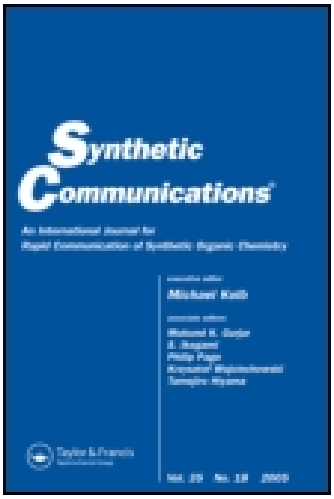

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Lactam Coupling as a Versatile Route to Indoprofen Analogs

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LACTAM COUPLING AS A VERSATILE ROUTE TO INDOPROFEN ANALOGS

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A convergent synthesis of indoprofen via a Buchwald coupling approach is reported. Using this methodology, indoprofen and a set of analogs of indoprofen were readily prepared.

Keywords: Buchwald–Hartwig cross-coupling; indoprofen; palladium

INTRODUCTION

Indoprofen (**1**), a nonsteroidal anti-inflammatory drug that was withdrawn from the world market in the 1980s after postmarketing reports of severe gastrointestinal bleeding, has resurfaced within the drug discovery realm.[1] In 2004, Stockwell and coworkers found through high-throughput screening that indoprofen increases production of the survival motor neuron protein, suggesting that it may provide insight into the treatment of spinal muscular atrophy.[1]

A number of syntheses of indoprofen (**1**) have been reported,[2] but we felt none of these were attractive for readily preparing an array of analogs. To obtain a variety of derivatives of indoprofen (**1**), new synthetic methods were explored. Herein we report a new convergent approach to obtain the indoprofen scaffold via a palladium-mediated Buchwald–Hartwig cross-coupling reaction.

RESULTS AND DISCUSSION

The preparation of indoprofen and a small set of analogs substituted on the aryl portion of isoindolin-1-one was accomplished using a carbon–nitrogen cross-coupling. Buchwald, Hartwig, and coworkers[3] have previously described both the palladium- and copper-catalyzed coupling of amides and aryl halides. Using the Buchwald–Hartwig palladium-catalyzed coupling method, we found that the indoprofen core structure could be constructed in a quick and efficient manner by

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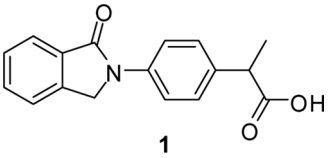

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Figure 1. Indoprofen.

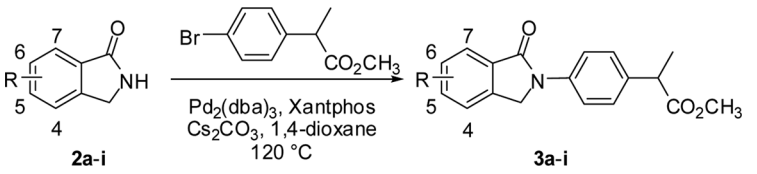
coupling the appropriately substituted isoindolin-1-ones with 2-(4-bromophenyl)-propanoate. The preparations of the coupling partners were carried out using standard synthetic organic transformations, and in most cases the isoindolin-1-ones were commercially available unless otherwise noted in this text. The synthesis of methyl 2-(4-bromophenyl)propanoate has previously been reported.[4]

Table 1 illustrates the results from the palladium-mediated cross-coupling conditions of isoindolin-1-ones **2a**–**i** utilizing $Pd_2(dba)_3$/Xantphos. The methyl ester of indoprofen **3a** was obtained in 56% yield, and products containing the methoxy groups **3b**–**e** on all positions of the benzo ring gave comparable yields (57–78%) in the palladium coupling system investigated. With the chloro groups, however, the yields ranged considerably. In the case of the 4-Cl **3f** and 7-Cl **3i** analogs, the yields were poor, 8% and 36%, respectively. In contrast, the 5-Cl **3g** and 6-Cl **3h** analogs were obtained in 73% and 59% yields, respectively.

Based on the encouraging biological activities[5] demonstrated by the C-6 substituted analogs, we further explored substitution at this position with a variety of substituents (Table 2).

The C-6 substituted isoindolin-1-ones **4c**–**e**, **h**, and **i** have been previously described in the literature, and isoindolin-1-ones **4a**, **b**, **f**, and **g** were prepared by similar methods.

