Synthesis and structure analysis of 1-(3-methoxybenzoyl)-3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine

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1-(3-Methoxybenzoyl)-3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine was prepared from 3-methoxybenzoyl chloride and 3,6-diphenyl-1,2(or 1,4)-dihydro-1,2,4,5-tetrazine, and its structure was determined by X-ray diffraction. This reaction yields the title compound rather than 1-(3-methoxybenzoyl)-3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine. The central tetrazine ring of the title compound exhibits a boat conformation and therefore, is not homoaromatic.

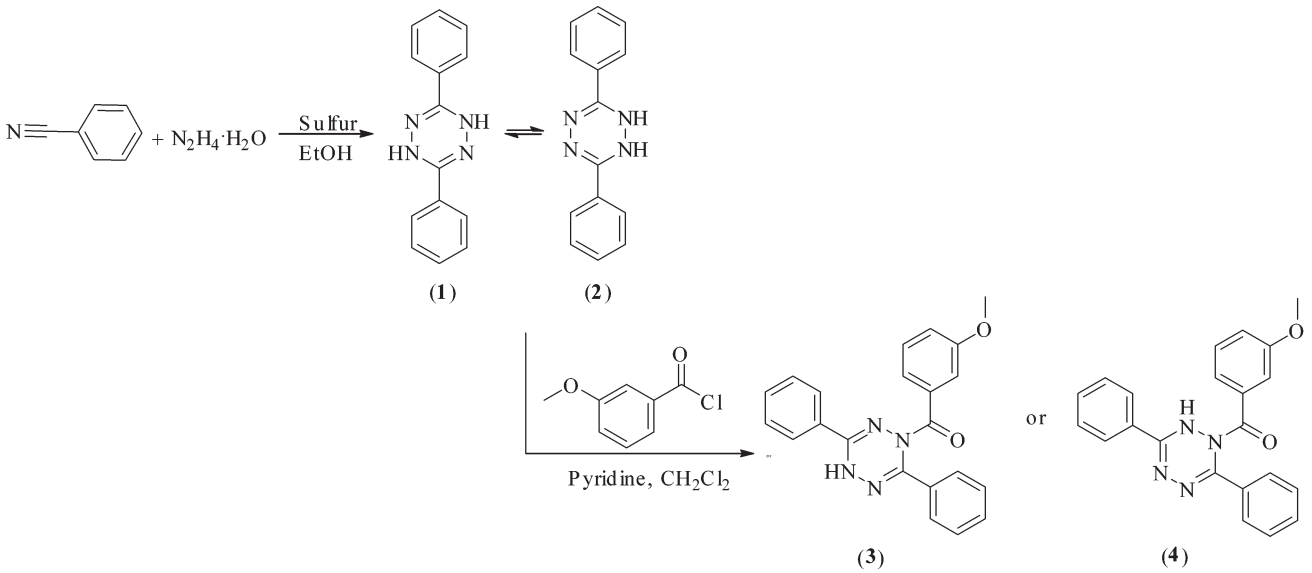
Keywords: 1,2,4,5-tetrazine, X-ray diffraction, boat conformation

1,2,4,5-Tetrazine derivatives have high reactivities,[1,2] good potential for biological activities, and have been widely used in organic synthetic chemistry and medicinal chemistry.[3–6] Dihydro-1,2,4,5-tetrazine has four isomers, 1,2-, 1,4-, 1,6- and 3,6-dihydro-1,2,4,5-tetrazine. Homoaromatic structures have been demonstrated by X-ray diffraction in the 1,6-dihydro structures.[7] There seems to be some doubt as to whether the 1,4-dihydro structures have homoaromaticity. For example, X-ray diffraction reportedly showed 3,6-bis(4-chlorobenzyl)-1,4-dihydro-1,2,4,5-tetrazine to have an obvious chair conformation without a homoaromatic structure,[8] but 1,3,4,6-tetramethyl-1,4-dihydro-1,2,4,5-tetrazine was analysed by X-ray diffraction and a possible homoaromatic structure was identified.[9] There seems to be much confusion over the structures of 1,2- and 1,4-dihydro-1,2,4,5-tetrazine isomers, and the same compound is often formulated as both structures. In most cases, the dihydro structure which would be the first reaction product is presented. Some scientists believe that rearrangement can occur between 1,2- and 1,4-dihydro-1,2,4,5-tetrazine isomers.[10]

