# Benzothienoindolizidines *via* Intramolecular Aryl Radical Cyclization or Palladium Catalyzed Cyclization

Pascal Pigeon and Bernard Decroix[*]

Laboratoire de Chimie, Faculté des Sciences et des Techniques de l'Université du Havre,
30, rue Gabriel-Péri, 76600 Le Havre, France

Abstract: Indolizidines 4,7 fused to both benzene and thiophene rings were synthesized *via* intramolecular aryl radical cyclization of enamide 3 or intramolecular Heck reaction of enamidone 5. Copyright © 1996 Elsevier Science Ltd

As a part of our continuing studies towards the synthesis of polyheterocycles containing an indolizidine moiety, the central system of a number of pharmacologically interesting indolizidine alkaloids[1], we recently examined different ionic cyclizations using a carboxylic group[2,3] or a formyl group[4] attached to N-thienylmethylpyrrolidine or pyrrole system. Now, we wish to report our initial studies of annulation of cyclic enamides **1** and **5** respectively *via* aryl radical cyclization or Heck reaction. Recently, indolizidines 167B and 209D have been synthesized stereoselectively *via* radical cyclization of β-aminoacrylates[5] using tributyltin hydride and AIBN in refluxing benzene, and lennoxamine was obtained via radical cyclization of linear enamide[6] using tributyltin hydride and AIBN in refluxing toluene (Scheme 1).

R = Me indolizine167 B
R = Bu indolizine 209D

Lennoxamine
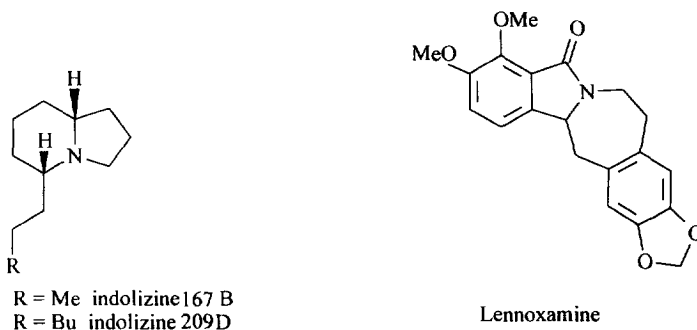
Scheme 1

The required enamide **3** was prepared in excellent yield (98%) in two steps by the selective addition of organometallic (R=butyl, phenylethynyl) upon the imide function of the reported phthalimide derivative **1**[7] (Scheme 2). The resulting hydroxylactam **2** (R=butyl) treated with PTSA in refluxing toluene gave enamide **3** with a E configuration as the major product. The intermediate N-acyliminium ion did not react with the thiophene nucleus to afford the possible five membered ring. In the case of R=phenylethynyl a Meyer-Schuster rearrangement[8] occurred under an acidic treatment leading to the enamidone **5** with a E configuration and a S-*cis* conformation. The ^{1}H NMR spectrum of **5**[9] shows a high value for the chemical shift of Ha benzene (δ=8.80 ppm) due to the proximity of the carbonyl function.

Enamide **3** was then subjected to the usual radical cyclization conditions (Bu$_3$SnH, AIBN, toluene). The rate of generation of the aryl radical from **3** was rather slow and a complex mixture was obtained after three days. From this mixture the expected indolizidine **4** was separated by column chromatography (silicagel - dichloromethane). The ^{1}H NMR spectrum[10] of this product reveals only one diastereomer. Actually, a *cis* coupling constant of 4 Hz is observable between H$_{10b}$ (δ=4.80 ppm) and H$_{11}$ (δ=3.44 ppm).

