Heteroaromatization with ketene dithioacetals: Part I. Synthesis of some novel 5-amino-1-(1,3,4-thiadiazol-2-yl) and 1-(1,3,4-thiadiazin-2-yl)pyrazole-4-carbonitriles

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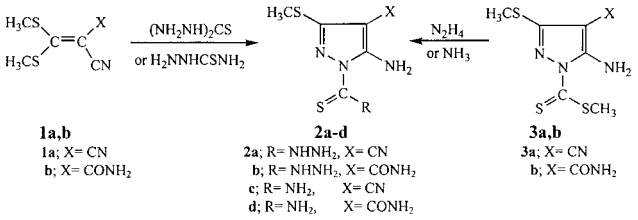
Saber M. Hassan*, Hussein A. Emam and Mahmoud M. Abdelall

Chemistry Department, Faculty of Science, Al-Azhar University, Nasr City, 11884 Cairo, Egypt.

5-Amino-3-methylthio-1-(1,3,4-thiadiazol-2-yl) and 1-(1,3,4-thiadiazin-2-yl)pyrazole-4-carbonitriles have been prepared from 5-aminopyrazoles using ketene dithioacetals as starting materials.

Ketene dithioacetals[5–14] are one of the most common starting materials for the synthesis of pyrazoles. The reactions of ketene dithioacetals **1a,b** with thiocarbohydrazide or thiosemicarbazide in hot ethanol afford the corresponding pyrazole derivatives **2a–d,** respectively (Scheme 1). In addition, the syntheses of **2a–d** could also be achieved through hydrazinolysis or ammonolysis of pyrazolyldithio-carbonate **3a,b**, Scheme 1.



Scheme 1

The structure of **2** was confirmed on the basis of elemental analyses and spectral data. The mass spectrum of **2a** was compatible with the molecular formula $C_6H_8N_6S_2$ (M^+ 228) and the base peak at *m/e* 154 (100%) was formed due to loss of CH_2N_2S (N_2H_2, CS) from the parent ion peak.

Interestingly, it was found that enaminonitrile **3a** reacted with triethyl orthoformate in the presence of acetic anhydride giving rise to 5-ethoxymethyleneamino-3-methylthio-1-[(methylthio)thiocarbonyl]pyrazole-4-carbonitrile **(4)**.

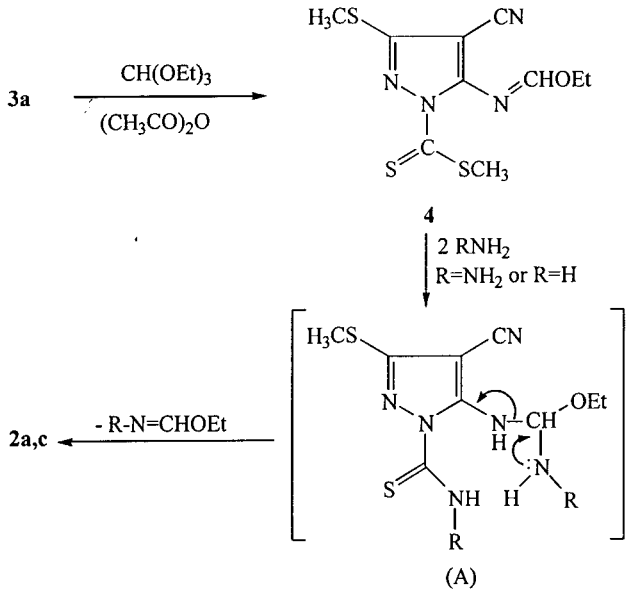
Compound **4** treated with hydrazine hydrate or ammonia in stirred ethanol at room temperature led to the formation of products which were found to be identical in all respects (m.p., mixed m.p. and spectral data) with **2a** and **2c**, respectively. The formation of **2a** or **2c** was assumed to proceed via hydrazinolysis or ammonolysis of the dithioester site and addition of the nucleophile at the N=CH site to give the intermediate (A) followed by elimination of ethyl formate hydrazone[15,16] and ethyl formate imine, respectively, Scheme 2.

