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

CYCLOADDITION REACTIONS OF MESOIONIC THIAZOL-5-ONES

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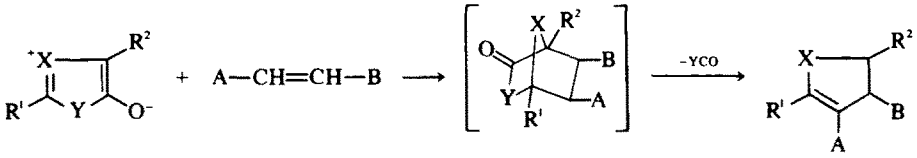
Abstract—In contrast with the behaviour of mesoionic oxazol-5-ones, corresponding thiazol-5-ones give stable cycloadducts with electron-deficient alkenes. However, the thiazolones undergo cycloaddition-extrusion reactions with alkynes and with heterocumulenes, in many cases giving products identical with those from corresponding oxazolones. Examples of the influence of thiazolone substituents on the course of these cycloaddition reactions are provided by comparison of results of reactions of differently-substituted mesoionic thiazol-5-ones with phenyl isocyanate, phenyl isothiocyanate, or dimethyl furmarate.

A feature of 1,3-dipolar cycloaddition reactions of mesoionic oxazol-5-ones,[2] the ready loss of CO_2 from an initially-formed cycloadduct (Scheme), is the basis of useful new synthetic procedures in heterocyclic chemistry.[3] Corresponding reactions reported for mesoionic thiazol-5-ones (**1**)[4-7] involve a similar ready loss of carbonyl sulphide from corresponding 1,3-dipolar cycloadducts. Although a large number of examples of reactions represented by Scheme 1 are to be found in the literature, only in very few cases have cycloadducts been isolated from reactions of mesoionic heterocycles with unsaturated systems (from an oxazol-5-imine,[8] from a 1,3-dithiol-5-one,[9] from a 1,3,4 - thiadiazole - 5 - imine,[10] and from a thiazol - 5 - one[6]).

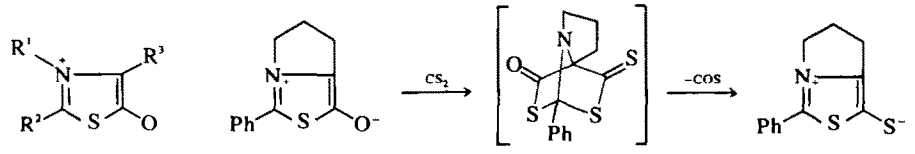
We now report cycloaddition reactions performed under mild conditions with a mesoionic 4-substituted 2 - phenylthiazol - 5 - one (**2**),[11] providing examples of addition reactions leading to different types of products in most cases from those obtained in corresponding oxazolone reactions. After the completion of this work,[12] the isolation of stable cycloadducts formed under mild conditions between a mesoionic thiazol - 5 - one lacking a 4-substituent (**1**; R^1 = Me, R^2 = Ph or p-Cl-C_6H_4, R^3 = H) and either N-phenylmaleimide or dimethyl fumarate was reported.[6] Comparison of our results with those reported by Potts *et al.*[6] reveals a measure of control by thiazolone substituents on the course of the addition reaction in some cases.

Mesoionic thiazol - 5 - ones (**1**, **2**) are readily available[4-6,11,13] from N - substituted - N - thiobenzoyl - α - amino-acids, and we have used **2**, prepared from proline by successive thiobenzoylation and cyclisation with acetic anhydride or with trifluoroacetic acid,[11] in the present work.

The ease with which a mesoionic thiazol - 5 - one undergoes cycloaddition reactions with heterocumulenes, and the instability of the initially-formed cycloadduct, is shown in the reaction of **2** with carbon disulphide to give **3**,[5] which is formed by dissolving **2** in carbon disulphide and evaporating the solution at room temperature in a stream of cold air. Reactions of **2** with phenyl isothiocyanate and with phenyl isocyanate gave **4** and **5** respectively as the products of a cycloaddition-extrusion sequence, **5** being formed by condensation of the initial cycloadduct with excess phenyl isocyanate. Potts *et al.*[6] found that an N - arylthiazol - 5 - one with a proton at C-4 (**1**; R^1 = Me, R^2 = Ph, R^3 = H) reacted with phenyl isothiocyanate to give the cycloaddition-extrusion products (**6** and **7**); we find that under mild conditions, **2** gives a 1:2-adduct corresponding to **6**, which on recrystallisation from benzene gives **4** by extrusion of PhNCS. The reaction products from (**1**; R^1 = Me, R^2 = Ph, R^3 = H) and phenyl isocyanate reported by Potts *et al.*[6] are the initial cycloadduct (**8**) and the oxygen analogue of **7**, providing another substantial contrast with the corresponding reaction with **2**, which gives instead the cycloaddition-



Scheme 1.



