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Copper-Catalyzed Cross-Coupling Reactions of Methyl 13-Iodo-O-methylpodocarpate and Amides

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Abstract: Copper iodide was utilized as a relatively inexpensive catalyst (versus palladium) for the high-yield synthesis of amide derivatives of podocarpic acid. The reaction involved the one-step cross-coupling reaction of methyl 13-iodo-O-methylpodocarpate with amides.

Keywords: Aryl amides, copper(I) iodide, methyl O-methylpodocarpate, podocarpic acid

INTRODUCTION

Amines and amides are of great interest in organic synthesis because many compounds in this class have biological activity.[1,2] The synthesis of amides is also an important step for many intermediate organic molecules including natural product derivatives.[3] Metal catalysts have been employed for synthesis of aryl amines. Wolfer and Buchwald first synthesized aryl amines by the utilization of palladium-catalyzed reactions of primary amines and aryl iodides.[4] These investigators later utilized an 18-crown-6 catalyst to improve the yield of the amine products.[5] Applications of the cross-coupling reaction between aryl halides and amines have also been performed in the pharmaceutical

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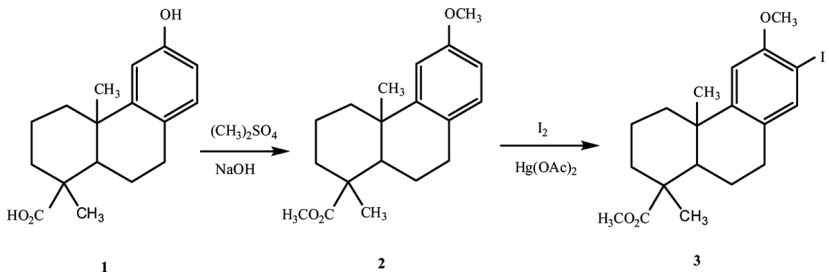
industry through the utilization of a palladium catalyst.[6] It is logical that metal-catalyzed cross-coupling reactions could be extended to aryl halides and amides. Thus, this work involved the synthesis of amide derivatives of podocarpic acid by an alternative methodology that utilized an inexpensive copper-mediated catalyst.[7] The generality of the methodology for the cross-coupling reaction of aryl iodides and amides was demonstrated by its application to the synthesis of seven novel amide derivatives of methyl O-methylpodocarpate.

RESULTS AND DISCUSSION

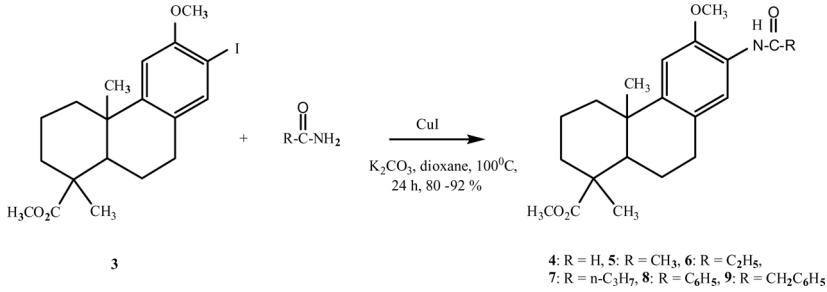
Methyl 13-iodo-O-methylpodocarpate (**3**) was synthesized in 71% overall yield from podocarpic acid (**1**) (Scheme 1). This conversion involved the methylation of podocarpic acid (**1**) in 82% yield by the utilization of dimethyl sulfate in sodium hydroxide solution. The resulting product was identical to methyl O-methylpodocarpate (**2**) upon comparison with the melting point, IR, NMR, and mass spectra with an authentic sample of compound **2**.[8] Methyl O-methylpodocarpate (**2**) was iodinated in 86% yield by treatment with iodine in mercury(II) acetate to give compound **3**, as was confirmed by NMR, IR, and high-resolution mass spectroscopic (HRMS) analysis. The high-resolution mass spectrum showed a molecular ion at 428.0844, which was consistent with the assigned molecular formula of $C_{19}H_{25}IO_3$. The IR spectrum showed an additional absorption for a C−I bond in the fingerprint region at 650 cm^{-1}. Of special significance was the disappearance of the proton attached to carbon 13 that was present in the starting material (compound **2**) at 6.80 δ and the downfield shift of carbon 13 from 131 ppm to 140 ppm in the ^{13}C NMR.

