Efficient Solvent-Free Synthesis of Benzothiazine-Fused Pyrrolo[3,4-*c*]coumarins: Cycloaddition Reactions between Coumarin-Based Dihydrobenzothiazoles and Isocyanides

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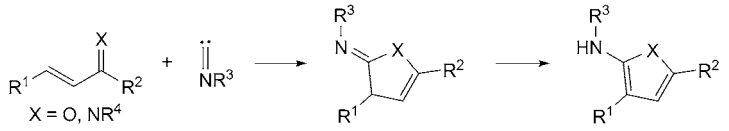
A new and unusual synthesis of benzothiazine-fused pyrrolo[3,4-*c*]coumarins, involving the ring-opening of coumarin-based dihydrobenzothiazoles and subsequent [4 + 1] cycloaddition reaction with isocyanides, was described. Thus, simple heating of various 3-(2,3-dihydro-2-methylbenzo[*d*]thiazol-2-yl)coumarins with isocyanides produced the title compounds in good yields under solvent-free conditions.

Introduction. – Cycloaddition reactions are an important route to the formation of cyclic compounds from acyclic substrates. A [4 + 1] cycloaddition reaction of a conjugated 1,3-π system with isocyanides is a straightforward and attractive method for the construction of five-membered compounds, such as furan and pyrrole derivatives (X = O and N, *Scheme 1*) [1]. *Quai et al.* reported the reaction of α,β-unsaturated carbonyl compounds with isocyanides to afford quite unstable furan-2-imines, which are oxidized quickly by *triplet* O_2 leading to 5-hydroxy-*N*-substituted-2*H*-pyrrole-2-ones [2].

Nair and co-workers described the reaction of *in situ* generated quinone methides from 4-hydroxycoumarin with various aldehydes, which underwent reaction with isocyanides to produce furocoumarins [3].

Scheme 1. *[4 + 1] Cycloaddition Reaction of Conjugated 1,3-π Systems with Isocyanides*



Coumarins (2*H*-1-benzopyran-2-ones) and their annulated derivatives are an important class of compounds, as they display a wide spectrum of biological activities [4]. Especially polycyclic coumarin derivatives have been shown to be potent inhibitors of tumor induction by carcinogenic polycyclic aromatic hydrocarbon [5]. Pyrrolo-annulated benzopyranones were found to possess promising biological features such as antitumor activity, reversal of multidrug resistance (MDR), and HIV-1 integrase inhibition activity [6]. Lamellarins are pyrrolo-annulated benzopyranone alkaloids isolated from mollusks and ascidians. Of the family of lamellarins, Lam-D is one of the most potent lead candidates for cancer chemotherapy. There is substantial evidence that Lam-D is an inhibitor of topoisomerase I and a potent pro-apoptotic agent [7]. In the light of the significance of pyrrolo-annulated coumarin systems and their diverse pharmacological properties, there has been a continuous effort to develop new, convenient, and versatile methods for modification of this class of compounds.

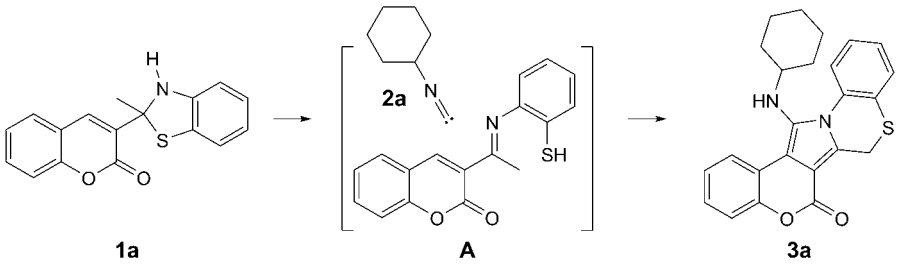
Results and Discussion. – As part of our continuing efforts on the development of efficient routes for the preparation of biologically active coumarin-based compounds [8][9], we have now synthesized new benzothiazine-fused pyrrolo[3,4-*c*]coumarins using a simple reaction between 3-(dihydrobenzothiazol-2-yl)coumarins and isocyanides without using any solvent or catalyst.

