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Comparison of Different Reducing Systems in the Synthesis of Functionally Substituted Benzylamines from Alkyl Aryl Ketones and Aromatic Aldehydes

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Abstract—Different synthetic approaches to functionally substituted benzylamines were examined: reductive amination of alkyl aryl ketones and reduction of aromatic aldehyde oximes. The most efficient procedures were used to prepare a series of previously unknown hydroxy-, alkoxy-, and halogen-substituted benzylamines.

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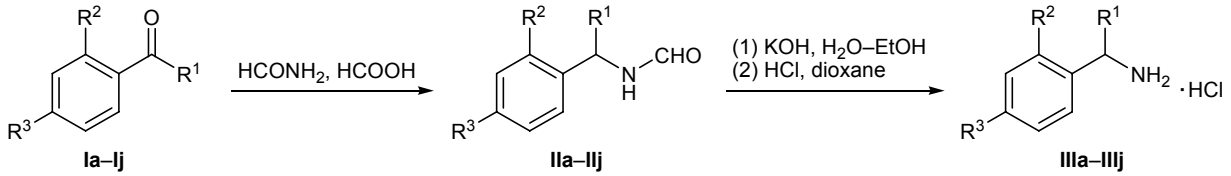
Benzylamines are widely used in the synthesis of enzyme inhibitors [1–5] and compounds exhibiting analgesic [3], antithrombotic [2], antibacterial [6], fungicidal [7], and other kinds of biological activity. Benzylamines are usually prepared by reductive amination of carbonyl compounds [8–12] and reduction of the corresponding oximes, nitriles, or azines. Oximes can be reduced with sodium amalgam [13], metallic sodium in liquid ammonia [14, 15], Mg–$HCOONH_4$–MeOH [16], Raney nickel–EtOH–base [17–19], $LiAlH_4$ [10], $NaBH_4$–$TiCl_4$ [20], and $NaBH_4$–LiCl–Amberlyst [21]. Oxime ethers, nitriles, and azines were also reduced in the presence of Pd/C [19, 22, 23]. However, despite diversity of methods for the preparation of benzylamines, there are very limited published data on the synthesis of benzylamines with hydroxy and alkoxy groups in the aromatic ring [11, 13, 16–18, 21].

In the present work we examined different synthetic approaches to functionally substituted benzylamines, primarily to those containing hydroxy and alkoxy substituents. In particular, such standard procedures as hydride reduction of aldehyde and ketone oximes with $LiAlH_4$, reduction of ketone oximes with sodium in liquid ammonia, and reductive amination of ketones according to Leuckart–Wallach were studied.

In the first step of our study we examined the possibility for synthesizing functionally substituted 1-phenylalkan-1-amines by reduction of the corresponding aromatic ketone oximes with $LiAlH_4$; as model substrates we used acetophenone oxime and its *O*-methyl ether. Both these substrates were completely reduced in boiling THF in 3 h, but the reactions were not selective: apart from the target 1-phenylethanamine, secondary *N*-ethylaniline was formed as a result of side Beckmann rearrangement followed by reduction of intermediate acetanilide. In the reaction with acetophenone oxime the ratio 1-phenylethanamine–*N*-ethylaniline was 1 : 1.5, and in the reduction of acetophenone *O*-methyloxime both products were formed in equimolar amounts. The reduction of acetophenone oxime with the system $LiAlH_4$–Me_3SiCl was more selective, and the ratio of 1-phenylethanamine and *N*-ethylaniline was 3 : 1. With a view to obtain functionally substituted benzylamine, 1-(4-hydroxyphenyl)ethanamine, the corresponding oxime was reduced with sodium in liquid ammonia. This reaction was not accompanied by side Beckmann rearrangement, and the target product was formed in high yield. As far as we known, we were the first to apply this procedure for the reduction of an aromatic ketone oxime having a hydroxy group in the aromatic ring. However, the use of sodium in liquid ammonia for the reduction of ketone oximes is strongly limited. For example, alkoxy-substituted benzylamines cannot be obtained in such a way, for alkoxy group is readily converted to hydroxy by the action of sodium.

Our further study showed that, unlike reduction of ketone oximes, reductive amination of ketones with

Scheme 1.



Ia–Ij **IIa–IIj** **IIIa–IIIj**

For substituents R^1–R^3, see Table 1.

formamide in the presence of formic acid (Leuckart–Wallach) provides the most convenient and universal method for the synthesis of various functionally substituted benzylamines (Scheme 1). Under the optimal conditions (130°C, reaction time 20 h for ketones **Ia**–**Ig** and 50 h for hydroxyphenyl ketones **Ih**–**Ij**), we synthesized a series of alkoxy-, hydroxy-, and halogen-substituted benzylamines with different numbers and positions of the substituents. As follows from the data in Table 1, the nature of substituents in the benzene ring affects the yield of the resulting benzylamines. The highest yield (64%) was obtained for 1-(2,4-difluorophenyl)ethanamine. Hydroxy-substituted derivatives require longer reaction time, and their yields are lower (40–45%). The final products were isolated as hydrochlorides which were characterized by ^{1}H NMR and mass spectra and elemental analyses.