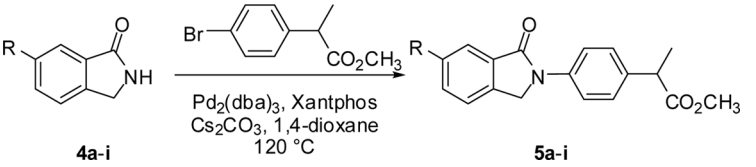
Table 1. Palladium coupling products



2a-i **3a-i**

Compound	R	Yield (%)
3a	H	56
3b	4-OCH_3	73
3c	5-OCH_3	57
3d	6-OCH_3	78
3e	7-OCH_3	66
3f	4-Cl	8
3g	5-Cl	73
3h	6-Cl	59
3i	7-Cl	36

Table 2. Palladium coupling products of C-6 substituted isoindolin-1-ones



4a-i **5a-i**

Compound	R	Yield (%)
5a	$N(CH_3)_2$	78
5b	$OCH(CH_3)_2$	63
5c	CH_3	72
5d	C_6H_5	70
5e	F	57
5f	CF_3	51
5g	CN	16
5h	SO_2CH_3	8
5i	NO_2	0

From the results tabulated in Table 2, it was evident that as one moved from electron-donating to electron-withdrawing groups, the overall yield of the palladium-catalyzed coupling decreased to the point where no reaction occurred, as shown in entry **5i**. One possible explanation is that strongly electron-withdrawing groups affect the pKa of the amide, resulting in increased acidity and therefore reduced nucleophilicity, leading to poor reaction efficiency. Shakespeare[3d] noted this with the cross-coupling of aliphatic amides.

Indoprofen (**1**) and the substituted indoprofen analogs were readily obtained by saponification of the coupled products under conventional conditions using lithium hydroxide in yields of 72–98%.

In conclusion, a new convergent method based on C-N cross-coupling for the synthesis of indoprofen and its analogs has been developed. The desired coupling partners can be prepared in a straightforward manner using standard organic transformations.

EXPERIMENTAL

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Proton nuclear magnetic resonance spectra were obtained on a Bruker Avance 300 spectrometer at 300 MHz and Bruker Avance 500 spectrometer at 500 MHz. Spectra are given in parts per million (δ), and coupling constants, J values, are reported in hertz. Tetramethylsilane was used as an internal standard. Mass spectra were obtained on a Thermo Finnigan AQA Mass Spectrometer (electrospray ionization) or a Finnigan LCQ Duo liquid chromatograph–mass spectrometer (APCI). All compounds were purified using ISCO combi-flash column chromatography.

General Palladium Coupling Procedure

A mixture of the appropriately substituted isoindolin-1-one (1.2 mmol), 2-(4-bromophenyl)propanoate (1 mmol), tris(dibenzylideneacetone) dipalladium (3 mol%), Xantphos (8 mol%), cesium carbonate (1.4 mmol), and 1,4-dioxane (2 mL) was heated under argon in a sealed tube at 120 °C overnight. After cooling to room temperature, the mixture was diluted with dichloromethane and filtered. The filtrate was concentrated, and the residue was purified by chromatography to afford the desired product. The data for the compounds in Tables 1 and 2 are shown.

Selected Data

Compound 3a. White solid: mp 110–111 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, $J = 9.0$ Hz, 2H), 7.78 (d, $J = 7.5$ Hz, 1H), 7.68 (m, 2H), 7.54 (t, $J = 7.5$ Hz, 1H), 7.34 (d, $J = 8.5$ Hz, 2H), 5.01 (s, 2H), 3.82 (q, $J = 7.0$ Hz, 1H), 3.59 (s, 3H), 1.41 (d, $J = 7.5$ Hz, 3H); ESI MS m/z 296 $[M + H]^+$.

Compound 3b. Off-white solid: mp 105–106 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.87 (d, $J = 8.5$ Hz, 2H), 7.52 (t, $J = 7.7$ Hz, 1H), 7.36 (d, $J = 7.5$ Hz, 1H), 7.33 (d, $J = 8.5$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 1H), 4.92 (s, 2H), 3.93 (s, 3H), 3.81 (q, $J = 7.0$ Hz, 1H), 3.59 (s, 3H), 1.40 (d, $J = 7.5$ Hz, 3H); ESI MS m/z 326 $[M + H]^+$.

