Pergamon

Tetrahedron Letters, Vol. 38, No. 6, pp. 1041-1042, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02497-5

Synthesis of Dibenz[c,e]azepine and Benzo[e]thieno[c]azepine *via N*-Acyliminium ion 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: Dibenz[c,e]azepine **4a** and benzo[e]thieno[c]azepine **4b** have been synthesized utilizing the acid-catalyzed cyclization of hydroxylactams **3a,b** as key step.

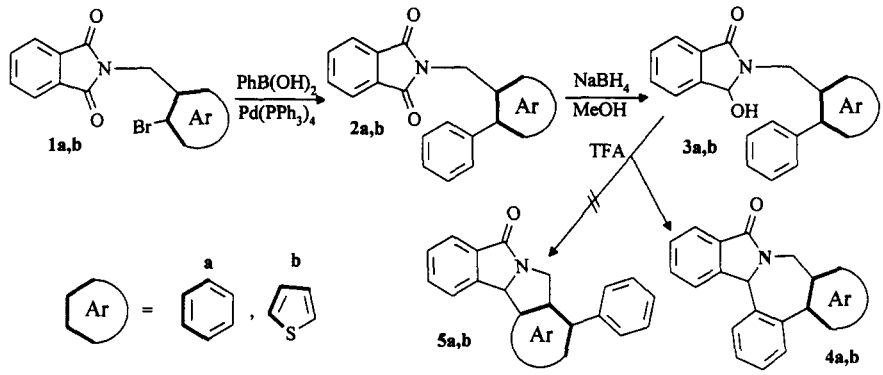
Over the last ten years many synthetic efforts have been directed toward synthesis of [2] or [3] benzazepines annelated to various rings (isoindole, pyrrolidine, benzene...) because a number of natural products as Chilenine[1], Lennoxamine[2], Cephalotaxine[3] contains this moiety and present potential biological activities. Any number derivatives of dibenz[c,e ; b,e ; b,f]azepines are known and present hypolipidermic activity[4], central nervous system activity[5], antiarrhythmic activity[6] respectively. With our interest in the synthesis of diversely substituted polycyclic systems[7-10] we wish to report herein an interesting approach to dibenzazepine or thienobenzazepine annelated to an isoindole moiety as **4a** or **4b**.

We have shown[11] that 3-phenyl-2-(2'-bromothien-3'-ylmethyl)phthalimide subjected to the usual radical cyclization conditions (AIBN, Bu_3SnH, toluene) or intramolecular Heck reaction did not give the expected [2]benzazepine **4b**. On the other hand it was reported[12] that cyclodehydration of N-(o-biphenyl)hydroxyphthalimidine under refluxing of trifluoroacetic acid occurred leading to a new isoindolophenanthridine.

From these results we suggested to use the hydroxylactam **3a** for the synthesis of the dibenzazepine derivative **4a**. *N*-acyliminium ion precursor **3a** was prepared from phthalimide derivative **1a**. A palladium (0) catalyzed cross coupling of bromo derivative **1a** with phenylboronic acid provided the biphenyl compound **2a** in good yield (76%). Reduction of imide **2a** by sodium borohydride in the presence of acid[13], afforded the hydroxylactam **3a** (82%). This latter was then subjected to trifluoroacetic acid at room temperature and according to the Baldwin's rules[14] led to the expected formation of a 7-membered ring, the new dibenz[c,e]azepine **4a** annelated to an isoindole moiety in a yield of 95%. The structure of **4a** was supported by NMR (^1H, ^{13}C) spectroscopic analyses[15]. A study of the long range heteronuclear shift correlation (HETCOR) spectrum of **4a** further substantiated our conclusions. The spectrum showed seven different signals for the benzenic correlation. Such correlations would not be expected from the isomeric structure **5a**.

This promoted result allied to the fact that a *N*-acyliminium ion cyclization gave a 5 or 6-membered ring from the α position of thiophene and only a 6-membered ring from the β position of the thiophene[16] we tested

the hydroxylactam **3b**. In similar conditions (CF_3COOH, room temperature), cyclization of **3b** gave a 7-membered ring (**4b**) as in the above benzene series rather than a 5-membered one (**5b**).



