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Novel method of synthesis of N-methyl-3-phenyl piperazine and some alkylpiperazine and Phenylpiperazine derivatives

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Abstract: The novel method for synthesis of N- methyl -3-phenyl piperazine and it's derivatives are described in this novel approach, aromatic aldenhyde (Benzaldehyde) condensed with substituted halo amine (2-chloroethylamine) in same mole ratio to give imine tautomer, (2-chloro-*N*-[(1*E*)-phenylmethylene]ethanamine). Furthermore cyclize with substituted alkyl haloamine (1-chloro-*N*-methylmethanamine) to form substituted tetrahydro pyrazine (1-methyl-3-phenyl-1,2,3,6-tetrahydropyrazine) which concomitantly fallowed by reduction with metal hydride (sodium borohydride) giving the targeted compound (N- methyl -3-phenyl piperazine).

Keywords: N-methyl-3-phenyl piperazine, 3-ethenyl-1-methyl-5-phenylpiperazine, 2-benzyl-1-methyl-3-phenylpiperazine, 2-ethyl-1-methyl-5-phenylpiperazine,2-chloro-*N*-[(1*E*)-phenylmethylene]ethanamine,1-methyl-3-phenyl-1,2,3,6-tetrahydropyrazine, reduction , cyclization.

Introduction

Mirtazapine is the only tetracyclic antidepressant that has been approved by the USFDA (United States Food and Drug Administration) to treat depression. Because of its unique pharmacologic profile, mirtazapine is virtually devoid of anticholinergic effects, serotonin-related side effects,[1] and adrenergic side effects (orthostatic hypotension and sexual dysfunction). It is most useful as an add on medication to enhance the effectiveness of agents such as duloxetine and venlafaxine in severe and treatment resistant depression [2].

Introduction of our novel method of synthesis of "N-methyl-3-phenyl piperazine from benzaldehyde" will be very much useful for worldwide manufacturer of N-methyl-3-phenyl piperazine and hence Mirtazapine also with respect to simplicity in operation, cost and eco-friendliness.

A number of synthetic strategies have been reported for the preparation of N-methyl -3-phenyl piprerazine so far. The method describe by Divvela V. [3] involves the selective protection of amine in 1-alkyl 2-oxo-3-phenyl piperazine but this step afford less yield because of non selectivity of benzyl chloride [10] and BOC anhydride [13] and furthermore, N- methylation by alkyl iodide and reduction with lithium aluminium hydride and finally, deprotection by hydrogeneation . from the above said method there is several disadvantages likes uses of hazardous chemicals, alkyl iodide, lithium aluminium Hydride and hydrogenation [16] [17] which is not suitable for industrial point of view.

By the route of Dolitzky,[4] [9] the piperazine was made from *N*- (2-chloroethyl)- *N*-methyl-β-chloro-β-phenylethylamine and this method afforded by product 1-methyl-2- phenylpiperazine. This may be because of the non-selectivity in the reaction of starting material preparation.

The method described by Roderick,[5] [10] involves the methylation of 2-phenylpiperazine and this step afforded low yields [13] [14] because it was not selective and produces unwanted product 1,4-dimethylpiperazine.

The method described by Guo,[6] [11] involves the use of excess of lithium aluminum hydride,[7] for the unsubstituted amide reduction. From above said synthesis methods for preparation of N- methyl -3-phenyl piperazine ,there is still need to improve the strategies which circumvents theses problems.

