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Manjeera Yalavarty [a], Courtney M. Paradise [a], Travis A. L. Klein [a] & D. Howard Miles [a]

[a] Natural Products Research Laboratory, Department of Chemistry, University of Central Florida, Orlando, Florida, USA

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COPPER-CATALYZED CROSS-COUPLING REACTIONS OF METHYL 13-IODO-O-METHYLPODOCARPATE AND ALCOHOLS

Manjeera Yalavarty, Courtney M. Paradise, Travis A. L. Klein, and D. Howard Miles
Natural Products Research Laboratory, Department of Chemistry, University of Central Florida, Orlando, Florida, USA

Copper iodide was utilized as a relatively inexpensive catalyst for the synthesis of podocarpic acid ether derivatives in excellent yields through the one-step cross-coupling reaction of methyl 13-iodo-O-methylpodocarpate with alcohols.

Keywords: Aryl ethers; copper(I) iodide; methyl 13-iodo-O-methylpodocarpate; podocarpic acid

INTRODUCTION

The goal of this work was to synthesize novel ether derivatives of podocarpic acid at the C-13 aromatic position. In regard to the synthesis of aryl ethers, it is known that aromatic ethers can be prepared from aryl halides.[1] The most general synthesis of diaryl ethers, which has the disadvantage of requiring strong reaction conditions, has been the copper-mediated Ullmann coupling of aryl bromides and aryl iodides with phenols.[2] Goldberg[3] also used a copper catalyst to study the formation of ethers from aryl bromides. However, the yields were poor, separations were difficult, and high temperatures were required (200 °C). Thus, a search for more optimal reaction conditions was needed.

Palladium has been utilized as a catalyst for the formation of ethers at moderate temperatures and has resulted in relatively good product yield.[4] However, the palladium catalyst is expensive, and for this reason, a search was conducted for an inexpensive copper catalyst[5,6] for the coupling of an aryl halide with an alcohol that would yield an aryl ether. The advantages of a copper catalyst are that it is not only cheap but also can be used in versatile conditions such as in the presence of moisture or oxygen. For these reasons, this study utilized a copper catalyst for the synthesis of novel ether derivatives of podocarpic acid.

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Address correspondence to D. Howard Miles, Natural Products Research Laboratory, Department of Chemistry, University of Central Florida, Orlando, FL 32816, USA. E-mail: dhmiles@pegasus.cc.ucf.edu

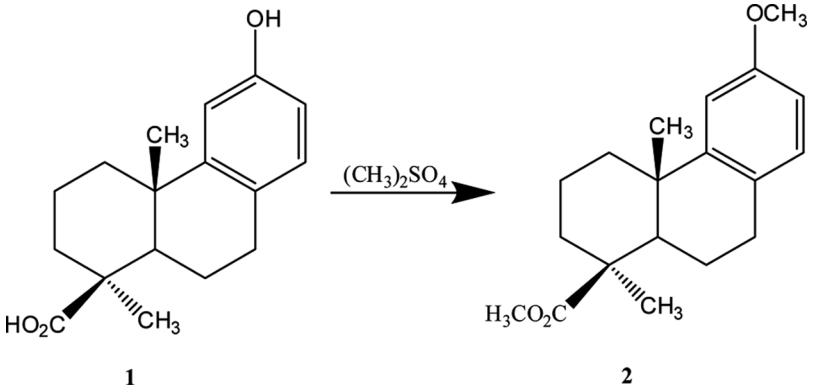
RESULTS AND DISCUSSION

The first step toward achieving the goal of the synthesis of novel C-13 ether derivatives of podocarpic acid involved the methylation of podocarpic acid (**1**)[6] (Scheme 1) to form methyl O-methylpodocarpate (**2**). This process resulted in the formation of the desired compound **2** in 84% yield with a melting point of 127 °C. The infrared (IR), NMR, and mass spectra (MS) of compound **2** were identical with those of an authentic sample of methyl O-methylpodocarpate (**2**).[7]

The formation of methyl 13-iodo-O-methylpodocarpate (**3**) in 94% yield (melting point of 149 °C) was achieved by the reaction of iodine with methyl O-methylpodocarpate (**2**) as shown in Scheme 2. The IR, NMR, and MS data of compound **3** were identical with those of an authentic sample of methyl 13-iodo-O-methylpodocarpate (**3**).[8]

