

Short Note

2-Benzyl-3-morpholino-7-(thiophen-2-yl)-6-(thiophen-2-ylmethyl)-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one

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Abstract: The new polyheterocyclic compound 2-benzyl-3-morpholino-7-(thiophen-2-yl)-6-(thiophen-2-ylmethyl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (**1**) was synthesized via a one-pot process involving an Ugi-Zhu three-component reaction coupled to a cascade *aza*-Diels-Alder cycloaddition/*N*-acylation/decarboxylation/dehydration process, using toluene as the solvent, ytterbium (III) triflate as the Lewis acid catalyst, and microwave-dielectric heating to increase the overall yield by up to 73%, while decreasing the reaction time to less than one hour. Product **1** was fully characterized by its physicochemical properties and using spectroscopic techniques (IR, HRMS and NMR).

Keywords: multicomponent reactions; Ugi-Zhu reaction; thiophene; pyrrolo[3,4-*b*]pyridin-5-one

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1. Introduction

Multicomponent reactions (MCRs) are convergent one-pot processes in which at least three substrates are sequentially combined to synthesize products incorporating most of the atoms coming from the reagents [1]. In addition, MCRs are distinguished from conventional multistep synthetic methodologies by their high efficiency, atom economy, and selectivity toward both, chemical libraries of small compounds of high interest in medicinal chemistry [2], and/or complex polyheterocycles [3]. The wide diversity of MCR products is due to modularity of the stereoelectronic nature of reagents by modifying their structural decoration but retaining the main functional groups [4]. For these reasons and features, MCRs have gained attention in various fields of science and technology, but mainly in both pharmacological and pharmaceutical industries [5]. One of the polyheterocyclic systems that can be efficiently synthesized via MCRs is the pyrrolo[3,4-*b*]pyridin-5-one, which is present in some compounds exhibiting biological activity, for instance the antidiabetic **A** [6]. In addition, it is known that pyrrolo[3,4-*b*]pyridin-5-ones are *aza*-analogues of isoindolin-1-ones, which in turn are found in many bioactive compounds such as the antiviral **B** [7] and the antitumoral **C** [8] agents (Figure 1a). Moreover, within heterocyclic compounds of high interest in both medicinal chemistry and agrochemistry, thiophene has been considered as a privileged moiety because it is found in several bioactive compounds like antimicrobials [9], analgesics [10], insecticides [11], and fungicides [12]. Additionally, this heterocycle is present in many drugs approved by FDA, for example, the antifungal Tioconazole [13], platelet antiaggregant Clopidogrel [14], and Canagliflozin [15], the latter being an efficient treatment for type-2 diabetes (Figure 1b). Moreover, it is known that thiophene is considered as a benzene surrogate, even its bio-isostere, as it was masterfully described by Berger and co-workers [16]. Thus, in the present work, the synthesis of a polyheterocycle containing a couple of thiophene rings and one pyrrolo[3,4-*b*]pyridin-5-one in its structure is described. The synthetic strategy involved an Ugi-Zhu reaction coupled to a cascade sequence, but without losing its one pot nature.