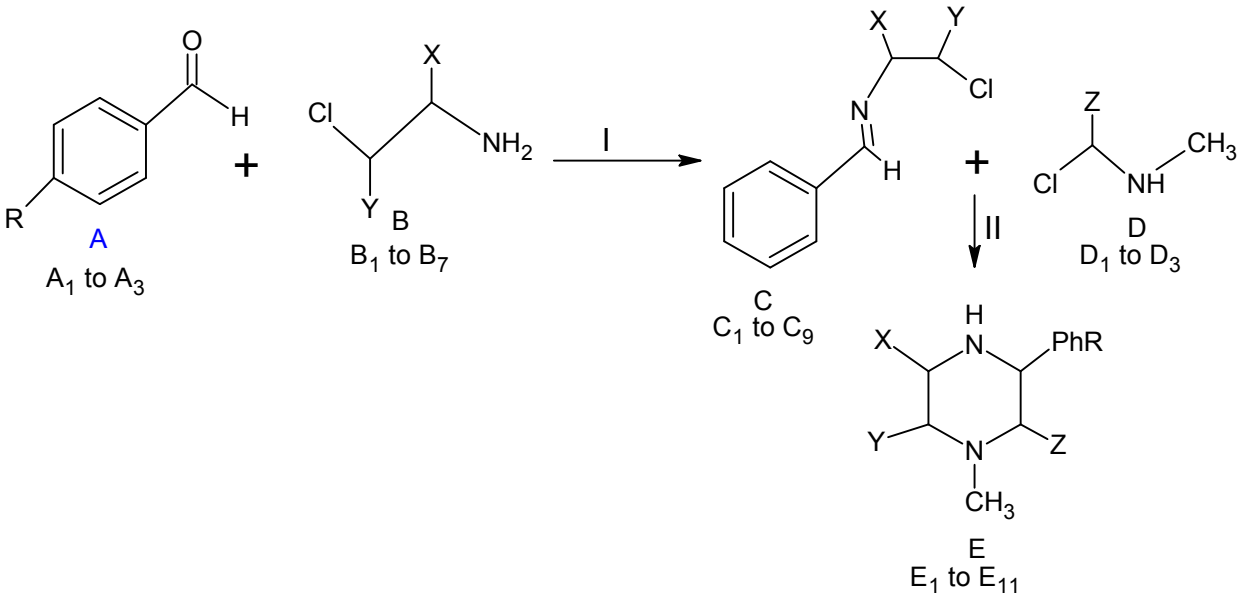
In our novel approach, first step involves condensation of aromatic aldenhyde (Benzaldehyde) with substituted

halo amine (2- chloroethylamine) in stricometric way to give imine tautomer, (2-chloro-*N*-[(1*E*)-phenylmethylene]ethanamine) which furthermore cyclize with substituted alkyl haloamine (1-chloro-*N*-methylmethanamine) to form substituted tetrahydro pyrazine (1-methyl-3-phenyl-1,2,3,6-tetrahydropyrazine) which concomitantly fallowed by reduction with metal hydride (sodium boro hydride) giving the targeted compound (N- methyl -3-phenyl piperazine).The above said novel approach for preparation of N- methyl -3-phenyl piperazine is well efficient over the existing prior art.

Results and Discussion

From the above said synthesis methods and their several disadvantages over this novel approach for preparation of 1and 3 substituted piperazine and it's derivatives. This method involves simple three steps in which finial step is insitu way. Aromatic aldenhyde (Benzaldehyde) condensed with substituted halo amine (2-chloroethylamine) in same mole ratio to give imine tautomer, (2-chloro-*N*-[(1*E*)-phenylmethylene]ethanamine) which furthermore cyclize with substituted alkyl haloamine (1-chloro-*N*-methylmethanamine) to form substituted tetrahydro pyrazine (1-methyl-3-phenyl-1,2,3,6-tetrahydropyrazine) which concomitantly fallowed by reduction with metal hydride (sodium boro hydride) giving the title compound (N- methyl -3-phenyl piperazine).

Route:1



Wherein,

I. Imine formation; Toulene, MDC, at reflux temp.

II. Cyclization and reduction (insitu); sodium borohydride, methanol, at cool temperature. 6N HCl, 50% NaOH.

Table: 1

A_1, R=H		X	Y		R	X	Y	D_1, Z=H
	B_1	H	H	C_1	H	H	H	
A_2, R=CH_3	B_2	CH=CH_2	H	C_2	H	H	CH3	D_2, Z=CH=CH_2
A_3, R=CH2 CH_3	B_3	CH_2CH_3	H	C_3	H	H	CH2CH3	D_3, Z=CH_2Ph
	B_4	CH_2Ph	H	C_4	H	CH=CH_2	H	
	B_5	H	CH_2CH_3	C_5	H	CH_2CH_3	H	
	B_6	H	CH=CH_2	C_6	H	CH_2Ph	H	
	B_7	H	CH_2Ph	C_7	H	H	CH_2CH_3	
				C_8	H	H	CH=CH_2	
				C_9	H	H	CH_2Ph	

So E_1 to E_{11} will be as follows.