Recently, we have studied the synthesis and biological activities of new coumarin derivatives of type **1** containing the 2-methylbenzothiazole motif. These compounds were easily prepared in excellent yields using the standard protocol developed in our laboratory [9].

Considering the ring-opening ability of the dihydrobenzothiazole derivatives **1** and generation of intermediate **A** [10], our attention was directed to develop a [4 + 1] cycloaddition reaction of this 1,3-conjugated system with isocyanides. As far as we know, there is no report on the reaction of 3-imino-substituted coumarin with isocyanides. We initiated our studies with dihydrobenzothiazole **1a**, which, upon treatment with a 1.5 equiv. of cyclohexyl isocyanide **2a**, afforded the product **3a** in 77% yield (*Scheme 2*).

Product **3a** was characterized on the basis of its spectroscopic data. The IR spectrum showed a strong absorption band at 1721 cm^{-1}, which is characteristic for the coumarin C=O group. In the ^{1}H-NMR spectrum, the aromatic H-atoms of coumarin and benzene rings appeared at 7–8 ppm and the H–N resonated at 4.93 ppm (exchangeable by D_2O) [3]. Also, two CH_2 H-atoms of the benzothiazine ring were observed as a *singlet*

Scheme 2. *Synthesis of Densely Functionalized Pyrrole Derivatives* **3a**



at 4.37 ppm. The ^{1}H-decoupled ^{13}C-NMR spectrum of **3a** exhibited 22 signals. For example, the CH_2 group of the benzothiazine ring which absorbed at 56.5 ppm was confirmed with DEPT spectra. The mass spectrum of **3a** displayed a molecular-ion peak at *m*/*z* 402, and a fragmention peak at *m*/*z* 319, indicating the loss of the cyclohexyl group. Furthermore, an X-ray crystallographic study was carried out on compound **3a**, after recrystallization from MeCN (*Fig.*).

Several examples of this prototype reaction which confirm the synthetic utility of this protocol are outlined in the *Table*.

To explain the formation of the products, we propose a reaction mechanism, which is outlined in *Scheme 3*. On the basis of the well-established chemistry of isocyanides [11], it is reasonable to assume that cycloaddition of the initially generated intermediate **A** and isocyanide **2** leads to compound **B**. The formation of the benzothiazine scaffold certainly involves a complex multistep sequence of events and probably proceeds by intramolecular addition of the SH group to alkene. It is conceivable that compound **B** can tautomerize under the reaction condition to an intermediate **C**. In the next step, the intramolecular addition of SH to the exocyclic group C=C results in the formation of compounds **D**, which is converted to compound **E** by tautomerization. Finally, compound **3** can be formed after further tautomerization and air oxidation and aromatization.

Conclusions. – We have introduced a new and unusual synthetic procedure to prepare benzothiazine-fused pyrrolo[3,4-*c*]coumarins involving the ring opening of coumarin-based dihydrobenzothiazoles and subsequent [4 + 1] cycloaddition reaction with isocyanides. The present method offers the advantages that the reaction is

