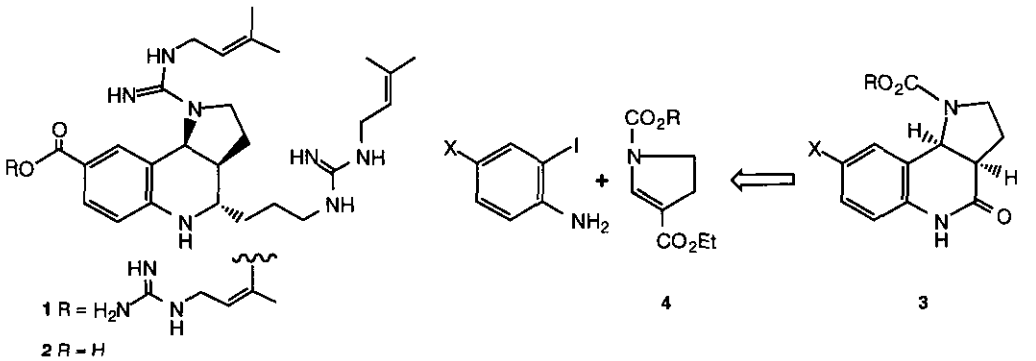
STUDIES DIRECTED TOWARD THE SYNTHESIS OF MARTINELLINES : ONE POT SYNTHESIS OF PYRROLOQUINOLONE RING SYSTEM

Mukund K Gurjar*, Shashwati Pal, and A V Rama Rao

Indian Institute of Chemical Technology, Hyderabad *500 007*, India

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 isolated[1] new alkaloids martinelline (**1**) and martinellic acid (**2**), from the roots of tropical plant *Martinella iquitosensis*, possess potent Bradykinin (BK) B_1 ad 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.

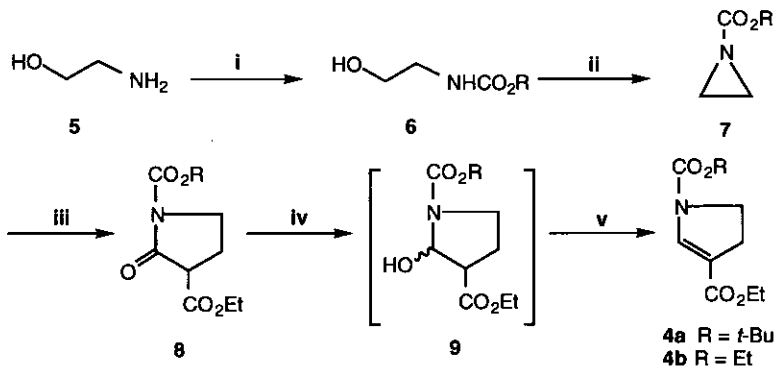


These features prompted us to device a potential general strategy to construct the new tricyclic pyrroloquinoline ring system based on Heck reaction.[2] This communication describes the Pd-catalysed arylation of *N*-substituted 3-carbethoxy-4,5-dihydropyrrole (**4**) to efficiently obtain pyrroloquinolone 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_3N in MeCN at room temperature to furnish the aziridine derivative (**7**) in 82 % yield (Scheme 1). Subsequently, **7** was treated[4] with sodium

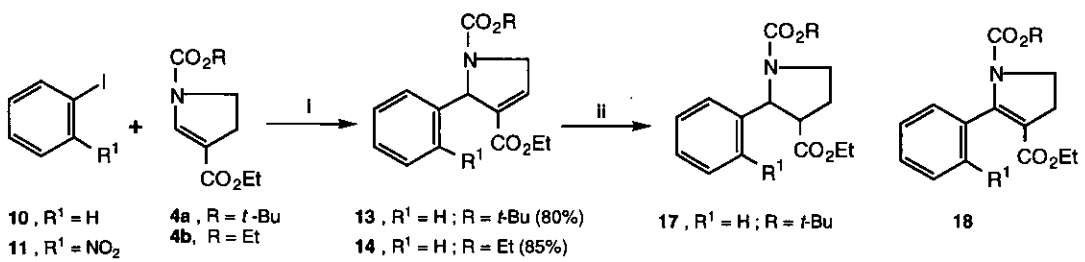
Scheme 1



i) $(Boc)_2O$, THF, H_2O, room temperature, 2 h; ii) PPh_3, CCl_4, Et_3N, MeCN, room temperature, 12 h; iii) NaH, $CH_2(CO_2Et)_2$, THF, reflux, 7 h; iv) $NaBH_4$, MeOH, -40 °, 30 min; v) MsCl, Et_3N, room temperature, 2 h.

