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Synthesis of Naratriptan using new intermediate N-Benzyl-N-Methyl Ethenesulfonamide

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ABSTRACT

*A novel intermediate N-benzyl-N-methylethenesulfonamide **(3)** synthesis has been reported. This on reaction with 5-bromo-3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indole **(4)** under heack condition gave N-benzyl-N-methyl-2-[3-(1-methyl-1, 2, 3, 6,-tetrahydro pyridine -4-yl)-1H-indol-5-yl] ethene sulfonamide **(5)** . Later on **5** was subjected to the hydrogenation, followed by debenzylation to afford naratriptan **(1)** with high purity.*

Keywords: N-benzyl-N-methylethenesulfonamide, Indole derivatives, Heack reaction, Nartriptan, Debenzylation.

INTRODUCTION

Triptans are a new class of compounds developed for the treatment of migraine attacks,[1] The first of the class, sumatriptan,[2] and the newer triptans that are zolmitriptan,[3] naratriptan,[4] rizatriptan,[5] eletriptan,[6] almotriptan,[7] and frovatriptan [8] display high agonist activity mainly at the serotonin 5-HT1B and 5-HT1D receptor subtypes. Among these triptans, naratriptan is one of the important drug for the treatment of acute attacks of migraine exhibiting high affinity for 5-HT1D receptors, a serotonin (5-hydroxytryotamine, 5-HT) receptor. All triptans have an indole structure identical to the neurotransmitter 5-HT. Classic triptan structure contains side chain on the indole ring, and basic nitrogen in a similar distance from the indole structure. The main structural difference of the triptans is the position of the sulfonamide and the side chain attached to it. In rizatriptan and zolmitriptan, instead of a sulfonamide, a triazole and 2-oxazolidone rings are present respectively. Another exception to the classic structure is seen on eletriptan, in which dimethyl-pyrrolidine ring is attached to the indole. Similarly, in naratriptan, 1-methyl-piperidine ring is attached to the indole.

Several methods for the synthesis of naratriptan have been reported. Oxford et. al. [9] used N-methylvinylsulfonamide in the synthesis which is not commercially available. Preparation of N-methyl vinyl sulfonmide[10] is difficult due to its polymerization property and poor yields. Bela et. al. [11] reported multi step synthesis and over all yield of naratriptan base is 4%. Laszlo et. al. [12] reported novel synthesis but requires expensive raw materials such as indoline-5-carbaldehyde, titaniumtetrachloride etc. In this paper we have reported a new intermediate N-benzyl-N-methylethenesulfonamide for the synthesis of naratiptan with good yields and high purity.

MATERIALS AND METHODS

All the reagents used for reactions are of L.R. Grade. Solvents were routinely distilled before use. IR spectra were recorded as KBr pellets on Thermo Nicolet Avatar 330 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a 100 MHz Varian or 200 MHz Tecmag instruments using TMS as internal standard. Melting points are uncorrected and were determined in open capillaries on Mettler FP-90 apparatus. TLC was recorded on Merck silica gel 60 F_{254} Plates and spots were detected using iodine chamber or U.V lamp at 254nm.

Preparation of N-benzyl-N-methylethenesulfonamide (3): 2-Chloroethanesulfonylchloride **(1)** (50.0 gm) was dissolved in dichloromethane (500.0 mL) and cooled to -20 to –15 ^{O}C. To the cooled solution triethylamine (31.2 gm) was added at -20 to –15 ^{O}C. The reaction mixture was stirred at –10 ^{O}C for 0.5 hours.Then a mixture of N-methylbenzylamine (33.0 gm) and triethylamine (31.2 gm) was added to the reaction mixture at –10 ^{O}C. After completion of the addition, the temperature of the reaction was raised to 0 ^{O}C and water (100.0 mL) was added. The reaction mixture was stirred for 10 to 20 minutes and the organic layer was separated, dried over anh.Na_2SO_4 and concentrated. The residue obtained was repeatedly titurated with diethylether. The ether extract, on concentration, gave an oil 42 gm of N-benzyl-N-methyl ethene sulfonamide with 95% pure (by GC) and was used without further purification.

