A facile one pot synthesis of substituted pyrazole derivatives

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Diazo compounds derived from aromatic aldehydes were reacted with derivatives of (*Z*)-2-arylidene-2*H*-benzofuran-3-ones to give new highly substituted heterocyclic pyrazoles. The structures of the synthesised compounds were determined on the basis of their elemental analyses and spectroscopic data.

Keywords: benzofuran-3-one, aryldiazomethane, 1,3-dipolar cycloaddition, pyrazoles

Pyrazoles and their variously substituted derivatives are important biological agents and a significant amount of research activity has been directed to study these compounds.[1] In particular, they are used as anti-tumour, anti-bacterial and anti-fungal, anti-viral, anti-parasitic, anti-tubercular and insecticidal agents. Some of these compounds also have anti-inflammatory, anti-diabetic, anesthetic and analgesic properties.[2–4] Several methods for the synthesis of pyrazoles and their derivatives have been reported, most of them involving construction of the pyrazole moiety by reaction of α,β-unsaturated aldehydes or ketones with hydrazines.[5–9] In another route, these products can be obtained by 1,3-dipolar cycloaddition of diazoalkanes with acetylenes.[10–13]

Lévai *et al.*[14] described the addition of diazomethane to arylidenebenzofuranone as a route to a spiropyrazoline *via* a regioselective condensation of the dipole onto the C=C double bond of the benzofuranone skeleton. Also, Fathi *et al.*[15] studied the reaction of a spiropyrazoline with trifluoroacetic acid to afford a trisubstitued pyrazole.

We were prompted to study the 1,3-dipolar cycloaddition reaction of aryldiazomethanes with benzofuranones in order to synthesise some new highly substituted pyrazoles and we report here our results.

Results and discussion

The aryldiazomethane was generated *in situ* by condensation of *p*-toluenesulfonyl hydrazide with an aromatic aldehyde **1a–c** followed by treatment with an aqueous solution of sodium hydroxide to give a solution of the sodium salt of the aromatic aldehyde tosylhydrazone, which upon warming to 50 °C gave a reddish solution of a diazo compound **2a–c**.[16,17] The initial starting compounds (*Z*)-2-arylidene-2*H*-benzofuran-3-ones **3a–c** were prepared by cyclisation of 2-hydroxychalcones in the presence of mercury acetate in pyridine according to the literature procedure.[18]

Thus we achieved our first aim of reacting the diaryldiazomethanes **2a–c** with compounds **3a–c** to access the spiropyrazolinic skeleton **4a–i**, but, the unexpected products **5a–i** were obtained. Structures were assigned on the basis of their spectral data and are new pyrazoles (Scheme 1). The loss of starting materials was shown by TLC.

The mass spectra recorded in ES^+ mode, of compound **5b** for example, showed a molecular ion *m/z* = 339.1 $[M+H]^+$. The 1,3-dipolar cycloaddition of aryldiazomethane is in each case regiospecific. Unambiguous proof for the obtained cycloadducts came from their spectral data. The ^1H NMR spectrum of compound **5b** recorded at 300 MHz in $CDCl_3$, showed a singlet at 2.27 ppm corresponding to the methyl group, a broad singlet at 4.69 ppm which corresponds to the NH of the pyrazole moiety. Also, the same spectrum showed the aromatics protons between 6.69 ppm and 8.02 ppm and the presence of another signal at 11.90 ppm directly linked to a hydroxyl proton. Here we can state that, in this case, we have not isolated the spiranic cycladducts which we were attempting to prepare but rather we obtained the rearrangement products possessing the pyrazole structures. In the light of this finding, we have suggested a mechanism in order to give a plausible explanation for the observed results. In Scheme 1, **4a–i** is able to undergo 1,3 prototropic rearrangement and opening of the benzofuranone ring at the 2-position gives fully aromatised pyrazole derivatives **5a–i**.