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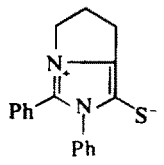
extrusion product (**5**), presumably by way of an initial cycloadduct corresponding to **8**. The structure assigned to the 1:3-adduct is based upon spectroscopic and analytical data, and although the adduct (**5**) represents a novel type of cycloaddition-extrusion product, evidence for the incorporation of isocyanate dimers into cyclic structures has been obtained in other studies.[14]



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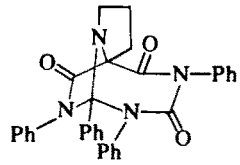

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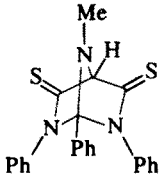

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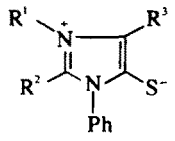

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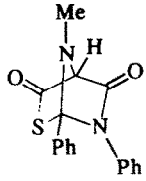

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In cycloaddition reactions with alkynes, mesoionic thiazol - 5 - ones behave like their oxygen analogues in giving pyrroles;[4,6] this applies also to the 4-substituted thiazol - 5 - one (**2**), which gives the pyrrole (**9**) with dimetyl acetylenedicarboxylate, although we find that conditions milder than those used in reported studies[4,6] are adequate. Even so, attempts to isolate the putative initial cycloadduct from which **9** is derived by loss of COS have not been successful, and the stable cycloadduct formed from a mesoionic oxazol - 5 - imine and ethyl phenylpropiolate[8] remains the only example of this structural type.

Maleic anhydride reacts with **2** to give the stable cycloadduct (**10**) under mild conditions, as have been used[6] in the preparation of an analogue of **10** from N - arylthiazol - 5 - ones (**1**) and N-phenylmaleimide. However, the cycloaddition-extrusion product (**11**) was obtained from **2** and dimethyl fumarate under mild conditions; this contrasts with the reported[6] formation of a cycloadduct corresponding to **10**, from **1** and dimethyl fumarate. Extrusion of COS from **10** is a prominent fragmentation mode under electron impact, the mass spectrum containing a peak at *m/e* 60 as base peak, with fragment of largest mass appearing at *m/e* 255 (M-60).

Attempted cycloaddition of **2** to morpholinocyclohexene gave N-thiobenzoylproline morpholide **12**. Although similar results are obtained with the corresponding non-mesoionic thiazol-5(4H)-ones[1] (which are readily aminolysed[15]), the mesoionic thiazolone **2** is not cleaved by amines,[11] and it is difficult to account for this result.

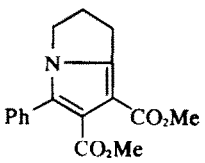
A mesoionic thiazol-5-one (**1**; R^1 = Me, R^2 = R^3 = Ph) has been reported to give the 1,2,4-triazole (**13**) together with tetra - ethyl hydrazinetetracarboxylate by reaction with diethyl azodicarboxylate;[7] however, **2** gives only diethyl hydrazine - 1,2 - dicarboxylate in this reaction, possibly because the reaction depends upon stabilisation of the intermediate azomethine ylide by substituents, provided in **1** (R^1 = Me, R^2 = R^3 = Ph) but not present in **2**.

EXPERIMENTAL

General. Procedures and instrumentation applied in experimental work are as described in Part II.[1]

Reaction of anhydro - 5 - hydroxy - 2 - phenyl - 3,4 - trimethylenethiazolium hydroxide (**2**) *with carbon disulphide*

The thiazolone (0·434 g) was dissolved in excess CS_2 (10 ml), and resulting golden yellow soln was evaporated in a stream of cold air. The residue on crystallisation from acetone gave **3**, orange needles, m.p. 194–6° (Found: C, 61·45; H, 5·05, N, 6·1; S, 27·6. $C_{12}H_{11}NS_2$ requires: C, 61·75; H, 4·75; N, 6·0; S, 27·5%); MS: *m/e* 233 (98%), 218 (20), 121 (100).



