Synthesis and X-ray crystal studies of 6-(2-chlorophenyl)-3-methyl[1,2,4] triazolo[4,5-*b*][1,3,4]thiadiazole.

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The compound 6-(2-chlorophenyl)-3-methyl[1,2,4]triazolo[4,5-*b*][1,3,4]thiadiazole, was synthesised using different reagents and conditions, characterised by spectroscopic techniques and finally confirmed by X-ray crystal structure analysis. The title compound crystallises in monoclinic class under the space group $P2_1/c$ with cell parameters, *a*=10.6710 (6)Å, *b*=7.3660 (4)Å, *c*=14.3900 (8)Å, β=110.403 (3)°, *Z=2* and R_1= 0.0396 for 2715 reflections [$I>2\Sigma I$]. The structure exhibits inter-molecular hydrogen bonding.

Keywords: 6-(2-chlorophenyl)-3-methyl[1,2,4]triazolo[4,5-*b*][1,3,4]thiadiazole, pharmacological activity

Compounds of 1,2,4-triazole and 1,3,4-thiadiazole derivatives exhibit diverse pharmacological activities[1] such as fungicidal, insectidical, bactericidal, herbicidal, anti-tumor,[2] anti-inflammatory,[3] CNS stimulant properties.[4] They also find applications as dyes, lubricants and analytical reagents.[5]

We have synthesised the compound, 4-amino-3-ethyl-5-mecarpto[1,2,4]triazole **1** using a reported procedure.[6]

In continuation of our studies on the synthesis of condensed nitrogen and sulfur heterocycles,[7,8] we now report, an efficient and one-pot method for the synthesis of 6-(2-chlorophenyl)-3-methyl[1,2,4]triazolo[4,5-*b*][1,3,4]thiadiazole **2** by the condensation of 4-amino-3-methyl-5-mercapto[1,2,4]triazole **1** with 2-chlorobenzoic acid under different conditions including microwave irradiation in DMF solvent.

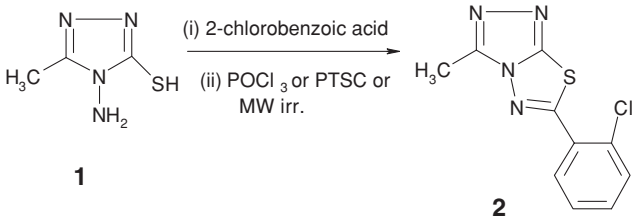
Condensation of 4-amino-3-methyl-5-mercapto[1,2,4]triazole **1** with 2-chlorobenzoic acid either in $POCl_3$ at reflux temperature for overnight or with *p*-toluene sulfonyl chloride in toluene for 12 h at 65–70 °C or microwave irradiation (kenstar) in DMF as a solvent for about 30–40 s at 60 power unit produced **2** with 65, 72 and 85% yield respectively (Scheme 1, Table 1).

The condensation reaction with $POCl_3$ as cyclising agent resulted in the lower yield of **2** than both of *p*-toluene sulfonyl chloride, a mild cyclising agent and microwave-assisted synthesis, which is a selective reaction at that irradiation.

ORTEP[9] drawing of the molecule **2** with thermal ellipsoids at 50% probability is shown in Fig. 1. The condensed triazolo-thiadiazole ring and the adjacent phenyl ring are co-planar with each other. The structure exhibits intermolecular bond of the type C–H----Cl (C_6–H_6...Cl_1; bond length: 3.7004(2)Å and bond angle: 164.43° with symmetry equivalent code *x*, $^1/_2 - y$ and $-\,^1/_2 + z$ respectively.)

Bond length: C2–Cl1: 1.7293(18)Å, C7–C8: 1.4847(18)Å, C8–S12: 1.7706(15)Å, C11–N10: 1.359(2)Å, N15–N14: 1.410(2)Å.

Bond angle: C7–C8–N9: 117.96(14)°, C8–S12–C11: 87.66(7)°, C11–N15–N14: 105.18(14)°, N9–N10–C13: 134.68(13)°.



Scheme 1

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Table 1 The different conditions and reagents used for the condensation reaction

Sample no.	Reagent	Condition	Yield/%
1	$POCl_3$	Reflux for overnight	65
2	PTSC	Toulene, 12 h, 65–70 °C	72
3	MW irradiation	DMF, 30 s, 60 W	85

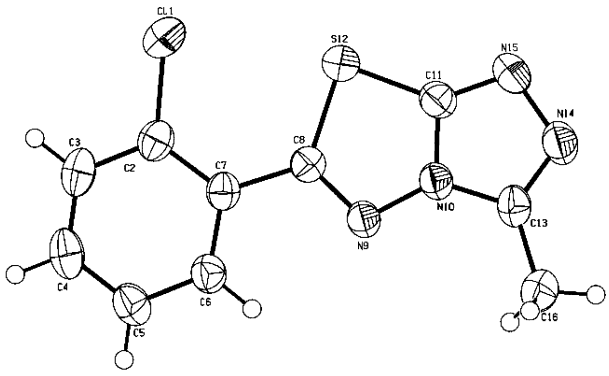

Fig. 1 ORTEP diagram of the molecule at 50% probability with some selected bond lengths and bond angles.