IR (neat): 3030, 3059, 1606,1338, 1152,978,779. 1H NMR: ($CDCl_3$) δ 2.69 (s, 3H), 4.25 (s, 4H), 6.02 (d, 1H,), 6.27 (d, 1H,), 6.45 (d, 1H,), 7.31 (m, 6H). M+1: 212. Anal. Calcd. for ($C_{10}H_{13}NO_2S$) requires: C, 56.85; H, 6.20; N, 6.63 % Found: C, 56.79; H, 6.27; N, 6.60%.

Preparation of N-benzyl-N-methyl-2-[3-(1-methyl-1, 2, 3, 6,-tetrahydro pyridine -4-yl)-1H-indol-5-yl] ethene sulfonamide (5): In a round bottom flask fitted with a mechanical stirrer and condenser, were charged N,N- dimethylformamide (100.0 mL), 5-bromo-3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indole **(4)** (25.0 gm), **3** (30.0 gm), triethylamine (32.1 gm), triorthotolylphosphine (7.75 gm) and palladium aceate (0.42 gm). The reaction mixture was gradually heated to 100-110 ^{O}C under stirring and maintained for 8 hours. The reaction mass was cooled to 60 ^{O}C, filtered. The filtrate was diluted with water (300.0 ml) and extracted with ethyl acetate (3x100.0 mL). The ethyl acetate layer was washed with water (75.0 mL) and dried over anhydrous sodium sulphate and concentrated. The residue was stirred with methanol (100.0 mL), cooled to 0-5 ^{O}C and solid formed was filtered and dried to give 27.0 gm of the product. An analytical sample was recrystalised from methanol m.p 205-210 ^{O}C.IR (KBr,pallet): 3416,3027,2847,2890,1647,1607,1494,1445,1337,1148,1073,938,846. ^{1}H NMR: ($CDCl_3$) δ1.65 (s, 2H), 2.43 (s, 3H), 2.24 (t, 2H,), 2.40 (s, 3H), 2.78 (s, 3H), 2.78 (m, 1H), 3.06 (d, 2H), 3.26 (d,

4H), 4.33 (s, 2H), 6.96 (m, 1H), 7.34 (m, 6H), 7.44 (s, 1H), 8.73 (s,1H). M +1: 422. Anal. Calcd. for ($C_{24}H_{27}N_3O_2S$) requires: C, 68.38; H, 6.46; N, 9.97 % Found: C, 68.30; H, 6.51; N, 9.92%.

