Solvent-Free Heck–Jeffery Reactions under Ball-Milling Conditions Applied to the Synthesis of Unnatural Amino Acids Precursors and Indoles

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Abstract: The syntheses of various amino- and hydroxy-substituted dehydrophenylalanine derivatives using the Heck–Jeffery protocol under non-solvent conditions in a ball mill are presented. The influences of electron-withdrawing groups and of the location of the heteroatom substituent relative to the halide are discussed. Suitably substituted ortho-amino dehydrophenylalanine derivatives undergo a cyclization–elimination reaction to the corresponding 2-substituted indoles.

Key words: cyclizations, indoles, green chemistry, Heck reaction, palladium

The Heck reaction is a palladium-catalyzed coupling reaction for the formation of a C–C bond between an aryl halide and an olefin. In the infancy of this transformation, the catalytic species Pd(0) was often stabilized with phosphine ligands but in more recent years much effort has been devoted to the development of phosphine-free conditions, especially since it was observed that the addition of tetraalkylammonium salts to phosphine-free reaction mixtures led to higher catalytic activities. Furthermore, in some cases, a reduction of catalytic activity has been observed upon addition of phosphines. The rationale behind this behavior is that the tetraalkylammonium salts stabilize the catalytic species, i.e. Pd(0) nanoparticles, by forming a monomolecular layer around the metal core and thereby preventing undesirable agglomeration.

The existence of these Pd(0) nanoparticles has been observed by in situ electron microscopy and the catalytic activity of the tetraalkylammonium-encapsulated Pd(0) has been verified by independent and conclusive experiments. Among the phosphine-free Heck conditions, the Heck–Jeffery protocol extends the scope of this reaction to the synthesis of unnatural amino acids derived from phenylalanine. The reaction is carried out in N,N-dimethylformamide with a stoichiometric amount of tetrabutylammonium halide and sodium bicarbonate as base. Unnatural amino acids derived from this methodology have been the subject of a number of papers in our group. Recently, we further modified this methodology to avoid the use of N,N-dimethylformamide and to shorten the reaction times. This was achieved by ball-milling in which the reaction was carried out under non-solvent conditions. In that study we ascertained the crucial importance of the tetraalkylammonium salt (in stoichiometric amounts) for the successful outcome of the reaction. Aryl halides possessing electron-donating groups or with no extra substitution, proved to be the best coupling partners together with the amido acrylates. The most successful amino aryl halide in that study was 4-iodoaniline. This encouraged us to test the coupling of halo anilines in general. In some cases the resulting substituted α-amino dehydrophenylalanine derivatives spontaneously cyclized to form 2-carboxy substituted indole derivatives under mildly acidic or thermal conditions. The literature describes many methods to cyclize unprotected ortho-ethyl anilines to 2-substituted indoles, but unprotected ortho-ethyl counterparts are somewhat more scarce. Syntheses of methyl-1H-indole-2-carboxylate derivatives in the literature include a Fischer synthesis, reductive cyclization of methyl-2-nitro cinnamate and cyclization of azidoesters. The compound itself, has been used as starting material for the synthesis of HIV-1 integrase inhibitors.

In this report we describe the coupling of various halo anilines with an amido acrylate under solvent- and phosphine-free conditions and the subsequent cyclization of suitably substituted coupling products to their corresponding indole derivatives. Our results for the coupling reactions are summarized in Table 1 and Scheme 1. As olefin for the reactions we selected 2-tert-butoxycarbonylalinoacrylic acid methyl ester which gave the best results in our previous study. It will henceforth be abbreviated as AA. Aryl iodides were

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The above observation that electron-withdrawing substituents on the aryl halide had a detrimental effect on the yields in the coupling reactions, is consistent with observations in previous studies.\(^6,12\) The effect of the heteroatom substituents adjacent to the halide, can be rationalized by increased steric hindrance to some extent but it could also be an electronic effect due to coordination of nitrogen to palladium. Indeed, in a recent study, 4-membered palladacycles were synthesized, isolated and subjected to X-ray analysis.\(^26\) Moreover, a slight shortening of the ArC–Pd bond length indicated that the presence of nitrogen influences the electronic properties of Pd(II) in the oxidative addition complex. This, in turn, may slow down or completely stop subsequent steps in the Heck reaction. Indeed, theoretical calculations on the strength of coordination of ethylene to cationic methyl and ethyl palladium complexes, show that when ammonia ligands are introduced to the system, the energy released upon coordination of ethylene drops significantly.\(^27\) Although the system studied in the theoretical calculations is not comparable with our system, it offers an insight into the influence exerted by nitrogen ligands on Pd (II) species.

