

Short Note

4'-Methyl-2'-(quinolin-8-ylcarbamoyl)-biphenyl-4-carboxylic Acid Ethyl Ester

Hamad H. Al Mamari *  and Anfal Al Hasani

Department of Chemistry, College of Science, Sultan Qaboos University, PO Box 36, Al Khoudh, PC 123 Muscat, Oman; s116398@student.squ.edu.om

* Correspondence: halmamari@squ.edu.om; Tel.: +968-24142472; Fax: +968-24141469

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Abstract: In this short note communication, we report the synthesis of a novel amide 4'-methyl-2'-(quinolin-8-ylcarbamoyl)-biphenyl-4-carboxylic acid ethyl ester by the Ru-catalyzed C(sp²)-H bond arylation reaction. The catalytic C-H bond functionalization reaction was employed, amongst other reaction reagents and conditions, [RuCl₂(*p*-cymene)]₂ as a precatalyst and (*p*-tol)₃P as a ligand. The arylation product was characterized by various spectroscopic methods (¹H NMR, ¹³C NMR, IR, GC-MS, and IR spectroscopy), and its composition was confirmed by elemental analysis.

Keywords: organic synthesis; catalysis; bidentate directing groups; benzamides; chelation assistance; C-H bond functionalization

1. Introduction

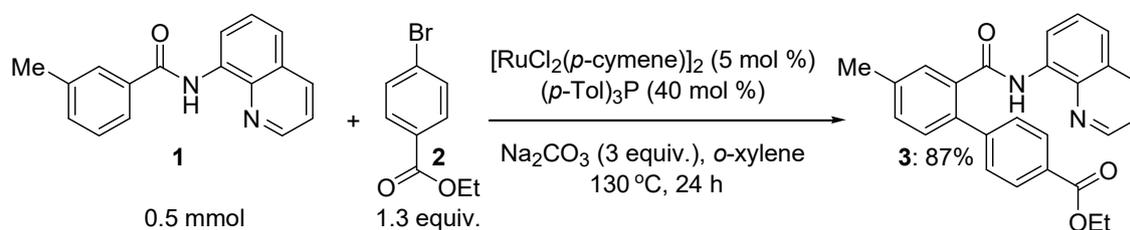
Functionalization of C-H bonds has emerged as a powerful method for the construction of chemical bonds [1,2]. The strategy is centered on the functionalization of otherwise inert or nonreactive C-H bonds that are ubiquitous in nature. Therefore, C-H bond functionalization chemical science allows rapid access of target functional bonds or desired molecules from simple starting materials. Hence, it could reduce materials, reagents, conditions, and ultimately, the number of steps required to achieve target molecules using conventional methods, a demonstration of step economy. Given the abundance of C-H bonds in nature, functionalization science could result in a reduction of waste and a reduction of the emission of noxious substances into the environment. Therefore, functionalization of C-H bonds could be green and environmentally benign. Given the abundance of C-H bonds in molecules, controlling which C-H bond to be functionalized (or site-selectivity) remains a significant challenge for the scientific community. One approach is to control or circumvent the site-selectivity to use groups that can direct the functionalization of C-H bonds to occur at a specific site or position [3,4]. The essence of directing groups is the utilization of their Lewis basic properties toward the reaction with a Lewis acidic metal, by which the C-H bond functionalization is catalyzed. Lewis basic directing groups coordinate Lewis acidic metals, bringing them in proximity to C-H bonds to be functionalized. The regiocontrol provided by directing groups is determined by the thermodynamic stability of the reaction intermediate, cyclometalated complexes, or chelates [5]. The thermodynamic stability of an appropriately sized chelate or cyclometalated complex determines which C-H bond undergoes cleavage and thus C-H functionalization. The use of directing groups, via chelation assistance, is demonstrated by monodentate and bidentate directing groups via a mono-chelate or bis-chelate respectively [6–8].

C-H bond functionalization is typically catalyzed by transition metals with second row transition metals such as Pd [9,10], Rh [11,12], and Ru [13], which are established as metal catalysts for the reaction. The use of first row transition metals such as Ni [14,15], Fe [16], and Mn [17,18] is also established. The use of 8-aminoquinoline as a directing group in metal-catalyzed C-H bond functionalization is now well developed [7,8]. In 2013, Chatani et al. disclosed a pioneering Ru-catalyzed C(sp²)-H bond

arylation using 8-aminoquinoline as a directing group [19]. In the reported work, $[\text{RuCl}_2(p\text{-cymene})]_2$ was used as a precatalyst and PPh_3 as a ligand. It is also reported that the latter was essential for the reaction as no reaction was observed without it [19]. In the continuation of our program [20–23] of the development of directed metal-catalyzed C-H bond functionalization, we wish to report herein the synthesis of a novel amide '4'-methyl-2'-(quinolin-8-ylcarbamoyl)-biphenyl-4-carboxylic acid ethyl ester' by the Ru-catalyzed $\text{C}(\text{sp}^2)\text{-H}$ bond arylation reaction. The functionalization method employed $[\text{RuCl}_2(p\text{-cymene})]_2$ as a precatalyst and $(p\text{-tol})_3\text{P}$ as a ligand.