The yields of benzylamines in the reductive amination of aromatic aldehydes **IV** were somewhat lower, and the reaction time was considerably longer. However, unlike the examined ketone oximes, aldehyde oximes **V** with various substituents in the aromatic ring are selectively reduced with $LiAlH_4$ in high yield at room temperature in 4–5 h (Scheme 2, Table 2). An exception was aldehyde oxime **Vn**. We failed to reduce it do 2-hydroxy-3-methoxybenzylamine (**VIIn**) with an acceptable yield. Amine **VIIn** was synthesized in 47% yield by reductive amination.

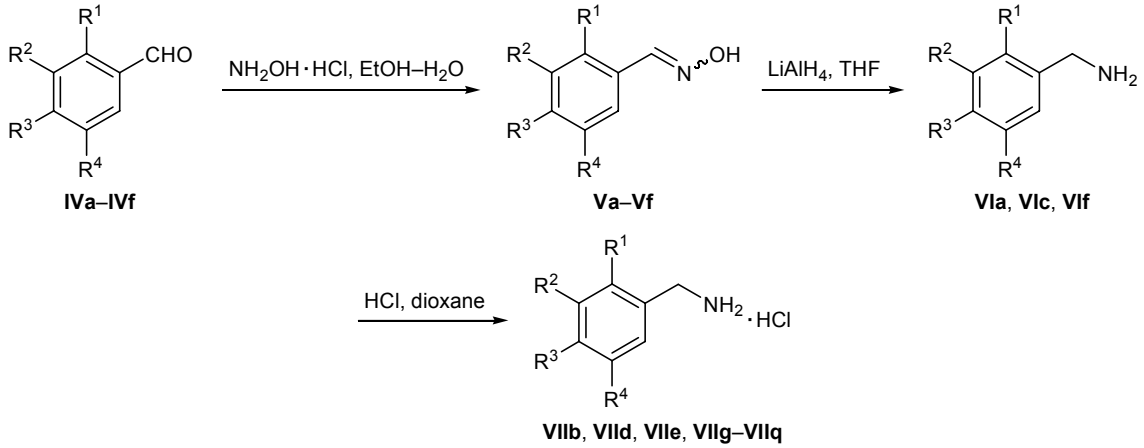
Thus our results showed that the most effective procedure for the synthesis of hydroxy-, alkoxy-, and halogen-substituted benzylamines from the corresponding alkyl aryl ketones is reductive amination according to Leuckart–Wallach and that reduction of aldehyde oximes with $LiAlH_4$ is most appropriate for the preparation of functionally substituted benzylamines from aromatic aldehydes.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker Avance II 300 spectrometer. The melting points were determined on a Boetius melting point apparatus and were not corrected. The mass spectra (electron impact, 70 eV) were obtained on a Kratos MS-30 instrument.

Reduction of 4-hydroxyacetophenone oxime with sodium in liquid ammonia. Ammonia, 100 ml, was distilled into a flask equipped with a stirrer and a reflux condenser and cooled with dry ice, 10.9 g (0.072 mol) of 4-hydroxyacetophenone oxime [11] and 29 ml of methanol were added, and 7.1 g (0.31 mol) of metallic sodium was added in portions over a period of 2.5–3 h. The mixture was stirred for 2 h and left to

Scheme 2.



IVa–IVf **Va–Vf** **VIa**, **VIc**, **VIf**

VIIb, **VIId**, **VIIe**, **VIIg–VIIq**

For substituents R^1–R^4, see Table 2.

Table 1. Synthesis of benzylamines **IIIa**–**IIIj** by reductive amination of functionally substituted alkyl aryl ketones **Ia**–**Ij**

Product	R^1	R^2	R^3	Yield of hydrochloride **III**,[a] %	mp, °C
IIIa	Et	H	H	59	182–183
IIIb	Me	EtO	H	56	148–150
IIIc	Me	PrO	H	53	153–154
IIId	Me	H	PrO	63	157–158
IIIe	Et	H	EtO	60	209–211 (decomp.)
IIIf	Et	H	PrO	59	163–164
IIIg	Me	F	F	64	154–155
IIIh	Me	OH	H	40	150–152
IIIi	Me	H	OH	45	185–186
IIIj	Et	H	OH	43	200–202

[a] Calculated on the initial ketone.

Table 2. Synthesis of benzylamines **VIa**, **VIc**, and **VIf** and hydrochlorides **VIIb**, **VIId**, **VIIe**, and **VIIg**–**VIIq** by reduction of aromatic aldehyde oximes **V** with $LiAlH_4$

Product	R^1	R^2	R^3	R^4	Yield, %	mp, ºC
VIa	PrO	H	H	H	77	131–132[a]
VIIb	H	PrO	H	H	67	141–142
VIc	H	*i*-PrO	H	H	82	125–126[a]
VIId	H	H	*i*-PrO	H	70	188–190
VIIe	*s*-BuO	H	H	H	62	96–97
VIf	H	*s*-BuO	H	H	79	128–130[a]
VIIg	H	H	*s*-BuO	H	67	
VIIh	EtO	MeO	H	H	72	187–188
VIIi	PrO	MeO	H	H	65	105–106
VIIj	H	MeO	PrO	H	72	186–187 (decomp.)
VIIk	H	MeO	*i*-PrO	H	75	195–200
VIIl	H	MeO	BuO	H	69	180–185 (decomp.)
VIIm	H	MeO	*i*-AmO	H	69	199–200
VIIn[b]	OH	MeO	H	H	47	194–196
VIIo	PrO	H	H	Cl	72	154–156
VIIp	*i*-PrO	H	H	Cl	72	147–149
VIIq	Cl	H	Cl	H	71	188 decomp.)