Table: 2

E_1	R=H and X, Y, Z=H_2, 1-methyl-3-phenylpiperazine
E_2	R=CH_3 and X, Y, Z=H_2, 1-methyl-3-(4-methylphenyl) piperazine
E_3	R=CH_2CH_3 and X, Y, Z=H_2, 3-(4-ethylphenhyl)-1-methylphenylpiperazine
E_4	R=H, X= CH=CH_2 and Y, Z= H_2, 3-ethenyl-1-methyl-5-phenylpiperazine
E_5	R=H, X=CH_2CH_3, Y,Z=H_2, 3-ethyl-1-methyl-5-phenylpiperazine
E_6	R=H, X=CH_2Ph and Y,Z=H_2, 3-benzyl-1-methyl-5-phenylpiperazine
E_7	R=H, Y= CH_2CH_3, X,Z=H_2, 2-ethyl-1-methyl-5-phenylpiperazine
E_8	R=H, Y= CH=CH_2, X,Z=H_2, 2-ethenyl-1-methyl-5-phenylpiperazine
E_9	R=H, Y= CH_2Ph, X,Z=H_2, 2-benzyl-1-methyl-5-phenylpiperazine
E_{10}	R=H, Z=CH=CH_2 and X,Y=H_2, 2-ethenyl-1-metyl-3-phenylpiperazine
E_{11}	R=H, Z=CH_2Ph and X,Y=H_2, 2-benzyl-1-methyl-3-phenylpiperazine

In summary, we report novel approach of reaction via imine formation .Initially by imine formation ,fallowed by cyclization anf concomitantly with reduction yield a title compound in good overall yield and purity.However, intermediate obtained (Route-1)by the following method may be useful for making some biological important compounds owing to the available free NH group.

Experimental section :

General Procedures:

Melting points were measured by using capillary tube method apparatus. Proton NMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard ($CDCl^3$ solution). IR spectra were recorded from KBr disk on FT-IR Bruker,All steps and final product were characterized by spectra and physical data.

E_1: N-methyl-3-phenyl piperazine

Benzaldehyde and 2-chloroethanamine in same mole proportion was refluxed with 300 ml of toluene for 12 hrs. Residue was dissolved in MDC and washed by NaHCO3 solution. Crude product was distilled U/V (< 1 mbar) and obtained a colorless oil with narrow boiling range, which solidified upon standing in the refrigerator. The product was identified as the imine toutomer neat (IR). Taken 1 mole of this substance and 1.5 to 1.7 moles of 1-chloro-N-methylmethanamine and 2 moles of sodium borohydride in methanol under cooling for 3 hrs. Distilled out the solvent u/v below 30°C to get oily residue, added water. Residue cooled to 10-15°C and aq. solution of 6 N HCL is added to pH 1 (11ml) (exothermic reaction) Resulting white suspension stirred at 20°C for 1 hour. Suspension cooled to 10-15°C and basify with 50% NaOH to pH 12-14 (5-6 ml). RM extracted with 3X10 ml of diethyl ether. Diethyl ether layer concentrated U/V and obtained yellow liquid residue of N-methyl-3-phenyl piperazine, which on subsequent work up with iso propyl alcohol and then by drying at 35°C, obtained light yellow crystals of title compound.