The seven novel amide derivatives of compound (**3**) (compounds **4–10** in Schemes 2 and 3) were synthesized by the reaction of methyl



1 2 3

Scheme 1. Synthesis of methyl 13-iodo-O-methylpodocarpate.

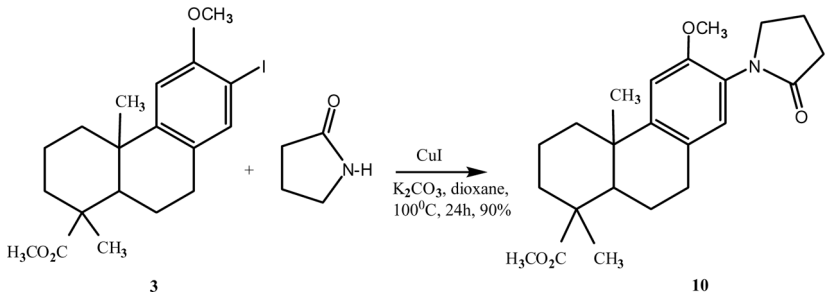


Scheme 2. Synthesis of amide derivatives of methyl O-methylpodocarpate.

13-iodo-O-methylpodocarpate (**3**) with amides using copper(I) iodide catalyst and potassium carbonate in dioxane under reflux at 100 °C for a period of 24 to 48 h. The amides utilized were formamide, acetamide, propionamide, butyramide, benzamide, benzylamide, and 2-pyrrolidinone.

N,N′-dimethylethylenediamine was used in this reaction as a ligand in order to dissolve the copper(I) iodide catalyst. The yields for compounds **4–10** were 82, 84, 81, 81, 80, 92, and 90% respectively.

The structures of the derivatives were determined through the utilization of MS, IR, and NMR analysis. HRMS confirmed the molecular ions of compounds **4–10** respectively as 345.1927, 359.2096, 373.2264, 387.2411, 421.2253, 435.2410, and 385.2253. These results were consistent with the formulas of $C_{20}H_{27}NO_4$, $C_{21}H_{29}NO_4$, $C_{22}H_{31}NO_4$, $C_{23}H_{33}NO_4$, $C_{26}H_{31}NO_4$, $C_{27}H_{33}NO_4$, and $C_{23}H_{31}NO_4$ respectively. The IR spectra for all of the derivatives (except compound **10,** which is a tertiary amide) showed (in addition to those absorptions shown in the starting compound **3**) a single absorption for a secondary amide at 3400 cm^{-1} and an absorption in the range of 1640–1680 cm^{-1} for the amide carbonyl group.



Scheme 3. Synthesis of methyl 13-pyrrolidinone-O-methlpodocarpate.

The ^{1}H NMR spectra for derivatives **4**–**9** indicated the presence of a singlet secondary N–H proton as a singlet at 8.00 δ in addition to the signals shown for starting compound **3**. This was consistent with the formation of an amide moiety. The presence of the desired aldehyde functionality in compound **4** was indicated by a one-proton singlet at 8.42 δ. Compound **5** possessed an additional (versus starting material) 3 proton singlet at 2.20 δ, which could be assigned to a carbonyl methyl group. Compound **6** showed additional (versus starting material) overlapping multiplets at 2.35 and 1.75 δ, which integrated for a total of five protons. This is consistent with the presence of an ethyl group. The additional multiplets (versus starting material) in the proton NMR spectrum of compound **7** at 2.22 and 1.30 δ integrated for a total of seven protons, which is consistent with the presence of a propyl group. Compound **8** displayed signals at 7.5 and 7.9 δ, which is consistent with the presence of five additional aromatic protons. Compound **9** showed signals that were not present in compound **3**, at 3.7 and 7.3 δ, which integrated for two and five protons respectively. This result was consistent with the presence of two benzylic protons and five aromatic protons in compound **9**. Compound **10** possessed signals that were not present in the starting compound **3,** at 3.8 and 2.2 δ, which integrated for six protons. This is consistent with the presence of the desired pyrrolidinone moiety in compound **10**.

The ^{13}C NMR spectra showed signals for the amide carbons (in compounds **4–10)** at 160, 168, 172, 171.5, 165, 169, and 176 ppm respectively. In addition, the chemical shift of carbon 13 in all derivatives was downfield versus that shown by carbon 13 in the ^{13}C spectrum of the starting compound **3**.

