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Synthesis of 5,6-dicyanobenzofurans based on 4-bromo-5-nitrophthalonitrile

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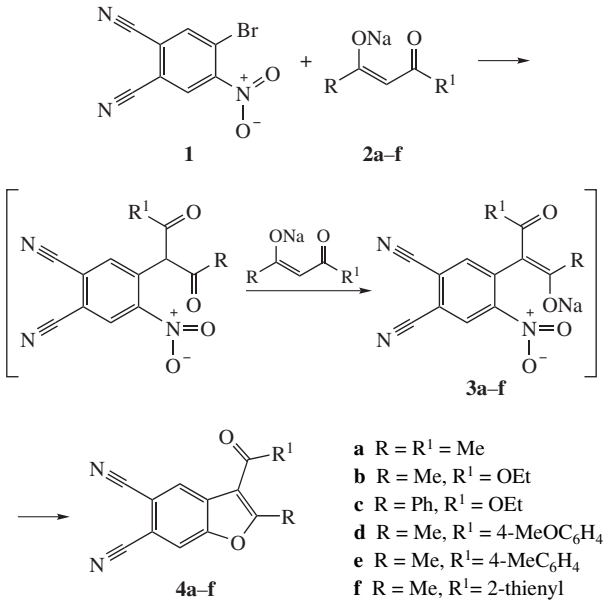
A new stereoselective method for the synthesis of substituted 5,6-dicyanobenzofurans by activated aromatic nucleophilic replacement of a bromine atom and a nitro group in 4-bromo-5-nitrophthalonitrile has been developed.

Owing to the diversity of practical applications of benzofurans,[1,2] interest in this class of heterocycles remains high.[3,4] Although diverse methods are known to synthesise these compounds, information on syntheses of benzofurans with electron-withdrawing substituents is relatively scarce,[5–7] and only three papers on the synthesis of *ortho*-dicarbonitriles containing the benzofuran moiety are available. Two syntheses of dicyanobenzofurans are based on a high-temperature reaction of brominated derivatives with metal cyanides,[8,9] and nucleophilic replacement of the nitro group in 4-nitrophthalonitrile with dimedone[10] at 100 °C is used in one case. Note that substituted *ortho*-dicarbonitriles are precursors for synthesising phthalocyanines,[11–13] hexazocyclanes[14] and other compounds containing anhydride, imide, isoindoline and tetrazole moieties.

We have developed a new method for the synthesis of substituted 5,6-dicyanobenzofurans **4a–f** by activated aromatic nucleophilic replacement of a bromine atom and a nitro group[15,16] in 4-bromo-5-nitrophthalonitrile (BNPN) **1** with sodium salts of 1,3-diketones **2a–f**† (Scheme 1). The reaction occurs at 25–35 °C in DMF and requires 12–20 h to be completed (the reaction time decreases to 2 h in case of aliphatic substituents). The reaction yield exceeds 75%, which is attributable to the high reactivity of BNPN in strongly basic media. The behaviour of this substrate in S_NAr reactions was considered previously.[11–14,17–19] In reactions with mono- and bifunctional O-, N-, S-nucleophiles, the reactive bromine atom was first replaced in this compound an then the nitro group; as a result, a wide range of derivatives were obtained with diverse aliphatic, aromatic and heterocyclic substituents.

A specific feature of this method is that sodium salts of 1,3-dicarbonyl compounds **2a–f** were used not only as reagents but also as deprotonating agents; therefore, they were needed in a two-fold molar excess. Attempts to decrease the amount of compounds **2a–f** using other bases (TEA, K_2CO_3, NaOH and MeONa) resulted in a considerable decrease in the yields of target benzofurans **4a–f**. This reaction was carried out in DMSO, DMF, acetonitrile and ethanol; however, the best results were obtained in DMF.

We believe that the formation of the benzofuran ring in **4a–f** starts with an attack of nucleophilic reagent **2a–f** at the BNPN carbon atom bound to the bromine atom to give intermediate **3a–f**.[20] The formation of C–C bonds in electron-deficient aromatic compounds was considered by Artamkina *et al.*[21] Compound **3** is not accumulated in the reaction mixture; instead,



Scheme 1

immediately after the formation, it undergoes deprotonation to give an O-nucleophile.

