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Short Note

Methyl 5-Imino-2-methyl-1,10a-dihydro-5*H*-chromeno[2,3-*b*]pyridine-3-carboxylate

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Abstract: Multicomponent reactions are valuable synthetic tools to deliver highly functionalized motifs starting from simple building blocks in only one step and in an atom-economical way. Herein we disclose the structure of a new and unexpected compound, the methyl 5-imino-2-methyl-1,10a-dihydro-5*H*-chromeno[2,3-*b*]pyridine-3-carboxylate, which was formed in the ohmic-heating-assisted multicomponent Hantzsch reaction of 3-formylchromone with methyl acetoacetate and ammonium acetate, in aqueous medium, in the presence of tetrabutylammonium bromide as phase transfer catalyst. The title compound was isolated with no need of chromatographic separation and was analyzed by nuclear magnetic resonance (^{1}H and ^{13}C-NMR, HSQC and HMBC) spectroscopy, mass spectrometry (MS) and high-resolution mass spectrometry (HRMS). Its formation as the main reaction product was observed when the reaction was performed using ohmic heating, which may lead to some speculations about the possible existence of specific effects of ohmic heating in the reactivity pathway because of the passage of an alternating electric current of high frequency within the reaction media, opening new opportunities for further investigations of the potential of this thermal processing method in organic synthesis and reactivity optimization.

Keywords: multicomponent reactions; Hantzsch reaction; 1,4-dihydropyridines; 3-formylchromone; ohmic heating; aqueous phase synthesis; phase transfer catalyst; NMR spectroscopy

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1. Introduction

Multicomponent reactions allow the sustainable construction of highly functionalized and biologically important molecules in a one-step process, with high atom economy, by combination of simple building blocks [1–3]. Therefore, there has been an increasing interest in the use of this kind of reaction in medicinal chemistry and drug discovery [4]. Specifically, the multicomponent Hantzsch reaction offers an efficient way to prepare 1,4-dihydropyridines (1,4-DHPs) by reaction of an aldehyde with a β-ketoester and a nitrogen donor compound such as ammonia or ammonium acetate [5,6].

The 1,4-DHPs are small molecules that occupy a prime place in medicinal chemistry as privileged pharmacophores because of their significant biological activities as calcium channel modulators, antioxidants, bronchodilators, antiartherosclerotic agents and candidates for Alzheimer's disease therapy, among other activities [7,8]. In turn, 4*H*-chromen-4-ones have been extensively studied as bioactive compounds and are well-recognized as, for example, antioxidant, anti-inflammatory, antiviral, antimicrobial, anticancer and neuroprotectant compounds [9,10]. When 4-oxo-4*H*-chromene-3-carbaldehyde (also known as 3-formylchromone) is used as the aldehyde counterpart in the Hantzsch reaction, the reaction affords dihydropyridines functionalized at C-4 with the 3-chromonyl substituent thus combining these two important pharmacophores in a single molecule [11].

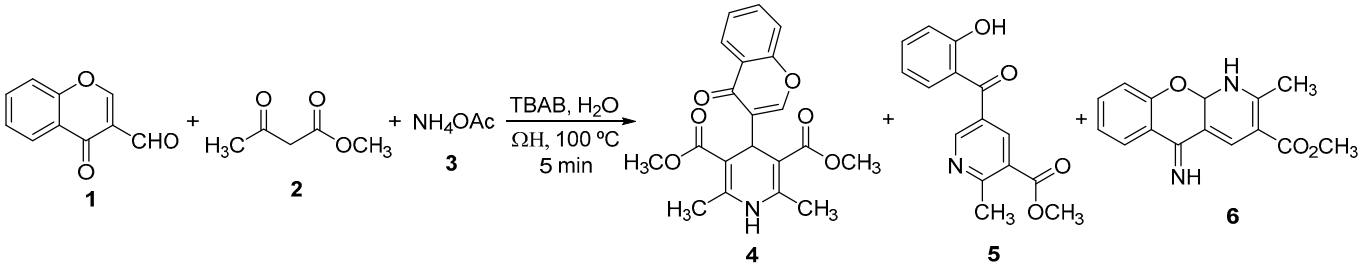
In our group, we have been investigating the use of ohmic heating to assist different chemical reactions for example, Diels–Alder reactions, C-C cross coupling reactions, *N*-alkylations, nucleophilic substitutions, Knoevenagel condensation, indium-promoted

