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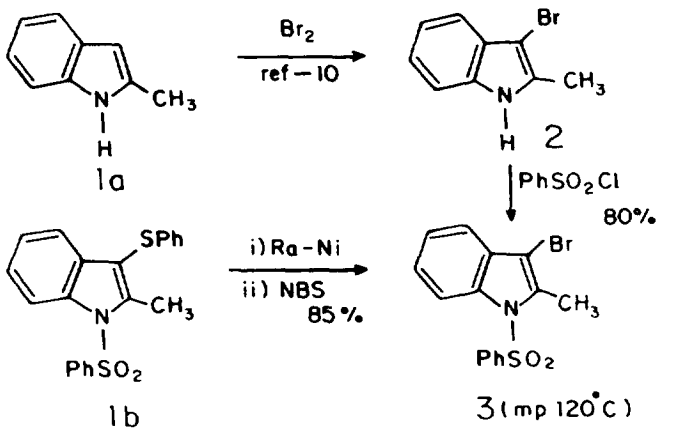
Synthesis of 4-Substituted-1,2,3,4-Tetrahydro-ß-Carbolines via Intramolecular Radical Cyclisation and Heck Reaction

Arasambattu K. Mohanakrishnan and Panayencheri C. Srinivasan*

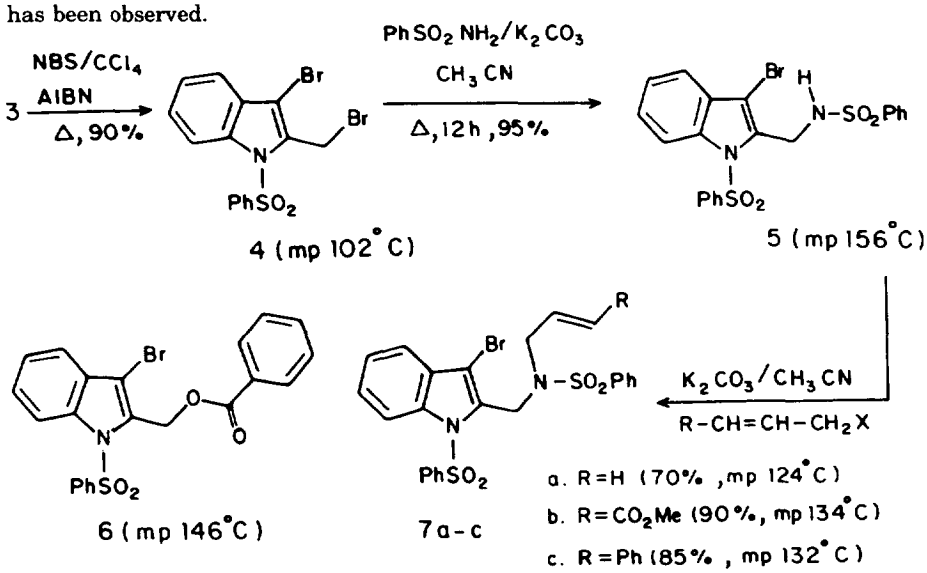
Department of Organic Chemistry, University of Madras,
Guindy Campus, Madras - 600 025, INDIA

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

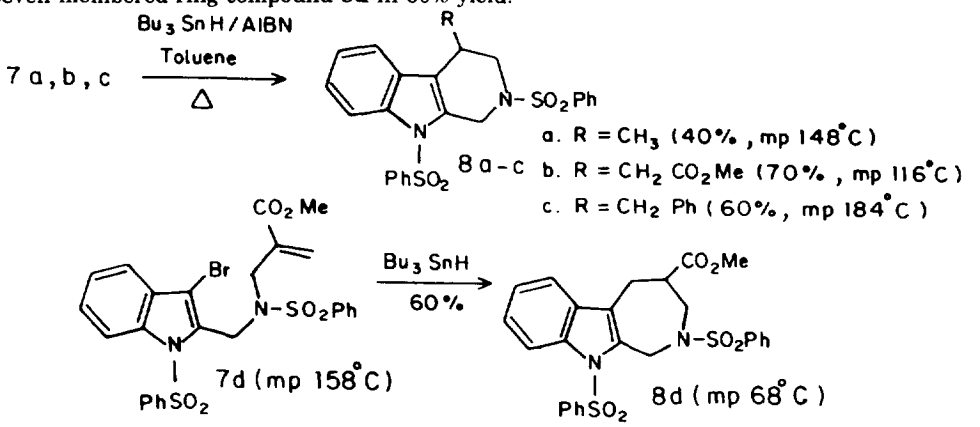
The generation of aryl radicals by the homolysis of aryl halides using n-Bu_3SnH is well documented[1]. Recently several natural product syntheses based on radical cyclisation have been reported[2]. Eventhough the radical cyclisation and intramolecular Heck reactions are well exploited for the synthesis 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.



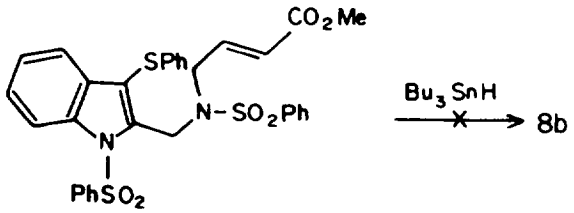
The side chain bromination of **3** in boiling CCl_4 gave **4** in 90% yield. Then it was converted to the corresponding sulfonamide **5** in 95% yield and subsequently to the corresponding N-allyl derivative **7**. During alkylation of **5** a small amount of ester **6** was also isolated (less than 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.



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.

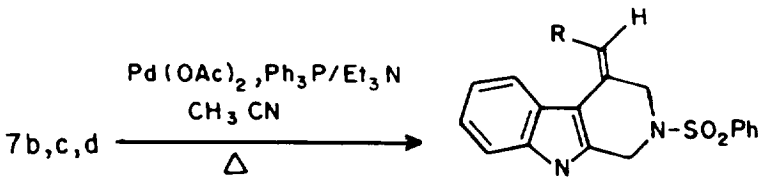


Attempted radical generation at the indole-3-position using the corresponding thiophenyl derivative **9** was unsuccessful.



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.

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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).

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