Utility of [(*p*-Sulfonamidophenyl)azo]malononitrile in the Synthesis of Polyfunctionally Substituted Pyrimidine, Pyrazole, Isoxazole and Pyridazine Derivatives

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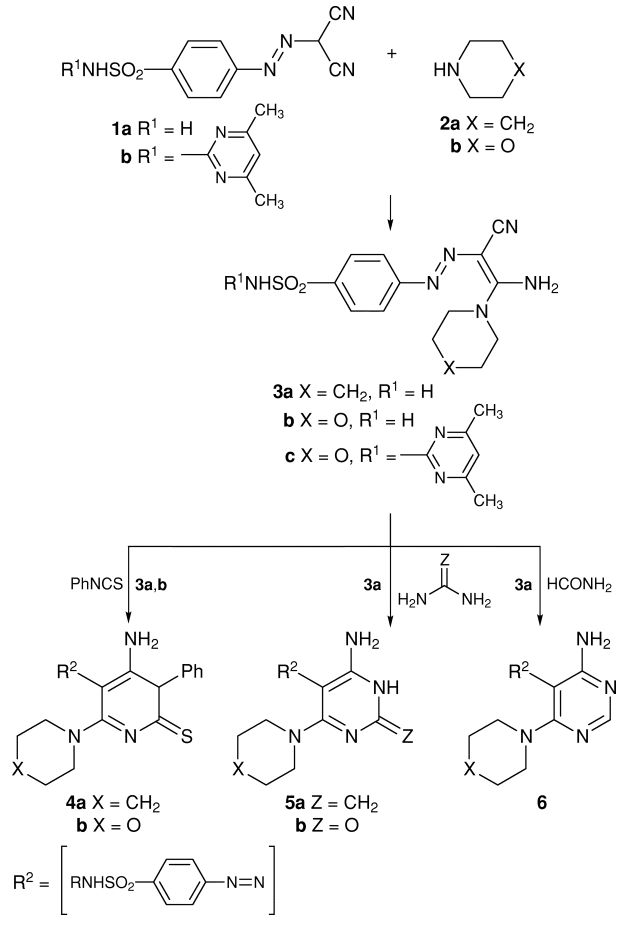
[(*p*-Sulfonamidophenyl)azo]malononitrile and/or [(*p*-sulfonamidophenyl)azo]acrylonitrile derivatives react with various reagents to afford pyrimidine, pyrazole, isooxazole and pyridazine derivatives with interesting biological activities *via* initial addition to either the cyano or amino group followed by cyclization.

Sulfonamide drugs were the first effective chemotherapeutic agents to be employed systematically for the prevention and cure of bacterial infections in human beings.[1] Phenylazomalonitrile has been extensively used as a starting material for preparing analogous heteroaromatics.[3] In view of the aforesaid versatile benefits and in connection with our previous efforts directed towards the facile synthesis of heterocyclic ring systems,[4,5] we aimed to incorporate the [(*p*-sulfonamidophenyl)azo] or *p*-sulfonamidophenyl moieties with a variety of pyrimidine, pyrazole, isoxazole and pyridazine moieties to obtain some new heterocyclic compounds with an expected wide spectrum of potential applications.



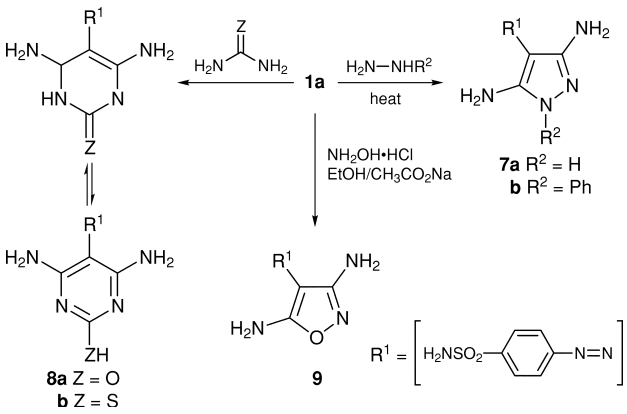
Scheme 1

The key precursor [(*p*-sulfonamidophenyl)azo]malononitrile derivatives (**1a**,**b**) were prepared by diazotizing the amino group of sulfanilamide or its derivatives and coupling with malononitrile in ethanolic sodium acetate solution at 0–5 °C. Compound **1** reacted with each of piperidine or morpholine (**2a**,**b**), respectively, in refluxing ethanol to afford the corresponding 1:1 acyclic enaminonitrile adducts **3a**–**c**.

