ISSN: 0974 - 7516 Volume 7 Issue 2

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Short Communication

OCAIJ, 7(2), 2011 [105-107]

A simple and efficient synthesis of calcium channel blocker Flunarizine

A.Venkat Narsaiah*, J.Kranthi Kumar

Organic Chemistry Division, Indian Institute of Chemical Technology, Hyderabad, 500007, (INDIA)

E-mail : vnakkirala2001@yahoo.com

Received: 30th August, 2010 ; Accepted: 9th September, 2010

ABSTRACT

T-type calcium channel blocker and anti-ischemic drug 1-[bis (4-fluorophenyl) methyl]-4-cinnamylpiperazine **(1)** synthesis has been carried out in four steps with an average of 70% yield. This route is very convenient and can be applied for large scale preparation of Flunarizine with high yields.

KEYWORDS

Keto reduction;
Calcium chloride blocker;
Piperazine;
Cinnamylbromide.

INTRODUCTION

The Ca^{2+} channel blockers have been used extensively in the treatment of neuropathetic pain, hypertension and angina pectoris. These are classified mainly in to high voltage activated (HVA) and low voltage activated (LVA) channels on the basis of depolarization. Based on pharmacological studies HVA channels are again sub-divided into L, N, P, Q and R-types. The LVA are sub-divided into L and T type which are co-existing in neurons, heart, vascular smooth muscle and endocrine cells. Most of the Ca^{2+} channel blockers interact with L-type calcium channel[1-4]. However, these drugs showed some extent feature of unwanted effects such as negative inotropism, atrioventricular blockade or neurohormonal activation. Recently more attention has been paid on the development of active T-type blockers for the reduction of side effects. Flunarizine **(1)**, 1-[bis (4-fluorophenyl) methyl]-4-cinnamylpiperazine which belongs to T-type calcium channel blocker is effective in preventing attacks in migraine patients[5-7]. The reported methods in literature for the synthesis of Flunarizine involves the Grignard and reductive amination reactions[8,9].

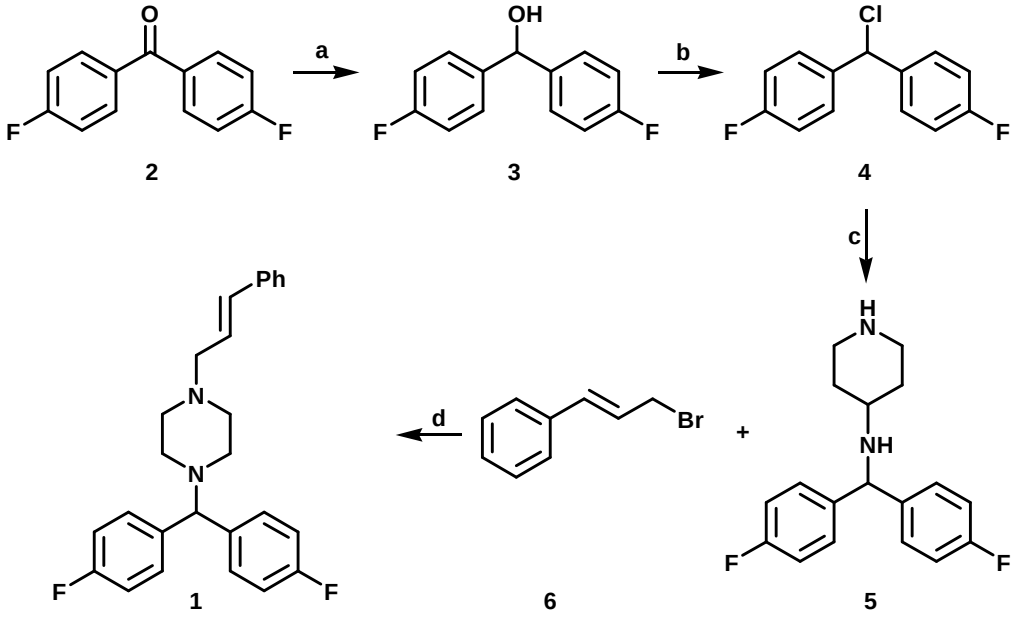
RESULTS AND DISCUSSIONS

As part of our research program in design and synthesis of biologically active compounds[10-15], herein we report a highly efficient route for the synthesis of T-type calcium channel blocker Flunarizine **(1)** as shown in the scheme 1. Our synthetic strategy started from commercially available bis (4-fluorophenyl) methanone **(2)**, which on reduction with sodium borohydride ($NaBH_4$) in methanol at room temperature to afford the corresponding product bis (4-fluorophenyl) methanol 3 in excellent yields.[16] Thus obtained bis (4-fluorophenyl) methanol was reacted with hydrochloric acid at reflux condition to yield the corresponding derivative of 4,4′-(chloromethylene) bis (fluoro benzene) **(4)** in very good yields. This chloro compound was used for further reaction without purification.

