Synthesis of 1,3-diaryl-4-cyanopyrazoles from the corresponding aldoximes using dimethylformamide-thionylchloride complex

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A mild and convenient method for the synthesis of 1,3-diaryl-4-cyanopyrazoles from the corresponding aldoximes using dimethylformamide-thionylchloride complex is reported.

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Nitriles are versatile intermediates as they can be readily converted into biologically interesting heterocycles like thiazoles, tetrazoles, imidazoles and triazoles. They can also be transformed into functional groups like carboxylic acids, amides and amines. The recent emergence of Celecoxib as COX-2 inhibitor and Sildenafil citrate as phosphodiesterase inhibitor indicates the importance of pyrazole nucleus as an active pharmacophore in these drugs, hence the synthesis of functionally substituted pyrazoles gained much importance. In view of this, and in pursuit of developing a library on pyrazoles, we became interested in a more common synthesis of 4-cyanopyrazoles and the results are reported herein.

4-Cyanopyrazoles can be synthesized by reaction of 4-bromopyrazoles with cuprous cyanide in DMSO at 140°C. They can also be prepared by the non-aqueous diazotization of the corresponding 4-cyano-5-aminopyrazoles with isopentyl nitrite in refluxing tetrahydrofuran. Hassanseen et al. reported a single step method for the preparation of these compounds by reaction of nitri leimines with fumaronitriles via elimination of hydrogen cyanide. They can also be prepared by oximation followed by dehydration of the corresponding 4-formylpyrazoles. Dehydrating agents such as n-butylamine and trichloroacetylchloride in presence of triethylamine have been used. However, all these methods suffer from drawbacks like use of expensive, hazardous and commercially non-available reagents, harsh reaction condition, long reaction times and tedious work-up procedures.

In view of the above disadvantages, we report herein a mild and facile method for the synthesis of 4-cyanopyrazoles making use of inexpensive and commercially available reagents. Thus, 1,3-diaryl-4-formylpyrazoles were prepared by Vilsmeier-Haack reaction on acetophenonephenylhydrazones. Reaction of I with hydroxylamine-hydrochloride in refluxing ethanol gave the corresponding aldoximes in excellent yields. The structures of 2 were characterized by 1H NMR spectra which exhibited characteristic signals for –NOH and –N=CH protons around δ 11.80 and 8.91-9.3 ppm respectively. The dehydration of oximes is effected by the use of N,N-dimethyl chlorosulfitemethaniminium chloride complex obtained from dimethylformamide-thionylchloride. This reagent is relatively unexplored and has been used in the activation of carboxylic acids in the synthesis of Cephalosporins, as a dehydrating agent, in the synthesis of azetidinones, sydnones, nitriles from thioamides and in situ preparation of mesoionic oxazolones. The aldoximes were reacted with the above reagent in dichloromethane at 0°C followed by stirring at room temperature to give the 4-cyanopyrazoles in 65-70% yields. All the products reported in Table I were characterized by IR and 1H NMR spectra and further supported by elemental analyses and mass spectra of representative compounds. In the IR spectra, the compounds exhibited characteristic absorption around 2225 cm⁻¹ for nitrile group. 1H NMR spectra of 4 exhibited a singlet around δ 8.2-8.4 ppm for pyrazole proton apart from other aromatic signals.

In conclusion, we report a mild and convenient method for the synthesis of 1,3-diaryl-4-cyanopyrazoles making use of commonly available reagents. The dehydration of aldoximes undergoes presumably via the intermediate 5 (Scheme I).

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; 1H NMR
Table I — Characterization data of compounds 4a-j