An additional confirmation of the regiochemistry of the cycloaddition products was determined from the NOESY spectrum which allowed us to distinguish a clear spatial correlation between the hydroxyl proton (11.92 ppm) and the NH proton (4.69 ppm). Also, the absence of any nOe between the hydroxyl proton and the aromatic protons of the aryl group linked to the pyrazole moiety, confirms the structure of the obtained compounds **5a–i** (Scheme 2).

Conclusion

Here we describe an effective approach to a novel class of new highly substituted pyrazole systems achieved via the 1,3-cycloaddition reaction between the (*Z*)-2-arylidene-*2H*-benzofuran-3-ones with aryldiazomethane. We have shown that these reactions proceed with excellent regiospecificities.

Experimental section

Caution: Aryldiazomethane is highly toxic and potentially explosive. All operations should be carried out in an efficient hood behind a protective screen.

IR spectra were recorded on a Perkin-Elmer IR-197 spectrophotometer. The mass spectra were acquired with a Kratos MS80RF double focusing mass spectrometer of Nier-Johnson geometry. Melting points were determined on a Buchi-510 capillary melting point apparatus and were not corrected. TLC was performed on silica gel 254 plates (Merck) with UV (254 nm) visualisation, and preparative chromatographic separations were conducted on silica gel Si-60-7734 (Merck). NMR spectra were obtained on a Bruker AC 300 spectrometer operating at 300 MHz for ^1H and at 75.64 MHz for ^{13}C. Elemental analyses were performed on a Perkin-Elmer 240B microanalyser. All reagents were of commercial quality or purified by standard procedures.

Synthesis of pyrazoles; typical procedure

Aromatic aldehydes were added to a solution of *p*-toluenesulfonylhydrazide (1.5 mmol). After stirring for 3 h at room temperature, a solution of NaOH (5 M, 300 µL, 1.5 mmol) was added and the mixture was stirred for a further 20 min. The derivatives of the (Z)-2-arylidene-2H-benzofuran-3-ones (7.5 mmol) were added and the mixture was stirred at 50 °C for 48 h. The volatiles were evaporated under reduced pressure and the residue was dissolved in a 1:1 mixture of water:ethyl acetate (70 mL). The organic layer was separated and dried over $MgSO_4$. After filtration and removal of the solvent under reduced pressure, the crude material was purified by flash chromatography (eluent petroleum ether/ethyl acetate 4:1) to afford compounds **5a–i**. These products were crystallised from ethanol.