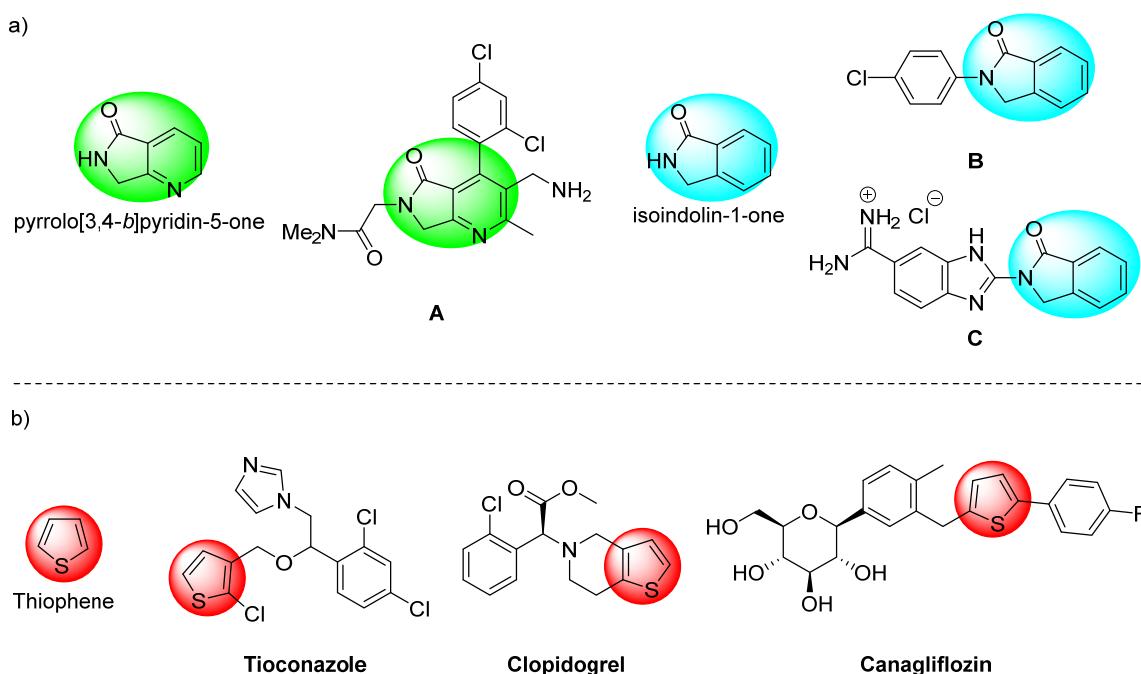


Figure 1. (a) a fused-pyrrolo[3,4-*b*]pyridin-5-one and isoindolin-2-ones of interest in medicinal chemistry, (b) thiophene-based current drugs.

2. Results and Discussion

Behind the synthesis of the objective molecule **1**, it was first necessary to synthesize the corresponding α -isocyanoacetamide **4** starting from racemic phenylalanine, in three reaction steps: (1) aminoacid *N*-formylation, (2) peptidic coupling, and (3) Ugi dehydration, all according to the protocol published by Zhu and Bienaymé [17]. In our own previous reports [18,19], it was found that microwaves, dichloromethane (DCM) and scandium (III) triflate (ScOTf_3) were the best heat source, catalyst, and solvent, respectively, to synthesize novel and complex pyrrolo[3,4-*b*]pyridine-5-ones. However, for the present work, it was necessary to optimize the reaction conditions due to the special nature of reactants, mainly due to the presence of a couple of thiophene rings (Figure 2). A series of both Lewis ($\text{Sc}(\text{OTf})_3$, $\text{Yb}(\text{OTf})_3$, InCl_3) and Bronsted acids (NH_4Cl) were tested. Additionally, the reaction was run in a panel of solvents: MeOH , EtOH , CH_3CN and toluene, from 65 to 80 °C using MW as a heating source. However, it was found that toluene worked well because it better solubilized all reactants, even at room temperature. In the same way, the use of ytterbium (III) triflate gave the highest yield (Table 1, entry 6).

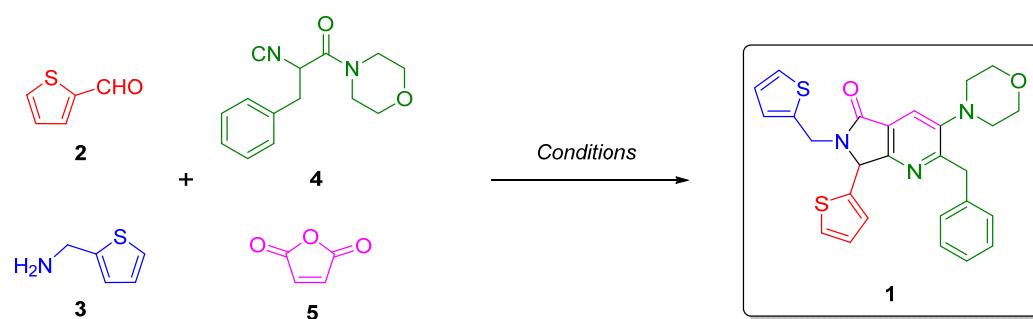


Figure 2. Screening conditions.

Table 1. Effect of catalysts and solvents in the synthesis of pyrrolo[3,4-*b*]pyridin-5-ones.