reductive dehalogenation and reductive elimination reactions, aiming to improve the sustainability of synthetic processes [12–17]. Ohmic heating (ΩH) is a thermal process in which the reaction mixture, which behaves as an electrical resistor, is heated by passing an alternating electrical current (AC) of high frequency (25 kHz) through it, by using electrodes in direct contact with a conductive reaction medium. Thermal energy is generated by the motion of the charged species in solution because of the high frequency AC electric current. The thermal energy transfer occurs mostly between the electrode plates cross-session region and surroundings. Electrical energy is dissipated into heat with high efficiency, providing a high-speed heating rate, rapid, and uniform heating (temperature homogeneity), as well as an enhancement of the charged-species dynamics, which may conduct to a distinct reactivity. Ohmic heating has similar effects as microwave activation on the reaction, mostly by reducing the reaction time. Our ohmic reactor operates at atmospheric pressure, under open-vessel conditions, and typically at the boiling temperature of the solvent [18–20].

Aiming to investigate the applicability of ohmic heating to multicomponent chemical reactions, we decided to study the Hantzsch reaction of 3-formylchromone with methyl acetoacetate (also known as methyl 3-oxobutanoate) and ammonium acetate, in aqueous medium, using water to replace organic solvents. Besides the 1,4-DHP functionalized at C-4 with the 3-chromonyl substituent, which is the expected Hantzsch reaction product, two other compounds were obtained. One of them resulted from the opening of the chromone ring in the reaction conditions, which is not surprising, but most intriguing was the formation of the title compound, the methyl 5-imino-2-methyl-1,10a-dihydro-5*H*-chromeno[2,3-*b*]pyridine-3-carboxylate that will be discussed in the next sections.

2. Results

The practical use of water as solvent in the Hantzsch reaction is often limited by the hydrophobic nature of the organic reagents used in the synthesis of 1,4-DHPs and the sensitivity of catalysts to moisture. Nonetheless, water is a very good solvent for ohmic heating, and it was the selected solvent for the Hantzsch reaction of 3-formylchromone **1** with methyl acetoacetate **2** and ammonium acetate **3** studied in this work (Scheme 1).



Scheme 1. Multicomponent ohmic heating assisted Hantzsch reaction in aqueous media.

Initially, the reaction was performed in water at 100 °C in the presence of tetrabutylammonium bromide (TBAB) as a phase transfer catalyst using conventional heating for 2 h. In these conditions, two products, the dimethyl 2,6-dimethyl-4-(4-oxo-4*H*-chromen-3-yl)-1,4-dihydropyridine-3,5-dicarboxylate (**4**) and the methyl 5-(2-hydroxybenzoyl)-2-methylnicotinate (**5**), were obtained in low yields, 6% and 24%, respectively (Table 1, entry 1). Compound **4** is the expected product of this reaction while compound **5** was formed due to the opening of the chromone ring as explained in the next section. Then, the reaction was performed in the ohmic heating reactor and after 30 min the heating was stopped, and the reaction mixture was cooled to room temperature. During the cooling a solid was formed and it was filtrated and dried. The analysis of the ^{1}H- and ^{13}C-NMR spectra of this compound allowed the elucidation of its structure which corresponds to the unexpected title compound, the methyl 5-imino-2-methyl-1,10a-dihydro-5*H*-chromeno[2,3-*b*]pyridine-3-carboxylate (**6**) which was obtained in a low yield (6%) (Table 1, entry 2). No other products were isolated in these conditions. To improve the reaction yield, it

was decided to double the amount of methyl acetoacetate and the reaction was heated at 100 °C for 15 min. Three products were isolated which corresponded to compounds **4** (7%), **5** (31%) and **6** (40%), with a significant increase of the overall reaction yield (Table 1, entry 3). In these conditions, compound **6** was the main reaction product. Finally, attempting to improve the overall reaction yield, a higher excess of methyl acetoacetate (6.0 equiv) was added. After 5 min of reaction, complete consumption of 3-formylchromone was observed by thin-layer chromatography and the heating was stopped. Compound **6** which precipitated from the reaction mixture was filtered and recrystallized from ethanol being obtained with 48% yield. After isolation of this compound, the aqueous solution was extracted with ethyl acetate and the organic residue was purified by thin-layer chromatography (ethyl acetate/hexane, 3:2) to isolate compounds **4** and **5** with 9% and 28% yield, respectively. In the presence of a higher excess of methyl acetoacetate, not only did the overall reaction yield increase, but also a reduction in the reaction time from 15 to 5 min was achieved. It is noteworthy that the formation of compound **6** was observed only when the reaction was performed in the ohmic heating reactor which led to some speculation about the specific effects of ohmic heating in the dynamic of charged particles in solution which may led to a distinct reactivity pathway and formation of unexpected products. However, further studies are needed to investigate the existence of these effects.