When pyrazolylcarbothiohydrazide **(2a)** was subjected to the reaction with formic acid, cyclization took place to give 3-methylthio-1-(1,3,4-thiadiazol-2-yl)pyrazolo-[3,4-d] pyrimidin-4-one **(5)**, Scheme 3.

The structure of the latter compound was established on the basis of elemental analysis, spectral data and alternative routes. The reaction of **2b** with triethyl orthoformate or with formic acid gave the same pyrazolo[3,4-d]pyrimidin-4-one **(5)** (identical spectral data, m.p. and mixed m.p.)

Reaction of pyrazolylcarbothiohydrazide **(2a)** with benzoic acid in the presence of phosphorus oxychloride[17] produced 5-benzoylamino-3-methylthio-1-(5-phenyl-1,3,4-thiadiazol-2-yl)pyrazole-4-carbonitrile **(6a)**, Scheme 3.

Treatment of pyrazolylcarbothiohydrazide **(2a)** with triethyl orthoformate in acetic anhydride at reflux temperature

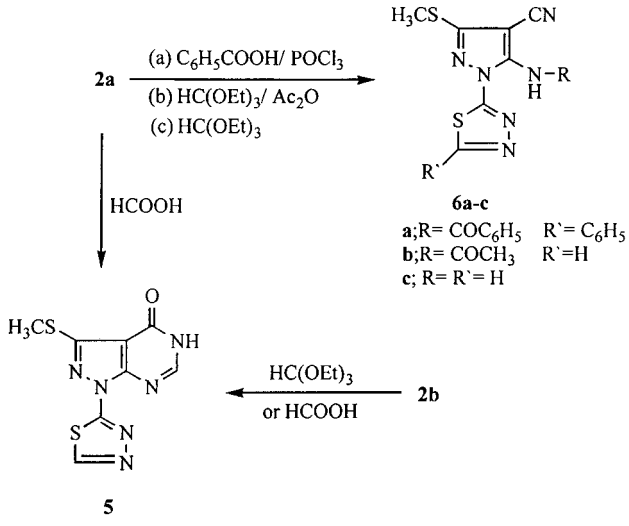


Scheme 2

afforded a product which was identified as 5-acetylamino-3-methylthio-1-(1,3,4-thiadiazol-2-yl)pyrazole-4-carbonitrile **(6b)** on the basis of elemental analysis and spectral data, Scheme 3.

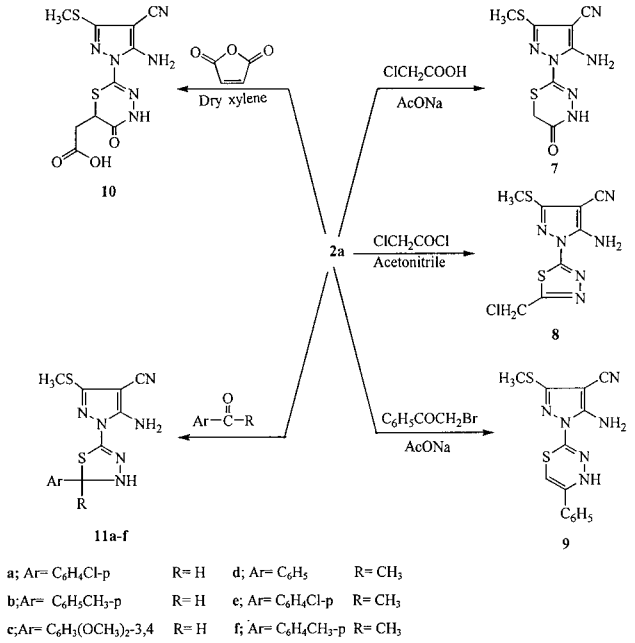
On the other hand, when compound **2a** was allowed to react with triethyl orthoformate in absence of acetic anhydride, 5-amino-3-methylthio-1-(1,3,4-thiadiazol-2-yl)pyrazole-4-carbonitrile **(6c)** was formed, Scheme 3.