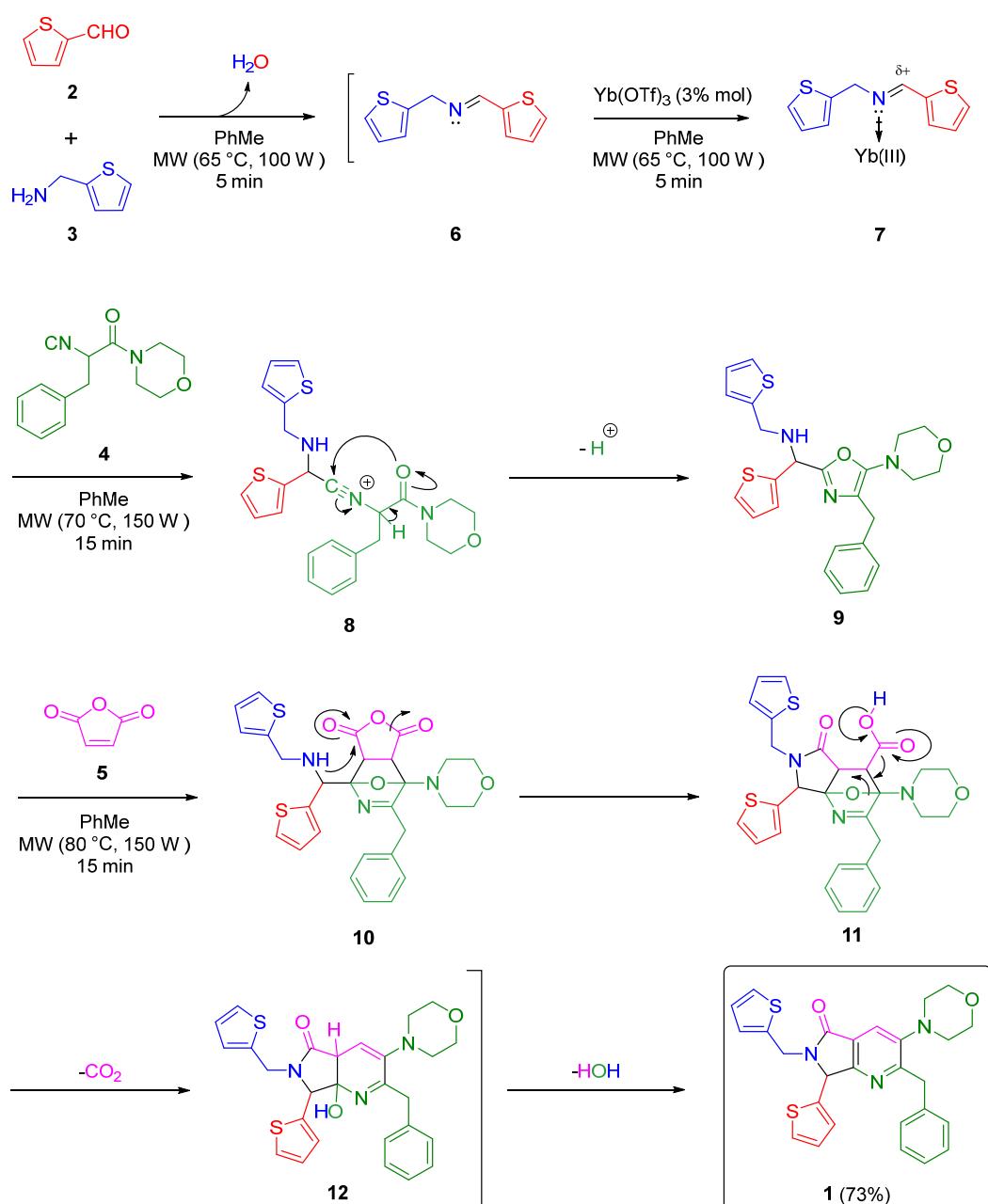
Entry ^a	Solvent	Catalyst ^b	Yield (%)
1	MeOH	Sc(OTf) ₃	30
2	EtOH	Sc(OTf) ₃	17
3	CH ₃ CN	Sc(OTf) ₃	traces
4	PhMe	Sc(OTf) ₃	60
5	PhMe	NH ₄ Cl	24
6	PhMe	Yb(OTf) ₃	73
7	PhMe	InCl ₃	50

^a Experiments were carried out using equimolar amounts of aldehyde and amine. ^b 3% mol was used.

Once the optimal reaction conditions were found, it was proceeded with the synthesis of the corresponding *bis*-thienyl-pyrrolo[3,4-*b*]pyridin-5-one (**1**) in a one pot fashion through an Ugi-Zhu three component reaction (UZ-3CR) [20] coupled to a cascade process as follows: a condensation between 2-thiophenecarboxaldehyde (**2**) and 2-thiophenemethylamine (**3**) occurs to give the corresponding imine **6** using toluene as a solvent at 65 °C under microwave-dielectric heating (100 W). Then, the imine **6** was activated with catalytic amounts (3% mol) of the Lewis acid ytterbium (III) triflate [21] to generate the Lewis' iminium ion **7**, which through an α -nucleophilic attack from the isocyanide **4** to the cation intermediate formed the 5-aminooxazole **9** via a non-prototropic chain-ring tautomerization of the intermediate **8**. Finally, the addition of maleic anhydride (**5**) to **9** promoted the one pot cascade sequence *aza*-Diels Alder cycloaddition followed by an *N*-acylation of **10**, decarboxylation of **11** and dehydration of intermediate **12** towards the *bis*-thienyl-pyrrolo[3,4-*b*]pyridin-5-one (**1**) in 73% overall yield (Scheme 1).