Nevertheless, 2-halo aniline substrates gave products resulting from Heck-coupling but some of the primary coupling products easily cyclized to give indole derivatives (see Table 2, products \(21, 24, 28, 31\) and \(32\)). During the reaction of 2-iodoaniline (\(20\)) with the olefin TLC analysis clearly indicated the formation of only one compound, which upon chromatographic workup, was converted into two new compounds. The crude product apparently underwent a reaction in contact with the slightly acidic silica. When the reaction was repeated and the coupling product was purified on a pre-neutralized silica column \([10\%\) triethylamine in heptane–ethyl acetate \((1:1)\)] this behavior was not observed. In this case the expected product was isolated and it could be analyzed by \(^1\)H NMR spectroscopy if an acid free solvent was used. The initial coupling product cyclized easily in refluxing acetic acid or acetic anhydride to give the corresponding methyl-2-indole carboxylate \(21\) in near quantitative yield. For the coupling product between \(22\) and \(AA\), the silica neutralization was left out. This resulted in the serendipitous isolation of a substance that on \(^1\)H NMR analysis in CDCl\(_3\) was shown to be \(23\) (see Figure 2).

\[
\text{Figure 2 Intermediate in the cyclization to form indole 24}
\]

When this material was treated with refluxing acetic anhydride overnight, it exclusively gave indole derivative \(24\). Dehydroindole derivatives such as \(23\) with a quaternary carbon adjacent to the nitrogen are known from the literature.\(^28\) Upon acidic treatment, this labile intermediate loses the equivalent of tert-buty carbamate to form the
indole. Upon searching the literature for other examples of this type of cyclization–elimination, we could only find one relevant reference (see Scheme 2). Acidic treatment of 25 with HCl in refluxing methanol afforded the indole 26 in near quantitative yield. The authors did not comment on the mechanism.

**Scheme 2** Details from a known reaction sequence comprising a cyclization–elimination reaction forming an indole derivative

Those ortho-amino dehydrophenylalanine intermediates prone to form indoles were so unstable that characterisation of these intermediates was not practical. In fact, the onset of the cyclization–elimination was also observed in neat samples after an overnight storage in an open flask. Therefore, the entire reaction sequence depicted in Scheme 3 was carried out without fully characterizing any intermediates until products could be isolated as stable indoles. The results from these coupling–cyclization reactions are shown in Scheme 3 and Table 2.

The results in the Table 2 suggest that the cyclization–elimination reaction was very sensitive to the nature of the substituents. Thus, when the sequence was performed with ortho-aminoryl iodides containing electron-drawing substituents such as 1 and 2, the intermediate ortho-amino dehydrophenylalanine derivatives 11 and 12, respectively, failed to form the indole even after several days of refluxing in acetic anhydride. When the imino tautomer 18 obtained from the coupling between 9 and AA was subjected to cyclization conditions, in an attempt to form the corresponding benzofuran derivative, no product was formed either. The unsubstituted 2-iodoaniline (20) and the electron-donating substituted substrate 27 both gave the corresponding indole derivatives 21 and 28 in fair yields, whereas substrates 22, 29 and 30 containing mildly electron-donating substituents gave the corresponding indoles 24, 31 and 32, respectively, in more modest yields. The yield-determining process in the reaction sequence was invariably the coupling reaction as determined by the weight of the residue remaining after a short workup prior to cyclization, whereas the cyclization–elimination reaction was nearly quantitative. The failure of aryl bromides to couple with AA enabled a regioselective coupling of 30 followed by cyclization to form indole 32 in modest yield. The indole derivative 32 has been used as starting material for Suzuki and Sonagashira coupling reactions.

