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Short Note

(*Z*)-4-(Carbomethoxymethylene)-2-(4-fluorophenyl)-4*H*-benzo[*d*][1,3]oxazine

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Academic Editor: Norbert Haider

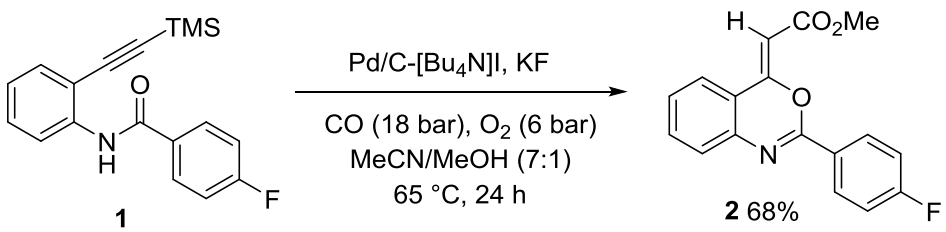
Received: 20 December 2016; Accepted: 9 January 2017; Published: 13 January 2017

Abstract: The title compound, (*Z*)-4-(carbomethoxymethylene)-2-(4-fluorophenyl)-4*H*-benzo[*d*][1,3]oxazine, was synthesized in 68% isolated yield by palladium-catalyzed oxidative cyclization-methoxycarbonylation of 4-fluoro-*N*-(2-((trimethylsilyl)ethynyl)phenyl)benzamide. This new heterocyclic derivative was fully characterized by IR, ^{1}H-NMR, ^{13}C-NMR spectroscopies, MS spectrometry, and elemental analysis. The *Z* configuration around the double bond was unequivocally established by 2D NOESY experiments.

Keywords: palladium; benzoxazines; carbonylation; Heterocyclization; 2D NMR experiments

1. Introduction

Palladium-catalyzed oxidative alkoxycarbonylation of alkynes is a simple and powerful tool for the synthesis of complex heterocyclic compounds from easily available starting reagents [1–5]. Over the years, we have successfully applied this effective methodology to access carbonylated compounds in a one-pot fashion [6–13]. In particular, some years ago, we reported a facile and efficient route for the synthesis of new functionalized benzo[*d*][1,3]oxazines by in situ deprotection of 2-(trimethylsilanyl)ethynylaniline derivatives followed by palladium-catalyzed cyclization-alkoxycarbonylation [14]. The benzo[*d*][1,3]oxazine scaffold is found in many biologically active molecules, including anti-tumor, anti-inflammatory, anti-convulsant, and anti-fungal agents [15–19]. In this Note, we report the preparation of the fluorinated benzoxazine **2**—that is, (*Z*)-4-(carbomethoxymethylene)-2-(4-fluorophenyl)-4*H*-benzo[*d*][1,3]oxazine—by adopting the same catalytic carbonylative strategy (Scheme 1). We provide a full characterization of compound **2**, including NMR spectra and a complete assignment of all ^{1}H and ^{13}C-NMR signals.



Scheme 1. Pd/C-catalyzed synthesis of the title compound **2** (TMS = trimethylsilyl).

2. Results and Discussion

As shown in Scheme 1, the synthesis of (*Z*)-4-(carbomethoxymethylene)-2-(4-fluorophenyl)-4*H*-benzo[d][1,3]oxazine (**2**) was achieved in one step, through palladium-catalyzed oxidative alkoxycarbonylation of 4-fluoro-*N*-(2-((trimethylsilyl)ethynyl)phenyl)benzamide (**1**). The reaction was carried out in 7:1 MeCN/MeOH mixture at 65 °C in the presence of a catalytic amount of 10% Pd/C in conjunction with $[Bu_4N]I$ and KF and under 24 bar of a 3:1 mixture of CO-air. Under these reaction conditions, the target product **2** was obtained in 68% isolated yield. The structure of compound **2** was confirmed by NMR, IR, and mass spectral data. In particular, the *Z* stereochemistry of the methoxycarbonylmethylene moiety was confirmed by a 2D NOESY experiment, while 2D HSQC/HMBC experiments enabled the unequivocal assignment of all proton and carbon signals (Figures 1 and 2).

