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4-(((4-Methoxyphenyl)amino)methyl)-*N*,*N*-dimethylaniline and 2-Methoxy-5-((phenylamino)methyl)phenol

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Abstract: Molecular structures of 4-(((4-methoxyphenyl)amino)methyl)-*N*,*N*-dimethylaniline and 2-methoxy-5-((phenylamino)methyl)phenol synthesized via Schiff bases reduction route are reported. The compounds consist of asymmetric units of $C_{16}H_{20}N_2O$ (**1**) and $C_{14}H_{15}NO_2$ (**2**) in orthorhombic and monoclinic crystal systems, respectively. Compound **1** consist of intermolecular C11—H11···N2 hydrogen bonding with C11···N21 = 3.463(4) Å. The hydroxyl group in **2** is also involved in intermolecular O2—H2···O2 and O2—H2···O21 hydrogen bonding with O2···O11 = 2.8885(15) Å and O1···O21 = 2.9277(5) Å. The molecular structures of the compounds are stabilized by secondary intermolecular interactions of C1—H1B···O11 and C5—H···(C41, C51, C61, C71) for **1** and H···C, C—H···O and N—H···C for **2**. The reported compounds are important starting material for the synthesis of many compounds such as azo dyes and dithiocarbamate.

Keywords: secondary amines; crystal structure; sodium borohydride; supramolecular structure

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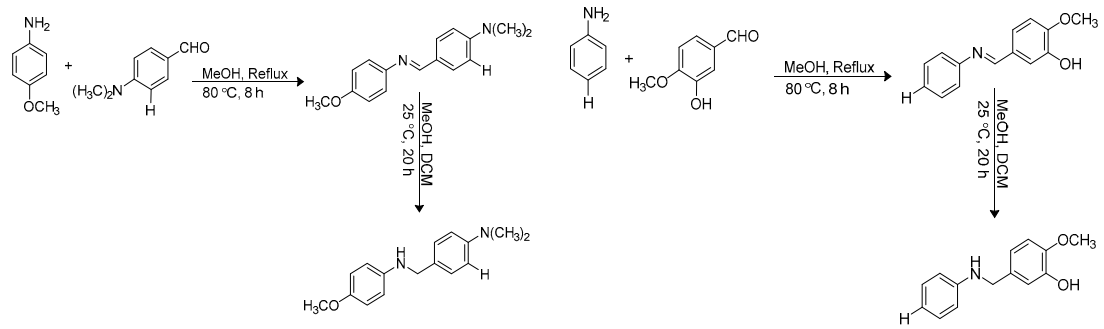
1. Introduction

N-alkylation of primary amines and ammonia, reduction of nitriles and amides in the presence of catalyst such as $LiAlH_4$ and $NaBH_4$, tin, or iron have been used for the preparation of secondary amines [1–5]. $NaBH_4$ is a powerful reducing agent that has been used for the reduction of different functional groups [6] due to its selectivity; it also does not affect reducible substituents such as nitro and chloride during the reduction process [7]. Secondary amines are important starting materials for the preparation of compounds such as dithiocarbamates and dyes, among others, and form the constituents of many pharmaceuticals such as antidepressants (clomipramine, desipramine) psychedelic and opiate analgesics (phenethylamines, codeine, heroin, morphine), and agrochemicals, among others [8–17]. Related secondary amines to the title compounds that have been reported include 2-[(4-chlorophenyl)aminomethyl]-6-methoxyphenol [18], 2-[(4-methoxyanilino) methyl]phenol [19], 2-(anilinomethyl)phenol [20]. Herein we report the synthesis and crystal structures of 4-(((4-methoxyphenyl)amino)methyl)-*N*,*N*-dimethylaniline (**1**) and 2-methoxy-5-((phenylamino)methyl)phenol (**2**).

2. Results and Discussion

2.1. Synthesis of the Compounds

The compounds were synthesized by condensation of the primary amines with the corresponding aldehydes in methanol and sequential reduction of the resulting Schiff bases with sodium borohydride in methanol and dichloromethane at room temperature (Scheme 1).