[a] Boiling point (5 mm).
[b] Obtained by reductive amination.

stand for 24 h at room temperature until complete evaporation of ammonia. The white precipitate was dissolved in 200 ml of water, the mixture was acidified with 4.5 N hydrochloric acid to pH 3–4 and then made alkaline by adding aqueous ammonia to pH 8–9. The aqueous phase was washed with diethyl ether, and water was distilled off. The residue was dissolved in ethanol, the undissolved material was filtered off, the filtrate was acidified to pH 1–2, and the precipitate of 1-(4-hydroxyphenyl)ethanamine hydrochloride (**IIIi**) was filtered off, washed with diethyl ether, and dried under reduced pressure. Yield 10.5 g (75%).

Reductive amination of ketones Ia–Ig (*general procedure*). A mixture of 1 mol of ketone **I**, 465 ml of formamide, and 310 ml of formic acid was heated for 30 h under reflux (130°C). The mixture was then poured into ice water and extracted with ethyl acetate. The organic phase was washed with water, a saturated aqueous solution of $NaHCO_3$, and a saturated solution of NaCl and dried over $MgSO_4$. The solution was filtered through a layer of silica gel, the solvent was distilled off on a rotary evaporator, and the solid residue was recrystallized from ethyl acetate–hexane (2 : 1). Formamide derivative **II** thus obtained was dissolved in 1 l of ethanol, 0.5 l of water and 200 g of potassium hydroxide were added, and the mixture was heated for 20 h under reflux. The mixture was then poured into 1 l of methylene chloride, the organic phase was separated, washed with water and a saturated solution of NaCl, and dried over $MgSO_4$, the solvent was removed, and the residue was distilled under reduced pressure. The resulting amine was dissolved in ethyl acetate, a 6 N solution of HCl in dioxane was added, and the precipitate was filtered off, washed with diethyl ether, and dried under reduced pressure. The yields of compounds **IIIa**–**IIIg** are given in Table 1.

***N*-(1-Phenylpropyl)formamide (IIa)** was obtained from 148 g of ethyl phenyl ketone (**Ia**). Yield 130 g (80%). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.81 m (3H, CH_3), 1.70 m (2H, CH_2), 4.79 m (1H, CH), 7.31 m (5H, H_{arom}), 8.10 s (1H, CHO), 8.43 d (1H, NH).

1-Phenylpropan-1-amine hydrochloride (IIIa). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.82 t (3H, CH_3), 1.93 m (1H, CH_2), 2.18 m (1H, CH_2), 4.01 m (1H, CH), 7.33 m (3H, H_{arom}), 7.49 d (2H, H_{arom}), 8.85 br.s (3H, NH_3^+). Mass spectrum, *m*/*z* (I_{rel}, %): 135 (2) $[M]^{+\cdot}$, 118 (4), 106 (100), 91 (5), 78 (30), 63 (5). Found, %: C 63.24; H 8.28; Cl 20.83; N 7.65. $C_9H_{13}N \cdot HCl$. Calculated, %: C 62.97; H 8.22; Cl 20.65; N 8.16. *M* 135 (free amine).

1-(2-Ethoxyphenyl)ethanamine hydrochloride (IIIb). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.48 t (3H, $CH_2C\mathbf{H}_3$), 1.59 d (3H, $CHC\mathbf{H}_3$), 4.11 m (2H, OCH_2), 4.63 m (1H, CH), 6.87 d (1H, H_{arom}), 6.93 t (1H, H_{arom}), 7.21 t (1H, H_{arom}), 7.57 d (1H, H_{arom}), 8.72 br.s (3H, NH_3^+). Mass spectrum, *m*/*z* (I_{rel}, %): 165 $[M]^{+\cdot}$ (8), 150 (100), 136 (5), 133 (22), 122 (27), 105 (22), 95 (31), 91 (24), 77 (43), 65 (12). Found, %: C 59.70; H 8.08; Cl 17.68; N 6.71. $C_{10}H_{15}NO \cdot HCl$. Calculated, %: C 59.55; H 8.00; Cl 17.58; N 6.94. *M* 165 (free amine).

