The Reaction of Nitriles with Mercaptoacetic Acid. A New Synthesis of Thiazole Derivatives

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The reaction of mercaptoacetic acid with nitriles was investigated. Whereas 4-hydroxythiazole derivative could be obtained from the reaction of benzoylacetonitrile and of ethyl cyanoacetate with mercaptoacetic acid, a bithiazole derivative was obtained on treatment of benzonitrile with the same reagent. The behaviour of the synthesised thiazole derivatives towards aromatic aldehydes and hydrazines is reported.

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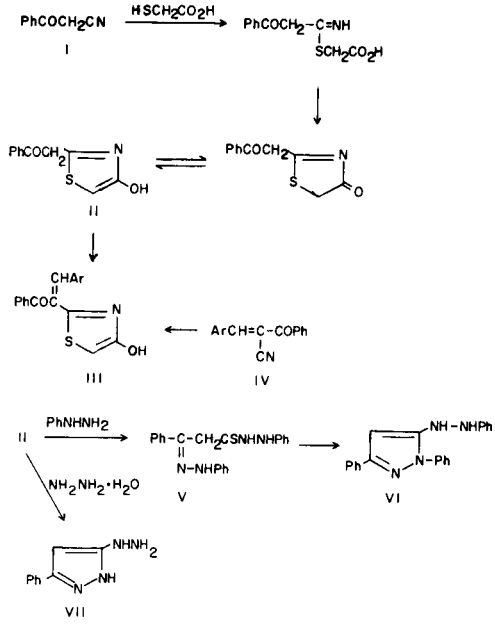
In spite of enormous literature reported for the synthesis of thiazole derivatives (1), relatively few successful syntheses of 5-unsubstituted 2-thiazolin-4-one derivatives have been reported (1). The instability of these derivatives has certainly hindered attempted syntheses (2-4). In a previous paper we have reported the synthesis of several 2-cyanomethyl-2-thiazolin-4-one derivatives from the reaction of mercaptoacetic acid with malononitrile derivatives (5). The products obtained were fairly stable under both acidic and basic conditions in contrast to 2-alkyl- and 2-aryl-2-thiazolin-4-ones.

In the present paper we report the synthesis of several other stable 2-thiazolin-4-one derivatives *via* the reaction of activated nitriles with mercaptoacetic acid. Thus, it has been found that benzoylacetonitrile (I) reacts with mercaptoacetic acid to yield a colourless product of molecular formula $C_{11}H_9NO_2S$ (M^+ 219). The ir of this product revealed strong absorptions at 1730 cm^{-1} and at 1620 cm^{-1} indicating a carbonyl group and a carbon carbon double bond, respectively, and a band extending from 2100 cm^{-1} to 3120 cm^{-1} indicating a chelated hydroxyl group. The ^1H nmr of this product exhibits a multiplet for five protons at δ 7.4-7.9 ppm and two sharp singlets at δ 6.75 and 3.80 ppm for one and two protons, respectively. Based on these data, a 4-hydroxythiazole structure II was suggested for this product. Thus prepared, compound II proved to be stable compared with 2-aryl-4-hydroxythiazoles. Thus, it did not dimerize or polymerize on heating in solvents like ethanol, pyridine, or acetic acid.

Compound II condensed with aromatic aldehydes to yield the arylidene derivatives III. The latter could also be obtained from the reaction of α-(arylmethylene)benzoylacetonitrile (IV) and mercaptoacetic acid. The thiazole ring in II was cleaved by the action of phenylhydrazine to yield the *N*-phenylhydrazide derivative of the thiocarboxylic acid V. When II was treated with phenylhydrazine in the absence of a solvent, the phenylhydrazinopyrazole derivative VI was formed. Compound VI could be also obtained from the reaction of V and phenylhydrazine in the absence of solvent. Hydrazine hydrate reacted with II to yield the hydrazinopyrazole derivative VII. The structures of V-VII were inferred from analytical and spectral data.

An investigation was undertaken to explore the potential utility of the reactions of some activated nitriles with mercaptoacetic acid as a route for the synthesis of thiazoles. It has been found that ethyl cyanoacetate reacts with mercaptoacetic acid in refluxing acetic acid to yield the previously reported thiazole derivative VIII (4). However, in refluxing pyridine a resin from which no simple product could be isolated was formed. Compound VIII reacted with benzaldehyde to yield the benzylidene derivative for which structure IX or X seemed possible. Structure X could be excluded because the benzylidene derivative thus prepared was different from the authentic X synthesised from ethyl cyanocinnamate (XI) and mercaptoacetic acid. Attempts to effect condensation of the exocyclic activated methylene in VIII with aromatic aldehydes were unsuccessful. The unreactivity of the