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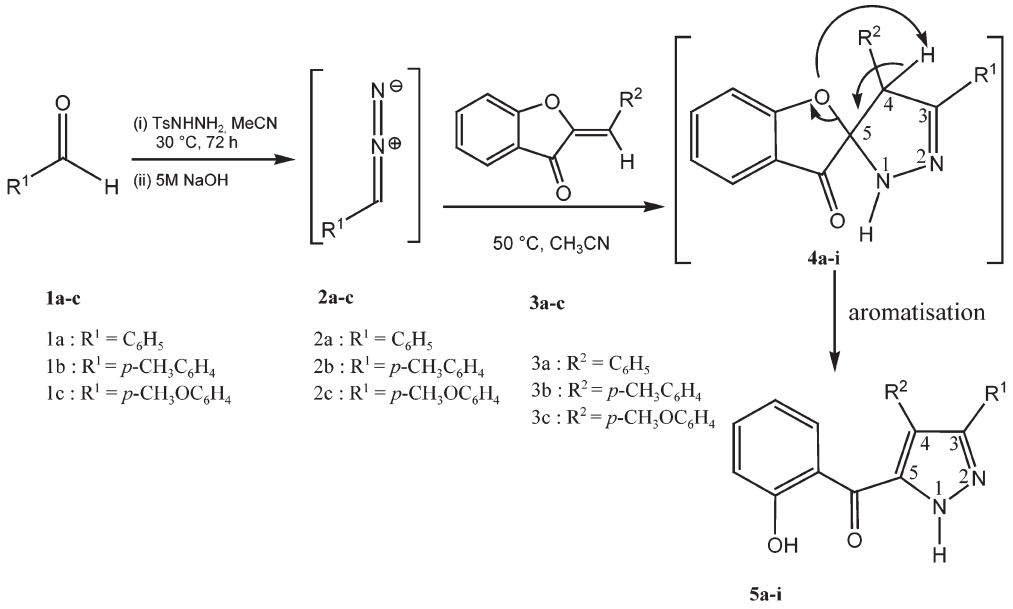
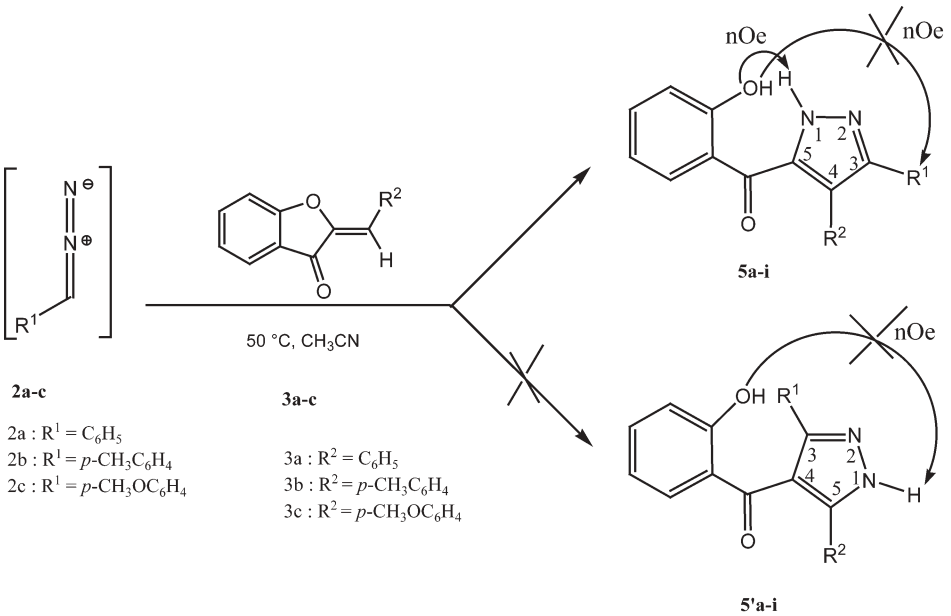


Compound **5**	R^1	R^2
a	C_6H_5	C_6H_5
b	*p*-$CH_3C_6H_4$	C_6H_5
c	*p*-$CH_3OC_6H_4$	C_6H_5
d	C_6H_5	*p*-$CH_3C_6H_4$
e	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$
f	*p*-$CH_3OC_6H_4$	*p*-$CH_3C_6H_4$
g	C_6H_5	*p*-$CH_3OC_6H_4$
h	*p*-$CH_3C_6H_4$	*p*-$CH_3OC_6H_4$
i	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$

Scheme 1 Synthesis of pyrazoles using aryldiazomethanes and (Z)-2-arylidene-2H-benzofuran-3-ones.



Scheme 2 Regiochemistry of cycloaddition.

(4,5-Diphenyl-2H-pyrazol-3-yl)-(2-hydroxyphenyl)-methanone (**5a**): Yellow solid (75.4%); m.p. 197–199 °C. Anal. Calcd for $C_{22}H_{16}N_2O_2$: C, 77.64; H, 4.70; N, 8.23. Found: C, 77.61; H, 4.58; N, 8.33%; IR (KBr): ν_{cm}^{-1} = 1600 (C=N), 1623 (C=O), 3223 (OH), 3435 (NH); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.80 (br s, 1H, NH), 6.73–8.05 (m, 14-Harom), 11.98 (br s, 1H, OH). $^{13}C\{^1H\}$NMR (75.47 MHz, $CDCl_3$): δ (ppm) = 117.9–136.4 (C_{arom}), 123.2 (C_4), 131.5 (C_5), 145.2 (C_3), 163.2 (COH), 193.4 (C=O).

