Polyheterocyclic ring systems with bridgehead nitrogen atoms: a facile route to some novel Azolo-1,2,4-triazine derivatives

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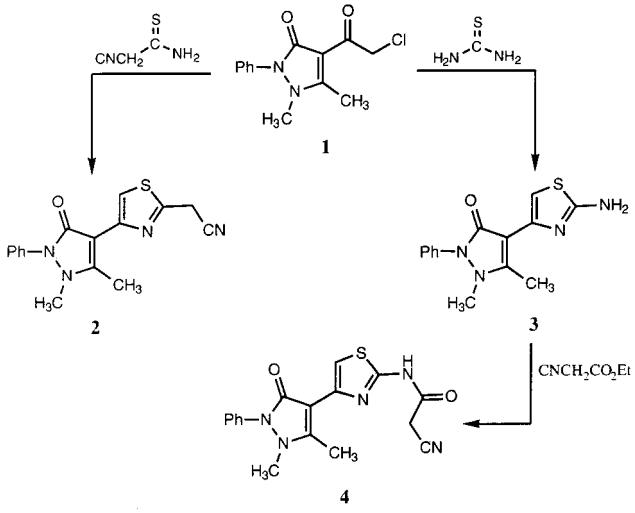
The synthesis of the entitled azolo-1,2,4-triazines *via* the reaction of some functionalized thiazole derivatives with several heterocyclic diazonium salts is described.

The pharmacological activity of antipyrine (phenazone) derivatives are of great interest in the field of medicinal chemistry.[1–3] On the other hand, 2-aminothiazole derivatives have also a wide pharmaceutical applications.[4–6] This perception has inspired us to find an efficient way for the synthesis of a new class of polyheterocyclic ring systems containing an antipyrine moiety pendent to a thiazole nucleus for biological screening. For this purpose, we performed a series of reactions using 4-chloroacetylantipyrine (**1**) as a precursor for the versatile functionalized thiazoles **2** and **4** which are useful for the fulfillment of our objective *via* their coupling with a variety of heterocyclic diazonium salts.

Thus, when 1,2-dihydro-1,5-dimethyl-2-phenyl-4-chloroacteyl-3H-pyrazol-3-one (**1**) was treated with 2-cyanoethanethioamide in refluxing ethanol, in the presence of a catalytic amount of triethylamine it afforded a single product identified as [4-(1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3H-pyrazol-4-yl)-thiazol-2-yl]acetonitrile (**2**) on the basis of its spectral data.



Scheme 1

Compound **1** reacted also with thiourea, in refluxing ethanol to afford 2-amino-4-(1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3H-pyrazol-4-yl)thiazole (**3**).

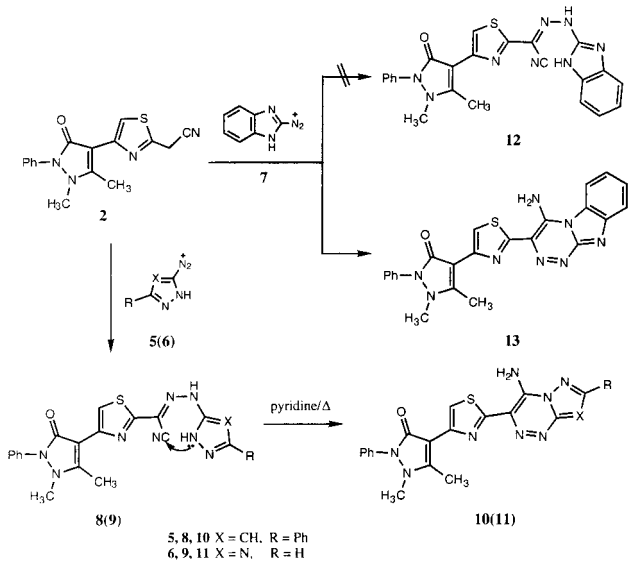
Fusion of the 2-aminothiazole derivative **3** with ethyl cyanoacetate afforded a single product for which structure **4** was assigned on the basis of the elemental and spectral analyses of the isolated product.

The behaviour of compound **2** towards some heterocyclic diazonium salts was investigated. Thus, it was found that **2** couples smoothly with 3-phenyl-pyrazol-5-diazonium chloride (**5**), in pyridine, at room temperature to afford the corresponding hydrazone **8**. The latter compound undergoes an intramolecular cyclization upon heating in pyridine to afford the corresponding pyrazolo[5,1-*c*]-1,2,4-triazine derivative **10** (Scheme 2).

In a similar manner, compound **2** coupled readily with diazonium salt of 3-amino-1,2,4-triazole (**6**) and afforded the corresponding hydrazone **9** (Scheme 2). Compound **9** underwent an intramolecular cyclization upon boiling in pyridine giving the corresponding 4-amino-3-[4-(1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3H-pyrazol-4-yl)thiazol-2-yl]-1,2,4-triazolo[5,1-*c*]-1,2,4-traizine (**11**) in a high yield. The structure of the latter product was established on the basis of its spectral data.

In contract to its behaviour toward the diazonium salts **5** and **6**, compound **2** reacted with diazotized 2-aminobenzimidazole **7** under the same conditions and afforded directly the 1,2,4-triazino[4,3,-*a*]benzimidazole derivative **13** rather than its isomeric acyclic hydrazone structure **12**. The lack of nitrile absorption and appearance of NH_2 absorption bands at 3351 and 3199 cm^{-1} in the IR spectrum of the isolated product assisted the assigned structure **13**. All attempts to isolate the acyclic hydrazone **12** were unsuccessful.

Prompted by the forgoing results, we studied the reactivity of **4** towards similar diazonium salts. Thus, when compound **4** was treated with the heterocyclic diazonium salts **6**, **7**, under similar experimental conditions, it afforded the respective cyanohydrazones **14**, **15** as depicted in Chart 1. Refluxing the latter cyanohydrazones in pyridine furnished, in all cases, new coloured products which were identified as the corresponding fused triazines **16**, **17**, respectively (Chart 1). The structure assignment of both acyclic hydrazones **14**, **15** and the cyclic fused triazines **16**, **17** was established by means of spectral data.



Scheme 2

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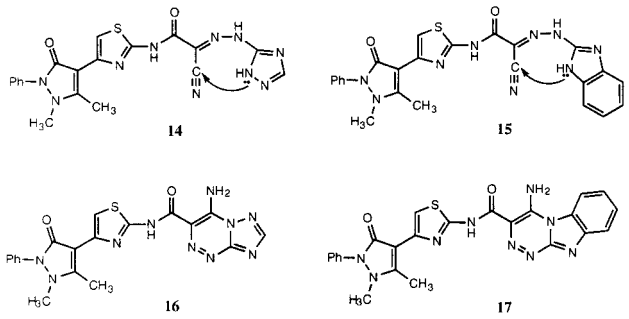

Chart 1

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Techniques used: IR, ^{1}H NMR, and mass spectrometry

References: 10

Schemes: 2

Charts: 1

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