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Synthesis of 2-oxo- and 2-thioxo-5-(benzofuran-2-yl)tetrahydropyrimidines

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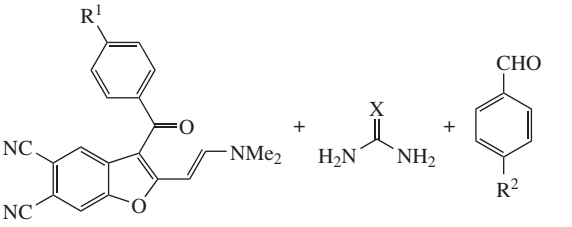
New 5,6-dicyanobenzofurans bearing a 2-(thi)oxotetrahydropyrimidine moiety at the 2-position were synthesized from 2-(2-dimethylaminovinyl)-5,6-dicyanobenzofurans, benzaldehydes and (thio)urea in AcOH.

Recently, the area of heterocyclic chemistry dealing with the syntheses of substituted tetrahydropyrimidin-2-ones and their thio analogues was growing rapidly; these syntheses are based on the three-component Biginelli reaction[1] catalysed both by acids and bases.[2,3] The resulting 6-aryl-2-(thi)oxotetrahydropyrimidines show various biological activities, *e.g.*, they can act as calcium channel modulators and be employed for the therapy of cardiovascular diseases.[4] Compounds of benzofuran series capable of uric acid liberation, such as amiodarone – a third class antiarhythmic compound, benzbromarone and benziodarone,[5] are also widely used in practical medicine. Thus, combining benzofuran and pyrimidine moieties in the same molecule creates promising opportunities for development of new pharmaceuticals.

Here, we describe a synthesis of new substituted 5,6-dicyanobenzofurans bearing a dihydropyrimidin-2-one(thione) moiety at the 2-position. Syntheses of similar compounds based on amino enones available from the corresponding R-carboxymethyl derivatives are known,[6,7] but data on the use of catalysts reported in those publications are contradictory.

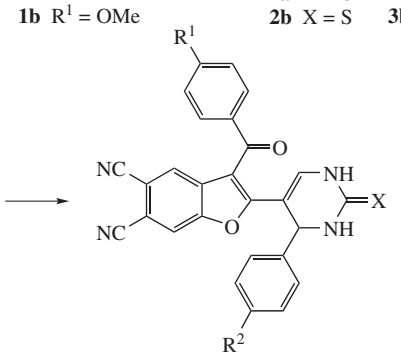
In our experiments, substituted 2-(2-dimethylaminovinyl)-5,6-dicyanobenzofurans are used for the first time as the substrate analogous to amino enones, with glacial acetic acid being used as the catalyst and solvent (Scheme 1).



1a R^1 = Me
1b R^1 = OMe

2a X = O
2b X = S

3a R^2 = H
3b R^2 = OMe



4a R^1 = Me, R^2 = H, X = O
4b R^1 = Me, R^2 = OMe, X = O
4c R^1 = Me, R^2 = H, X = S
4d R^1 = Me, R^2 = OMe, X = S
4e R^1 = R^2 = OMe, X = S

Scheme 1

The starting compounds **1a**,**b** were obtained by heating of 3-aroyl-5,6-dicyano-2-methylbenzofurans[8] in excess of dimethylformamide dimethylacetal.[9] Tetrahydropyrimidin-2-ones(thiones) **4a**–**e** were synthesized in 50–75% yield by heating (thio)urea **2** and aromatic aldehydes **3a**,**b** for 8–18 h with equimolar amounts of compounds **1** in glacial acetic acid. The process occurs selectively to give one regioisomer. The reaction with urea proceeds more quickly than that with thiourea and the yields of the corresponding derivatives are generally higher than those of the thioxo analogues, since the longer heating results in greater resinification.

The structures of the products **4** were confirmed by IR and NMR spectroscopy and mass spectrometry.† ^{1}H NMR spectra

† IR spectra were measured on a Perkin-Elmer RX-1 spectrometer in the range of 700–4000 cm^{-1} using suspensions of substances in Nujol. 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 DMSO-d_6. Signals of residual protons of the solvent in ^{1}H NMR spectra (δ_H 2.50) or the signal of DMSO-d_6 in ^{13}C spectra (δ_C 39.5) were used as references for chemical shift measurements.

The starting benzofurans were synthesized according to procedure published elsewhere,[8] whereas aminovinyl compounds **1a**,**b** were obtained by another reported method.[9]

General procedure for the synthesis of compounds **4a**–**e**. A mixture of corresponding compounds **1**–**3** (0.01 mol each) was refluxed in glacial acetic acid (20 ml) for 8–18 h at 100 °C, cooled and diluted with water (20 ml); the precipitate formed was filtered off and dissolved in dichloromethane. The solution was washed with water; flash chromatography on silica gel was carried out, the solvent was evaporated, and the precipitate was filtered off and washed with ethanol.