1-(2-Propoxyphenyl)ethanamine hydrochloride (IIIc). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.08 t (3H, $CH_2C\mathbf{H}_3$), 1.59 d (3H, $CHC\mathbf{H}_3$), 1.87 m (2H, $OCH_2C\mathbf{H}_2$), 3.99 m (2H, OCH_2), 4.63 m (1H, CH), 6.89 d (1H, H_{arom}), 6.98 t (1H, H_{arom}), 7.25 t (1H, H_{arom}), 7.58 d (1H, H_{arom}), 8.72 br.s (3H, NH_3^+). Mass spectrum, *m*/*z* (I_{rel}, %): 179 (3) $[M]^{+\cdot}$, 164 (100), 147 (7), 136 (24), 122 (92), 104 (14), 95 (58), 77 (16), 65 (11), 59 (18). Found, %: C 61.42; H 8.45; Cl 16.55; N 6.20. $C_{11}H_{17}NO \cdot HCl$. Calculated, %: C 61.25; H 8.41; Cl 16.43; N 6.49. *M* 179 (free amine).

1-(4-Propoxyphenyl)ethanamine hydrochloride (IIId). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.02 t (3H, $CH_2C\mathbf{H}_3$), 1.60 d (3H, $CHC\mathbf{H}_3$), 1.80 m (2H, $OCH_2C\mathbf{H}_2$), 3.88 m (2H, OCH_2), 4.25 m (1H, CH), 6.84 d (2H, H_{arom}), 7.44 d (2H, H_{arom}), 8.75 br.s (3H, NH_3^+). Mass spectrum, *m*/*z* (I_{rel}, %): 179 (23) $[M]^{+\cdot}$, 164 (70), 136 (32), 122 (64), 107 (14), 95 (65), 77 (100), 65 (41). Found, %: C 61.40; H 8.47; Cl 16.55; N 6.18. $C_{11}H_{17}NO \cdot HCl$. Calculated, %: C 61.25; H 8.41; Cl 16.43; N 6.49. *M* 179 (free amine).

1-(4-Ethoxyphenyl)propan-1-amine hydrochloride (IIIe). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.80 t (3H, $OCH_2C\mathbf{H}_3$), 1.39 t (3H, $CHCH_2C\mathbf{H}_3$), 1.91 m (1H, $CHC\mathbf{H}_2CH_3$), 2.15 m (1H, $CHC\mathbf{H}_2CH_3$), 3.99 m (3H, CH, OCH_2), 6.84 d (2H, H_{arom}), 7.40 d (2H, H_{arom}), 8.73 br.s (3H, NH_3^+). Mass spectrum, *m*/*z* (I_{rel}, %): 178 (1) $[M-1]^{+\cdot}$, 163 (3), 150 (89), 133 (8), 122 (100), 106 (10), 95 (53), 76 (40), 59 (24). Found, %: C 61.39; H 8.44; Cl 16.53; N 6.22. $C_{11}H_{17}NO \cdot HCl$. Calculated, %: C 61.25; H 8.41; Cl 16.43; N 6.49. *M* 179 (free amine).

1-(4-Propoxyphenyl)propan-1-amine hydrochloride (IIIf). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.74 t (3H, $OCH_2CH_2C\mathbf{H}_3$), 0.95 t (3H, $CHCH_2C\mathbf{H}_3$), 1.75 m (3H, $CHC\mathbf{H}_2CH_3$, $OCH_2C\mathbf{H}_2CH_3$), 1.99 m (1H, $CHC\mathbf{H}_2CH_3$), 3.91 t (2H, OCH_2), 4.01 m (1H, CH), 6.96 d (2H, H_{arom}), 7.41 d (2H, H_{arom}), 8.59 br.s (3H, NH_3^+). Mass spectrum, *m*/*z* (I_{rel}, %): 193 (6) $[M]^{+\cdot}$, 177 (40), 164 (100), 150 (17), 133 (16), 122 (75), 107 (63), 95 (77), 76 (80). Found, %: C 62.87; H 8.82; Cl 15.56; N 5.84. $C_{12}H_{19}NO \cdot HCl$. Calculated, %: C 62.73; H 8.77; Cl 15.43; N 6.10. *M* 193 (free amine).

1-(2,4-Difluorophenyl)ethanamine hydrochloride (IIIg). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.60 d (3H, $CHC\mathbf{H}_3$), 4.59 m (1H, CH), 6.88 t (1H, H_{arom}), 7.01 m (1H, H_{arom}), 7.90 m (1H, H_{arom}), 9.01 br.s (3H, NH_3^+). Mass spectrum, *m*/*z* (I_{rel}, %): 157 (3) $[M]^{+\cdot}$, 156 (17), 142 (100), 121 (27), 115 (73), 101 (50), 95 (57),

75 (19), 63 (25). Found, %: C 49.74; H 5.23; Cl 18.45; F 19.83; N 6.75. $C_8H_9F_2N \cdot HCl$. Calculated, %: C 49.63; H 5.21; Cl 18.31; F 19.62; N 7.23. *M* 157 (free amine).

