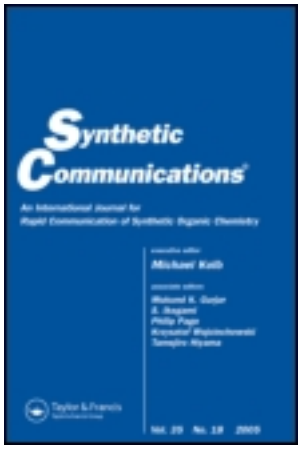

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Polycyclic N-Heterocyclic Compounds, Part 77: Synthesis of [1]Benzothieno[3′,2′:2,3]oxepino[4,5-d]pyrimidines and Evaluation of Their Antiplatelet Aggregation Activity

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POLYCYCLIC *N*-HETEROCYCLIC COMPOUNDS, PART 77: SYNTHESIS OF [1]BENZOTHIENO[3′,2′:2,3]OXEPINO[4,5-*d*]PYRIMIDINES AND EVALUATION OF THEIR ANTIPLATELET AGGREGATION ACTIVITY

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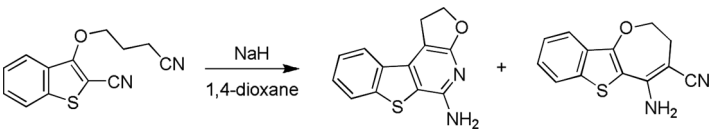
GRAPHICAL ABSTRACT



Abstract *Reaction of 3-(3-cyanopropoxy)[1]benzothiophene-2-carbonitrile with sodium hydride gave 5-amino-1,2-dihydro[1]benzothieno[3,2-*d*]furo[2,3-*b*]pyridine and 5-amino-2,3-dihydro[1]benzothieno[3,2-*b*]oxepin-4-carbonitrile. The latter compound served as a convenient scaffold for the synthesis of the new heterocycles [1]benzothieno[3′,2′:2,3]oxepino[4,5-*d*]pyrimidines and the parent 1,2,4,5-tetrahydro[1]benzothieno[2′,3′:6,7]oxepino[4,5-*e*]imidazo[1,2-*c*]pyrimidine heterocyclic system. The new compounds described in this report were evaluated as inhibitors of platelet aggregation in vitro.*

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Keywords Antiplatelet aggregation; cyclization; Thorpe–Ziegler reaction; Truce–Smiles rearrangement; Vilsmeier reagent

INTRODUCTION

As part of our research to develop new medicinally active compounds, we have been investigating the syntheses and biological evaluation of heterocycles containing new ring systems that are accessible by rearrangement reactions. During the course

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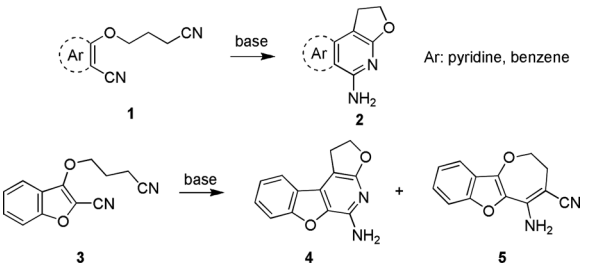
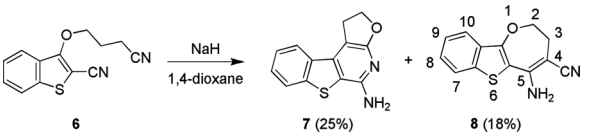


Scheme 1. Substrates (**1** and **3**) with base and products (**2**, **4**, and **5**).

