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Article

Synthesis, Crystal Structure and Antibacterial Activity of (*E*)-*N*-(2,3,4-Trimethoxy-6-methylbenzylidene)-4-methylbenzenamine

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Abstract: The title compound (*E*)-*N*-(2,3,4-trimethoxy-6-methylbenzylidene)-4-methylbenzenamine ($C_{18}H_{21}NO_3$, M_r = 299.36) was synthesized and characterized by elemental analysis, IR spectra and single crystal X-ray diffraction. The crystal belongs to monoclinic, space group $P2_1/c$, with a = 7.7239(9), b = 27.287(2), c = 8.4128(11) Å,β= 111.529(2) °, V = 1649.4(3) Å^3, Z = 4, D_c = 1.206 g/cm^3, λ= 0.71073 Å, μ(Mo $K\alpha$) = 0.082 mm^{-1}, F(000) = 640. The final refinement gave R = 0.0525, $wR(F^2)$= 0.1130 for 2899 observed reflections with $I > 2\sigma(I)$. X-ray diffraction analysis reveals that the dihedral angle between the two phenyl rings is 137.8 (2)°. The molecule adopts a *trans* configuration about the central C=N functional bond. The crystal structure is stabilized by an intermolecular hydrogen bonding and weak π-π interactions. The title compound possesses moderate antibacterial activity.

Keywords: *N*-(2,3,4-Trimethoxy-6-methylbenzylidene)-4-methylbenzenamine; Synthesis; Crystal structure; Antibacterial activity

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Introduction

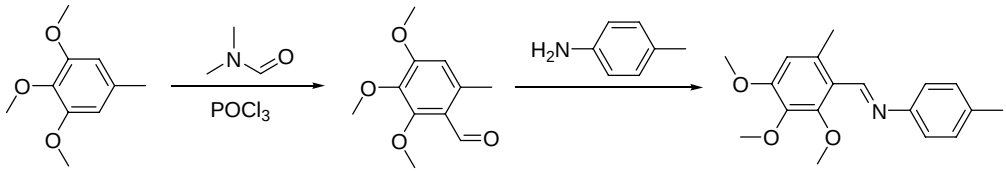
Schiff bases are used as substrates in the preparation of a number of industrial and biologically active compounds via ring closure, cycloaddition and replacement reactions [1]. Schiff bases are known to have biological activities such as antimicrobial [2-7], antitumor [8-10], and herbicidal properties [11]. They have also been widely used as versatile ligands involved in various metal chelation reactions to form metal complexes [12-15], which are very intreresting in many fields, such as catalysis and enzymatic reactions [16,17] and magnetism [18]. Recently, a few Schiff base compounds with antibacterial activity have been investigated [19-23]. However, to the best of our knowledge, the Schiff base (*E*)-*N*-(2,3,4-trimethoxy-6-methylbenzylidene)-4-methylbenzenamine and the complexes derived from it have never been reported so far. Investigation of the structure and antibacterial property of the Schiff base compound may help us to explore the interactions among the molecules, design and synthesize new metal complexes, as well as evaluate the potential medicinal applications. In this paper, the synthesis, crystal structure and antibacterial activities of the title compound are reported.

Results and Discussion

Synthesis

(*E*)-*N*-(2,3,4-trimethoxy-6-methylbenzylidene)-4-methylbenzenamine was prepared in high yield from 3,4,5-trimethoxytoluene as shown in Scheme 1.

Scheme 1. Synthesis of the title compound.



X-ray structure

The molecular structure of the title compound is shown in Figure 1 and the crystal packing of the compound is depicted in Figure 2. Selected bond lengths and angles are given in Table 1.

As seen from Figure 1, the dihedral angle between the two phenyl rings is 137.8 (2)° . The molecule adopts an *E* configuration about the central C=N functional bond. All the bond lengths and bond angles in the title compound are within normal ranges [24, 25] and comparable to those in the similar compounds [19, 20]. The crystal structure is stabilized by an intermolecular hydrogen bonding and weak π-π interactions (Figure 2 and Table 2).

Figure 1. Molecular structure of the title compound at 30% probability thermal ellipsoids.