Reductive amination of ketones Ih–Ij (*general procedure*). A mixture of 1 mol of ketone **Ih–Ij**, 465 ml of formamide, and 310 ml of formic acid was heated for 30 h under reflux (130°C). Excess formamide and formic acid were distilled off from the mixture at a residual pressure of 20 mm on heating on a water bath, and the residue was subjected to alkaline hydrolysis. The resulting amines was treated with ~450 ml of concentrated hydrochloric acid which was added in portions until pH 2–3. The salt was filtered off, and the mother liquor was evaporated. The solid residue was dissolved in propan-2-ol, and the undissolved material was filtered off. After removal of the solvent, benzylamine hydrochloride **IIIh–IIIj** was recrystallized from propan-2-ol–diethyl ether (1 : 1). The yields are given in Table 1.

1-(2-Hydroxyphenyl)ethanamine hydrochloride (IIIh). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.45 d (3H, CHC**H**$_3$), 4.51 m (1H, CH), 6.81 t (1H, H$_{arom}$), 6.96 d (1H, H$_{arom}$), 7.15 t (1H, H$_{arom}$), 7.39 d (1H, H$_{arom}$), 8.38 br.s (3H, NH_3^+), 10.01 br.s (1H, OH). Found, %: C 55.52; H 7.03; Cl 20.57; N 7.82. $C_8H_{11}NO \cdot HCl$. Calculated, %: C 55.34; H 6.97; Cl 20.42; N 8.07.

1-(4-Hydroxyphenyl)ethanamine hydrochloride (IIIi). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.47 d (3H, CHC**H**$_3$), 4.24 m (1H, CH), 6.79 d (2H, H$_{arom}$), 7.31 d (2H, H$_{arom}$), 8.43 br.s (3H, NH_3^+), 9.67 br.s (1H, OH). Mass spectrum, *m*/*z* (I_{rel}, %): 137 (34) $[M]^{+\cdot}$, 122 (100), 95 (77), 91 (24), 76 (44), 65 (54). Found, %: C 55.57; H 7.03; Cl 20.56; N 7.84. $C_8H_{11}NO \cdot HCl$. Calculated, %: C 55.34; H 6.97; Cl 20.42; N 8.07.

1-(4-Hydroxyphenyl)propan-1-amine hydrochloride (IIIj). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.23 t (3H, $CH_2C\mathbf{H}_3$), 1.76 m (1H, CHC**H**$_2$CH$_3$), 1.98 m (1H, CHC**H**$_2$CH$_3$), 3.95 m (1H, CH), 6.81 d (2H, H$_{arom}$), 7.29 d (2H, H$_{arom}$), 8.51 br.s (3H, NH_3^+), 9.71 br.s (1H, OH). Mass spectrum, *m*/*z* (I_{rel}, %): 151 (5) $[M]^{+\cdot}$, 133 (32), 133 (22), 122 (73), 105 (27), 95 (78), 76 (100), 65 (30). Found, %: C 57.85; H 7.60; Cl 19.01; N 7.08. $C_9H_{13}NO \cdot HCl$. Calculated, %: C 57.60; H 7.52; Cl 18.89; N 7.46. *M* 151 (free amine).

Reduction of aldehyde oximes IVa–IVq with $LiAlH_4$ (*general procedure*). A solution of 77.4 g (1.2 mol) of hydroxylamine hydrochloride and 48 g (1.2 mol) of sodium hydroxide in 0.5 l of water was added to a solution of 1 mol of aldehyde **IV** in 0.5 l of methanol, and the mixture was heated under reflux for 8 h. The mixture was poured into cold water, and the product was extracted into methylene chloride. The extract was washed with water, a saturated solution of $NaHCO_3$, and a saturated solution of NaCl and dried over $MgSO_4$, and the solvent was distilled off. The residue (oxime **V**) was subjected to reduction without additional purification; it was added in portion to a suspension of 38.7 g (1.02 mol) of $LiAlH_4$ in 1 l of THF at such a rate that the mixture weakly boiled. When the entire amount of oxime **V** was added, the mixture was stirred for 3 h at room temperature and heated for 1 h under reflux. Excess reducing agent was quenched by treatment with ~100 ml of 40% aqueous sodium hydroxide, the solution was separated by decanting, and the precipitate was treated with THF on heating under reflux over a period of 1 h. The solution was filtered, the organic phases were combined, the solvent was removed, and the residue (amine **VI**) was distilled under reduced pressure. Hydrochlorides **VII** were obtained as described above. The yields are given in Table 2.

2-Propoxyphenylmethanamine (VIa). bp 131–132°C (5 mm). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.09 t (3H, CH_3), 1.82 m (4H, $CH_3C\mathbf{H}_2$, $NH_2C\mathbf{H}_2$), 3.98 t (2H, OCH_2), 4.83 s (2H, $N\mathbf{H}_2CH_2$), 6.90 m (2H, H$_{arom}$), 7.22 m (2H, H$_{arom}$). Mass spectrum, *m*/*z* (I_{rel}, %): 165 (35) $[M]^{+\cdot}$, 148 (44), 133 (38), 122 (100), 106 (94), 95 (54), 77 (44), 69 (17), 57 (22). Found, %: C 72.83; H 9.21; N 8.21. $C_{10}H_{15}NO$. Calculated, %: C 72.69; H 9.15; N 8.48. *M* 165.

