Indian Journal of Chemistry
Vol. 46B, January 2007, pp. 201-203

Note

Synthesis of *N*-(3′,5′-dimethyl-4′-hydroxybenzyl)-*N*-tosyl-3,4-dimethoxybenzyl amine†

B China Raju*, Parvathi Neelakantan & U T Bhalerao*#

Organic Chemistry Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India

E-mail: chinaraju@iict.res.in

Received 12 July 2004; accepted (revised) 2 November 2006

Reaction of 4-benzyloxy-3,5-dimethyl benzyl bromide **4** and *N*-tosyl-3,4-dimethoxy benzyl amine **5** gives the *N*-(4′-benzyloxy-3′,5′-dimethylbenzyl)-*N*-tosyl-3,4-dimethoxybenzyl amine **6**. The obtained product on debenzylation affords *N*-(3′,5′-dimethyl-4′-hydroxybenzyl)-*N*-tosyl-3,4-dimethoxybenzyl amine **7** in 94% yield, which is key intermediate in the synthesis of isoindolines.

Keywords: *N*-(3′,5′-dimethyl-4′-hydroxybenzyl)-*N*-tosyl-3,4-dimethoxybenzyl amine, Isoindolines

IPC:Int.Cl.[8] C07C

Endothelins are potent vasoconstrictor and mitogenetic peptides isolated from vascular endothelial cells[1]. These peptides are known to elicit a number of biological effects contributes to cardiovascular and renal dysfunctions[2]. Substituted isoindolines are important intermediates for the synthesis of endothelones[3]. Our continuing interest in the research on synthesis of heterocyclic compounds[4], herein we report the synthesis of *N*-(3′,5′-dimethyl-4′-hydroxybenzyl)-*N*-tosyl-3,4-dimethoxybenzyl amine **7** which is key intermediate for the synthesis of isoindolines. 4-Benzyloxy-3,5-dimethylbenzoic acid **1** was prepared according to earlier procedure[4a] starting from the 2,6-dimethyl phenol.

4-Benzyloxy-3,5-dimethylbenzoic acid **1** on esterification furnished 4-benzyloxy-3,5-dimethyl benzoate **2**. The ester on reduction with LAH gave alcohol **3** and the obtained alcohol on bromination[5] with CBr_4/ PPh_3 gave 4-benzyloxy-3,5-dimethylbenzyl bromide **4** (**Scheme I**). The *N*-tosyl-3,4-dimethoxybenzyl amine **5** was treated with sodium hydride[6] in dry DMF at 0°C under nitrogen atmosphere. The reaction mixture slowly brought to room temperature, 4-benzyloxy-3,5-dimethylbenzyl bromide **4** was added over a period of 30 min. and the reaction mixture was stirred for one hr at the same temperature. Then the reaction mixture was heated to 90° C for 16 hr, cooled, workup and on column chromatography gave *N*-(4′-benzyloxy-3′,5′-dimethylbenzyl)-*N*-tosyl-3,4-dimethoxybenzyl amine **6**. The compound **6** on debenzylation with palladium charcoal under hydrogen atmosphere in ethyl acetate solvent gave *N*-(3′,5′-dimethyl-4′-hydroxybenzyl)-*N*-tosyl-3,4-dimethoxybenzyl amine **7** (**Scheme II**). All the new compounds were well characterized by its IR, ^{1}H NMR, Mass and CHN analysis.

Experimental Section

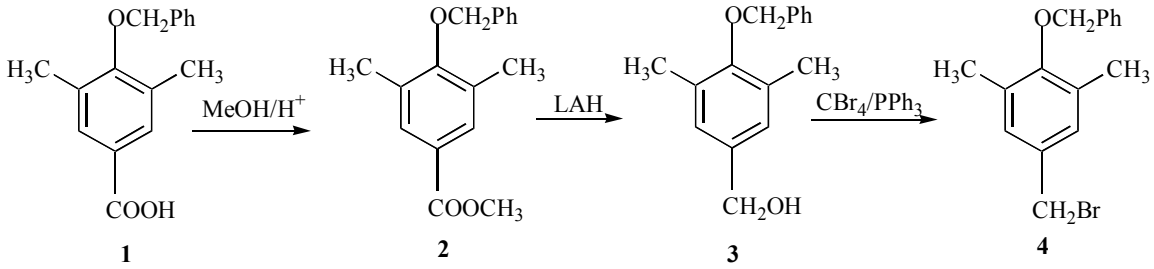
The ^{1}H NMR spectra were recorded on a Gemini 200 MHz spectrometer in $CDCl_3$ with TMS as internal standard. IR spectra were recorded on a Nicollet 740 FT IR spectrometer and Mass spectra were obtained on a VG Micro mass 7070H. Melting points were obtained on a Toshniwal melting point apparatus and are uncorrected.