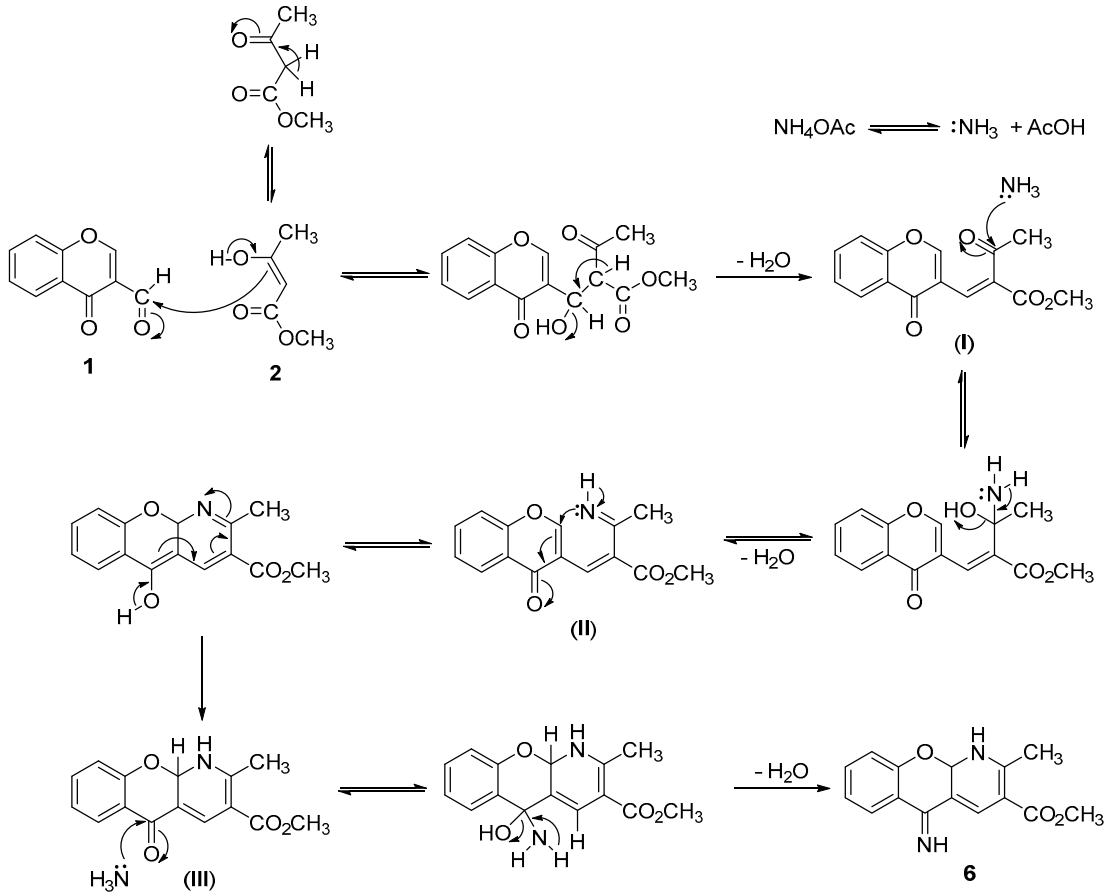
Table 1. Reaction conditions and yields for the Hantzsch reaction of 3-formylchromone **1** with methyl acetoacetate **2** and ammonium acetate **3**. [a].

