Palladium-catalysed heteroannulation of vinylic compounds: a highly convenient method for the synthesis of *N*-aryl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acids

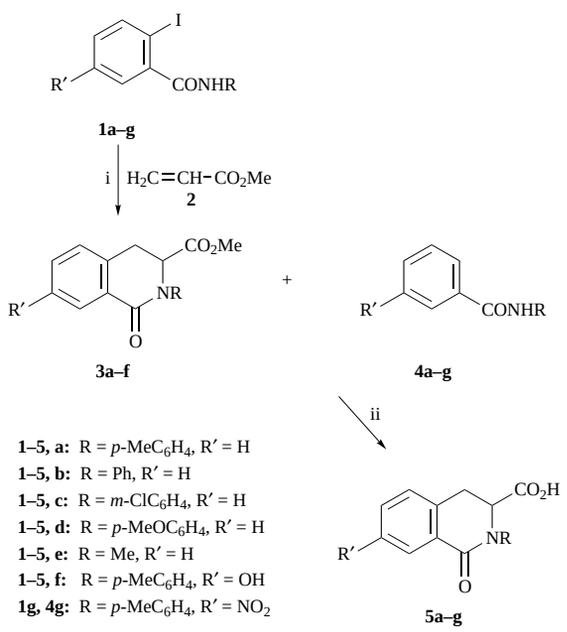
Jyan S. Mahanty, Mahuya De and Nitya G. Kundu *

Department of Organic Chemistry, Indian Association for the Cultivation of Science Jadavpur, Calcutta-700 032, India

***N*-Aryl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acids have been synthesized by facile palladium-catalysed olefination of *N*-aryl-2-iodobenzamides**

Although scarce in nature,[1–6] 1(2*H*)-isoquinolones and their perhydro derivatives are constituents of several compounds of medicinal importance.[7–11] For example, 1(2*H*)-isoquinolones have been described as analgesics, antiinflammatory and anticonvulsive agents and tranquilizers. Some Amaryllidaceae alkaloids, *e.g.* pancratistatin, containing the 1(2*H*)-isoquinolone moiety, is reported to possess antitumour activity.[12] Also, substituted perhydroisoquinoline-3-carboxylic acids have been reported to be potent, systemically active, competitive AMPA receptor antagonists.[13]

Various methods are known for the synthesis of 1(2*H*)-isoquinolones[14–21] and the synthesis of 1,2,3,4-tetrahydro-1(2*H*)-isoquinolones has also been reported.[22–24] However, palladium-catalysed procedures for the synthesis of 1(2*H*)-isoquinolones and 1,2,3,4-tetrahydro-1(2*H*)-isoquinolones are limited in number. Hegedus and co-workers[25] reported the synthesis of two isoquinolones starting from *o*-allybenzamides through palladium-mediated reactions, although nearly equivalent amounts of the palladium catalyst were needed. Similar reactions needing equivalent amounts of palladium catalysts leading to a few isoquinolones have also been reported by Kasihara and co-workers.[26] Only a few examples of the synthesis of a small number of isoquinolone derivatives using palladium-catalysed reactions have been reported in the literature.[27–31] With this background it seemed desirable to develop facile palladium-catalysed procedures for the synthesis of substituted 1(2*H*)-isoquinolones. In continuation of our studies on the synthesis of various heterocyclic structures[32–35] by palladium-catalysed reactions, we have recently developed a facile method for the synthesis of the title compounds **5** through palladium-catalysed olefination of *N*-aryl-2-iodobenzamides **1** with methyl acrylate **2** (Scheme 1) which we here report.



