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Unexpected ring-opening of 3-aroylbenzo[*b*]furans at room temperature: a new route for the construction of phenol-substituted pyrazoles

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ABSTRACT

A new and convenient route for the synthesis of phenol-substituted pyrazoles **11–18** is starting from 3-aroylbenzo[*b*]furans **1–8** and hydrazine hydrate at room temperature.

The construction of pyrazoles has gained significant interest among the azole family[1–3] due to their diverse therapeutic potential as versatile anticancer,[4] antifungal,[5] antimicrobial,[6], and anti-inflammatory agents[7] and osteogenesis activity.[8] The pyrazole moiety is the main pharmacophore in the established anti-inflammatory drugs, Celecoxib[9] and SC-558.[10] On the other hand, phenolic compounds have received considerable attention owing to their widespread occurrence in a large number of natural products, and for their useful biological and pharmacological properties, for example, as antioxidant,[11] antibacterial,[12] and cardiovascular agents,[13] in addition to their estrogen receptor activity.[14] As part of an ongoing research program devoted to study benzofurans and pyrazoles with potential chemical activities,[15–17] in the present communication, we have investigated the reactions of 3-aroylbenzo[*b*]furans with hydrazine hydrate (Scheme 1).

The structures of benzofurans **4–8**[18] were confirmed from their spectroscopic data and elemental analyses[19] in addition to X-ray single crystal analysis of compound **6** (Fig. 1).[20] Benzofurans **1–8** reacted rapidly with hydrazine hydrate at room temperature to produce phenol-substituted pyrazoles **11–18** (Scheme 1).

The structures of pyrazoles **11–18** were established on the basis of their elemental analyses, spectral data[21] and single crystal X-ray analysis of compound **16** (Fig. 2).[20] Scheme 1 illustrates the mechanism of the formation of compounds **11–18** which are suggested to be formed through intermediate **9** followed by the nucleophilic attack on the electron-deficient C-2 of furan to produce compounds **11–18**. The formation of compounds **11–18** via intermediate **10** is more possible under basic conditions of hydrazine. However, all attempts to isolate intermediates **9** and **10** failed.

The ^{1}H NMR ($CDCl_3$) spectra of the isolated reaction products revealed the existence of the pyrazole NH around δ 7.59 and the phenolic OH in the region δ 8.4–8.9. The appearance of the pyrazole C-5 proton in a pattern in DMSO-d_6 that was different from that in $CDCl_3$[21] is probably due to the tautomerism of 1*H*-3(5)-R pyrazoles.[22] Owing to the latter tautomerism, 1*H*-3(5)-R pyrazoles can exist in two tautomeric forms, 1*H*-3-R and 1*H*-5-R in solution in a ratio that depends on the temperature.[23] Moreover, these pyrazoles showed ^{1}H chemical shifts for the N–H proton in DMSO-d_6 that differed from the corresponding shifts in $CDCl_3$, which can be explained by the presence of intra- or intermolecular hydrogen bonding.[24]

In the solid state, the most common situation is the presence of only one tautomer of 1*H*-3(5)-R pyrazoles.[22] The single crystal X-ray structure of pyrazole **16** not only provided unambiguous confirmation of the structure of pyrazoles **11–18**, but also confirmed the presence of only one tautomeric form, that is, that of the 1*H*-3-R pyrazole (Fig. 2).

In conclusion, the electron-deficient C-2 of 3-aroylbenzo[*b*]furans is extremely reactive toward the nitrogen nucleophilic ring-opening, and this reactivity is employed for the development of an effective new route for the construction of 3,4-disubstituted-pyrazoles.