2. Results

The requisite starting amide, 3-methylbenzamide bearing 8-aminoquinoline as a directing group (**1**) was prepared according to literature procedures from the corresponding acid chloride [19,24]. The benzamide was then subjected to the Ru-catalyzed C-H bond arylation conditions. Thus, amide (**1**) was reacted with ethyl 4-bromobenzoate upon treatment with $[\text{RuCl}_2(p\text{-cymene})]_2$ (5 mol %) as a precatalyst and $(p\text{-tol})_3\text{P}$ (40 mol %) as a ligand in the presence of Na_2CO_3 (3 equiv.) as a base (Scheme 1).



Scheme 1. Ru-catalyzed C-H bond arylation of amide **1** to afford the target arylation product **3**.

The Ru-catalyzed $\text{C}(\text{sp}^2)\text{-H}$ bond monoarylation successfully took place at the *ortho* position with respect to the amide, to afford the desired arylation product (**3**) in a decent 87% yield. No double-arylation product was observed. The arylation product (**3**) was then characterized by various spectroscopic methods (^1H NMR, ^{13}C NMR, GC-MS, and IR spectroscopy, Supplementary Materials). The elemental composition of the product was analyzed by elemental analysis.

3. Discussion

While the reported Ru-catalyzed $\text{C}(\text{sp}^2)\text{-H}$ arylation reaction by Chatani et al. employed $[\text{RuCl}_2(p\text{-cymene})]_2$ as a precatalyst and PPh_3 as a standard phosphine ligand, the present Ru-catalyzed $\text{C}(\text{sp}^2)\text{-H}$ bond arylation reaction, reported herein (Scheme 1), employed $(p\text{-tol})_3\text{P}$ as a ligand with $[\text{RuCl}_2(p\text{-cymene})]_2$. This is a demonstration that substituted triphenylphosphines can also promote the reaction. The electron-rich phosphine ligand has proven to be successful and efficient in promoting the Ru-catalyzed arylation reaction presented. Given the fact that the arylation product (**3**) obtained was new, there was no direct comparison with literature reports given herein. However, Chatani et al. reported that the 3-methylbenzamide bearing 8-aminoquinoline (**1**) underwent Ru-catalyzed $\text{C}(\text{sp}^2)\text{-H}$ bond arylation with bromobenzene using $[\text{RuCl}_2(p\text{-cymene})]_2$ as a precatalyst and PPh_3 as a ligand, to give the corresponding arylation product in a 74% yield [19]. A similar electron-deficient aryl bromide, methyl 4-bromobenzoate under Ru-catalyzed C-H arylation reaction with a 3-phenylbenzamide bearing 8-aminoquinoline, was also reported by Chatani et al. [19]. The arylation product was obtained in a 78% yield [19].

4. Materials and Methods

General Methods

All chemicals, reagents, and solvents were purchased from chemical companies (Sigma-Aldrich Chemie GmbH, Taufkirchen, Germany) and were used as received without prior purification. Reactions

that required dry conditions were performed in an inert atmosphere with Ar gas. Syringes and needles for the transfer of reagents were oven dried and cooled in a desiccator over silica gel before use. The reaction's progress was monitored by thin-layer chromatography (TLC) on glass plates pre-coated with Merck silica gel. TLC plates were examined under UV lamplight (UVGL-58 Handheld 254/365 nm). Büchi-USA rotary evaporators were used to evaporate solvents using appropriate temperatures. Flash column chromatography was performed using silica gel (Kieselgel) (70–230) mesh as an adsorbent. The purified products were characterized using NMR (^1H NMR, ^{13}C NMR), IR, mass spectra, and melting point analyses. Melting points were recorded on the Gallenkamp-MPd350.bm2.5 melting point apparatus (Gallenkamp, Kent, U.K.). Attenuated total-reflectance IR spectra were recorded on pure samples on Agilent Technologies Cary 630 FTIR (Agilent, Santa Clara, CA, USA). ^1H NMR spectra were recorded in CDCl_3 on JEOL ECX-400 spectrometers (JEOL Ltd., Tokyo, Japan). ^1H NMR chemical shifts (δ) were assigned in parts per million (ppm) downfield using an internal standard trimethylsilane (TMS) and were referenced to CDCl_3 , $\delta = 7.24$. Abbreviations s, d, t, q, quin, sept, and m refer to singlet, doublet, triplet, quartet, quintet, septet, and multiplet, respectively. Chemical shifts in ^{13}C spectra (175 MHz) were quoted in ppm and referenced to the central line of the CDCl_3 triplet, $\delta \text{ C } 77.0$. Coupling constants (J) were recorded in hertz (Hz). GC-MS spectra were obtained using an Agilent mass spectrometer (Agilent, Santa Clara, CA, USA). Elemental analysis was performed using an EuroEA Elemental Analyzer (configuration CHN (EuroVector Instruments & Software, Milano, Italy) with a calibration type of K-factor.