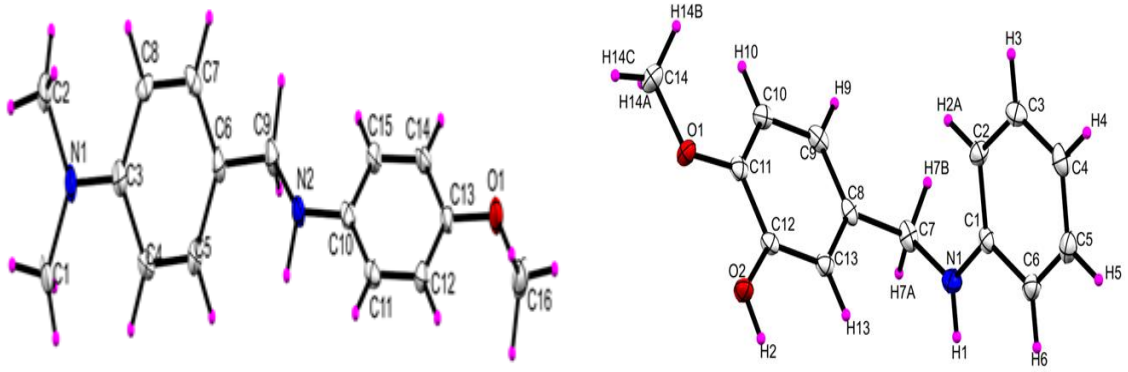


(**Compound 1**) Yield = 78% (**Compound 2**) Yield = 80%

Scheme 1. Synthetic routes for the preparation of secondary amines (**1**,**2**).

2.2. Molecular Structures of the Compounds

The molecular structures of **1** and **2** are presented in Figure 1. The crystal data and structure refinement are presented in Table 1 while the packing diagrams are presented in Figure 2. The molecular structures of both compounds consist of a monomeric unit in the asymmetric unit. Compound **1** consist of *N*,*N*-dimethylaniline and methoxyphenylamino moieties while **2** consist of phenylamino and phenol moieties. The phenyl rings in both compounds lie in distinct planes with dihedral angles of 73.89° for **1** and 86.61° for **2** between the planes (Figure 3). Compound **1** is involved in intermolecular C11—H11···N2 hydrogen bonding (C11···N2^{1} = 3.463(4) Å); symmetry operation of $^{1}1/2 + x, -y, +z$. The hydroxyl group of **2** is involved in intermolecular hydrogen bonding arising from O2—H2···O2 (methoxy oxygen of the neighboring molecule) and O2—H2···O2^{1} (hydroxyl oxygen of the neighboring molecule), with O2···O1^{1} = 2.8885(15) Å and O1···O2^{1} = 2.9277(5) Å; symmetry operation of $^{1}1 - x, -1/2 + y, 1 - z$. The molecular structures of **1** and **2** (Figure 3) are held together by secondary intermolecular interactions of C1—H1B···O1^{1} and C5—H···(C4^{1}, C5^{1}, C6^{1}, C7^{1}) for **1** and H···C, C—H···O and N—H···C for **2** (Table 2). The values of the short contact lengths are less than the sum of their *Vander Waal radii* [21]. All bond lengths and angles are in the expected ranges of similar compounds that have been reported [18–20].

