

# Synthesis of 2,6-diaminopyridine substituted $\alpha$ -oxoketene $S,N$ -acetals: Crystal structure and hydrogen bonding interactions

OKRAM MUKHERJEE SINGH<sup>a,\*</sup>, LAISHRAM RONIBALA DEVI<sup>a</sup> and NEELADRI DAS<sup>b,\*</sup>

<sup>a</sup>Department of Chemistry, Manipur University, Canchipur 795 003, India

<sup>b</sup>Department of Chemistry, Indian Institute of Technology Patna, Patna 800 013, India

e-mail: ok\_mukherjee@yahoo.co.in; neeladri@iitp.ac.in

MS received 15 August 2012; revised 19 March 2013; accepted 4 July 2013

**Abstract.** Polyaza  $\alpha$ -oxoketene  $S,N$ -acetals can exist as either enamino or imino tautomeric forms. Based on the spectroscopic data and structural analysis of one of the  $S,N$ -acetals, the stereochemistry was unambiguously assigned as an *all-E*-configuration. The crystal structure confirms the enamino structure and shows extensive use of C-H...X (X = N, O, and S) weak hydrogen bonding interactions, thereby generating a 3-dimensional network in solid state.

**Keywords.** Polyaza; heterocycles; conformation; synthesis; crystal structure.

## 1. Introduction

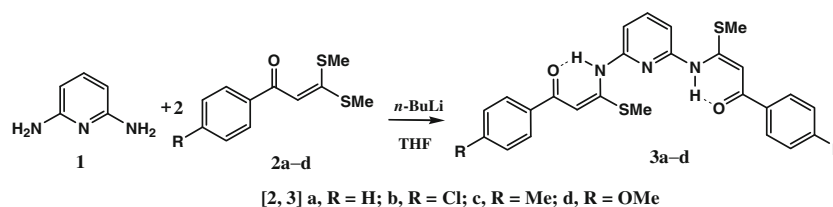
Polyaza heterocyclic ligands have been used extensively in many self-assembly reactions involving metal ions and the synthetic strategies for these compounds have been a central theme in supramolecular chemistry.<sup>1</sup> However, synthetic methods for the preparation of polyaza heterocyclic ligands are extremely limited.<sup>2</sup> The preparation of 2,4-disubstituted polypyrimidines and related derivatives by reaction of  $\alpha$ -oxoketene dithioacetals with different carboxamides in benzene or benzene-DMF solution in the presence of NaH, has been reported by Potts *et al.*<sup>3</sup> Lehn *et al.* have described the synthesis of new aza heterocyclic structures containing 1,3-pyrimidine units using a procedure which involved Pd(II)-catalysed cross coupling reactions.<sup>4</sup> In this prospect we are reporting here with a convenient synthesis of polyaza pyridine substituted ligands commonly known as  $\alpha$ -oxoketene  $S,N$ -acetals and explored the interesting conformational features exhibited by this class of compounds.

The synthetic utility of  $\alpha$ -oxoketene  $S,N$ -acetals as versatile intermediates in organic synthesis has been well-recognized, particularly, as 1,3-bielectrophilic C<sub>3</sub> synthons.<sup>5</sup> They have been widely applied in the synthesis of substituted and fused aromatic structural frameworks, using annulation strategies.<sup>6</sup> In this report, we describe the synthesis of new polyaza  $\alpha$ -oxoketene  $S,N$ -acetals **3a–d** (scheme 1). These compounds were prepared in good yields by using our earlier reported method,<sup>7</sup> which involves the thiomethyl displacement reactions of  $\alpha$ -oxoketene dithioacetals with lithiated 2,6-diaminopyridine.

## 2. Experimental

### 2.1 Materials and measurements

All NMR spectra were recorded on Varian Unity 300 or Varian XL-300 spectrometers. <sup>1</sup>H chemical shifts are reported relative to the residual protons of deuterated



**Scheme 1.** Synthesis of  $S,N$ -acetals (**3a–d**).

\*For correspondence

dimethylsulphoxide (D<sub>6</sub>)DMSO ( $\delta = 2.50$  ppm) or relative to the residual protons of CDCl<sub>3</sub> ( $\delta = 7.27$  ppm). IR spectra were recorded on a Shimadzu IR-408 spectrometer in KBr pellets. M.p. were determined on a Veego (Capillary method) apparatus and are uncorrected. The FAB mass spectra were recorded on a JEOL SX 102/DA-6000 Mass Spectrometer/Data System. Elemental analyses were carried out on a Perkin Elmer 240B elemental analyzer.