Scheme 1 *Reagents and Conditions:* i, $Pd(Ph_3P)_2Cl_2$, DMF, Et_3N, 80 °C, 24 h; ii, NaOH (1.5 equiv.), MeOH

Results and discussion

N-Aryl-2-iodobenzamides **1**, when stirred with methyl acrylate **2** in the presence of bis(triphenylphosphine)palladium(II) chloride (3–3.6 mol% based on **1**) in DMF with triethylamine as base, at 80 °C for 24 h gave *N*-aryl-3-methoxycarbonyl-1,2,3,4-tetrahydro-1(2*H*)-isoquinolones **3** together with the deiodinated benzamides **4**. Partial deiodination of *N*-aryl-2-iodobenzamides **1** could not be avoided irrespective of the reaction conditions employed and furthermore, occurred even in the absence of methyl acrylate. Thus, a mixture of **1** (R = *p*-MeC_6H_4) and $Pd(Ph_3P)_2Cl_2$ in DMF with triethylamine as base when stirred at 80 °C for 24 h gave compound **4** in 37.0% yield. Although separation of products **3** and **4** by column chromatography was difficult, hydrolysis with base of the esters **3** gave the corresponding acids **5** (Table 1) which could be easily separated. The overall yields of the product **5** were in the range 28–71%.

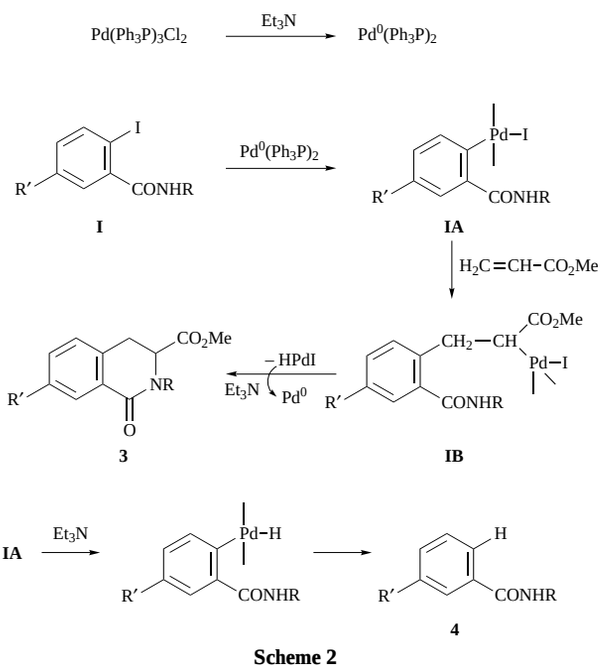
Studying the effect of temperature on the course of the reaction, we found that at 50 °C, only partial deiodination occurred, whereas at 60 °C trace amounts of the isoquinolone esters **3** could be identified (^{1}H NMR). The optimum temperature appeared to be 80 °C, product yields not increasing at higher temperature (entries 1, 2, 3; Table 1). The addition of copper(I) iodide was found not to be essential for the success of the reaction and, in fact, its presence suppressed the yields (entry 1 *vs.* 4). Bis(triphenylphosphine)palladium(II) dichloride was found to be the catalyst of choice, other palladium catalysts, *e.g.* palladium(II) acetate or tetrakis(triphenylphosphine)-palladium(0) resulting in decreased yields (entries 5 and 6). DMF was found to be the best solvent for the reactions, acetonitrile with triethylamine as base giving a lower yield (entry 7) and dimethyl sulfoxide (entry 8) giving deiodinated product (56%) along with starting material. No reaction occurred in benzene (entry 9).

Although we have also studied an alternative approach towards the synthesis of the carboxylic acid **5** involving palladium-catalysed olefination with acrylonitrile followed by hydrolysis under basic conditions, this resulted in a lower product yield (entry 11). It was noted that electron-donating substituents on the *N*-aryl group increased the yield of the cyclised products (entry 13 *vs.* 10) whereas electron-withdrawing substituents decreased the yields; substitution on the aromatic ring (benzamide part) reduced the yields considerably, the

Table 1 Synthesis of *N*-aryl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acids **5**[a,b] (Scheme 1)