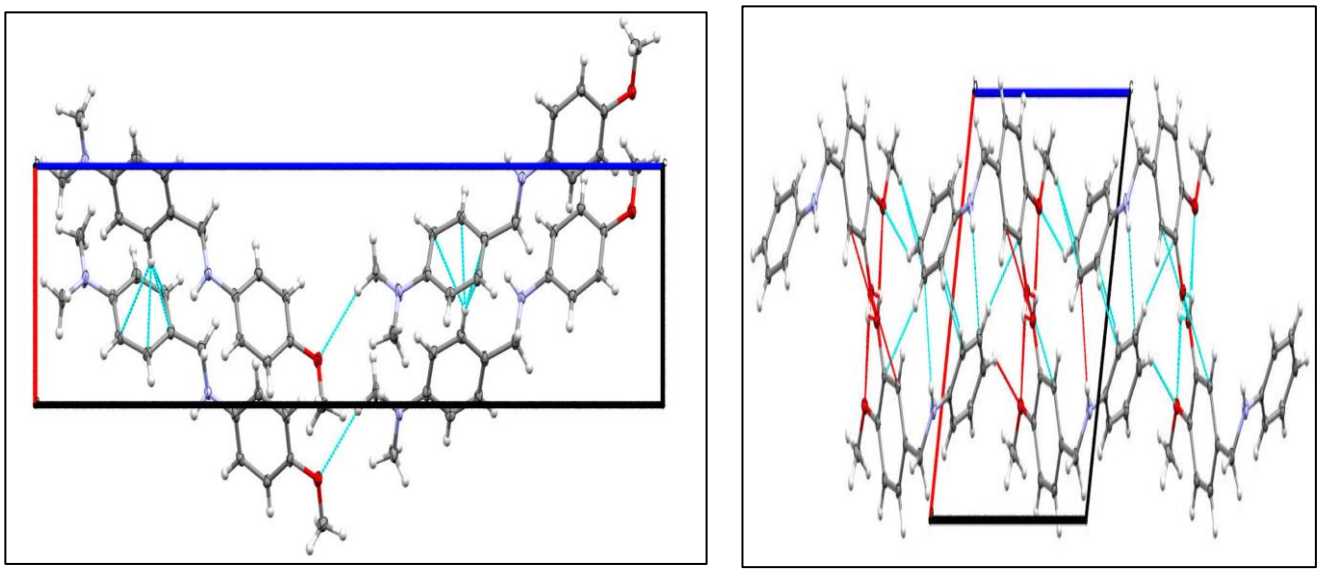


(**1**) (**2**)

Figure 1. Molecular structures of **1** and **2** displacement ellipsoid drawn at 50% probability.

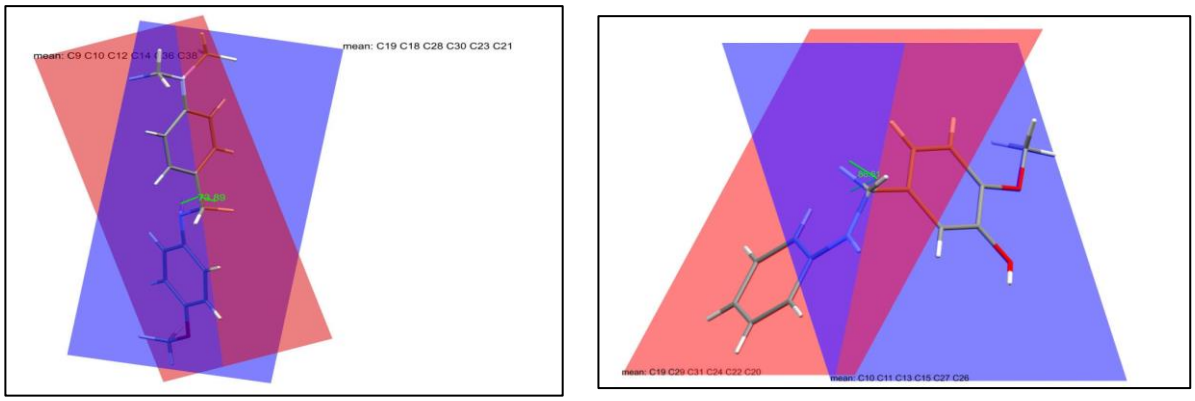
Table 1. Crystal data and refinement details.

	1	**2**
Formula	$C_{16}H_{20}N_2O$	$C_{14}H_{15}NO_2$
D_{calc}/g cm^{-3}	1.230	1.330
μ(MoK$_\alpha$)/mm^{-1}	0.077	0.089
Formula Weight	256.34	229.27
Colour	colourless	colourless
Shape	block	Plank
Size/mm^3	0.78 × 0.34 × 0.32	0.38 × 0.21 × 0.14
Crystal System	orthorhombic	monoclinic
Space Group	$Pca2_1$	$P2_1$
a/Å	6.590(1)	9.9964(2)
b/Å	7.278(1)	5.65940(10)
c/Å	28.870(4)	10.6027(2)
α/°	90	90
β/°	90	107.3100(10)
γ/°	90	90
V/Å^3	1384.6(3)	572.666(19)
Z/Z′	4/1	2/1
Wavelength/Å	0.71073	0.71073
Θ_{min}/°	1.411	2.012
Θ_{max}/°	25.969	28.390
Measured Refl.	8346	11733
Independent Refl.	2612	2860
Reflections Used	2521	2767
R_{int}	0.0268	0.0190
Parameters	176	156
Largest Peak	0.289	0.252
Deepest Hole	−0.200	−0.177
GooF	1.189	1.047
wR_2 (all data)	0.1507	0.0766
wR_2	0.1483	0.0756
R_1 (all data)	0.0433	0.0290
R_1	0.0418	0.0279



(**1**) (**2**)

Figure 2. Unit cell packings of **1** and **2** viewed along b-axis with hydrogen bonds shown as dash lines.



