Synthesis of some new 1-(6-fluorobenzothiazol-2-yl)-3-(4-fluoro-phenyl)-5-arylpyrazolines and their iodine(III) mediated oxidation to corresponding pyrazoles

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The reaction of fluorinated chalcones 2 and 6-fluorobenzothiazol-2-ylhydrazine 1 in presence of catalytic amount of glacial acetic acid in refluxing ethanol yields 1-(6-fluorobenzothiazol-2-yl)-3-(4-fluorophenyl)-5-arylpyrazolines 3, which undergo facile oxidation to the corresponding pyrazoles 4 in good yield using iodobenzene diacetate (IBD). The structures of the synthesized compounds have been established on the basis of their elemental analysis, MS and $^{1}$H and $^{13}$C NMR spectroscopy.

Keywords: Fluorinated chalcones, pyrazolines, iodobenzene diacetate, pyrazoles, NMR spectroscopy

Pyrazoline derivatives constitute an interesting class of organic compounds, which are associated with diverse chemical and pharmacological properties$^{1-4}$. These compounds are known for their antitumor, analgesic, anti-inflammatory, insecticidal, antiarthritic, cerebroprotective effect and antidepressant properties$^{5-8}$. Several substituted pyrazolines are found to be effective bleaching agents, luminescents and fluorescents$^{9}$. They are also useful as biodegradable agrochemicals$^{10}$.

Moreover, several pyrazole derivatives have emerged as a group of compounds possessing a broad spectrum of useful medicinal properties such as analgesic, antipyretic, anti-inflammatory, germicidal and antifungal activity$^{11,12}$.

The biological properties of fluorine or multifluorine containing compounds have been recently investigated. Owing to their unique properties, such as high thermal stability and lipophilicity, fluoro-organic compounds have been frequently used as biorelated materials, medicines and agrochemicals$^{13,14}$.

Encouraged by these results and in continuation with the work related to the synthesis, spectral studies and biological properties of heteroarylpyrazoles$^{15}$, herein is reported the synthesis of some novel fluorine incorporated 1-heteroarylpyrazolines 3 and pyrazoles 4.

Results and Discussion

Synthesis of 1-(6-fluorobenzothiazol-2-yl)-3-(4-fluorophenyl)-5-arylpyrazolines 3a-f and their oxidation to corresponding pyrazoles 4a-f is summarized in Scheme 1.

The starting compounds 1-(4-fluorophenyl)-3-arylprop-2-enones (chalcones) 2a-f were prepared by the Claisen-Schmidt condensation of $p$-fluoroacetophenone with various substituted aromatic aldehydes in presence of methanol/KOH$^{16}$. The reaction of 6-fluorobenzothiazol-2-ylhydrazine 1 with chalcones 2a-f in refluxing ethanol under the influence of glacial acetic acid gave 1-(6-fluorobenzothiazol-2-yl)-
3-(4-fluorophenyl)-5-arylpyrazolines 3a-f in good yield.

The compounds 3a-f were characterized by the combined application of elemental analysis, mass spectrometry, ¹H and ¹³C NMR spectroscopy. The ¹H NMR spectra of pyrazolines 3a-f displayed the three characteristic signals due to diastereotopic protons (Hₐ, Hₖ and Hₜ). The Hₐ proton which is cis to Hₜ resonates upfield in the range δ 3.25-3.35 as a doublet of doublet (dd, Jₕₕₕ = ~ 17.7 Hz, Jₕₕₕ = ~ 5.4 Hz) while Hₖ, the other proton which is trans to Hₜ resonates downfield in the range δ 3.89-3.99 as a dd (Jₕₕₕ = ~ 17.7 Hz, Jₕₕₕ = ~ 12 Hz). The Hₜ proton which is vicinal to two methylene protons (Hₐ and Hₖ) resonates as dd in the range δ 5.81-5.87 (Jₕₕₕ = ~ 12 Hz, Jₕₕₕ = ~ 5.4 Hz).

The structures of 3a-f were further supported by their ¹³C NMR in which C-3, C-4 and C-5 resonated at δ 149-146, 108 and 145-146 ppm, respectively. These values are in close agreement with the reported values¹⁷ for pyrazoline carbons 3, 4 and 5.

It may be mentioned here that many conventional oxidizing agents namely potassium ferricyanide, silver nitrate, mercuric nitrate, colloidal platinum, manganese oxide, mercuric acetate and lead oxide have been used for the dehydrogenation of pyrazolines. A careful examination of the literature reveals that most of the methods suffer from one drawback or the other. To illustrate, catalytic dehydrogenation using colloidal platinum results in the formation of a mixture containing the corresponding pyrazoles and pyrazolidines¹⁸. Similarly, the oxidation of pyrazolines involving manganese dioxide results in the formation of bi-phenyl in addition to the desired pyrazoles¹⁹. Moreover, toxicity associated with the mercury and lead reagents makes their use rather undesirable.