3-Propoxyphenylmethanamine hydrochloride (VIIb). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.97 t (3H, CH_3), 3.95 m (4H, OCH_2, NCH_2), 1.41 m (3H, $C\mathbf{H}_3CH_2CH_2$), 1.72 m (2H, $CH_3C\mathbf{H}_2$), 6.90 d (1H, H$_{arom}$), 7.03 d (1H, H$_{arom}$), 7.16 s (1H, H$_{arom}$), 7.39 t (1H, H$_{arom}$), 8.61 br.s (3H, NH_3^+). Mass spectrum, *m*/*z* (I_{rel}, %): 165 (62) $[M]^{+\cdot}$, 148 (79), 136 (12), 133 (18), 122 (67), 106 (80), 95 (55), 77 (100), 66 (33). Found, %: C 59.71; H 8.10; Cl 18.01; N 6.58. $C_{10}H_{15}NO \cdot HCl$. Calculated, %: C 59.55; H 8.00; Cl 17.58; N 6.94. *M* 165 (free amine).

3-Isopropoxyphenylmethanamine (VIc). bp 125–126°C (5 mm). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.32 d [6H, $(C\mathbf{H}_3)_2CH$], 1.43 br.s (2H, NCH_2), 3.83 s (2H, NH_2), 4.59 m (1H, OCH), 6.87 m (3H, H$_{arom}$), 7.22 m (1H, H$_{arom}$). Mass spectrum, *m*/*z* (I_{rel}, %): 165

$[M]^{+\cdot}$ (81), 149 (78), 133 (21), 122 (67), 107 (100), 95 (62), 77 (69), 69 (55), 56 (32). Found, %: C 72.84; H 9.20; N 8.11. $C_{10}H_{15}NO$. Calculated, %: C 72.69; H 9.15; N 8.48. *M* 165.

4-Isopropoxyphenylmethanamine hydrochloride (VIId). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.29 d [6H, CH(C**H**$_3$)$_2$], 3.91 m (2H, NCH$_2$), 4.55 m (1H, OCH), 6.82 d (2H, H$_{arom}$), 7.43 d (2H, H$_{arom}$), 8.70 br.s (3H, NH_3^+). Mass spectrum, *m*/*z* (I_{rel}, %): 165 (48) $[M]^{+\cdot}$, 149 (21), 122 (68), 107 (100), 95 (63), 76 (56), 65 (11). Found, %: C 59.72; H 8.08; Cl 17.72; N 6.69. $C_{10}H_{15}NO\cdot HCl$. Calculated, %: C 59.55; H 8.00; Cl 17.58; N 6.94. *M* 165 (free amine).

2-(1-Methylpropyloxy)phenylmethanamine hydrochloride (VIIe). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.01 t (3H, C**H**$_3$CH$_2$), 1.34 d (3H, CHC**H**$_3$), 1.69 m (1H, CH$_3$C**H**$_2$), 1.82 m (1H, CH$_3$C**H**$_2$), 3.38 m (1H, OCH), 3.98 m (2H, NCH$_2$), 6.89 m (2H, H$_{arom}$), 7.24 t (1H, H$_{arom}$), 7.59 d (1H, H$_{arom}$), 8.65 br.s (3H, NH_3^+). Mass spectrum, *m*/*z* (I_{rel}, %): 179 (19) $[M]^{+\cdot}$, 162 (27), 146 (73), 133 (60), 122 (62), 107 (100), 95 (70), 77 (87), 57 (71). Found, %: C 61.41; H 8.45; Cl 16.58; N 6.01. $C_{11}H_{17}NO\cdot HCl$. Calculated, %: C 61.25; H 8.41; Cl 16.43; N 6.49. *M* 179 (free amine).

3-(1-Methylpropyloxy)phenylmethanamine (VIIf). bp 128–130°C (5 mm). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.00 t (3H, C**H**$_3$CH$_2$), 1.40 br.s (2H, NH$_2$), 1.59 d (3H, CHC**H**$_3$), 1.70 m (2H, CH$_3$C**H**$_2$), 3.65 s (2H, NCH$_2$), 4.62 m (1H, OCH), 6.63 m (3H, H$_{arom}$), 7.43 t (1H, H$_{arom}$). Mass spectrum, *m*/*z* (I_{rel}, %): 179 $[M]^{+\cdot}$ (29), 163 (32), 148 (5), 133 (6), 122 (85), 107 (100), 94 (23), 78 (45), 69 (17), 56 (21). Found, %: C 73.84; H 9.59; N 7.53. $C_{11}H_{17}NO$. Calculated, %: C 73.70; H 9.56; N 7.81. *M* 179.

4-(1-Methylpropyloxy)phenylmethanamine hydrochloride (VIIg). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.92 t (3H, C**H**$_3$CH$_2$), 1.21 d (3H, CHC**H**$_3$), 1.60 m (2H, CH$_3$C**H**$_2$), 3.91 br.s (2H, NCH$_2$), 4.40 m (1H, OCH), 6.92 d (2H, H$_{arom}$), 7.42 d (2H, H$_{arom}$), 8.55 br.s (3H, NH_3^+). Mass spectrum, *m*/*z* (I_{rel}, %): 179 (46) $[M]^{+\cdot}$, 162 (12), 150 (11), 133 (9), 123 (89), 107 (100), 95 (35), 89 (35), 76 (80), 65 (23). Found, %: C 61.38; H 8.46; Cl 16.57; N 6.02. $C_{11}H_{17}NO\cdot HCl$. Calculated, %: C 61.25; H 8.41; Cl 16.43; N 6.49. *M* 179 (free amine).