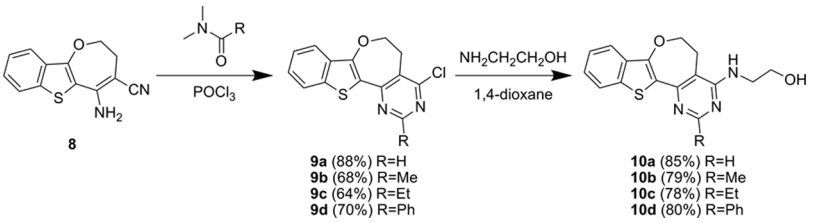
of this work, we have developed a new synthetic method for aromatic fused 2,3-dihydrofuro[2,3-*b*]pyridines (**2**) based on reactions of 2-(3-cyanopropoxy)aryl-1-carbonitriles (**1**) with bases (Scheme 1). This process involves a Truce–Smiles rearrangement followed by intramolecular cyclization.[1–5] When we applied this strategy to 3-(3-cyanopropoxy)[1]benzofuran-2-carbonitriles (**3**), we found that the formation of the expected product, 5-amino-1,2-dihydro[1]benzofuro[3,2-*d*]furo[2,3-*b*]pyridines (**4**), was accompanied by formation of 5-amino-2,3-dihydro[1]benzofuro[3,2-*b*]oxepin-4-carbonitrile (**5**).[6] Thus, because the key step of Truce–Smiles rearrangement is a nucleophilic attack at an *ipso* position of an aromatic ring, the less-reactive electron-rich benzofuran is a poor substrate for this rearrangement and the Thorpe–Ziegler reaction can compete to give **5**. This was the first time we had observed a product of the Thorpe–Ziegler reaction in our studies.

Previously, we found that the reaction of 3-(3-cyanopropoxy)[1]benzothiophene-2-carbonitrile (**6**) with base gave 5-amino-1,2-dihydro[1]benzothieno[3,2-*d*]furo[2,3-*b*]pyridine (**7**) in modest yield.[3] Because benzothiophene is also a somewhat electron-rich aromatic, we reasoned that 5-amino-2,3-dihydro[1]benzothieno[3,2-*b*]-oxepin-4-carbonitrile (**8**) could also be a product of this reaction. Here we describe the synthesis of **8**, which is formed along with **7**. We also describe the preparation of tetracyclic [1]benzothieno[3′,2′:2,3]oxepino[4,5-*d*]pyrimidines (**9** and **10**) and pentacyclic 1,2,4,5-tetrahydro[1]benzothieno[2′,3′:6,7]oxepino[4,5-*e*]imidazo[1,2-*c*]pyrimidine (**11**), which are accessible from **8**. Because current antiplatelet drugs are known to have certain detrimental side effects and low efficacy and thus much research is directed to the development of new drugs in this class,[7–13] we tested these new analogs for antiplatelet aggregation activity.

Reaction of **6** and sodium hydride in dry 1,4-dioxane gave **8** in 18%, as we had anticipated, as well as **7**, which was formed in 25% (Scheme 2). The characteristic amino and cyano bands in the infrared (IR) spectrum of **8** clearly supported the isomer identification. In Contrast to the case of benzofuran,[6] in which the Truce–Smiles



Scheme 2. Substrate (**6**) with base and products (**7** and **8**).



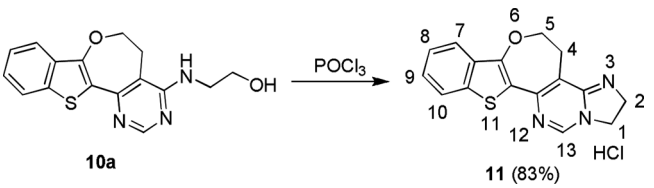
Scheme 3. Synthesis of **9** and **10**.

rearrangement product **4** is the minor product and the Thorpe–Ziegler reaction product **5** is a major product, the Truce–Smiles rearrangement product **7** is the major product and the Thorpe–Ziegler reaction product **8** is a minor product.

To access additional potential pharmaceuticals, the functionality present in compound **8** was exploited for the construction of a pyrimidine ring leading to the new heterocyclic ring system [1]benzothieno[3′,2′:2,3]oxepino[4,5-*d*]pyrimidine. Thus, reaction of **8** with Vilsmeier reagent gave **9a–d** in 64–88% yield. Structures of **9a–d** were determined based on the disappearance of the enamine and nitrile groups and appearance of chlorine atoms in their IR and mass (MS) spectra. In addition, the NMR spectra and elemental analyses supported these structures. Next, **9a–d** were treated with ethanolamine to give **10a–d** in 78–85% yield (Scheme 3). Finally, unprecedented pentacyclic 1,2,4,5-tetrahydro[1]benzothieno [2′,3′:6,7]oxepino[4,5-*e*]imidazo[1,2-*c*]pyrimidine (**11**) was prepared in 83% yield by cyclodehydration of **10a** (Scheme 4).