Entry	Heating Method	2 (equiv)	3 (equiv)	Time (min)	4 (%)	5 (%)	6 (%)
1	CH [b]	2	2	120	6 [d]	24 [d]	- [e]
2	ΩH [c]	2	2	30	- [e]	- [e]	6 [g]
3	ΩH	4	2	15	7 [f]	31 [f]	40 [g]
4	ΩH	6	2	5	9 [f]	28 [f]	48 [g]

[a] Reaction conditions: 3-formylchromone **1** (1.0 mmol), methyl acetoacetate **2** (2.0-6.0 equiv), ammonium acetate **3** (2.0 equiv), TBAB (0.25 equiv), H_2O (5 mL), 100 °C. [b] CH stands for conventional heating. [c] ΩH stands for ohmic heating. [d] Yield of isolated compound after purification by thin-layer chromatography. [e] Compound not isolated in the experiment. [f] Compound isolated after extraction and purification by thin-layer chromatography of the aqueous solution obtained after filtration of compound **6**. [g] Compound **6** was isolated by filtration of the solid formed in the reaction after being cooled to room temperature and recrystallization in ethanol.

3. Discussion

The formation of the dimethyl 2,6-dimethyl-4-(4-oxo-4*H*-chromen-3-yl)-1,4-dihydropyridine-3,5-dicarboxylate (**4**) can be explained based on the Hantzsch reaction mechanism (see Scheme S1 on the Supplementary Information) [21,22]. Likewise, the formation of the methyl 5-(2-hydroxybenzoyl)-2-methylnicotinate (**5**) was not surprising since it is already described in the literature [11]. In fact, the opening of the chromone ring in certain reaction conditions is well-documented and has been observed for 3-formylchromones in the presence of amines as nucleophiles [23–25]. Primary amines can produce aminoenones by nucleophilic attack at C-2 of the chromone ring as shown in Scheme S2 (see Supplementary Information). In turn, to the best of our knowledge, the main compound obtained when the reaction was performed in the ohmic heating reactor, the methyl 5-imino-2-methyl-1,10a-dihydro-5*H*-chromeno[2,3-*b*]pyridine-3-carboxylate (**6**), was never reported. A plausible mechanism was proposed to explain the formation of this compound (Scheme 2). The mechanism starts with the Knoevenagel condensation of methyl acetoacetate **2** (enolic form) with 3-formylchromone **1** and subsequent formation of intermediate (**I**). Afterwards, the nucleophilic attack of ammonia in the methyl ketone of **I** and elimination of water originates the intermediate (**II**) which upon nucleophilic attack of the nitrogen atom at C-2 of the chromone ring and further rearrangement gives intermediate (**III**). Finally, a second nucleophilic attack of ammonia in the carbonyl group of **III** and subsequent water elimination affords the title compound **6**.



Scheme 2. Plausible mechanism for the formation of the title compound **6**.

The structure of compound **6** (Figure 1) was confirmed based on the analysis of the ^{1}H- and ^{13}C-NMR spectra and the correlations observed in the 2D NMR spectra (HSQC and HMBC). The most characteristic signals of this compound are the singlet at δ_H 2.82 ppm (δ_C 24.6 ppm) due to the resonance of the protons of the 2-methyl group, the singlet at δ_H 3.88 ppm (δ_C 52.2 ppm) due to the resonance of the protons of the ester group, and the doublet due to the resonance of the proton H-10a at δ_H 6.54 ppm (δ_C 91.5 ppm) which couples with the proton of the NH group (^{3}J 6.2 Hz). In the aromatic region of the NMR spectra three typical signals are observed, among other signals: a singlet corresponding to the resonance of H-4 at δ_H 8.22 ppm (δ_C 136.3 ppm), a doublet due to the resonance of H-6 at δ_H 8.26 ppm (δ_C 124.4 ppm), and another doublet assigned to the resonance of H-9 at δ_H 7.09 ppm (δ_C 117.8 ppm). Based on the correlations observed in the HMBC spectrum (H-4, H-6→C-5) it was possible to identify the quaternary carbon C-5 of the imine group at δ_C 147.8 ppm, and the correlations (H-10a→C-9a) and (H-4→C-2) allowed the assignment of C-9a (δ_C 153.5 ppm) and C-2 (δ_C 159.3 ppm) at higher chemical shifts because of the oxygen atom effect. Also characteristic is the signal of the carbonyl carbon of the ester group observed at δ_C 165.9 ppm (H-4, OC$\underline{H}_3$→C=O). Other correlations observed in the HMBC spectrum (H-9, H-7→C-5a), (H-1→C-4a) and (C$\underline{H}_3$→C-3) allowed the identification of the quaternary carbons C-5a (δ_C 120.3 ppm), C-4a (δ_C 124.2 ppm) and C-3 (δ_C 123.4 ppm) (Figure 1).