(**1**) (**2**)

Figure 3. Dihedral angles between the two benzene rings viewed along b-axis for **1** and b-axis for **2**.

Table 2. Hydrogen Bond information for 1 and 2.

	D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/Deg
1	C11	H11	N2[1]	0.95	2.63	3.463(4)	146.4
2	O2	H2	O1[1]	0.84	2.14	2.8885(15)	148.9
	O2	H2	O2[1]	0.84	2.29	2.9277(5)	133.2

Symmetry codes: **1**, [1]1/2 + x, −y, +z; **2**, [1]1 − x, −1/2 + y, 1−.

3. Materials and Methods

All solvents and chemical reagents such as p-anisidine, aniline, 4-(dimethylamino) benzaldehyde, 3-hydroxy-4-methoxybenzaldehyde were obtained from Sigma Aldrich and used as obtained without further purification. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker (Billerica, MA, USA) Avance III 400 MHz spectrometer. The proton and carbon shifts are quoted in ppm relative to the solvent signals. FTIR spectra were recorded in the region 4000 to 650 cm^{-1} using a Cary 630 FTIR spectrometer (Agilent Technologies, Santa Clara, CA, USA). Single mass analysis was carried out using the Waters Micromass LCT Premier TOF-MS (Waters, Milford, MA, USA). The spectra are presented in Supplementary Figures S1–S8. Single crystal X-ray crystallography of the compounds were recorded on a Bruker (Billerica, MA, USA) APEX-II CCD diffractometer.

*3.1. Synthesis of 4-(((4-Methoxyphenyl)amino)methyl)-*N,N*-dimethylaniline (1)*

P-anisidine (1.1084 g, 0.009 mol) dissolved in 20 mL methanol was placed in a two neck flask and 4-(dimethylamino)benzaldehyde (1.4919 g, 0.01 mol) was added, the resulting mixture was refluxed at 80 °C for 8 h. The solvent was then removed under vacuum to give a yellow oily product. The yellow oily product was dissolved in 1:1 dichloromethane:methanol (20 mL) and added in portion to sodium borohydride (0.7566 g, 0.02 mol) at room temperature and stirred for 20 h. The solvent was removed under vacuum and the product extracted with dichloromethane and washed with water. The whitish solid product obtained was recrystallized in methanol to give single crystals suitable for X-ray crystallography. Yield, 1.7995, 78%, ^{1}H NMR (400 MHz, (CD3)2CO, δ, ppm); 7.21(d, 2H), 6.71(t, 4H), 6.62(d, 2H), 4.75(s, 1H), 4.15(d, 2H), 3.67(s, 3H), 2.90(s, 6H), ^{13}C NMR (400 MHz, $(CD_3)_2CO$, δ, ppm); 40.80($(CH_3)_2N$—), 48.78(—CH_2—NH—), 55.84(—OCH_3), 114.57, 115.43, 150.90, 152.56 (—NH—C_6H_4—), 113.49, 128.19, 129.14, 144.33(N—C_6H_4—), IR (solid, cm^{-1}); 3387 (s), 3031 (s), 2992 (m), 1610 (s), 1506 (s), 1444 (s), 1347 (s), 1228 (s), TOF MS ES^{+}, *m*/*z* (%); 255.1503 (100) [M^{+}]

