Chemistry and tautomerism of coupling products of diazotised sulfamethoxazole with some compounds containing an active methylene group

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Azo compounds **(2–5)** bearing a sulfamethoxazole moiety were prepared. The action of hydrazinecarbodithioate derivatives on (**2–4**) afforded pyrazoledithiocarboxylates **(8–10)**.

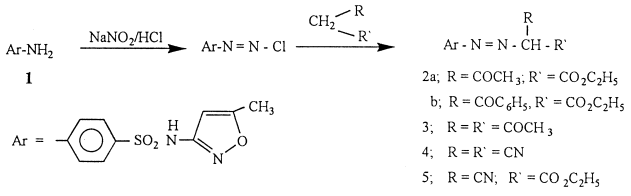
Keywords: sulfamethoxazole, hydrazinecarbodithioate, tautomerism and pyrazole-dithiocarboxylate

In a continuation of our previous work[11,12] on the synthesis of pyrazole-dithiocarboxylates, we report here several new approaches to these derivatives.

Diazotisation of *p*-[(5-methylisoxazol-3-yl)aminosulfonyl]aniline **1** followed by coupling with ethyl acetoacetate or ethyl benzoylacetate in ethanol in the presence of sodium acetate afforded the corresponding arylazo-β-ketoester derivatives **2a and 2b**, Scheme 1.

The structures of **2a and 2b** were confirmed on the basis of elemental analyses and spectral data. ^{1}H-NMR spectra showed that the products **2a and 2b** exist in DMSO-d_6 as an equilibrium mixture of three tautomeric forms **2A–C,** Scheme 2, as ^{1}H-NMR for **2a** revealed three signals for one proton at δ 7.66, 11.35 and 11.58 ppm where for **2b** these signals appear at δ 7.55, 11.32 and 11.48 ppm. These signals are assigned for the CH proton in the azo form **2A**, the OH proton in enolazo *E*-form **2B** and the NH proton in arylhydrazone *Z*-form **2C**. **2B** and **2C** forms are stabilised by intramolecular hydrogen bonding which is indicated by the appearance of carbonyl ester absorption bands at ν 1698 and 1666 cm^{-1} for **2a** and **2b**, respectively.

When diazotised sulfamethoxazole **1** was coupled with acetylacetone in ethanolic sodium acetate solution, *p*-[(5-methylisoxazol-3-yl)aminosulfonyl]-phenylazoacetylacetone **3** was obtained, Scheme 1.

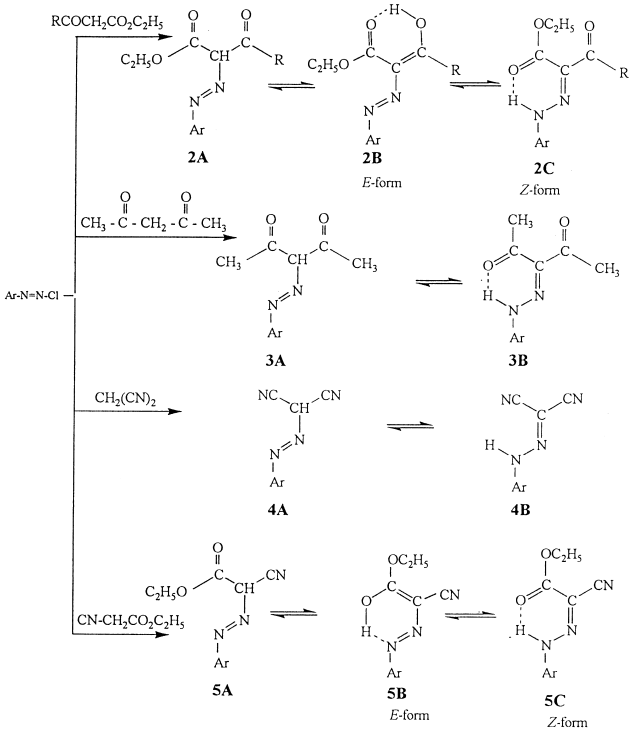


Scheme 1

The ^{1}H-NMR spectrum of compound **3** in DMSO-d_6 indicated the presence of two tautomeric structures **3A and 3B**, as the ^{1}H-NMR revealed two signals for one proton at δ 8.3 and 11.4 ppm. The signal at δ 8.15 is assigned to the CH proton in the azo form **3A** while the signal at δ 11.43 ppm which exchanged with D_2O is assigned to the NH proton in the hydrazo form **3B**, Scheme 2. From ^{1}H-NMR intergrals, it could be calculated that the major constituent in this equilibrium mixture is the hydrazo form (**3B**; 58%) which is stabilised by intramolecular hydrogen bonding while the azo form (**3A**; 42%) is the minor tautomer.

