reaction of anhydro - 2 - phenyl - 3,4 - trimethylenethiazol - 5 - thiolium hydroxide (**4**) *with other unsaturated systems*

Reaction mixtures containing excess maleic anhydride, dimethyl acetylenedicarboxylate, acrylonitrile, phenyl isocyanate, 4-phenyltriazolin-3,5-dione, diethyl azodicarboxylate, or N-morpholino-1-cyclohexene and **4** remained unchanged after 24 hr at room temp. with Et_2O or acetone as solvent. However, in refluxing benzene or toluene during 1–12 hr, the mixture darkened and gave on working up only intractable black tars.

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