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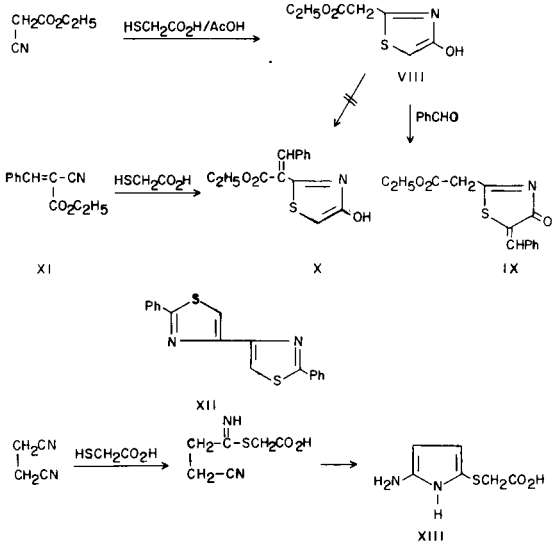
methylene group of VIII towards benzaldehyde as compared to that in II can be interpreted in terms of the increased acidity of the methylene hydrogen induced by replacing the carbonyl group by an ester group.

Mercaptoacetic acid did not react with acetonitrile under a variety of conditions. However, it reacted with benzonitrile in boiling pyridine to yield the bithiazole derivative XII.

Succinonitrile reacted with mercaptoacetic acid to yield a monoaddition product. The ir spectrum of this product revealed the absence of a cyano group absorption. The presence of a free acidic function could also be indicated from the observed reactivity of this product with aqueous sodium hydrogen carbonate. Structure XIII was thus suggested for this product. Further investigations on the reactivity of other mercaptocarboxylic acids towards nitriles is now being undertaken and work in progress will be the subject of other communications.



EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded in potassium bromide on a Pye Unican Sp 1000. ^{1}H Nmr spectra were measured in DMSO-d_6 on a Varian A-60 HZ using TMS as internal standard and chemical shifts are expressed as δ in ppm. Analytical data were obtained from the analytical data unit at Cairo University.

2-Phenacyl-4-hydroxythiazole (II).

A solution of I (0.1 mole) in pyridine or acetic acid (100 ml) was treated with mercaptoacetic acid (0.1 mole). The reaction mixture was refluxed for six hours and evaporated *in vacuo*, the remaining product was collected by filtration and crystallized from ethanol.

Compound II formed colourless crystals, m.p. 212°, yield 56%; ir: 3120-2100 (conjugated OH), 1730 (CO) and 1620 cm^{-1} (C=C); ^{1}H nmr: 7.9-7.7 (2H, the two *ortho* aromatic protons), 7.7-7.4 (m, 3H, *meta* and *para* phenyl protons), 6.73 (s, 1H, thiazole proton) and 3.8 (s, 2H, CH_2).

Anal. Calcd. for $C_{11}H_9NO_2S$: C, 60.3; H, 4.1; N, 6.4; S, 14.6. Found: C, 60.5; H, 4.5; N, 5.9; S, 14.4.

3-Aryl-1-phenyl-2(4-hydroxythiazolyl)-2-propen-1-one (III).

Method A.

A solution of II (0.1 mole) in ethanol (100 ml) was treated with the appropriate aromatic aldehyde (0.12 mole) and a few drops of piperidine. The reaction mixture was refluxed for three hours and then evaporated *in vacuo*. The remaining product was triturated with water and the resulting solid product was collected by filtration and crystallised from ethanol.

Compound III (Ar = Ph).

This compound formed yellow crystals, m.p. 189°, yield 70%; ir 3100-2300 (conjugately chelated OH), 1700 (CO) and 1610 cm^{-1} (C=C); ^{1}H nmr: 7.8-7.3 (m, 11H, 2 Ph and arylmethylene protons) and 6.6 (s, 1H, thiazole proton).

Anal. Calcd. for $C_{18}H_{13}O_2NS$: C, 70.3; H, 4.2; N, 4.6; S, 10.4. Found: C, 70.0; H, 4.3; N, 4.8; S, 10.0.

Compound III (Ar = C_6H_5Cl-*p*).

This compound formed orange crystals, m.p. 210°; yield 70%; ir: 3300-2300 (chelated OH), 1725 (CO) and 1630 cm^{-1} (C=C).

Anal. Calcd. for $C_{18}H_{12}ClNO_2S$: C, 63.2; H, 3.5; N, 4.0; S, 9.4. Found: C, 63.2; H, 3.5; N, 4.0; S, 9.8.

Method B.

A solution of IV (0.1 mole) in glacial acetic acid (100 ml) was treated with mercaptoacetic acid (0.1 mole). The reaction mixture was refluxed for 10 hours and then evaporated *in vacuo*. The remaining product was triturated with water and the resulting solid product was collected by filtration and identified (m.p. and mixed m.p.) as III, Ar = Ph and C_6H_4Cl-*p*, respectively, in 56 and 62% yield, respectively.

3,*N*-Diphenyl-3-(phenylhydrazono)propanethionohydrazide (V).

A solution of II (0.1 mole) in ethanol (20 ml) was treated with phenylhydrazine (0.1 mole) and the reaction mixture was refluxed for three hours. The solvent was then evaporated and the remaining product was triturated with water. The solid product thus formed was collected by filtration and crystallised from ethanol.

