Molbank **2015**, M859; doi:10.3390/M859

OPEN ACCESS

molbank

ISSN 1422-8599

www.mdpi.com/journal/molbank

Short Note

3-({5-Bromo-4-[pyrrolidin-1-yl]pyrimidin-2-yl}amino)phenol

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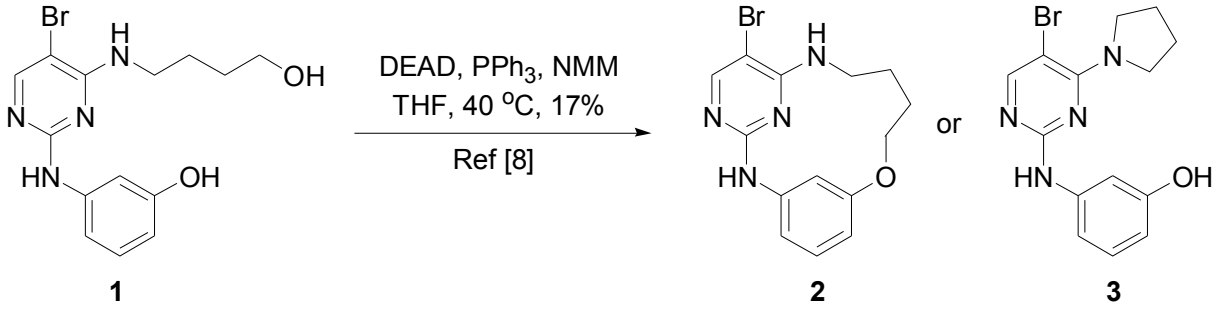
Academic Editor: Norbert Haider

Received: 25 April 2015 / Accepted: 18 May 2015 / Published: 21 May 2015

Abstract: Re-investigation of the ^{1}H-NMR spectrum reported for 1^{5}-bromo-4-oxa-2,9-diaza-1(2,4)-pyrimidine-3(1,3)-benzenacyclononaphane (**2**) prepared via a Mitsunobu-mediated macroether cyclisation led to a proposed structural isomer (**3**). The title compound (**3**) was prepared via a two-step protocol and assigned using ^{1}H, ^{13}C-NMR and LC-MS.

Keywords: macrocyclic ether; Mitsunobu; macrocyclisation

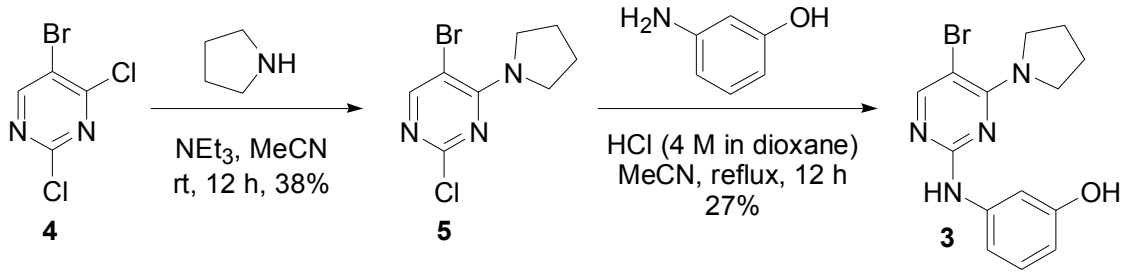
Macrocycles are an important class of organic compounds defined as containing cyclic systems of 12 or more atoms [1]. Macrocycles have garnered much attention recently in medicinal chemistry due to their ability to access biologically relevant conformations [2–4]. There are a variety of macrocyclisation strategies available [5] in particular we were interested in the *intra*-molecular Mitsunobu reaction that has been used to prepare kinase inhibitor scaffolds [6,7]. Lücking *et al.* [8] have reported a high dilution *intra*-molecular Mitsunobu reaction to macrocycle **2** (Scheme 1) that possessed micromolar activity against CDK2 and anti-proliferative effects towards MCF7 cells. We were intrigued by the stated ^{1}H-NMR spectrum for **2** which showed the four methylene groups occurred at 3.30 ppm (m, 4H) and 1.90 ppm (m, 4H). We therefore considered whether there is a choice of two *intra*-molecular Mitsunobu reactions—one that delivers compound **2** and one that delivers compound **3**. To address this question we prepared the novel isomer, **3**.



1 **2** **3**

Scheme 1. Lücking *et al.* [8] route to macrocyclic scaffold **2** and our postulated isomer **3**.

Our synthesis of **3** (Scheme 2) commenced with pyrrolidine mediated displacement of the more reactive C-Cl bond in **4** which afforded **5** in modest yield after trituration. The synthesis of **3** was accomplished using an analogous S_NAr procedure to that reported by Lücking *et al.* [8]. Chromatographic separation and trituration afforded a sample of **3** in modest yield under identical elution conditions. ^1H and ^{13}C NMR spectra of intermediate **5** and product **3** are provided in the supplementary materials.