Interestingly, in a further attempt to perform the coupling between 2-iodoaniline (20) and AA under conventional conditions, using N-methyl-2-pyrrolidone as solvent, no coupling product was formed after 24 hours at 80 °C. This is remarkable as the temperature attained in the ball mill after one hour of milling seldom rises above this level but it is sufficient to form product. However, heating to 130 °C, gave the indole in 50% yield. This fact was puzzling because the reaction mixture used for coupling, irrespective if performed in solvent or without solvent, is inherently basic. This suggested that the cyclization could be performed simply by heating the coupled intermediate in

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**Table 2** Yields of Methyl-1H-indole-2-carboxylate Derivatives

<table>
<thead>
<tr>
<th>ArX</th>
<th>Product</th>
<th>R1</th>
<th>R2</th>
<th>R4</th>
<th>R5</th>
<th>Yield (%)</th>
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<td>H</td>
<td>CN</td>
<td>H</td>
<td>–</td>
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<td>H</td>
<td>–</td>
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<td>–</td>
<td>OH</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>–</td>
</tr>
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<td>H</td>
<td>H</td>
<td>H</td>
<td>60</td>
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<td>Cl</td>
<td>H</td>
<td>26</td>
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<tr>
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<td>32</td>
<td>NH2</td>
<td>H</td>
<td>Br</td>
<td>H</td>
<td>35</td>
</tr>
</tbody>
</table>

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**Scheme 3** General reaction scheme for the formation of the indole derivatives
an appropriate solvent and indeed we found that the cyclization could be effected thermally by refluxing in toluene but conversion was slower and the yields were poorer than when the coupled intermediate was heated at reflux in acetic acid or anhydride.

The coupling of amido acrylate AA with various iodo anilines and iodo phenols under ball-milling conditions proceeded in modest to good yields. The reaction was performed under solvent- and phosphine-free conditions and has the added advantage of being rapid and easily worked up. Suitably substituted ortho-aminoaryl dehydrophenylalanine derivatives cyclized efficiently to the corresponding methyl 1H-indole-2-carboxylates. This methodology provides a useful and direct synthesis of some of these derivatives.

All reagents were used as delivered from Aldrich without further purification. 2-tert-Butoxycarbonylaminocarboxylic acid methyl ester (AA) and 2-iodo-3-nitrophenol was synthesized according to the literature procedures. Inorganic salts were dried in an oven at 110 °C overnight. Chromatographic workup was performed with a mixture of methanol and ethyl acetate (95:5) with a Teflon gasket. The following components were added to the reaction vessels: aryl bromide (1.00 equiv), AA (1.05 equiv), NaHCO3 (2.50 equiv), HCO2Na (0.20 equiv), n-Bu4NCl (1.20 equiv), Pd(OAc)2 (0.05 equiv) and NaCl (5 mg/mg aryl halide). Then, 8 steel balls were added and the vessel was purged with argon and closed with lid and gasket. To balance the rotor of the ball mill, two similarly loaded gaskets were added and the vessel was purged with argon and closed with lid and gasket. After the vessels had cooled down, the contents were transferred to a 50 mL vial containing 10% Et3N and the solution was heated at 90 °C for 3 h and then cooled to 25 °C. The reaction was quenched with a solution of sodium thiosulfate in water, extracted with Et2O (3 × 50 mL) and the combined organic phases were dried with Na2SO4. After filtering and removal of the solvent under reduced pressure, the residue was purified by chromatographic workup using heptane–EtOAc (8:1) as eluent. The amine was obtained as a pale brown liquid (1.29 g, 37%).

HRMS (FAB+): m/z calcd for C20H17F3I: 426.9149; found: 426.9142.

It was not possible to obtain satisfactory elemental analysis for this compound. The 1H NMR data were in accordance with literature data.

2-Iodo-3-methoxyphenylamine (27)

Methyl iodide (0.32 mL, 3.8 mmol) was added to a suspension of 2-iodo-3-nitrophenol (0.92 g, 3.5 mmol) and K2CO3 (2.4 g, 17 mmol) in DMF (5 mL). The mixture was stirred at r.t. overnight and then 2 M NaOH (5 mL) was added. The mixture was extracted with Et2O (3 × 20 mL) and the combined organic phases were dried with Na2SO4. After filtration and removal of the solvent under reduced pressure, the title compound was obtained as a yellow powder (0.9 g, 97%). The melting point (100.9–102.9 °C) was in agreement with the literature data (Lit.10 102.5–103.5 °C). This compound was used directly in the next step without further purification.