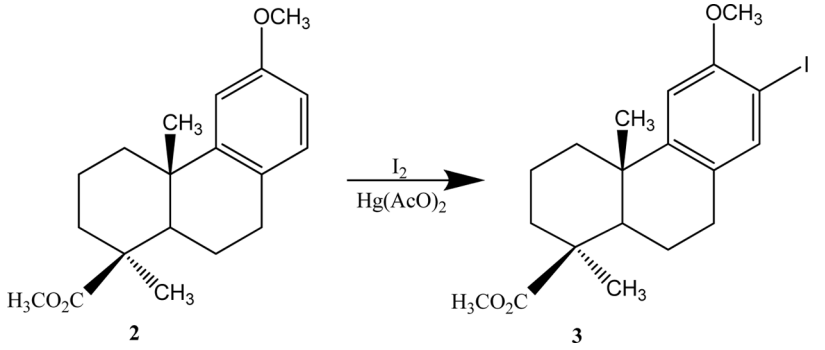
As shown in Scheme 3, the novel derivatives of compound **3** (compounds **4**, **5**, and **6**) were synthesized via the reaction of methyl 13-iodomethylpodocarpate (**3**) with aliphatic alcohols using copper(I) iodide catalyst. The general procedure involved the utilization of 1 molar equivalents of compound **3** with 1.5 molar equivalents of the corresponding alcohol, 0.1 molar equivalents of copper(I) iodide, and 2 molar equivalents of potassium carbonate. This mixture was then refluxed in N,N-dimethylformamide for 4 h. The alcohols utilized were methanol, ethanol, and 1-propanol, and the resulting yields for compounds **4**, **5**, and **6** were 84, 88, and 84% respectively.

The structures of derivatives **4**, **5**, and **6** were determined through the utilization of MS, IR, and NMR analysis. The IR spectrum of compounds **4**, **5**, and **6** gave signals at 1730 cm^{-1}, which corresponded to the methyl ester they all have in common. The signals at 1450, 1490, and 1600 cm^{-1} confirmed the presence of an aromatic ring in the aryl ether derivatives, whereas a signal at 1200 cm^{-1} corresponded to the C-O bond present in the ether and ester functionalities that are present in all three compounds. High-resolution mass spectra (HRMS) confirmed the molecular ions of compounds **4, 5**, and **6** to be, respectively, 332.4243, 346.4404, and 360.4756. These results are consistent with the formulas of $C_{20}H_{28}O_4$(332.4240), $C_{21}H_{30}O_4$ (346.4500), and $C_{22}H_{32}O_4$ (360.4760) respectively.



1 **2**

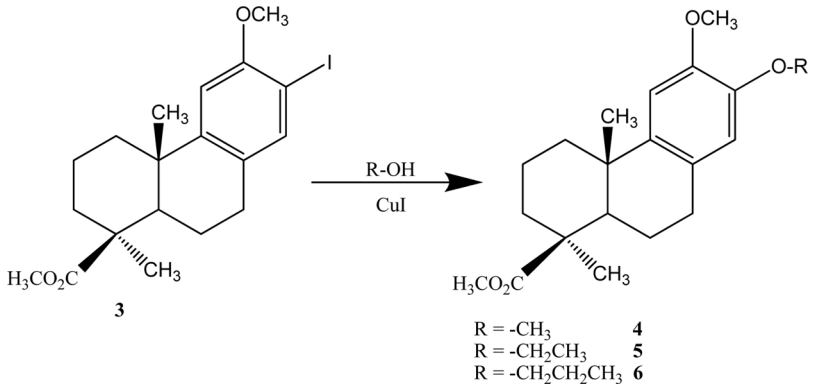
Scheme 1. Formation of methyl O-methylpodocarpate.



Scheme 2. Formation of methyl 13-iodo-O-methylpodocarpate.

In comparison to the data of compound **3**, the ^{1}H NMR spectra of compound **4** indicated that the C-13 aryl hydrogen had disappeared and that an additional 3H peak was present at δ 3.62 ppm as a singlet. This information corresponds to the presence of the desired methoxy group at the C-13 position of compound **4**. Also, in comparison with the NMR data for compound **3**, the spectra of compound **5** gave a new signal at δ 3.98 ppm (q), which could be assigned to the CH_2-O moiety that is present in compound **5** at the C-13 aryl position. Additionally, a methyl group appeared as a triplet at δ 1.33 ppm. Thus, the presence of a triplet and quartet along with the chemical shift value of the quartet indicated that the desired ethoxy group was present. The NMR for compound **6** (in comparison with compound **3**) indicated that a propoxy group was present at the C-13 position. This is supported both by the absence of the C-13 aromatic proton and the presence of the signals expected for a propoxy group (3H signal at 1.10 ppm as a triplet, 2H signal at 1.75 ppm as a sextet, and a 2H signal at δ 1.10 ppm as a triplet).