Purity 99.9% (by HPLC); mp 58-60 °C (lit,[6] 53-55°C); IR (KBr, cm^{-1}) 3253, 2942, 2816, 2792, 1603, 761, 703; ^{1}H-NMR(300 MHz, CDCl3) δ 1.76 (bs, 1H), 1.92-1.99 (m, 1H), 2.10-2.15 (m, 1H), 2.31 (s, 3H), 2.80-2.89 (m, 2H), 3.01-3.11 (m, 2H), 3.87 (dd, 1H, *J*=10.6, 2.7 Hz), 7.27-7.41 (m, 5H); ^{13}C-NMR(300 MHz, CDCl3) δ 46.6, 46.7, 55.6, 60.8, 63.7, 127.3, 127.9, 128.8, 142.9; MS (ESI, *m/z*):

177.0 $[M+H]^+$. Anal. Calcd. For $C_{11}H_{16}N_2$ (176.26): C, 74.96; H, 9.15; N, 15.89. Found: C, 74.90; H, 9.22; N, 15.88.

In the same way prepared the derivatives E_1 to E_{11} . Below given is structure interpretation data:

E_2: R=CH_3 and X, Y, Z=H_2, 1-methyl-3-(4-methylphenyl) piperazine,

A_2 and B_1 were refluxed in toluene, crude product was solidified upon standing refrigerator, then treated this C_2 with D_1 with the same process as in E_1 to get E_2 and drying was carried out at 35°C.

Purity 99.9% (by HPLC); mp 56-58 °C, IR (KBr, cm^{-1}) 3253, 2942, 2816, 2792, 1603, 761, 703, 618; ^{1}H-NMR(300 MHz, CDCl3) δ 1.76 (bs, 1H), 1.92-1.99 (m, 1H), 2.10-2.15 (m, 1H), 2.31 (s, 3H), 2.34 (s,

3H), 2.80-2.89 (m, 2H), 3.01-3.11 (m, 2H), 3.87 (dd, 1H, *J*=10.6, 2.7 Hz), 7.27-7.41 (m, 4H); ^{13}C-NMR(300 MHz, CDCl3) δ 24.9 46.7, 56.6, 60.8, 63.7, 127.3, 127.9, 128.8, 156.9; MS (ESI, *m/z*):

191 $[M+H]^+$. Anal. Calcd. For $C_{12}H_{18}N_2$ (190): C, 78.96; H, 4.15; N, 15.89.

E_3: R=CH_2CH_3 and X, Y, Z=H_2, 3-(4-ethylphenhyl)-1-methylphenylpiperazine

A_3 and B_1 were refluxed in toluene, crude product was solidified upon standing refrigerator, then treated this C_3 with D_1 with the same process as in E_1 to get E_3 and drying was carried out at 35°C.

Purity 99.9% (by HPLC); mp 70-72 °C, IR (KBr, cm^{-1}) 3253, 2942, 2816, 2792, 1603, 761,609, 508,703; ^{1}H-NMR(300 MHz, CDCl3) δ 1.76 (bs, 1H), 1.92-1.99 (m, 1H), 2.10-2.15 (m, 1H), 2.31 (s, 3H), 2.4 (m, 2H), 2.80-2.89 (m, 2H), 3.01-3.11 (m, 2H), 3.87 (dd, 1H, *J*=10.6, 2.7 Hz), 7.27-7.41 (m, 4H); ^{13}C-NMR(300 MHz, CDCl3) δ20.3, 46.7, 55.6, 60.8, 63.7, 127.3, 127.9, 128.8, 159.3; MS (ESI, *m/z*):

204.0 $[M+H]^+$. Anal. Calcd. For $C_{13}H_{18}N_2$ (203): C, 79.96; H, 4.15; N, 15.89.

E_4: R=H, X= CH=CH_2 and Y, Z= H_2, 3-ethenyl-1-methyl-5-phenylpiperazine

A_2 and B_1 were refluxed in toluene, crude product was solidified upon standing refrigerator, then treated this C_2 with D_1 with the same process as in E_1 to get E_2 and drying was carried out at 35°C.

