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Synthesis of 7,8-dicyanopyrimido[2,1-*b*][1,3]benzothiazoles

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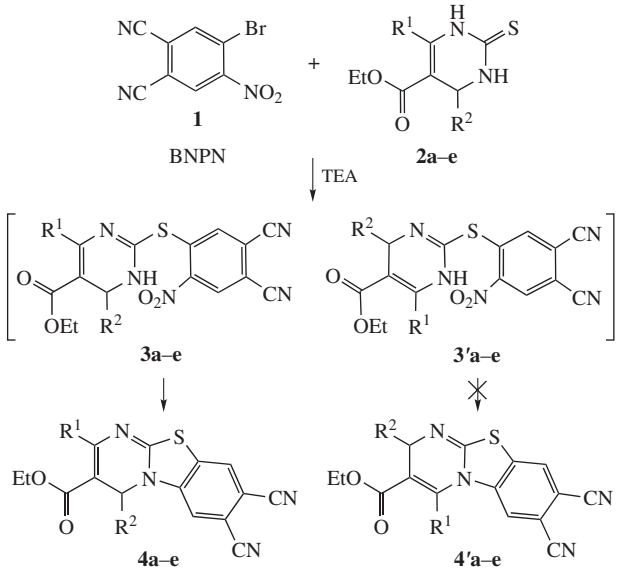
Reaction between 4-bromo-5-nitrophthalonitrile and Biginelli pyrimidinethiones affords 7,8-dicyanopyrimido[2,1-*b*][1,3]benzothiazoles.

Biginelli compounds[1–3] are currently subject to intense studies due to their wide-ranging bioactivity. On the other hand, sulfanyl derivatives of phthalonitriles behave as powerful inhibitors of monoamine oxidase B (MAO-B) and can be used for the treatment of neurodegenerative disorders, such as Parkinson disease.[4] In view of this, the reaction of 4-bromo-5-nitrophthalonitrile (BNPN) **1** with 2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid esters **2a–e** to give tricyclic compounds of the benzothiazole series is of particular interest. For example, a method was proposed for synthesizing pyrimido[2,1-*b*][1,3]benzothiazoles by modified Biginelli three-component condensation where aminobenzothiazole was used instead of thiourea, which was carried out by prolonged heating above 100 °C.[5,6] A synthesis of similar compounds at 90–95 °C by nucleophilic substitution using substituted chlorodinitrobenzenes as the substrates and aqueous potassium hydroxide as the deprotonating agent was reported.[7] Previously, we described the preparation of benzofuran-5,6-dicarbonitriles having a 2-oxo(thioxo)-1,2,3,4-tetrahydropyrimidine moiety at 2-position using a three-component modified Biginelli reaction.[8] No data on the synthesis of substituted 7,8-dicyanopyrimido[2,1-*b*][1,3]benzothiazoles is available in the literature.

The aim of this work was to study the reaction of 4-bromo-5-nitrophthalonitrile **1**[9] with substituted 1,2,3,4-tetrahydropyrimidine-2-thiones obtained by the classical three-component Biginelli reaction.[1]

The reaction of BNPN **1** with compounds **2a–e** was carried out in DMF solution at room temperature for 12–20 h (until the BNPN TLC spot disappeared) using TEA as the deprotonating agent. The reaction gave substituted 7,8-dicyanopyrimido-[2,1-*b*][1,3]benzothiazole-3-carboxylates **4a–e** in 55–78% yields (Scheme 1). A similar product was obtained in refluxing isopropyl alcohol (reaction was completed in 4–8 h). According to ^{1}H NMR data, each pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxylate is formed as one isomer. On the other hand, bearing in mind the assumed reaction scheme, two isomeric products **4** and **4′** with different structures can be formed. However, even if reactant **2e** with both aromatic substituents R^1 and R^2 was used, nothing of isomeric product **4′e** was detected.†

NOESY spectroscopy was used to determine the structure of benzothiazoles **4a–e**. The cross peaks of coupling of the H-6 proton in the phthalonitrile moiety with aromatic protons of the adjacent substituent and with H-4 of the heterocycle (the most intense signal) are the key signals for identification. This experiment showed that the H-6 and H-4 hydrogen atoms are located nearly in the same plane and at the minimum spatial distance,



a R^1 = Me, R^2 = Ph
b R^1 = Me, R^2 = 4-MeC_6H_4
c R^1 = Me, R^2 = 4-$MeOC_6H_4$
d R^1 = Me, R^2 = 2-thienyl
e R^1 = Ph, R^2 = 4-$MeOC_6H_4$