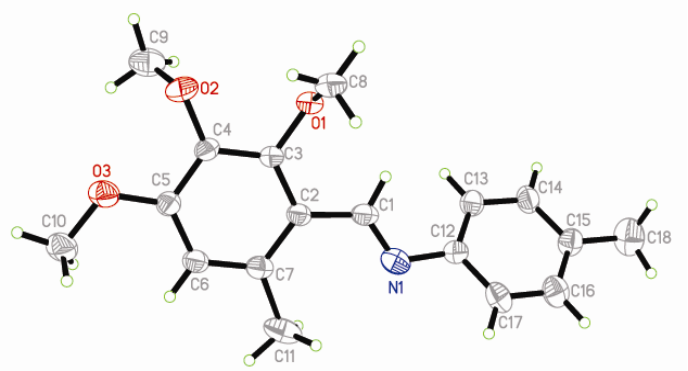


Figure 2. Crystal packing of the title compound.

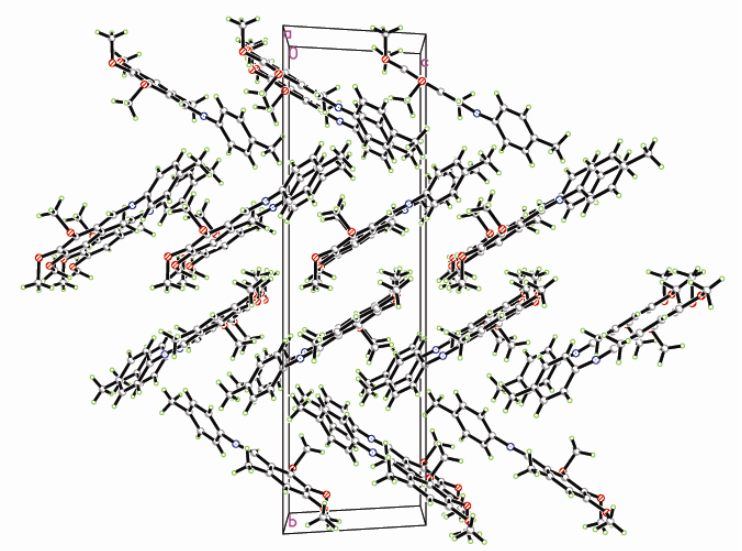


Table 1. Select Bond Lengths (Å) and Bond Angles (°).

Bond	**Dist.**	**Bond**	**Dist.**
N(1)-C(1)	1.263(3)	O(3)-C(5)	1.361(3)
N(1)-C(12)	1.419(4)	O(3)-C(10)	1.423(3)
O(1)-C(3)	1.386(3)	C(1)-C(2)	1.453(3)
O(1)-C(8)	1.431(3)	C(7)-C(11)	1.512(4)
O(2)-C(4)	1.377(3)	C(15)-C(18)	1.505(4)
O(2)-C(9)	1.419(4)		
Angle	**(°)**	**Angle**	**(°)**
C(1)-N(1)-C(12)	118.8(3)	C(3)-C(4)-O(2)	119.9(3)
C(3)-O(1)-C(8)	113.1(2)	O(2)-C(4)-C(5)	121.7(3)
C(4)-O(2)-C(9)	113.8(2)	O(3)-C(5)-C(6)	124.6(3)
C(5)-O(3)-C(10)	118.2(2)	O(3)-C(5)-C(4)	115.4(3)
N(1)-C(1)-C(2)	125.9(3)	C(6)-C(7)-C(11)	117.5(3)
C(3)-C(2)-C(1)	117.5(2)	C(2)-C(7)-C(11)	123.1(3)
C(7)-C(2)-C(1)	124.9(3)	C(17)-C(12)-N(1)	118.6(3)
C(4)-C(3)-O(1)	118.3(3)	C(13)-C(12)-N(1)	123.5(3)
O(1)-C(3)-C(2)	118.8(3)	C(14)-C(15)-C(18)	120.9(3)

Table 2. Hydrogen-bond geometry (Å, °).