Purity 99.9% (by HPLC); mp 75-80 °C ,IR (KBr, cm^{-1}) 3253, 2942, 2816, 2792, 1603, 1400, 761, 703; ^{1}H-NMR(300 MHz, CDCl3) δ 1.76 (bs, 1H), 1.92-1.99 (m, 1H), 2.10-2.15 (m, 1H), 2.31 (s, 3H), 2.80-2.89 (m, 1H), 2.9 (t, D, 2H),3.0 (d, 2H), 3.01-3.11 (m, 2H), 3.87 (dd, 1H, *J*=10.6, 2.7 Hz), 7.27-7.41 (m, 5H); ^{13}C-NMR(300 MHz, CDCl3) δ 39.3, 44.4, 46.7, 55.6, 60.8, 63.7, 127.3, 127.9, 128.8, 142.9; MS (ESI, *m/z*):

203 $[M+H]^+$. Anal. Calcd. For $C_{13}H_{18}N_2$ (202): C, 76.96; H, 7.15; N, 15.89.

E_5: ,R=H, X=CH_2CH_3, Y,Z=H_2, 3-ethyl-1-methyl-5-phenylpiperazine

A_1 and B3 were refluxed in toluene, crude product was solidified upon standing refrigerator, then treated this C5 with D_1 with the same process as in E_1 to get E_5 and drying was carried out at 35°C.

Purity 99.9% (by HPLC); mp 93-95 °C ,IR (KBr, cm^{-1}) 3253, 2942, 2816, 2792, 1603, 1329, 761, 703; ^{1}H-NMR(300 MHz, CDCl3) δ 1.76 (bs, 1H), 1.92-1.99 (m, 1H), 2.10-2.15 (m, 1H), 2.31 (s, 3H), 2.80-2.89 (m, 1H), 2.9 (m, 2H). 3.0 (t, 3H), 3.01-3.11 (m, 2H), 3.87 (dd, 1H, *J*=10.6, 2.7 Hz), 7.27-7.41 (m, 5H); ^{13}C-NMR(300 MHz, CDCl3) δ 35.2, 46.7, 55.6, 60.8, 63.7, 127.3, 127.9, 128.8, 142.9; MS (ESI, *m/z*):

205 $[M+H]^+$. Anal. Calcd. For $C_{13}H_{20}N_2$ (204): C, 75.96; H, 8.15; N, 15.89. Found: C,

74.90; H, 9.22; N, 15.88.

E_6: R=H, X=CH_2Ph and Y,Z=H_2, 3-benzyl-1-methyl-5-phenylpiperazine,

A_1 and B_4 were refluxed in toluene, crude product was solidified upon standing refrigerator, then treated this C_6 with D_1 with the same process as in E_1 to get E_6 and drying was carried out at 35°C.

Purity 99.9% (by HPLC); mp 105-107 °C , IR (KBr, cm^{-1}) 3253, 2942, 2816, 2805, 2792, 1603, 761, 703; ^{1}H-NMR(300 MHz, CDCl3) δ 1.76 (bs, 1H), 1.92-1.99 (m, 1H), 2.10-2.15 (m, 1H), 2.31 (s, 3H), 2.4 (s, 2H), 2.80-2.89 (m, 1H), 3.01-3.11 (m, 2H), 3.87 (dd, 1H, *J*=10.6, 2.7 Hz), 7.27-7.41 (m, 10H); ^{13}C-NMR(300 MHz, CDCl3) δ 44.9, 46.7, 55.6, 60.8, 63.7, 103.2,127.3, 127.9, 128.8, 142.9; MS (ESI, *m/z*):

267.0 $[M+H]^+$. Anal. Calcd. For $C_{18}H_{22}N_2$ (266): C, 82.96; H, 1.15; N, 15.89. Found: C,

74.90; H, 9.22; N, 15.88.

E_7: R=H, Y= CH_2CH_3, X,Z=H_2, 2-ethyl-1-methyl-5-phenylpiperazine

A_1 and B_5 were refluxed in toluene, crude product was solidified upon standing refrigerator, then treated this C_7 with D_1 with the same process as in E_1 to get E_7 and drying was carried out at 35°C.

