A direct single step synthesis of 1,3-diaryl-4-cyanopyrazoles and their conversion to 1,3-diaryl-4-(4,6-diamino-1,3,5-triazin-2-yl)pyrazoles

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A series of 1,3-diaryl-4-(4,6-diamino-1,3,5-triazin-2-yl)pyrazoles 6a-g have been synthesized. 1,3-Diaryl-4-cyanopyrazoles 5a-i required as intermediates have been prepared in a single step from acetophenone hydrazones 4a-i.

Keywords: 1,3-diaryl-4-cyanopyrazoles, 1,3-diaryl-4-(4,6-diamino-1,3,5-triazin-2-yl)pyrazoles

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Nitriles are interesting intermediates as they can be converted into a variety of functional groups and also serve as precursors in the synthesis of biologically active heterocycles. s-Diaminotriazinines are important class of compounds possessing diverse types of biological activities. Similarly, pyrazoles have got wide application such as anti-inflammatory, non-nucleoside HIV agents, nonbenzodiazepine anxioylytics and anticoagulant agents. Furthermore, several vicinal bisaryl, heteroaryl heterocyclic templates have been reported as COX-2 inhibiting agents (e.g. Celecoxib, Rofecoxib and etoricoxib). In view of this and in continuation of our work on pyrazoles, we report herein a direct synthesis of 4-cyanopyrazoles and their conversion to 4,6-diamino-s-triazin-2-yl pyrazoles.

In the present work, a number 1,3-diaryl-4-cyanopyrazoles 5 are required as starting intermediates. A detailed literature survey indicated the lack of a general method for the synthesis of a variety of 4-cyanopyrazoles. Thus, dehydration of oximes derived from 4-formylpyrazoles with n-butylamine, acetic anhydride and trichloroacetylchloride-triethylamine has been reported. Cyanation of 4-bromo-pyrazoles with cuprous cyanide in refluxing DMSO has been reported by Khan et al. These can also be prepared by deamination of 4-cyano-5-aminopyrazoles via non-aqueous diazotization with isoamyl-nitrite. Hassaneen et al. have reported a single step method involving the reaction of nitrileimines with fumaronitriles by elimination of hydrogen cyanide.

All these methods, involve the use of expensive, hazardous and commercially unavailable reagents involving multi-steps and low overall yields. Hence, continuous efforts are being made for a direct synthesis of functionally substituted pyrazoles which result in higher yields and avoid multi-step synthesis. Our synthetic strategy involves in combining the two reactions namely formylation and oximation into a single step, although such reactions are known, this has received little attention in the direct synthesis of cyanosubstituted heterocycles. Recently, we have reported a direct synthesis of 3-cyanochromones from 2-hydroxyacetophenones following this methodology. In the present work, this reaction has been extended to acetophenonehydrazones resulting in the direct synthesis of 4-cyanopyrazoles (Scheme 1).

Thus various acetophenones were reacted with phenylhydrazines to get the corresponding phenylhydrazone derivatives. These were subjected to Vilsmeier-Haack reaction, with dimethylformamide and phosphoryl chloride at 0°C. After diluting the reaction mixture with dichloromethane it was reacted with hydroxylamine hydrochloride at room temperature to give 1,3-diaryl-4-cyanopyrazoles 5 in fair to good yields. The structures of 5 were established on the basis of spectral data. In the IR spectra, the products exhibited a nitrile absorption band around 2230 cm⁻¹. In the ¹H NMR spectra showed a characteristic singlet for the pyrazole ring proton around δ 8.4. Reaction of 5 with dicyanamide in 2-methoxyethanol in the presence of potassium hydroxide gave the desired diamino-triazinylpyrazoles 6 in good yields. The structures of 6 (Table 1) were established based on their IR, ¹H NMR (characterized by the presence of signals bs, 2 × NH₂ and a singlet for pyrazole proton around δ 6.65
and 8.81 respectively), mass spectra and elemental analyses. The conversion of 4 to 5 is likely to proceed through a double formylation leading to pyrazole-4-iminium species and oxime on reaction with hydroxylamine hydrochloride. It is presumed that the chloro iminium salt [(CH$_3$)$_2$N$^+$=CHCl.Cl$^-$] formed under the reaction conditions acts as a dehydrating agent in the conversion of the oximes to cyano-pyrazoles according to a similar mechanism reported by us.

In conclusion, we have reported the synthesis of 4-(diamino-s-triazinyl)pyrazoles via 4-cyanopyrazoles. The method reported for the synthesis of 5, is a direct single step, simple and general that is applicable to a variety of acetophenones and phenylhydrazines with high yields when compared to multi-steps and expensive methods reported in the literature.

**Experimental Section**

Melting points were determined in open capillaries and are uncorrected. The purity of all the compounds was routinely checked by TLC on silica gel coated plates. IR spectra were recorded in KBr pellets on a Perkin-Elmer system 2000 FT IR spectrometer; $^1$H NMR spectra in CDCl$_3$ or DMSO-$d_6$ on a Varian 200 MHz instrument with TMS as internal standard (chemical shifts in $\delta$, ppm); and mass spectra on a Hewlett Packard mass spectrometer operating at 70 eV.

**General procedure for the preparation of 1,3-diaryl-4-cyanopyrazoles 5.** To a cooled solution of DMF (7.74 g, 0.106 mole) and POCl$_3$ (16.2 g, 0.106 mole) at 0$^\circ$C was added a solution of acetophenone hydrazone 4 (0.036 mole) in DMF (10 mL) dropwise at 0$^\circ$C, then warmed to room temperature for 30 min, and the mixture heated to 70-80$^\circ$C for 5 hr. It was cooled to room temperature and diluted with CH$_2$Cl$_2$ (200 mL). A solution of NH$_2$OH.HCl (5.00 g, 0.072 mole) in DMF (50 mL) was added and stirred at room temperature for 4-6 hr. After completion of the reaction (as monitored by TLC), it was diluted with cold water (500 mL) and extracted with CH$_2$Cl$_2$ (2×100 mL). The combined extracts were washed with water (2×100 mL), saturated NaHCO$_3$ solution (1×100 mL), water (2×100 mL) and dried (anhyd. Na$_2$SO$_4$). The solvent was removed in vacuo and the resulting solid purified by column chromatography (5% ethyl acetate - hexane) to give pure 5 as white crystalline solids.

Compounds 5a-i were prepared similarly and their characterization data are listed in Table I.
General procedure for the preparation of 1,3-diaryl-4-(4,6-diamino-1,3,5-triazin-2-yl)pyrazoles 6.

To a mixture of KOH (0.002 mole) and ethoxyethanol (20 mL) was added dicyandiamide (0.012 mole) and 1,3-diaryl-4-cyanopyrazole (0.01 mole) and the mixture slowly heated to reflux. Refluxing was continued for 2 hr to get a clear solution. After completion of the reaction (as monitored by TLC), the reaction mixture was poured onto crushed ice, the separated solid was filtered and recrystallized from ethyl acetate to give pure 6 as white crystalline solids.

Compounds 6a-g were prepared similarly and their characterization data are listed in Table I.

References