Entry	Amide[c]	Catalyst[d]	Solvent	Temp (°C)	Products	
					5 (% Yield)[e]	**4** (% Yield)[e]
1	**1a**	A	DMF	80	61	13.5
2	**1a**	A	DMF	100	60	15.3
3	**1a**	A	DMF	130	60.2	15.7
4[f]	**1a**	A	DMF	80	54.2	23.7
5	**1a**	B	DMF	80	47.5	23.7
6	**1a**	C	DMF	80	42.4	23.8
7	**1a**	A	CH_3CN	80	47.4	23.7
8	**1a**	A	DMSO	80	—	55.9
9	**1a**	A	C_6H_6	80	*g*	
10	**1b**	A	DMF	80	56	12.9
11[h]	**1b**	A	DMF	80	36.1	19
12	**1c**	A	DMF	80	47.3	13.7
13	**1d**	A	DMF	80	71.1	9.1
14	**1e**	A	DMF	80	53.7	15.4
15	**1e**	A	DMF	80	35.5	26.6
16	**1f**	A	DMF	80	28	50
17	**1g**	A	DMF	80	—	91.3

[a] Satisfactory spectroscopic and analytical data were obtained for all the compounds **5** (see Experimental Section). Compounds **4** were identified from mp (comparison with literature mp) and ^{1}H NMR spectroscopic data. [b] Triethylamine (≈ 4 equiv. based on **1**) was used as base. [c] Amides were obtained by condensing *o*-iodobenzoyl chloride with the corresponding amines. [d] A: 3–3.6 mol% $(Ph_3P)_2PdCl_2$ used, B: 5–8 mol% $Pd(OAc)_2$ used, C: 3.66 mol% $(Ph_3P)_4Pd$ used. [e] Refers to the isolated yields of **4** and **5** based on the starting material **1**. [f] 6 Mol% copper(I) iodide used. [g] Only starting material recovered. [h] Acrylonitrile was used for olefination.



Scheme 2

Heck reaction being completely inhibited by a nitro substituent and affording only the deiodinated product.

The use of other substituted vinylic compounds in their reaction with **1** was also studied. Allylic halides in contrast to the observation of Larock and co-workers[36] failed to give any *N*-heterocycles under our conditions, the vinylic group needing to be activated by conjugation with an ester or a nitrile group for the desired reaction to take place. Conjugated aldehydes (*e.g.* acrolein) led only to deiodinated products whereas conjugated vinylic ketones (*e.g.* methyl vinyl ketone) gave a mixture of cyclic product and the deiodinated compound **4** which were not easily separable by column chromatography. *N*-Aryl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acids **5** were characterised by their spectroscopic data. IR absorption at 1650–1660 cm^{-1} clearly indicated the presence of a δ-lactam ring. In the ^{1}H NMR spectra the presence of an ABX pattern corresponding to the H_2C_4-C_3H part of the ring was clearly discernible, establishing the formation of the six-membered 1,2,3,4-tetrahydroisoquinolone moiety.

The mechanism of formation of **3** may be explained as follows: the σ-aryl palladium complex (**IA**) undergoes a Heck reaction with methyl acrylate **2** leading to **IB** which on elimination of 'HPdI' leads to the isoquinolones **3**. A competitive reduction of **IA** with triethylamine will lead to the deiodinated product **4**.[37]

Thus, we have described for the first time a palladium-catalysed procedure for the heteroannulation of *N*-aryl-2-iodobenzamides with acrylic esters to afford products which upon alkaline hydrolysis gave *N*-aryl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acids. This constitutes a general and facile method for the synthesis of this type of compound from readily available starting materials. The importance of oxoquinoline-3-carboxylic acids (ciprofloxacin, norfloxacin and others) as antibacterial agents[38,39] underlines the need for the facile synthesis of the corresponding isoquinoline analogues in order to study further their biological properties.