Structure of compound **1** was determined by 1D and 2D NMR spectroscopy, high resolution mass spectrometry, and IR (See the Electronic Supplementary Material for further details). In ¹H NMR spectra (Figure S1), the pyrrolo[3,4-*b*]pyridin-5-one key signals are a singlet at 7.90 ppm (C23-pyridine group), a singlet at 5.71 ppm (C5-methyne group), a doublet AX-spin system at 5.46 and 4.20 ppm (C4-methylene diasterotopic group), and doublet AB-spin system at 4.27 ppm (C15-methylene group). Heteronuclear single quantum coherence spectroscopy (HSQC) was employed to correlate ¹³C signals, as shown in Figure S4. To complement assignment of ¹H, ¹³C was used ¹H-¹H (COSY), ¹H-¹³C (HMBC) correlations as exposed in Figures S3, S5 and S6, respectively. Additionally, a HRMS spectrum confirmed unequivocally the minimal formula for the molecular cation (C₂₇H₂₆N₃O₂S₂⁺) with an error less than 5 ppm (Figure S7). Finally, an FT-IR spectrum showed all absorption characteristic bands, being the most representative of the C=O stretching at 1694 cm⁻¹.

It is important to highlight the formation of several C–C and C–H bonds in a one pot fashion, as well as structural complexity of compound **1**, which denotes a very high atom economy (more than 80%). Additionally, the structural decoration of pyrrolo[3,4-*b*]pyridin-5-one placing a couple of thiophene rings had not been reported in the literature.



Scheme 1. Synthesis of bis-thienyl-pyrrolo[3,4-*b*]pyridin-5-one via a one pot cascade process (Ugi-Zhu 3CR/aza Diels-Alder/*N*-acylation/decarboxylation/dehydration).

3. Materials and Methods

3.1. General Information, Instrumentation, Software, and Chemicals

All starting reagents and solvents were used as received (without further purification, distillation, or dehydration). A mixture of hexanes (Hex) and ethyl acetate (EtOAc) in 3:2 (*v/v*) proportion was used to run TLC, silica-gel column, preparative plate, and to measure the retention factor (*R_f*) value. Microwave-assisted reactions were performed in closed-vessel mode on a CEM Discover SP MW-reactor (Matthews, North Carolina, CA, USA). Reaction progress was monitored by thin-layer chromatography (TLC) and the spots were visualized under ultraviolet (UV) light (254 or 365 nm). Flash column packed with silica-gel 60, 230–400 mesh particle size and a glass preparative plate (20 × 20 cm) coated with silica-gel 60 doped with UV indicator (F₂₅₄) were used to purify the product. ¹H and ¹³C nuclear magnetic resonance (NMR) spectra were acquired on a Bruker AMX

Advance III spectrometer (500 MHz, Fällande, Uster, Switzerland). The solvent used for NMR experiments was deuterated chloroform (CDCl_3). Chemical shifts are reported in parts per million (δ/ppm). Coupling constants are reported in Hertz (J/Hz). Internal reference for NMR spectra was tetramethylsilane (TMS) at 0.00 ppm. Multiplicities of the signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t) and multiplet (m). NMR spectra were analyzed using the MestReNova software (Version 12.0.0-20080). High-resolution mass spectroscopy (HRMS) spectrum was acquired by Electrospray ionization (ESI^+) on a Micro-TOF II spectrometer Bruker Daltonics GmbH (Bremen, Germany). The HRMS sample was injected directly (Apollo source) and analyzed by the time-of-flight method (TOF). HRMS spectrum was analyzed using the Compass 1.5 software. The Infrared (IR) spectrum was acquired on a Perkin Elmer 1600 spectrometer (Norwalk, CT, USA) using the Attenuated Total Reflectance (ATR) method. The maximum absorbance peaks are reported in reciprocal centimeters ($\nu_{\text{max}}/\text{cm}^{-1}$). The IR spectrum was analyzed using the Report Builder software (Version 2.01). Chemical structures were drawn using the ChemDraw Professional software (Version 15.0.0.106, Perkin Elmer Informatics, Cambridge, MA, USA). The purity for the synthesized compound **1** (>98%) was assessed by NMR.