D─H…A	D─H	H…A	D…A	D─H…A
C1─H1…O1	0.93	2.36	2.7427(4)	104.7
C9─H9C…O3	0.96	2.43	2.9966(5)	117.3

Antibacterial activity

Antibacterial tests were performed according to the literature [26, 27]. The concentration of the title compound solution in the preliminary antibacterial tests was 0.5 mg/mL, and the test results are given in Table 3. The data show that the title compound exhibits moderate antibacterial activities against four bacterial species: *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi* and *Staphylococcus aureus*, with corresponding inhibition zones of 9.6, 8.1, 3.5 and 6.2 mm.

Table 3. Antibacterial activities tests of the title compound.

Bacterial strain	Inhibitory zone (mm)	Bactericidal efficiency assay	Agar media
Escherichia coli	9.6	positive	negative
Pseudomonas aeruginosa	8.1	positive	negative
Salmonella typhi	3.5	positive	negative
Staphylococcus aureus	6.2	positive	negative

Experimental

General

All reagents for synthesis and analyses were of commercially available analytical grade and were used as received without further purification. Elemental analyses were performed on a Perkin-Elmer 240C analyzer. IR spectra were measured on a TENSOR 27 (Bruker) FT-IR spectrometer with KBr pellets in the range 4000-400 cm^{-1}. ^1H NM R spectra were recorded on a Varian INOVA 600 spectrometer at ambient temperature and the chemical shifts were given in ppm relative to Me_4Si in $CDC1_3$. The X-ray powder diffraction (XRPD) was recorded on a Rigaku D/Max-2500 diffractometer at 40 kV, 100 mA for a Cu-target tube and a graphite monochromator.

Synthesis of 2,3,4-trimethoxy-6-methylbenzaldehyde

To a solution of 3,4,5-trimethoxytoluene (9.1 g, 0.05 mol) in *N*,*N*-dimethylformamide (10 mL), $POCl_3$ (7.5 mL, 0.09 mol) was added dropwise for about 1.5 h at 0~5°C. The solution was stirred magnetically for 1 h at 40 °C and then for 5 h at reflux temperature. The solution was poured into ice-water, and the pH value was adjusted to 7~8 by adding 30% NaOH solution, giving a white solid.

After cooling to room temperature, the product was filtered and dried. Yield 93.1%. m.p. 61~61.5 °C (lit. [28] 61~61.4 °C).

Synthesis of the title compound

To a solution of *p*-toluidine (5 mmol) and potassium acetate (10 mmol) in distilled water (10 mL), 2,3,4-trimethoxy-6-methylbenzaldehyde (5 mmol) in ethyl alcohol (20 mL) was added dropwise and the solution was stirred magnetically for 1 h at reflux temperature. After cooling to room temperature, the product was filtered and dried. Yield 91%. Anal. Calcd. (%) for $C_{18}H_{21}NO_3$: C 72.14, H 7.01, N 4.68. Found (%): C 72.28, H 7.14, N 4.75; IR (cm^{-1}): 1635 (s, -C=N), 1200 (s, -O-Ar). ^{1}H-NMR: (CD_3COCD_3, ppm): δ= 8.63 (s, 1H), 7.13 (d, 4H), 6.20 (s, 1H), 3.81 (s, 9H), 2.42 (s, 6H).

X-ray single crystal structure determination

A brown crystal with dimensions of 0.45 mm × 0.43 mm × 0.40 mm was selected for X-ray diffraction. It was obtained by evaporation from ethanol solution after a week. The reflection data were collected on a Bruker Smart Apex II CCD area diffractometer with graphite monochromatized Mo*Kα* radiation (λ=0.71073 Å) at 298 (2) K. A total of 8258 reflections were collected in the range of 1.49 <θ< 25.01° by using ω scans mode. And a total of 2899 observed reflections with $I > 2\sigma(I)$ were used in structure solution and refinement. 1457 independent reflections and R_{int} = 0.1195. *LP* corrections were applied to the data.