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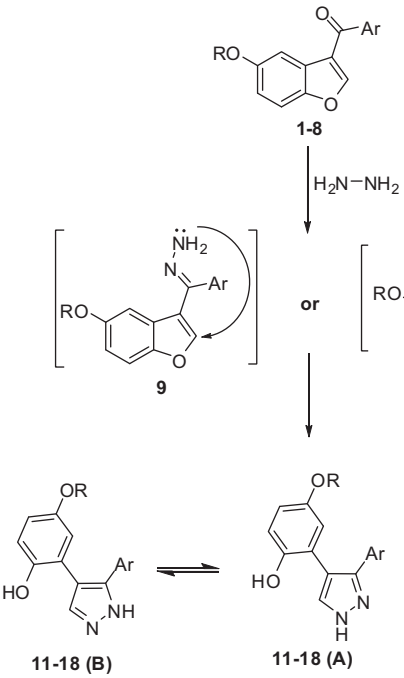

Product	Ar	R	Yield (%)
11	Ph	H	67
12	4-MeC_6H_4	H	64
13	4-ClC_6H_4Ph	H	70
14	Ph	Me	65
15	Ph	CH_2COOMe	70
16	Ph	CH_2COOEt	78
17	4-MeC_6H_4	Me	69
18	4-ClC_6H_4	Me	73

Scheme 1. The reaction of benzofurans **1**–**8** with hydrazine hydrate at room temperature.

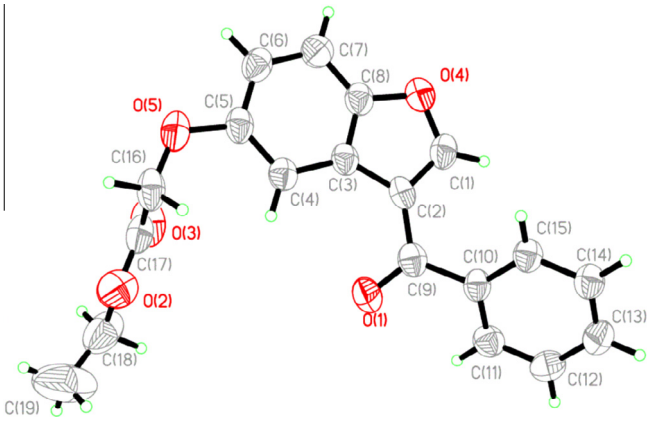

Figure 1. ORTEP diagram of **6**.

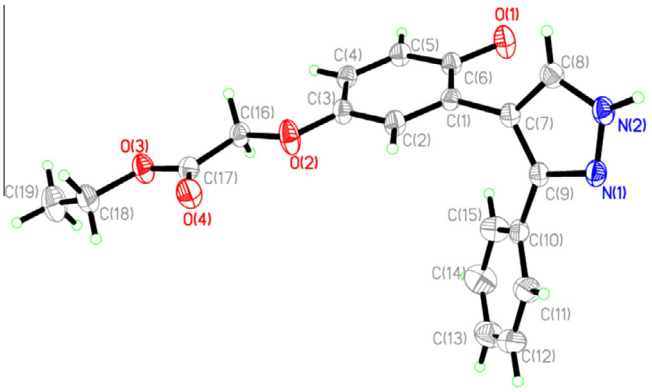

Figure 2. ORTEP diagram of **16**.

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18. (a) Benzofurans **1**–**3** were synthesized by the reaction of enaminones with benzoquinone in acetic acid.; (b) Antczak, C.; Shum, D.; Bassit, B.; Li, Y.; De Stanchina, E.; Scheinberg, D. A.; Djaballah, H.; Frattini, M. G. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4528–4532.

