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NEW SYNTHESIS OF 10-ALKOXY-5*H*-DIBENZ[b,f]AZEPINES

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Abstract-The reaction of 5-acetyl-5*H*-dibenz[b,f]azepines with sodium-hypochlorite led to the 5-acetyl-10,11-epoxy-10,11-dihydro-5*H*-dibenz[b,f] azepine (**1**). The lithium iodide induced rearrangement of **1** gave the keton **2** which was reacted with trialkyl-orthoformates leading to the vinyl ethers **3a,b**.

The title compounds play important rule in the preparation of oxcarbazepine(5-carboxamide-10-oxo-10,11-dihydro-5*H*-dibenz[b,f]azepine) one of the recently introduced antiepileptic drugs[1].

The preparation of these compounds usually occurs *via* the synthesis of the 10,11-dibromo derivative followed by a reaction with sodium alcoholates[2].

Now we report here a new and simple synthesis using the oxirane **1** and the 5-acetyl-10-oxo-10,11-dihydro-5*H*-dibenz[b,f]azepine (**2**) as key intermediates.

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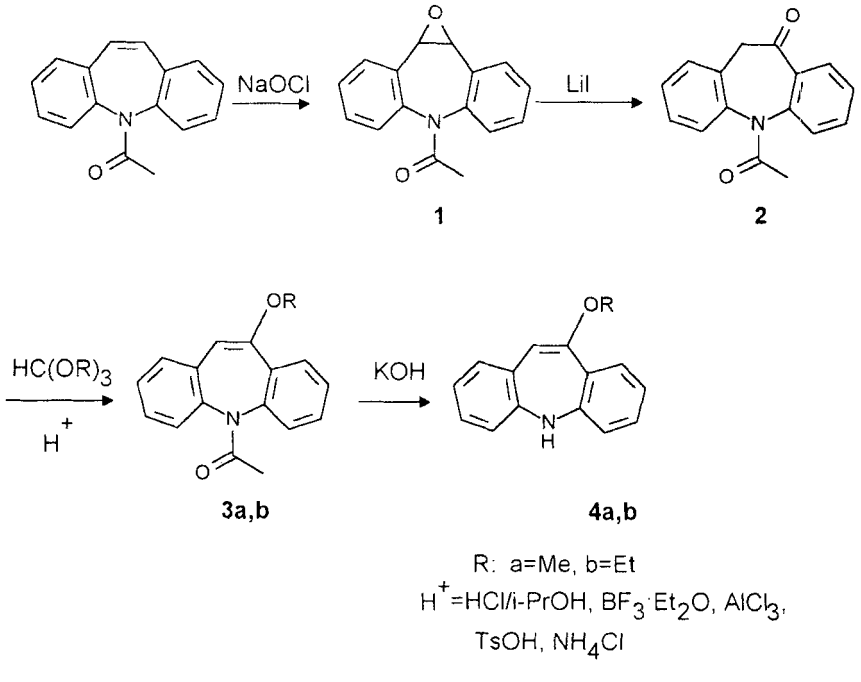
The epoxidation of electrophilic alkenes proceeds well with sodium-hypochlorite in the presence of alumina[3] or silica gel[4]. This phenomenon was utilized when the 5-acetyl-5*H*-dibenz[b,f]azepine was reacted with sodium-hypochlorite in the presence of silica gel yielding the oxirane **1**(Scheme). Our previous results[5] showed that one of the best reagents for the rearrangements of **1** to the keto compound **2** is the lithium iodide. The acid-catalysed reactions of **2** with trialkyl orthoformates smoothly gave the vinyl ethers **3a,b** which were reacted with potassium-hydroxide in ethylene glycol yielding the 10-alkoxy-5*H*-dibenz[b,f]azepines (**4a,b**).

The preparation of **4a,b** was performed either with or without the isolation and purification of **3a,b** and **1**.



Scheme

EXPERIMENTAL

Melting points are uncorrected. ^{1}H-NMR spectra were taken on a VARIAN GEMINI-200 instrument (Chemical shifts are in ppm, the spectra were recorded in $CDCl_3$. TMS was used as internal standard) MS spectra were determined with a VG TRIO-2 quadropol mass spectrometer EI 70 eV instrument.