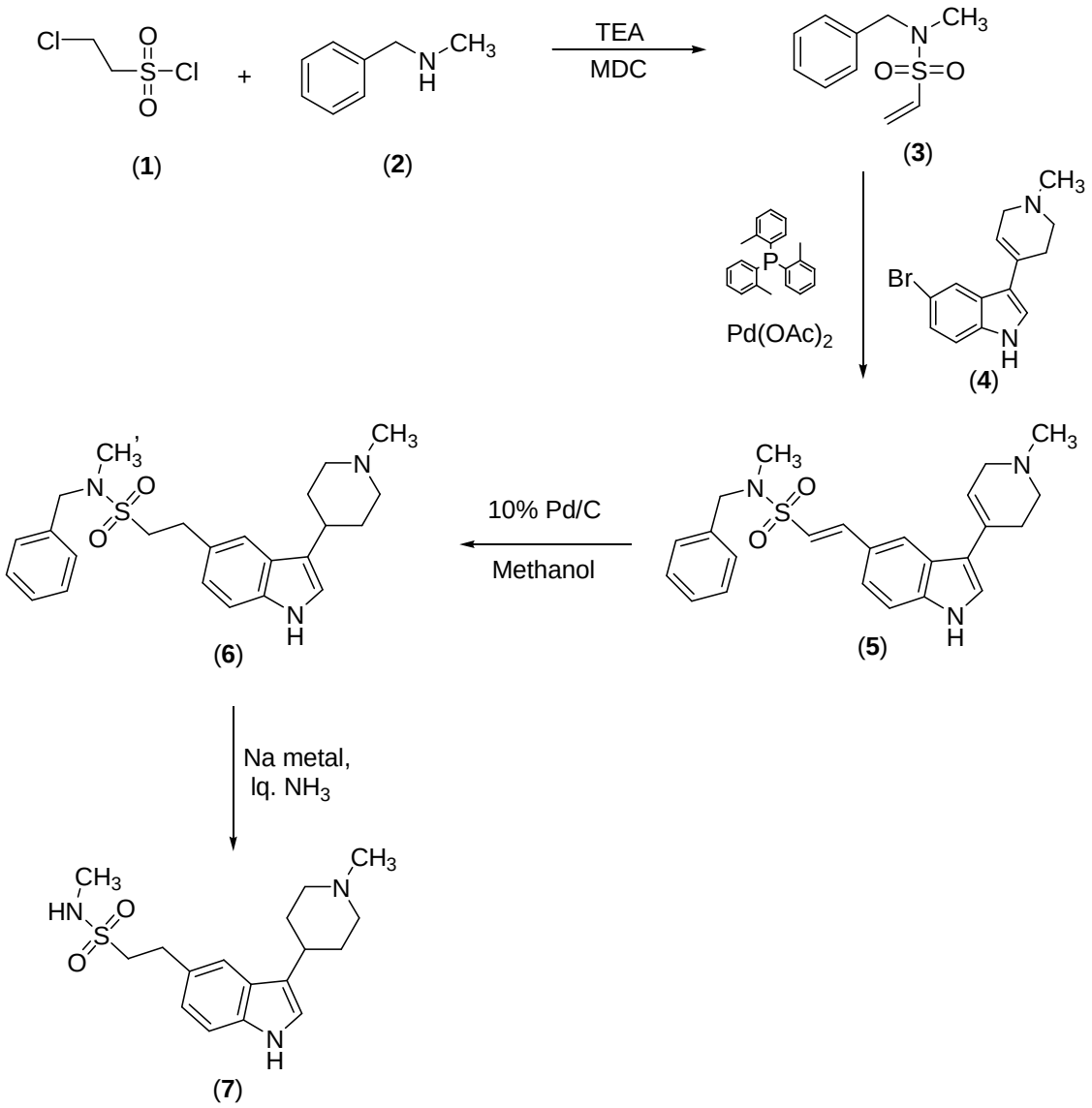
Preparation of N-benzyl-N-methyl-2-[3-(1-methylpiperdin-4-yl)-1H-indol-5-yl]ethanesulfon amide (6): A hydrogenation kettle was charged with methanol (500.0 mL) and **5** (30,0 gm), and 10% Pd/C (20.0 gm). Hydrogenation was carried out at 6kg/cm^{-2} pressure and continued for 20-24hours till hydrogen gas adsorption ceased. The reaction mass was filtered and filtrate was concentrated under reduced reduced pressure. The resulting residue was dissolved in methanol (100.0 mL), cooled to 20-25 ^{0}C and solid formed was filtered and dried to give 21.0 gm of the product with m.p: 155-160 ^{O}C. IR (KBr): 3441, 3127, 2913,1448,1323,1144,987. ^{1}H NMR: ($CDCl_3$) δ 1.92 (m, 2H), 2.05 (m, 2H), 2.24 (t, 2H), 2.40 (s, 3H), 2.78 (s, 3H), 2.78 (m, 1H), 3.06 (d, 2H), 3.26 (d, 4H,), 4.33 (s, 2H), 6.96 (m, 1H), 7.34 (m, 6H), 7.44 (s, 1H), 8.73 (s,1H). M +1: 425. Anal. Calcd. for ($C_{24}H_{31}N_3O_2S$) requires: C, 67.73; H, 7.34; N, 9.87 % Found: C, 67.30; H, 7.51; N, 9.89%.

Preparation of N-methyl-2-[3-(1-methylpiperdine-4-yl)-1H-indol-5-yl] ethane sulfonamide (naratriptan) (7): To a stirred solution of N-benzyl-N-methyl 2-[3-(1-methylpiperdine -4-yl)-1H-indol-5-yl] ethane sulfonamide (25.0 gm) in liquid ammonia (250.0 mL) and THF (100.0 mL), was added sodium metal (18.0 gm) at –80 ^{O}C over a period of 30 min. The reaction mixture was stirred for another one hour at –80 ^{O}C. The reaction mass was treated with aqueous ammonium chloride solution (25.0 gm in 75.0 mL water) at –80 ^{O}C. The reaction mixture was allowed to warm to room temperature and extracted with dichloromethane (3x150.0 mL). The organic layer was washed with water (75.0 mL), dried over anhydrous sodium sulphate and concentrated. The residue was stirred with methanol (100.0 mL), cooled to 0-5 ^{O}C and the solid was filtered and dried to give 17.0 gm of the crude naratriptan base, m.p 170-172 ^{O}C.