In summary, amides derivatives of pododcarpic acid were synthesized in high yield by utilizing copper-catalyzed cross-coupling reactions between amides and methyl 13-iodo-O-methylpodocarpate. Thus this work provides a new and efficient method of synthesizing amide derivatives of podocarpic acid. In addition, seven novel amide derivatives of podocarpic acid were prepared, and these derivatives will be evaluated for their potential as new drug leads for the treatment of tuberculosis and cancer.

EXPERIMENTAL

Podocarpic acid (**1**) was recrystallized from methanol and dried in vacuo. IR spectra were recorded in chloroform with a Perkin-Elmer spectrometer; NMR spectra were recorded in deuterated chloroform with the utilization of Mercury 300-MHz and Varian 500-MHz spectrometers.

Preparation of Methyl O-Methylpodocarpate (2)[8]

Compound **1** (50 g of podocarpic acid) was placed in a 300-mL beaker, and 50 g of ice and then 50 mL of methanol were added. This mixture was stirred, and then 24 g of sodium hydroxide pellets were added. The resulting solution was continually stirred until the podocarpic acid (**1**) and sodium hydroxide were completely dissolved. The resulting mixture was then cooled to 15 °C in an ice-water bath. To this solution, 42.5 mL of dimethyl sulfate was added over an hour while the temperature was maintained at 15 °C. The solution was then allowed to solidified with stirring. One hundred mL of water were then added, and the resulting mixture was filtered under vacuum to obtain approximately 45 g of a white solid (yield 82%). The resulting solid was recrystallized from 2-propanol to obtain 20 g of methyl O-methylpodocarpate (**2**) as white needles with mp 125 °C. IR ($CHCl_3$): 1720, 1600, 1540, 1490, 1460, 1200, 1190, 1150 cm^{-1}. ^{1}HNMR (Mercury 300 MHz): 6.95 (d), 6.80 (d), 6.65 (d), 3.85 (s), 3.65 (d), 2.80 (m), 2.25 (m), 1.95 (m), 1.60 (m), 1.50 (m), 1.40 (m), 1.22 (m), 1.20 (s), 1.15 (m), 1.05 (m), 1.00 (s) ppm. ^{13}CNMR (Mercury 300 MHz): 178, 158, 150, 130, 128, 114, 112, 56, 52, 51, 44, 39.5, 38, 32, 28, 25, 22.5, 20.5, 20 ppm. HRMS (Finnigan spectrometer): 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)

Compound **2** (3.025 g) was weighed and transferred into a 500-mL flask and then dissolved in 60 mL of acetic acid. In a separate 250-mL beaker, 2 g of mercury(II) acetate was dissolved in 60 mL of acetic acid, which was then poured into the flask containing compound **2.** The resulting solution was equipped with a magnetic stir bar and then stirred on a hot plate at 70 °C for 15 min. A solution of iodine was prepared by dissolving 2.614 g of iodine in 240 mL of warm acetic acid in a 500-mL Erlenmeyer flask. The iodine solution was then added dropwise, with stirring, over a period of 45 min into the reaction flask while the temperature was maintained at 70 °C. This solution was stirred for an additional hour, after which it was cooled to 15 °C in an ice-water bath and filtered. The filtrate was then stirred into 500 mL of cold water in a 1-L beaker, and the resulting white precipitate was filtered to yield 3.70 g of crude product **3** (86% yield). The product was recrystallized from acetic acid to obtain 3.0 g of a white powder, mp 149 °C. IR ($CHCl_3$): 1720, 1600, 1495, 1470, 1440, 1200, 1150, 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), 1.60 (m), 1.50 (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), 227 (15), 211 (4), 172 (6), 140 (5), 129 (8), 115 (6), 101 (3), 91 (2).

General Procedure for the Preparation of Amides 4–10

To 1.5 molar equivalents of each amide in a 100-mL flask, 0.1 g of copper(I) iodide, 3.46 g of potassium carbonate, 0.1 g of N,N′-dimethylethylenediamine, and 15 mL of dioxane were added. This was followed by the addition of 2.15 g of compound **3**. After attaching a condenser, the mixture was stirred (with a magnetic stirring bar) under nitrogen while heating at 100 °C for 24 h. After cooling to room temperature, a precipitate was obtained, which was filtered and washed with 100 mL of ethyl acetate. The filtrate was evaporated under reduced pressure to yield a solid material which was further purified by open column chromatography with 63- to 200-mesh silica gel. Hexane and ethyl acetate (1:1) were used as the eluents.