## 2.2 General procedure for the synthesis of 2,6-(lithio-diamino) pyridine and its reaction with $\alpha$ -oxoketene dithioacetals: preparation of *S,N*-acetals **3a–d**

*n*-Butyllithium (20 mmol) was added to a stirred solution of 2,6-diaminopyridine (10 mmol) in dry tetrahydrofuran (THF) (20 mL) under a dry and inert atmosphere over a period of 20 min at room temperature (rt) (25°C). Stirring was continued for 30 min at the same temperature. Appearance of a reddish brown colour indicated that lithiation had occurred. This was followed by addition of an oxoketene *S,S*-acetal (10 mmol) soln in dry THF (25 mL) and stirring the reaction mixture for 2–3 h at rt. The progress of the reaction was monitored by thin-layer chromatography. The reaction was worked up by pouring the mixture into saturated aq. NH<sub>4</sub>Cl (100 mL), and extracting the organic portion with CHCl<sub>3</sub> (2  $\times$  50 mL). The combined extracts were washed with H<sub>2</sub>O (2  $\times$  50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to yield a crude product, which was purified by either crystallization from CHCl<sub>3</sub>/hexane solution or by passage through a column of silica gel with AcOEt/hexane (1:9) as eluent (**3a–d**).

## 2.3 Spectroscopic and analytical data

**2.3a 2,6-Bis[*N,N'*-1-(methylthio)-3-phenyl-3-oxoprop-2-en-1-yl]aminopyridine (**3a**):** Yellow crystals. Yield: 1.46 g (65%). M.p. 145–148°C. IR(KBr): 3385, 3307, 3193, 3055, 1625, 1548. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 2.50 (*s*, 6H), 6.01 (*s*, 2H), 6.87 (*d*, *J* = 6, 2H) 7.44–7.64 (*m*, 7H), 7.92–7.94 (*m*, 4H), 14.38 (*s*, 2H). <sup>13</sup>C-NMR (75.5 MHz, CDCl<sub>3</sub>): 16.1, 91.3, 109.4, 127.2, 128.4, 131.2, 139.7, 140.1, 150.4, 165.7, 186.4. MS: *m/z* = 461 (M<sup>+</sup>, 100%). Anal. calc. for C<sub>25</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub> (461.12): C 65.05, H 5.02, N 9.10; found: C 65.08, H 5.01, N, 9.12.

**2.3b 2,6-Bis[*N,N'*-1-(methylthio)-3-(4-chlorophenyl)-3-oxoprop-2-en-1-yl]aminopyridine (**3b**):** Yellow crystals. Yield: 1.55 g (60%). M.p. 167–169°C. IR (KBr): 3285, 3193, 3060, 1716, 1598. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):

2.51 (*s*, 6H), 5.95 (*s*, 2H), 6.88 (*d*, *J* = 6, 2H), 7.43 (*d*, *J* = 6.3, 4H), 7.63–7.67 (*m*, 1H), 7.86 (*d*, *J* = 6.3, 4H), 14.36 (*s*, 2H). <sup>13</sup>C-NMR (75.5 MHz, CDCl<sub>3</sub>): 16.1, 90.9, 109.7, 128.5, 128.6, 137.4, 138.4, 139.8, 150.3, 166.2, 184.9. MS: *m/z* 529 (M<sup>+</sup>, 80%). Anal. calc. for C<sub>25</sub>H<sub>21</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub> (529.05): C 56.60, H 3.99, N 7.92; found: C 56.62, H 4.01, N 7.89.

