

Short Note

1,4-Phenylenebis[(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone]

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Abstract: The compound named in the title was prepared from N^1, N^4 -diphenethylterephthalamide **1**. The resulting bis terephthalamide was subjected to an intramolecular α -amidoalkylation reaction with paraformaldehyde in the presence of heterogeneous catalyst TfOH/SiO₂ to obtain 1,4-phenylenebis[(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone]. The structure of the newly synthesized compound was determined using ¹H, ¹³C-NMR, UV, IR and mass spectral data.

Keywords: TfOH/SiO₂; α -amidoalkylation; terephthaloyl chloride; homoveratrylamine; bis terephthalamide

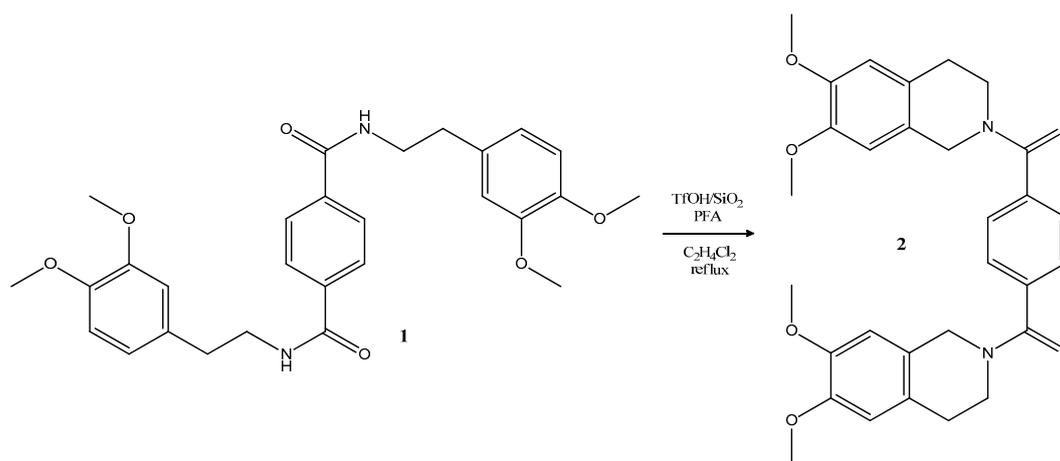
1. Introduction

The alkaloids containing an isoquinoline skeleton are one of the largest classes of plant alkaloids which display a broad spectrum of biological activities [1]. In recent years, acid catalysts have increasingly found use as catalytic systems of acid absorbed on silica [2]. In addition to promoting a successful reaction, their ability to be recovered and consistently reused in subsequent reactions identifies them as environmentally friendly “green reagents” [3]. Based on our previous experience of the application of intramolecular α -amidoalkylation for the synthesis of isoquinoline compounds, we have successfully obtained 1,4-phenylenebis[(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone] using triflic acid absorbed on silica, as a green catalyst, in an intramolecular α -amidoalkylation reaction.

2. Results

In this work we report the successful synthesis of 1,4-phenylenebis[(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone] as shown in Scheme 1.

The starting amide **1** was synthesized through the application of the Saidov [4] synthetic procedure. Based on our previous experience [5], initial cyclization reactions were performed for amide **1** (Scheme 1) using paraformaldehyde in dichloroethane in the presence of the catalytic system of acid absorbed on silica. In our previous experiments we have reported the use of heterogeneous catalytic systems of polyphosphoric acid absorbed on silica as a new “green” agent for the synthesis of *Cherylline* derivatives [6]. In search of other new “green” agents, we studied the possibility of applying a TfOH/SiO₂ system as a heterogeneous acid catalyst in an intramolecular α -amidoalkylation reaction. Triflic acid (TfOH) is termed a “super acid”, as it is perhaps one of the most versatile Brønsted acid catalysts that can be used in a vast array of organic reactions. Because of its high corrosiveness and due to the fact that it is a fuming liquid, difficulties remain in storage, transportation, handling and waste disposal that severely restrict their application in industry [7].



Scheme 1. Synthesis of 1,4-phenylenebis[(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone] **2**.