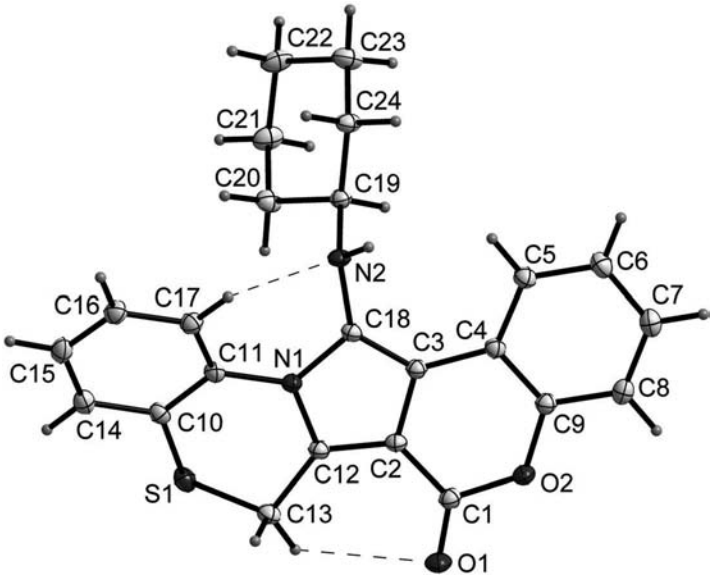
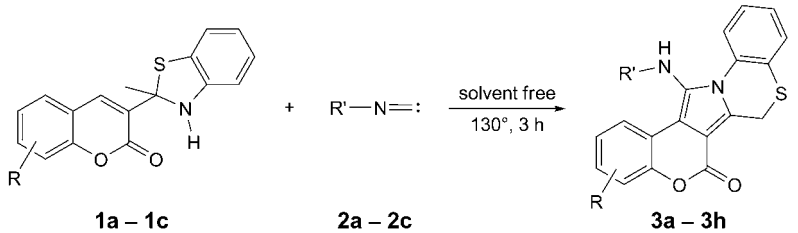


Figure. *X-Ray structure of compound* **3a** *with the atom numbering scheme and the intramolecular C–H⋯O/N contacts* (dashed lines). Displacement ellipsoids are shown at the 50% probability level.

Table. *Synthesis of Benzothiazine-Fused Pyrrolo[3,4-c]coumarins* **3a**–**3h**

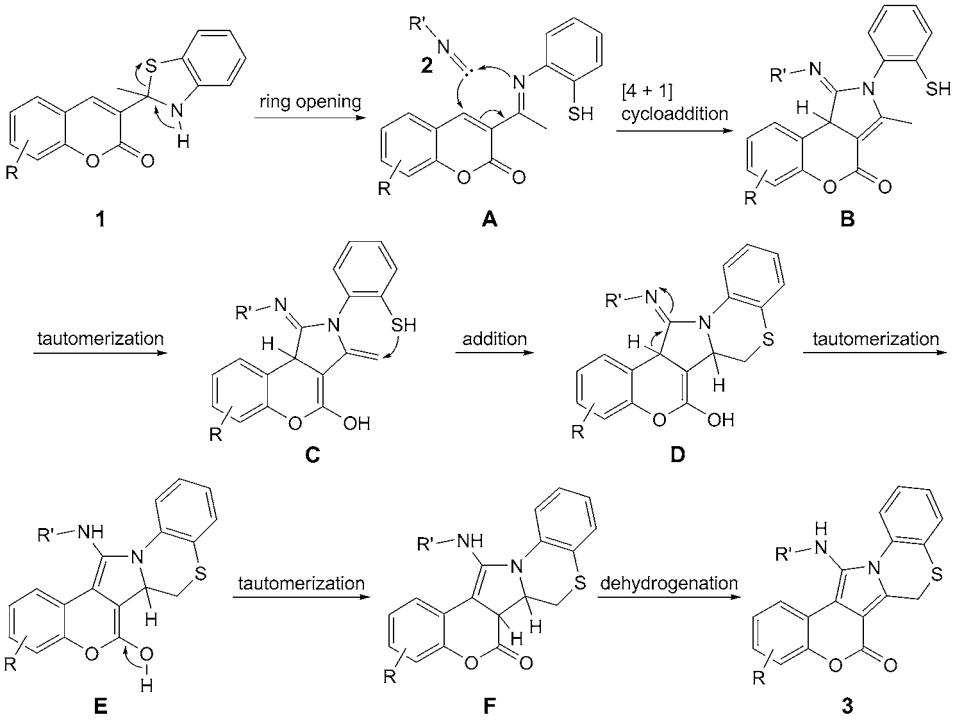


1a – 1c **2a – 2c** **3a – 3h**

Compound	R	R′	Yield [%][a])
3a	H	Cyclohexyl	77
3b	6-Br	Cyclohexyl	73
3c	8-MeO	Cyclohexyl	74
3d	H	*t*Bu	70
3e	8-MeO	*t*Bu	77
3f	H	1,1,3,3-Tetramethylbutyl	67
3g	8-MeO	1,1,3,3-Tetramethylbutyl	68
3h	6-Br	1,1,3,3-Tetramethylbutyl	64

[a]) Yield of isolated product.

