SYNTHESIS OF TETRAHYDRO AND HEXAHYDRO TETRACYCLIC 1,5-BENZOXAZEPINES

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Abstract: Tetrahydro-tetracyclic-1,5-benzoxazepines (4a-c) and hexahydro-tetracyclic-1,5-benzoxazepines (4d-e) from tetracyclic-1,5-benzoxazepines (1a-e) were prepared in presence of Pd/C under medium pressure hydrogenation. The structures of the final products were confirmed by spectral and elemental data.

Introduction: A number of papers have been published on the chemistry and biological activity[1] of 1,5-benzothiazepines containing an additional bicyclic system fused to different positions of the seven membered ring. Tetracyclic indolo-[2], benzofuro-[3], pyrazolopyrido-[4], quino-[5], benzopyrano-[6], benzothiopyrano-[7], quinazolinone-[8], quinoxylino-1,5-benzothiazepines[9] are known. Surprisingly, little work has been reported in the literature on the preparation of tetracyclic-1,5-benzoxazepines. In a broad programme to synthesize such polycyclic heterocycles and in continuation of our studies[3,10-14] concerning the synthetic utility of heterocyclic β-chlorovinylaldehydes and to meet the need for water soluble lead candidates[15-18], the syntheses of new tetrahydro- and hexahydro-tetracyclic-1,5-benzoxazepines have been achieved successfully in a simple way. This communication describes the syntheses of these tetracyclic-1,5-benzoxazepines (4a-e) as detailed below.

Synthesis and Results: In our previous communication[14], the attempted reduction of the imine double bond in 1a-e using $NaBH_4$ and $LiAlH_4$ to generate the corresponding dihydro- (2a-c) and tetrahydro- (2d-e) derivatives, however was unsuccessful. Catalytic hydrogenation of 1a-e in the presence of palladium on carbon (Pd/C) in acetic acid and acetic anhydride medium failed to give the desired product 2a-e. Instead, hydrogenolysis[14] occurred to result in the acetoxy derivatives (3a-e).

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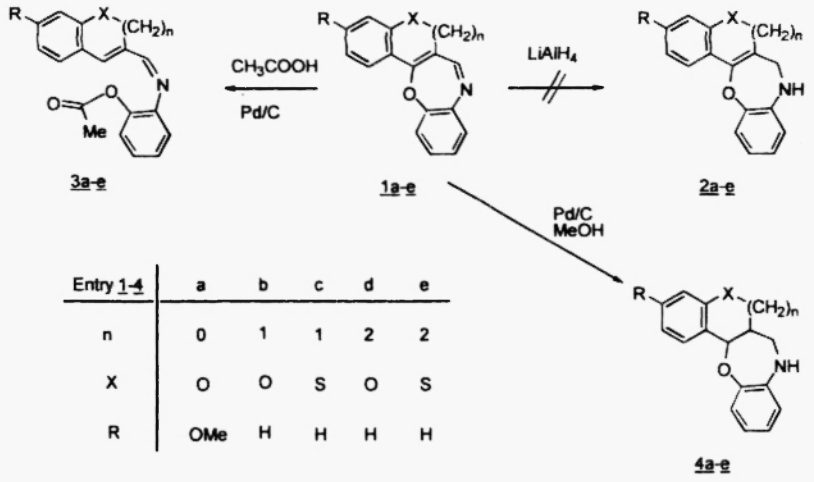
Scheme - 1



Entry 1-4	a	b	c	d	e
n	0	1	1	2	2
X	O	O	S	O	S
R	OMe	H	H	H	H

For the first time, we report a hydrogenation method on tetracyclic-1.5-benzoxazepine systems, which affords good yield of tetrahydro-tetracyclic-1.5-benzoxazepine (4a-c) and hexahydro-tetracyclic-1.5-benzoxazepine (4d-e) systems. The advantages of this method are simpler experimental conditions, easy isolation procedures, shorter reaction times and delivery of the desired product in good purity in excellent yields.

Hydrogenation of tetracyclic-1.5-benzoxazepines (1a-e) with 5% Pd/C in methanol at 60-70°C and at 110 psi pressure of hydrogen in 2-3hrs gave compounds 4a-e respectively. The structures of the compounds were established on the basis of IR. ^{1}H-NMR and mass spectral data and by elemental analysis (see Table - 1).