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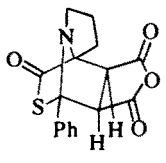

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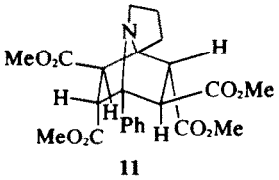

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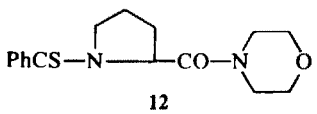

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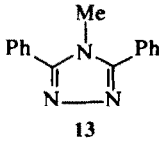

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Reaction of anhydro - 5 - hydroxy - 2 - phenyl - 3,4 - trimethylenethiazolium hydroxide (2) *with phenyl isothiocyanate*

(i) A suspension of the thiazolone (2·4 g) in excess phenyl isothiocyanate (10 ml) was stirred at room temp for 15 min, during which time a clear soln had formed, followed by the formation of a yellow ppt. The ppt was filtered off and recrystallised from benzene, giving **4**, (2·6 g; 81%), m.p. 208° (dec). (Found: C, 73·9; H, 5·4; N, 9·8; S, 10·9. $C_{18}H_{16}N_2S$ requires: C, 73·95; H, 5·5; N, 9·6; S, 10·95%); UV(MeOH): λ_{max} 210 nm (log ϵ 4·41), 230 (4·31), 348 (3·94); MS: *m/e* 77 (44%), 78 (100), 105 (33), 180 (17), 291 (2), 292 (M^+, 3).

(ii) The ppt from an identical mixture was washed with MeOH and Et_2O to give **6** (R^1R^1 = $-CH_2-CH_2-CH_2-$, R^2 = Ph), m.p. 210° (dec) (Found: C, 70·0; H, 5·0; N, 9·8; S, 15·0. $C_{25}H_{21}N_3S_2$ requires: C, 70·5; H, 5·9; N, 9·85; S, 15·0%).

Reaction of anhydro - 5 - hydroxy - 2 - phenyl - 3,4 - trimethylenethiazolium hydroxide (2) *with phenyl isocyanate*

The thiazolone (0·868 g) was dissolved in excess anhyd phenyl isocyanate (5 ml) at 100°; after 45 min at 100° the soln was evaporated *in vacuo* giving a yellow oil, which on trituration with CCl_4 gave a yellow solid from which **5** was obtained on crystallisation from CCl_4-ether, yield 0·45 g (22%), m.p. 225–6° (dec). (Found: C, 74·4; H, 5·15; N, 10·6. $C_{32}H_{26}N_4O_3$ requires: C, 74·75; H, 5·1; N, 10·9%); NMR (C^2HCl_3): τ 2·5–3·0 (20H, ArH, m), 6·45 (2H, $-CH_2-N=$, t, J = 6·0 Hz), 7·20 (2H, $-C-CH_2-CH_2-$, t, J = 6·0 Hz), 7·5–8·0 (2H, $-CH_2-CH_2-CH_2-$, m); MS: *m/e* 77 (100%), 119 (65), 130 (19), 180 (90), 22 (11), 222 (14), 276 (42), 276 (42), 514 (M^+, 15).

Reaction of anhydro - 5 - hydroxy - 2 - phenyl - 3,4 - trimethylenethiazolium hydroxide (2) *with dimethyl acetylenedicarboxylate*

(i) A soln of **2** (0·434 g, 2 mmol) and dimethyl acetylenedicarboxylate (0·71 g, 5 mmol) in toluene (10 ml) was heated under reflux during 6 hr. The soln was evaporated *in vacuo*, and the residual oil on trituration with petrol (b.p. 60–80°) gave a pale yellow solid (0·65 g, 90%), m.p. 150–5°, from which on recrystallisation from MeOH, **9**, (0·50 g, 80%), m.p. 156–8° was obtained. (Found: C, 68·3; H, 5·8; N, 4·65. $C_{17}H_{17}NO_4$ requires: C, 68·2; H, 5·7; N, 4·7%); MS: *m/e* 180 (40%; 181 (86), 209 (30), 210 (18), 267 (32), 268 (100), 299 (M^+, 84).