Reagents and reaction conditions: (a) $NaBH_4$, methanol, rt, 2 h, 96%. (b) $CaCl_2$, con. HCl, 90-95°C, 10 h, 90%. (c) Piperazine, K_2CO_3, THF, reflux, 8 h, 90%. (d) Cinnamylbromide, acetonitrile, K_2CO_3, reflux, 10h, 90%.

The above obtained 4,4′-(chloromethylene) bis (fluorobenzene) compound was subjected to further reaction with piperazine in presence of potassium car-

Short Communication



Scheme 1

bonate at THF reflux to yield the corresponding product of 1-[bis (4-fluorophenyl) methyl] piperazine **(5)** in very good yields. Thus obtained piperazine derivative was reacted with cinnamyl bromide in presence of potassium carbonate in acetonitrile at reflux condition to afford the target molecule 1-[bis (4-fluorophenyl) methyl]-4-cinnamylpiperazine **(1)** in very good yields. All the products were characterized by their ^{1}H NMR, IR and mass specrtroscopy data.

CONCLUSION

In conclusion, we have demonstrated a simple and efficient five step synthetic pathway for the preparation of Ca^{2+} channel blocker drug Flunarizine **(1)** in very good yields. This route is very convenient and easy for large scale preparation of Flunarizine with out any difficulty.

EXPERIMENTAL

General Methods. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectro photometer using KBr optics. ^{1}H NMR spectra were recorded on Gemini-200 spectro meter in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

Bis (4-fluorophenyl) methanol (3)

To a stirred solution of bis (4-fluoro phenyl) methanone **(2)** (2 g, 9.16 mmol) in methanol (20 mL) was added $NaBH_4$ (0.52 g, 13.76 mmol) in portions at 0°C. The resulting reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction as indicated by TLC, the reaction mixture was quenched by adding crushed ice. Then, the solvent was removed under reduced pressure and extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude product was purified by column chromatography. The pure product bis (4-fluorophenyl) methanol 3 was obtained as colorless thick syrup, yield 1.92g (96%). IR (KBr): υ 3379, 2884, 1604, 1508, 1414, 1298, 1226, 1182, 1157, 1099, 1015, 865, 833, 778 cm^{-1}.; ^{1}H NMR ($CDCl_3$): δ 2.35 (brs, 1H, OH), 5.68 (s, 1H), 6.90-7.02 (m, 4H), 7.20-7.30 (m, 4H).

4,4′-(chloromethylene) bis (fluorobenzene) (4)

To a mixture of alcohol 3 (1.92g, 8.72 mmol) in con. Hydrochloric acid (10 mL) was added $CaCl_2$ (1.34 g, 12.2 mmol) at room temperature. The resulting reaction mixture was heated at 90-95°C for 10 hours. Then, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude product as a thick

syrup, 2 g (90%).; ^{1}H NMR ($CDCl_3$): δ 6.18 (s, 1H), 7.03 (t, 4H, J = 7.8 Hz), 7.33 (t, 4H, J = 7.8 Hz).

1-[bis (4-fluorophenyl) methyl] piperazine (5)

To a stirred mixture of the above chloro compound **(4)** (2 g, 8.4 mmol) in THF (20 mL) was added piperazine (0.72 g, 8.4 mmol) and potassium carbonate (2.32 g, 16.8 mmol) and a catalytic amount of tertiary butyl ammonium iodide (PTC) at room temperature. The resulting reaction mixture was refluxed for 8 hours. After completion of the starting material as indicated by TLC, the solvent was removed under reduced pressure. The afforded residue was extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude product, which was purified by column chromatography. The pure product was obtained as a thick liquid, yield 2.22g, (90%). IR (KBr): υ 3428, 2924, 2850, 1603, 1567, 1506, 1385, 1220, 1152, 1092, 1046, 1005, 871, 826, 783, 717 cm^{-1}.; ^{1}H NMR ($CDCl_3$): δ 2.35 (brs, 1H, OH), 5.68 (s, 1H), 6.90-7.02 (m, 4H), 7.20-7.30 (m, 4H). EIMS m/z (%): 289 (m^{+1} 60), 242 (27), 204 (42), 203 (100), 95 (10), 76 (20), 51 (10).