Compound 3c. White solid: mp 114–115 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.82 (d, $J = 8.5$ Hz, 2H), 7.78 (d, $J = 8.5$ Hz, 1H), 7.32 (d, $J = 8.5$ Hz, 2H), 7.21 (d, $J = 1.5$ Hz, 1H), 7.08 (dd, $J = 8.5$, 2.0 Hz, 1H), 4.94 (s, 2H), 3.87 (s, 3H), 3.81 (q, $J = 7.0$ Hz, 1H), 3.59 (s, 3H), 1.41 (d, $J = 7.0$ Hz, 3H); ESI MS m/z 326 $[M + H]^+$.

Compound 3d. White solid: mp 130–131 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.84 (d, $J = 8.5$ Hz, 2H), 7.56 (d, $J = 8.5$ Hz, 1H), 7.34 (d, $J = 9.0$ Hz, 2H), 7.27–7.23 (m, 2H), 4.93 (s, 2H), 3.85 (s, 3H), 3.82 (q, $J = 7.0$ Hz, 1H), 3.60 (s, 3H), 1.41 (d, $J = 7.5$ Hz, 3H); ESI MS m/z 326 $[M + H]^+$.

Compound 3e. Off-white solid: mp 105–107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (m, 2H), 7.52 (m, 1H), 7.34 (m, 2H), 7.06 (d, $J = 7.4$ Hz, 1H), 6.93 (d, $J = 8.3$ Hz, 1H), 4.78 (s, 2H), 4.00 (s, 3H), 3.73 (q, $J = 7.2$ Hz, 1H), 3.67 (s, 3H), 1.51 (d, $J = 7.2$ Hz, 3H); ESI MS m/z 326 $[M + H]^+$.

Compound 3f. White solid: mp 160–162 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.81 (m, 3H), 7.56 (dd, $J = 7.9$, 0.9 Hz, 1H), 7.48 (t, $J = 7.7$ Hz, 1H), 7.39–7.36 (m, 2H), 4.82 (s, 2H), 3.75 (q, $J = 7.2$ Hz, 1H), 3.68 (s, 3H), 1.52 (d, $J = 7.2$ Hz, 3H); ESI MS m/z 330 $[M + H]^+$.

Compound 3g. Off-white solid: mp 160–162 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85–7.78 (m, 3H), 7.48 (m, 2H), 7.37 (m, 2H), 4.82 (s, 2H), 3.75 (q, $J = 7.0$ Hz, 1H), 3.67 (s, 3H), 1.52 (d, $J = 7.5$ Hz, 3H); ESI MS m/z 330 $[M + H]^+$.

Compound 3h. White solid: mp 160–161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, $J = 1.8$ Hz, 1H), 7.79 (dd, $J = 6.8$, 2.0 Hz, 2H), 7.56 (dd, $J = 8.0$, 2.0 Hz, 1H), 7.45 (dd, $J = 8.1$, 0.5 Hz, 1H), 7.37 (dd, $J = 7.0$, 1.8 Hz, 2H), 4.83 (s, 2H), 3.75 (q, $J = 7.1$ Hz, 1H), 3.67 (s, 3H), 1.52 (d, $J = 7.2$ Hz, 3H); ESI MS m/z 330 $[M + H]^+$.

Compound 3i. Off-white solid: mp 110–113 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.82 (d, $J = 8.5$ Hz, 2H), 7.66–7.63 (m, $J = 7.5$, 5.5 Hz, 2H), 7.54 (d, $J = 7.5$ Hz, 1H), 7.35 (d, $J = 8.5$ Hz, 2H), 4.98 (s, 2H), 3.82 (q, $J = 7.0$ Hz, 1H), 3.59 (s, 3H), 1.41 (d, $J = 7.0$ Hz, 3H); ESI MS m/z 330 $[M + H]^+$.

Compound 5a. Off-white solid: mp 169–170 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, $J = 8.6$ Hz, 2H), 7.35 (d, $J = 8.6$ Hz, 2H), 7.33 (d, $J = 8.2$ Hz, 1H), 7.19 (d, $J = 2.4$ Hz, 1H), 6.96 (dd, $J = 8.4$, 2.4 Hz, 1H), 4.74 (s, 2H), 3.74 (q, $J = 7.2$ Hz, 1H), 3.67 (s, 3H), 3.02 (s, 6H), 1.51 (d, $J = 7.2$ Hz, 3H); ESI MS m/z 339 $[M + H]^+$.