19. *Synthesis of benzofurans* ***4–8***. A mixture of benzofuran derivative **1–3** (10 mmol), the appropriate haloalkane (10 mol), and anhydrous K_2CO_3 (2.76 g, 20 mmol) in dry DMF (30 mL) was stirred for 6 h. Next, H_2O (100 mL) was added to the mixture and the precipitated solid was filtered off and recrystallized from an appropriate solvent to afford the corresponding alkoxy derivatives **4–8**.
Methyl 2-(3-benzoylbenzofuran-5-yloxy)acetate (**5**). White powder, 68% yield; mp 105–107 °C; IR (KBr) ν 1751, 1637 (2C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.80 (s, 3H, $-OCH_3$), 4.72 (s, 2H, CH_2), 7.08 (d, J = 8.5 Hz, 1H, ArH), 7.44–7.51 (m, 3H, ArH), 7.58–7.59 (m, 1H, ArH), 7.68 (s, 1H, ArH), 7.83–7.85 (m, 2H, ArH), 8.04 (s, 1H, furan); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.29 ($-OCH_3$), 65.96 ($-CH_2$), 105.63, 112.40, 116.00, 121.24, 125.90, 128.71, 132.50, 139.21, 151.01, 153.14, 155.44, 169.35 (*C*=O ester), 190.28 (*C*=O ketone); MS (ESI) m/z 311.1 $[M+1]^+$, 333.1 $[M+23]^+$. Anal. Calcd for $C_{18}H_{14}O_5$ (310.30): C, 69.67; H, 4.55. Found: C, 69.51; H, 4.73.
Ethyl 2-(3-benzoylbenzofuran-5-yloxy)acetate (**6**). Colorless crystals, 75% yield; mp 85–87 °C; IR (KBr) ν 1744, 1643 (2C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, J = 7.0 Hz, 3H, $-CH_3$), 4.22 (q, J = 7.0 Hz, 2H, $-OCH_2CH_3$), 4.66 (s, 2H, $-OCH_2CO$), 7.04 (dd, J = 2.0, 8.5 Hz, 1H, ArH), 7.39–7.47 (m, 3H, ArH), 7.53–7.56 (m, 1H, ArH), 7.64 (d, J = 8.5 Hz, 1H, ArH), 7.79–8.05 (m, 2H, ArH), 7.99 (s, 1H, furan); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.16 (CH_2CH_3), 60.37 (CH_2CH_3), 65.00 ($-CH_2$), 104.62, 111.32, 115.00, 120.21, 124.83, 127.68, 131.44, 138.20, 149.95, 152.08, 154.46, 167.86 (*C*=O ester), 189.23 (*C*=O ketone); MS (ESI) m/z 325.0 $[M+1]^+$. Anal. Calcd for $C_{19}H_{16}O_5$ (324.33): C, 70.36; H, 4.97. Found: C, 70.09; H, 5.21.
20. Crystallographic data for the structures **6** (914845) and **16** (914846) have been deposited with the Cambridge Crystallographic Data Centre (CCDC). Copies of the data can be obtained, free of charge, on application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk].
21. *Synthesis of pyrazoles* **11–18**. A solution of benzofuran **1–8** (1 mmol) in MeOH (50 ml) and hydrazine hydrate (1 mmol) was stirred for 6 h. The separated solid was recrystallized from the appropriate solvent to afford the corresponding pyrazoles **11–18**, respectively.
2-(3-Phenyl-1H-pyrazol-4-yl)benzene-1,4-diol (**11**). Colorless crystals, 67% yield; mp 230–232 °C; IR (KBr) ν 3450–2700 (OH+NH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.40 (s, 1H, ArH), 6.51 (d, J = 8.5 Hz, 1H, ArH), 6.75 (d, J = 8.5 Hz, 1H, ArH), 7.24–7.31 (m, 3H, ArH), 7.41–7.46 (m, 2H, ArH), 7.59 (s, 1H, pyrazole), 8.48, 8.60, 8.73 (3s, D_2O-exch., 3H, 2OH+NH); ^1H NMR (500 MHz, DSMO-d_6) δ 6.44 (s, 1H, ArH), 6.52 (dd, J = 2.8, 8.5 Hz, 1H, ArH), 6.68 (d, J = 8.5 Hz, 