For the cyclization step, to amide **1** (Scheme 1) dissolved in dichloroethane we added paraformaldehyde in excess and TfOH/SiO₂. Compound **2** was successfully obtained by refluxing the reaction mixture for 10 min. After completion of the reaction, the reaction mixture was cooled, and the catalyst was removed via filtration. The solvent was then distilled via rotary evaporator.

Compound **2** was obtained as a light yellow solid (93% yield) with a melting point recorded at 199–202 °C. The UV spectrum exhibited absorption maxima λ_{\max} 203, 234 and 284 nm. The mass of the compound in the HRMS spectrum was found at $[M + Na]^+$, $m/z = 539.2128$ (Calculated: 539.2158). The signals in the NMR spectra are doubled due to rotamers in nearly a 1:1 ratio.

3. Materials and Methods

All the reagents and chemicals were purchased from commercial sources (Sigma-Aldrich, Sofia, Bulgaria) and used as received. Melting points were determined on a Boetius hot stage apparatus and are uncorrected. The spectral data were recorded on a Bruker Avance II + 600 spectrometer (BAS-IOCCP—Sofia, Sofia, Bulgaria). The ¹H-NMR and ¹³C-NMR spectra for compound **2** were taken in DMSO at 600 MHz and 150.9 MHz, respectively. Chemical shifts are given in ppm relative and were referenced to TMS ($\delta = 0.00$ ppm) as an internal standard with the coupling constants indicated in Hz. The NMR spectra were taken at room temperature (ac. 295 K). TLC was carried out on precoated 0.2 mm Fluka silica gel 60 plates, using diethyl ether/*n*-hexane = 1/1 as chromatographic system. The catalyst TfOH/SiO₂ was prepared using the procedure detailed by Liu et al. [3].

Synthesis of 1,4-Phenylenebis[(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone] **2**

To a solution of *N*¹,*N*⁴-diphenethylterephthalamide **1** (3 mmol) and paraformaldehyde (5 mmol) in C₂H₄Cl₂ (10 mL) was added 0.06 g of catalyst (TfOH/SiO₂, 0.5 mmol/g). The reaction mixture was placed under reflux for 10 min. After the completion of the reaction, the reaction mixture was cooled and the catalyst was separated by simple filtration.

1,4-Phenylenebis[(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone] (**2**). White solid (M.p. 199–202 °C). ¹H-NMR (600 MHz, DMSO) δ ppm 2.71 (s, 2H), 2.85 (s, 2H), 3.55 (m, 2H), 3.73–3.81 (m, 12H), 3.93 (m, 2H), 4.41 (s, 2H), 4.77 (s, 2H), 6.33 (s, 1H), 6.56–6.61 (m, 3H), 7.44 (s, 4H); ¹³C-NMR (150.9 MHz, DMSO) δ ppm 146.9, 136.6, 126.4, 126.3, 110.5, 110.3, 108.2, 107.5, 54.9, 48.5, 44.3, 42.5. λ_{\max} , MeOH: 203, 234, 284 nm. HRMS (ESI) m/z calcd for C₃₀H₃₂N₂O₆ $[M + Na]^+ = 539.2158$, found 539.2128. IR (KBr) ν_{\max} , cm⁻¹: 760 γ (C_{sp}²-H), 847 γ (C_{sp}²-H), 1037 ν_s (C_{sp}²-O-C), 1207 ν_{as} (C_{sp}²-O-C), 1442 δ (R₂=N-CH₂-), 1518 ν (C_{sp}²-C_{sp}²), 1631 γ (N-C=O), 2835 δ_{as} (OCH₂-H), 2933 ν_{as} (CH₂), 3067 ν (C_{sp}²-H).

Copies of all spectra and ESI-HRMS (Figures S1–S5) are provided in the Supplementary Materials.

Supplementary Materials: The molefiles and the other supplementary materials can be found at <http://www.mdpi.com/1422-8599/2016/3/M902>.

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Author Contributions: Both authors contributed equally to both the experimental and writing work.

Conflicts of Interest: The authors declare no conflict of interest.

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