Malononitrile also coupled with diazotised sulfamethoxazole **1** to give *p*-(5-methylisoxazol-3-yl)aminosulfonyl]phenylhydrazonemalononitrile **4**, Scheme 1. The ^{1}H-NMR of **4** in DMSO-d_6 showed that this compound exists in the hydrazo form **4B** only; a signal at 11.42 ppm, which exchanged with D_2O being exhibited to the NH proton, Scheme 2.

Similarly, ethyl *p*-[(5-methylisoxazol-3-yl)aminosulfonyl]-phenylazocyano-acetate **5** could be synthesised via reaction of diazotised sulfamethoxazole with ethyl cyanoacetate. ^{1}H-NMR of **5** in DMSO-d_6 showed that this compound exists in three tautomeric forms **5A–C** Scheme 2, as ^{1}H-NMR revealed three signals for one proton at δ 7.71, 11.28, 12.42 ppm. The signal at δ 7.71 ppm is assigned to the CH proton in azo form **5A** while the signal at δ 11.28 ppm is assigned to the OH proton in enolazo *E*-form **5B** and the one at δ 12.42 ppm is assigned to the NH proton in the hydrazone *Z*-form **5C**.



Scheme 2

Treatment of **2a** with phenylhydrazine in refluxing ethanol yielded 3-methyl-4-[*p*-(5-methylisoxazol-3-yl)aminosulfonylphenylazo]-1-phenylpyrazolin-5-one **6**. The structure **6** was confirmed on the basis of elemental analyses and spectral data. Further confirmation of **6** was obtained through its synthesis via another reaction route. Thus, reaction of diazotised sulfamethoxazole **1** with 3-methyl-1-phenyl-pyrazolin-5-one[13,14] in ethanolic sodium acetate solution afforded a product which was found to be identical with **6** (the same m.p., mixed m.p. and IR spectrum).

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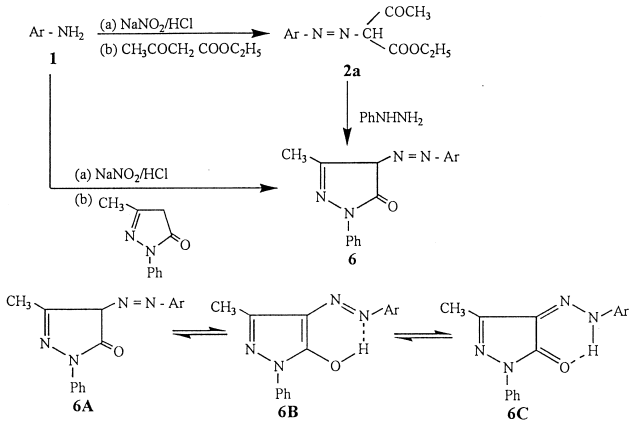
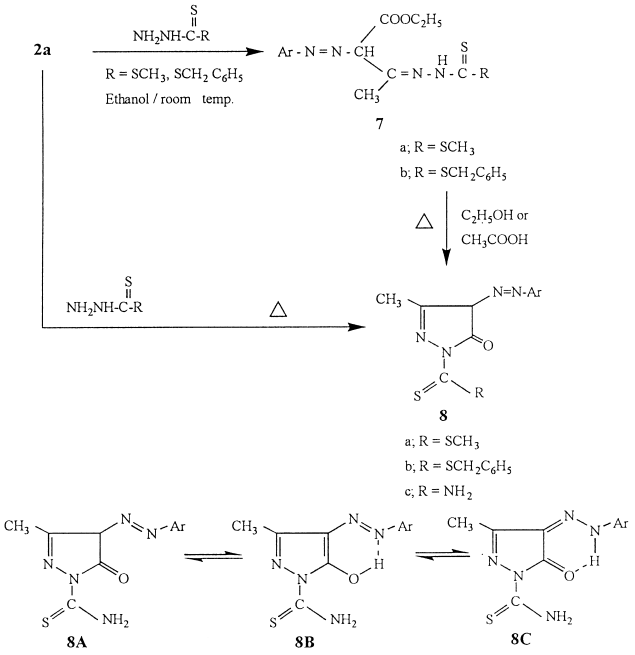