With these compounds in hand, the antiplatelet aggregation activities were examined to explore the structure–activity relationships using a random in vitro screening test for atherothrombosis. The inhibitory activities of compounds **9–11** using dimethylsulfoxide (DMSO, final concentration 0.83%) as a cosolvent against platelet aggregation induced by collagen (final concentration 14.3 μg/ml) was assayed to demonstrate the possible therapeutic potential of these compounds.

The inhibitory assay was executed by a turbidimetric method developed by Born and Cross[14] using an aggregometer. Comparison of the inhibition rate of **10a** ($21.7 \pm 2.1\%$), **10b** ($17.4 \pm 1.8\%$), and **11** ($22.3 \pm 2.8\%$) at a final concentration of 25 μM with that of aspirin ($15.7 \pm 1.0\%$) revealed that **10a**, **10b**, and **11** had potency comparable to aspirin. Unfortunately, other compounds **9–10** did not have sufficient water solubility to execute this assay. We are currently exploring development of derivatives with antiplatelet aggregation activity that possess good solubility.



Scheme 4. Synthesis of **11**.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-melting-point apparatus and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-5 CHN Corder elemental analyzer. The electron impact (EI) mass and fast atom bombardment (FAB) mass (*m*-nitrobenzyl alcohol was used as the matrix) were obtained on a VG70-SE mass spectrometer. The IR spectra were recorded on a Japan Spectroscopic diffraction grating A-102 spectrophotometer and frequencies are expressed in cm^{-1}. The ^1H NMR spectra were recorded on a Varian VXR-200 instrument operating at 200 MHz or a Hitachi R-1500 instrument operating at 60 MHz with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in parts per million (ppm) (δ) and *J* values in hertz (Hz), and the signals are designated as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; br, broad; m, multiplet.

5-Amino-2,3-dihydro[1]benzothieno[3,2-*b*]oxepin-4-carbonitrile (8)

NaH (60% oil dispersion, 2.05 g, 51.3 mmol) and 3 drops of *tert*-BuOH were added to a solution of **6**[3] (9.95 g, 41.1 mmol) in 1,4-dioxane (200 mL) and the resulting mixture was refluxed for 5 h. After removal of solvent in vacuo, ice water (200 mL) was added to the residue. The resulting mixture was extracted with ethyl acetate (100 mL × 3). The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and then evaporated in vacuo. The residue was chromatographed on silica gel. The eluate of benzene was evaporated in vacuo, and the solid residue was recrystallized from benzene to give **8** (1.80 g, 18%) as pale yellow prisms, mp 159–161 °C; IR (KBr) cm^{-1}: 3440, 3320, 3230 (NH), 2175 (CN); ^1H NMR (60 MHz, $CDCl_3$): δ 2.65–2.90 (m, 2H, H3), 4.39–4.69 (m, 2H, H2), 4.57 (br s, 2H, deuterium oxide exchangeable, NH_2), 7.24–7.58 (m, 2H, H8 and 9), 7.58–7.88 (m, 2H, H7 and 10); FAB-ms *m/z* 243 (MH^+). Anal. calcd. for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56. Found: C, 64.20; H, 4.31; N, 11.39.

The further eluate of benzene–ethyl acetate (4:1) was evaporated in vacuo, and the solid residue was recrystallized from acetonitrile to give **7** (2.53 g, 25%) as pale brown prisms, mp 269–271 °C.[3]

Preparation of 2-Substituted 4-Chloro-5,6-dihydro[1]benzothieno[3′,2′:2,3]oxepino[4,5-*d*]pyrimidine (9)

A mixture of the corresponding *N,N*-dimethylamide (3.00 mmol) and phosphorus oxychloride (0.840 mL, 9.01 mmol) was stirred at 0 °C for 30 min. Then **8** (242 mg, 1.00 mmol) was added, and the resulting mixture was stirred at 70–80 °C for 1 h. After removal of solvent in vacuo, ice water (100 mL) was added to the residue, followed by basification with sodium bicarbonate. The aqueous mixture was extracted with ethyl acetate (30 mL × 3). The combined organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was purified by recrystallization to give **9**.

