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Synthesis of *N*-aryl indole-2-carboxylates via an intramolecular palladium-catalysed annulation of didehydrophenylalanine derivatives

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Abstract

Nitrogen substituted indole-2-carboxylates can be prepared via an intramolecular palladium-catalysed amination reaction of didehydrophenylalanine derivatives using $PdCl_2$(dppf) and KOAc in DMF at 90°C to form the indole nucleus. The specific formation of (*Z*)-isomers from Horner–Wadsworth–Emmons reaction of phosphonylglycinates and 2-iodobenzaldehydes was crucial to the success of the process. The product *N*-substituted indole-2-carboxylates were isolated in high yield.

Keywords: amination; Horner–Wadsworth–Emmons; indole-2-carboxylate; palladium catalysis.

Indole-2-carboxylates substituted on nitrogen with an aryl or acyl group are a relatively poorly described class of compounds. Previous syntheses of *N*-arylindole-2-carboxylates have relied on Ullmann coupling, transition metal mediated coupling or aromatic nucleophilic attack to arylate the indole nitrogen. These methods are not entirely satisfactory, for example, the copper mediated Ullmann coupling which has remained the standard method of construction of the *N*-aryl bond. Although useful for compounds with activated aryl halides, this method usually requires high temperatures and gives variable yields.[1,2] Alternatively, Barton et al. have described a copper-catalysed phenylation of indole derivatives using triphenylbismuth bis-trifluoroacetate. Using this methodology they found that ethyl indole-2-carboxylate undergoes *N*-phenylation in a yield of 30%.[3] Russell et al. have demonstrated nucleophilic aromatic substitution in the synthesis of these compounds.[4] Their method uses the sodium salt of indole-2-carboxylates to displace aryl fluorides bearing strongly electron withdrawing groups in the *ortho* or *para* position to give products in yields of between 9 and 84%. Alternative preparations reliant upon formation of the heterocyclic portion built from an aromatic amino group are known, for example the Nenitzescu reaction, but this and other methods involving cyclisation require lengthy syntheses.[5] Ischii and coworkers have shown that the Fischer indolisation of ethyl pyruvate 2-(4-methoxyphenyl)phenylhydrazone can yield an *N*-aryl indole-2-carboxylate derivative in moderate yield,[6,7] however, this reaction is limited

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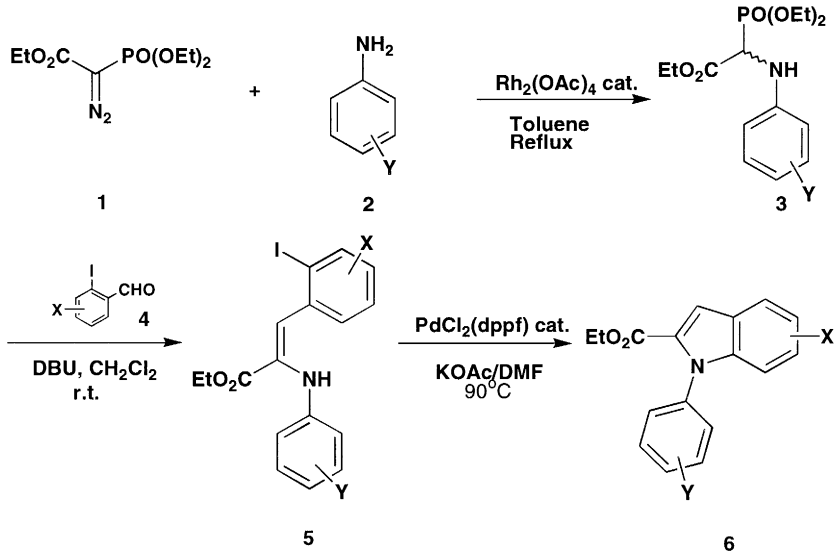
to the formation of compounds in which the phenyl portion of indole nucleus bears an electron donating substituent. Thus, the need for a flexible procedure compatible with a wide range of functionality is clear.

