Pergamon

Tetrahedron Letters, Vol. 37, No. 15, pp. 2659-2662, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00354-1

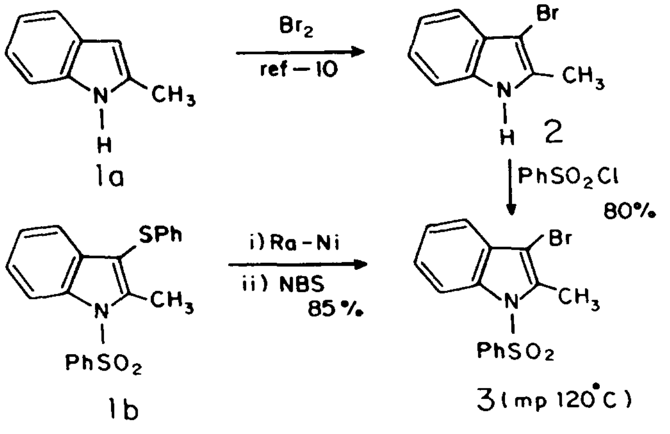
Synthesis of 4-Substituted-1,2,3,4-Tetrahydro-ß-Carbolines via Intramolecular Radical Cyclisation and Heck Reaction

Arasambattu K. Mohanakrishnan and Panayencheri C. Srinivasan*

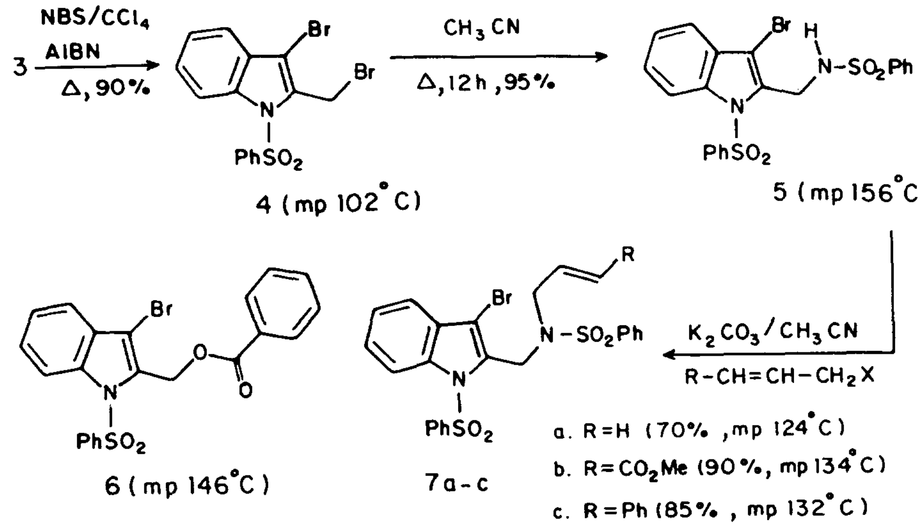
Department of Organic Chemistry, University of Madras,
Guindy Campus, Madras - 600 025, INDIA

Abstract : A convenient method for the synthesis of 4-substituted-ß-carbolines from the corresponding N-allylisogramine derivative is reported using intramolecular free radical cyclisation or Heck reaction. Copyright © 1996 Elsevier Science Ltd

The generation of aryl radicals by the homolysis of aryl halides using n-Bu_3SnH is well documented[1]. Recently several natural product syntheses based on radical cyclisation have been reported[2]. Eventhough the radical cyclisation and intramolecular Heck reactions are well exploited for the synthesis of indole derivatives[3], the generation of heteroaryl radical particularly indolyl-3-radical is not very common. There is only one report[4] of indolyl-3-radical by Sundberg. Intramolecular radical cyclisation is well exploited for the synthesis of fused[1,2-a]indoles involving both radical addition and radical generation at indole-2-position[5]. Kibayashi *et al* have developed[6] a synthesis of carbazoles using intramolecular cyclisation of enaminones involving arylpalladium complexes. Recently synthesis of 4-oxo-ß-carboline was reported[7] using zerovalent palladium. Traditionally ß-carboline alkaloids are synthesized from tryptamine derivatives using Pictet-Spengler reaction[8]. Till this date there is no report on the synthesis of ß-carbolines by radical cyclisation or intramolecular Heck reaction from the corresponding indole-3-halides. In continuation of our studies[9] with N-benzenesulfonyl-2(or)3-bromomethylindoles, we report here a facile synthesis of 1,2,3,4-tetrahydro-ß-carboline from 3-bromo-2-substituted indoles. 2-Methylindole **1a** was converted to the corresponding 3-bromo-2-methylindole **2** by the published[10] procedure and the latter was phenylsulfonylated under PTC conditions[11]. Compound **3** was also prepared from 2-methyl-N-benzenesulfonylindole[12] by adopting the reported[13] procedure.