Preparation of methyl-4-benzyloxy-3,5-dimethyl benzoate 2. The 4-benzyloxy-3,5-dimethylbenzoic acid **1** (10 g, 0.037 mole) was refluxed in dry methanol (15 mL) with catalytic amount of sulfuric acid (0.4 g) for 8 hr. The solvent was removed under reduced pressure and extracted with chloroform and the organic layer was washed with water and dried over sodium sulfate, concentrated and on column chromatography using hexane and ethyl acetate (9:1) gave methyl 4-benzyloxy-3,5-dimethylphenyl acetate **2** (8.9 g, yield: 84%) as liquid.

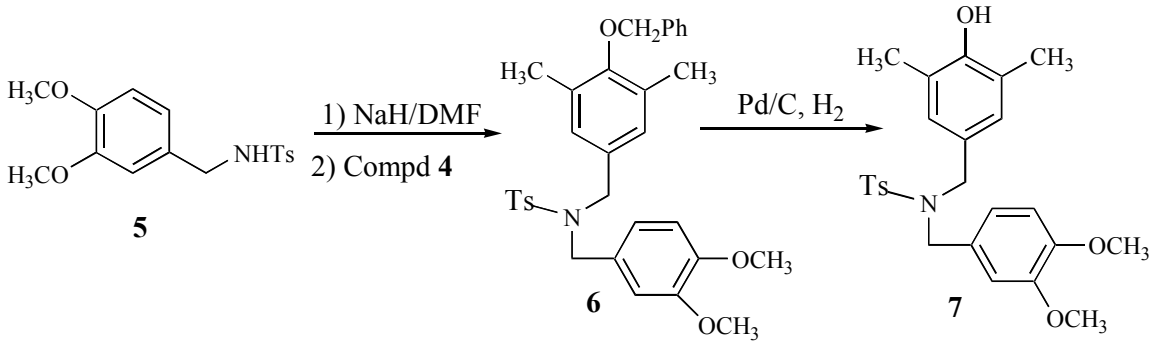
^{1}H NMR: δ 2.3 (s, 6H, $2CH_3$), 3.88 (s, 3H, OCH_3), 4.82 (s, 2H, OCH_2), 7.3-7.46 (m, 5H, aromatic), 7.71 (s, 2H, aromatic); IR ($CHCl_3$): 1720, 1610, 1320 & 1120 cm^{-1}; Mass: *m/e* 270; Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.55; H, 6.66. Found: C, 75.58; H, 6.62%.

Preparation of 4-benzyloxy-3,5-dimethylbenzyl alcohol 3. A solution of methyl 4-benzyloxy-3,5-dimethylphenyl acetate **2** (3 g, 0.0011 mole) in dry ether was added at room temperature to a well stirred suspension of $LiAlH_4$ (0.84 g, 0.022 mole) in dry ether (10 mL) under nitrogen atmosphere for 12 hr. Excess reagent was decomposed by cautious addition of cold

* Corresponding author, *#Former Director, IICT, Hyderabad 500 007, India.
† IICT Communication No. 061212



Scheme I



Scheme II

water and extracted with ether. The organic layer was washed with brine solution, dried over sodium sulfate, solvent removed under reduced pressure and purified by column chromatography using hexane and ethyl acetate gave 4-benzyloxy-3,5-dimethyl benzyl alcohol **3** (2 g, yield: 74.4%) as liquid.

^{1}H NMR: δ 2.22 (s, 6H, $2CH_3$), 4.48 (s, 2H, CH_2OH), 4.72 (s, 2H, OCH_2) 6.94 (s, 2H, aromatic), 7.26-7.42 (m, 5H, aromatic); IR (Neat): 3375, 1380, 1320, 1220 & 1140 cm^{-1}. Mass: *m/e* 242; Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.33; H, 7.43. Found: C, 79.42; H, 7.38%.

Preparation of 4-benzyloxy-3,5-dimethylbenzyl bromide 4. Triphenylphosphine (0.97 g, 0.002 mole) was added to a stirred solution of carbontetrabromide (1.23 g, 0.002 mole) and benzyl alcohol **3** (0.45 g, 001 mole) in dichloromethane (20 mL) at room temperature. The resulting solution was stirred for 4 hr, after which the solvent was removed under reduced pressure. The crude residue on column chromatography purification afforded 4-benzyloxy-3,5-dimethylbenzyl bromide **4** (0.38 g, yield: 67%) as solid, m.p. 64.5-65.3° C.

^{1}H NMR: δ 2.24 (s, 6H, $2CH_3$), 4.36 (s, 2H, H_2C-Br) 4.76 (s, 2H, OCH_2), 7.00 (s, 2H, aromatic), 7.28-7.45 (m, 5H, aromatic); IR (KBr): 1490, 1365, 1310, 1200, 1150 & 950 cm^{-1}; Mass: (*m/e*) 304, 306.