Experimental

Mps were determined on a Reichert (285980) (Austria) bath and are uncorrected. UV spectra were recorded on a Hitachi 200-20 spectrometer in spectrophotometric grade ethanol (Baker). IR spectra were taken on a Perkin-Elmer 298 instrument as KBr plates. ^{1}H NMR spectra were recorded on a Varian EM-360 spectrometer, Bruker DPX-300 and Bruker 200 spectrometers in solvents as indicated with tetramethylsilane as internal reference; *J* values given in Hz. Silica gel TLC was performed on 60F-254 pre-coated sheets (E. Merck) and column chromatography was done on silica gel (60–120 mesh). Elemental analyses were performed on a Perkin-Elmer 240C analyser.

General procedure for the synthesis of *N*-substituted 1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acids

To a solution of *N*-substituted 2-iodobenzamide (300 mg, 0.89 mmol) in DMF (5 cm^3) were added bis(triphenylphosphine)-palladium(II) dichloride (0.028 mmol, 3.15 mol%), triethylamine (3.56 mmol, 4 equiv.) and methyl acrylate (2.67 mmol, 3 equiv.). The mixture was stirred under a nitrogen atmosphere at 80 °C for 24 h after which it was evaporated under reduced pressure and the residue purified by column chromatography on silica gel using 2.5% ethyl acetate in chloroform as eluent. *N*-Substituted 3-methoxycarbonyl-1,2,3,4-tetrahydro-1(2*H*)iso-

quinolones **3** were eluted together with the deiodinated benzamides **4**. The mixture was easily separated by hydrolysis of the ester (240 mg, 0.49 mmol) with a refluxing solution of NaOH (1.5 equiv.) in MeOH (10 cm^3) during a period of 1.5 h. After removal of solvent from the mixture, the residue was diluted with water (25 cm^3) and filtered. The filtrate upon neutralisation regenerated the acid **5**. The deiodinated product **4** remained in the residue.

***N-p*-Tolyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid 5a.** Mp 195–196 °C; ν_{max}(KBr)/cm^{-1} 1730s, 1660s, 1520, 1430, 1400; λ_{max}(EtOH)/nm 281.2 (log ε 4.00) and 228.2 (log ε 4.14); δ_H(200 MHz, [$^2H_6$]-DMSO) 2.33 (s, 3H, Ar-Me), 2.51 (dd, *J* 7.4, *J* 16.3, 1H, H-4ax), 2.87 (dd, *J* 3.8, *J* 16, 1H, H-4eq), 5.61 (dd, *J* 3.8, *J* 7.3, 1H, H-3) and 7.24–7.78 (m, 8H, ArH) (Found: C, 72.59; H, 5.63; N, 5.26. $C_{17}H_{15}NO_3$ requires C, 72.58; H, 5.38; N, 4.98%).

***N*-Phenyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid 5b.** Mp 184–185 °C; ν_{max}(KBr)/cm^{-1} 1730s, 1650s, 1600, 1500 and 1420; λ_{max}(EtOH)/nm 274.8 (log ε 4.01) and 228.6 (log ε 4.12); δ_H(100 MHz, [$^2H_6$]-DMSO) 2.60 (dd, *J* 8, *J* 16, 1H, H-4ax), 2.92 (dd, *J* 4, *J* 16, 1H, H-4eq), 5.72 (dd, *J* 4, *J* 8, 1H, H-3), 7.16–8.12 (m, 9H, ArH) and 12.40 (br s, 1H, CO_2H); δ_C(75 MHz, [$^2H_6$]-DMSO) 36.820 (C-4), 57.917 (C-3), 123.787, 124.080, 124.759, 126.322, 129.418, 129.792, 132.548, 133.127, 137.498, 145.570 (Ar-C), 167.007 and 171.815 (CO); δ_C(75 MHz, [$^2H_6$]-DMSO DEPT 135) 36.527 (inverted, C-4), 57.626 (C-3), 123.503, 123.797, 124.472, 126.038, 129.136, 129.510 and 132.845 (Ar-C) (Found: C, 71.77; H, 5.03; N, 5.36. $C_{16}H_{13}NO_3$ requires C, 71.90; H, 4.90; N, 5.24%).