3-(4-Methylbenzoyl)-2-(2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)-1-benzofuran-5,6-dicarbonitrile **4a**: yield 71%, mp 208–210 °C. IR (ν/cm^{-1}): 3287 (N–H), 2234 (C≡N), 1656, 1640 (C=O), 1286 (C–O–C). ^{1}H NMR, δ: 2.40 (s, 3H, Me), 5.42 (d, 1H, H-4′, *J* 3.0 Hz), 7.16–7.28 (m, 8H), 7.43 (d, 2H, H-2″, H-6″, *J* 8.1 Hz), 7.72 (s, 1H, H-7),

contain signals of all protons of the benzofuran and pyrimidine moieties; furthermore, pyrimidine ring protons are manifested by vicinal coupling constants, and the $^4J_{NH^1–NH^3}$ long-range constant can sometimes be observed for urea protons.

The structure of compound **4a** was ultimately proved by X-ray diffraction (Figure 1).‡ A unit cell contains a molecule of compound **4a** and two disordered THF molecules. The benzofuran ring is planar; the pyrimidine ring also has a planar structure and is coplanar to benzofuran, which results in π-conjugation between the rings. This is indicated by the shortening of the C(2)–C(16) bond [1.439(7) Å] and by the C(16)=C(17) bond length [1.334(7) Å] typical of conjugated systems (the average statistical lengths of similar bonds are 1.478 and 1.330 Å, respectively[10]).

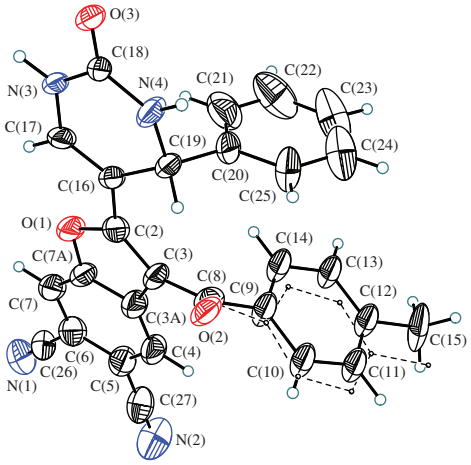


Figure 1 General view of molecule **4a**. The atoms are presented as thermal vibration ellipsoids at 50% probability level; the second component of the disordered 4-MeC_6H_4 moiety is shown by dashed lines and dots (hydrogen atoms are not shown).

In the crystal structure, one of the amide protons is involved in H-bonding [N(3)–H(3)···O(3), H···O 1.88 Å, N···O 2.782(6) Å, ∠NHO 176°], which leads to formation of centrosymmetrical dimers, whereas the N(4)–H(4) fragment is bound to one of the THF molecules.

In conclusion, new benzofurans containing 2-positioned tetrahydropyrimidin-2-one(thione) moiety have been selectively synthesized from substituted 5,6-dicyanobenzofurans with acetic acid as the catalyst.

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7.82 (d, 1H, H-3′, *J* 3.0 Hz), 8.49 (s, 1H, H-4), 9.41 (br. s, 1H, H-1′). ^{13}C NMR, δ: 21.22, 54.07, 100.34, 108.98, 109.67, 112.50, 116.07, 116.18, 117.22, 126.06, 126.34 (2C), 127.78, 128.55 (2C), 129.22 (2C), 129.31 (2C), 132.35, 134.14, 134.61, 142.56, 144.35, 150.77, 160.61, 188.80. MS, *m/z* (%): 458 [M$^+$] (14.7), 339 [M$^+$ – MeC_6H_4CO] (16.6), 119 [$MeC_6H_4CO^+$] (100), 91 [$MeC_6H_5^+$] (61.5). Found (%): C, 73.22; H, 4.01; N, 12.15. Calc. for $C_{28}H_{18}N_4O_3$ (%): C, 73.35; H, 3.96; N, 12.22.

2-[4-(4-Methoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl]-3-(4-methylbenzoyl)-1-benzofuran-5,6-dicarbonitrile **4b**: yield 75%, mp 227–229 °C. IR (ν/cm^{-1}): 3328, 3200 (N–H), 2236 (C≡N), 1656, 1644 (C=O), 1282 (C–O–C). ^{1}H NMR, δ: 2.40 (s, 3H, Me), 3.65 (s, 3H, OMe), 5.36 (d, 1H, H-4′, *J* 2.9 Hz), 6.67 (d, 2H, *J* 8.6 Hz), 7.04 (d, 2H, *J* 8.6 Hz), 7.25 (s, 1H, H-6′), 7.26 (d, 2H, H-3″, H-5″, *J* 8.2 Hz) 7.37 (d, 2H, H-2″, H-6″, *J* 8.2 Hz), 7.57 (s, 1H, H-7), 7.56 (d, 1H, H-3′, *J* 2.9 Hz), 8.39 (s, 1H, H-4), 9.37 (s, 1H, H-1′). MS, *m/z* (%): 488 [M$^+$] (3.8), 309 (23.3), 285 (21.7), 134 (54.8), 119 [$MeC_6H_4CO^+$] (95), 91 [$MeC_6H_5^+$] (100). Found (%): C, 71.10; H, 3.97; N, 11.52. Calc. for $C_{29}H_{20}N_4O_4$ (%): C, 71.30; H, 4.13; N, 11.47.