Preparation of *N*-(4′-Benzyloxy-3′,5′-dimethyl-benzyl)-*N*-tosyl-3,4-dimethoxybenzyl amine 6. To a suspension of NaH (0.15 g, 3.6 mmole) in dry DMF (5 mL), the *N*-tosyl-3,4-dimethoxy benzyl amine **5** (0.5 g, 1.5 mmole) in dry DMF (5 mL) was added at 0°C, under nitrogen atmosphere over a period of 30 min. The temperature was slowly raised to room temperature (3 hr) and then the benzyl bromide (0.52 g, 1.7 mmole) in dry DMF (5 mL) was added over a period of 30 minutes and the reaction mixture was stirred for 1 hr at room temperature. The temperature was then raised to 90°C and the reaction mixture was stirred for 16 hr. The contents were cooled; water was added and extracted repeatedly with ether. The ether layer was washed with water, dried over sodium sulfate, solvent removed under reduced pressure and on column chromatography over silica gel using hexane and ethyl acetate afforded *N*-(4′-benzyloxy-3′,5′-dimethylbenzyl)-*N*-tosyl-3,4-dimethoxybenzylamine **6** (0.32 g, yield: 34.3%) as solid, m.p. 97.4-98°C; ^{1}H NMR: δ 2.12 (s, 6H, $2CH_3$), 2.42 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.14 (s, 2H, NCH_2), 4.20 (s, 2H, NCH_2), 4.7 (s, 2H, OCH_2) 6.5-6.7 (m, 5H, aromatic), 7.22-7.45 (m, 7H, aromatic), 7.72 (d, 2H, aromatic); IR (KBr): 1580, 1510, 1330 & 1160 cm^{-1}; Mass: *m/e* 546 (M^{+1}); Anal. Calcd for $C_{32}H_{35}NSO_5$: C, 70.45; H, 6.42; N, 2.56. Found: C, 70.38; H, 6.46; N, 2.58%.

Preparation of *N*-(3′,5′-Dimethyl-4′-hydroxy-benzyl)-*N*-tosyl-3,4-dimethoxybenzyl amine 7. To the benzyl derivative (0.32 g, 0.59 mmole) in ethyl

acetate (5 mL), Pd-C (10%, 0.032 g) was added and the reaction mixture was stirred under hydrogen atmosphere (balloon) at room temperature for 6 hr (TLC). The charcoal was filtered using celite as filter aid, the solvent removed under reduced pressure and on chromatography over silica gel afforded *N*-(3′,5′-Dimethyl-4′-hydroxybenzyl)-*N*-tosyl-3,4-dimethoxy-benzylamine **7** (0.25 g, yield: 94%) as solid. m.p.113-14°C;^{1}H NMR: δ 2.12 (s, 6H, $2CH_3$), 2.48 (s, 3H, CH_3), 2.46 (t, 2H, CH_2), 3.7 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.14 (s, 2H, NCH_2), 4.22 (s, 2H, NCH_2), 4.48 (s, 1H, OH, D_2O exchangeable), 6.52-6.76 (m, 5H, aromatic), 7.3 (d, 2H, aromatic), 7.74 (d, 2H, aromatic); IR (KBr): 3480, 1580, 1510, 1335 & 1150 cm^{-1}; Mass: m/e 455; Anal.Calcd for $C_{25}H_{29}NSO_5$: C, 65.93; H, 6.37; N, 3.07. Found: C, 65.89; H, 6.39; N, 3.12%.

Acknowledgement

One of the authors (B China Raju) is thankful to the Director, IICT for constant encouragement.

References

1 Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, Yazaki Y, Goto K & Masaki T, *Nature*, 332, **1988**, 411.

2 Doherty A M, *J Med Chem*, 35, **1992**, 1493.

3 Kukkola P J, Bilci N A & Ikeler B T, *Tetrahedron Lett*, 37, **1996**, 5065.

4 (a) Bhalerao U T, China Raju B & Neelakantan P, *Synth Commun*, 25, **1995,** 1433.

(b) Bhalerao U T, China Raju B & Neelakantan P, *Indian J Chem,* 31B, **1994**, 1197.

(c) Bhalerao U T, China Raju B & Neelakantan P, *Indian J Chem*, 35B, **1996**, 530.

(d) China Raju B, Jayathirtha Rao V & Raghavan K V, *US Patent*, **2004**, 6,737,529.

(e) China Raju B & Jayathirtha Rao V, *US Patent*, **2003**, 6,566,528.

(f) Ganga Dasu B, China Raju B & Jayathirtha Rao V, *US Patent*, **2002**, 6,479,664.

(g) China Raju B & Jayathirtha Rao V, *Indian J Chem*, 41B, **2002**, 2180.

5 Hooz J & Gilani S S H, *Can J Chem*, 46, **1968**, 86.

6 Tietze L F & Schimpt R, *Chem Ber*, 127, **1994**, 2235.