***N-m*-Chlorophenyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid 5c.** Mp 161–162 °C; ν_{max}(KBr)/cm^{-1} 1720s, 1660s, 1590 and 1490; λ_{max}(EtOH)/nm 275.8 (log ε 3.95); δ_H(100 MHz, [$^2H_6$]-DMSO) 2.66 (dd, *J* 8, *J* 16, 1H, H-4ax), 2.92 (dd, *J* 4, *J* 16, 1H, H-4eq), 5.72 (dd, *J* 4, *J* 8, 1H, H-3), 7.20–8.16 (m, 8H, Ar-H), 12.40 (br s, 1H, CO_2H) (Found: C, 63.52; H, 4.27; N, 4.70. $C_{16}H_{12}ClNO_3$ requires C, 63.69; H, 4.01; N, 4.64%).

***N-p*-Methoxyphenyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid 5d.** Mp 216–218 °C; ν_{max}(KBr)/cm^{-1} 1720s, 1660s, 1520s and 1400; λ_{max}(EtOH)/nm 281.8 (log ε 3.99) and 228.6 (log ε 4.18); δ_H(200 MHz, [$^2H_6$]-DMSO) 2.51 (dd, *J* 7.3, *J* 16, 1H, H-4ax), 2.83 (dd, *J* 4, *J* 16, 1H, H-4eq), 3.78 (s, 3H, Ar-OMe), 5.55 (dd, *J* 4.1, *J* 7.86, 1H, H-3), 7.01 (d, *J* 9, 2H, Ar-H_m) and 7.44–7.77 (m, 6H, ArH) (Found: C, 68.35; H, 5.25; N, 4.69. $C_{17}H_{15}NO_4$ requires C, 68.67; H, 5.08; N, 4.71%); δ_C(75 MHz, [$^2H_6$]-DMSO) 36.858 (C-4), 55.515 (OCH_3), 57.885 (C-3), 95.947, 114.413, 123.147, 123.456, 126.150, 128.685, 129.615, 132.167, 145.021, 157.467 (Ar-C), 166.203 and 171.410 (CO); δ_C(75 MHz, [$^2H_6$]-DMSO, DEPT 135) 37.082 (inverted, C-4), 55.729 (OCH_3), 58.103 (C-3), 114.625, 123.355, 123.666, 126.359, 128.894 and 132.387 (Ar-C).

***N*-Methyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid 5e.** Mp 165–167 °C; ν_{max}(KBr)/cm^{-1} 1700s, 1660s, 1450 and 1400; λ_{max}(EtOH)/nm 279.2 (log ε 3.24) and 239.8 (log ε 3.82); δ_H(60 MHz, [$^2H_6$]-DMSO) 2.71 (dd, *J* 8, *J* 16.3, 1H, H-4ax), 2.87 (dd, *J* 4.2, *J* 16, 1H, H-4eq), 3.13 (s, 1H, N-Me), 4.83 (dd, *J* 4, *J* 8, 1H, H-3) and 7.53–7.73 (m, 4H, Ar-H) (Found: C, 64.05; H, 5.44; N, 6.88. $C_{11}H_{11}NO_3$ requires C, 64.37, H, 5.40, N, 6.83%).

***N-p*-Tolyl-7-hydroxy-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid 5f.** Mp >260 °C; ν_{max}(KBr)/cm^{-1} 1720s, 1660s, 1520 and 1390; λ_{max}(EtOH)/nm 281.6 (log ε 3.97); δ_H(60 MHz, [$^2H_6$]-DMSO) 2.38 (s, 3H, Ar-Me), 2.51 (dd, *J* 7.4, *J* 16, 1H, H-4ax), 2.73 (dd, *J* 4, *J* 16, 1H, H-4eq), 5.36 (dd, *J* 4, *J* 8, 1H, H-3) and 7.13–7.66 (m, 7H, ArH) (Found: C, 67.03; H, 5.49; N, 4.70. $C_{16}H_{15}NO_4$ requires C, 67.36; H, 5.29; N, 4.91%.

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