The side chain bromination of **3** in boiling CCl_4 gave **4** in 90% yield. Then it was converted to the corresponding sulfonamide **5** in 95% yield and subsequently to the corresponding N-allyl derivative **7**. During alkylation of **5** a small amount of ester **6** was also isolated (less than 10%) when allyl chloride or methyl α-bromomethyl acrylate was the alkylating agent. The structure of **6** was confirmed by crystallographic studies[14]. It is obvious that CO_2 probably from K_2CO_3 gets incorporated in to the molecule connecting the phenyl ring of phenylsulfonyl group and the indole-2-methylene group. Still the precise mechanism of formation of ester **6** in the present case is not clear. Literature search indicated[15] that incorporation of CO_2 in amino function in Cs_2CO_3/DMF has been observed.



4 (mp 102°C)

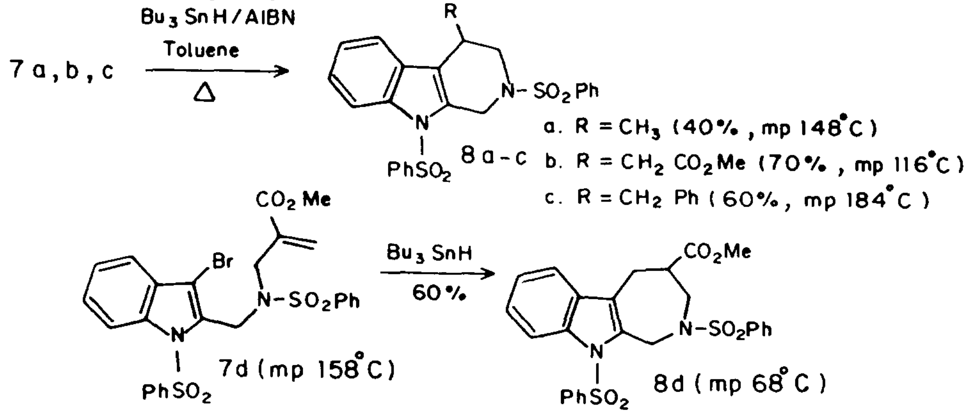
5 (mp 156°C)

6 (mp 146°C)

7a-c

a. R=H (70%, mp 124°C)
b. R=CO_2Me (90%, mp 134°C)
c. R=Ph (85%, mp 132°C)

Cyclisation of **7** in boiling toluene by 1.5 eq of n-Bu_3SnH gave the corresponding 4-substituted-ß-carboline derivatives **8** in 40-70% yield. In the case of **8a** a small amount of starting material was recovered. All of these compounds were characterized by ir, pmr[16] and mass spectra. Structure of **8c** was confirmed by crystallographic studies[14]. Cyclisation of **7d** gave the seven membered ring compound **8d** in 60% yield.



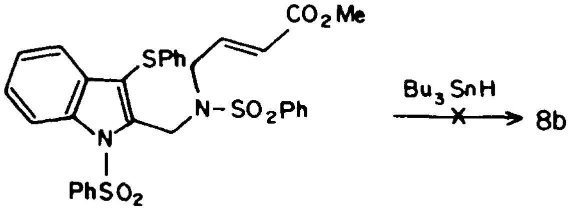
8a-c

a. R = CH_3 (40%, mp 148°C)
b. R = CH_2CO_2Me (70%, mp 116°C)
c. R = CH_2Ph (60%, mp 184°C)

7d (mp 158°C)

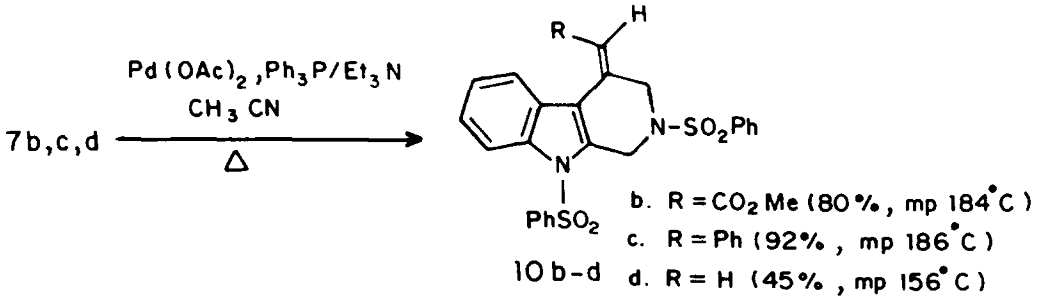
8d (mp 68°C)

Attempted radical generation at the indole-3-position using the corresponding thiophenyl derivative **9** was unsuccessful.



9 (mp 118°C)

Intramolecular Heck arylation of compound **7** gave the ß-carboline derivative **10** with an exocyclic methylene group. The mechanism of ester cleavage in the case of **7d** is not clear. The structures of compounds **10** were confirmed by ir, pmr[16] and mass spectra.



10 b-d
b. R = CO_2Me (80%, mp 184°C)
c. R = Ph (92%, mp 186°C)
d. R = H (45%, mp 156°C)

In summary we have developed a new and convenient synthesis of 4-substituted-ß-carbolines using hitherto unknown radical cyclisation and Heck reaction of the corresponding 3-bromo-N-allylisogramine derivatives. Related work regarding the generality and scope of this synthesis for more complex ß-carboline derivatives is under investigation.