Under similar radical conditions enamidone **5** gave no cyclic product. In the presence of toluene, reduction of the double bond occurred to furnish compound **6** while in the presence of benzene the starting material was recovered. A reduction with Bu$_3$SnH, without AIBN, had been reported for the selective reduction of the double bond of an enone[11].
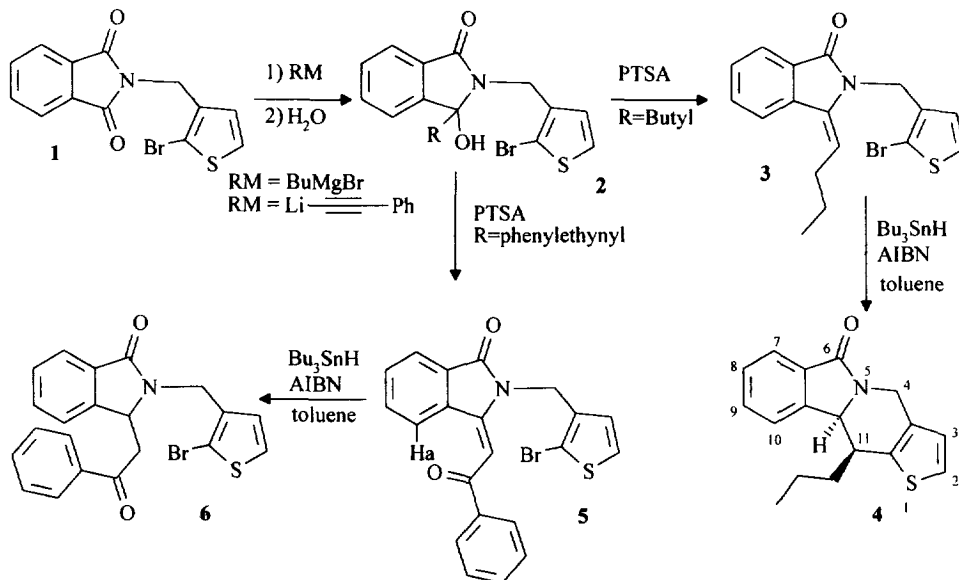
Scheme 2

From this result we were then led to examine a palladium-catalyzed cyclization (intramolecular Heck reaction)[12,13] of the enamidone **5**. Actually, it has been reported[14] that the α position of the carbonyl of an enaminoester reacted under the Heck conditions leading to a five membered ring. Also, we suggested that an enamidone would react in a similar manner. Recently, Comins[15] has shown that possibility. Therefore enamidone **5** was treated with a stoichiometric quantity of palladium (II) acetate, triphenylphosphine (4.4 eq), triethylamine in refluxing acetonitrile (Scheme 3). After six days a TLC showed two products, one of them, **8**, has the same retention time as the starting material, and the second, **7**, exhibited a more intense yellow color. A chromatography of the resulting mixture allowed to separate them (63% of **7** and 37% of **8**). The ^{1}H NMR of the indolizidine **7**[16] shows a S-*trans* conformation since the benzenic proton H_{10} (δ<7.8 ppm) is shifted toward high field compared to the starting material (δ=8.78 ppm) or enamidone **8** (δ=8.83 ppm). This latter compound was identical to that prepared directly from N-thien-3-ylmethylphthalimide instead of 2-bromo derivative **1** *via* the Meyer-Schuster rearrangement in an overall yield of 98%.
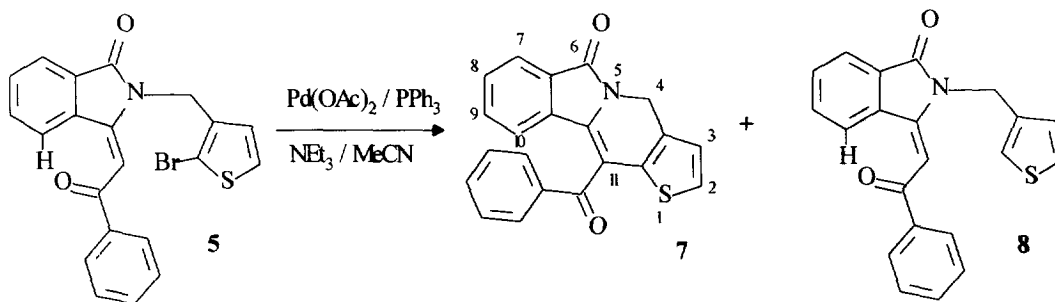
Scheme 3

This work shows that enamide **3** or enamidone **5** are suitable precursors to indolizidines fused to both benzene and thiophene rings via an intramolecular radical cyclization or palladium catalyzed cyclization respectively. Further studies to improve the accessibility of the indolizidine nucleus are now in progress.

REFERENCES AND NOTES

1. Daly, J.W.; Spande, T.F. *In Alkaloïds: Chemical and Biological perspectives*; ed. Pelletier, S.W.; Wiley: New-York, **1986**, vol. 4, chapter 1.