The ^{13}C NMR spectrum of compound **4** gave a signal at δ 57.2 ppm corresponding to the methoxy group at C-13 of compound **4**. The spectrum for compound **5** showed new signals at δ 65.0 ppm and δ 14.8 ppm, which corresponded to the CH_2-O and CH_3 moieties of the ethoxy group. The C-13 NMR spectrum of



Scheme 3. General reaction for the formation of novel ethers of podocarpic acid.

compound **6** showed signals at δ 73.5, 22.7, and 14.2 ppm for the carbons in the desired propoxy group.

In summary, the reaction of methyl 13-iodo-O-methylpodocarpate (**3**) with aliphatic alcohols gave ether derivatives of podocarpic acid in good yield. Thus, this work provides a new and efficient method of synthesizing ether derivatives of podocarpic acid that will be evaluated for their potential as new drug leads for the treatment of tuberculosis and cancer.

EXPERIMENTAL

Preparation of Methyl-O-methylpodocarpate (2)

Podocarpic acid (25 g) was weighed into a 300-mL beaker to which 25 g of ice were added. Methanol (25 ml) was then added to the beaker, and the resulting mixture was stirred while 12 g of sodium hydroxide pellets were added. After continually stirring this solution to completely dissolve the podocarpic acid and sodium hydroxide, it was cooled to 15 °C in an ice bath. Next, 21.5 mL of dimethyl sulfate was added to the cooled solution over a period of 1 h.[4] The solution solidified, but stirring was continued for an additional 30 min. Additional water (50 mL) was added, and the solid material was removed by filtration. The solid was then dried to obtain 22 g of a white solid. This solid was recrystallized to obtain 20 g of methyl O-methylpodocarpate (**2**) with a melting point of 125 °C (82% yield). IR ($CHCl_3$): 3000, 2950, 2900, 2860, 1720, 1600, 1540, 1490, 1460, 1400, 1360, 1300, 1240, 1200, 1190, 1150, 1060, 1020, 950, 760, 740. ^{1}H NMR: (300 MHz): 6.95 (d), 6.8 (s), 6.65 (d), 3.85 (s), 3.65 (s), 2.8 (m), 2.25 (m), 1.95 (m), 1.6 (m), 1.5 (m), 1.4 (m), 1.22 (m), 1.2 (s), 1.15 (m), 1.05 (m), 1.00 (s) ppm. ^{13}C NMR (300 MHz): 178, 158, 150, 130, 128, 114, 112, 56, 52, 51, 44, 39.5, 38, 31, 28, 25, 22.5, 20.5, 20 ppm. MS: 302 (44), 287 (6), 228 (16), 227 (100), 173 (6), 170 (23), 147 (10), 121 (6), 91 (4).

Preparation of Methyl 13-Iodo-O-methylpodocarpate (3)

Three g of methyl-O-methylpodocarpate (**2**) were weighed, transferred into a 500-mL volumetric flask, and then dissolved in 60 mL of acetic acid. In a separate beaker, 2 g of mercury(II) acetate were weighed and dissolved in 60 mL of acetic acid. This solution was then added to the flask containing compound **2**. The resulting solution was heated to 70 °C and stirred for 15 min. A solution of iodine was prepared by dissolving 7.6 g of iodine in 240 mL of warm acetic acid. This iodine solution was then added dropwise over a period of 45 min into the flask while the temperature was maintained at 70 °C. The solution was then filtered, and the resulting filtrate was added into 500 mL of cold water in a 1-L beaker. A precipitate formed and was removed by filtration to give 3 g of crude product **3**. This material was recrystallized from acetone to obtain 2 g of pure compound **3** with a melting point of 149 °C and yield of 95%. IR: 3000, 2940, 2850, 2400, 1720, 1600, 1495, 1470, 1440, 1390, 1350, 1300, 1250, 1200, 1150, 1050, 950, 900, 800, 750, 650 cm^{-1}. ^{1}H NMR (300 MHz): 7.45 (s), 6.65 (s), 3.95 (s), 3.85 (s), 2.70 (m), 2.20 (m), 1.95 (m), 1.6 (m), 1.5 (m), 1.25 (s), 1.15 (m), 1.02 (s), 0.95 (m) ppm. ^{13}C NMR (300 MHz): 178, 156, 150, 140, 131, 108, 83, 56.5, 52.5, 52, 44,

