Communication

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 C16H20N2O (I) and C16H22NO (II) in orthorhombic and monoclinic crystal systems, respectively. Compound I consists of intermolecular C11⋯N2 hydrogen bonding with C11⋯N21 = 3.463(4) Å. The hydroxyl group in II is also involved in intermolecular O2⋯H2⋯O2 and O2⋯H2⋯O2 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 I and H⋯C, C⋯H⋯O and N⋯H⋯C for II. 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

1. Introduction

N-alkylation of primary amines and ammonia, reduction of nitriles and amides in the presence of catalyst such as LiAlH4 and NaBH4, tin, or iron have been used for the preparation of secondary amines [1–5]. NaBH4 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 (I) and 2-methoxy-5-((phenylamino)methyl)phenol (II).

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).
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 = 3.463(4) Å); symmetry operation of 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 (hydroxyl oxygen of the neighboring molecule), with O2⋯O1 = 2.8885(15) Å and O1⋯O2 = 2.9277(5) Å; symmetry operation of 1/2−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 and C5—H⋯(C4i, C5i, C6i, C7i) 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].

Figure 1. Molecular structures of (A,B) displacement ellipsoid drawn at 50% probability.
Figure 2. Unit cell packings of (A, B) viewed along b-axis with hydrogen bonds shown as dash lines.

Table 1. Crystal data and refinement details.

|                      | 1        | 2        |
|----------------------|----------|----------|
| Formula              | C₆H₁₀N₂O | C₆H₁₀N₂O |
| Dₐ₀/g cm⁻³           | 1.230    | 1.330    |
| μ(MoKα)/mm⁻¹         | 0.077    | 0.089    |
| Formula Weight       | 256.34   | 229.27   |
| Colour               | colourless | colourless |
| Shape                | block    | Plank    |
| Size/mm³             | 0.78 × 0.34 × 0.32 | 0.38 × 0.21 × 0.14 |
| Crystal System       | orthorhombic | monoclinic |
| Space Group          | Pca2₁    | P₁       |
| a/Å                  | 6.590(1) | 9.996(2) |
| b/Å                  | 7.278(1) | 5.659(10) |
| c/Å                  | 28.870(4) | 10.602(2) |
| α/°                  | 90       | 90       |
| β/°                  | 90       | 107.310(10) |
| γ/°                  | 90       | 90       |
| V/Å³                 | 1384.6(3) | 572.666(19) |
| Z/Z’                 | 4/1      | 2/1      |
| Wavelength/Å         | 0.71073  | 0.71073  |
| θ<sub>meas</sub>/°   | 1.411    | 2.012    |
| θ<sub>ref</sub>/°    | 25.969   | 28.390   |
| Measured Refl.       | 8346     | 11733    |
| Independent Refl.    | 2612     | 2860     |
| Reflections Used     | 2521     | 2767     |
| R<sub>int</sub>      | 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<sub>2</sub> (all data) | 0.1507 | 0.0766 |
| wR<sub>2</sub>       | 0.1483   | 0.0756   |
| R<sub>i</sub> (all data) | 0.0433 | 0.0290   |
| R<sub>i</sub>        | 0.0418   | 0.0279   |
Figure 3. Dihedral angles between the two benzene rings viewed along b-axis for (A) and b-axis for (B).

### 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     |

Symmetry codes: 1, \(\frac{1}{2} + x, -y, +z\); 2, \(-1 - x, -\frac{1}{2} + y, 1-z\).

### 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 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). Single mass analysis was carried out using the Waters Micromass LCT Premier TOF-MS. The spectra are presented in supplementary Figures S1-S8. Single crystal X-ray crystallography of the compounds were recorded on a Bruker 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, (CD\(_3\))\(_2\)CO, \(\delta\) 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\(_3\))\(_2\)CO, \(\delta\) ppm): 40.80(CH\(_3\):CO), 48.78(−CH−NH−), 55.84(−OCH\(_3\)), 114.57, 115.43, 150.90, 152.56 (−NH−C\(_6\)H\(_5\)−), 113.49, 128.19, 129.14, 148.93(N−C\(_6\)H\(_5\)−), 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 several times 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% 1H NMR (400 MHz, (CD3)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), 4C NMR (400 MHz, (CD3)2CO, δ, ppm): 159.6 (OCH3), 147.56 (s), 147.56 (s), 143.4 (s), 136.5 (s), 136.5 (s), 136.5 (s), 122.0 (s), TOF MS ESi, 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 mm3 and (0.38 × 0.21 × 0.14) mm3 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 Pca21 and P21 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 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 1H, 13C NMR, FTIR, and TOF mass-spectra for the compounds 1 and 2 (Figure S1–Figure S8). Figure S1: 1H NMR spectra of 4-(((4-methoxyphenyl)amino)methyl)-N,N-dimethylaniline (1); Figure S2: 13C NMR Spectra of 4-(((4-methoxyphenyl)amino)methyl)-N,N-dimethylaniline (1); Figure S3: 1H NMR spectra of 2-methoxy-5-((phenylamino)methyl)phenol (2); Figure S4: 13C 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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References

1. Roese, P.; Eller, K.; Henkes, E.; Rossbacher, R.; Höke, H. Ullmann’s Encyclopedia of Industrial Chemistry; Weinheim Wiley-VCH-Verl: Weinheim, Germany, 2015; pp. 1–55.