The structure of the thienobenzazepine **4b** was supported by NMR (^1H, ^{13}C) spectroscopic analyses[17]. The two protons of the thiophene ring appear as doublets (AB system) with chemical shifts of 7.13 ppm and 7.38 ppm and a coupling constant of 5 Hz characteristic of a α,β substituted thiophene.

The present investigation has thus led to a new method of synthesis of dibenzo[c,e]azepine or benzo[e]thieno[c]azepine annelated to an isoindole moiety starting from hydroxylactams.

REFERENCES AND NOTES

1. Mazzocchi, P.H.; King, C.R.; Ammon, H.L. *Tetrahedron Lett.*, **1987**, *28*, 2473-2476.
2. Ishibashi, H.; Kawanami, H.; Iriyama, H.; Ikeda, M. *Tetrahedron Lett.*, **1995**, *36*, 6733-6734.
3. Weinreb, S.M.; Auerbach, J. *J. Am. Chem. Soc.*, **1975**, *97*, 2503-2506.
4. Hall, I.; Murthy, A.R.K.; Wyrick, S.D. *J. Pharm. Sci.*, **1986**, *75*, 622-626.
5. Steiner, G.; Franke, A.; Haedicke, E.; Lenke, D.; Teschendorf, H.; Hofmann, H.; Kreiskott, H.; Worstmann, W. *J. Med. Chem.*, **1986**, *29*, 1877-1888.
6. Wunderlich, H.; Strak, A.; Carstens, E.; Lohmann, D.; Gritsenko, A.N.; Skoldinov, A.P. *Pharmazie*, **1985**, *40*, 827-830.
7. Marchalin, S.; Decroix, B. *Heterocycles*, **1995**, *41*, 689-696.
8. Daich, A.; Ohier, P.; Decroix, B. *Tetrahedron Lett.*, **1995**, *36*, 83-86.
9. Pigeon, P.; Decroix, B. *J. Heterocyclic Chem.*, **1996**, *33*, 129-135.
10. Othman, M.; Decroix, B. *Synth. Commun.*, **1996**, *26*, 2803-2809.
11. Pigeon, P., PhD University Le Havre, **1996**.
12. Hitchings, G.J; Heliwell, M.; Vernon, J.M. *J. Chem. Soc. Perkin Trans. I*, **1990**, 83-87.
13. Wijnberg, J.B.P.A.; Schoemaker, H.J.; Speckamp, W.N. *Tetrahedron*, **1978**, *34*, 179-187.
14. Baldwin, J.E. *J. Chem. Soc. Chem. Comm.*, **1976**, 734-736.
15. The HETCOR spectrum of **4a** was acquired using the standard Bruker microprogram XHCORR.AU (Bax, A.; Morris, G. *J. Mag. Res.*, **1981**, *42*, 501). Yield: 95%; mp: 196°C; IR: 1686 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 3.89 (d, 1H, NCH_2, J = 14 Hz), 5.05 (d, 1H, NCH_2, J = 14 Hz), 5.31 (s, 1H, CH), 7.05 (d, 1H, H_{arom}, J = 7 Hz), 7.28 (t, 1H, H_{arom}, J = 7 Hz), 7.31-7.72 (m, 9H, H_{arom}), 7.92 (d, 1H, H_{arom}, J = 7 Hz). ^{13}C NMR: δ 44.2 (CH_2), 60.2 (CH), 123.5 (CH), 123.8 (CH), 124.8 (CH), 128.0 (CH), 128.1 (2CH), 128.4 (CH), 128.5 (CH), 128.8 (2CH), 128.9 (CH), 130.6 (CH), 133.2 (C), 133.4 (C), 133.7 (C), 140.0 (C), 140.0 (C), 141.3 (C), 165.1 (CO).
16. Othman, M.; Pigeon, P.; Decroix, B. *Tetrahedron*, submitted.
17. Yield: 88%; mp: 241°C; IR: 1684 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 4.07 (d, 1H, NCH_2, J = 15 Hz), 5.20 (d, 1H, NCH_2, J = 15 Hz), 5.60 (s, 1H, CH), 6.99-7.77 (m, 7H, H_{arom}), 7.13 (d, 1H, $H_{\beta thiophene}$, J = 5 Hz), 7.38 (d, 1H, $H_{\alpha thiophene}$, J = 5 Hz), 7.95 (d, 1H, H_{arom}, J = 6 Hz).

(*Received in France* 20 *November* 1996; *accepted* 20 *December* 1996)