Purification: In to a round bottom flask fitted with a mechanical stirrer and condenser was charged methanol (100.0 mL) and crude naratriptan (25.0 gm). The reaction mixture was gradually heated to about 45- 50 ^{O}C under stirring and maintained for 30 min. Oxalic acid (17.0 gm) was added at 40-45 ^{O}C and stirred for another 30min. The reaction mixture was then slowly cooled to 10-15 ^{O}C, and filtered to give naratriptan oxalate with a purity of 99.5% (HPLC). The wet cake of Naratriptan oxalate was taken in water (200.0 mL) and basified with potassium carbonate to P^H 9.5 and stirred for 20 minutes. The solid was filtered, washed with water and dried to give 20.0 gm of pure naratriptan with HPLC purity >99.8%. IR (KBr): 3441, 3127, 2913,1448,1323,1144,987. ^{1}H NMR: ($CDCl_3$) δ1.92 (m, 2H), 2.05 (m, 2H,J=9.3Hz), 2.24 (t, 2H,J=10.9 Hz), 2.40 (s, 3H), 2.78 (s, 3H), 2.78 (m, 1H), 3.06 (d, 2H, J=9.8 Hz), 3.26 (d, 4H,J=11.4 Hz), 4.33 (s, 2H), 6.96 (m, 1H), 7.34 (m, 6H), 7.44 (s, 1H), 8.73 (s,1H). M+1: 336. Anal. Calcd. for ($C_{17}H_{25}N_3O_2S$) requires: C, 60.87; H, 7.51; N, 12.53 % Found: C, 60.85; H, 7.51; N, 12.50%.

RESULTS AND DISCUSSION

The required starting materials 2-chloroethanesulfonamides purchased from Aldeich Company. 5-Bromo-3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indole **(4)** was prepared from 5-bromoindole and N-methyl-4-piperidone as per the literature procedure[9].



Scheme-I

A new compound N-benzyl-N-methylethanesulfonamide **(3)** has been prpared. This intermediate was synthesized by reacting 2-chloroethanesulfonylchloride **(1)** with N-methyl benzyl amine **(2)** in the presence of triethylamine at -20 to –10 ^{O}C. This reaction was studied in different solvents such as dimethylformamide, solvent ether, diisopropylether, tetrahydrofuron, dichloromethane, ethylene dichloride and chloroform using triethylamine as a base. Among all the solvents, dichloromethane was gave better yields.

3 was reacted with 5-Bromo-3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indole **(4)**, in the presence of palladium acetate, tri-o- tolylphosphine and triethylamine at 100 to 110 ^{O}C in dimethylformamide. The Heck reaction product N-((1E)-2-(3-(1,2,3,6-tetrahydro-1-methylpyridin-4-yl)-1H-indol-5-l)vinylsulfonyl)-N-methyl(phenyl) methanamine **(5)** was obtained in around 90% yield. The product **5** was hydrogenated to give N-benzyl-N-methyl-2-[3-

(-methyl piperdine-4-yl)-1H-indole-5-yl] ethane sulfonamide **(6)**. The hydrogenation of **5** was effected smoothly in methanol using Pd/C.

The debenzylation of **6** was tried catalytically and reaction did not proceed. However, the reaction was successful when the Birch reduction conditions were employed. The reaction was conducted in liquid ammonia containing tetrahydrofuran and sodium metal at temperature–80 to-85 ^{O}C to give naratriptan **(8)** with 92% purity by HPLC.

In order to achieve a pharmacopeal product of 99.5% purity by HPLC as well as single impurity of <0.1%, the crude product had to be purified. Crystallisation in different solvents did not help. Hence other methods of purification like salt formation were tried. Of the several salts viz., hydrochloride sulphate succinate, maleate,oxalate ete, oxalate salt was most favourable. Naratriptan oxalate on basification yielded naratriptan of 99.8% HPLC purity.

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