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Short Note

9-Methoxynaphtho[1,2-*b*]benzofuran

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Abstract: A highly selective one-pot microwave-assisted synthesis of 9-methoxynaphtho[1,2-*b*]benzofuran was obtained by treating 1-naphthol with 1-bromo-4-methoxy-2-nitrobenzene and two molar equivalents of potassium *tert*-butoxide in dimethyl sulfoxide. The selectivity in the production of the title compound was addressed by the suitable position of the bromine and nitro group on the aryl reagent. Moreover, we highlight how the nitro group plays a dual role, as activator in the first nucleophilic substitution with the release of bromide ion and then as the leaving group in the furan cyclization. Eventually, the product was structurally characterized by MS and extensive NMR analyses.

Keywords: naphthobenzofuran; α-brasan; nucleophilic aromatic substitution; nitro group replacement; microwave-assisted reaction; chemoselectivity

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1. Introduction

Fused heteroaromatic molecules are of interest for several and various applications, including the development of electronic devices based on organic semiconductor materials [1]. In particular, derivatives of benzo[b]naphtha[2,1-*d*]furan (also referred to as α-brasan) are polycondensed heteroaromatic compounds studied as precursors for building dimers specifically designed to extend the π-conjugation, with the aim of increasing the intermolecular π electrons overlap in the solid state and obtaining a higher electron mobility [2]. Moreover, furanoacenes have attracted recent interest as functional materials and as bioactive molecules and different synthetic procedures have been developed. In detail, polyhydroxy benzo[b]naphtha[2,1-*d*]furan was obtained by an acid-catalyzed reaction of α-naphthoquinone and substituted phenol [3], and the synthesis of a series of furanoacenes was recently reported starting from aryloxy-disilylenynes through a three-step Pd-catalyzed sequence [4].

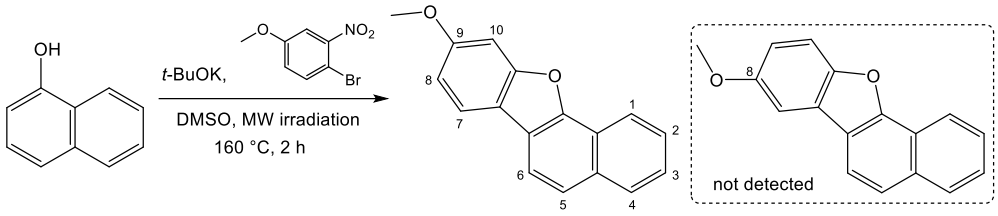
When substituents are present on the aryl units, the synthesis of these fused heteroaromatic structures can produce a mixture of isomeric products, pointing out the missing regiospecific preparations. This is the case of the title compound 9-methoxynaphtho[1,2-*b*]benzofuran, which was obtained in mixture with the 8-methoxy isomer (12% and 10% yield, respectively) by reaction of 1-naphthol and 1,2-dibromo-4-methoxybenzene with cesium carbonate, triphenylphosphine, and a catalytic amount of palladium acetate in anhydrous dimethylformamide [2]. The pure 9-methoxy compound was recovered by chromatographic separation from its regioisomer and used in the following preparation of the desired molecules.

We report here the highly selective synthesis of the title compound, through an efficient single-pot procedure starting from a suitable reagent. Structural characterization was supported by extensive NMR analysis.

2. Results and Discussions

The synthesis of 9-methoxynaphtho[1,2-*b*]benzofuran was achieved by reacting 1-bromo-4-methoxy-2-nitrobenzene with two molar equivalents of 1-naphthol and potassium *tert*-butoxide in dry dimethyl sulfoxide (DMSO) under microwave (MW) irradiation

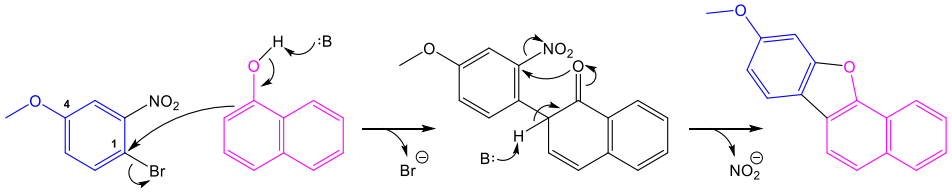
for 2 h (Scheme 1). The replacement of conventional heating by microwave irradiation was reported to be a powerful tool for reducing the volume of solvent used, shortening reaction times and increasing the reaction yield, often associated with a decrease in by-products and for all these reasons also employed in the preparation of organic products for electronic devices [5].