Scheme 1

whereas the substituent at the H-4 atom is in the axial position. This arrangement of the substituents in the pyrimido[2,1-*b*][1,3]-benzothiazoles remains the same as in the original Biginelli

† 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 ppm) or the signal of DMSO-d_6 in ^{13}C NMR spectra (δ_C 39.5 ppm) were used as references for chemical shift measurements.

Two-dimensional spectra were recorded using standard Bruker techniques. The mixing time in NOESY spectra was 0.3 s.

BNPN **1** was synthesized according to a published procedure.[20] Pyrimidinethiones **2a–e** were synthesized using a reported technique.[21]

General procedure for the synthesis of compounds **4a–e**. *Method A.* Pyrimidinethione **2a–e** (0.01 mol) and BNPN **1** (0.01 mol) were dissolved in DMF (10 ml). TEA (0.022 mol) was added to the solution and the mixture was stirred for 12–20 h at room temperature. The reaction mixture was poured into water. The resulting resinous precipitate was separated and crystallized from ethanol.

compounds whose configuration was determined by XRD.[10,11] In turn, this specifies the regioselectivity in the formation of target products **4a–e**.

The data derived from NMR studies were ultimately confirmed by XRD data for compound **4c**.‡ The general view of compound **4c** is shown in Figure 1. The benzothiazole moiety is planar, while the dihydropyrimidine ring annelated with it deviates from a planar structure towards a boat conformation [the N(1) and C(4) atoms deviate from the plane]. In agreement with the prediction based on NMR data, the methoxyphenyl substituent occupies an axial position. It is rotated almost perpendicularly relative to the plane of the tricyclic moiety [the interplanar angle is 82.46(2)°], whereas the pseudo-torsional angle H(4)C(4)C(6)H(6) is 47°, which corresponds to the closest approach of the hydrogen atoms.

The most interesting feature in the process we studied is that the rare for thioamides sequential intramolecular S_NAr reactions[12,13] readily occur. This can be explained by the Smiles rearrangement.[14–16] In reactions between BNPN and mono- or bifunctional O-, N-, S-nucleophiles, the reactive bromine atom was replaced first, usually to stall on monosubstitution products.[17]

In order to study the regularities of the reaction of substrate **1** with bifunctional pyrimidine S,N-nucleophiles **2a–e** in detail, monitoring of the process was attempted by NMR spectroscopy.

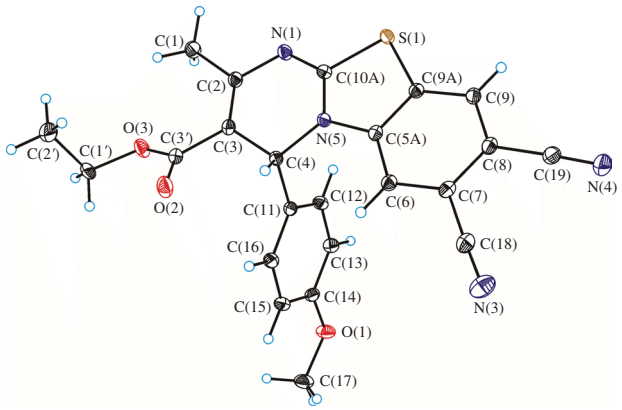


Figure 1 General view of molecule **4c** in representation of atoms by thermal displacement ellipsoids at 50% probability level.

Method B. Pyrimidinethione **2a–e** (0.01 mol), BNPN **1** (0.01 mol) and TEA (0.022 mol) were mixed in isopropyl alcohol (20 ml). The mixture was refluxed for 4–8 h, then cooled. The precipitate that formed was filtered off and recrystallized from ethanol. The yield is somewhat higher in this method and the product is well purified by recrystallization, so the yields are given for method B.