Scheme 3. *Proposed Mechanism for the Formation of the Title Compounds* **3**



1 **A** **B** **C** **D** **E** **F** **3**

performed under neutral conditions and the substances can be mixed under solvent-free conditions, and without any promoters such as acids, *Lewis* acids, or transition-metal complexes. The products are polycyclic molecules of potential synthetic and pharmacological interest.

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Experimental Part

General. IR Spectra: *Nicolet FT-IR Magna 550* spectrometer; KBr disks; $\tilde{\nu}$ in cm^{-1}. ^{1}H-NMR Spectra: *Bruker 400* or *500* MHz instruments; δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: *HP 5937*, mass selective detector (*Agilent* technologies); in *m/z*. Elemental analyses: *CHN-Rapid Heraeus* elemental analyzer, the results of elemental analyses (C, H, N) were within $\pm 0.4\%$ of the calculated values.

General Procedure. A mixture of 3-(2-methyl-2,3-dihydrobenzo[*d*]thiazol-2-yl)-2*H*-chromen-2-ones **1** (2 mmol) and the appropriate isocyanide **2** (3 mmol) was stirred at 130° for 3 h in a sealed tube. The mixture was cooled to r.t. and the residue was purified by column chromatography (CC) with hexane/AcOEt 1:2. The product was recrystallized from hexane/AcOEt 1:1.

14-(Cyclohexylamino)[1]benzopyrano[3′,4′:3,4]pyrrolo[2,1-c][1,4]benzothiazin-6(7H)-one (**3a**). Red solid. M.p. 217–219°. IR: 3332 (NH), 1721 (C=O). ^{1}H-NMR ($CDCl_3$): 0.90–1.03 (*m*, 5 H); 1.37–1.58 (*m*, 5 H); 2.54 (*m*, 1 H); 4.37 (*s*, 2 H); 4.93 (*s*, 1 H); 7.29–7.32 (*m*, 4 H); 7.42 (*t*, $J = 7.7$, 1 H); 7.60 (*d*, $J = 7.7$, 1 H); 8.30 (*d*, $J = 7.3$, 1 H); 8.46 (*d*, $J = 8.2$, 1 H). ^{13}C-NMR ($CDCl_3$): 23.8; 24.1; 25.2; 32.6; 56.5; 100.0; 112.0; 116.7; 117.0; 122.6; 123.5; 124.1; 126.6; 126.7; 127.1; 127.7; 129.4; 129.8; 130.7; 133.8; 150.3; 158.1. ESI-MS: 402 (85, M^+), 319 (100), 305 (51), 280 (48). Anal. calc. for $C_{24}H_{22}N_2O_2S$ (402.50): C 71.62, H 5.51, N 6.96; found: C 71.41, H 5.86, N 6.69.

2-Bromo-14-(cyclohexylamino)[1]benzopyrano[3′,4′:3,4]pyrrolo[2,1-c][1,4]benzothiazin-6(7H)-one (**3b**). Yellow solid. M.p. 222–224°. IR: 3328 (NH), 1720 (C=O). ^{1}H-NMR ($CDCl_3$): 0.87–0.97 (*m*, 5 H); 1.39–1.54 (*m*, 5 H); 2.09 (*s*, 1 H); 4.36 (*s*, 2 H); 5.13 (*s*, 1 H); 7.26 (*d*, $J = 8.5$, 1 H); 7.33 (*t*, $J = 7.5$, 1 H); 7.44 (*t*, $J = 7.5$, 1 H); 7.48 (*d*, $J = 8.5$, 1 H); 7.62 (*d*, $J = 7.5$, 1 H); 8.42 (*d*, $J = 8.5$, 1 H); 8.48 (*s*, 1 H). Anal. calc. for $C_{24}H_{21}BrN_2O_2S$ (481.40): C 59.88, H 4.40, N 5.82; found: C 59.56, H 4.22, N 5.61.