**2.3c 2,6-Bis[*N,N'*-1-(methylthio)-3-(4-methylphenyl)-3-oxoprop-2-en-1-yl]aminopyridine (**3c**):** Yellow crystals. Yield: 1.78 g (75%). M.p. 135–138°C. IR (KBr): 3485, 3299, 3184, 3026, 1627, 1556. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): 2.34 (*s*, 6H), 2.42 (*s*, 6H), 5.92 (*s*, 2H), 6.77 (*d*, *J* = 6, 2H), 7.18 (*d*, *J* = 6, 4H), 7.52–7.56 (*m*, 1H), 7.75 (*d*, *J* = 6, 4H), 14.28 (*s*, 2H). <sup>13</sup>C-NMR (75.5 MHz, CDCl<sub>3</sub>): 16.1, 21.5, 91.3, 109.3, 127.3, 129.1, 137.4, 139.7, 141.8, 150.5, 165.3, 186.3. MS *m/z* 489 (M<sup>+</sup>, 80%). Anal. calc. for C<sub>27</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub> (489.15): C 66.23, H 5.56, N 8.58; found: C 66.21, H 5.55, N 8.61.

**2.3d 2,6-Bis[*N,N'*-1-(methylthio)-3-(4-methoxyphenyl)-3-oxoprop-2-en-1-yl]aminopyridine (**3d**):** Yellow crystals. Yield: 2.03 g (80%). M.p. 150–152°C. IR (KBr): 3480, 3290, 3181, 3026, 1625, 1550. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): 2.50 (*s*, 6H), 3.88 (*s*, 6H), 5.98 (*s*, 2H), 6.84 (*d*, *J* = 6, 2H), 6.96 (*d*, *J* = 6.6, 4H), 7.60–7.63 (*m*, 1H), 7.91(*d*, *J* = 6.6, 4H), 14.32 (*s*, 2H). <sup>13</sup>C-NMR (75.5 MHz, CDCl<sub>3</sub>): 16.1, 55.4, 90.9, 109.1, 113.6, 129.1, 132.63, 139.6, 150.3, 166.2, 164.7, 185.5. MS *m/z* 521 (M<sup>+</sup>, 100%). Anal. calc. for C<sub>27</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub> (521.14): C 62.17, H 5.22, N 8.06; found: C 62.15, H 5.23, N 8.09.

## 2.4 X-ray crystallography

**2.4a X-ray data collection, structure solution, and refinement:** Data for **3b** were collected at room temperature with a *Nonius Kappa CCD* diffractometer equipped with MoK $\alpha$  radiation ( $\lambda = 0.71073$  Å). Data were collected at 150(1) K with an oscillation range of 1°/frame and an exposure time of 20 s/frame.<sup>8</sup> The structure was solved by a combination of direct methods and heavy atom using SIR 97.<sup>9</sup> All of the non-hydrogen atoms were refined with anisotropic displacement coefficients. Hydrogen atoms were located and refined isotropically using SHELXL97.<sup>10</sup> The weighting scheme employed was  $w = 1/[\sigma^2(F_o^2) + (0.0340P)^2 + 0.8974P]$  where  $P = (F_o^2 + 2F_c^2)/3$ . The refinement converged to R1 = 0.0387, wR2 = 0.0850, and S = 1.033 for 4367 reflections with I > (I), and R1 = 0.0570,

$wR2 = 0.0948$ , and  $S = 1.033$  for 5559 unique reflections and 392 parameters.<sup>1</sup> The maximum  $\Delta/\sigma$  in the final cycle of the least-squares was 0.002, and the residual peaks on the final difference-Fourier map ranged from  $-0.351$  to  $0.319 e/\text{\AA}^3$ . All calculations and molecular graphics were done using the WinGX package.<sup>11,12</sup>

**2.4b Crystallographic description of 3b:**  $C_{25}H_{21}Cl_2N_3O_2S_2$ ;  $M_r = 530.47$ ; crystal dimension (mm)  $0.33 \times 0.20 \times 0.13$ ; crystal system = triclinic, space group  $P\bar{1}$ ;  $a = 7.9092(2) \text{\AA}$ ,  $b = 8.6131(2) \text{\AA}$ ,  $c = 19.6517(5) \text{\AA}$ ;  $\alpha = 87.7854(11)^\circ$ ,  $\beta = 89.8452(11)^\circ$ ,  $\gamma = 65.6010(13)^\circ$ ,  $V = 1218.13(5) \text{\AA}^3$ ;  $Z = 2$ ;  $\rho_{\text{cal}} = 1.446 \text{ Mg/m}^3$ ;  $\text{MoK}\alpha$  radiation ( $\lambda = 0.71073 \text{\AA}$ ),  $\nu(\text{mm}^{-1}) = 0.467$ ;  $F(000) = 548$ ; reflection collected/unique = 10499/5559; refinement method full-matrix least-squares on  $F^2$ ; final  $R$  indices [ $I > 2\sigma_1$ ]  $R1 = 0.0387$ ,  $wR2 = 0.0850$ ,  $R$ indices (all data)  $R1 = 0.0570$ ,  $wR2 = 0.0948$ ; goodness of fit on  $F^2 = 1.033$ .

