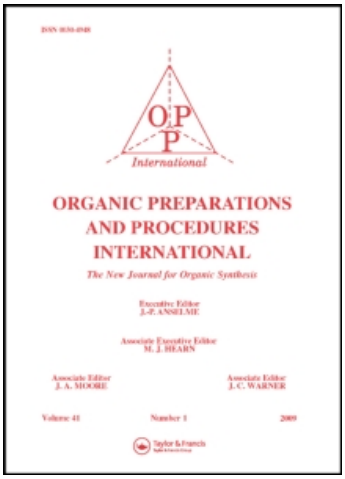

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A PRACTICAL SYNTHESIS OF 4-ACETYL-2,3,4,5-TETRAHYDRO-1*H*-1,4-BENZODIAZEPINE

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A PRACTICAL SYNTHESIS OF 4-ACETYL-2,3,4,5-TETRAHYDRO-1*H*-1,4-BENZODIAZEPINE

Submitted by (05/03/08)

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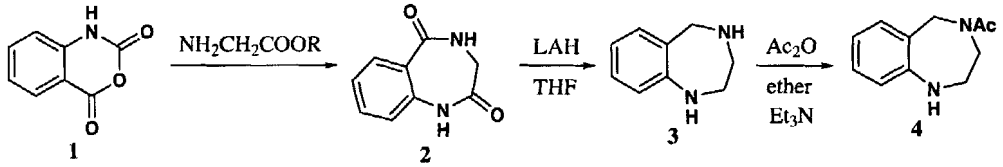
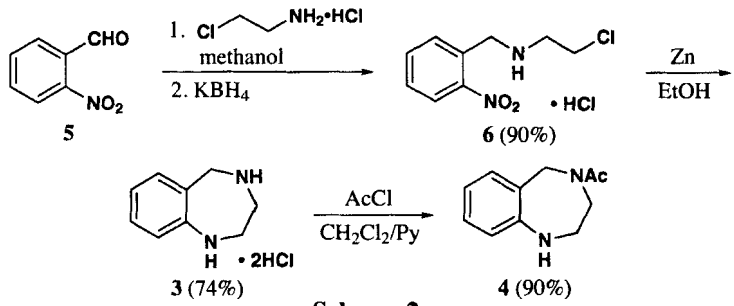
2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**3**) and 4-acetyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**4**) as important intermediates are used in many aspects such as 5-HT_{2C} receptor agonists for the treatment of obesity,[1] dopamine D_3 receptor ligands,[2] inhibitors of phenylethanolamine *N*-methyltransferase,[3] inhibitors of Farnesyl transferase,[4] etc. The most applicable existing approach for preparation of title compound **1** involved synthesis of key intermediate benzodiazepinedione **2** which was obtained by condensation of isatoic anhydride[5-7] with glycine or glycine ethyl ester hydrochloride (R = Et) at elevated temperature.[4,8] Then compound **2** was reduced with lithium aluminum hydride (LAH) in THF to give **3**[4, 9-10] which was mono-acylated with acetic anhydride in triethylamine to form **4** (*Scheme 1*).[11]



Scheme 1

Though the route seems elegant and straightforward, the process suffers from several disadvantages such as the use of expensive LAH and anhydrous THF; in addition, LAH is not a good choice due to safety concerns because it is highly flammable and moisture sensitive and the work-up procedure for LAH is not very convenient as small deviations will result in unfilterable suspended solids. These factors made the process less viable for commercial production. We report here a short, economic, and efficient route to **4** free from undesirable reagents (LAH) and conditions (high temperature) starting from commercial available 2-nitrobenzaldehyde (**5**) in an overall yield of around 60% (*Scheme 2*).

Of all the methods used for the synthesis of **6**, the reaction of aromatic aldehydes with amines followed by reduction of the intermediate imines with $NaBH_4$ proved to be the best one with respect to economy and yields.[12] Thus condensation of 2-nitrobenzaldehyde



Scheme 2

with 2-chloroethylamine hydrochloride at room temperature in methanol gave the Schiff's base which was reduced with less expensive KBH_4 to give compound **6**, isolated as its hydrochloride by crystallization with HCl(g)/ethanol in 90% yield. Although reduction of nitro group could be achieved by many metal-acid reducing systems such as Sn/HCl and Zn/HCl, the use of the latter two reagents gave **3** in poor yields presumably because these reducing agents are too potent. Thus mild reducing conditions were explored and reduction of the nitro group was achieved with zinc in ethanol, albeit requiring more than 24 h to be complete at room temperature. When the reaction temperature was raised to 45-50°C, the reduction was complete in 5 h to give cyclization product **3** as the crystalline dihydrochloride salt in 74% yield. Acylation of the more basic 4-amine to form **1** was originally accomplished by condensation with acetic anhydride in the presence of triethylamine in ether;[11] however, the yield was low. An improved yield was obtained when the reduction was carried out by addition of acetyl chloride to a solution of **3** in CH_2Cl_2 in the presence of pyridine at 0°C; after 2 h at room temperature with stirring, the organic layer was evaporated to give an oil which was crystallized in ether to give **4** in 90% yield.