14-(Cyclohexylamino)-4-methoxy[1]benzopyrano[3′,4′:3,4]pyrrolo[2,1-c][1,4]benzothiazin-6(7H)-one (**3c**). Yellow solid. M.p. 188–190°. IR: 3326 (NH), 1723 (C=O). ^{1}H-NMR ($CDCl_3$): 0.92–1.04 (*m*, 5 H); 1.34–1.48 (*m*, 5 H); 2.48 (*m*, 1 H); 3.94 (*s*, 3 H); 4.39 (*s*, 2 H); 5.01 (*s*, 1 H); 6.91 (*d*, $J = 7.5$, 1 H); 7.23 (*t*, $J = 7.5$, 1 H); 7.44–7.58 (*m*, 5 H); 8.44 (*d*, $J = 8.5$, 1 H). Anal. calc. for $C_{25}H_{24}N_2O_3S$ (432.53): C 69.42, H 5.59, N 6.48; found: C 69.21, H 5.80, N 6.69.

*14-[(*tert*-Butyl)amino][1]benzopyrano[3′,4′:3,4]pyrrolo[2,1-c][1,4]benzothiazin-6(7H)-one* (**3d**). Yellow solid. M.p. 231–233°. IR: 3332 (NH), 1715 (C=O). ^{1}H-NMR ($CDCl_3$): 0.81 (*s*, 9 H); 4.06 (*d*, $J = 1.5$, 1 H); 4.67 (*d*, $J = 1.5$, 1 H); 4.80 (*s*, 1 H); 7.28–7.32 (*m*, 4 H); 7.40 (*t*, $J = 7.6$, 1 H); 7.62 (*d*, $J = 7.6$, 1 H); 8.36 (*d*, $J = 8.0$, 1 H); 8.50 (*d*, $J = 7.6$, 1 H). Anal. calc. for $C_{22}H_{20}N_2O_2S$ (376.47): C 70.19, H 5.35, N 7.44; found: C 70.34, H 5.13, N 7.18.

*14-[(*tert*-Butyl)amino]-4-methoxy[1]benzopyrano[3′,4′:3,4]pyrrolo[2,1-c][1,4]benzothiazin-6(7H)-one* (**3e**). Yellow solid. M.p. 204–206°. IR: 3330 (NH), 1722 (C=O). Anal. calc. for $C_{23}H_{22}N_2O_3S$ (406.50): C 67.96, H 5.46, N 6.89; found: C 67.73, H 5.71, N 6.66.

14-[(1,1,3,3-Tetramethylbutyl)amino][1]benzopyrano[3′,4′:3,4]pyrrolo[2,1-c][1,4]benzothiazin-6(7H)-one (**3f**). Yellow solid. M.p. 169–171°. IR: 3335 (NH), 1720 (C=O). ^{1}H-NMR ($CDCl_3$): 0.86 (*s*, 9 H); 0.95 (*s*, 6 H); 1.40 (*s*, 2 H); 4.04 (*d*, $J = 1.5$, 1 H); 4.62 (*s*, 1 H); 4.68 (*d*, $J = 1.5$, 1 H); 7.29–7.33 (*m*, 4 H); 7.42 (*t*, $J = 7.3$, 1 H); 7.62 (*d*, $J = 7.3$, 1 H); 8.31 (*d*, $J = 7.8$, 1 H); 8.48 (*d*, $J = 7.3$, 1 H). ^{13}C-NMR ($CDCl_3$): 27.2; 28.7; 30.1; 31.5; 55.8; 60.4; 100.1; 114.7; 116.8; 117.3; 123.5; 124.3; 124.5; 126.6; 127.4; 128.5; 128.8; 129.4; 131.5; 134.3; 150.4; 158.2. Anal. calc. for $C_{26}H_{28}N_2O_2S$ (432.58): C 72.19, H 6.52, N 6.48; found: C 72.32, H 6.33, N 6.69.