3.2. Synthesis and Characterization of 2-Benzyl-3-morpholino-7-(thiophen-2-yl)-6-(thiophen-2-ylmethyl)-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one (**1**)

2-Thiophenecarboxaldehyde (**2**, 83 μL , 0.883 mmol) and 2-thiophenemethylamine (**3**, 92 μL , 0.1 mmol, 0.883 mmol) were placed in a sealed CEM Discover microwave reaction tube (10 mL) and diluted in toluene (1.0 mL). Then, the mixture was stirred and heated using microwave irradiation (65 °C, 100 W) for 5 min, and ytterbium (III) triflate (16 mg, 0.026 mmol) was added. The mixture was stirred and heated using microwave irradiation (65 °C, 100 W) for 5 min, and then 2-isocyano-1-morpholino-3-phenylpropan-1-one (**4**, 260 mg, 1.060 mmol) was added. The new mixture was stirred and again heated using microwave irradiation (70 °C, 150 W) for 15 min, and then maleic anhydride (**5**, 121 mg, 1.240 mmol) was added. Finally, the reaction mixture was stirred and heated using microwave irradiation (80 °C, 150 W) for 15 min. Then, the solvent was removed to dryness under vacuum. The crude was extracted using dichloromethane ($3 \times 25.0 \text{ mL}$) and $\text{Na}_2\text{CO}_3\text{(aq.)}$ ($3 \times 25 \text{ mL}$), and then washed with brine ($3 \times 25 \text{ mL}$). The organic layer was dried using anhydrous Na_2SO_4 , filtered, and concentrated to dryness under vacuum. The new crude was purified by silica-gel column chromatography followed by preparative TLC using a mixture of hexanes (Hex) and ethyl acetate (EtOAc) in 3:2 (v/v) proportions as mobile phase to isolate 73.1 mg of the polyheterocycle **1** in 73% yield as yellow oil; $R_f = 0.36$ (Hex– $\text{AcOEt} = 3:2, v/v$); FT-IR (ATR) $\nu_{\text{max}}/\text{cm}^{-1}$ 1694 (C=O); ^1H NMR (500 MHz, CDCl_3): δ 7.90 (s, 1H), 7.33 (dd, $J = 5.1, 1.3 \text{ Hz}$, 1H), 7.21 (dd, $J = 5.0, 1.2 \text{ Hz}$, 1H), 7.19–7.10 (m, 4H), 7.04 (dd, $J = 5.1, 3.5 \text{ Hz}$, 1H), 6.97–6.95 (m, 1H), 6.93 (dd, $J = 5.0, 3.4 \text{ Hz}$, 1H), 5.71 (s, 1H), 5.46 (d, $J = 15.4 \text{ Hz}$, 1H), 4.31 (d, $J = 13.8 \text{ Hz}$, 1H), 4.24 (d, $J = 13.8 \text{ Hz}$, 1H), 4.20 (d, $J = 15.5 \text{ Hz}$, 1H), 3.81–3.77 (m, 4H), 2.88–2.75 (m, 4H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ 166.0, 162.2, 159.5, 148.2, 139.2, 139.0, 138.2, 128.8, 128.5, 128.2, 127.2, 127.0, 127.0, 126.7, 126.2, 125.8, 124.1, 67.1, 59.8, 53.0, 40.1, 38.1 ppm; HRMS (ESI^+): m/z calcd for $\text{C}_{27}\text{H}_{26}\text{N}_3\text{O}_2\text{S}_2$ 488.1461 [$\text{M} + \text{H}]^+$, found 488.1469.

4. Conclusions

A one pot synthesis of the new *bis*-thienyl-pyrrolo[3,4-*b*]pyridin-5-one **1** in 73% yield was achieved. It is noteworthy the molecular complexity of the compound **1**, that several C-C, C-H and C-N bonds form in a one pot manner, and the high atom economy of the process (>85%). Furthermore, the potential of compound **1** for further *in silico* and *in vitro* studies is also worth highlighting due mainly to the placement into the same structure, of at least three pharmacophoric motifs, such as a couple of thiophene rings and a fused-polyheterocycle pyrrolo[3,4-*b*]pyridin-5-one.

Supplementary Materials: The following supporting information can be downloaded online. Copies of ^1H -NMR, ^{13}C -NMR, 2D-NMR (COSY, HSQC, and HMBC), HRMS and FT-IR spectra.

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