Scheme 1. Synthesis of 9-methoxynaphtho[1,2-*b*]benzofuran. The indicated numbering is in agreement with the previously reported for α-brasan [3].

The synthesis of the title compound described by Itoh et al. [2] used 1,2-dibromo-4-methoxybenzene, but the presence of the two bromine atoms did not allow a regioselective cyclization. Conversely, we selected 1-bromo-4-methoxy-2-nitrobenzene as starting reagent to obtain the single 9-methoxy isomer where the suitable position of bromine and nitro group drives the reaction.

The proposed reaction mechanism (Scheme 2) involves the initial production of naphthalen-1-olate, which acts as a *C*-nucleophile by substitution of bromine in the C-1 position. Moreover, the presence of the nitro electron-withdrawing group in the *ortho*-position promotes aromatic nucleophilic substitution [6,7]. Subsequently, the second equivalent of base promotes the formation of the furan heterocycle by releasing a nitrite ion, known to be a relatively good leaving group [8,9]. Therefore, the nitro group plays a dual role in this synthesis, namely as activator in the first nucleophilic substitution and as the leaving group in the final step of furan cyclization. The solvent, dimethyl sulfoxide, was selected for its dipolar aprotic properties to favor substitutions involving anionic nucleophiles.



Scheme 2. Proposed mechanism for the formation of 9-methoxynaphtho[1,2-*b*]benzofuran by a base-mediated annulation of 1-bromo-4-methoxy-2-nitrobenzene with 1-naphthol.

The reaction was monitored by TLC, where the formation of the product was easily highlighted thanks to its characteristic fluorescence under 365 nm UV light. The crude reaction mixture was purified using column chromatography on silica gel, recovering the product with a yield of 30%. Its molecular structure was established by the presence of $[M + H]^+$ ion at m/z 249 in the ESI(+)MS spectrum and by a complete NMR signals assignment (see experimental part).

Further support was found in perfect agreement with the reported data, where the discrimination between 8-methoxy and 9-methoxy compounds was certainly achieved by X-ray analysis for a 9-methoxy derivate [2].

3. Materials and Methods

3.1. General

All chemicals and reagents were purchased from Sigma Aldrich (Taufkirchen, Germany). MW irradiation was performed using a CEM microwave reactor (Matthews, NC, USA). The yield is referred to purified compound and was not optimized. Thin-layer chromatography

(TLC) was performed using Merck silica gel F_{254} (VWR, Milan, Italy), using short-wave UV light as the visualizing agent, and $KMnO_4$ as developing agent upon heating. Column chromatography was performed using Merck Si 40–60 μm (VWR, Milan, Italy) as stationary phase. NMR spectra were recorded on a Bruker Avance 400 instrument (Billerica, MA, USA) equipped with a 5 mm BBI probe ^{1}H at 400 MHz and ^{13}C at 100 MHz and calibrated using residual undeuterated solvent for $CDCl_3$ (relative to δ_H 7.25 ppm and δ_C 77.0 ppm, respectively) with chemical shift values in ppm and *J* values in Hz. The following abbreviations were used to describe multiplicities: s = singlet and d = doublet. Signals assignment was established by ^{1}H-^{1}H correlation by COSY experiment, ^{1}H-^{13}C hetero-correlation by HSQC, and ^{1}H-^{13}C long-range hetero-correlation by HMBC experiments and 2D NOESY (delay 0.5 s) experiment. NMR data were analyzed using BrukerTopspin software 3.6.1 version (Billerica, MA, USA). ESI-MS spectrum was recorded in positive ion mode using a Bruker Esquire-LC mass spectrometer (Billerica, MA, USA), injecting a methanolic solution of the sample, after the addition of a few drops of formic acid.