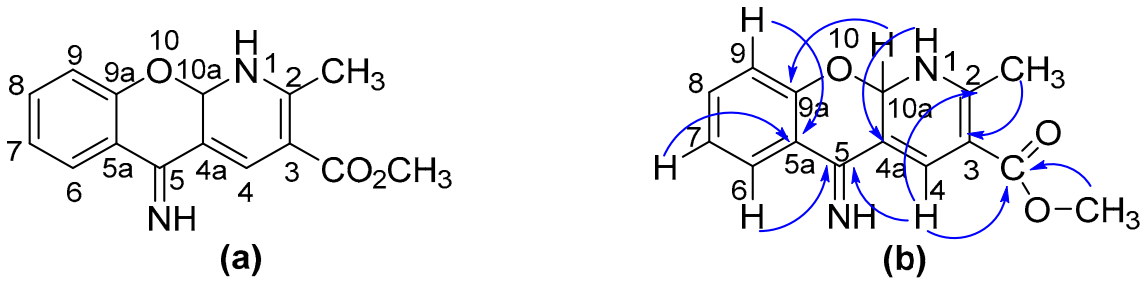


Figure 1. (**a**) Structure and numbering of the title compound **6** and (**b**) main correlations observed in the HMBC spectrum.

4. Materials and Methods

All reagents were used as purchased without any further purification. Preparative thin-layer chromatography was carried out with silica gel (60 DGF254) plates and plates were observed under a UV light at 254 and 365 nm. Melting points were determined on a Büchi melting point B-540 apparatus and are uncorrected. The solvent used for recrystallization is indicated after the melting point. NMR spectra were recorded on a 300 MHz or 500 MHz NMR spectrometer [300.13 MHz (^{1}H), 75.47 MHz (^{13}C) or 500.13 MHz (^{1}H), 125.77 MHz (^{13}C)] with TMS as an internal reference and with DMSO-d_6 as solvent. Chemical shifts (δ) are quoted in ppm relative to TMS. Coupling constants (J) are quoted in Hz. Unequivocal ^{13}C assignments were made based on 2D *g*HSQC (^{1}H/^{13}C) and *g*HMBC (delays for one bond and long-range $J_{C/H}$ couplings were optimized for 145 and 7 Hz, respectively) experiments. Positive-ion ESI mass spectra and high-resolution mass spectra [ESI(+)-HRMS] were performed using a LTQ Orbitrap XL mass spectrometer (Thermo Fischer Scientific, Bremen, Germany) controlled by LTQ Tune Plus 2.5.5 and Xcalibur 2.1.0. The capillary voltage of the electrospray ionization (ESI) was set to 3100 V. The capillary temperature was 275 °C. The sheath gas flow rate (nitrogen) was set to 5 (arbitrary unit as provided by the software settings). The capillary voltage was 36 V and the tube lens voltage 110 V. For experiments carried out under ohmic heating, the 10 mL reactor was filled with the reaction mixture, closed, and the mixture was heated to 100 °C. For 5 mL of reaction mixture the length of electrodes immersed in the reaction medium was approximately 9 mm; the distance between the electrodes was 10 mm. Medium magnetic stirring speed (740 rpm) was used in all the experiments carried out in the ohmic heating reactor. Experiments were performed using sinusoidal waveform and a 25 kHz AC current. Temperature measurement was done using a type J glass-sheathed thermocouple inside the reactor. For the experiments carried out in conventional heating (oil bath), medium magnetic stirring speed (740 rpm) was used.