4'-Methyl-2'-(quinolin-8-ylcarbamoyl)-biphenyl-4-carboxylic acid ethyl ester (3), *3-Methyl-N-(quinolin-8-yl)benzamide (1)* [19,24] (0.131 g, 0.499 mmol), *ethyl-4-bromobenzoate (2)* (100 μL , 0.612 mmol), Na_2CO_3 (0.160 g, 1.51 mmol), $[\text{RuCl}_2(p\text{-cymene})]_2$ (5 mol %), and $\text{P}(p\text{-Tol})_3$ (60.9 mg, 0.200 mmol, 40 mol %) were added to *o*-xylene (3 mL) in an oven-dried Schlenk tube under Ar atmosphere. The reaction mixture was stirred for 24 h at 130 $^\circ\text{C}$. The reaction was quenched with saturated NH_4Cl (5 mL). The mixture was extracted with CH_2Cl_2 (3 \times 10 mL). The combined organic extracts were dried over anhydrous MgSO_4 and filtered. Concentration under reduced pressure gave a crude product, which was purified by flash chromatography (SiO_2) using hexane:EtOAc (4:1) to give the C-H arylation product (**3**) as a white solid; $R_f = 0.4$ (hexane:EtOAc (1:1)); mp = 176–177 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ (ppm) 9.66 (s, 1H), 8.74 (dd, $J = 7.2, 1.8$ Hz, 1H), 8.60 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.08 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.89 (d, $J = 8.6$ Hz, 2H), 7.66 (dd, $J = 12.0, 6.9$ Hz, 1H), 7.59 (d, $J = 8.6$ Hz, 2H), 7.56–7.30 (m, 5H), 4.25 (q, $J = 7.1$ Hz, 2H), 2.53 (s, 3H), 1.29 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ (ppm) = 168.0, 166.5, 148.2, 145.1, 138.7, 136.8, 136.3, 136.1, 134.2, 132.2, 132.1, 130.2, 129.6, 129.4, 129.3, 128.8, 128.7, 128.5, 127.9, 127.6, 127.4, 122.0, 121.6, 60.9, 19.9, 14.4. IR (neat) (cm^{-1}): 3325, 2925, 2850, 1725, 1676, 1600, 1525, 1487, 1275. MS (ESI) m/z (relative intensity): 410 (50), 365 (10), 267 (15), 221 (7), 195 (100), 165 (47), 144 (15), 89 (6), 55 (3). Elemental analysis, calculated: C (76.08), H (5.40), N (6.82), found: C (75.70), H (5.71), N (6.76).

5. Conclusions

The title compound, *4'-methyl-2'-(quinolin-8-ylcarbamoyl)-biphenyl-4-carboxylic acid ethyl ester (3)*, was synthesized by Ru-catalyzed C(sp²)-H bond arylation of 3-methylbenzamide bearing 8-aminoquinoline as a directing group, with ethyl 4-bromobenzoate. The reaction employed $[\text{RuCl}_2(p\text{-cymene})]_2$ as a precatalyst with the (*p*-tol)₃P ligand and Na_2CO_3 as a base. The desired monoarylation product, the title compound (**3**), was obtained in a highly regioselective manner with an 87% yield. The structure of the arylation product was characterized by various spectroscopic methods (^1H NMR, ^{13}C NMR, GC-MS, and IR spectroscopy), and its composition was confirmed by elemental analysis measurements.

Supplementary Materials: The following are available online, Figure S1: ^1H NMR of the title compound, Figure S2: ^{13}C NMR of the title compound, Figure S3: IR of the title compound, Figure S4: GC-MS of the title compound.

Author Contributions: A.A.H. carried out all experimental work under the supervision of H.H.A.M. All authors have read and agreed to the published version of the manuscript.

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

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