<table>
<thead>
<tr>
<th>Compd</th>
<th>R₁</th>
<th>R₂</th>
<th>m.p. °C</th>
<th>Yield (%)</th>
<th>Mol. formula</th>
<th>Found (Calc.) %</th>
<th>Spectral data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C₁₇H₁₃N₃</td>
<td>78.37 (78.76)</td>
<td>1H NMR: 8.32(s, 1H), 7.94(d, 2H), 7.71(d, 2H), 7.39(m, 5H), 2.45(s, 3H); Mass: M⁺ 259</td>
</tr>
<tr>
<td>4a</td>
<td>4-CH₃</td>
<td>H</td>
<td>124</td>
<td>77</td>
<td>C₁₇H₁₃N₃</td>
<td>78.37 (78.76)</td>
<td>1H NMR: 8.32(s, 1H), 7.94(d, 2H), 7.71(d, 2H), 7.39(m, 5H), 2.45(s, 3H); Mass: M⁺ 259</td>
</tr>
<tr>
<td>4b</td>
<td>4-OCH₃</td>
<td>H</td>
<td>142</td>
<td>75</td>
<td>C₁₇H₁₃N₃O</td>
<td>74.46 (74.14)</td>
<td>1H NMR: 8.43(s, 1H), 7.82(d, 2H), 7.63(d, 2H), 7.32(m, 5H), 3.86(s, 3H); Mass: M⁺ 275</td>
</tr>
<tr>
<td>4c</td>
<td>4-SCH₃</td>
<td>H</td>
<td>149</td>
<td>69</td>
<td>C₁₇H₁₃N₃S</td>
<td>70.24 (70.10)</td>
<td>1H NMR: 8.34(s, 1H), 8.00(d, 2H), 7.73(d, 2H), 7.31-7.55(m, 5H), 2.53(s, 3H); Mass: M⁺ 291</td>
</tr>
<tr>
<td>4d</td>
<td>4-Cl</td>
<td>H</td>
<td>156</td>
<td>72</td>
<td>C₁₀H₁₀ClN₃</td>
<td>69.12 (68.69)</td>
<td>1H NMR: 8.35(s, 1H), 8.01(d, 2H), 7.72(d, 2H), 7.54(m, 5H); Mass: M⁺ 281</td>
</tr>
<tr>
<td>4e</td>
<td>2,4-diCl</td>
<td>5-F</td>
<td>H</td>
<td>172</td>
<td>C₁₆H₈Cl₂FN₃</td>
<td>58.23 (58.00)</td>
<td>1H NMR: 8.40(s, 1H), 7.39-7.75(m, 7H); Mass: M⁺ 332</td>
</tr>
<tr>
<td>4f</td>
<td>4-F</td>
<td>2-F</td>
<td>172</td>
<td>74</td>
<td>C₁₆H₉F₂N₃</td>
<td>68.97 (68.81)</td>
<td>1H NMR: 8.45(s, 1H), 8.13(m, 3H), 7.34(m, 5H); Mass: M⁺ 281</td>
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<tr>
<td>4g</td>
<td>4-F</td>
<td>4-F</td>
<td>175</td>
<td>72</td>
<td>C₁₆H₉F₂N₃</td>
<td>68.72 (68.81)</td>
<td>1H NMR: 8.36(s, 1H), 8.05(m, 2H), 7.74(m, 2H), 7.27(m, 4H); Mass: M⁺ 281</td>
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<tr>
<td>4h</td>
<td>4-F</td>
<td>2,4-diF</td>
<td>159</td>
<td>71</td>
<td>C₁₆H₈F₃N₃</td>
<td>65.23 (64.86)</td>
<td>1H NMR: 8.42(s, 1H), 8.04(m, 3H), 7.16(m, 4H); Mass: M⁺ 299</td>
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<tr>
<td>4i</td>
<td>4-F</td>
<td>2-CH₃</td>
<td>115</td>
<td>65</td>
<td>C₁₇H₁₂FN₃</td>
<td>74.27 (73.91)</td>
<td>1H NMR: 8.35(s, 1H), 7.24-8.15(m, 8H), 2.43(s, 3H); Mass: M⁺ 277</td>
</tr>
<tr>
<td>4j</td>
<td>4-F</td>
<td>4-CH₃</td>
<td>182</td>
<td>68</td>
<td>C₁₇H₁₂FN₃</td>
<td>74.34 (73.91)</td>
<td>1H NMR: 8.37(s, 1H), 8.12(m, 2H), 7.64(d, 2H), 7.35(d, 2H), 1.15(m, 2H), 2.45(s, 3H); Mass: M⁺ 277</td>
</tr>
</tbody>
</table>

Scheme I
spectra on a Varian 200 MHz instrument with TMS as internal standard (chemical shifts in δ, ppm); and mass spectra on a Hewlett Packard Mass spectrometer operating at 70eV.

**General procedure for preparation of 1,3,diarylpyrazole-4-aldoximes 2.** A mixture of 1 (0.05 mole) and hydroxylamine-hydrochloride (0.1 mole) in ethanol (25 mL) was refluxed for 6 hr. The separated solid was filtered, washed with water, ethanol and dried to give the product 2 in 90% yield. Compounds 2a-j were used as such in the next step without further purification. The melting points and 1H NMR spectral data of compounds 2a-j are given below.