Scheme 3

IR and ^{1}H-NMR spectra of **6** indicate the presence of tautomeric structures. Thus, IR spectrum showed absorption bands for an enolic OH at 3444.3 cm^{-1} and a C = O at 1654 cm^{-1}. The ^{1}H-NMR spectrum of this compound showed that it exists in DMSO-d_6 as an equilibrium mixture of **6A–C** forms Scheme 3, as evidenced by three signals for a single proton at δ 7.9, 11.42 and 13.12 ppm. These signals are assigned to CH, OH and NH protons in azopyrazolinone **6A**, azohydroxypyrazole **6B** and hydrazopyrazolinone **6C** respectively, Scheme 3.

When compound **2a** was condensed with methyl or benzyl hydrazine-carbodithioate[15,16] in ethanol at room temperature, it led to the formation of products which were found to be hydrazone derivatives **7a,b** on the basis of elemental analyses and spectral data, Scheme 4. Thus, IR spectra of **7a** and **7b** revealed absorption bands for carbonyl ester groups at ν 1720 and 1710 cm^{-1} respectively and showed no absorption bands for acetyl groups. Also the ^{1}H-NMR spectrum of **7b** in DMSO-d_6 showed triplet and quartet signals at δ 1.38 and 4.33 ppm for methyl and methylene residues of ethyl ester respectively. This indicate that the above reaction proceed via



Scheme 4

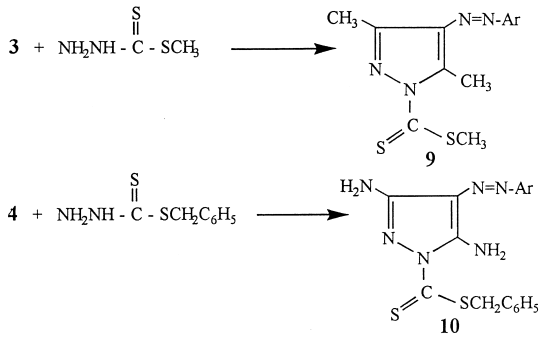
elimination of water through condensation of the acetyl group with the hydrazine derivatives.

Cyclisation of hydrazones **7a,b** could be achieved by refluxing in ethanol or acetic acid to give methyl and benzyl 3-methyl-4-[*p*-(5-methylisoxazol-3-yl)amino-sulfonylphenylazo]-5-oxopyrazolin-1-dithiocarboxylates (**8a,b**) respectively, Scheme 4. IR spectra of **8a,b** revealed the absence of carbonyl ester bands and the ^{1}H-NMR of **8b** showed the disappearance of ethyl ester signals. Pyrazolones **8a,b** were also prepared in one step by refluxing **2a** with methyl or benzyl hydrazinecarbodithioate in ethyl alcohol and acetic acid respectively, Scheme 4.

Compound **2a** was also cyclised with thiosemicarbazide in refluxing ethanol via elimination of water and ethanol to give 3-methyl-4-[*p*-(5-methylisoxazol-3-yl)-aminosulfonylphenylazo]-5-oxopyrazolin-1-thiocarboxamide **8c**, Scheme 4. The ^{1}H-NMR spectrum of pyrazole **8c** showed that it exists in DMSO-d_6 as an equilibrium mixture of three toutomeric forms **8A–C** Scheme 4, with three signals attributed to a single proton at δ 8.88, 9.49 and 11.44 ppm, these signals are assigned as the CH proton in azopyrazolinone **8A**, the OH proton in azohydroxypyrazole **8B** and the NH proton in hydrazopyrazolinone **8C**.

When compound **3** was allowed to react with methyl hydrazinecarbodithioate in refluxing ethanol, methyl 3,5-dimethyl-4-[*p*-(5-methylisoxazol-3-yl)aminosulfonyl-phenylazo]pyrazole-1-dithiocarboxylate **9** was obtained, Scheme 5.

Finally, compound **4** condensed with benzyl hydrazinecarbodithioate in refluxing ethanol produced benzyl 3,5-diamino-4-[*p*-(5-methylisoxazol-3-yl)amino-sulfonylphenylazo] pyrazole-1-dithiocarboxylate **10**, Scheme 5.



Scheme 5

Techniques used: IR, 1H NMR, mass spectra and microanalysis.

References: 16

Schemes: 5

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