The enaminonitrile moiety in **3** proved to be highly reactive towards nitrogen nucleophiles. Thus, compounds **3a**,**b** reacted with phenylisothiocyanate, in refluxing pyridine, to afford the corresponding pyrimidinethione derivatives **4a**,**b**, respectively. In addition, **3a** was condensed with urea and thiourea to give **5a**,**b**.

Similarly, condensation of **3a** with formamide afforded 4-amino-5-[(*p*-sulfonamidophenyl)azo]-6-piperidinopyrimidine (**6**) (Scheme 1).

As an extension of this synthetic route the behaviour of **1a** towards some other nitrogen nucleophiles was investigated. Thus, **1a** reacted with equimolar amounts of hydrazine or phenylhydrazine[8] in refluxing ethanol to afford the corresponding arylazo derivatives **7a**,**b**, respectively. Similarly, compound **1a** reacted with urea and thiourea to yield **8a**,**b**. The reaction of **1a** with hydroxylamine hydrochloride in ethanolic sodium acetate solution, boiled under reflux, provided **9** (Scheme 2).



Scheme 2

We have also investigated the possible utility of **1a** to develop a facile and a convenient route to polyfunctionally substituted 4-amino-1-(*p*-sulfonamidophenyl)-1,6-dihydropyridazine derivatives that are expected to have a wide spectrum of biological and physiological potential.[9] Thus, compound **1a** reacted with malonitrile in refluxing EtOH/

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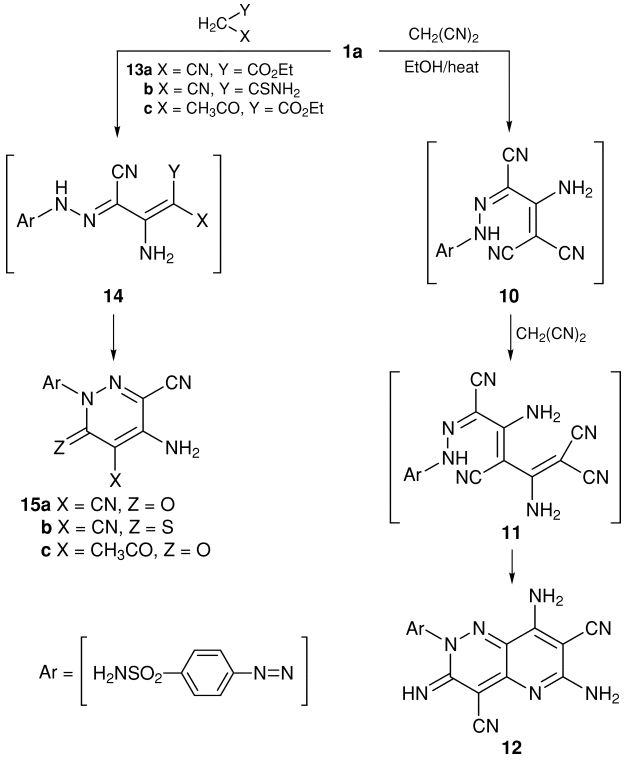

Scheme 3

Et_3N solution to yield the corresponding 1:2 adduct *via* intermediates **10** and **11**. In addition, the reaction of **1a** with equimolar proportions of ethyl cyanoacetate, cyanothioacetamide and ethyl acetoacetate under the same experimental conditions afforded the corresponding 4-amino-1-(*p*-sulfonamidophenyl)pyridazine-3-carbonitrile derivatives (**15a**–**c**)[11] (Scheme 3).

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

References: 12

Schemes: 3

Table 1: % Yields and elemental data for the reaction products **3a**–**9**, **12** and **15**

Table 2: IR, ^{1}H NMR and MS data for the reaction products **3a**–**9**, **12** and **15**

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