4-Methoxy-14-[(1,1,3,3-tetramethylbutyl)amino][1]benzopyrano[3′,4′:3,4]pyrrolo[2,1-c][1,4]benzothiazin-6(7H)-one (**3g**). Yellow solid. M.p. 143–145°. IR: 3328 (NH), 1720 (C=O). Anal. calc. for $C_{27}H_{30}N_2O_3S$ (462.60): C 70.10, H 6.54, N 6.06; found: C 70.33, H 6.21, N 6.27.

2-Bromo-14-[(1,1,3,3-tetramethylbutyl)amino][1]benzopyrano[3′,4′:3,4]pyrrolo[2,1-c][1,4]benzothiazin-6(7H)-one (**3h**). Yellow solid. M.p. 179–181°. IR: 3334 (NH), 1718 (C=O). Anal. calc. for $C_{26}H_{27}BrN_2O_2S$ (511.47): C 61.05, H 5.32, N 5.48; found: C 61.29, H 5.09, N 5.26.

X-Ray Crystallography. Yellow-brown single crystals of **3a** were obtained from MeCN soln. by slow evaporation at r.t. over several days. The yellow-brown single crystals were filtered, washed with cold MeCN, and dried at r.t. (m.p. 216°). Compound **3a**: $C_{24}H_{22}N_2O_2S$, M_r 402.50; yellow-brown block, crystal dimensions, $0.40 \times 0.32 \times 0.26$ mm^3; orthorhombic; space group, *Pbca*; $a = 7.267(2)$ Å, $b = 18.636(4)$ Å, $c = 28.259(4)$ Å, $V = 3827.1(14)$ Å^3, $T = 100(2)$ K, $Z = 8$, $\rho_{calc} = 11.397$ g/cm^3, $\mu = 0.19$ mm^{-1} (for MoK_α, $\lambda = 0.71073$ Å); $F(000) = 1696$, reflections collected, 28350; reflections independent, 7480 [$R_{int} = 0.022$]; reflections observed, 6031 [$I > 2\sigma(I)$]; θ range, 2.62–38.46°, h, k, l range, $-10 \le h \le 11$, $-28 \le k \le 26$, $-39 \le l \le 41$, full-matrix least-squares on F^2, parameters, 266; restraints, 0; $R_1 = 0.046$, $wR_2 = 0.115$ [$F^2 > 2\sigma(F^2)$], GoF = $S = 1.09$, largest difference in peak and hole, $\Delta\rho_{max}$ and $\Delta\rho_{min}$ 0.54 and -0.36 e/Å^3; resp. CCDC-851379 contains supplementary crystallographic data for this article. These data can be obtained free of charge from *the Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/data_request/cif or by e-mailing deposit@ccdc.cam.ac.uk.

The crystallographic measurement was performed on a κ-geometry *Xcalibur PX* four-circle diffractometer with graphite-monochromatized MoK_α radiation (ω and φ scans). Data were corrected for *Lorentz* and polarization effects. Data collection, cell refinement, and data reduction and analysis were carried out with the Xcalibur PX software, CRYSALIS CCD, and CRYSALIS RED, resp. (*Oxford Diffraction Ltd.*, Abingdon, England, 2009). Empirical absorption correction was applied to the data with the use of CRYSALIS RED. The structure was solved by direct methods with the SHELXS-97 program, and refined using SHELXL-97 [12] with anisotropic thermal parameters for non-H-atoms. All H-atoms were found in difference *Fourier* maps, and were refined isotropically. In the final refinement cycles, all C-bonded H-atoms were treated as riding atoms in geometrically optimized positions, with C–H of 0.95–1.00 Å, and with $U_{iso}(H) = 1.2U_{eq}(C)$. The figure was drawn using DIAMOND program (ver. 3.0d, K. Brandenburg, *Crystal Impact GbR*, Bonn, Germany, 2005).

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