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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~~

New address: Université du Havre, URCOM, 25 rue Philippe Lebon, BP 1123, 76063 Le Havre cedex, 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.

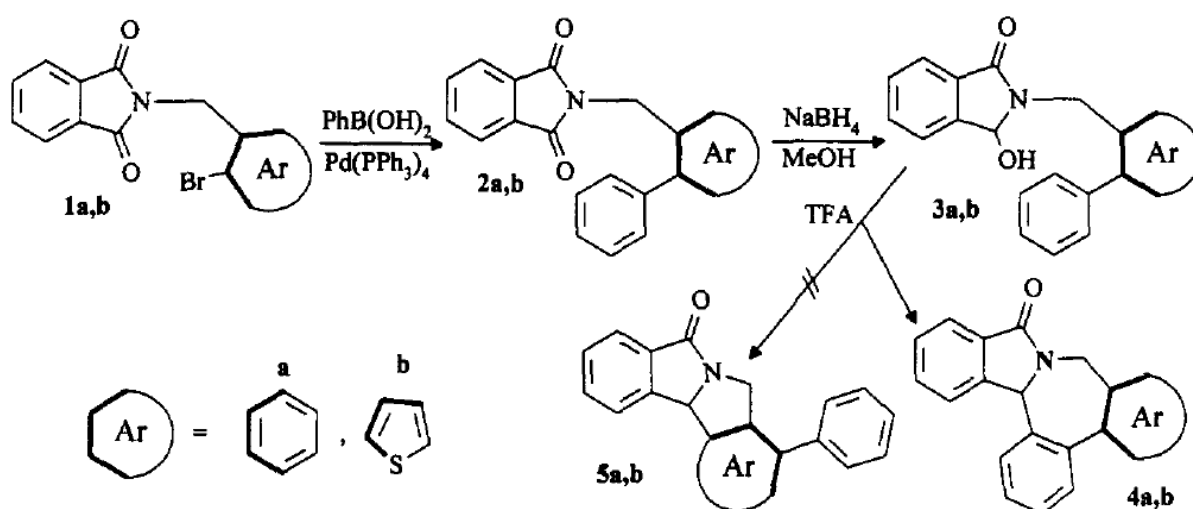
Over the last ten years many synthetic efforts have been directed toward synthesis of [2] or [3] benzazepines annelated to various rings (isoindole, pyrrolidine, benzene...) because a number of natural products as Chilenine ¹, Lennoxamine ², Cephalotaxine ³ contains this moiety and present potential biological activities. Any number derivatives of dibenz[c,e ; b,e ; b,f]azepines are known and present hypolipidemic 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, Bu₃SnH, 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, ¹³C) 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 (CF₃COOH, 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, ¹³C) 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.

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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 (CDCl₃): δ 3.89 (d, 1H, NCH₂, J = 14 Hz), 5.05 (d, 1H, NCH₂, 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). ¹³C NMR: δ 44.2 (CH₂), 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).
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17. Yield: 88%; mp: 241°C; IR: 1684 cm⁻¹ (C=O); ¹H NMR (CDCl₃): δ 4.07 (d, 1H, NCH₂, J = 15 Hz), 5.20 (d, 1H, NCH₂, J = 15 Hz), 5.60 (s, 1H, CH), 6.99-7.77 (m, 7H, H_{arom}), 7.13 (d, 1H, H_βthiophene, J = 5 Hz), 7.38 (d, 1H, H_αthiophene, J = 5 Hz), 7.95 (d, 1H, H_{arom}, J = 6 Hz).