A) 5-Acetyl-10,11-epoxy-10,11-dihydro-5*H*-dibenz[b,f]azepine, **1**

5-Acetyl-5*H*-dibenz[b,f]azepine (20.00g ,85mmol) , 40 cm^3 acetonitrile, 300 cm^3 sodium-hypochlorite (4M/dm^3) and 30 g silica gel (0.06-0.2 mm) were stirred for 1.5 hrs at reflux temperature. The silica gel was filtered at room temperature and was washed with 100 cm^3 $CHCl_3$.

The two phases were separated and the aqueous layer was extracted with 100 cm^3 $CHCl_3$. The collected organic phase was washed with 100 cm^3 water and dried (Na_2SO_4).

This solution was reacted with LiI without further purification (B) or the solvent was evaporated and the crude product was recrystallized from EtOH (yield: 75,1 %, mp: 151-152^0).

^{1}H-NMR:1.95(s,3H), 4.28(s,2H), 7.2-7.5(m,8H)

B) 5-Acetyl-10-oxo-10,11-dihydro-5*H*-dibenz[b,f]azepine, **2**

The oxirane 1 (20.00g, 79 mmol) was solved in 180 cm^3 $CHCl_3$. LiI (9.05g 80 mmol) was added and after 20 minutes stirring at reflux temperature the solution was cooled to 20^0 and was washed with 10 % Na_2SO_3 (50 cm^3) and water (100 cm^3).

The organic phase was dried and the $CHCl_3$ was evaporated. The crude product was recrystallyzed from EtOH yielding **2** in 85 %. The reaction

performed without isolation of **1** yielded **2** in 67 % based on 5-Acetyl-5*H*-dibenz[b,f]azepine.

mp: 142-143 (ethanol)

^{1}H-NMR:2.13(s,3H), 3.89(d,1H,15Hz), 4.36(d,1H,15Hz), 7.2-8.2(m,8H)

MS(%):251(20), 209(100), 195(30), 180(55), 152(20)

C) 5-Acetyl-10-alkoxy-5*H*-dibenz[b,f]azepine , **3a,b**

The keto compound **2** (10.00 g, 40 mmol) was solved in the appropriate alcohol (90 cm^3). To this solution were added the trialkyl-orthoformates (52mmol)and the catalytic amount of the acid (for example 0.1 cm^3 of 14 % HCl in i-PrOH).

After two hours stirring at reflux temperature the solution was cooled to 20^0, and water was added (200 cm^3). The resulted oil was extracted with $CHCl_3$ (3x100 cm^3).The organic layer was washed with saturated Na_2CO_3 solution and water and dried (Na_2SO_4).

The crude products formed after evaporation of the solvent was recrystallyzed from ethanol.

3a: yield: 90 %, mp:124-25^0. ^{1}H-NMR:1.91(s,3H), 3.92(virt.d.,4.5Hz,3H) 6.15(virt.d.,13.5Hz,1H), 7.2-7.8(m,8H)

MS(%):265(50), 222(100), 180(80), 152(20)

3b: yield: 82 %, mp:156-57^0, ^{1}H-NMR: 1.42(t, 8.0 Hz, 3H), 4.1(m, 2H), 6.35(s, 1H), 7.2-7.8(m, 8H)

MS(%):279(50), 236(60), 208(45), 180(100), 152(25)

D) 10-alkoxy-5*H*-dibenz[b,f]azepines, **4a,b**

The compounds **3** (12mmol) ethylene glycol (4cm^3) and KOH (0.678g, 12mmol) were stirred for 5hrs at reflux temperature. The crude products **4a,b** were filtered off after cooling to 0-5^0 for two hours.

The recrystallization from ethanol yielded **4a** in 80 % and **4b** in 75 %.

4a, mp:123-24^0. ^{1}H-NMR:3.93(s,3H), 5.15(s,br,1H), 5.86(s,1H)

4b, mp:132-33^0, ^{1}H-NMR:1.48(t,6.9Hz,3H), 4.07(q,6.9Hz,2H), 5.15(s,br,1H), 5.89(s,1H), 6.6-7.6(m,H)

This reaction(D) was performed with the concentrated reaction mixture of C) without the isolation of compound **3** yielding the compounds **4a,b** in 72% and 65 % calculated to the keton **2**.

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