3.2. Synthesis of 2-Methoxy-5-((phenylamino)methyl)phenol (2)

Aniline (1.46 mL, 0.016 mol) dissolved in 20 mL methanol was placed in a two-neck flask and 3-hydroxy-4-methoxybenzaldehyde (2.7387 g, 0.018 mol) was added, the resulting mixture was refluxed at 80 °C for 8 h. The solvent was then removed under vacuum to give a yellow oily product. This was dissolved in 1:1 dichloromethane:methanol (20 mL), and sodium borohydride (1.3619 g, 0.036 mol) were added in portion at room temperature and stirred for 20 h. The solvent was removed under vacuum and after which the product was extracted with dichloromethane and washed severally with water. The solvent was removed to give a whitish solid product that was recrystallized in methanol to obtain single crystals suitable for X-ray crystallography. Yield, 2.9347, 80% ^{1}H NMR (400 MHz, $(CD_3)_2CO$, δ, ppm); 7.41 (s, 1H), 7.06 (t, 2H), 6.88 (d, 2H), 6.81 (d, 1H), 6.65 (d, 2H), 6.55 (t, 1H), 5.27 (s, 1H), 4.21 (s, 2H), 3.81 (s, 3H), ^{13}C NMR (400 MHz, $(CD_3)_2CO$, δ, ppm); 56.80(—OCH_3), 47.80 (—CH_2—NH—), 113.50, 119.15, 129.69, 149.87 (C_6H_5—NH—), 112.47, 115.10, 117.15, 134.17, 147.33, 147.56 (—C_6H_3OH—), IR (solid, cm^{-1}); 3399 (b), 3026 (m), 2955 (m), 1596 (s), 1506 (s), 1434 (s), 1365 (s), 1220 (s), TOF MS ES$^+$, *m*/*z* (%); 230.1189 (100) [M$^+$]

3.3. Single Crystal X-ray Crystallography

Single colorless block and plank-shaped crystals of **1** and **2** were obtained from slow evaporation of methanolic solution of the compounds. Suitable crystals (0.78 × 0.34 × 0.32) mm^3 and (0.38 × 0.21 × 0.14) mm^3 of **1** and **2** were selected and mounted on a MITIGEN holder in paratone oil on a Bruker APEX-II CCD diffractometer [22] and data were collected using Olex2 [23] with the crystal temperature kept at T = 100(2) K. The structures were solved in a space group $Pca2_1$ and $P2_1$ for **1** and **2,** respectively, with ShelXS-2013 [24] structure solution program, using the direct solution method. The model was refined with version 2016/6 of ShelXL [25] using least squares minimization.

4. Conclusions

The molecular structures of the compounds 2-methoxy-5-((phenylamino) methyl) phenol (**1**) and 4-(((4-methoxyphenyl)amino)methyl)-*N*,*N*-dimethylaniline (**2**) are reported. The compounds crystallized as monomeric entity of in an orthorhombic and monoclinic crystal system for **1** and **2,** respectively. Each compound is held together in the unit cell by the combination of both intramolecular covalent and intermolecular secondary interactions. The compounds are useful starting materials for the synthesis of many important organic compounds.

Supplementary Materials: The following are available online, including copies of ^{1}H, ^{13}C NMR, FTIR, and TOF mass-spectra for the compounds **1** and **2** (Figure S1–Figure S8). Figure S1: ^{1}H NMR spectra of 4-(((4-methoxyphenyl)amino)methyl)-*N*,*N*-dimethylaniline (1); Figure S2: ^{13}C NMR Spectra of 4-(((4-methoxyphenyl)amino)methyl)-*N*,*N*-dimethylaniline (1); Figure S3: ^{1}H NMR spectra of 2-methoxy-5-((phenylamino)methyl)phenol (2); Figure S4: ^{13}C NMR spectra of 2-methoxy-5-((phenylamino)methyl)phenol (2); Figure S5: FTIR spectra of 4-(((4-methoxyphenyl)amino)methyl)-*N*,*N*-dimethylaniline (1); Figure S6: FTIR spectra of 2-methoxy-5-((phenylamino)methyl)phenol (2); Figure S7: Single mass spectrum of 4-(((4-methoxyphenyl)amino)methyl)-*N*,*N*-dimethylaniline (1); Figure S8: Single mass spectrum of 2-methoxy-5-((phenylamino)methyl)phenol (2).

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Data Availability Statement: CCDC 1841554 and 1853350 contain supplementary crystallographic data can be obtained from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: + 44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Conflicts of Interest: The authors declare no conflict of interest.

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