Methyl 5-Imino-2-methyl-1,10a-dihydro-5H-chromeno[2,3-b]pyridine-3-carboxylate

A stirred suspension of 4-oxo-4*H*-chromene-3-carbaldehyde (**1**) (3-formylchromone) (174.2 mg, 1.0 mmol), methyl acetoacetate (**2**) (0.65 mL, 6.0 mmol), ammonium acetate (**3**) (154.2 mg, 2.0 mmol) and TBAB (81.3 mg, 0.25 mmol) in water (5 mL) was heated in the ohmic heating reactor, using the 10 mL glass vessel reactor, for 5 min. After that period, the reaction was cooled to room temperature and the solid formed was filtrated and recrystallized from ethanol. After filtration the title compound methyl 5-imino-2-methyl-1,10a-dihydro-5*H*-chromeno[2,3-*b*]pyridine-3-carboxylate (**6**) (130.9 mg, 48% yield) was isolated as a white solid, mp 233-234 °C (from ethanol); ^{1}H-NMR (500.13 MHz, DMSO-d_6): δ 8.26 (d, J = 7.5 Hz, 1H, H-6), 8.22 (s, 1H, H-4), 7.69 (d, J = 6.2 Hz, 1H, N*H*-1), 7.46 (ddd, J = 8.2, 7.5 and 0.8 Hz, 1H, H-8), 7.17 (t, J = 7.5 Hz, 1H, H-7), 7.09 (d, J = 8.2 Hz, 1H, H-9), 6.54 (d, J = 6.2 Hz, 1H, H-10a), 3.88 (s, 3H, 3-CO_2CH_3), 2.82 (s, 3H, 2-CH_3) ppm. ^{13}C-NMR (125.77 MHz, DMSO-d_6): δ 165.9 (3-CO_2CH_3), 159.3 (C-2), 153.5 (C-9a), 147.8 (C-5), 136.3 (C-4), 132.1 (C-8), 124.4 (C-6), 124.2 (C-4a), 123.4 (C-3), 121.8 (C-7), 120.3 (C-5a), 117.8 (C-9), 91.5 (C-10a), 52.2 (3-CO_2CH_3), 24.6 (2-CH_3) ppm. MS (ESI$^+$) m/z (%):

272 $[M+H]^+$ (100). HRMS (ESI^+) $[M+H]^+$ calculated for $C_{15}H_{15}N_2O_3$ 272.09230; found, 272.09075.

In turn, the aqueous solution was extracted with ethyl acetate (4 × 10 mL) and the organic layer was collected and dried with anhydrous sodium sulfate. The solution was concentrated under reduced pressure and purified by thin layer chromatography (ethyl acetate/hexane, 3:2). The isolated products were analyzed by NMR spectroscopy and their structures corresponded to the dimethyl 2,6-dimethyl-4-(4-oxo-4*H*-chromen-3-yl)-1,4-dihydropyridine-3,5-dicarboxylate (**4**) (33.0 mg, 9%) and methyl 5-(2-hydroxybenzoyl)-2-methylnicotinate (**5**) (75.7 mg, 28%) (see Supplementary Information for the NMR data of these compounds).

5. Conclusions

In conclusion, the methyl 5-imino-2-methyl-1,10a-dihydro-5*H*-chromeno[2,3-*b*]pyridine-3-carboxylate (**6**) was formed as the main compound in the ohmic heating assisted Hantzsch reaction of 3-formylchromone **1** with methyl acetoacetate **2** and ammonium acetate **3,** in aqueous medium, together with the two products **4** and **5** expected for this reaction. The use of water as solvent, short reaction time (only 5 min) and simple workup procedure for the isolation of the formed compounds are the main advantages of this method. Compound **6** was isolated with no need of chromatographic separation. The ester group at C-3 of compound **6** can be hydrolyzed to the corresponding carboxylic acid allowing additional transformation at this position. Further studies to test the general scope of this reaction by using other substituted 3-formylchromones will be conducted. Since the formation of compound **6** was observed when the reaction was performed using ohmic heating, this work raised some questions about the existence of specific effects of ohmic heating on the reactivity pathway due to the passage of electric current through the reaction media that need to be further investigated.

Supplementary Materials: The following supporting information can be downloaded online. Scheme S1: Hantzsch reaction scheme and mechanism for the formation of compound **4**; Scheme S2: Plausible mechanism for the formation of compound **5**; Figure S1: ^{1}H-NMR spectrum of compound **6** (500.13 MHz, DMSO-d_6); Figure S2: Expansion of ^{1}H-NMR spectrum of compound **6** (500.13 MHz, DMSO-d_6); Figure S3: ^{13}C-NMR spectrum of compound **6** (125.77 MHz, DMSO-d_6); Figure S4: Expansion of ^{13}C-NMR spectrum of compound **6** (125.77 MHz, DMSO-d_6); Figure S5: HSQC spectrum of compound **6**; Figure S6: Expansion of HSQC spectrum of compound **6**; Figure S7: HMBC spectrum of compound **6.** Figure S8: Expansion of HMBC spectrum of compound **6.** Page S8: NMR structural characterization data for compounds **4** and **5**.

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Data Availability Statement: The presented data are available in this article.

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