In a continuation of our studies of structure–activity relationships in 1,2,4,5-tetrazine derivatives,[8,11,12] we have obtained a yellow crystalline compound that was the product of the reaction of 3-methoxybenzoyl chloride and 3,6-diphenyl-1,2(or 1,4)-dihydro-1,2,4,5-tetrazine (compound **1** or **2**). The latter was prepared according to the literature procedure.[8] As Scheme 1 shows, there are two possible compounds, (**3**) and (**4**), that could be the product. However, IR, NMR and MS studies failed to confirm whether the product has a homoaromatic structure and whether the hydrogen on the nitrogen is located at the 4 or 2 position. The structure of the product was confirmed by single-crystal X-ray diffraction.

The molecular structure of compound **3** is illustrated in Fig. 1. Selected bond lengths are listed in Table 1. In the molecule (Fig. 1), the N2=C3 [1.283(2) Å] and N5=C6 [1.269(2) Å] bonds correspond to typical double bonds of C=N, and the C3–N4 [1.370(2) Å], N4–N5 [1.387(2) Å], C6–N1 [1.415(2) Å] and N1–N2 [1.436(2) Å] bond lengths are typical for single bonds. Therefore, the tetrazine ring is the 1,4-dihydro structure with the N-substituted group at the 1-position and the N-hydrogen at the 4 and not the 2-position, the compound being 1-(3-methoxybenzoyl)-3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine, (**3**), rather than 1-(3-methoxybenzoyl)-3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine, (**4**).

In compound **3**, atoms N2, C3, N5 and C6 are coplanar, with the largest deviation from the plane (plane 1) being –0.0219 (8) Å for atom N5. The least-squares plane is listed in Table 2. The adjacent N1 and N4 atoms deviate from plane 1 by 0.4291 (24) and 0.3403 (23) Å, respectively. The dihedral angle between plane 1 and the N1/N2/C6 plane is 34.04 (13) °, and between plane 1 and the N4/N5/C3 plane is 28.35 (13) °. The difference in the dihedral angles is presumably due to a steric effect of the substituent at the 1-position. The central tetrazine ring of compound **3** exhibits an obvious boat conformation (Fig. 2) and is therefore not homoaromatic. The dihedral angles



Scheme 1 Synthesis of **3**.

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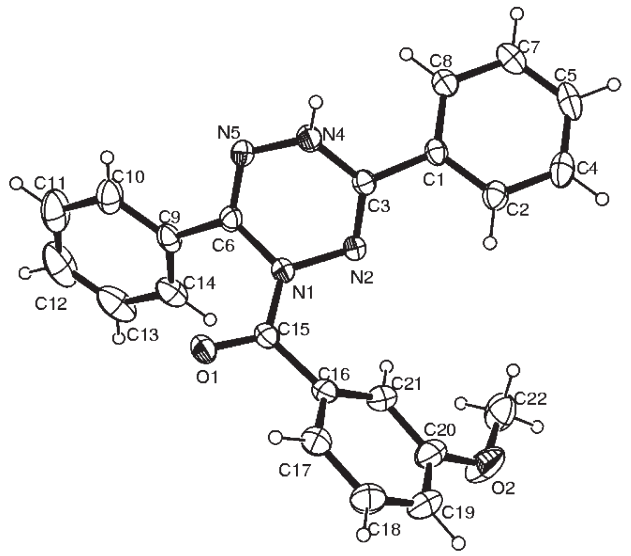

Fig. 1 The molecular structure of **3**, shown with 30% probability displacement ellipsoids.