Compound V formed colourless crystals, m.p. 147°, yield 50%; ir: 3480-3050 (chelated NH), 1630 cm^{-1} (NH_2 deformation). ^{1}H nmr: 4.2 (br, 5H, CH_2 and NH integrated for 2H after deuterium oxide exchange) and 6.95-7.80 (m, 15H, 3Ph).

Anal. Calcd. for $C_{21}H_{20}N_4S$: C, 69.9; H, 5.5; N, 15.6. Found: C, 69.8; H, 5.5; N, 16.0.

1,3-Diphenyl-5-phenylhydrazinopyrazole (VI)

A mixture of II (2.0 g) and phenylhydrazine (2.0 ml) was heated at 130° (bath temperature) for two hours. The resulting product was then dissolved in hot ethanol and left to cool to room temperature. The crystals that separated on standing were collected by filtration and recrystallised from ethanol. Compound VI formed colourless crystals, m.p. 132°, yield 50% ir: 3480-3100 (chelated NH) and 2980 cm^{-1} (CH).

Anal. Calcd. for $C_{21}H_{18}N_4$: C, 77.2; H, 5.6; N, 17.1. Found: C, 76.9; H, 5.6; N, 17.0.

Compound VI was also obtained in 60% yield by heating an equimolecular mixture of V and phenylhydrazine for 2 hours at 130° (bath temperature) and working up the reaction mixture as described above.

3-Hydrazino-5-phenylpyrazole (VII).

A solution of II (2.0 g) in ethanol (20 ml) was treated with hydrazine hydrate (1 ml, 99%) and the reaction mixture was refluxed for three hours. The solvent was then evaporated and the remaining product was triturated with ethanol. The solid product, so formed, was collected by filtration and crystallised from ethanol. Compound VII formed colourless crystals, m.p. 265°, yield 50%; ir: 3420-3100 cm^{-1} (chelated NH).

Anal. Calcd. for $C_9H_{10}N_4$: C, 62.0; H, 5.8; N, 32.2. Found: C, 61.8; H, 5.4; N, 32.5.

2-Ethoxycarbonylmethyl-4-hydroxythiazole (VIII).

A solution of VIII (2.0 g) in pyridine (15 ml) was refluxed for two hours

then evaporated *in vacuo*. The remaining product was collected by filtration and crystallised from ethanol. Compound VIII was found to be identical (m.p. and mixed m.p.) with an authentic specimen prepared according to the procedure described by Behringer and Weber (3).

5-Benzylidene-2-ethoxycarbonylmethyl-2-thiazolin-4-one (IX).

A solution of VIII (0.1 mole) in ethanol (100 ml) was treated with benzaldehyde (0.1 mole) and then with one ml of piperidine. The reaction mixture was refluxed for three hours and then evaporated *in vacuo*. The remaining product was triturated with ethanol and the resulting solid was collected by filtration. Compound IX formed yellow crystals from ethanol, m.p. 185°, yield 60%; ir: 3000-2900 (CH and CH_2), 1725 (ester CO) and 1690 cm^{-1} (thiazole CO).

Anal. Calcd. for $C_{14}H_{13}NO_3S$: C, 61.0; H, 4.7; N, 5.1; S, 11.6. Found: C, 61.3; H, 5.0; N, 5.4; S, 12.0.

Ethyl 2-(4-Hydroxythiazol-2-yl)cinnamate (X).

A solution of XI (0.1 mole) in acetic acid (60 ml) was treated with mercaptoacetic acid (0.1 ml). The reaction mixture was refluxed for ten hours then evaporated *in vacuo*. The remaining product was triturated with water and the resulting solid product was collected by filtration and crystallised from ethanol.

Compound X formed pale yellow crystals, m.p. 60°, yield 68%; ir: 3300-2300 (conjugately chelated OH), 1700 (ester CO) and 1625 cm^{-1} (C=C).

Anal. Calcd. for $C_{14}H_{13}NO_3S$: C, 61.0; H, 4.7; N, 5.1; S, 11.6. Found: C, 61.2; H, 5.0; N, 5.0; S, 11.3.

Reaction of Benzonitrile with Mercaptoacetic Acid.

A solution of benzonitrile (0.1 mole) in pyridine (50 ml) was treated with mercaptoacetic acid (0.1 mole). The reaction mixture was refluxed for five hours and then evaporated to one half of its volume and left to cool. The solid product was collected by filtration and crystallised from ethanol. The product (22% yield) was found identical with an authentic sample of XII prepared after the procedure described by Chabrier, *et al.* (6).

2-Amino-5-(carboxymethylthio)pyrrole (XIII).

A solution of succinonitrile (0.1 mole) in pyridine (30 ml) was treated with mercaptoacetic acid (0.1 mole). The reaction mixture was refluxed for three hours and then treated as previously described for the reaction of mercaptoacetic acid with other nitriles. Compound XIII formed brown crystals, m.p. 320°, yield 60%; ir: 3400-2400 (chelated OH and NH), 1670-1690 cm^{-1} (carboxy CO and NH_2).

Anal. Calcd. for $C_6H_8N_2O_2S$: C, 41.9; H, 4.7; S, 18.6. Found: C, 42.0; H, 4.9; S, 18.4.

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