(ii) The reactants as in (i), in acetone (20 ml) gave the pyrrole (0·19 g, 32%) after 24 hr at room temp.

Reaction of anhydro - 5 - hydroxy - 2 - phenyl - 3,4 - trimethylenethiazolium hydroxide (2) *with maleic anhydride*

A suspension of the thiazolone (1·19 g, 5·5 mmol) in a soln of maleic anhydride (1·62 g, 16·5 mmol) in ether (50 ml) gave a clear soln, then a pale yellow suspension, on stirring at room temp. during 30 min. The ppt (1·1 g, 70%) on crystallisation from CCl_4-ether, gave **10**, (0·58 g; 37%), m.p. 175–8° (dec). (Found: C, 63·2; H, 6·75; N, 9·15; S, 10·4. $C_{16}H_{13}NO_4S$ requires: C, 63·15; H, 6·6; N, 9·2; S, 10·53%); IR (Nujol): ν_{max} 1860, 1780 (anhydride C=O), 1690 (S–CO), 1220 cm^{-1}; NMR (acetone-$^2H_6$): τ 2·5 (5H, ArH, s), 5·35 (1H, $-CH-CH-$, d, J = 7·0 Hz), 6·35 (1H, $-CH-CH-$, d, J = 7·0 Hz), 6·6–7·0 (1H, $N-CH_2-$, m), 7·5–7·9 (4H, $-CH_2-CH_2-$, m); MS: *m/e* 60 (100%), 182 (28), 183 (42), 211 (3), 255 (11), no M^+.

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

A suspension of the thiazolone (0·434 g, 2 mmol) in a soln of dimethyl fumarate (0·864 g, 6 mmol) in acetone (20 ml) was stirred at room temp. during 3 hr. The resulting clear soln was evaporated *in vacuo*, trituration with MeOH of the residual oil giving colourless solid (0·105 g, 12%) which on recrystallisation from MeOH gave **11**, (0·95 g; 11%), m.p. 164–6°. (Found: C, 62·0; H, 6·1; N, 2·9. $C_{23}H_{27}NO_8$ requires: C, 62·0; H, 6·1; N, 3·15%); NMR (C^2HCl_3): τ 2·2–2·5 (5H, ArH, m), 5·5 (1H, $-CH-CH-$, d, J = 6·0 Hz), 5·9–7·2 (5H, 3 methine protons, $-CH_2-N$, m), 6·18 (3H, CH_3O-, s), 6·20 (3H, CH_3O-, s), 6·28 (3H, CH_3O-, s), 6·60 (3H, CH_3O-, s), 7·7–8·0 (4H, $-CH_2-CH_2-C$, broad s); MS: *m/e* 182 (72%), 21 (33), 242 (100), 301 (26), 445 (M^+, 5).

Reaction of anhydro - 5 - hydroxy - 2 - phenyl - 3,4 - trimethylenethiazolium hydroxide (2) *with morpholinocyclohexene*

The thiazolone (0·217 g) was heated under reflux with N - morpholino - 1 - cyclohexene (0·35 g, 2 mmol) in toluene (5 ml) during 1 hr. The residue obtained on evaporation of the soln gave **12** after trituration with ether and recrystallisation from MeOH; yield 30%, m.p. 165–7°. (Found: C, 63·2; H, 6·75; N, 9·15; S, 10·4. $C_{16}H_{20}N_2O_2S$ requires: C, 63·15; H, 6·6; N, 9·2; S, 10·55%); MS: *m/e* 121 (100), 304 (M^+, 40%).

Attempted reaction of anhydro - 5 - hydroxy - 2 - phenyl - 3,4 - trimethylenethiazolium hydroxide (2) *with diethyl azodicarboxylate*

The thiazolone (0·217 g, 1 mmol) and diethyl azodicarboxylate (2–5 mmol) were reacted (a) in refluxing toluene during 2 hr, (b) in refluxing toluene during 12 hr, (c) in acetone during 2 hr at room temp, and (d) in ether during 24 hr at room temp, giving in every case diethyl hydrazine - 1,2 - dicarboxylate as sole isolatable product, m.p. 134–5° (lit.[15] m.p. 135°); IR (Nujol): 3250, 3030, 2990, 1750, 1700 and 1530 cm^{-1}.

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