Recently the arylation of amines and anilines using aryl halides with palladium or nickel catalysis has been well documented by Hartwig and Buchwald.[8] In addition Buchwald has recently shown the palladium-catalysed cyclisation of secondary amides and carbamates to give indanes and indanones.[9] In this communication, we present an approach to *N*-substituted indole-2-carboxylates using an intramolecular palladium-catalysed amination reaction to form the heterocyclic core of the indole nucleus with the nitrogen substituent installed prior to cyclisation (Scheme 1).



Scheme 1.

N-Aryl-α-phosphonylglycines (**3**) were prepared according to the rhodium carbenoid insertion method developed by Haigh and Moody.[10] Thus, ethyl 2-diazo-2-diethoxyphosphonylacetate (**1**) (1 equiv.) and the appropriate aniline (**2**) (1 equiv.) were heated in toluene at 110°C with catalytic $Rh_2(OAc)_4$ for between 4 and 18 h by which time the reaction was complete. Horner–Wadsworth–Emmons (HWE) reaction of the *N*-aryl-α-phosphonylglycine (**3**) derivatives with 2-iodobenzaldehydes (**4**: X=H, 5-NO_2, 4-NO_2, 5-OMe) using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base in dichloromethane at room temperature gave the corresponding didehydro compounds (**5**) in excellent yield. Although the HWE reaction of *N*-acyl-α-phosphonylglycine derivatives with aldehydes is well known,[11] we believe this is the first report of *N*-aryl-α-phosphonylglycine derivatives being used in this reaction. In each case a single geometrical isomer was formed which on the basis of ROESY experiments the double bond was assigned as *Z*. Treatment of these compounds with $PdCl_2$ (dppf) (0.05 equiv.) and KOAc (3 equiv.) in DMF at 90°C cleanly gave the substituted indoles (**6**) in good yield, typically, reactions were complete within 4 h.[12] The electronic nature of the substituents on the phenyl ring bearing the iodine atom had little effect on the yield of cyclisation, compounds with electron withdrawing, neutral or electron donating groups reacting equally well (Table 1). It is noteworthy that the final *N*-substituted products are formed with little, if any, concomitant formation of de-iodinated products.

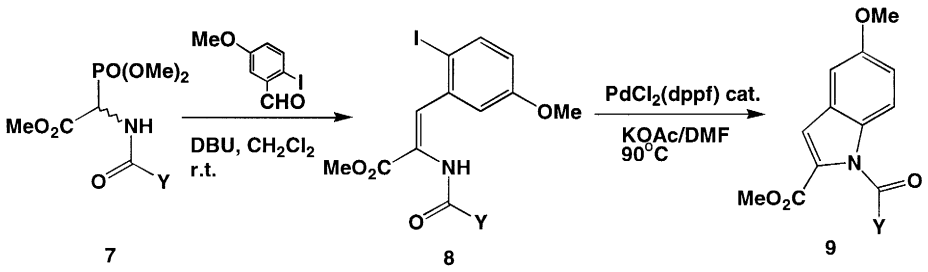
The cyclisation of *N*-acyl didehydroamino acid derivatives was an obvious extension to this methodology. The necessary *N*-acyl-α-phosphonylglycines (**7**) were prepared from commercially available *N*-Cbz-α-phosphonylglycine methyl ester via removal of the protecting group followed by an EDC coupling with the appropriate acid. HWE reaction with 2-iodo-4-methoxybenzaldehyde gave (*Z*)-didehydro com-

Table 1
N-Aryl indole-2-carboxylates

Entry	X[a]	Y	**3** Yield[b] /%	**5** Yield[b] /%	**6** Yield[b] /%
1	H	4-CO_2Et	91	87	89
2	6-NO_2	2-Br	89	92	83
3	6-NO_2	4-CH_2CO_2Et	90	88	93
4	6-NO_2	3,4-OCH_2O	88	96	94
5	5-NO_2	2-Br	89	78	90
6	H	3,4-OCH_2O	88	93	92
7	5-OMe	4-CO_2Et	91	84	94
8	5-OMe	3,4-OCH_2O	88	88	90

[a]position of substituent on final indole nucleus **6**
[b]isolated yield

pounds (**8**) in high yield which were cyclised to give *N*-acyl indole-2-carboxylates (**9**) in the same manner as above (Scheme 2) again in good overall yield (Table 2).