### 3. Results and discussion

It is known that polarized ketene *S,N*-acetals<sup>13</sup> exist in tautomeric equilibrium between enamino **A** and imino **B** forms (scheme 2). The presence of intramolecular

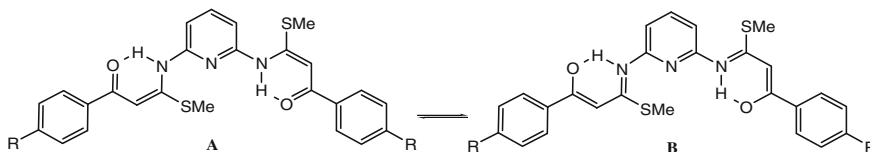
hydrogen-bonded NH is obvious from the stretching vibration band at  $3300 \text{ cm}^{-1}$ . The merging of the band characteristic of the carbonyl stretching vibration with bands around and below  $1600 \text{ cm}^{-1}$  suggests that the carbonyl group is in conjugation and it acts as a hydrogen-bond acceptor.  $^1\text{H}$  NMR spectra of these *S,N*-acetals in  $\text{CDCl}_3$  showed NH protons far downfield near  $\delta$ <sup>13,14</sup>. This indicates that the participation of the NH protons in strong hydrogen bond with the O-atom of the carbonyl group (scheme 2). Thus, on the basis of IR and NMR data, it can be concluded that ketene *S,N*-acetals **3** exist in the enamino tautomeric form.

However, single-crystal X-ray diffraction led to interesting conclusions on the unambiguously identification of their possible tautomeric conformations.

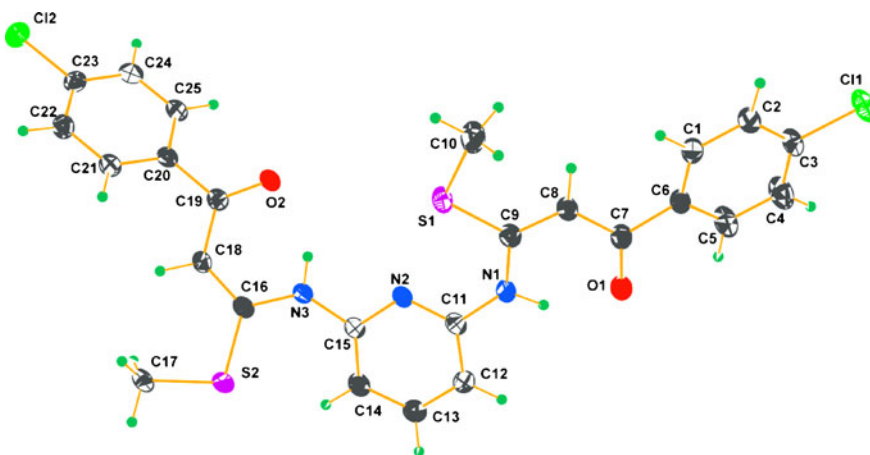
However, single crystal X-ray diffraction technique confirmed the existence of one tautomer over the other. X-ray data show a slightly distorted planar tautomeric structure **A**, depicted in scheme 2. ORTEP representation of **3b** is shown in figure 1.

X-ray quality single crystals of **3b** were obtained by evaporation of a  $\text{CH}_2\text{Cl}_2$  solution. The crystals of the compound belong to triclinic crystal system with  $P\bar{1}$  space group.