2-Ethoxy-3-methoxyphenylmethanamine hydrochloride (VIIh). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.30 t (3H, C**H**$_3$CH$_2$), 3.82 s (3H, OCH$_3$), 4.03 m (4H, OCH$_2$, NCH$_2$), 7.21 m (3H, H$_{arom}$), 8.50 br.s (3H, NH_3^+). Mass spectrum, *m*/*z* (I_{rel}, %): 181 (28) $[M]^{+\cdot}$, 164 (20), 152 (100), 133 (40), 121 (11), 107 (32), 93 (37), 76 (27), 65 (34). Found, %: C 55.27; H 7.46; Cl 16.45; N 6.07. $C_{10}H_{15}NO_2\cdot HCl$. Calculated, %: C 55.17; H 7.41; Cl 16.29; N 6.43. *M* 181 (free amine).

3-Methoxy-2-propoxyphenylmethanamine hydrochloride (VIIi). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.98 t (3H, C**H**$_3$CH$_2$), 1.71 m (2H, CH$_3$C**H**$_2$), 3.80 s (3H, OCH$_3$), 3.97 m (4H, OCH$_2$, NCH$_2$), 7.08 m (3H, H$_{arom}$), 8.49 br.s (3H, NH_3^+). Mass spectrum, *m*/*z* (I_{rel}, %): 195 (38) $[M]^{+\cdot}$, 180 (5), 178 (29), 164 (13), 152 (75), 136 (100), 122 (26), 106 (81), 93 (54), 77 (24), 65 (38). Found, %: C 57.17; H 7.86; Cl 15.46; N 5.78. $C_{11}H_{17}NO_2\cdot HCl$. Calculated, %: C 57.02; H 7.83; Cl 15.30; N 6.04. *M* 195 (free amine).

3-Methoxy-4-propoxyphenylmethanamine hydrochloride (VIIj). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.94 t (3H, CH$_3$), 1.70 m (2H, CH$_3$C**H**$_2$), 3.78 s (3H, OCH$_3$), 3.89 m (4H, OCH$_2$, NCH$_2$), 6.96 m (2H, H$_{arom}$), 7.28 s (1H, H$_{arom}$), 8.60 br.s (3H, NH_3^+). Mass spectrum, *m*/*z* (I_{rel}, %): 195 (75) $[M]^{+\cdot}$, 180 (6), 164 (46), 152 (100), 136 (70), 122 (62), 109 (24), 93 (37), 77 (22), 65 (38). Found, %: C 57.20; H 7.88; Cl 15.46; N 5.78. $C_{11}H_{17}NO_2\cdot HCl$. Calculated, %: C 57.02; H 7.83; Cl 15.30; N 6.04. *M* 195 (free amine).

4-Isopropoxy-3-methoxybenzaldehyde oxime (Vk). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.23 d [6H, CH(C**H**$_3$)$_2$], 3.71 s (3H, OCH$_3$), 4.54 m [1H, C**H**(CH$_3$)$_2$], 6.71 d (1H, H$_{arom}$), 7.01 d (1H, H$_{arom}$), 7.48 s (1H, H$_{arom}$), 8.19 s (1H, CH=N), 9.59 br.s (1H, OH).

4-Isopropoxy-3-methoxyphenylmethanamine hydrochloride (VIIk). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.23 d [6H, CH(C**H**$_3$)$_2$], 3.77 s (3H, OCH$_3$), 3.90 m (2H, NCH$_2$), 4.52 m (1H, OCH), 6.96 m (2H, H$_{arom}$), 7.28 s (1H, H$_{arom}$), 8.53 br.s (3H, NH_3^+). Mass spectrum, *m*/*z* (I_{rel}, %): 195 (78) $[M]^{+\cdot}$, 180 (3), 164 (15), 152 (100), 136 (58), 124 (90), 110 (31), 105 (13), 93 (27), 77 (29), 65 (27), 59 (13). Found, %: C 57.18; H 7.88; Cl 15.45; N 5.77. $C_{11}H_{17}NO_2\cdot HCl$. Calculated, %: C 57.02; H 7.83; Cl 15.30; N 6.04. *M* 195 (free amine).