Experimental

Silica gel GF-254 was used for TLC. Melting point was recorded on a SEALCO-605 melting point apparatus and is uncorrected. IR spectra was recorded on a FT-IR 8000 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AMX-400 MHz, 100 MHz spectrometer respectively using $CDCl_3$ as solvent with TMS as internal standard. Elemental analysis was obtained on a Vario-EL instrument.

Synthesis of 6-(2-chlorophenyl)-3-methyl[1,2,4]triazolo[4,5-b] [1,3,4]thiadiazole (2): Method 1: A mixture of 4-amino-3-methyl-5-mercapto[1,2,4]triazole **1** (2.5 g, 0.0192 mol), 2-chlorobenzoic acid (3.30 g, 0.02112 mol) and $POCl_3$ (5 ml) were refluxed overnight. After completion of the reaction (benzene: ethyl acetate: 7.5:2.5 used for TLC), the reaction mixture was cooled and poured slowly, with stirring into ice water. The pH of the mass was adjusted to basic (pH=7.5-8.0) with NH_4OH solution and the resulting compound was extracted with ethyl acetate. The organic layer was washed with 10% $NaHCO_3$ solution to remove the unreacted 2-chlorobenzoic acid, dried (Na_2SO_4), filtered and the solvent was evaporated under vacuum. To the residue obtained, 3 volumes of hexane were added, stirred well and filtered at cold condition. A good quality single crystal was obtained from the slow evaporation technique using ethyl acetate as solvent. M.p.: 180 °C; IR (nujol): frequency 3110; 1235; 734; 1539 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 22 °C): δ 2.2–2.5 (s, 3H, –CH_3); 7.15–7.3 (m, 2H, Ar–H); 7.35 (d, 1H, Ar–H); 7.7 (d, 1H, Ar–H).^{13}C NMR (100 MHz, $CDCl_3$, 22 °C): δ 16.8, 158.3, 146.5, 164.6, 161.2, 129.6, 122.4, 130.12, 133,2, 135.3. Elemental analysis: C: 47.91, H. 2.81, N. 22.35, S. 12.79, found: C: 47.42, H. 2.71, N. 22.14, S. 12.92 %.

Method 2: The compound 4-amino-3-methyl-5-mercapto[1,2,4] triazole **1** (2.5 g, 0.0192 mol), 2-chorobenzoic acid (3.30 g, 0.02112 mol) and *p*-toluenesulfonyl chloride (3.638 g, 0.0192 mol) were added to toluene (5–8 ml) and stirred at 65–70 °C, 12 hours. After completion of the reaction, the solvent was evaporated under vacuum and the resulting compound was isolated as described in the earlier method.

Method 3: The compound 4-amino-3-methyl-5-mercapto[1,2,4] triazole **1** (2.5 g, 0.0192 mol) and 2-chlorobenzoic acid (3.30 g, 0.02112 mol) were dissolved in 6 ml of DMF and kept for 30–40 s in a microwave oven at 60% power. After completion of the reaction, the dark yellow reaction mass was poured into ice-cold water and worked up as described earlier.

Single crystal X-ray crystallography: A single crystal of size $0.2 \times 0.25 \times 0.2$ mm was chosen for single crystal X-ray diffraction studies. The measurements were made on a DIPLABO Image Plate diffractometer. The data were collected and processed using Denzo[10] data reduction program. The structure was solved by direct methods using SHELXS-97[11] and refined by full-matrix least squares method using SHELXL-97[12] program. Full Crystallographic details deposited at Cambridge Crystallographic Database Centre (CCDC No. 261782). Copies of the data can be obtained by free of charge, on application to CCDC, 12 Union road, Cambridge, CB2 IEZ, UK (fax: +44(0) 1223336033 or e-mail: deposit@ccdc.cam.ac.uk).

In summary, we developed one-pot synthesis and crystal structure of possible biologically active title compound **2,** by two-component condensations reaction with high yield.

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References

1 F. Kurtzer, A.R, Katritzky and A.J. Boulton (Eds.). *Advances in Heterocyclic Chemistry,*. vol. 5 Academic Press, New York, 1965, 165.
2 B. Shivarama Holla, K. Narayana Poojary, B. Sooryanarayana Rao and M.K.Shivananda *Eur. J. Med.,* 2002, **37**, 511.
3 K. Cooper and J. Steele, EP 329357 *Chem. Abstr*., 1990, **112**, 76957.
4 N.D. Heindel and J.R. Reid, *J. Heterocycl. Chem*., 1980, **17**, 1087.
5 Z.Y. Zhang and S Xiago-Wen, *Heterocycles*, 1998, **48** 561.
6 T. George, R. Tahilramani and D.A. Dabholkar *Ind. J. Chem.*, 1969, **5B** 5959.
7 B. Prabhuswamy and S.Y. Ambekar, *Synth. Commun.*, 1999, **29**, 3487.
8 Basappa, M. Sathish Kumar, S. Nanjundaswamy, M. Mahendra, B.S. Vishwanath, J. Shashidhara Prasad and K.S. Rangappa *Bioorg. Med. Chem. Lett.,* 2004, **14**, 3679-3681.
9 C.K. Johnson, ORTEP-II, A Fortran Thermal-Ellipsoid Plot Program, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, USA, 1976.
10 Z. Otwinowski and W. Minor, *Meth. Enzymol.*, 1997, **276**, 307-326.
11 Sheldrick G M, SHELXS-97. Program for Crystal Structure Solution, University of Göttingen, Germany, 1997.
12 Sheldrick G M, SHELXL-97, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 1997.