Iron powder (0.77 g, 14 mmol) was added to a solution of 2-iodo-1-methoxy-3-nitrobenzene (0.9 g, 3.3 mmol) in a mixture of AcOH (8 mL) and EtOH (8 mL). The grey slurry thus obtained was heated at reflux for 3.5 h and then left to cool. The mixture was diluted with water, neutralized with solid Na2CO3 and extracted with CH2Cl2 (3 × 20 mL). The combined organic phases were dried with Na2SO4. After filtration and removal of the solvent under reduced pressure, the title compound was obtained as a brown oil (0.51 g, 60%). The 1H NMR spectrum of this compound was in agreement with the literature data.

Heck Couplings: General Procedure

The following components were added to the reaction vessels: aryl halide (1.00 equiv), AA (1.05 equiv), NaHCO3 (2.50 equiv), HCO2Na (0.20 equiv), n-Bu4NCl (1.20 equiv), Pd(OAc)2 (0.05 equiv) and NaCl (5 mg/mg aryl halide). Then, 8 steel balls were added and the vessel was purged with argon and closed with lid and gasket. To balance the rotor of the ball mill, two similarly loaded vessels were always run at the same time. The ball mill was then run at full speed for an hour. After the vessels had cooled down, the contents were poured into a round-bottomed flask together with silica and the solvent was removed in vacuo. The solid residue absorbed on silica was placed on a neutralized silica column (the appropriate eluent containing 10% Et2O in hexane was used to pack the column) and purified by chromatographic workup with eluent system as indicated.

Reactions were typically run on a 0.5 mmol scale with regard to the aryl halide. The total weight of the reaction mixture in the reaction vessel was in the order of 1 g. The following compounds were prepared using this procedure.
3-(2-Amino-5-cyanophenyl)-2-tert-butoxycarbonylamino-
acrylic Acid Methyl Ester (11)
Eluent: pentane–EtOAc (3:2); pale yellow needles (pentane–
EtOAc); mp 151.8–152.2 °C.
IR (KBr): 3409, 2222, 1716, 1624 cm⁻¹.
1H NMR (300 MHz, CDCl₃): δ = 7.52 (d, J = 1.8 Hz, 1 H, ArH),
7.35 (dd, J = 1.9, 8.4 Hz, 1 H, ArH), 7.03 (s, 1 H, Hc=), 6.71 (d,
J = 8.4 Hz, 1 H, ArH), 6.54 (br, 1 H, NH), 4.38 (br, 2 H, NH₂), 3.87
(s, 3 H, CO₂CH₃), 1.35 [s, 9 H, C(CH₃)₃].
13C NMR (100 MHz, CDCl₃): δ = 165.2, 151.4, 148.2, 133.3, 133.1,
126.9, 121.5, 120.3, 119.8, 116.0, 100.5, 81.6, 53.1, 28.1.
HRMS (FAB⁺): m/z calc'd for C₁₆H₁₉N₃O₄: 317.1376; found:
317.1376.
Anal. Calc'd for C₁₆H₂₆N₃O₄: C, 60.56; H, 6.03; N, 13.20. Found:
C, 60.40; H, 5.96; N, 13.20.

4-Amino-3-(2-tert-butoxycarbonylamino-2-methoxycarbonyl-
vinyl)benzoic Acid Methyl Ester (12)
Eluent: petroleum ether–EtOAC (3:2); yellow powder (pentane–
EtOAc); mp 185.2–186.1 °C.
IR (KBr): 3419, 1733, 1716, 1652 cm⁻¹.
1H NMR (400 MHz, CDCl₃): δ = 7.96 (d, J = 1.8 Hz, 1 H, ArH),
7.81 (dd, J = 1.9, 8.5 Hz, 1 H, ArH), 7.11 (s, 1 H, Hc=), 6.71 (d,
J = 8.5 Hz, 1 H, ArH), 6.47 (br, 1 H, NH), 4.25 (br, 2 H, NH₂), 3.88
(s, 3 H, CO₂CH₃), 3.85 (s, 3 H, CO₂CH₃), 1.36 [s, 9 H, C(CH₃)₃].
13C NMR (100 MHz, CDCl₃): δ = 167.0, 165.6, 152.4, 148.6, 131.7,
131.6, 126.7, 123.3, 123.0, 119.2, 115.5, 83.1, 53.0, 51.9, 28.5.
HRMS (FAB⁺): m/z calc’d for C₁₆H₂₆N₃O₄: 350.1478; found:
350.1482.
Anal. Calc'd for C₁₆H₂₆N₃O₄: C, 58.28; H, 6.33; N, 8.00. Found:
C, 58.20; H, 6.29; N, 7.88.