4-Chloro-5,6-dihydro[1]benzothieno[3′,2′:2,3]oxepino[4,5-*d*]pyrimidine (9a). Yield 88%, brown prisms from benzene, mp 179–181 °C.

4-Chloro-2-methyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]oxepino[4,5-*d*]-pyrimidine (9b). Yield 68%, colorless plates from ethyl acetate, mp 188–190 °C.

4-Chloro-2-ethyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]oxepino[4,5-*d*]-pyrimidine (9c). Yield 64%, colorless plates from cyclohexane, mp 129–130 °C.

4-Chloro-2-phenyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]oxepino[4,5-*d*]-pyrimidine (9d). Yield 70%, colorless prisms from benzene, mp 169–170 °C.

Preparation of 2-Substituted 2-(5,6-Dihydro[1]benzothieno[3′,2′:2,3]-oxepino[4,5-*d*]pyrimidin-4-yl)amino]ethanols (10)

2-Aminoethanol (0.605 mL, 10.0 mmol) was added to a solution of **9** (1.00 mmol) in a few mL of 1,4-dioxane, and the mixture was then stirred at 60–80 °C for 2 h. Ice water (50 mL) was added to the reaction mixture. The precipitate was collected by filtration, washed with cold water, and then recrystallized to give **10**.

2-(5,6-Dihydro-[1]benzothieno[3′,2′:2,3]oxepino[4,5-*d*]pyrimidin-4-yl)amino]ethanol (10a). Yield 85%, brown scales from acetonitrile, mp 185–187 °C.

2-[(2-Methyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]oxepino[4,5-*d*]pyrimidin-4-yl)amino]ethanol (10b). Yield 79%, pale yellow needles from ethyl acetate, mp 194–196 °C.

2-[(2-Ethyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]oxepino[4,5-*d*]pyrimidin-4-yl)amino]ethanol (10c). Yield 78%, colorless prisms from benzene, mp 170–171 °C.

2-[(2-Phenyl-5,6-dihydro[1]benzothieno[3′,2′:2,3]oxepino[4,5-*d*]pyrimidin-4-yl)amino]ethanol (10d). Yield 80%, brown powder from benzene, mp 220–221 °C.

1,2,4,5-Tetrahydro[1]benzothieno[2′,3′:6,7]oxepino[4,5-*e*]imidazo-[1,2-*c*]pyrimidine Hydrochloride (11)

A mixture of **10a** (157 mg, 0.501 mmol) and phosphorus oxychloride (2.0 mL, 21.4 mmol) was stirred at 70–80 °C for 1 h. After removal of solvent in vacuo, ice water (50 mL) was added to the residue. The precipitate was collected by filtration, washed with cold water, and then recrystallized from methanol to give **11** (138 mg, 83%) as yellow scales; mp 279–281 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.21 (br t, 2H, $J = 3.7$ Hz, H4), 4.00 (t, 2H, $J = 9.9$ Hz, H1 or 2), 4.60–4.72 (m, 4H, H1 or 2 and 5), 7.42–7.62 (m, 2H, H8 and 9), 7.83 (d, 1H, $J = 7.7$ Hz, H7 or 10), 7.96 (d, 1H, $J = 7.9$ Hz, H7 or 10), 8.82 (s, 1H, H13), 10.32 (s, 1H, deuterium oxide exchangeable, N^+H); FAB-ms m/z 296 (MH^+-HCl). Anal. calcd. for $C_{16}H_{14}ClN_3OS$: C, 57.91; H, 4.25; N, 12.66. Found: C, 58.10; H, 4.38; N, 12.80.

SUPPLEMENTARY MATERIAL

Full spectroscopic and characterization data for **9a–d** and **10a–d** including elemental analysis, NMR spectra of all new compounds, and details for the platelet aggregation assay are available online in the Supplementary Material.

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