*Ethyl 7,8-dicyano-2-methyl-4-phenyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxylate* **4a**: yield 67%, mp 218–220 °C (decomp.). IR (ν/cm^{-1}): 2232 (C≡N), 1684 (C=O), 1605 (C=C), 1588 (Ar), 1243 (C–O–C). ^{1}H NMR, δ: 1.21 (t, 3H, Me, *J* 7.1 Hz), 2.34 (s, 3H, Me), 4.08 (dq, 2H, CH_2, *J* 7.1 Hz), 6.58 (s, 1H, 4-H), 7.25 (t, 1H, 4′-H, *J* 7.5 Hz), 7.33 (t, 2H, 3′-H, 5′-H, *J* 7.5 Hz), 7.51 (d, 2H, 2′-H, 6′-H, *J* 7.5 Hz), 8.28 (s, 1H, 9-H), 8.47 (s, 1H, 6-H). MS, *m*/*z* (%): 400 [M$^+$] (24), 371 [M$^+$ – Et] (27), 327 (72), 323 (100), 295 (42), 249 (29), 225 (44), 184 (24), 128 (19), 115 (15), 77 (18). Found (%): C, 65.85; H, 3.96; N, 13.93. Calc. for $C_{22}H_{16}N_4O_2S$ (%): C, 65.99; H, 4.03; N, 13.99.

*Ethyl 7,8-dicyano-2-methyl-4-(2-thienyl)-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxylate* **4d**: yield 78%, mp 246–248 °C (decomp.). IR (ν/cm^{-1}): 2233 (C≡N), 1670 (C=O), 1602 (C=C), 1245 (C–O–C). ^{1}H NMR, δ: 1.23 (t, 3H, Me, *J* 7.1 Hz), 2.35 (s, 3H, Me), 4.13 (dq, 2H, CH_2, *J* 7.1 Hz), 6.93 (dd, 1H, 4′-H, *J* 3.5 Hz, *J* 5.0 Hz), 6.95 (s, 1H, 4-H), 7.25 (d, 1H, 3′-H, *J* 3.5 Hz), 7.42 (d, 1H, 5′-H, *J* 5.0 Hz), 8.50 (s, 1H, 9-H), 8.57 (s, 1H, 6-H). MS, *m*/*z* (%): 406 [M$^+$] (38), 377 [M$^+$ – Et] (21), 361 [M$^+$ – OEt] (18), 333 [M$^+$ – COOEt] (72), 250 (15), 225 (18), 184 (30), 101 (28), 58 (100), 42 (51). Found (%): C, 58.98; H, 3.56; N, 13.72. Calc. for $C_{20}H_{14}N_4O_2S_2$ (%): C, 59.10; H, 3.47; N, 13.78.

For characteristics of compounds **4b**,**c**,**e**, see Online Supplementary Materials.

However, the possible intermediates were never detected. One should take into account that alkylation of Biginelli compounds with dibromoethane[18] or haloacetic acids[19] under mild conditions initially gives a product of substitution at the sulfur atom, which then undergoes intramolecular cyclization at the N(1) atom.[18] Therefore, in our case it can be assumed that initially the reaction in the presence of TEA affords intermediate **3** with the most energetically preferable system of conjugated bonds [C(4)=N(3)], whose stabilization is favoured by the carboxy moiety, which leads to individual isomers **4a–e**.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.07.012.

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‡ *Crystal data for* **4c**. Crystals of $C_{23}H_{18}N_4O_3S$ are monoclinic, space group $P2_1/n$: a = 13.1107(3), b = 10.8298(3) and c = 14.6076(4) Å, β = = 104.2200(10)°, V = 2010.53(9) Å^3, Z = 4, M = 430.47, d_{calc} = 1.422 g cm^{-3}, μ = 0.196 mm^{-1}. 27 642 reflections were collected by a SMART APEX II CCD diffractometer [λ(MoKα) = 0.71073 Å, graphite monochromator, ω-scans, 2θ < 62°] at 100 K. The structure was solved by the direct methods and refined by the full-matrix least-squares procedure in anisotropic approximation. 6399 independent reflections (R_{int} = 0.0332) were used in the refinement procedure that converged to wR_2 = 0.0937 calculated on F^2_{hkl} [GOF = 1.020, R_1 = 0.0354 calculated on F_{hkl} using 5308 reflections with $I > 2\sigma(I)$].

CCDC 923901 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, 2013.