Table – 1 : Melting point and elemental analysis

Compd. No.	n	x	R	Yield (%)	mp (°C)	Analysis Found % (Calcd.) C	H	N
4a	0	O	OMe	78	156	71.17 (71.37)	5.40 (5.57)	5.10 (5.20)
4b	1	O	H	75	164	75.68 (75.88)	5.80 (5.92)	5.43 (5.53)
4c	1	S	H	76	170	71.15 (71.37)	5.47 (5.57)	5.10 (5.20)
4d	2	O	H	82	202	76.20 (76.40)	6.25 (6.36)	5.04 (5.24)
4e	2	S	H	80	208	71.85 (72.08)	5.85 (6.00)	4.75 (4.94)

The ^{1}H-NMR spectra of compounds 4a-e (Table-2) are quite interesting that the N-H protons are observed in the range of 11.8-12.2 ppm. In addition, these 1,5-benzoxazepines (4a-e) did not possess the high field ^{1}H-NMR signal of the iminic proton (δ 7.8-8.0 ppm) as in the corresponding aldimines (-CH=N-) in 1a-e[5a,5b,14]. The synthesis of the starting compounds 1a-e were carried out according to the literature procedure[14]. The reaction is believed to proceed via the formation of dihydro-, tetrahydro- intermediates but the intermediates could not be isolated.

Table – 2 : Spectral data

Compd. No.	IR data (ν_{max})	^{1}H-NMR (ppm)	Mass m/z (M+1)
4a	3386 (N-H). 3050 (C-H). 1590 (C=C)	3.24 (d. 2H. J=14. 7). 3.8 (s. 3H). 4.6 (m. 1H). 5.0 (d. 1H. J=8.7). 6.3-8.3 (m. 7H)	270
4b	3398 (N-H). 3045 (C-H). 1600 (C=C)	2.788 (m. 1H). 3.29 (dd. 2H. J=14. 4). 4.08 (dd. 2H. J=10.7. 7.7). 4.975 (d. 1H. J=7). 5.96-7.36 (m. 8H)	254
4c	3378 (N-H). 3040 (C-H). 1588 (C=C)	2.48 (m. 1H). 3.0 (dd. 2H. J=13. 7.7). 3.46 (dd. 2H. J=14. 4). 5.0 (d. 1H. J=7). 6.2-7.2 (m. 8H)	270
4d	3385 (N-H). 3035 (C-H). 1590 (C=C)	1.62 (m. 2H). 1.674 (m. 1H). 3.53 (dd. 2H. J=14. 7). 3.96 (m. 2H). 5.17 (d. 1H. J=8). 5.30-7.30 (m. 8H)	268
4e	3390 (N-H). 3025 (C-H). 1590 (C=C)	1.52 (m. 1H). 2.31 (m. 2H). 3.23 (m. 2H). 3.4 (dd. 2H. J=14. 7). 6.0 (d. 1H. J=8). 6.35-7.22 (m. 8H)	284

Experimental : Melting points were determined on Buchi 535 melting point apparatus and are uncorrected. IR spectra were recorded in KBr on Perkin-Elmer Spectrometer. ^{1}H-NMR were recorded in $CDCl_3$ using 200 MHz Varian Gemini spectrometer. Mass spectra were recorded on an MS Engine – Hewlett Packard model at DIP 20eV.

General procedure for the preparation of tetrahydro-tetracyclic-1,5-benzoxazepines (4a-c) and hexahydro-tetracyclic-1,5-benzoxazepines (4d-e):

A solution of tetracyclic-1,5-benzoxazepines (2 mmol) in methanol was hydrogenated in an autoclave in presence of 5% Pd/C (0.5g) at 100-120 psi at 60°C for 2-3 hrs. The mixture was allowed to cool and filtered on a pad of Celite. Evaporation of the methanol gave a solid, which was chromatographed on a column of silica gel (1:40). Elution with hexane/ethyl acetate (9:1) afforded the title compounds (4a-e) in a pure form.

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