In view of the difficulties encountered in these methods and encouraged by previous observations²⁰ resulting in the successful conversion of pyrazolines to pyrazoles using IBD, this reagent has been adopted to convert the pyrazoline 3 to pyrazoles 4.

The pyrazolines 3a-f were treated with one equivalent of iodobenzene diacetate (IBD) in dichloromethane at RT for 4 hr. The reaction smoothly afforded the desired products 4a-f in good yield.

The compounds 4a-f were also characterized on the basis of NMR and mass spectrometry, and elemental analysis. The ¹H NMR spectra of pyrazoles 4a-f showed a characteristic singlet due to C₄-H at δ ~6.6. In ¹³C NMR spectra of the compound 4a-f, the three carbon atoms C-3, C-4 and C-5 of pyrazole nucleus resonated at δ 152-153, 108 and 145-146, respectively²¹.

The complete assignments of the carbon signals of the compounds 3 and 4 are given in Tables I and II.

**Experimental Section**

Melting points were determined in open capillaries in electrical apparatus and are uncorrected. ¹H and ¹³C NMR spectra were run on a Brucker instrument at 300 MHz and 75 MHz, respectively using TMS as an internal standard. ¹⁹F NMR spectra were run on DRX 300 and DPX 400 at 282 and 376 MHz, respectively, using CDCl₃ as solvent. The internal standard for ¹⁹F spectra was CFCl₃, setting the CFCl₃ signal at δ 0.00. High resolution mass spectra (HRMS) were measured in EI mode on a Kratos MS-50 spectrometer.
6-Fluorobenzothiazol-2-ylhydrazine was prepared according to literature procedure.22

General procedure for synthesis of 1-(6-fluorobenzothiazol-2-yl)-3-(4-fluorophenyl)-5-arylpyrazolines, 3
1-(6-fluorobenzothiazol-2-yl)-3-(4-fluorophenyl)-5-phenylpyrazoline, 3a.

A solution of 1-(4-fluorophenyl)-3-phenylprop-2-enone 2a (0.45 g, 0.002 mole) and 6-fluorobenzothiazol-2-ylhydrazine 1 (0.37 g, 0.002 mole) in ethanol (25 mL) containing 4-5 drops of glacial acetic acid was heated under reflux for 8 hr. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure and then allowed to cool when a solid product crystallized out. The product was collected by filtration & washed with ethanol to give 3a. This was further purified by recrystallization from ethanol. Yield 80%; m.p. 182-83°C. 1H NMR (CDCl3): δ 3.27-3.35 (dd, 1H, Hα, JHαHβ = 17.7 Hz, JHαHβ = 5.4 Hz), 3.89-3.98 (dd, 1H, Hβ, JHβHα = 17.4 Hz, JHβHα = 12 Hz), 5.82-5.87 (dd, 1H, Hε, JHεHδ = 11.7 Hz, JHεHδ = 5.4 Hz), 6.95-7.02 (m, 1H, 5'-H), 7.11-7.17 (m, 2H, 3', 5'-H), 7.28-7.37 (m, 6H, Ph-O-H, 7'-H), 7.44-7.48 (dd, 1H, 4'-H, JH = 9 Hz, JH = 4.8 Hz), 7.75-7.79 (m, 2H, 2', 6'-H); 19F NMR (CDCl3): δ -120 (s, 1F, 6'-F), -109 (s, 1F, 4'-F); HRMS: m/z M+ C22H15F2N3S requires 391.0954. Found: 391.0943. Anal. Calcd. for C22H15F2N3S: N, 3.23-3.39 (dd, 1H, Hα, JHαHβ = 17.7 Hz, JHαHβ = 5.4 Hz)

The compounds 3b-f were similarly prepared.

3b: Yield 76%; m.p. 146°C; 1H NMR (CDCl3): δ 3.28-3.38 (dd, 1H, Hα, JHαHβ = 17.7 Hz, JHαHβ = 5.4 Hz, JHαHβ = 5.4 Hz).
3c: Yield 78%; m.p. 186°C; 1H NMR (CDCl3): $\delta$ 3.25-3.32 (dd, 1H, Hα, $J_{HAHB} = 17.5$ Hz, $J_{HAHX} = 5.4$ Hz), 3.90-4.00 (dd, 1H, Hβ, $J_{HBHX} = 12$ Hz), 5.86-5.91 (dd, 1H, HX, $J_{HBHX} = 11.7$ Hz, JIXHX = 5.4 Hz), 6.78-7.06 (m, 1H, 5'-H), 7.04-7.07 (dd, 1H, 3', 3''-H), 7.33-7.38 (m, 2H, 3'', 5''-H), 7.00-7.08 (m, 2H, 3'', 5''-H), 7.04-7.07 (d, 1H, 4'-H, $J_o = 9$ Hz, $J_{(m)HF} = 4.8$ Hz), 7.74-7.78 (m, 2H, 2'', 6''-H); 19F NMR (CDCl3): $J_{HAHB} = 17.5$ Hz, $J_{HAHX} = 5.4$ Hz, 3.87-3.96 (dd, 1H, Hα, $J_{HAHB} = 17.4$ Hz, $J_{HBHX} = 12$ Hz), 5.74-5.79 (dd, 1H, HX, $J_{IXHX} = 11.7$ Hz, JIXHX = 5.4 Hz), 6.94-7.78 (m, 11H, FBz', p-FPh'' and p-FPh'''-H); 19F NMR (CDCl3): $\delta$ 120 (s, 1F, 4''-F), -109 (s, 1F, 4''-F)*; MS: m/z M+ 409. Anal. Calcd. for C22H14F3N3S: N, 10.27. Found 9.94%.