1H, ArH), 7.10–7.50 (m, 5H, ArH), 7.58 (s, 0.49H, pyrazole), 7.75 (s, 0.51H, pyrazole), 8.53 (s, D_2O-exch., 1H, OH), 8.61 (s, D_2O-exch., 1H, OH), 12.89 (br s, D_2O-exch., 0.51H, NH), 13.10 (br s, D_2O-exch., 0.49H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 114.50, 115.25, 116.07, 117.42, 126.72, 127.98, 128.43, 129.69, 147.45, 149.45; MS (ESI) m/z 253.2 $[M+1]^+$. Anal. Calcd for $C_{15}H_{12}N_2O_2$ (252.27): C, 71.42; H, 4.79; N, 11.10. Found: C, 71.26; H, 4.82; N, 10.88.
Methyl 2-[4-hydroxy-3-(3-phenyl-1H-pyrazol-4-yl)phenoxy]acetate (**15**). Colorless crystals, 70% yield; mp 187–189 °C; IR (KBr) ν 3500–2700 (OH+NH), 1748 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 3H, $-OCH_3$), 4.66 (s, 2H, $-OCH_2CO$), 6.58 (s, 1H, ArH), 6.71 (d, J = 8.5 Hz, 1H, ArH), 6.82 (d, J = 8.5 Hz, 1H, ArH), 7.17–7.20 (m, 3H, ArH), 7.23–7.37 (m, 2H, ArH), 7.59 (s, 1H, pyrazole), 8.75 (br s, D_2O-exch., 2H, OH+NH); ^1H NMR (500 MHz, DSMO-d_6) δ 3.75 (s, 3H, $-OCH_3$), 4.51 (s, 2H, $-OCH_2CO$), 6.55 (s, 1H, ArH), 6.69 (dd, J = 2.8, 8.5 Hz, 1H, ArH), 6.77 (d, J = 8.5 Hz, 1H, ArH), 7.29–7.43 (m, 5H, ArH), 7.58 (s, 0.42H, pyrazole), 7.79 (s, 0.58H, pyrazole), 8.90 (s, D_2O-exch., 1H, OH), 12.91 (br s, D_2O-exch., 0.58H, NH), 13.15 (br s, D_2O-exch., 0.42H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.03 ($-OCH_3$), 65.88 ($-CH_2$), 106.07, 112.40, 116.74, 120.67, 126.89, 129.19, 132.78, 139.97, 151.11, 153.89, 155.29, 168.28 (*C*=O ester); MS (ESI) m/z 325.1 $[M+1]^+$, 347.2 $[M+23]^+$. Anal. Calcd for $C_{18}H_{16}N_2O_4$ (324.33): C, 66.66; H, 4.97; N, 8.64. Found: C, 66.42; H, 5.15; N, 8.83.
Ethyl 2-[4-hydroxy-3-(3-phenyl-1H-pyrazol-4-yl)phenoxy]acetate (**16**). Colorless crystals, 78% yield; mp 166–168 °C; IR (KBr) ν 3500–2750 (OH+NH), 1745 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.17 (t, J = 7.0 Hz, 3H, $-CH_3$), 4.13 (q, J = 7.0 Hz, 2H, $-OCH_2CH_3$), 4.35 (s, 2H, $-OCH_2CO$), 6.55 (s, 1H, ArH), 6.72 (d, J = 8.5 Hz, 1H, ArH), 6.84 (d, J = 8.5 Hz, 1H, ArH), 7.19–7.21 (m, 3H, ArH), 7.26–7.38 (m, 2H, ArH), 7.59 (s, 1H, pyrazole), 8.77 (br s, D_2O-exch., 2H, OH+NH); ^1H NMR (500 MHz, DSMO-d_6) δ 1.17 (t, J = 7.0 Hz, 3H, $-CH_3$), 4.10 (q, J = 7.0 Hz, 2H, $-OCH_2CH_3$), 4.53 (s, 2H, $-OCH_2CO$), 6.57 (s, 1H, ArH), 6.70 (dd, J = 2.8, 8.5 Hz, 1H, ArH), 6.78 (d, J = 8.5 Hz, 1H, ArH), 7.29–7.45 (m, 5H, ArH), 7.58 (s, 0.44H, pyrazole), 7.81 (s, 0.56H, pyrazole), 8.93 (s, D_2O-exch., 1H, OH), 12.96 (br s, D_2O-exch., 0.56H, NH), 13.15 (br s, D_2O-exch., 0.44H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.11 (CH_2CH_3), 60.33 (CH_2CH_3), 65.17 ($-CH_2$), 115.30, 116.00, 116.19, 117.60, 126.50, 127.58, 127.94, 128.43, 134.29, 143.23, 147.60, 150.50, 168.17 (*C*=O ester); MS (ESI) m/z 339.2 $[M+1]^+$, 361.1 $[M+23]^+$. Anal. Calcd for $C_{19}H_{18}N_2O_4$ (338.36): C, 67.44; H, 5.36; N, 8.28. Found: C, 67.70; H, 5.23; N, 8.43.

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