1-[bis (4-fluorophenyl) methyl]-4-cinnamylpiperazine (1)

To a stirred solution of piperazine compound 5 (2 g, 6.94 mmol) in acetonitrile (20 mL) was added (*E*)-(3-bromoprop-1-enyl) benzene **(6)** (1.36g, 6.9 mmol) and potassium carbonate (1.92g, 13.88 mmol) and a catalytic amount of tertiarybutyl ammonium iodide (PTC) at room temperature. The resulting reaction mixture was refluxed for 10 hours. After completion of the starting material as indicated by TLC, the solvent was removed under reduced pressure. The afforded residue was extracted with ethyl acetate (230 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude product, which was purified by column chromatography. The pure product was obtained as syrup, yield 2.6g (90%). IR (KBr): υ 3029, 2928, 2812, 1658, 1602, 1504, 1452, 1330, 1290, 1224, 1146, 1095, 1005, 969, 828, 788, 750, 695 cm^{-1}.; ^{1}H NMR ($CDCl_3$): δ 2.30-2.60 (m, 8H), 3.20 (d, 2H, J = 8.0 Hz), 4.20 (s, 1H), 6.10-6.30 (m, 1H), 6.45 (d, 1H, J = 14.5 Hz), 6.95 (t, 4H, J = 8.5 Hz), 7.18-7.48 (m, 9H). ^{1}H NMR ($CDCl_3$): 153.4, 160.1, 136.7, 129.2, 128.5, 127.5, 126.3, 115.5, 115.2, 74.4, 60.8, 53.2, 51.1. EIMS m/z (%): 406 (m^{+2} 30), 405 (m^{+1} 100), 303 (10), 289 (10), 203 (18), 95 (10), 76 (25), 51 (20).

ACKNOWLEDGEMENT

JKK is thankful to UGC-New Delhi for providing Fellowship.

REFERENCES

[1] B.Holmes, R.N.Brogden, R.C.Heel, T.M.Speight, G.S.Avery; Drugs, **27**, 6 **(1984)**.

[2] H.Annoura, K.Nakanishi, M.Uesugi, A.Fukunaga, A.Miyajima, Y.T.Horikawa, S.Tamura; Bioorg. Med.Chem.Lett., **9**, 2999 **(1999)**.

[3] K.Ayajiki, T.Okamura, N.Toda; Eur.J.Pharmacol., **329**, 49 **(1997)**.

[4] S.Younesl, G.B.Mouyssetl, G.S.Sannesl, J.L.Stiglianil, M.Payard, R.Bonnafous, J.T.Versailles; Eur. J.Med.Chem., **28**, 943 **(1993)**.

[5] L.J.S.Knutsen, C.J.Hobbs, C.G.Earnshaw, A.Fiumana, J.Gilbert, S.L.Mellor, F.Radford, N.J.Smith, P.J.Birch, J.R.Burley, S.D.C.Ward, I.F.James; Bioorg.Med.Chem.Lett., **17**, 662 **(2007)**.

[6] M.R.Kilbourn; Appl.Radiar.Isor., **42**, 109 **(1991)**.

[7] X.C.Cheng, X.Y.Liu, W.F.Xu, X.L.Guo, N.Zhang, Y.N.Song; Bioorg.Med.Chem., **17**, 3018 **(2009)**.

[8] H.Annoura, K.Nakanishi, M.Uesugi, A.Fukunaga, S.Imajo, A.Miyajima, Y.T.Hori yawa, S.Tamura; Bioorg.Med.Chem., **10**, 371 **(2002)**.

[9] G.W.Zamponi, Z.P.Feng, L.Zhang, H.Pajouhesh, Y.Ding, F.Belardett, H.Pajouhesh, D.Dolphin, L.A.Mitscher, T.P.Snutch; Bioorg.Med.Chem.Lett., **19**, 6467 **(2009)**.

[10] D.S.Bose, A.V.Narsaiah; Bioorg.Med.Chem., **13**, 627 **(2005)**.

[11] A.V.Narsaiah; Synth.Commun., **36**, 1897 **(2006)**.

[12] A.V.Narsaiah; Catal.Lett., **121**, 81 **(2008)**.

[13] A.V.Narsaiah, J.K.Kumar; Synthesis., 1989 **(2010)**.

[14] A.V.Narsaiah, B.Nagaiah; Synthesis., 2705 **(2010)**.

[15] A.V.Narsaiah, P.Narsimha, G.Navitha; Int.J.App. Biol.Pham. Tech., **1**, 736 **(2010)**.

[16] A.R.Chamberlin, J.S.Daniel; ‚Comprehensive Organic Synthesis', 3rd Edn., Pergamon Press, New York, 923 **(1991)**.