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_3N in CH_2Cl_2 at room temperature to give 4,5-dihydropyrrole (**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 2



10 , R^1 = H
11 , R^1 = NO_2
12 , R^1 = Me

4a , R = *t*-Bu
4b, R = Et

13 , R^1 = H ; R = *t*-Bu (80%)
14 , R^1 = H ; R = Et (85%)
15 , R^1 = NO_2 ; R = Et (20%)
16 , R^1 = Me ; R = *t*-Bu (70%)

17 , R^1 = H ; R = *t*-Bu

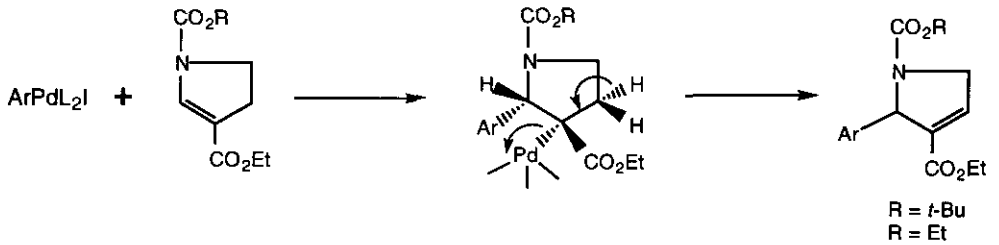
18

i) $Pd(OAc)_2$, PPh_3, Bu_3N, MeCN, reflux, 24 h; ii) 10% Pd-C, MeOH, H_2, room temperature, 12 h.

After several conditions tried we concluded that $Pd(OAc)_2$ in refluxing MeCN with PPh_3 and Bu_3N 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_3N (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

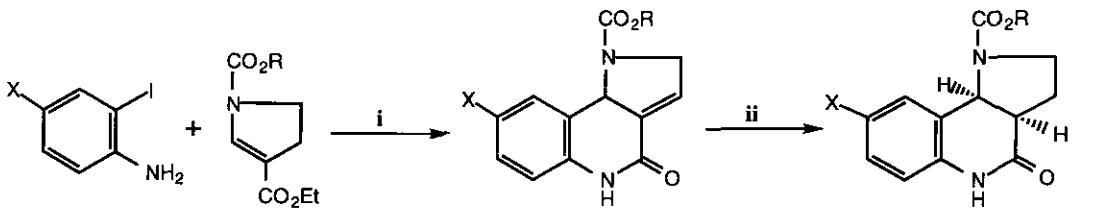
^{1}H-nmr and mass spectral data. The benzylic protons of **13/14** were distinctly located in their ^{1}H-nmr spectrum thereby omitting the regiomeric structure (**18**). The identification of these structures led to an interesting observation in which the less stable non-aromatic ring system (**13/14**) 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



19, X= H
20, X=CO_2Me

4a, R = *t*-Bu
4b, R = Et

21, X = H ; R = *t*-Bu (46%)
22, X = H ; R = Et (41%)
23, X = CO_2Me ; R = *t*-Bu (48%)

24, X = H ; R = *t*-Bu
25, X = CO_2Me ; R = *t*-Bu

i) $Pd(OAc)_2$, PPh_3, Bu_3N, MeCN, 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 δ 5.26 with characteristic coupling constant (J = 6.8 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

1. K.M. Witherup, R.W. Ransom, A.C. Graham, A.M. Bernard, M.J. Salvatore, W.C. Lumma, P.S. Anderson, S.M. Pitzenberger, and S.L. Varga, *J. Am. Chem. Soc.*, 1995, **117**, 6682.
2. a) S.A. Godliski, *Comprehensive Organic Synthesis*, ed. by B.M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, Vol., **4**, p. 585; ed. by R.F. Heck, *Palladium Reagents in Organic Synthesis*, Academic Press, London, 1985; b) R.F. Heck, *Organic Reactions*, 1982, **27**, 345; c) A.M. Rouchi, *Chem. Engg. News*, (June 1), **1995**, 32; J. Tsuji, *Organic Synthesis with Palladium Compounds*, Springer-Verlag, 1980; J. Tsuji, *Synthesis*, **1990**, 739.
3. R. Appel and R. Kleinstuck, *Chem. Ber.*, 1974, **107**, 1075.
4. H. Stamm, *Chem. Ber.*, 1966, **99**, 2556.
5. ^{1}H-Nmr (200 MHz, $CDCl_3$) and mass spectral data of some selected compounds : Compound (**8**) : δ 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**) : δ 1.25 (m, 6H), 2.77 (t, 2H, *J* = 8.5 Hz), 3.82 (t, 2H, *J* = 8.5 Hz), 4.11 (m, 4 H), 7.42 (br s, 1H); ms - 213 (M+); Compound (**13**) : δ 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**) : δ 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**) : δ 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**) : δ 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**) : δ 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-ms - 289 (M++1), mp 150 - 151 °C; Compound (**25**) : δ 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-ms - 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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