*(2-Hydroxyphenyl)-(4-phenyl-5-*p*-tolyl-2H-pyrazol-3-yl)-methanone* (**5b**): Pale white solid (46.8%); m.p. 219–221 °C. Anal. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.96; H, 5.08; N, 7.90. Found: C, 78.00; H, 5.15; N, 8.05%; MS (ES^+): *m/z* = 339.1 $[M+H]^+$, IR (KBr): ν_{cm}^{-1} = 1597 (C=N), 1621 (C=O), 3253 (OH), 3440 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.27 (s, 3H, CH_3), 4.69 (br s, 1H, NH), 6.69–8.02 (m, 13-Harom), 11.90 (br s, 1H, OH). $^{13}C\{^1H\}$NMR (75.47 MHz, $CDCl_3$): δ (ppm) = 21,2 (CH_3), 116.9–138.9 (C_{arom}), 124.8 (C_4), 131.5 (C_5), 146.2 (C_3), 162.3 (COH), 192.6 (C=O).

(2-Hydroxyphenyl)-[5-(4-methoxyphenyl)-4-phenyl-2H-pyrazol-3-yl]-methanone (**5c**): Yellow solid (55.2%); m.p. 132–134 °C. Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.59; H, 4.86; N, 7.56. Found: C, 74.48; H, 4.77; N, 7.53%; IR (KBr): ν_{cm}^{-1} = 1599 (C=N), 1623 (C=O), 3258 (OH), 3446 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.83 (s, 3H, OCH_3), 4.79 (br s, 1H, NH), 6.84–8.15 (m, 13-Harom), 12.05 (br s, 1H, OH). $^{13}C\{^1H\}$NMR (75.47 MHz, $CDCl_3$): δ (ppm) = 54.7 (OCH_3), 113.9–136.3 (C_{arom}), 123.7 (C_4), 131.8 (C_5), 147.1 (C_3), 159.4 ($COCH_3$), 162.1 (COH), 191.8 (C=O).

(2-Hydroxyphenyl)-(5-phenyl-4-p-tolyl-2H-pyrazol-3-yl)-methanone (**5d**): Yellow solid (42.4%); m.p. 200–202 °C. Anal. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.96; H, 5.08; N, 7.90. Found: C, 77.90; H, 5.03; N, 7.85%; IR (KBr): ν_{cm}^{-1} = 1600 (C=N), 1629 (C=O), 3257 (OH), 3396 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.32 (s, 3H, CH_3), 4.69 (br s, 1H, NH), 6.75–8.07 (m, 13-Harom), 12.00 (br s, 1H, OH). $^{13}C\{^1H\}$NMR (75.47 MHz, $CDCl_3$): δ (ppm) = 21.2 (CH_3), 117.9–137.0 (C_{arom}), 123.2 (C_4), 130.5 (C_5), 143.8 (C_3), 163.2 (COH), 193.7 (C=O).

(4,5-Di-p-tolyl-2H-pyrazol-3-yl)-(2-hydroxyphenyl)-methanone (**5e**): Yellow solid (55.9%); m.p. 200–202 °C. Anal. Calcd for $C_{24}H_{20}N_2O_2$: C, 78.26; H, 5.43; N, 7.60. Found: C, 78.13; H, 5.48; N, 7.76%; IR (KBr): ν_{cm}^{-1} = 1593 (C=N), 1622 (C=O), 3219 (OH), 3425 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.00 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 4.67 (br s, 1H, NH), 6.77–8.09 (m, 12-Harom), 11.99 (br s, 1H, OH). $^{13}C\{^1H\}$NMR (75.47 MHz, $CDCl_3$): δ (ppm) = 21.2 (CH_3), 29.7 (CH_3), 117.9–137.1 (C_{arom}), 121.6 (C_4), 129.9 (C_5), 142.6 (C_3), 163.3 (COH), 193.7 (C=O).