3e: Yield 78%; m.p. 186°C; 1H NMR (CDCl3): $\delta$ 3.25-3.32 (dd, 1H, Hα, $J_{HAHB} = 17.5$ Hz, $J_{HAHX} = 5.4$ Hz), 3.90-4.00 (dd, 1H, Hβ, $J_{HBHX} = 12$ Hz), 5.85-5.90 (dd, 1H, HX, $J_{IXHX} = 11.7$ Hz, JIXHX = 5.4 Hz), 6.78-7.06 (m, 1H, 5'-H), 7.04-7.07 (m, 2H, 3'', 5''-H), 7.33-7.38 (m, 5H, p-CIphph''-H, 7'-H), 7.43-7.51 (dd, 1H, 4'-H, $J_o = 9$ Hz, $J_{(m)HF} = 4.8$ Hz), 7.74-7.78 (m, 2H, 2'', 6''-H); 19F NMR (CDCl3): $J_{HAHB} = 17.5$ Hz, $J_{HAHX} = 5.4$ Hz, 3.87-3.96 (dd, 1H, Hα, $J_{HAHB} = 17.4$ Hz, $J_{HBHX} = 12$ Hz), 5.74-5.79 (dd, 1H, HX, $J_{IXHX} = 11.7$ Hz, JIXHX = 5.4 Hz), 6.94-7.78 (m, 11H, FBz', p-FPh'' and p-FPh'''-H); 19F NMR (CDCl3): $\delta$ 120 (s, 1F, 4''-F), -109 (s, 1F, 4''-F)*; HRMS: m/z M+ C22H14F3N3S requires 425.0565 for lower iso-}

### General procedure for synthesis of 1-(6-fluorobenzothiazol-2-yl)-3-(4-fluorophenyl)-5-arylpazoles, 4

To a stirred solution of 1-(6-fluorobenzothiazol-2-yl)-3-(4-fluorophenyl)-5-arylpyrazoles. Yield 84%; m.p. 152°C; 1H NMR (CDCl3): $\delta$ 7.61-7.66 (dd, 1H, 4'-H, $J_o = 8.1$ Hz, $J_{(m)HF} = 5.4$ Hz), 7.36-7.39 (m, 4H, 3''', 4''', 5''', 7'-H), 7.47-7.53 (m, 4H, 3''', 4''', 5''', 7'-H), 6.77 (s, 1H, 4-H), 7.09-7.20 (m, 3H, 5', 3'', 5''-H), 7.12-7.18 (m, 2H, 3'', 5''-H), 7.33-7.39 (dd, 1H, 7'-H, $J_o = 8.1$ Hz, $J_{(m)HF} = 5.4$ Hz), 7.75-7.79 (m, 2H, 2'', 6''-H); 19F NMR (CDCl3): $\delta$ -116 (s, 1F, 4''-F), -112 (s, 1F, 4''-F); HRMS: m/z M+ C22H14F3N3S requires 407. Anal. Calcd. for C22H14F3N3S: N, 10.37. Found 10.26%.

### The compounds 4b-f were similarly prepared.

4b: Yield 84%; m.p. 152°C; 1H NMR (CDCl3): $\delta$ 6.79 (s, 1H, 4-H), 6.98-7.15 (m, 1H, FBz', p-FPh'' and p-FPh'''-H); 19F NMR (CDCl3): $\delta$ -116 (s, 1F, 4''-F), -112 (s, 1F, 4''-F)*; -114 (s, 1F, 4''-F)*; MS: m/z M+ 407; Anal. Calcd. for C22H14F3N3S: N, 10.32. Found 10.52%.

4d: Yield 83%; m.p. 182-83°C; 1H NMR (CDCl3): δ 2.38 (s, 3H, CH3), 6.67 (s, 1H, 4'-H), 7.00-7.44 (m, 8H, 5', 7', 3', 5', 6'-F, p-CH3Phâ°-H), 7.57-7.61 (dd, 1H, 4'-H, Jm = 9 Hz, Jm (m) HF = 4.8 Hz), 7.82-7.87 (m, 2H, 2'', 6''-H); 19F NMR (CDCl3): δ -116 (s, 1F, 6'-F), -112 (s, 1F, 4''-F); MS: m/z M+ 403. Anal. Calcd. for C22H14F2N4O2S: N, 12.90. Found 12.78%.

References
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