The subsequent intramolecular nucleophilic replacement of the nitro group in intermediate **3a–f** by the O-nucleophilic centre formed *in situ* completes the formation of target 5,6-dicyanobenzofurans **4a–f**. Note that, due to the tautomerism of the double bond, cyclisation of intermediate **3** can produce two isomers of 2-Me or 3-Ac-benzofurans **4a**,**b**,**d–f**; however, the reaction occurs stereoselectively under the conditions used to give only one 2-Me isomer in all cases, which was proved by ^{13}C NMR spectroscopy (the methyl proton signal at δ 14–15 ppm). This follows from an analysis of ^{13}C NMR chemical shifts for compound **4a** (the only compound with an acetyl substituent) with the following values for methyl carbons: δ 15.27 (2-Me) and 30.75 (3-Ac), respectively.

The structures of compounds **4a–f** were confirmed by a combination of IR- and NMR-spectroscopic and mass-spectrometric data. Typical signals in ^1H NMR spectra include two signals of phthalonitrile protons at about δ 8.5 ppm and a methyl group signal at about δ 2.55–2.86 ppm. Furthermore, the ^{13}C NMR spectra of benzofurans **4a**,**d–f** contain a characteristic

signal of the carbonyl carbon in the region of δ 180–190 ppm, whereas the signal of the carbonyl carbon of the ester group in compounds **4b**,**c** is observed in the region of δ 160–164 ppm. Compound **4c** is the only one in the presented series that has a phenyl substituent at the 2-position. Its structure was confirmed by an analysis of data of a NOESY spectrum containing medium-intensity cross-peaks of ethyl group protons with one of the protons of the phthalonitrile ring and the phenyl substituent.

† IR spectra were measured on a Perkin-Elmer RX-1 spectrometer in the range of 700–4000 cm^{-1} using suspensions of substances in Vaseline oil. Mass spectra were obtained using a FINNIGAN MAT.INCOS 50 mass spectrometer; the ionization energy was 70 eV. NMR spectra were recorded on a Bruker DRX-500 instrument at 30 °C for solutions in [$^2H_6$]DMSO. Signals of residual protons of the solvent in ^{1}H NMR spectra (δ_H 2.50) or the signal of [$^2H_6$]DMSO in ^{13}C spectra (δ_C 39.5) were used as references for chemical shift measurements.

BNPN (**1**) was synthesised using a published procedure.[17] The sodium salts of 1,3-dicarbonyl compounds **2a**–**f** were synthesised by the procedure reported elsewhere.[22]

General procedure for the synthesis of compounds **4a**–**f**. Compound **2a**–**f** (4.4 mmol) was added to a solution of BNPN (2.0 mmol) in 3 ml of DMF, the mixture was stirred for 2–20 h at 25–35 °C and poured into 10 ml of 1% hydrochloric acid solution. The resulting resinous precipitate was extracted with CH_2Cl_2, thoroughly washed with water, and chromatographed on silica gel using a hexane–dichloromethane mixture (1:2) as the eluent. The eluent was evaporated; the resulting precipitate was filtered off and recrystallised from ethanol.

3-Acetyl-2-methyl-1-benzofuran-5,6-dicarbonitrile **4a**: yield 61%, mp 205–207 °C. ^{1}H NMR, δ: 2.66 (s, 3H, Me), 2.87 (s, 3H, 2-Me), 8.56 (s, 1H, 7-H), 8.57 (s, 1H, 4-H). ^{13}C NMR, δ: 15.27 (2-Me), 30.75 (3-Ac), 109.67 (C-5), 110.13 (C-6), 115.99 (C≡N), 116.11 (C≡N), 116.87 (C-3), 117.72 (4-C), 127.74 (7-C), 130.19 (C-3a), 152.86 (C-7a), 168.09 (C-2), 193.12 (C=O). IR (ν/cm^{-1}): 2234 (C≡N), 1666 (C=O), 1286 (C–O–C). MS, *m*/*z* (%): 224 (M$^+$, 30), 209 (M$^+$ – Me, 100), 181 (M$^+$ – Ac, 4). Found (%): C, 69.42; H, 3.57; N, 12.52. Calc. for $C_{13}H_8N_2O_2$ (%): C, 69.64; H, 3.60; N, 12.49.