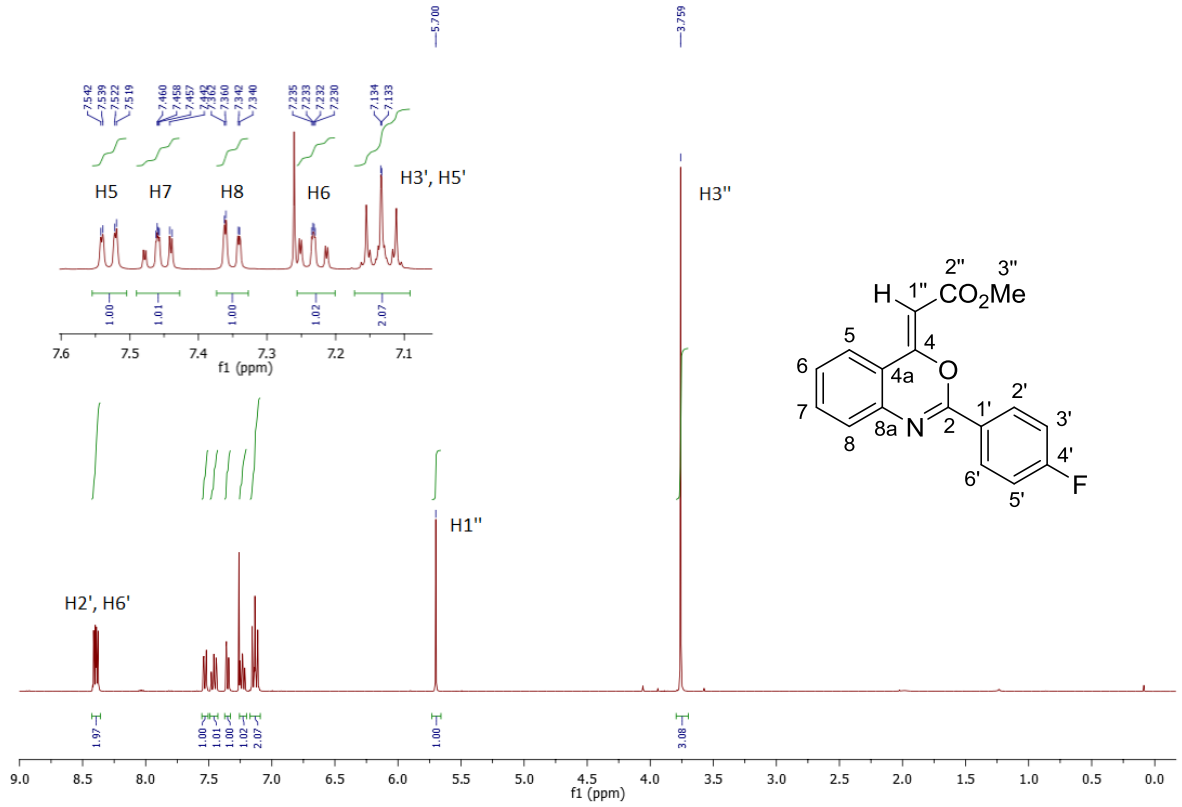


Figure 1. ^{1}H-NMR spectrum of compound **2** (400 MHz, $CDCl_3$) and related assignments.

3. Materials and Methods

Compound **1** was prepared according to procedures reported in the literature [14]. Other chemicals were obtained from commercial sources and were used without further purification. Gas chromatography analyses were performed with an Agilent Technology 7820A instrument (Agilent Technologies, Santa Clara, CA, USA) using a 30 m SE-30 capillary column. Column chromatography was carried out on silica gel (Merck, Darmstadt, Germany, 0.063–0.200 mm) and Thin-Layer Chromatography (TLC) on Merck $60F_{254}$ plates. Electron ionization (EI) mass spectra were obtained with an Agilent Technology instrument (Agilent Technologies, Santa Clara, CA, USA) working at 70 eV ionization energy. NMR spectra were recorded in $CDCl_3$, using the solvent residual signals as internal reference (7.26 and 77.00 ppm, respectively, for ^{1}H and ^{13}C) on a Bruker AVANCE 400 spectrometer (Bruker, Milan, Italy). IR spectrum was run on a Nicolet FT-IR 5700 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) paired with a Diamond Smart Orbit

accessory. Melting point was determined with an Electrothermal apparatus. Elemental analysis was performed with a Carlo Erba EA 1108-Elemental Analyzer (Carlo Erba, Milan, Italy).

