STUDIES DIRECTED TOWARD THE SYNTHESIS OF MARTINELLINES: ONE POT SYNTHESIS OF PYRROLOQUINOLONE RING SYSTEM

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Abstract - The Pd-catalysed coupling between aryl iodides and 3-carbethoxy-4,5-dihydropyrroles has been described. With ortho-iodoanilines, tandem cyclisation leading to pyrroloquinolones present in martinellines, was observed.

Recently isolated1 new alkaloids martinelline (1) and martinellic acid (2), from the roots of tropical plant Martinella iquitosensis, possess potent Bradykinin (BK) B_1 and B_2 receptor antagonist activity. 1 and 2 are the only nonpeptide BK antagonists reported so far. More importantly, 1 and 2 are characterised by the presence of unknown pyrroloquinoline skeleton which has not been observed so far in naturally occurring compounds.

These features prompted us to device a potential general strategy to construct the new tricyclic pyrroloquinoline ring system based on Heck reaction.2 This communication describes the Pd-catalysed arylation of N-substituted 3-carbethoxy-4,5-dihydropyrrole (4) to efficiently obtain pyrroloquinolone derivatives (3).

The synthesis of 4 was initiated from 2-aminoethanol (5) which was protected as the N-BOC derivative
and then subjected to the treatment\(^3\) with a mixture of PPh\(_3\) - CCl\(_4\) - Et\(_3\)N in MeCN at room temperature to furnish the aziridine derivative (7) in 82% yield (Scheme 1). Subsequently, 7 was treated\(^4\) with sodium salt of diethyl malonate in refluxing THF to obtain the pyrrolidone derivative (8) in 73% yield. In order to effect unsaturation, compound (8) was partially reduced with NaBH\(_4\) - MeOH at -40 °C and the corresponding hemiaminal intermediate (9) was immediately reacted with MsCl-Et\(_3\)N in CH\(_2\)Cl\(_2\) at room temperature to give 4,5-dihydropyrole (4a, R=t-Bu) in 60% yield. Similarly, compound (4b) (R=Et) was prepared and structures of both these products were confirmed by \(^1\)H-nmr\(^5\) and mass spectral data.\(^6\) We next examined the Pd-catalysed arylation reaction of 4a/b to establish optimum conditions for this reaction.

**Scheme 1**

\[
\begin{align*}
\text{HO} & \xrightarrow{i} \text{HO} \xrightarrow{\text{ii}} \text{CO}_2R \\
\text{NH}_2 & \xrightarrow{\text{iii}} \text{CO}_2R \\
\text{N} & \xrightarrow{\text{iv}} \text{CO}_2R \\
\text{7} & \xrightarrow{\text{v}} \text{CO}_2Et
\end{align*}
\]

i) (Boc\(_2\))O, THF, H\(_2\)O, room temperature, 2 h; ii) PPh\(_3\), CCl\(_4\), Et\(_3\)N, MeCN, room temperature, 12 h; iii) NaH, CH\(_2\)(CO\(_2\)Et\(_2\)), THF, reflux, 7 h; iv) NaBH\(_4\), MeOH, -40 °C, 30 min; v) MsCl, Et\(_3\)N, room temperature, 2 h.

After several conditions tried we concluded that Pd(OAc)\(_2\) in refluxing MeCN with PPh\(_3\) and Bu\(_3\)N as promoters gave satisfactory yields. For instance, iodobenzene (10) (1.0 mmol), and 4a/b (1.2 mmol) were heated under reflux with Pd(OAc)\(_2\) (0.2 mmol), PPh\(_3\) (0.4 mmol), and Bu\(_3\)N (1.0 mmol) in MeCN for 24 h to give the coupled product (13/14) in 80-85% yield. The structures of 13/14 were supported by

**Scheme 2**

\[
\begin{align*}
\text{R}^1 & \xrightarrow{i} \text{CO}_2R \\
\text{10, R}^1 = \text{H} & \quad 13, \text{R}^1 = \text{H} ; \text{R} = \text{t-Bu} (80\%) \\
\text{11, R}^1 = \text{NO}_2 & \quad 14, \text{R}^1 = \text{H} ; \text{R} = \text{Et} (85\%) \\
\text{12, R}^1 = \text{Me} & \quad 15, \text{R}^1 = \text{NO}_2 ; \text{R} = \text{Et} (20\%) \\
\text{4a, R} = \text{t-Bu} & \quad 16, \text{R}^1 = \text{Me} ; \text{R} = \text{t-Bu} (70\%) \\
\text{4b, R} = \text{Et} & \quad 17, \text{R}^1 = \text{H} ; \text{R} = \text{t-Bu} \\
\text{18} & \quad 18
\end{align*}
\]

i) Pd(OAc)\(_2\), PPh\(_3\), Bu\(_3\)N, MeCN, reflux, 24 h; ii) 10% Pd-C, MeOH, H\(_2\), room temperature, 12 h.
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\(^1\)H-nmr and mass spectral data. The benzylic protons of \(13/14\) were distinctly located in their \(^1\)H-nmr spectrum thereby omitting the regiomeretic structure \((18)\). The identification of these structures led to an interesting observation in which the less stable non-aromatic ring system \((13/14)\) was preferred over perfectly stable aromatic ring system \((18)\). The possibility of initial formation of \(18\) followed by isomerisation to \(13/14\) was rather remote (Scheme 2). Similarly compounds \(15\) and \(16\) were prepared from 2-nitro-iodobenzene \((11)\) and 2-methyl-iodobenzene \((12)\) respectively.