2. Marchalin, S.; Decroix, B.; Morel, J. *Acta. Chem. Scand.*, **1993**, *47*, 287-291.

3. Lebosquain, D.; Decroix, B. *Heterocycles*, **1993**, *36*, 2303-2314.

4. Daich, A.; Ohier, P.; Decroix, B. *Tetrahedron Lett.*, **1995**, *36*, 83-86.

5. Lee, E.; Li, K.S.; Lim, J. *Tetrahedron Lett.*, **1996**, *37*, 1445-1446.

6. Ishibashi, H.; Kawanami, H.; Iriyama, H.; Ikeda, M. *Tetrahedron Lett.*, **1995**, *36*, 6733-6734.

7. Pigeon, P.; Decroix, B. *J. Heterocyclic Chem.*, **1996**, *33*, 129-135.

8. Omar, E.A.; Tu, C.; Wigal, C.T.; Braun, L.L.; *J. Heterocyclic Chem.* **1992**, *29*, 947-951.

9. Physical data for **5**: yield 100%; mp 168°C, IR: 1708 (C=O), 1654 (C=O) cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 4.97 (s, 2H, CH$_2$), 6.59 (s, 1H, =CH), 6.72 (d, 1H, H$_3$, J = 6 Hz), 7.20 (d, 1H, H$_2$, J = 6 Hz), 7.30-7.90 (m, 8H, H$_{arom}$), 8.78 (d, 1H, H$_7$, J = 7 Hz); Anal. Calcd. for C$_{21}$H$_{16}$BrNO$_2$S: C, 59.16, H, 3.78, N, 3.29. Found: C, 58.98, H, 3.74, N, 3.34.

10. Physical data for **4** (oil): yield 40%; ^{1}H NMR (200 MHz, CDCl$_3$): δ 0.63 (t, 3H, CH$_3$, J = 7 Hz), 0.75-0.95 (m, 2H, CH$_2$), 1.00-1.20 (m, 2H, CH$_2$), 3.35-3.50 (m, 1H, H$_{11}$), 4.44 (d, 1H, H$_4$, J = 17 Hz), 4.80 (d, 1H, H$_{10b}$, J = 4 Hz), 5.09 (d, 1H,H$_4$, J = 17 Hz), 6.88 (d, 1H, H$_3$, J = 5 Hz), 7.18 (d, 1H, H$_2$, J = 5 Hz), 7.40-7.60 (m, 3H, H$_{arom}$), 7.88 (d, 1H, H$_{arom}$, J = 7Hz); ^{13}C NMR: δ 13.6 (CH$_3$), 19.7 (CH$_2$), 31.5 (CH$_2$), 37.8 (CH), 40.7 (CH$_2$), 60.6 (CH), 122.2 (CH), 123.3 (CH), 124.0 (CH), 124.9 (CH), 128.1 (CH), 130.2 (C), 131.2 (CH), 133.3 (C), 136.1 (C), 142.9 (C), 167.7 (CO).

11. Hutchinson, J.H.; Pattenden, G., *Tetrahedron Lett.*, **1987**, *28*, 1313-1316.

12. Heck, R.F. *Org. React.*, **1982**, *27*, 345-390.

13. De Meijere, A.; Meyer, F.E. *Angew. Chem. Int. Ed. Engl.*, **1994**, *33*, 2379-2411.

14. Michael, J.P.; Chang, S.F.; Wilson, C. *Tetrahedron Lett.*, **1993**, *34*, 8365-8368.

15. Comins, D.L.; Joseph, S.P.; Zhang, Y.M. *Tetrahedron Lett.*, **1996**, *37*, 793-796.

16. Physical data for **7**: yield 56%; mp 132°C; IR: 1715 (C=O, C=O) cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 5.18 (s, 2H, H$_4$), 6.99 (d, 1H, H$_3$, J = 5 Hz), 7.10-7.80 (m, 7H, H$_{arom}$+H$_2$), 7.87 (d, 1H, H$_{arom}$, J = 7 Hz), 8.08 (d, 2H, H$_{arom}$, J = 7Hz); ^{13}C NMR: δ 12.3 (CH$_2$), 112.9 (C), 123.1 (CH), 123.8 (CH), 125.6 (CH), 127.6 (CH), 129.0 (2CH), 129.1 (C), 129.6 (CH), 130.0 (C), 30.2 (2CH), 130.7 (C), 131.6 (CH), 132.4 (C), 132.9 (C), 134.5 (CH), 136.6 (C), 166.2 (CO), 193.4 (CO); Anal. Calcd. for C$_{21}$H$_{15}$NO$_2$S: C, 73.45, H, 3.82, N, 4.08. Found: C, 72.96, H, 3.75, N, 4.02.