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Synthesis of 11-(Piperazin-1-yl)-5*H*-dibenzo[b,e] [1,4]diazepine on Kilo Scale

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Abstract: A synthesis of 11-(piperazin-1yl)-5H-dibenzo[b,e][1,4]diazepine on kilo scale without any chromatographic purification step is reported. Key steps involved are Ullmann condensation, catalytic hydrogenation, and catalyzed cyclization.

Keywords: Antipsychotics, Dibenzodiazepine, Titanium tetrakisamine complex, Clozapine, Ullmann condensation

Introduction

Dibenzodiazepine derivatives have attracted much attention from the medicinal chemistry community owing to their potential use in the treatment of psychiatric disorders. The drugs in current clinical use from this class are few in number. Some of them are clozapine, olanzapine and flumezapine. In past years large number of derivatives from this class have been synthesized and tested for their pharmacological actions like muscarinic agonistic and dopamine antagonistic activities[1-7]. 11-(Piperazin-1-yl)-5*H*-dibenzo[b,e][1,4]diazepine is a structural analogue of clozapine, an important atypical antipsychotic. Atypical antipsychotics are preferred drugs over the conventional antipsychotics for the treatment as outcome of patients treated with conventional antipsychotics is unsatisfactory and adverse effects associated with them, in particular extrapyramidal adverse effects, can result in poor compliance[8].

We report herein a simple and high yielding method for kilo scale synthesis of 11-(piperazin-1-yl)-5H-dibenzo[b,e][1,4]diazepine.

Experimental

All solvents and reagents were purchased from the suppliers and used without further purification. Thin layer chromatography was performed on Merck precoated Silica-gel $60F_{254}$ plates. Mass spectra were obtained on Perkin Elmer Turbomass spectrometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ using 300 MHz, on a Jeol-300 NMR spectrometer. The chemical shifts were reported in δppm relative to TMS. The IR spectra were recorded in a solid state as KBr dispersion using Perkin Elmer FT-IR spectrophotometer. Melting points were obtained by using the open capillary method and are uncorrected.

*N-(2-Nitrophenyl) anthranilic acid (**3**)*

In a 20 liter RBF, equipped with a sealed mechanical stirrer and a reflux condenser, a mixture of 1-fluoro-2-nitrobenzene (3.4 kg, 24.1mol) **1**, anthranilic acid (3 kg, 21.89 mol) **2**, 30 gm Cu powder and K_2CO_3 (3 kg, 21.58 mol) in 5 liter DMF was refluxed for 12 h. After completion the reaction mixture was poured into 6 liter ice cold water and neutralised with glacial acetic acid maintaining the temperature below 25^0c. Orange colored solid was separated by filtration and recrystallized using glacial acetic acid. (4.8 kg, 85%); m.p.: 217-219 ^{0}c (lit. 219 ^{0}c)[9]; TLC R_f (silica, EtOAc) 0.56; IR (KBr, cm−1): 3337 (NH), 1500 (NO_2).

*N-(2-Aminophenyl)anthranilic acid (**4**)*

In a 5 liter stainless steel hydrogenation kettle, a solution of 1.5 kg of *N*-(2-nitrophenyl)anthranilic acid **3** in 2 liter DMF was hydrogenated for 2 h using 75 gm Raney Nickel W-2 as a catalyst at 70 psi pressure. The reaction mixture was filtered on bed of celite and DMF was evaporated under vacuum. Recrystallization from methanol gave methyl *N*-(2-aminophenyl)anthranilic acid. (1.1 kg, 83%). m.p.: 87-89 ^{0}c; IR (KBr, cm^{-1}): 3367, 3268 (NH_2).