Ethyl 5,6-dicyano-2-methyl-1-benzofuran-3-carboxylate **4b**: yield 54%, mp 129–132 °C. ^{1}H NMR, δ: 1.39 (t, 3H, Et, *J* 7.0 Hz), 2.83 (s, 3H, 2-Me), 4.40 (q, 2H, CH_2, *J* 7.0 Hz), 8.45 (s, 1H, 7-H), 8.62 (s, 1H, 4-H). ^{13}C NMR, δ: 13.96 (Me), 14.22 (2-Me), 60.88 (CH_2), 108.71 (C-5), 109.73 (C-6), 110.11 (C-3), 115.89 (C≡N), 115.97 (C≡N), 117.85 (C-4), 127.15 (C-7), 129.83 (C-3a), 152.98 (C-7a), 161.78 (C=O), 168.97 (C-2). IR (ν/cm^{-1}): 2235 (C≡N), 1716 (C=O), 1285 (C–O–C). MS, *m*/*z* (%): 254 (M$^+$, 53), 239 (M$^+$ – Me, 2), 226 (M$^+$ – Et + H, 100), 209 (M$^+$ – OEt, 82), 181 (M$^+$ – COOEt, 25). Found (%): C, 66.27; H, 3.73; N, 11.06. Calc. for $C_{14}H_{10}N_2O_3$ (%): C, 66.14; H, 3.96; N, 11.02.

Ethyl 5,6-dicyano-2-phenyl-1-benzofuran-3-carboxylate **4c**: yield 69%, mp 187–190 °C. ^{1}H NMR, δ: 1.34 (t, 3H, Et, *J* 7.0 Hz), 4.38 (q, 2H, CH_2, *J* 7.0 Hz), 7.58 (t, 2H, Ph, *J* 7.7 Hz), 7.64 (t, 1H, Ph, *J* 7.7 Hz), 8.00 (d, 2H, Ph, *J* 7.7 Hz), 8.52 (s, 1H, 7-H), 8.66 (s, 1H, 4-H). ^{13}C NMR, δ: 13.76 (Me), 61.23 (CH_2), 108.56 (C-5), 110.28 (C-6), 110.42 (C-3), 115.90 (C≡N), 116.03 (C≡N), 118.31 (C-4), 127.02 (C-1′), 128.34 (C-3′, C-5′), 128.44 (C-4′), 129.56 (C-2′, C-6′), 130.78 (C-7), 131.78 (C-3a), 153.16 (C-7a), 161.39 (C=O), 164.21 (C-2). IR (ν/cm^{-1}): 2232 (C≡N), 1727 (C=O), 1222 (C–O–C). MS, *m*/*z* (%): 316 (M$^+$, 79), 288 (M$^+$ – Et + H, 34), 271 (M$^+$ – OEt, 100), 244 (271 – HCN, 29), 215 (244 – 29, 87). Found (%): C, 72.18; H, 3.55; N, 8.83. Calc. for $C_{19}H_{12}N_2O_3$ (%): C, 72.15; H, 3.82; N, 8.86.