The structure was solved by direct methods using SHELXL-97 [29] and expanded using Fourier techniques. All non-hydrogen atoms and hydrogen atoms were refined anisotropically and isotropically, respectively. The final refinement by full-matrix least squares method was converged at R = 0.0525, and wR = 0.1130 ($w = 1/[\delta^2(F_o^2)+(0.0477P)^2 + 0.6503P]$, $P = (F_o^2+2F_c^2)/3)$, S = 1.020, $(\Delta/\sigma)_{max}$ = 0.001. The largest peak in the final difference Fourier map is 0.187 e/ Å^3 and the minimum peak is -0.181 e/ Å^3. Molecular graphics were drawn with the program package SHELXS-90 [30]. Crystallographic data for the structure of the title have been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC-687333. These data can be obtained free of charge from the CCDC via www.ccdc.cam.ac.uk/deposit. Telephone: (44) 01223 762910 Facsimile: (44) 01223 336033. Postal Address: CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

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References and Notes

1. Karia, F. D.; Parsania, P.H. Synthesis, biological and thermal properties of Schiff bases of bisphenol-C. *Asian J. Chem.* **1999**, *11*, 991-995.

2. More, P. G.; Bhalvankar, R. B.; Pattar, S. C. Synthesis and biological activities of Schiff bases of aminothiazoles. *J. Indian Chem. Soc*. **2001**, *78*, 474-475.
3. El-Masry, A. H.; Fahmy, H. H.; Abdelwaed, S. H. A. Synthesis and antimicrobial activity of some new benzimidazole derivatives. *Molecules* **2000**, *5*, 1429-1438.
4. Baseer, M. A.; Jadhav, V. D.; Phule, R. M.; Archana, Y. V.; Vibhute, Y. B. Synthesis and antimicrobial activity of some new Schiff bases. *Orient. J. Chem*. **2000**, *16*, 553-556.
5. Pandeya, S. N.; Sriram, D.; Nath, G.; De Clercq, E. Synthesis and antimicrobial activity of Schiff and mannich bases of isatin and its derivatives with pyrimidine. *Farmaco* **1999**, *54*, 624-628.
6. Singh, W. M.; Dash, B. C. Synthesis of some new Schiff bases containing thiazole and oxazole nuclei and their fungicidal activity. *Pesticides* **1988**, *22*, 33-37.
7. Wang, N.; Li, J. P.; Pu, Y.L. Synthesis and crystal structure of 2-hydroxybenzoic acid [1-(3,5-dibromo-2-hydroxyphenyl) methylidene] hydrazide methanol. *Chin. J. Struct. Chem*. **2007**, 26, 547-550.
8. Hodnett, E. M.; Dunn, W. J. Structure-antitumour activity correlation of some Schiff bases. *J. Med. Chem*. **1970**, *13*, 768-770.
9. Desai, S. B.; Desai, P. B.; Desai, K.R. Synthesis of some Schiff bases, thiazolidones, and azetidinones derived from 2,6-diaminobenzo[1,2-d:4,5-d']bisthiazole and their anticancer activities. *Heterocycl. Commun*. **2001**, *7*, 83-90.
10. Pathak, P.; Jolly, V. S.; Sharma, K.P. Synthesis and biological activities of some new substituted arylazo Schiff bases. *Orient. J. Chem*. **2000**, *16*, 161-162.
11. Samadhiya, S.; Halve, A. Synthetic utility of Schiff bases as potential herbicidal agents, *Orient. J. Chem*. **2001**, *17*, 119-122.
12. Aydogan, F.; Ocal, N.; Turgut, Z.; Yolacan, C. Transformations of aldimines derived from pyrrole-2-carboxaldehyde. Synthesis of thiazolidino-fused compounds. *Bull. Kor. Chem. Soc.* **2001**, *22*, 476-480.
13. Yu, T. Z.; Zhang, K.; Zhao, Y. L.; Yang, C. H.; Zhang, H.; Fan, D. W.; Dong, W. K. A new trinuclear zinc(II) complex possessing five- and six-coordinated central ions and its photolumine scent property. *Inorg. Chem. Commun*. **2007**, *10*, 401–403.
14. Yu, Y. Y.; Zhao, G. L.; Wen, Y. H. Syntheses, characterizations, crystal structures and antibacterial activities of two zinc (II) complexes with a Schiff base derived from *o*-vanillin and *p*-toluidine. *Chin. J. Struct. Chem*. **2007**, *26*, 1359-1402.
15. Chen, J.; Xu, X. Y.; Gao, J.; Li,Y. H.; Xu, G. X. Synthesis, crystal structure and characterization of a new mononuclear Zn (II) complex from Schiff-base ligand. *Chin. J. Struct. Chem*. **2007**, *26*, 632-636.
16. Kim, H. J.; Kim, W.; Lough, A. J.; Kim, B. M.; Chin, J. A. Cobalt(III)-salen complex with an axial substituent in the diamine backbone: Stereoselective recognition of amino alcohols. *J. Am. Chem. Soc.* **2005**, *127*, 16776-16777.
17. May, J. P.; Ting, R.; Lermer, L.; Thomas, J. M.; Roupioz, Y.; Perrin, D. M. Covalent Schiff base catalysis and turnover by a DNAzyme: A M^{2+}-independent AP-endonuclease mimic. *J. Am. Chem. Soc.* **2004**, *126*, 4145-4156.
18. Liu, Z.; Anson, F. C. Schiff base complexes of vanadium(III, IV, V) as catalysts for the electroreduction of O_2 to H_2O in acetonitrile. *Inorg. Chem*. **2001**, *40*, 1329-1333.

19. Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. The development of the first catalysed reaction of ketenes and imines: catalytic asymmetric synthesis of lactams. *J. Am. Chem. Soc*. **2002**, *124*, 6626-6635.
20. Siddiqui, H. L.; Iqbal, A.; Ahmad, S.; Weaver, G. W. Synthesis and spectroscopic studies of new Schiff bases. *Molecules* **2006**, *11*, 206–211.
21. Wang, N.; Li, J. P.; Pu, Y.L. Synthesis and crystal structure of 2-hydroxybenzoic acid [1-(3,5-dibromo-2-hydroxyphenyl)methylidene]hydrazide methanol. *Chin. J. Struct. Chem*. **2007**, *26*, 547-550.
22. Wang, N.; Shi, Q. Synthesis and crystal structure of (*E*)2-(3′-bromo-5′-chloro-salicylidene amino)-4-methyl pyridine. *Chin. J. Struct. Chem*. **2008**, *27*, 191-194.
23. Zhang, L.; Li, K. L. Synthesis, crystal structure and antimicrobial property of 4-bromo-2-[(3-methy-pyridin-2-ylimino)methyl]phenol. *Chin. J. Struct. Chem.* **2008**, *27*, 230-232.
24. El-Masry, A. H.; Fahmy, H. H.; Abdelwahed, S. H. A. Synthesis and antimicrobial activity of some new benzimidazole derivatives. *Molecules* **2000**, *5*, 1429-1438.
25. Li, C. H.; Song, B. A.; Yan, K.; Xu, G. F.; Hu, D. Y.; Yang, S.; Jin, L. H.; Xue, W.; Lu, P. One pot synthesis of α-aminophosphonates containing bromo and 3,4,5-trimethoxybenzyl groups under solvent-free. *Molecules* **2007**, *12*, 163-172.
26. Li, B. L.; Guo, J.; Zhang, X.Q.; Lai, Y. T.; Hu, H. M. Synthesis of 3,4,5-trimethoxy-4'-hydroxy stilbene derivatives and crystal structure of ethyl{4-[(*E*)-2-(3,4,5-trimethoxyphenyl)vinyl] phenoxy}acetate. *Z. Naturforsch.* **2007**, *62b*, 244-248.
27. You, Z. L.; Zhu, H. L. Solvolthermal syntheses and crystal structures of three linear trinuclear Schiff base complexes of Zinc(II) and Cadmium(II). *Z. Anorg. Allg. Chem*. **2004**, *630*, 2754-2760.
28. Wang, S. K.; Zhao, D. F. preparation of 6-methyl-2,3,4-trimethoxybenzaldehyde. *Dyestuffs and Coloration* **2003**, *40*, 163-164.
29. Sheldrick G.M. Program for the refinement of crystal structure. In *SHELXL*97; University of Göttingen: Göttingen, Germany, 1997.
30. Sheldrick G.M. *SHELXS97*. *Acta Crystallogr*. **1990**, *A46*, 467-473.

Sample Availability: Available from the authors.