Cyclocondensation of **2a** with chloroacetic acid[18] and fused sodium acetate in ethanol at reflux temperature afforded



Scheme 3

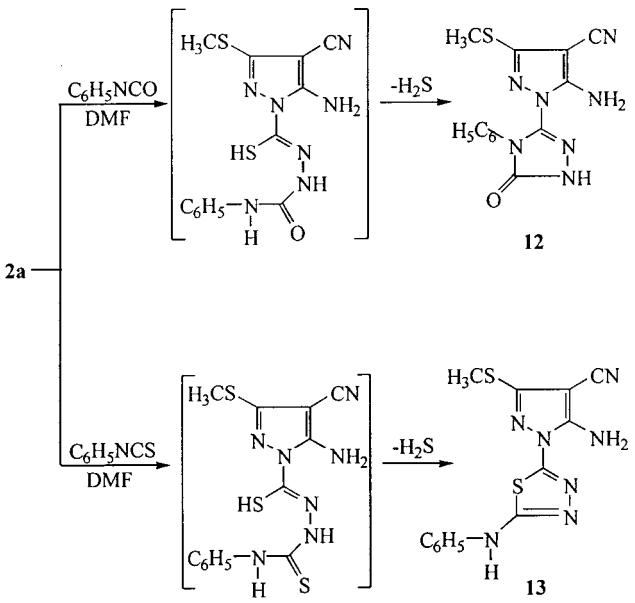
* To receive any correspondence. E-mail: saber_js@yahoo.com



Scheme 4

5-amino-3-methylthio-1-(5-oxo-1,3,4-thiadiazin-2-yl)-pyrazole-4-carbonitrile **(7)**. However, when chloroacetyl chloride was used instead of chloroacetic acid with the aim of obtaining the same product **7**, this gave the thiadiazolylpyrazole derivative **(8),** Scheme 4. The IR spectrum showed no C=O absorption band and this compound proved to be the thiadiazolylpyrazole derivative **(8)**.

Also, cyclocondensation of **2a** with an equimolar amount of phenacyl bromide in boiling absolute ethanol in the presence of fused sodium acetate yielded 5-amino-3-methylthio-1-(5-phenyl-1,3,4-thiadiazin-2-yl)pyrazole-4-carbonitrile **(9)**. Evidence for the structure **9** was provided on the bases of elemental analysis and spectral data.



Scheme 5

In another approach, reaction of compound **2a** with maleic anhydride in refluxing xylene afforded a product identified as 5-amino-3-methylthio-1-(6-carboxymethyl-5-oxo-1,3,4-thiadiazin-2-yl)pyrazole-4-carbonitrile **(10)** on the basis of elemental analysis and spectral data, Scheme 5.

Treatment of **2a** with aromatic aldehydes and with ketones in ethanol at reflux temperature afforded 1,3,4-thiadiazolylpyrazoles **11a-f** in good yield, Scheme 4.

Finally, refluxing compound **2a** with equimolar proportions of each of phenyl-isocyanate and phenylisothiocyanate in DMF as a solvent resulted in the formation of 5-amino-3-methylthio-1-(5-oxo-4-phenyl-1H-1,2,4-triazol-3-yl)pyrazole-4-carbonitrile **(12)** and 5-amino-3-methylthio-1-(5-phenylamino-1,3,4-thiadiazol-2-yl)pyrazole-4-carbonitrile **(13)**, respectively. The reaction was assumed to proceed via cyclization of the corresponding carbamoyl and thiocarbamoyl intermediates with loss of hydrogen sulfide, Scheme 5.

Techniques used: IR, 1H NMR, mass spectrometery, microanalysis.

References: 20

Schemes: 5

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