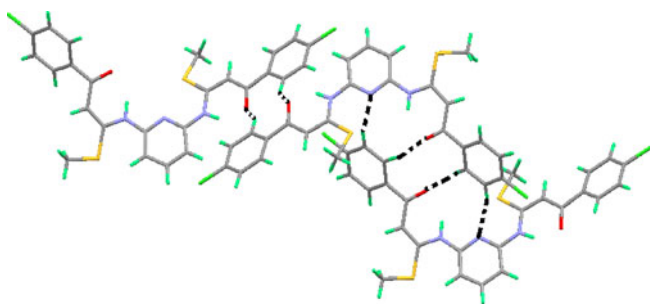
Intramolecular hydrogen bonding involving carbonyl oxygen and enamino nitrogen (as predicted by IR



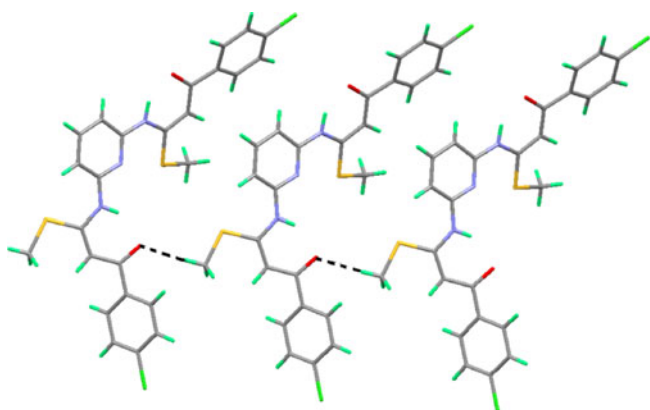
**Scheme 2.** Probable tautomers of  $\alpha$ -oxoketene *S,N*-acetals **3**.



**Figure 1.** An ORTEP view of **3b** with the atom labelling scheme.



**Figure 2.** CH...O and CH...N interactions in **3b** that accounts for association of each molecule of **3b** with two of its neighbouring molecules. CH...X interactions (X = N, O) indicated by dashed line in black colour.

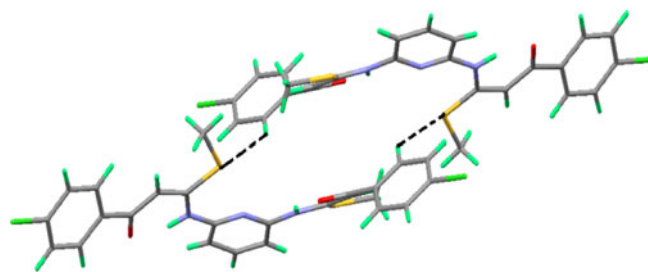


**Figure 3.** H-bonding interaction between the neighbouring molecules.

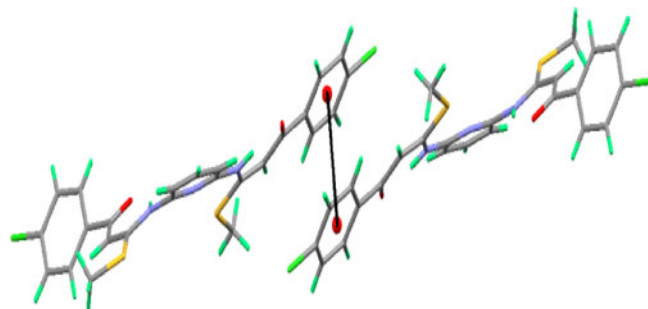
spectroscopy) was observed on either side of the pyridine ring. In this case, the average value for  $D$  ( $N \cdots O$ ) is 2.61 Å and that for  $d$  ( $H \cdots O$ ) is 1.84 Å.

Interesting feature of the solid state structure of **3b** is the existence of multiple  $C-H \cdots X$  ( $X = N, O,$  and  $S$ ) interactions which are basically weak hydrogen bonds having more van der Waals character than electrostatic nature (observed in 'normal' hydrogen bonds such as  $N-H \cdots O$  or  $O-H \cdots O$ ).<sup>10</sup> As shown in figure 2, the carbonyl oxygen atoms on either side of the pyridine moiety participate in self-complementary  $CH \cdots O$  interactions:  $C(3)-H(3C) \cdots O(1^i)$ ,  $O(1) \cdots H(3C^i)-C(3^i)$  on one side and  $C(19)-H(19C) \cdots O(2^{ii})$ ,  $O(2) \cdots H(19C^{ii})-C(19^{ii})$  on the other side. In addition, the nitrogen atom of the pyridine ring participates in  $CH \cdots N$  interaction as  $N(2) \cdots H(20C^{ii})-C(20^{ii})$ . This accounts for association of each molecule of **3b** with two of its neighbouring molecules by  $C-H \cdots O$  and  $C-H \cdots N$  weak hydrogen bonds.