3-(4-Methoxybenzoyl)-2-methylbenzofuran-5,6-dicarbonitrile **4d**: yield 64%, mp 163–166 °C. ^{1}H NMR, δ: 2.55 (s, 3H, Me), 3.89 (s, 3H, OMe), 7.07 (d, 2H, 5′-H, 3′-H, *J* 8.8 Hz), 7.80 (d, 2H, 2′-H, 6′-H, *J* 8.8 Hz), 8.10 (s, 1H, 7-H), 8.56 (s, 1H, 4-H). ^{13}C NMR, δ: 14.84 (2-Me), 55.70 (OMe), 109.66 (C-5), 109.83 (C-6), 114.21 (C-5′, C-3′), 116.25 (2C≡N), 116.61 (C-3), 117.95 (C-7), 127.24 (C-4), 130.16 (C-3a), 131.80 (C-2′, C-6′), 131.52 (C-1′), 153.43 (C-7a), 163.69 (C-4′), 165.62 (C-2), 187.80 (C=O). IR (ν/cm^{-1}): 2230 (C≡N), 1647 (C=O), 1265 (C–O–C). MS, *m*/*z* (%): 316 (M$^+$, 100), 301 (M$^+$ – Me, 30), 285 (M$^+$ – OMe, 100), 273 (M$^+$ – Ac, 6), 135 (COPhOMe, 57). Found (%): C, 72.27; H, 3.73; N, 8.90. Calc. for $C_{19}H_{12}N_2O_3$ (%): C, 72.15; H, 3.82; N, 8.86.

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2-Methyl-3-(4-methylbenzoyl)benzofuran-5,6-dicarbonitrile **4e**: yield 61%, mp 195–198 °C. ^{1}H NMR, δ: 2.47 (s, 3H, Me′), 2.52 (s, 3H, 2-Me), 7.40 (d, 2H, 5′-H, 3′-H, *J* 8.0 Hz), 7.72 (d, 2H, 2′-H, 6′-H, *J* 8.0 Hz), 8.15 (s, 1H, 7-H), 8.64 (s, 1H, 4-H). ^{13}C NMR, δ: 14.95 (2-Me), 21,31 (Me′), 109.77 (C-5), 109.92 (C-6), 116.22 (2C≡N), 116.53 (C-3), 117.98 (C-7), 127.28 (C-4), 129.34 (C-5′, C-3′), 129.48 (C-2′, C-6′), 131.40 (C-1′), 135.13 (C-3a), 144.23 (C-4′), 153.44 (C-7a), 166.33 (C-2), 189.13 (C=O). IR (ν/cm^{-1}): 2235 (C≡N), 1642 (C=O), 1288 (C–O–C). MS, *m*/*z* (%): 300 (M$^+$, 99), 285 (M$^+$ – Me, 100), 209 (M$^+$ – PhMe, 67), 181 (M$^+$ – COPhMe, 9), 119 (COPhMe, 68). Found (%): C, 76.13; H, 3.80; N, 9.25. Calc. for $C_{19}H_{12}N_2O_2$ (%): C, 76.00; H, 4.03; N, 9.33.

2-Methyl-3-(thien-2-ylcarbonyl)benzofuran-5,6-dicarbonitrile **4f**: yield 53%, mp 170–173 °C. ^{1}H NMR, δ: 2.68 (s, 3H, 2-Me), 7.26 (t, 1H, 4′-H, *J* 3.6 Hz, *J* 4.8 Hz), 7.85 (d, 1H, 3′-H, *J* 3.6 Hz), 8.21 (d, 1H, 5′-H, *J* 4.8 Hz), 8.32 (s, 1H, 7-H), 8.68 (s, 1H, 4-H). ^{13}C NMR, δ: 14.76 (2-Me), 109.80 (C-5), 109.92 (C-6), 116.23 (C≡N), 116.27 (C≡N), 116.58 (C-3), 118.01 (C-7), 127.25 (C-4′), 128.98 (C-4), 131.06 (C-3a), 136.10 (C-5′), 136.86 (C-3′), 143.21 (C-2′), 153.40 (C-7a), 165.26 (C-2), 180.79 (C=O). IR (ν/cm^{-1}): 2234 (C≡N), 1622 (C=O), 1291 (C–O–C). MS, *m*/*z* (%): 292 (M$^+$, 100), 277 (M$^+$ – Me, 8), 209 (M$^+$ – thienyl, 26), 111 (thienylcarbonyl, 99). Found (%): C, 65.77; H, 2.78; N, 9.74. Calc. for $C_{16}H_8N_2O_2S$ (%): C, 65.74; H, 2.76; N, 9.58.