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Synthesis of Dibenzo[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 76, France

Abstract: Dibenzo[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,c ; 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, 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 isoindolophenantridine.

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.
REFERENCES AND NOTES


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, Hₐr, J = 7 Hz), 7.28 (t, 1H, Hₐr, J = 7 Hz), 7.31-7.72 (m, 9H, Hₐr), 7.92 (d, 1H, Hₐr, 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).


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, Hₐr), 7.13 (d, 1H, Hₐr, J = 5 Hz), 7.38 (d, 1H, Hₐr, J = 5 Hz), 7.95 (d, 1H, Hₐr, J = 6 Hz).