*(2-Hydroxyphenyl)-[5-(4-methoxyphenyl)-4-*p*-tolyl-2H-pyrazol-3-yl]-methanone* (**5f**): Yellow solid (60.9%); m.p. 242–244 °C. Anal. Calcd for $C_{24}H_{20}N_2O_3$: C, 75.00; H, 5.20; N, 7.29. Found: C, 74.88; H, 5.22; N, 7.14%; IR (KBr): ν_{cm}^{-1} = 1593 (C=N), 1620 (C=O), 3239 (OH), 3432 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.32 (br s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.68 (br s, 1H, NH), 6.75–8.08 (m, 12-Harom), 11.98 (s, 1H, OH). $^{13}C\{^1H\}$NMR (75.47 MHz, $CDCl_3$): δ (ppm) = 21.2 (CH_3), 55.2 (OCH_3), 114.1–136.9 (C_{arom}), 121.3 (C_4), 137.1 (C_5), 145.6 (C_3), 159.9 ($COCH_3$), 163.3 (COH), 193.8 (C=O).

(2-Hydroxyphenyl)-[4-(4-methoxyphenyl)-5-phenyl-2H-pyrazol-3-yl]-methanone (**5g**): Yellow solid (62.1%); m.p 196–198 °C. Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.59; H, 4.86; N, 7.56. Found: C, 74.56; H, 4.90; N, 7.50%; IR (KBr): ν_{cm}^{-1} = 1599 (C=N), 1623 (C=O), 3217 (OH), 3437 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.79 (s, 3H, OCH_3), 4.80 (br s, 1H, NH), 6.76–8.07 (m, 13H-arom), 11.97 (br s, 1H, OH). $^{13}C\{^1H\}$NMR (75.47 MHz, $CDCl_3$): δ (ppm) = 55,1 (OCH_3), 113.9–136.4 (C_{arom}), 123.6 (C_4), 130.0 (C_5), 142.9 (C_3), 158.9 (OCH_3), 163.3 (OH), 193.6 (C=O).

*(2-Hydroxyphenyl)-[4-(4-methoxyphenyl)-5-*p*-tolyl-2H-pyrazol-3-yl]-methanone* (**5h**): Solid pale white (60.9%); m.p. 231–233 °C. Anal. Calcd for $C_{24}H_{20}N_2O_3$: C, 75.00; H, 5.20; N, 7.29. Found: C, 74.88; H, 5.30; N, 7.25%; IR (KBr): ν_{cm}^{-1} = 1596 (C=N), 1626 (C=O), 3260 (OH), 3440 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.38 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 4.80 (br s, 1H, NH), 6.83–8.15 (m, 12-Harom), 12.05 (br s, 1H, OH). $^{13}C\{^1H\}$NMR (75.47 MHz, $CDCl_3$): δ (ppm) = 21.3 (CH_3), 55.1 (OCH_3), 113.8–136.4 (C_{arom}), 123.6 (C_4), 129.6 (C_5), 142.8 (C_3), 158.8 ($COCH_3$), 163.7 (COH), 191.9 (C=O).

[*4,5-Bis-(4-methoxyphenyl)-2H-pyrazol-3-yl]-(2-hydroxyphenyl)-methanone* (**5i**): Yellow solid (57.6%); m.p. 245–247 °C. Anal. Calcd for $C_{24}H_{20}N_2O_4$: C, 72.00; H, 5.00; N, 7.00. Found: C, 72.04; H, 5.06; N, 7.07%; IR (KBr): ν_{cm}^{-1} = 1595 (C=N), 1624 (C=O), 3254 (OH), 3433 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.82 (s, 6H, $2OCH_3$), 4.77 (br s, 1H, NH), 6.84–8.10 (m, 12-Harom), 12.05 (br s, 1H, OH). $^{13}C\{^1H\}$NMR (75.47 MHz, $CDCl_3$): δ (ppm) = 54.6 (OCH_3), 54.7 (OCH_3), 113.3–135.9 (C_{arom}), 123.3 (C_4), 137.8 (C_5), 144.1 (C_3), 158.2 ($COCH_3$), 159.3 ($COCH_3$), 162.7 (COH), 193.4 (C=O).

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