3.2. Synthesis of 9-Methoxynaphtho[1,2-b]benzofuran

In a microwave vial, potassium *tert*-butoxide (192.6 mg, 1.72 mmol, 2 eq.) was added under nitrogen at room temperature to a solution of 1-naphthol (247.7 mg, 1.72 mmol, 2 eq.) dissolved in 3 mL of anhydrous DMSO. The reaction was stirred for two hours at 70 °C and the formed *tert*-butyl alcohol was removed under reduced pressure. 1-Bromo-4-methoxy-2-nitrobenzene (200.0 mg, 0.86 mmol, 1 eq.) was then added and the solution was MW irradiated at 160 °C for 2 h. After extraction with diethyl ether (x3), the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified via column chromatography on silica gel (*n*-hexane/CH_2Cl_2 60:40 *v*/*v*), providing the pure product (64.7 mg, 30% yield).

White solid. TLC: *n*-hexane/CH_2Cl_2 60:40 *v*/*v*, Rf = 0.59. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.42 (d, *J* = 7.3 Hz, 1H, H-1), 8.00 (d, *J* = 8.2 Hz, 1H, H-4), 7.96 (d, *J* = 8.5 Hz, 1H, H-6), 7.88 (d, *J* = 8.5 Hz, 1H, H-7), 7.78 (d, *J* = 8.5 Hz, 1H, H-5), 7.65 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H, H-2), 7.55 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H, H-3), 7.27 (d, *J* = 2.3 Hz, 1H, H-10), 7.03 (dd, *J* = 8.6, 2.3 Hz, 1H, H-8), 3.96 (s, 3H, OCH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 159.3 (C9), 157.2 (C-C10), 151.7 (O-C), 132.2 (C-C4), 128.3 (C4), 126.3 (C2), 125.4 (C3), 123.1 (C5), 121.3 (C-C1), 120.4 (C1), 120.3 (C7), 119.3 (C-C6), 118.2 (C-C7), 118.0 (C6), 111.3 (C8), 96.6 (C10), 55.6 (OCH_3). Significant correlations: ^{1}H,^{1}H COSY (Figure S3, Supplementary Materials): H-7/H-8 and H-8/H-10; HSQC (Figure S4) H-7/C7, H-8/C8, H-10/C10 and H-10/C-C7; HMBC (Figure S5): H-8/C9, H-10/C9, H-10/C-C10 and OCH_3/C9; NOESY (Figure S6): H-4/H-5; H-6/H-7. ESI(+)-MS: *m*/*z* 249 $[M + H]^+$.

4. Conclusions

An efficient method for the synthesis of 9-methoxynaphtho[1,2-*b*]benzofuran has been here proposed. This procedure takes advantage of the one-pot microwave-assisted procedure and of the selectivity addressed by the suitable position of the nitro and bromine groups on the methoxyaryl reagent. This avoids the drawbacks of the reported procedure where the product was obtained in a very low amount after chromatographic separation from its 8-methoxy isomer.

It should be remembered that this synthetic method can be adapted to prepare 8-methoxy isomer selectively, starting from the suitable 2-bromo-4-methoxy-1-nitro benzene reagent, which is commercially available.

Supplementary Materials: The following supporting information for the title compound is available online: Figure S1: ^{1}H-NMR spectrum; Figure S2: ^{13}C-NMR spectrum; Figure S3: ^{1}H,^{1}H correlation spectrum by COSY experiment; Figure S4: ^{1}H,^{13}C hetero-correlation spectrum by HSQC experiment; Figure S5: ^{1}H,^{13}C long-range hetero-correlation spectrum by HMBC experiment; Figure S6: 2D NOESY spectrum.

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