Preparation of Methyl 13-Formamido-O-methylpodocarpate (4)

Formamide (0.34 g) was utilized, according to the general procedure outlined previously, to obtain 1.40 g of 13-formamido methyl O-methylpodocarpate (**4**) with mp 145 °C (yield 82%). IR ($CHCl_3$): 3410, 1700, 1640, 1620, 1520, 1480, 1460, 1420, 1220, 1150 cm^{-1}. ^{1}H NMR (300 MHz): 8.42 (s), 8.02 (s), 7.80 (s), 6.80 (m), 3.95 (s), 3.85 (s), 2.80 (m), 2.30 (m), 1.95 (m), 1.65 (m), 1.6 (m), 1.4 (m), 1.30 (s), 1.20 (s) ppm. ^{13}C NMR (300 MHz): 178, 160, 147, 145, 128, 124.5, 120.5, 117.5, 56, 53, 44.5, 40, 39, 38, 32, 29, 23, 21.5, 20 ppm. HRMS: 346 (48), 345 (12), 302 (82), 300 (43), 219 (24), 154 (100).

Preparation of Methyl 13-Acetamido-O-methylpodocarpate (5)

Acetamide (0.45 g) was utilized, according to the general procedure outlined previously, to provide 1.50 g of methyl 13-acetamido-O-methylpodocarpate (**5**) with mp 157 °C in 84% yield. IR ($CHCl_3$): 3400, 1710, 1680, 1600, 1580, 1520, 1470, 1450, 1240, 1220, 1180, 1140, 1070 cm^{-1}. ^{1}H NMR (300 MHz): 8.00 (s), 7.65 (s), 6.70 (s), 3.95 (s), 3.85 (s), 2.80 (m), 2.20 (m), 1.95 (m), 1.65 (m), 1.50 (m), 1.35 (m), 1.22 (m), 1.05 (m), 1.00 (s) ppm. ^{13}C NMR (300 MHz): 178, 168, 146.5, 144, 128, 125.5, 120, 107, 56, 53, 44, 40, 39.5, 39, 32, 29, 25, 24, 22, 20.5 ppm. HRMS: 360 (22), 302 (24), 284 (90), 219 (10), 242 (100), 154 (100).

Preparation of Methyl 13-Propionamido-O-methylpodocarpate (6)

Propionamide (0.55 g) was utilized, according to the general procedure given previously, to obtain 1.51 g of 13-propionamido methyl O-methylpodocarpate (**6**) with mp 159 °C (81% yield). IR ($CHCl_3$): 3400, 1720, 1680, 1610, 1595, 1520, 1490, 1470, 1220, 1130, 1070, 1020 cm^{-1}. ^1H NMR (300 MHz): 8.02 (s), 7.65 (s), 6.65 (s), 3.95 (s), 3.85 (s), 2.80 (s), 2.35 (s), 2.20 (m), 1.95 (m), 1.75 (m), 1.60 (m), 1.50 (m), 1.30 (s), 1.20 (s), 1.05 (s) ppm. ^{13}C NMR (300 MHz): 178.2, 172, 146, 143.6, 128, 120, 107.8, 56, 54, 52, 44, 40, 38.6, 38, 32, 31.6, 28.8, 20, 10 ppm. HRMS: 374 (42), 358 (5), 350 (8), 302 (56), 300 (30), 219 (18), 154 (100).

Preparation of Methyl 13-Butyramido-O-methylpodocarpate (7)

Butyramide (0.66 g) was utilized, according to the general procedure previously given, to obtained 1.57 g of compound **7** with mp 162 °C (81% yield). IR ($CHCl_3$): 3395 1710, 1680, 1600, 1590, 1510, 1480, 1460, 1260, 1210, 1140 cm^{-1}. ^1H NMR (300 MHz): 8.00 (s), 7.62 (s), 6.65 (s), 3.92 (s), 3.82 (s), 2.80 (m), 2.22 (m), 2.15 (m), 1.95 (m), 1.6 (m), 1.50 (m), 1.30 (m), 1.20 (s), 1.00 (m) ppm. ^{13}C NMR (300 MHz): 178, 171.5, 146.5, 143.2, 128, 126, 120, 107, 56, 53, 52, 44, 40.5, 38.8, 32, 29, 23, 22, 20.5, 19.5, 14 ppm. HRMS: 388 (30), 302 (35), 219 (10), 154 (100).