4 **5** **3**

Scheme 2. Synthetic route to **3**.

Interestingly, the ^1H-NMR spectrum obtained for **3** matches the signals reported [8] for **2** for all the aryl and exchangeable protons. Two sets of multiplets consisting of 4 protons each was observed for **3**. However, the symmetrical methylene peaks adjacent to the nitrogen occurred further downfield at 3.75–3.70 ppm (m, 4 H) *versus* the 3.30 ppm (m, 4H) reported for **2** [9]. In conclusion, we have prepared a novel structural isomer **3** of compound **2**.

Experimental Section

General Information

Reactions were carried out under argon. Organic solutions were dried over Na_2SO_4. Starting materials and solvents were purchased from commercial suppliers and were used without further purification. Flash silica chromatography was performed using Merck silica gel 60 (0.025–0.04 mm). ^1H and ^{13}C-NMR spectra were recorded using a JEOL ECS 400 NMR Spectrometer. Chemical shifts (δ) are reported relative to TMS (δ = 0) and/or referenced to the solvent in which they were measured. High-resolution mass spectrometry analysis was performed on an Agilent 6450 LC-MS/MS.

Synthesis of 3-((5-Bromo-4-(pyrrolidin-1-yl)pyrimidin-2-yl)amino)phenol (**3**)

Triethylamine (1.0 mL, 7.3 mmol) and pyrrolidine (0.55 mL, 6.6 mmol) are added to a stirred solution of 5-bromo-2,4-dichloropyrimidine (**4**) (0.84 mL, 6.6 mmol) in acetonitrile (6 mL). The reaction mixture was stirred at room temperature overnight. After 12 h, the precipitate that formed was filtered off. The filtrate was concentrated *in vacuo* and triturated with isopropyl ether. 5-Bromo-2-chloro-4-(pyrrolidin-1-yl)pyrimidine (**5**) was obtained, 0.67 g (2.5 mmol, 38%) [10]. HCl (4 M in dioxane, 0.12 mL) is added to 3-aminophenol (53 mg, 0.49 mmol) and 5-Bromo-2-chloro-4-(pyrrolidin-1-yl)pyrimidine (**5**) (132 mg, 0.51 mmol) in acetonitrile (1.5 mL), and the reaction mixture was stirred at reflux for 12 h. After cooling to room temperature, the reaction mixture is concentrated *in vacuo*. Water (1.0 mL) was added, and the organic layer extracted with ethyl acetate (5 mL × 2). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (dichloromethane/methanol; 9:1), and the crude product obtained was triturated with isopropyl ether. The title compound **3** was obtained as a white powder, 44 mg (0.13 mmol, 27%).

^{1}H-NMR (400 MHz, d_6-DMSO) δ 9.20 (s, 1H), 9.10 (s, 1H), 8.03 (s, 1H), 7.23–7.21 (m, 1H), 7.12–7.09 (m, 1H), 6.99 (dd, J = 7.8 Hz, 1H), 6.33–6.29 (m, 1H), 3.75–3.70 (m, 4H), 1.89–1.84 (m, 4H).

^{13}C-NMR (100 MHz, d_6-DMSO) δ 159.0, 157.4, 156.9, 141.8, 128.9, 109.6, 108.2, 105.7, 90.1, 49.5, 25.1.

LC-MS (TOF, 2.0 min) Rt = 0.243 min; *m/z* (ESI) 335 (M^{79}Br+H), 337 (M^{81}Br+H).

Hi-Res LC-MS (ESI) *m/z* calcd for $C_{14}H_{16}{}^{79}BrN_4O$ (M+H) 335.0507, found 335.0477.

Melting point range: 159–160 °C.

Acknowledgments

AMJ thanks Manchester Metropolitan University for funding and MMU analytical services for running NMR and MS analyses.

Author Contributions

AMJ performed the experiments and wrote the manuscript.

Conflicts of Interest

The author declares no conflict of interest.

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10. Data obtained for 5-Bromo-2-chloro-4-(pyrrolidin-1-yl)pyrimidine (**5**). ^{1}H-NMR (400 MHz, d_6-DMSO) δ 8.24 (s, 1H), 3.75–3.69 (m, 4 H), 1.89–1.85 (m, 4H); ^{13}C-NMR (100 MHz, d_6-DMSO) δ 159.9, 157.8, 157.4, 100.0, 50.0, 25.1; LC-MS (TOF, 2.0 min) Rt = 0.173 min; *m/z* (ESI) 262 (M^{79}Br+H), 264 (M^{81}Br+H). Hi-Res LC-MS (ESI) *m/z* calcd for $C_8H_9{}^{79}BrClN_3$ (M+H) 261.9747, found 261.9743.