2. Wakamatsu, T.; Inaki, H.; Ogawa, A.; Watanabe, M.; Ban, Y. Reduction of nitriles and amides to amines with tetrabutylammonium borohydride in dichloromethane. Heterocycles 1980, 14, 1437–1440.

3. Severin, R.; Doye, S. The catalytic hydroamination of alkynes. Chem. Soc. Rev. 2007, 36, 1407–1420.

4. Hultzsch, K.C.; Gribkov, D.V.; Hampel, F. Non-metalloocene rare earth metal catalysts for the diastereoselective and enantioselective hydroamination of aminoketenes. J. Org. Chem. 2005, 69, 4401–4425.

5. Seayd, J.; Tillack, A.; Hartung, C.G.; Beller, M. Base-Catalyzed Hydroamination of Olefins: An Environmentally Friendly Route to Amines. Adv. Synth. Catal. 2002, 344, 795–813.

6. Aghera, A.K.; Parsania, P.H. A cleaner approach for reduction of some symmetric diimines using NaBH₄. Ind. J. Chem. 2009, 48B, 438–442.

7. Billman, J.H.; Delsing, A.C. Reduction of Schiff bases with sodium borohydride. J. Org. Chem. 1957, 22, 1068–1070.

8. Ajibade, P.A.; Andrew, F.P.; Fatokun, A.A.; Oluwalamo, A.E. Synthesis, characterization and in vitro screening for anticancer potential of Mn(II), Co(II), Cu(II), Zn(II), and Pt(II) methoxyphenyl dithiocarbamato complexes. J. Mol. Struct. 2021, 1230, 129894.

9. Paca, A.M.; Ajibade, P.A. Bis- (N-ethylphenyldithiocarbamato)palladium(II) as molecular precursor for palladium sulfide nanoparticles. J. Mol. Struct. 2021, 12435, 130777.

10. Ajibade, P.A.; Fatokun, A.A.; Andrew, F.P. Synthesis, characterization and anticancer studies of Mn(II), Cu(II), Zn(II) and Pt(II) dithiocarbamate complexes-crystal structures of the Cu(II) and Pt(II) complexes. Inorg. Chim. Acta 2020, 504, 119431.

11. Jones, R.S.G. Tryptamine: A neuromodulator or neurotransmitter in mammalian brain? Prog. Neurobiol. 1992, 38, 1, 117–139.

12. Knight, A.W.; Greenway, G.M. Relationship between structural attributes and observed electrogenerated chemiluminescence (ECL) activity of tertiary amines as potential analytes for the tris (2, 2-bipyridine) ruthenium(II) ECL reaction. A review. Analyst 1996, 121, 101R–106R.

13. Svejstrup, T.D.; Ruffoni, A.; Juliă, F.; Aubert, V.M.; Leonori, D. Synthesis of Arylamines via Aminium Radicals. Angew. Chem. Int. Ed. 2017, 129, 15144–15148.

14. Kumar, C.T.K.; Keshavayya, J.; Rajesh, T.N.; Pethambar, S.K.; Ali, A.R.S. Synthesis, characterization, and biological activity of 5-phenyl-1, 3, 4-thiadiazole-2-amine incorporated aza dye derivatives. Org. Chem. Int. 2013, 2013, 376026.

15. Pinheiro, H.M.; Touraud, E.; Thomas, O. Aromatic amines from aza dye reduction: Status review with emphasis on direct UV spectrophotometric detection in textile industry wastewaters. Dyes Pigments 2004, 61, 121–139.

16. Hogarth, G. Metal-dithiocarbamate complexes: Chemistry and biological activity. Mini Rev. Med. Chem. 2012, 12, 1202–1215.

17. Cozzi, P.G. Metal–Salen Schiff base complexes in catalysis: Practical aspects. Chem. Soc. Rev. 2003, 33, 410–421.

18. Liu, Y.F.; Xia, H.T.; Yang, S.P.; Wang, D.Q. 2-[(4-Chlorophenyl) aminomethyl]-6-methoxyphenol. Acta Cryst. 2007, E63, o3561.

19. Shu, H.; Yu, N.S.; Xie, G.L.; Chen, L.Z. 2-[(4-Methoxyanilino) methyl] phenol. Acta Cryst. 2011, E67, o2304.

20. Qu, Y.; Tian, L.J.; Dong, J. 2-(Anilinomethyl) phenol. Acta Cryst. 2007, E63, o4932.

21. Caracelli, I.; Magnani, S.H.; Cardoso, J.D.O.; Cunha, R.L.; Vega-Teijido, M.A.; Zukerman-Schpector, J.; Tiekink, E.R. Crystallographic and docking (Cathepsins B, K, L and S) studies on bioactive halotelluroxetanes. Z. Kristallogr. 2018, 233, 113.

22. Bruker: APEX2; Bruker AXS Inc.: Madison, WI, USA, 2011.

23. Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. A complete structure solution, refinement and analysis program. J. Appl. Cryst. 2009, 42, 339–341.

24. Sheldrick, G.M. A short history of SHELX Acta Cryst. 2008, A64, 339–341.

25. Sheldrick, G.M. Crystal structure refinement with SHELXL Acta Cryst. 2015, C27, 3–8.