4-Butoxy-3-methoxyphenylmethanamine hydrochloride (VIIl). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.90 t (3H, CH$_3$), 1.41 m (2H, CH$_3$C**H**$_2$CH$_2$), 1.67 m (2H, CH$_3$CH$_2$C**H**$_2$), 3.67 s (3H, OCH$_3$), 3.89 s (2H, NCH$_2$), 3.92 m (2H, OCH$_2$), 6.95 m (2H, H$_{arom}$), 7.27 s (1H, H$_{arom}$), 8.58 br.s (3H, NH_3^+). Mass spectrum, *m*/*z* (I_{rel}, %): 209 (72) $[M]^{+\cdot}$, 178 (10), 152 (100), 136 (62), 122 (28), 109 (34), 93 (13), 83 (15), 65 (21),

59 (75). Found, %: C 58.90; H 8.22; Cl 14.60; N 5.43. $C_{12}H_{19}NO_2 \cdot HCl$. Calculated, %: C 58.65; H 8.20; Cl 14.43; N 5.70. *M* 209 (free amine).

3-Methoxy-4-(3-methylbutoxy)phenylmethanamine hydrochloride (VIIm). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.89 d [6H, CH(C**H**$_3$)$_2$], 1.58 m (2H, CHC**H**$_2$CH$_2$), 1.75 m [1H, C**H**(CH$_3$)$_2$], 3.77 s (3H, CH$_3$O), 3.90 s (2H, NCH$_2$), 3.94 m (2H, OCH$_2$), 6.95 m (2H, H$_{arom}$), 7.28 s (1H, H$_{arom}$), 8.57 br.s (3H, NH_3^+). Mass spectrum, *m*/*z* (I_{rel}, %): 223 (68) $[M]^{+\cdot}$, 193 (16), 167 (6), 152 (100), 136 (77), 122 (65), 109 (17), 92 (10), 80 (11), 65 (10), 59 (19). Found, %: C 60.27; H 8.59; Cl 13.81; N 5.01. $C_{13}H_{21}NO_2 \cdot HCl$. Calculated, %: C 60.11; H 8.54; Cl 13.65; N 5.39. *M* 223 (free amine).

2-Hydroxy-3-methoxyphenylmethanamine hydrochloride (VIIn). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.81 s (3H, OCH$_3$), 3.93 m (2H, NCH$_2$), 6.81 m (1H, H$_{arom}$), 6.99 d (2H, H$_{arom}$), 8.41 br.s (3H, NH_3^+), 9.18 br.s (1H, OH). Mass spectrum, *m*/*z* (I_{rel}, %): 153 (35) $[M]^{+\cdot}$, 136 (100), 122 (72), 106 (64), 95 (26), 79 (28), 65 (43). Found, %: C 50.81; H 6.44; Cl 18.84; N 7.01. $C_8H_{11}NO_2 \cdot HCl$. Calculated, %: C 50.67; H 6.38; Cl 18.69; N 7.39. *M* 153 (free amine).

5-Chloro-2-propoxyphenylmethanamine hydrochloride (VIIo). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.96 t (3H, CH$_3$), 1.77 m (2H, CH$_3$C**H**$_2$), 3.96 m (4H, NCH$_2$, OCH$_2$), 7.07 d (1H, H$_{arom}$), 7.38 m (1H, H$_{arom}$), 7.55 s (1H, H$_{arom}$), 8.59 br.s (3H, NH_3^+). Mass spectrum, *m*/*z* (I_{rel}, %): 201/199 (15/45) $[M]^{+\cdot}$, 182 (39), 164 (45), 156 (100), 140 (90), 129 (36), 122 (80), 112 (78), 106 (40), 93 (15), 77 (40), 65 (40). Found, %: C 51.03; H 6.47; Cl 30.20; N 5.55. $C_{10}H_{14}ClNO \cdot HCl$. Calculated, %: C 50.86; H 6.40; Cl 30.03; N 5.93. *M* 200 (free amine).

5-Chloro-2-isopropoxyphenylmethanamine hydrochloride (VIIp). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.28 d [6H, CH(C**H**$_3$)$_2$], 3.91 s (2H, NCH$_2$), 4.63 m (1H, OCH), 7.08 d (1H, H$_{arom}$), 7.33 d (1H, H$_{arom}$), 7.56 s (1H, H$_{arom}$), 8.51 br.s (3H, NH_3^+). Mass spectrum, *m*/*z* (I_{rel}, %): 201/199 (10/30) $[M]^{+\cdot}$, 182 (41), 164 (17), 156 (81), 140 (100), 129 (22), 122 (70), 112 (70), 106 (40), 93 (15), 77 (39), 65 (26). Found, %: C 51.09; H 6.43; Cl 30.20; N 5.58. $C_{10}H_{14}ClNO \cdot HCl$. Calculated, %: C 50.86; H 6.40; Cl 30.03; N 5.93. *M* 200.

2,4-Dichlorophenylmethanamine hydrochloride (VIIq). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.07 s (2H, CH$_2$), 7.51 d (1H, H$_{arom}$), 7.70 m (2H, H$_{arom}$), 8.84 br.s (3H, NH_3^+). Mass spectrum, *m*/*z* (I_{rel}, %): 176 (21) $[M]^{+\cdot}$, 161 (10), 140 (100), 123 (9), 110 (15), 75 (17), 59 (24). Found, %: C 39.78; H 3.83; Cl 50.26; N 6.13. $C_7H_7Cl_2N \cdot HCl$. Calculated, %: C 39.56; H 3.79; Cl 50.05; N 6.59. *M* 176 (free amine).

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