Purity 99.9% (by HPLC); mp 67-69 °C , IR (KBr, cm^{-1}) 3253, 2942, 2816, 2792, 1895,1603, 761, 703; ^{1}H-NMR(300 MHz, CDCl3) δ 1.76 (bs, 1H), 1.92-1.99 (m, 1H), 2.10-2.15 (m, 1H), 2.31 (s, 3H), 2.80-2.89 (m, 2H), 2.9 (m, 2H), 3.0 (t, 3H), 3.01-3.11 (m, 1H), 3.87 (dd, 1H, *J*=10.6, 2.7 Hz), 7.27-7.41 (m, 5H); ^{13}C-NMR(300 MHz, CDCl3) δ 48.6, 46.7, 55.6, 60.8, 63.7, 127.3, 127.9, 128.8, 158; MS (ESI, *m/z*):

205 $[M+H]^+$. Anal. Calcd. For $C_{13}H_{20}N_2$ (204): C, 77.96; H, 6.15; N, 15.89. Found: C,

74.90; H, 9.22; N, 15.88.

E_8: R=H, Y= CH=CH_2, X,Z=H_2, 2-ethenyl-1-methyl-5-phenylpiperazine

A_1 and B_6 were refluxed in toluene, crude product was solidified upon standing refrigerator, then treated this C_8 with D_1 with the same process as in E_1 to get E_8 and drying was carried out at 35°C.

Purity 99.9% (by HPLC); mp 74-76 °C; IR (KBr, cm^{-1}) 3253, 2942, 2900, 2816, 2792, 1603, 761, 703; ^{1}H-NMR(300 MHz, CDCl3) δ 1.76 (bs, 1H), 1.92-1.99

(m, 1H), 2.10-2.15 (m, 1H), 2.31 (s, 3H), 2.4 (t, 1H), 2.1 (d, 2H), 2.80-2.89 (m, 2H), 3.01-3.11 (m, 1H), 3.87 (dd, 1H, *J*=10.6, 2.7 Hz), 7.27-7.41 (m, 5H); ^{13}C-NMR(300 MHz, CDCl3) δ 46.6, 46.7, 55.6, 60.8, 63.7, 127.3, 127.9, 128.8, 138.2, 142.9; MS (ESI, *m/z*):

203 $[M+H]^+$. Anal. Calcd. For $C_{13}H_{18}N_2$ (202): C, 79.96; H, 4.15; N, 15.89. Found: C,

74.90; H, 9.22; N, 15.88.

E_9: R=H, Y= CH_2Ph, X,Z=H_2, 2-benzyl-1-methyl-5-phenylpiperazine

A_1 and B_7 were refluxed in toluene, crude product was solidified upon standing refrigerator, then treated this C_9 with D_1 with the same process as in E_1 to get E_9 and drying was carried out at 35°C.

Purity 99.9% (by HPLC); mp 78-80 °C , IR (KBr, cm^{-1}) 3253, 2942, 2816, 2792, 2120, 1603, 761, 703; ^{1}H-NMR(300 MHz, CDCl3) δ 1.76 (bs, 1H), 1.92-1.99 (m, 1H),2.1 (m, 2H), 2.10-2.15 (m, 1H), 2.31 (s, 3H), 2.80-2.89 (m, 2H), 3.01-3.11 (m, 1H), 3.87 (dd, 1H, *J*=10.6, 2.7 Hz), 7.27-7.41 (m, 10H); ^{13}C-NMR(300 MHz, CDCl3) δ 46.6, 46.7, 55.6, 58.3, 60.8, 63.7, 127.3, 127.9, 128.8, 142.9; MS (ESI, *m/z*):

267$[M+H]^+$. Anal. Calcd. For $C_{18}H_{22}N_2$ (266): C, 81.96; H, 2.15; N, 15.89. Found: C,

74.90; H, 9.22; N, 15.88.

E_{10}: R=H, Z=CH=CH_2 and X,Y=H_2, 2-ethenyl-1-metyl-3-phenylpiperazine

A_1 and B_1 were refluxed in toluene, crude product was solidified upon standing refrigerator, then treated this C_1 with D_2 with the same process as in E_1 to get E_{10} and drying was carried out at 35°C.