3-(4-Methylbenzoyl)-2-(4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1-benzofuran-5,6-dicarbonitrile **4c**: yield 62%, mp 198–201 °C. IR (ν/cm^{-1}): 3285 (N–H), 2238 (C≡N), 1651, 1637 (C=O), 1299 (C–O–C). ^{1}H NMR, δ: 2.40 (s, 3H, Me), 5.41 (s, 1H, H-4′), 7.14–7.28 (m, 8H), 7.44 (d, 2H, H-2″, H-6″, *J* 8.1 Hz), 7.73 (s, 1H, H-7), 8.54 (s, 1H, H-4), 9.66 (br. s, 1H, H-3′), 10.60 (br. s, 1H, H-1′). MS, *m/z* (%): 474 [M$^+$] (1.5), 119 [$MeC_6H_4CO^+$] (100), 91 [$MeC_6H_5^+$] (56). Found (%): C, 70.42; H, 3.57; N, 11.72. Calc. for $C_{28}H_{18}N_4O_2S$ (%): C, 70.87; H, 3.82; N, 11.81.

3-(4-Methylbenzoyl)-2-[4-(4-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]-1-benzofuran-5,6-dicarbonitrile **4d**: yield 53%, mp 258–260 °C. IR (ν/cm^{-1}): 3387, 3146 (N–H), 2236 (C≡N), 1650, 1632 (C=O), 1273 (C–O–C). ^{1}H NMR, δ: 2.40 (s, 3H, Me), 3.63 (s, 3H, OMe), 5.32 (d, 1H, H-4′, *J* 3.3 Hz), 6.71 (d, 2H, *J* 8.7 Hz), 7.03 (d, 2H, *J* 8.7 Hz), 7.19 (d, 1H, H-6′, *J* 5.7 Hz), 7.26 (d, 2H, H-3″, H-5″, *J* 8.1 Hz), 7.41 (d, 2H, H-2″, H-6″, *J* 8.1 Hz), 7.71 (s, 1H, H-7), 8.53 (s, 1H, H-4), 9.59 (dd, 1H, H-3′, *J* 3.3 Hz, *J* 1.7 Hz), 10.54 (dd, 1H, H-1′, *J* 5.7 Hz, *J* 1.7 Hz). MS, *m/z* (%): 504 [M$^+$] (3.5), 119 [$MeC_6H_4CO^+$] (100), 91 [$MeC_6H_5^+$] (58). Found (%): C, 68.86; H. 3.84; N, 11.02. Calc. for $C_{29}H_{20}N_4O_3S$ (%): C, 69.03, H 4.00, N, 11.10.

3-(4-Methoxybenzoyl)-2-[4-(4-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]-1-benzofuran-5,6-dicarbonitrile **4e**: yield 58%, mp 262–264 °C, IR (ν/cm^{-1}): 3156 (N–H), 2236 (C≡N), 1650, 1632 (C=O), 1263 (C–O–C). ^{1}H NMR, δ: 3.65 (s, 3H, OMe), 3.88 (s, 3H, OMe), 5.33 (br. s, 1H, H-4′), 6.65 (d, 2H, *J* 8.2 Hz), 6.91 (d, 2H, *J* 8.5 Hz), 7.02 (d, 2H, *J* 8.2 Hz), 7.19 (br. s, 1H, H-6′), 7.46 (d, 2H, *J* 8.5 Hz), 7.63 (s, 1H, H-7), 8.41 (s, 1H, H-4), 9.47 (br. s, 1H, H-3′), 10.43 (br. s, 1H, H-1′). Found (%): C, 66.62; H, 3.74; N, 10.62. Calc. for $C_{29}H_{20}N_4O_4S$ (%): C, 67.00; H, 3.85; N, 10.79.

‡ *X-ray diffraction study.* Single crystals were obtained as very thin needles characterized by extremely weak reflection. Reflections for compound **4a** were collected with a SMART APEX2 diffractometer [λ(MoKα) = 0.71073 Å, graphite monochromator, ω-scans] at 100 K. The structure was solved by direct methods and refined by the full-matrix least-squares procedure against F^2 in anisotropic approximation (except for solvated THF molecules which were both disordered over two positions and refined isotropically). Hydrogen atoms of NH groups were found in the difference Fourier synthesis, normalized at the standard X-ray value (0.9 Å) and refined within the riding model. All the other hydrogen atoms were placed in geometrically calculated positions and refined within the riding model.

4a·2(C_4H_8O): $C_{28}H_{20}N_4O_3$·2(C_4H_8O), monoclinic, space group $P2_1/n$, a = 9.331(2), b = 18.448(4) and c = 18.476(4) Å, β = 103.077(3)°, V = = 3098.0(10) Å^3, Z = 4, M = 604.69, d_{calc} = 1.296 g cm^{-3}, μ = 0.087 mm^{-1}, $F(000)$ = 1280, wR_2 = 0.2418, GOF = 1.068 for 6076 independent reflections with $2\theta < 52°$, R_1 = 0.0963 for 2098 reflections with $I > 2\sigma(I)$.

CCDC 805524 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2011.