Table 1 Selected bond lengths (Å)

Bond lengths			
N1–N2	1.436(2)	N4–N5	1.387(2)
N2–C3	1.283(2)	N5–C6	1.269(2)
C3–N4	1.370(2)	N1–C6	1.415(2)

Table 2 Least-squares plane

Orthonormal equation of plane 1	8.8049 (31) x + 0.8076 (171) y – 6.4637 (82) z = 7.3787 (162)			
Atom	N2	C3	N5	C6
	–0.0213 (8)	0.0217 (8)	–0.0219 (8)	0.0214 (8)

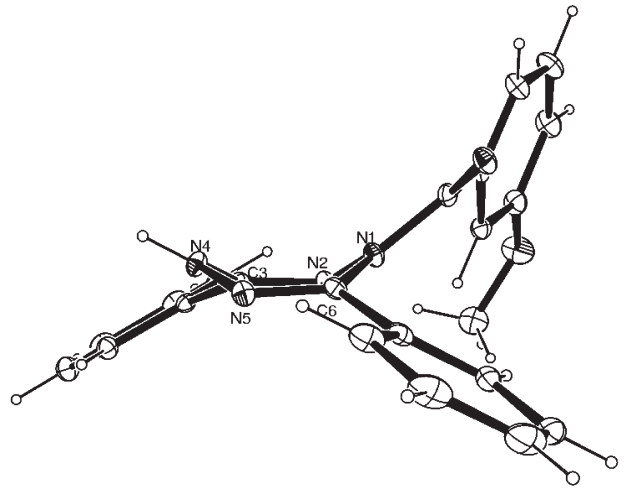

Fig. 2 A boat conformation of compound **3**, shown with 10% probability displacement ellipsoids.

between plane **1** and the three phenyl rings of the C1/C2/C4/C5/C7/C8, C9/C10/C11/C12/C13/C14 and C16/C17/C18/C19/C20/C21 plane are 29.18 (8), 30.67 (10) and 69.24 (9) °, respectively. The dihedral angle between the two phenyl rings of 3,6-positions is 59.10 (6) °.

As shown in the packing of compound **3** (Fig. 3), there exists one intramolecular hydrogen contact [C21–H21···N2] and weak intermolecular N—H···O and C—H···O hydrogen bonds (Table 3). Intramolecular and intermolecular interactions play a major role in stabilising the molecules in the unit cell.

Experimental

Melting points were determined on a X-4 melting point apparatus and uncorrected. IR spectra were taken on a Thermo Nicolet Avatar 370 FT-IR spectrophotometer (KBr pellets). H spectra were recorded on a Bruker Avance (500M) spectrometer. MS spectra were obtained on a Thermo Scientific ITQ 1100TM mass spectrometer.

1-(3-Methoxybenzoyl)-3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine (**3**): 3,6-Diphenyl-1,2(or 1,4)- dihydro-1,2,4,5-tetrazine (1.202g, 5.1 mmol), prepared according to the procedure of Rao *et al*.[8], and pyridine (1 mL) were dissolved in dichloromethane (40 mL) with stirring. 3-Methoxybenzoyl chloride (1.870 g, 11.0 mmol) and dichloromethane (20 mL) were added dropwise into the mixture at room temperature for 25 minutes. The mixture was stirred at room temperature for 10 h and at 32˚C for 9h. Then the solvent was removed *in vacuo* and the residue was washed with petroleum ether to afford the crude product. The crude product was purified by flash column chromatography on silica gel using petroleum ether/ethyl acetate (4:1, v/v) as eluent to afford compound **3** (1.133 g, 60.1%) as a yellow solid. A solution of the compound in ethanol was concentrated gradually at room temperature to afford yellow blocks which are suitable for X-ray diffraction, m.p. 162–164˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.84 (s, 3H, CH_3), 7.01 (d, J = 6.5 Hz, 1H, C_6H_4),7.32–7.72 (m, 13H, Ph and C_6H_4), 8.04 (s, H, NH). IR(KBr, cm^{-1}) ν: 3444, 3313, 1635, 1617, 1463, 1392, 1096, 1037, 1014, 968. MS (EI): *m/z*: 370 [*M*]$^+$. HRMS (EI): *m/z* [*M*]$^+$ Calcd for $C_{22}H_{18}N_4O_2$: 370.1430; found: 370.1426.