39, 38.5, 32, 31.5, 29.5, 23, 21, 20 ppm. HRMS: 428 (100), 413 (8), 381 (3), 368 (3), 353 (77), 313 (4), 287 (6), 272 (6), 227 (15), 211 (4), 172 (6), 140 (5), 129 (8), 115 (6), 101 (2), 91 (2).

General Procedure for the Preparation of Ethers 4–6

Methyl 13-iodo-O-methylpodocarpate (2.14 g) was weighed into a 100-mL, round-bottom flask and dissolved in 0.32 g of N,N-dimethylformamide. In addition, 0.405 g of sodium methoxide was added to 1.5 molar equivalents of the three respective alcohols in a separate beaker. The solution in the beaker was then added to the solution in the round-bottom flask. The resulting solution in the round-bottom flask was heated using a heating mantle with continuous stirring until the temperature of the solution reached 110 °C, at which time 0.1 g copper(I) iodide was added. A condenser was connected, and the solution was refluxed at 110 °C for 4 h while monitoring the reaction with thin-layer chromatography (TLC). After the completion of the reaction, the solution was allowed to cool. The precipitate formed and was filtered. The precipitate was washed with 100 mL ethyl acetate. The filtrate was evaporated to obtain either solid compound **4**, **5**, or **6**.

The first aryl ether derivative (**4**) was obtained in 84% yield (1.30 g) with a melting point of 143 °C. IR: 3000, 2940, 2850, 2400, 1720, 1600, 1495, 1470, 1440, 1390, 1350, 1300, 1250, 1200, 1150, 1050 cm^{-1}. ^{1}H NMR (300 MHz): 7.52 (s), 7.32 (s), 6.73 (s), 3.95 (s), 3.85 (s), 3.62 (s), 2.80 (m), 2.28 (m), 2.02 (m), 1.64 (m), 1.30 (s), 1.22 (s), 0.81 (s) ppm. ^{13}C NMR (300 MHz): 178, 158, 151, 148, 146.1, 132, 110.5, 57.2, 52, 50.2, 44.3, 38, 36, 30, 28, 22, 20, 18 ppm. MS: 333.4 (30), 332 (14), 302.4 (82), 220.3 (18), 155.1 (100).

Compound **5** was obtained in 88% yield (1.42 g) with a melting point of 146 °C. IR: 3000, 2940, 2850, 2400, 1720, 1600, 1495, 1470, 1440, 1390, 1350, 1300, 1250, 1200, 1150, 1050 cm^{-1}. ^{1}H NMR (300 MHz): 7.45 (s), 7.25 (s), 4.04 (m), 3.95 (s), 3.85 (s), 2.80 (m), 2.28 (m), 2.02 (m), 1.64 (m), 1.30 (s), 1.22 (s), 0.81 (s) ppm. ^{13}C NMR (300 MHz): 178, 150, 142, 140, 132, 108, 106, 65.2, 56, 52.2, 44.3, 40, 36, 30, 28, 22, 20, 18, 14 ppm. MS: 347.4 (25), 346 (10), 302.4 (58), 220.3 (18), 155.1 (100).

Compound **6** was obtained in 84% yield (1.41 g) with a melting point of 148 °C. IR: 3000, 2940, 2850, 2400, 1720, 1600, 1495, 1470, 1440, 1390, 1350, 1300, 1250, 1200, 1150, 1050 cm^{-1}. ^{1}H NMR (300 MHz): 6.82 (s), 6.73 (s), 4.01 (m), 3.95 (s), 3.85 (s), 3.12 (m), 1.80 (m), 1.60 (m), 1.40 (s), 1.02 (s), 0.81 (s) ppm. ^{13}C NMR (300 MHz): 178, 146, 144, 142, 132, 110.5, 108.2, 70.4, 58, 53.8, 52, 44.3, 38, 36, 32, 30, 28, 22, 20, 19, 18, 14 ppm. MS: 361.2 (16), 360 (5), 302 (68), 220.3 (18), 155.1 (100).

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