Compound 5b. White solid: mp 71 – 74 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, $J = 8.7$ Hz, 2H), 7.37 (m, 4H), 7.12 (dd, $J = 8.3$, 2.4 Hz, 1H), 4.77 (s, 2H), 4.65 (m, 1H), 3.74 (q, $J = 7.1$ Hz, 1H), 3.67 (s, 3H), 1.52 (d, $J = 6.9$ Hz, 3H), 1.37 (d, $J = 6.1$ Hz, 6H); ESI MS m/z 354 $[M + H]^+$.

Compound 5c. White solid: mp 139–142 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, $J = 8.7$ Hz, 2H), 7.72 (s, 1H), 7.39 (s, 2H), 7.35 (d, $J = 8.6$ Hz, 2H), 4.79 (s, 2H), 3.74 (q, $J = 7.2$ Hz, 1H), 3.67 (s, 3H), 2.46 (s, 3H), 1.51 (d, $J = 6.9$ Hz, 3H); ESI MS m/z 310 $[M + H]^+$.

Compound 5d. White solid: mp 155–158 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, $J = 1.3$ Hz, 1H), 7.84 (m, 3H), 7.66 (m, 2H), 7.58 (d, $J = 7.6$ Hz, 1H), 7.48 (t, $J = 7.6$ Hz, 2H), 7.39 (m, 3H), 4.89 (s, 2H), 3.75 (q, $J = 7.3$ Hz, 1H), 3.68 (s, 3H), 1.53 (d, $J = 6.9$ Hz, 3H); ESI MS m/z 372 $[M + H]^+$.

Compound 5e. White solid: mp 134–136 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, $J = 8.6$ Hz, 2H), 7.59 (dd, $J = 7.6$, 2.2 Hz, 1H), 7.48 (dd, $J = 8.2$, 4.3 Hz, 1H), 7.37 (d, $J = 8.6$ Hz, 2H), 7.29 (td, $J = 4.3$, 2.3 Hz, 1H), 4.82 (s, 2H), 3.75 (q, $J = 7.1$ Hz, 1H), 3.67 (s, 3H), 1.52 (d, $J = 7.3$ Hz, 3H); ESI MS m/z 314 $[M + H]^+$.

Compound 5f. White solid: mp 105–107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.86 (dd, $J = 7.9$, 1.0 Hz, 1H), 7.82–7.79 (m, 2H), 7.66 (d, $J = 7.9$ Hz, 1H), 7.40–7.37 (m, 2H), 4.92 (s, 2H), 3.76 (q, $J = 7.2$ Hz, 1H), 3.68 (s, 3H), 1.52 (d, $J = 7.0$ Hz, 3H); ESI MS m/z 364 $[M + H]^+$.

Compound 5g. Off-white solid: mp 186–187 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.88 (dd, $J = 7.8$, 1.4 Hz, 1H), 7.84 (d, $J = 8.7$ Hz, 1H), 7.77 (d, $J = 4.4$ Hz, 1H), 7.66 (d, $J = 7.9$ Hz, 1H), 7.39 (d, $J = 8.6$ Hz, 2H), 4.93 (s, 2H), 3.76 (q, $J = 7.2$ Hz, 1H), 3.68 (s, 3H), 1.52 (d, $J = 7.2$ Hz, 3H); ESI MS m/z 321 $[M + H]^+$.

Compound 5h. Off-white solid: mp 196–197 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, $J = 1.3$ Hz, 1H), 8.20 (dd, $J = 7.9$, 1.7 Hz, 1H), 7.80 (d, $J = 8.6$ Hz, 2H), 7.74 (d, $J = 7.9$ Hz, 1H), 7.39 (d, $J = 8.6$ Hz, 2H), 4.96 (s, 2H), 3.76 (q, $J = 7.2$ Hz, 1H), 3.68 (s, 3H), 3.12 (s, 3H), 1.53 (d, $J = 7.2$ Hz, 3H); ESI MS m/z 374 $[M + H]^+$.

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