2a (R1=4-CH3, R2=H): m.p. 142°C; 1H NMR (CDCl3): δ 11.81(s, 1H, NOH), 8.92(s, 1H, CH=N), 7.72(m, 4H, ArH), 7.37(m, 3H, ArH), 7.25(m, 2H, ArH), 2.38(s, 3H, CH3).

2b (R1=4-OCH3, R2=H): m.p. 162°C; 1H NMR (CDCl3): δ 11.80(s, 1H, NOH), 8.94(s, 1H, CH=N), 7.81(m, 4H, ArH), 7.41(m, 3H, ArH), 7.32(m, 3H, ArH), 3.82(s, 3H, OCH3).

2c (R1=4-SCH3, R2=H): m.p. 182°C; 1H NMR (CDCl3): δ 11.80(s, 1H, NOH), 8.92(s, 1H, CH=N), 7.78(m, 4H, ArH), 7.36(m, 3H, ArH), 7.29(m, 3H, ArH), 2.51(s, 3H, SCH3).

2d (R1=4-Cl, R2=H): m.p. 169°C; 1H NMR (DMSO-d6): δ 11.80(s, 1H, NOH), 8.93(s, 1H, CH=N), 7.56(m, 4H, ArH), 7.47(m, 3H, ArH), 7.21(m, 3H, ArH).

2e (R1=2,4-diCl,5-F, R2=H): m.p. 207°C; 1H NMR (DMSO-d6): δ 11.80(s, 1H, NOH), 9.13(s, 1H, CH=N), 8.00(m, 3H, ArH), 7.57(m, 4H, ArH), 7.06(s, 1H, ArH).

2f (R1=4-F, R2=2-F): m.p. 199°C; 1H NMR (DMSO-d6): δ 11.80(s, 1H, NOH), 8.97(s, 1H, CH=N), 7.94(m, 1H, ArH), 7.71(m, 2H, ArH), 7.43(m, 6H, ArH).

2g (R1=4-F, R2=4-F): m.p. 203°C; 1H NMR (DMSO-d6): δ 11.81(s, 1H, NOH), 8.96(s, 1H, CH=N), 7.92(m, 2H, ArH), 7.68(m, 2H, ArH), 7.39(m, 5H, ArH).

2h (R1=4-F, R2=2,4-diF): m.p. 229°C; 1H NMR (DMSO-d6): δ 11.80(s, 1H, NOH), 8.94(s, 1H, CH=N), 7.93(m, 1H, ArH), 7.67(m, 3H, ArH), 7.35(m, 4H, ArH).

2i (R1=4-F, R2=2-CH3): m.p. 177°C; 1H NMR (CDCl3): δ 11.82(s, 1H, NOH), 8.92(s, 1H, CH=N), 7.56(m, 5H, ArH), 7.32(m, 4H, ArH), 2.38(s, 3H, CH3).

2j (R1=4-F, R2=4-CH3): m.p. 185°C; 1H NMR (CDCl3): δ 11.80(s, 1H, NOH), 8.91(s, 1H, CH=N), 7.64(m, 3H, ArH), 7.53(s, 1H, ArH), 7.22(m, 5H, ArH), 2.39(s, 3H, CH3).

**General procedure for the preparation of N,N'-dimethylchlorosulfitemethaniminium chloride reagent 3.** To a solution of toluene (50 mL) and dimethylformamide (0.01 mole), thionyl chloride (0.011 mole) was added dropwise at 0°C. After 15 min the two phases were separated and the lower layer containing the reagent was taken and used as such in the next step.

**General procedure for the preparation of 1,3-diaryl-4-cyanopyrazoles 4a-j.** To a mixture of oxime (2, 0.01 mole) in dichloromethane (100 mL) above reagent 3 (0.015 mole) was added at 0-5°C. The reaction mixture was stirred at ambient temperature for 3-6 hr, as the reaction was monitored by TLC. At the end of the reaction, the reaction mixture was partitioned with cold water, the organic layer was washed with saturated NaHCO3 solution followed by drying (Na2SO4), solvent removed and purified by flash chromatography by eluting with CH2Cl2 to give 4a-j as crystalline solids (Table I).

**References**