Preparation of Methyl 13-Phenylamido-O-methylpodocarpate (8)

Benzamide (0.9 g) was utilized, according to the general procedure previously outlined (with the exception of heating for 48 h) to obtain 1.7 g of compound **8** with mp 128 °C (80% yield). IR: 3400, 1740, 1700, 1520, 1490, 1400, 1250, 1200, 1100, 1000 cm^{-1}, ^1H NMR(300 MHz): 8.5 (s), 8.2 (s), 7.9 (m), 7.5 (m), 6.8 (s), 3.9 (s), 3.7 (s), 2.8 (m), 2.3 (m), 2.0 (m), 1.6 (m), 1.4 (m), 1.3 (s), 1.1 (s). ^{13}C NMR: 178, 165, 147, 144, 135, 132, 129, 128, 127, 125, 120, 107, 56, 53, 51, 44, 40, 39, 38, 32, 28, 23, 21, 20. HRMS: 423 (26), 422 (100), 421 (69), 420 (8).

Preparation of Methyl 13-Benzylamido-O-methylpodocarpate (9)

Benzylamide (0.82 g) was utilized, according to the general procedure given previously, to obtain 2 g of compound **9** with mp 139 °C (yield 92%). IR: 3415, 1721, 1669, 1520, 1477, 1410, 1257, 1225, 1141, 1062, 1038 cm^{-1}. ^1H NMR (500 MHz): 8.0 (s), 7.7 (s), 7.3 (s), 6.6 (s), 3.7 (m),

3.65 (m), 2.6 (m), 2.2 (m), 2.0 (m), 1.9 (m), 1.6 (m), 1.2 (s), 1.0 (s). ^{13}C NMR: 178, 169, 146, 143, 135, 130, 129, 128, 127, 126, 120, 107, 56, 53, 51, 45, 44, 40, 39, 38, 32, 28, 23, 21, 20. HRMS: 437 (30), 435 (69), 436 (100), 434 (7).

Preparation of Methyl 13-Pyrrolidinone-O-methylpodocarpate (10)

2-Pyrrolidinone (0.55 g) was utilized according to the general procedure given previously, to obtain 1.7 g of compound **10** with mp 114 °C (yield 90%). IR: 1722, 1697, 1511, 1414, 1287, 1233, 1190 cm^{-1}. ^{1}H NMR (500 MHz): 6.95 (s), 6.85 (s), 3.8 (s), 3.7 (s), 2.8 (s), 2.6 (s), 2.2 (s), 2.0 (s), 1.6 (m), 1.3 (s), 1.2 (s), 1.1 (s). ^{13}C NMR: 178, 175, 153, 148, 129, 128, 125, 109, 55.73, 55.71, 53, 51.31, 51.28, 50.14, 44, 39.49, 38.75, 37.59, 31.27, 31.05, 29, 23, 21, 20, 19. HRMS: 387 (25), 385 (54), 386 (100), 384 (11).

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REFERENCES

1. Srivastava, S. K. Synthesis of some new bioactive aryl amides. *J. Ind. Chem. Soc.* **1991**, *68* (6), 358–359.
2. Schmeller, T.; Wink, M. Utilization of alkaloids in modern medicine. *Alkaloids* **1998**, 435–459.
3. Hayashi, Y.; Matsumoto, T.; Nishizawa, M. Total synthesis of nagilactone F, a biologically active norditerpenoid dilactone isolated from podocarpus nagi. *J. Org. Chem.* **1982**, *47*, 3428–3433.
4. Wolfe, J. P.; Buchwald, S. L. Palladium-catalyzed amination of aryl iodides. *J. Org. Chem.* **1996**, *61*, 1133–1135.
5. Wolfe, J. P.; Buchwald, S. L. Room temperature catalytic amination of aryl iodides. *J. Org. Chem.* **1997**, *62*, 6066–6068.
6. Richardson, C. F.; Schuster, D. I.; Wilson, S. R. Synthesis and characterization of water-soluble amino fullerene derivatives. *Org. Letts.* **2000**, *2* (8), 1011–1014.
7. Antilla, J. C. The copper-catalyzed N-arylation of indoles. *J. Am. Chem. Soc.* **2002**, *124* (39), 11684–11688.
8. Miles, D. H. The synthesis of tetracyclic diterpenoid alkaloids and related diterpenoids. *Thesis*. Georgia Institute of Technology, Atlanta, GA, 1969.