Acknowledgement

AKM thanks CSIR, New Delhi for the award of research associateship. PCS acknowledges the SAP programme of this department from UGC, Government of India.

References

1 (a) Jasperse, C.P.; Fevig, T.L.; Curran D.P. *Chem Review.* **1991**, 1237-86.
(b) Shankaran, K.; Sloan, C.P.; Snieckus, V. *Tetrahedron Lett.* **1985**, 6001-04.
(c) Sloan, C.P.; Cuevas, J.C.; Queshelle, C.; Snieckus, V. *Tetrahedron Lett.* **1988**, 4685-86.
(d) Rosa, A.M.; Prabhakar, S.; Lobo, A.M. *Tetrahedron Lett.* **1990**, 1881-84.
2 (a) Balasubramanian, T.; Balasubramanian, K.K. *Synlett.* **1994**, 946-948.
(b) Sato, T.; Chono, N., Ishibashi, H.; Ikeda, M. *J.Chem. Soc., Perkin Trans-I.* **1995**, 1115-20.

3 (a) Kizil, M.; Murphy, J.A. *J.Chem.Soc., Chem.Comm.,* **1995**, 1409-10.
  (b) Michael, J.P.; Chang, S-F.; Wilson, C. *Tetrahedron Lett.* **1993**, 8365-68.
  (c) Larock, R.C.; Yum, E.K. *J.Am.Chem. Soc.,* **1991**, 6689-90.
4 Sundberg, R.J.; Cherney, R.J. *J. Org. Chem.,* **1990**, 6028-37.
5 (a) Caddick, S.; Aboutayab, K.; West R.I. *Synlett.* **1993**, 231-232.
  (b) Caddick, S.; Aboutayab, K.; West, R.I. *J. Chem. Soc., Chem. Comm.,* **1995**, 1353-54.
  (c) Moody, C.J.; Norton, C.L. *Tetrahedron Lett.* **1995**, 9051-52.
  (d) Dobbs, A.P.; Jones, K.; Veal, K.T. *Tetrahedron Lett.* **1995**, 4857-60.
6 Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.,* **1980**, 2938-42.
7 Chen, L-C.; Yang, S-C.; Wang, H-M. *Synthesis.* **1995**, 385-386.
8 Cox, E.D.; Cook, J.M. *Chem Review.* **1995**, 1797-1812.
9 Mohanakrishnan, A.K.; Srinivasan, P.C. *J. Org. Chem.* **1995**, 1939-46.
10 Boccnl, V.; Palla, G. *Synthesis.* **1982**, 1096-97.
11 Selvakumaran, S.; Srinivasan, P.C. *Indian J. Chem., Sec B,* **1985**, 6.
12 Jeevanandam, A.; Srinivasan, P.C. J.*Chem.Soc., Perkin Trans-I.* **1995**, 2663-65.
13 a) Nagarathnam, D.; *Synthesis.* **1992**, 743-745.
  b) Zhang, P.; Liu, R.; Cook, J.M. *Tetrahedron Lett.* **1995**, 3103-06.
14 The authors thank Dr.D.Velmurugan, Reader, Department of Biophysics and Crystallography, University of Madras, for confirming the structure of compounds **6 and 8c**.
15 Butcher, K.J. *Synlett.* **1994**. 825-826.

16 H^1-nmr($CDCl_3$) data of some representative compounds.

7d δ 3. 5 (s, 3H), 4.2 (s, 2H), 4.9 (s, 2H), 5.8 (s, 1H), 6 (s, 1H), 7.2-8.1 (m, 14H).

8b δ 2.62-2.86 (m, 3H), 3.45 (d, 1H) 3.54 (s, 3H), 4-4.1 (m, 2H), 5.1-5.2 (d, 1H), 7.2-7.6 (m, 9H), 7.75-7.8 (m, 2H), 7.9 (m, 2H), 8.05-8.1 (d, J=7.5Hz, 1H).

8c δ 2.55 (dd, 1H), 2.9 (m, 1H), 3.1 (m, 2H), 3.85 (d, 1H), 4.06 (d, 1H), 5.15 (d, 1H), 7.2-7.6 (m, 14H), 7.8-7.85 (dd, 4H), 8.1 (d, J=7.5Hz, 1H).

10b δ 3.8 (s, 3H), 4.8 (s, 2H),4.98 (s, 2H) 6.26 (s,1H), 7.2-7.7 (m, 11H), 8 (m, 2H), 8.2 (d, J=7Hz, 1H).

10c δ 4.46 (s, 2H), 5.05 (s, 2H), 7 (s, 1H), 7.2-7.8 (m, 16H), 8 (d, 2H), 8.3 (d, J=7Hz, 1H).

(*Received in UK* 25 *January* 1996; *revised* 19 *February* 1996; *accepted* 23 *February* 1996)