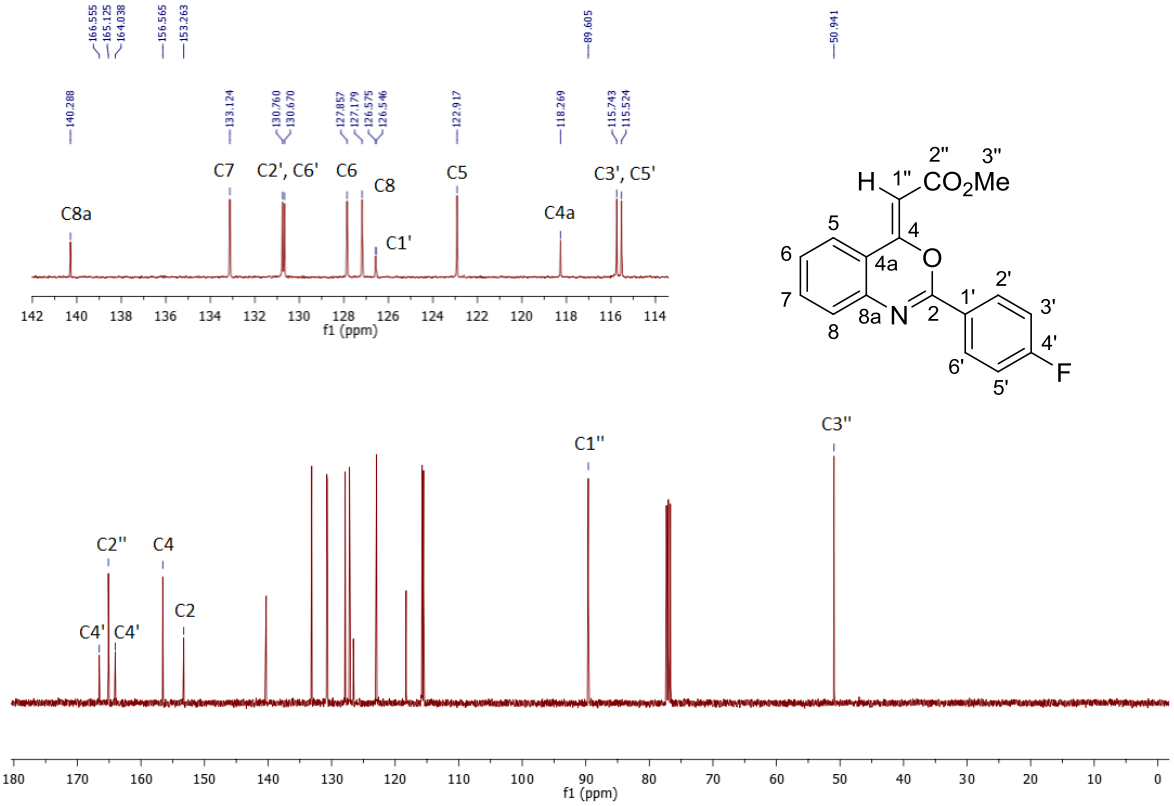


Figure 2. ^{13}C-NMR spectrum of compound **2** (100 MHz, $CDCl_3$) and related assignments.

The reaction in Scheme 1 was carried out in a 45 mL stainless steel autoclave with magnetic stirring. The autoclave was charged in the presence of air with amide **1** (0.31 g, 1.00 mmol), 10% Pd/C (0.011 g, 0.01 mmol), $[Bu_4N]I$ (0.369 g, 1.00 mmol), and $KF{\cdot}2H_2O$ (0.141 g, 1.50 mmol) in MeCN/MeOH (7/1 *v*/*v*, 5 mL). The autoclave was pressurized with CO (18 bar) and air (6 bar), reaching a total pressure of 24 bar at room temperature, and then heated with stirring for 24 h at 65 °C. After cooling, the autoclave was degassed, the solvent was evaporated under vacuum, and the residue was filtered through a short SiO_2 column using CH_2Cl_2 as eluent. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate 9:1 as eluent. Yield: 0.202 g (68% based on starting **1**). Pale yellow solid, mp 143–146 °C. IR (ATR diamond, cm^{-1}): ν = 2947 (w), 1714 (s), 1651 (s), 1608 (m), 1591 (m), 1507 (m), 1473 (m), 1276 (m), 1239 (m), 1147 (s), 1120 (m), 1089 (m), 761 (m); ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.44–8.36 (m, 2H, H2′, H6′), 7.53 (dd, *J* = 7.9, 1.2 Hz, 1H, H5), 7.46 (ddd, *J* = 8.0, 7.3, 1.3 Hz, 1H, H7), 7.35 (dd, *J* = 8.0, 0.9 Hz, 1H, H8), 7.23 (ddd, *J* = 8.0, 7.3, 1.3 Hz, 1H, H6), 7.17–7.09 (m, 2H, H3′, H5′), 5.70 (s, 1H, H1′′), 3.76 (s, 3H, H3′′); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 165.30 (d, *J* = 251.7 Hz, C4′), 165.12 (C2′′), 156.56 (C4), 153.26 (C2), 140.29 (C8a), 133.12 (C7), 130.71 (d, *J* = 9.1 Hz, C2′, C6′), 127.86 (C6), 127.18 (C8), 126.56 (d, *J* = 2.9 Hz, C1′), 122.92 (C5), 118.27 (C4a), 115.63 (d, *J* = 22.0 Hz, C3′, C5′), 89.60 (C1′′), 50.94 (C3′′); GC-MS: *m*/*z* = 297 (100) [M+], 266 (27), 252 (32), 239 (24), 224 (35), 210 (25), 183 (46); anal. calcd for $C_{17}H_{12}FNO_3$: C, C, 68.68; H, 4.07; F, 6.39; N, 4.71; O, 16.15; found C, 68.84; H, 4.01; N, 4.76.

Supplementary Materials: 1D and 2D NMR spectra are available online at www.mdpi.com/1422-8599/2017/1/M927.

Acknowledgments: This work was supported by University of Parma. The facilities of "Centro Interfacoltà di Misure"(University of Parma) were used for recording NMR spectra.

Author Contributions: N.D., M.C. and B.G. conceived and designed the experiments; F.P. performed the experiments; R.M. analyzed and confirmed the data analysis; E.M. performed and interpreted the 2D NMR experiments; N.D. wrote the paper.

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

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