*5H-dibenzo[b,e][1,4]diazepine-11(10H)-one (**5**)*

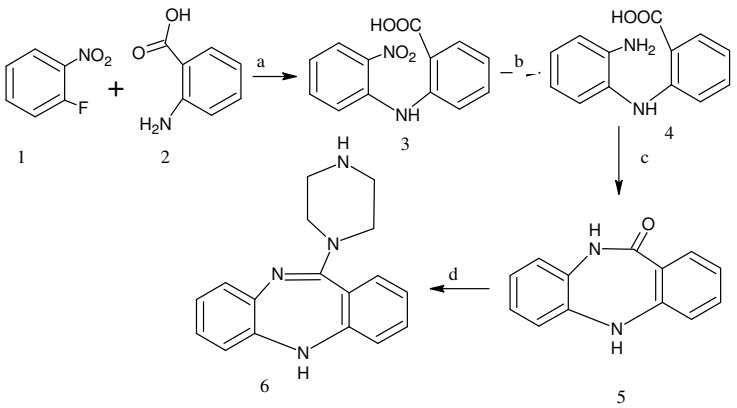
To a solution of 2 kg of N-(2-aminophenyl) anthranilic acid **4** in 5 liter of DMF was added 10 ml of concentrated H_2SO_4 and refluxed for 7-8 h after which reaction mixture was poured in ice cold water, solid was obtained which was filtered, dried in oven at 100 ^{0}C. This product is used without further purification for the next step. (1.5 kg, 81%); m.p.: 251-3^0c (lit. 254-55 ^{0}C)[1]; TLC: R_f (silica, EtOAc) 0.86; IR (KBr, cm^{-1}) 3634, 3017, 1659, 1215.

*11-Piperazinyl-5H-dibenzo[b,e][1,4]diazepine (**7**)*

To a solution of piperazine **6** (1.6 kg, 18.6 mol) in 7 liter anisole under nitrogen was added a solution of titanium tetrachloride (0.40 kg, 2.12 mol) in anisole and an immediate yellow/brown coloration was observed (titanium tetrakisamine complex). The mixture was warmed to 50-55 ^{0}C and a solution of 5H-dibenzo[b,e][1,4]diazepine-11(10H)-one **5** (1.5 kg, 7.14 mole) in anisole (3 liter) was added. The mixture was heated at 110^0c for 7-8 h and was filtered while hot. The filtrate was concentrated under vacuum to remove 80% of anisole. The concentrated filtrate was allowed to come at room temperature then cooled to 4 ^{0}C for 1 h. The green colored solid obtained which was filtered and recrystallized using methanol. (1.33 kg, 63%). TLC: R_f (Hexane : EtOAc, 1:9) 0.66; m.p.: 230-34 ^{0}C; IR (KBr, cm^{-1}): 3328, 1604, 1515, 1245; 1H NMR (CDCl3) (δ ppm): 1.60 (s, 8H, aliphatic CH_2), 5.55 (bs, 1H, Ar-NH-Ar), 6.7 (d, 1H, NH), 6.88-7.0 (m, 3H, aromatic), 7.3 (t, 1H, aromatic), 7.5 (bs, 1H, NH), 7.9 (d, 1H, aromatic); MS (m/z): 278 [M^+]; 249 (2), 222 (50), 193 (64), 209 (100). Anal. Cald. For $C_{17}H_{18}N_4$: C, 73.35; H, 6.52; N, 20.13. Found: C, 73.31; H, 6.54, N, 20.14

Results and Discussion

Key intermediate *N*-(2-nitrophenyl) anthranilic acid **3** was prepared by Ullmann condensation reaction between anthranilic acid **2** and 2-Fluoronitrobenzene **1**. The nitro group in intermediate **3** is reduced by catalytic hydrogenation using W-2 Raney Nickel to obtain *N*-(2-aminophenyl) anthranilic acid **4**. Cyclization of **4** was carried out in DMF by using H_2SO_4 in catalytic amount. The 5H-dibenzo [b,e][1,4]diazepine-11(10H)-one **5** formed showed the presence of cyclic lactam at 1659 cm^{-1} in IR. Finally **5** was condensed with piperazine **6** using $TiCl_4$ to get 11-piperazinyl-5H-dibenzo[b, e][1,4]diazepine **7** in 63% yield**,** which showed the absence of lactam in IR spectrum. Final compound was characterized by IR spectroscopy, mass spectrometry and ^{1}H-NMR at 300 MHz. Mass spectrum of **7** showed a molecular ion peak at m/z 278 which agreed with its molecular weight.



Scheme 1. (a) DMF, K_2CO_3, Cu powder, reflux, 12 h, 85%; (b) H_2, Raney Ni, 70 psi, 2 h, 83%; (c) DMF, H_2SO_4, reflux, 7-8 h, 81%; (d) anisole, piperazine, $TiCl_4$, reflux, 7-8 h, 63%.

Conclusion

We have devised the efficient, cheap and high yielding method for the synthesis of 11-piperazinyl-5H-dibenzo[b,e][1,4]diazepine bypassing any chromatographic purification step.

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