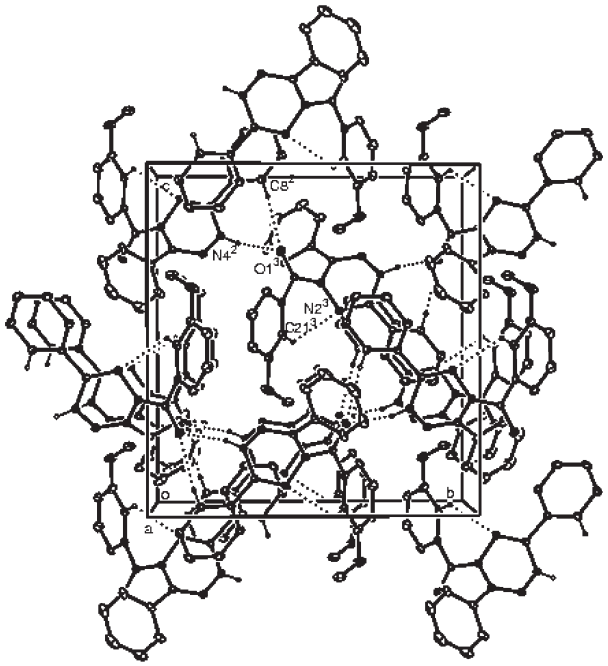

Fig. 3 A portion of the crystal packing of **3**. Hydrogen bonds are shown as dashed lines. H atoms not involved in hydrogen bonding were omitted for clarity.

Table 3 Hydrogen-bond geometry bond lengths(Å) and angles(°)

Donor–H···Acceptor	D–H	H···A	D···A	D–H···A
N4–H4···O1^i	0.86	2.55	2.970(2)	111.1
C8–H8···O1^i	0.93	2.49	3.376(2)	159.9
C21–H21···N2	0.93	2.40	2.867(2)	110.7

Symmetry code: (i) 2–x, y–1/2, 1/2–z.

Crystal data of **3**: A yellow block of dimensions 0.50 × 0.47 × 0.32 mm^3 was used for data collection with a Bruker SMART CCD area-detector diffractometer with graphite monochromated Mo *Kα* radiation (λ = 0.71073 Å). A summary of crystal data is presented in Table 4.

The structure was solved by direct method procedures as implemented in SHELXS97[13] program. The positions of all the non-hydrogen atoms were included in the full-matrix least-squares refinement using SHELXL97[14] program. H atoms were added at calculated positions and refined using a riding model. H atoms were given isotropic displacement parameters equal to 1.2 (or 1.5 for methyl H atoms) times the equivalent isotropic displacement parameters of their parent atoms, and C–H distances were set to 0.93 Å for phenyl H atoms, and 0.96 Å for methyl H atoms, while N-H distances were set to 0.86 Å.

Table 4 Crystal data and structure refinement

Chemical formula	$C_{22}H_{18}N_4O_2$
Colour/shape	Yellow/block
Formula weight	370.40
Temperature (K)	298(2)
Wavelength (Å)	0.71073
Crystal system	orthorhombic
Space group	$P\,2_12_12_1$
Unit cell dimensions	a = 9.8912(14) Å
	b = 13.426(2) Å
	c = 14.312(2) Å
Volume(Å^3)	1900.5(5)
Z	4
Density (calculated)(g cm^{-3})	1.295
Absorption coefficient (mm^{-1})	0.086
θ range for data collection(deg)	2.08–28.30
Limiting indices	–9/13, –17/17, –19/18
Reflections collected/unique	11487 / 4404 (R_{int} = 0.0238)
Absorption correction	Multi–scan
Max. and min. transmission	0.973, 0.958
Data/restraints/parameters	4404 / 0 / 254
Extinction coefficient	0.0096(17)
Goodness of fit on F^2	1.041
Final R indices [$I > 2\sigma(I)$]	R^1 = 0.0446, wR^2 = 0.1069
R indices (all data)	R^1 = 0.0535, wR^2 = 0.1116
Largest diff. peak and hole (e Å^{-3})	0.265, –0.195

Full crystallographic details have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 861589. Copies of available material can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or E-mail: deposit@ccdc.cam.ac.uk).

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