Scheme 3

Alternatively, an explanation for obtaining \((13 - 16)\) based on mechanistic consideration of the Heck reaction was sought.\(^7\) For instance, in the second step of the reaction (Scheme 3), the aryl palladium halide adds to the double bond in a syn fashion rendering the benzylic hydrogen and palladium halide groups anti to each other. The final and the preferred syn elimination of hydridopalladium halide occurs, as indicated, to provide \(13 - 16\) as sole products.

Scheme 4

i) \(\text{Pd(OAc)}_2, \text{PPh}_3, \text{Bu}_3\text{N}, \text{MeCN}, \text{reflux } 24\ h;\) ii) 10 % Pd-C, MeOH, H\(_2\), room temperature, 12 h.

In view of the above results we also examined the Pd-catalysed reaction between \(4a/b\) with ortho-iodoanilines \((19\) and \(20)\) (Scheme 4). As expected the C-C bond formation was accompanied with the tandem cyclisation between amine and carbethoxy group leading to the formation of tricyclic compounds \((21 - 23)\) in 41 - 47 % yield. Compounds \((21\) and \(23)\) were hydrogenated over 10 % Pd-C at room temperature and 1 atm pressure to give pyrroloquinolone derivatives \((24)\) and \((25)\). The stereochemistry at the ring junction of \(24\) was confirmed as cis by the \(^1\)H-nmr spectrum. The doublet due to benzylic proton appeared at \(\delta\) 5.26 with characteristic coupling constant \((J = 6.8\ \text{Hz})\) for cis geometry. This \(J\) value was consistent with the data\(^1\) for the natural products. The above methodology thus offers a fascinating direct entry to pyrroloquinoline system.
REFERENCES AND NOTES


5. $^1$H-NMR (200 MHz, CDCl$_3$) and mass spectral data of some selected compounds: Compound (8): $\delta$ 1.29 (t, 3H, $J = 8.3$ Hz), 1.50 (s, 9H), 2.10 - 2.45 (m, 2H), 3.45 (t, 1H, $J = 8.3$ Hz), 3.65 (m, 1H), 3.83 (m, 1H), 4.18 (q, 2H, $J = 4.2$ Hz); Compound (4b): $\delta$ 1.25 (m, 6H), 2.77 (t, 2H, $J = 8.5$ Hz), 3.82 (t, 2H, $J = 8.5$ Hz), 4.11 (m, 4H), 7.42 (br s, 1H); ms - 213 (M$^+$); Compound (13): $\delta$ 1.01 (m, 3H), 1.10 (s, 9H), 3.93 (m, 2H), 4.33 (m, 2H), 5.37 (m, 1H), 6.65 (s, 1H), 7.04 (m, 5H), mp 102 - 103 °C; Compound (14): $\delta$ 1.01 - 1.32 (m, 6H), 3.90 - 4.14 (m, 4H), 4.52 (m, 1H), 5.58 - 5.72 (m, 1H), 6.90 (s, 1H), 7.30 (s, 5H), ms - 289 (M$^+$); Compound (16): $\delta$ 1.13 (s, 9H), 1.17 (m, 3H), 2.48 (s, 3H), 4.01 (m, 2H), 4.42 (m, 2H), 5.75 (m, 1H), 6.77 (s, 1H), 7.04 (m, 4H), mp 90 - 91 °C; Compound (22): $\delta$ 1.25 (m, 3H), 4.22 (m, 3H), 4.53 (m, 1H), 5.73 (br s, 1H), 6.51 (s, 1H), 6.71 (d, 1H, $J = 7.5$ Hz), 6.95 (t, 1H, $J = 7.5$ Hz), 7.11 (t, 1H, $J = 7.5$ Hz), 7.37 (d, 1H, $J = 7.5$ Hz), 8.05 (s, 1H), CI-ms - 258 (M$^+$); Compound (24): $\delta$ 1.47 (s, 9H), 2.02 (m, 1H), 2.30 (m, 1H), 2.98 (m, 1H), 3.29 - 3.14 (m, 2H), 5.26 (d, 1H, $J = 6.8$ Hz), 6.73 (d, 1H, $J = 7.3$ Hz), 6.98 (t, 1H, $J = 7.3$ Hz), 7.13 (t, 1H, $J = 7.3$ Hz), 7.38 (d, 1H, $J = 7.3$ Hz), 9.13 (s, 1H), CI-m-s - 289 (M$^+$+1), mp 150 - 151 °C; Compound (25): $\delta$ 1.55 (s, 9H), 2.02 (m, 1H), 2.38 (m, 1H), 3.11 - 3.47 (m, 3H), 3.88 (s, 3H), 5.33 (d, 1H, $J = 6.6$ Hz), 6.88 (d, 1H, $J = 8.3$ Hz), 7.91 (d, 1H, $J = 8.3$ Hz), 8.25 (s, 1H), 9.42 (s, 1H), CI-m-s - 347 (M$^+$+1), mp 225 - 226 °C.

6. All the new compounds have satisfactory analysis by high resolution mass spectrum.

7. Ref. 2a, p. 833.

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