Purity 99.9% (by HPLC); mp 82-84 °C , IR (KBr, cm^{-1}) 3253, 2942, 2816, 2792, 1603, 1458, 761, 703; ^{1}H-NMR(300 MHz, CDCl3) δ 1.76 (bs, 1H), 1.92-1.99 (m, 1H), 2.10-2.15 (m, 1H), 2.2 (m, 1H), 2.3 (d, 2H), 2.31 (s, 3H), 2.80-2.89 (m, 1H), 3.01-3.11 (m, 2H), 3.87 (dd, 1H, *J*=10.6, 2.7 Hz), 7.27-7.41 (m, 5H); ^{13}C-NMR(300 MHz, CDCl3) δ 46.6, 46.7, 54.3, 55.6, 60.8, 63.7, 127.3, 127.9, 128.8, 142.9; MS (ESI, *m/z*):

203 $[M+H]^+$. Anal. Calcd. For $C_{13}H_{18}N_2$ (176.26): C, 76.96; H, 7.15; N, 15.89. Found: C,

74.90; H, 9.22; N, 15.88.

E_{11}: R=H, Z=CH_2Ph and X,Y=H_2, 2-benzyl-1-methyl-3-phenylpiperazine

A_1 and B_1 were refluxed in toluene, crude product was solidified upon standing refrigerator, then treated this C_1 with D_3 with the same process as in E_1 to get E_{11} and drying was carried out at 35°C.

Purity 99.9% (by HPLC); mp 98-100 °C , IR (KBr, cm^{-1}) 3253, 2942, 2816, 2792, 1603, 1156, 761, 703; ^{1}H-NMR(300 MHz, CDCl3) δ 1.76 (bs, 1H), 1.92-1.99 (m, 1H), 2.10-2.15 (m, 1H), 2.31 (s, 3H), 2.4 (m, 2H), 2.80-2.89 (m, 2H), 3.01-3.11 (m, 1H), 3.87 (dd, 1H, *J*=10.6, 2.7 Hz), 7.27-7.41 (m, 10H); ^{13}C-NMR(300 MHz, CDCl3) δ 46.6, 46.7, 55.6, 60.8, 63.7, 127.3, 127.9, 128.8, 132.5, 142.9; MS (ESI, *m/z*):

267 $[M+H]^+$. Anal. Calcd. For $C_{11}H_{16}N_2$ (266): C, 81.96; H, 2.15; N, 15.89. Found: C,

74.90; H, 9.22; N, 15.88.

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References and footnotes:

1. Gillman, PK (2006). "A systematic review of the serotonergic effects of mirtazapine: implications for its dual action status". *Human Psychopharmacology Clinical and Experimental* **21** (2): 117-25.]
2. Burrows GD, Kremer CM. (1997). "Mirtazapine: clinical advantages in the treatment of depression.". *Journal of Clinical Psychopharmacology* **17** (2S):
3. Divvela V. N. Srinivasa Rao, Ramesh Dand, General Papers,ARKIVOC 2006 (xiv) 1-9
4. Dolitzky, Ben-Zion. PCT Int. Appl. WO 00/63, 185: *Chem. Abstr*. **2000**, *133*, 321901.
5. Roderick, W. R.; Platte, H. J.; Pollard, C. B. *J. Med. Chem*. **1966**, *9*, 181-185.
6. Guo, B. S.; Yang, Y. S.; Ji, R. Y. *Chinese Chemical Lett.* **2003**, *14*, 365.
7. Lithium aluminum hydride reacts violently with water, liberating hydrogen,incompatible with strong oxidizing agents.Reactions to be carried out in anhydrous conditions.

8. Palladium on carbon is flammable, pyrophoric after activation with hydrogen. It should always be kept at inert atmosphere

9. US published patent application no. US4772765A1

10. US published reexamine patent application no. US6495685B1.

11. US published patent application no US204236107A1,

12. US granted patent no. US7041826.

13. US granted patent no US-4,772,705.

14. US published reexamine patent application no. US-6,339,156 B1.

15. US published patent application no US-2004/0236107 A1.

16. WIPO Published application no. WO-02/090339 A1 (with search result).

17. US published patent application no US-2004/0242879 A1.

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