In summary, we have developed a feasible route for the scaled up preparation of the title compound **4** from 2-nitrobenzaldehyde. Undesirable reagents and conditions were eliminated and the process proceeded very well in our pilot plant.

EXPERIMENTAL SECTION

All reagents were commercially obtained and used as received. ^1H NMR spectra were obtained on a Bruker AMX-400/600 at 300 MHz or 400 MHz using TMS as an internal standard. ^{13}C NMR spectra were obtained from a Gemini-300 spectrometer in deuterated solvents with TMS as an internal standard at room temperature. The melting points were determined by using the capillary method on a Buchi-510 melting point apparatus. The mass spectrum was recorded on a Finnigan MAT-95/711spectrometer.

N-(2-Chloroethyl)-2-nitrobenzylamine (6).- A solution of 2-nitrobenzaldehyde (300 g, 2 mol) and 2-chloroethylamine hydrochloride (248 g, 2.16 mol) in ethanol (1.5 L) was stirred for 3 h at ambient temperature. KBH_4 (49.8 g, 0.92 mol) was then added slowly at 0-10°C in four portions at intervals of 10 min and stirring continued for 2 h. The reaction mixture was evaporated to give

an oil and a saturated aqueous sodium hydrogen carbonate was added to the mixture to adjust the pH of the solution to 9-10, and extracted with methylene chloride (3 x 300 mL). The combined organic layers were washed with brine (500 mL), and dried over anhydrous Na_2SO_4. After removal of the drying agent, the solvent was evaporated under reduced pressure and the residue, so obtained, was treated with HCl(g)/ethanol to give **7** as the colorless crystalline hydrochloride (447 g, 90%). An analytical sample was obtained by recrystalization from ethanol, mp ~210°C (dec.). ^{1}H NMR ($CDCl_3$): δ 8.20 (d, 1H, J = 8.2 Hz), 7.87 (m, 2H); 7.71 (t, 1H, J = 7.3Hz), 4.50 (s, 1H); 3.99 (t, 1H, J = 6.1 Hz), 3.42 (t, 1H, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$): 39.18, 47.33, 48.53, 125.28, 127.04, 130.77, 133.47, 134.33, 148.43. HRMS (EI): Exact Mass: Calcd for $C_9H_{10}ClN_2O_2$ 213.0431. Found 213.0423.

Anal. Calcd for $C_9H_{12}Cl_2N_2O_2$: C, 43.05; H, 4.82; N, 11.16. Found: C, 43.22; H, 4.82, N, 10.99

2,3,4,5-Tetrahydro-1*H*-benzodiazepine (3).- N-(2-Chloroethyl)-2-nitrobenzylamine hydrochloride (375 g, 1.5 mol) was dissolved in ethanol (1.8 L), zinc powder (192 g, 2.94 mol) was added in portions. The resulting mixture was heated to 40-45°C for 3 h. After completion of the reaction (monitored by TLC), the mixture was filtered, and the filtrate was concentrated to give an oil. H_2O (1.2 L) was added, and the pH of aqueous layer was adjusted to 9-10 with 1 M aqueous NaOH solution and extracted with methylene chloride (2 x 600 mL). The organic layers were combined, and dried over Na_2SO_4, and evaporated under reduced pressure to give an oil. A solution of HCl(g)/ethanol was added with cooling whereupon, **3** precipitated as its colorless dihydrochloride (244 g, yield 74%). An analytical sample was obtained by recrystalization from ethanol, mp 96-97°C (*lit.*[9] 95-97°C).

4-Acetyl-2,3,4,5-tetrahydro-1*H*-benzodiazepine (4).- Acetyl chloride (70 mL, 0.99 mol) was added dropwise to a methylene chloride solution (1 L) of 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine dihydrochloride (220 g, 1 mol) and pyridine (160 mL) at 0°C. After stirring for 2 h at room temperature, the resulting mixture was poured into ice-water and the organic layer was separated and the aqueous layer was extracted with methylene chloride (2 x 400 mL). The organic layers were combined and dried over Na_2SO_4 and evaporated on a rotary evaporator under reduced pressure to give crude product as an oil. Crystallization from ether provides pure title compound (171 g, purity 98%, 90% yield) as a colorless solid, mp 85-86°C (*lit.*[11] 84-86°C). The spectroscopic data correspond to those reported in literature.[11]

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SYNTHESIS OF 3-(2-ARYL-1H-INDOL-3-YL)-4-AROYL-5-ARYLISOXAZOLINES

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Isoxazolines are useful as intermediates in organic synthesis and possess a broad range of biological activities such as antibacterial and antifungal,[1] antiinflammatory,[2] antiviral,[3] herbicidal,[4] neurotropic and antitumor,[5] vasodilating, anticoagulant and cardio-protective activities,[6] glycoprotein IIb/ IIIa antagonistic,[7] anti-HIV and antidepressant activities.[8] They also act as novel inhibitors of cyclooxygenase-2 with analgesic activity[9] and inhibitors of human leukocyte elastase (HLE) and cathepsin G (Cath G).[10] Isoxazolines have been utilized as scaffolds for peptidominetics,[11] and core structures in medicinal chemistry. Indole derivatives also constitute an important class of therapeutic agents in medicinal chemistry including anticancer,[12] antioxi-