Scheme 2.

Table 2
N-Acyl indole-2-carboxylates

Entry	Y	**7** Yield[a] /%	**8** Yield[a] /%	**9** Yield[a] /%
1	2-chloro-3-pyridyl	95	93	91
2	Ph	96	95	45
3	OBn	[b]	94	85

[a]isolated yield
[b]commercially available

In conclusion, we have demonstrated an efficient, general method for the synthesis of *N*-substituted indole-2-carboxylates, which uses a simple procedure and work up, giving the products in high overall yield and is complementary to existing strategies.

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12. Typical reaction conditions. For entry 7: (a) To a solution of the phosphonylacetate (**3**) (230 mg, 0.6 mmol) and 2-iodo-5-methoxybenzaldehyde (157 mg, 0.6 mmol) in dichloromethane (5 ml) at room temperature was added DBU (0.10 ml, 1.1 equiv.) The reaction was stirred for 30 min and then partitioned between EtOAc (50 ml) and water (50 ml). The organics were separated and washed with water (3×20ml), and brine (20 ml), and then dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by triturating with diethyl ether to give the product (**5**) as a yellow solid (249 mg, 84%.) FTIR ν_{max} (solid) 3346, 1707, 1689, 1601cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (3H, t, J=7.1 Hz), 1.40 (3H, t, J=7.1 Hz), 3.38 (3H, s), 4.28 (2H, q, J=7.1 Hz), 4.36 (2H, q, J=7.1 Hz), 6.43 (1H, dd, J=3.0, 8.8 Hz), 6.54 (2H, d, J=8.7 Hz), 6.56 (1H, s), 6.78 (1H, d, J=3.0 Hz), 7.14 (1H, s), 7.68 (1H, d, J=8.8 Hz), 7.74 (2H, d, J=8.7 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 14.4, 55.0, 60.5, 62.3, 89.8, 114.1, 116.1, 117.4, 122.3, 123.7, 127.6, 130.5, 138.5, 139.5, 145.1, 159.4, 165.9, 166.4 ppm. *m/z* (ESI+, 70 V) found MH+496. (b) To a solution of the iodoalkene (**5**) (148 mg, 0.3 mmol) in DMF (5 ml) under N_2 at room temperature was added KOAc (95 mg, 1 mmol) and $PdCl_2$(dppf) (14 mg, 6 mol%). The mixture was heated to 90°C for a period of 30 min, and then partitioned between EtOAc (50 ml) and water (50 ml). The aqueous was separated and the organics washed with water (4×25 ml), brine (30 ml), dried ($MgSO_4$), filtered and solvent removed in vacuo to give a brown oil. Column chromatography (eluant 4:1, hexane:EtOAc) gave the product (**6**) as a clear oil (111 mg, 94%). FTIR $\nu_{max.}$ (film) 2982, 1710, 1610cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24(3H, t, J=7.2 Hz), 1.43 (3H,t, J=7.2 Hz), 3.86 (3H, s), 4.23 (2H, q, J=7.1 Hz), 4.43 (2H, q, J=7.1 Hz), 6.95 (1H, dd, J=2.2, 9.1 Hz), 7.02 (1H, d, J=9.1 Hz), 7.11 (1H, d, J=2.1 Hz), 7.39 (2H, d, J=8.2 Hz), 7.42 (1H, s), 8.20 (2H, d, J=8.2 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 14.8, 56.1, 61.0, 61.6, 103.0, 112.2, 112.5, 117.5, 127.1, 128.3, 129.6, 130.3, 130.5, 130.8, 136.1, 143.1, 155.7, 161.5, 166.3 ppm. *m/z* (ESI+, 70 V) found MH+368.