3-(3-Aminophenyl)-2-tert-butoxycarbonylaminoacrylic Acid
Methyl Ester (13)
Eluent: heptane–EtOAc (3:2); white crystals (pentane–EtOAc); mp
134.9–135.6 °C.
IR (KBr): 3419, 1718, 1643 cm⁻¹.
1H NMR (400 MHz, CDCl₃): δ = 7.14 (m, 2 H, ArH), 6.93 (d, J =
7.7 Hz, 1 H, ArH), 6.85 (s, 1 H, Hc=), 6.66 (dd, J = 2.2, 7.9 Hz, 1 H,
ArH), 6.15 (br, 1 H, NH), 3.84 (s, 3 H, CO₂CH₃), 3.48 (br, 2 H,
NH₂), 1.41 [s, 9 H, C(CH₃)₃].
13C NMR (100 MHz, CDCl₃): δ = 166.4, 152.9, 146.5, 135.0, 130.3,
129.5, 124.8, 120.4, 116.2, 116.1, 81.0, 52.6, 28.2.
HRMS (FAB⁺): m/z calc’d for C₁₆H₂₆N₃O₄: 292.1423; found:
292.1423.
Anal. Calc’d for C₁₆H₂₆N₃O₄: C, 61.63; H, 6.90; N, 9.58. Found:
C, 61.56; H, 6.85; N, 9.45.

2-tert-Butyloxy carbamino-3-(3,5-diaminophenyl)acrylic
Acid Methyl Ester (14)
Eluent: pentane–EtOAc (1:1); amorphous white solid (pentane–
EtOAc); mp 127.5–128.5 °C.
IR (KBr): 3410, 1716, 1647 cm⁻¹.
1H NMR (300 MHz, CDCl₃): δ = 6.99 (s, 1 H, ArH), 6.29 (d, J = 2.2
Hz, 2 H, ArH), 6.08 (br. 1 H, NH), 6.01 (s, 1 H, Hc=), 3.83 (s, 3 H,
CO₂CH₃), 3.62 (br, 4 H, NH), 1.45 [s, 9 H, C(CH₃)₃].
13C NMR (100 MHz, CDCl₃): δ = 166.3, 152.2, 147.6, 135.8, 129.8,
125.1, 107.4, 102.9, 81.1, 52.6, 28.3.
HRMS (FAB⁺): m/z calc’d for C₁₆H₂₆N₃O₄: 307.1532; found:
307.1545.

2-tert-Butyloxycarbonylamino-3-(4-hydroxyphenyl)acrylic Acid Methyl Ester (19)

Eluent: petroleum ether–EtOAc (2:1); white amorphous solid (pentane–EtOAc); mp 145.2–147.0 °C.

IR (KBr): 3329, 1695, 1523 cm–1.

Methyl Ester (19)


Cyclization of Coupled Intermediates to Form Indole Derivatives; General Procedure

The above chromatographic workup was used to remove excess starting materials after which the column was flushed with heptane–EtOAc (1:1). The solvent was evaporated at reduced pressure and the residue was suspended in Ac2O (2 mL/100 mg residue). The brownish white residue was placed on a pad of silica and eluted with heptane–EtOAc (1:1). Removal of the solvent under reduced pressure afforded the starting materials after which the column was flushed with heptane–EtOAc; mp 211.8–213.6 °C.

IR (KBr): 3587, 3409, 1705, 1606 cm–1.

Methyl Ester (21)

HRMS (FAB+): m/z [M + H]+ calcd for C15H19NO5: 293.1263; found: 294.135.


1H-Indole-2-carboxylic Acid Methyl Ester (21)

White needles (toluene); mp 148.1–148.5 °C (Lit.24 145–147 °C).

IR (KBr): 3325, 1695, 1523 cm–1.

These data were in accordance with the literature data.41

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