Additionally, the molecule are interconnected through  $C-H \cdots O$  hydrogen bonds. This accounts for association of each molecule of **3b** with two additional neighboring molecules (figure 3).



**Figure 4.** Complementary  $CH \cdots S$  interactions in **3b** that accounts for association of each molecule of **3b** with another neighboring molecule.



**Figure 5.** Diagram showing  $\pi-\pi$  interactions in **3b**.

The values of  $C \cdots O/C \cdots N$  and  $H \cdots O/H \cdots N$  distances observed in **3b** are within the respective range of 3.00–4.00 Å (in case of  $D$ ) and 2.00–3.00 Å (in case of  $d$ ).

A very weak  $X-H \cdots A$  interaction has been observed in the solid state in case of **3b** in the form of a  $C-H \cdots S$  contact. There is a complementary set of two such interactions in the form of  $C(23)-H(23C) \cdots S(1)$  and  $S(1) \cdots H(23C^{iv})-C(23^{iv})$ . In this case, values of  $C \cdots S$  and  $H \cdots S$  distances observed are 3.660(2) Å and 2.93(2) Å, respectively. The two neighbouring molecules of **3b**, interacting with each other by virtue of two 'hydrogen bridges' involving  $C-H \cdots S$  interaction/short contact, is shown in figure 4. The term 'hydrogen bridges' was reintroduced by Desiraju in 2002 in order to extend the concept of hydrogen bonds to include weak  $X-H \cdots A$  interactions having van der Waals character.<sup>14</sup> This type of weaker  $C-H \cdots S$  hydrogen bonding interaction has been also reported by Chaudhuri and co-workers.<sup>15</sup>

In addition to the weak  $C-H \cdots X$  ( $X = N, O, S$ ) interactions mentioned above, each molecule of **3b** interacts with another neighbouring molecule by  $\pi-\pi$  interactions (figure 5). The distance between the centroids of the two interacting  $\pi$ -rings is 3.932(1) Å.

#### 4. Conclusion

In summary, a facile synthetic methodology for the preparation of pyridine substituted  $\alpha$ -oxoketene *S,N*-acetals from readily accessible  $\alpha$ -oxoketene *S,S*-acetals has been described. The presence of several electrophilic and nucleophilic reactive sites in *S,N*-acetals could be utilized in regioselective ring-closure strategies to yield interesting and novel molecules containing pyridine and other heterocycles. The *all-E*-configuration of the pyridine substituted  $\alpha$ -oxoketene *S,N*-acetals was unambiguously assigned using a combination of FT-IR,  $^1\text{H}$  NMR and single-crystal X-ray diffraction data. Crystal structure analysis of *S,N*-acetal **3b** indicates the presence of multiple C–H...X (X = N, O, and S) interactions. Together with a  $\pi$ – $\pi$  stacking interaction, these weak H-bonding contacts generate a 3-dimensional network in solid state. Further studies on the application of these functionalized *S,N*-acetals for synthesis of polyaza heterocycles and as building blocks for the construction of macro-molecular metal–organic frameworks are currently in progress.

#### Supplementary information

CCDC-749446 (3b) contains the supplementary crystallographic data for this article. These data can be obtained free of charge from *The Cambridge Crystallographic Data Centre* via [http://www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

#### Acknowledgements

Financial supports from the Council of Scientific and Industrial Research (CSIR), India (project No. 01(2387)/10/EMR-II) and the Department of Science and Technology (DST), India (project No. SR/S1/OC-31/2009) are gratefully acknowledged. We thank Atta M Arif (University of Utah, USA) for crystal structure analysis. We also thank (SAIF), (CDRI), Lucknow and SAIF, NEHU, Shillong for the spectral recordings.

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