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REGULAR ARTICLE

A novel reaction of 2-phenacyl mercaptoimidazole with acetic anhydride: formation of an imidazothiazole with loss of a phenyl group

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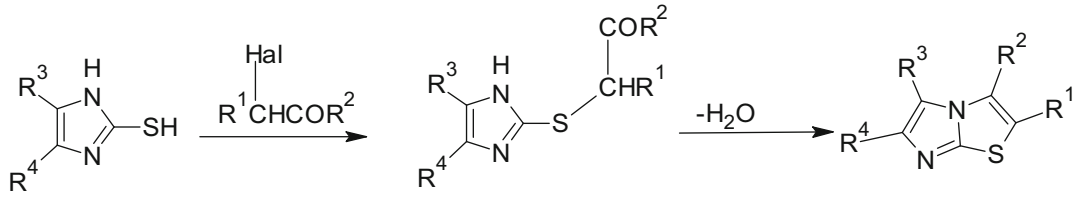
Abstract. Attempted cyclodehydration of phenacyl mercaptoimidazole hydrobromide with acetic anhydride gave an abnormal product lacking the phenyl group. The molecular structure is confirmed using X-ray crystal structure studies. Phenacyl mercaptobenzimidazole hydrobromide behaved similarly. Analysis of crystal structure revealed an intermolecular S…Br chalcogen bonding interaction.

Keywords. Phenacyl mercaptoimidazole; acetic anhydride; imidazo[2,1-b] thiazole; Single crystal.

1. Introduction

The imidazothiaoles and their precursors, thioacetophenones are frequently being used as a structural unit in the tailoring of pharmaceutical compounds with a wide range of activities.[1] Approaches for the synthesis imidazothiazoles *via* heteroaryl thioacetophenones are represented by many examples.[2–4] Mazur *et. al.*,[5] reported that the reaction of 2-mercaptoimidazole and its 4(5)-aryl-and 4,5-diaryl substituted derivatives with α-halogenoketones gives a number of alkyl-, acyl-, and aryl-substituted imidazo[2,1-b]thiazoles. They also reported that when 2-mercaptoimidazole (1) was boiled with aliphatic α-halogenoketones in ethanol or butanol in the absence of alkali, imidazo[2,1-b]thiazoles (3) are formed whereas the reaction of 2-mercaptoimidazole with aromatic halogenketones under similar condition stops at the stage of 2-imdazolylthioacetophenones (2). In the same literature, it was also reported that 2-imidazolylthioacetophenones cyclize to form aryl-substitute-dimidazo[2,1-b]thiazoles only under the action of strong



1 (R^3, R^4=H) **2** **3**

R^1=H, Ac: R^2=Alk, Ar: R^3=H, Ar: R^4=H, Ar

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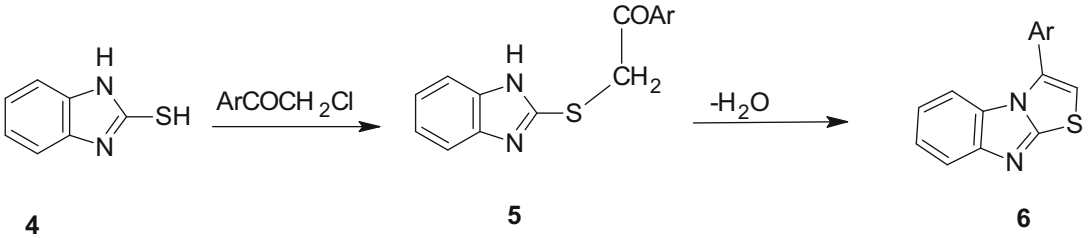
water abstracting reagents such as phosphorus oxychloride.

R^1 = H, Ac: R^2 = Alk, Ar: R^3 = H, Ar: R^4 = H, Ar

Abd EI-Wareth A. O. Sarhan *et. al.*,[6] reported the reaction of 2-mercaptobenzimidazole (4) with α-chloroaromatic ketones gave 2-benzimidazolylthioacetophenones (5) which on cyclization gave thiazolo[3,2-a]benzimidazoles (6).



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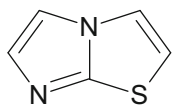
Thiazolo [2,1b] imidazole ring system (7) has been an attractive scaffold for medicinal chemistry to mine for biological activity.



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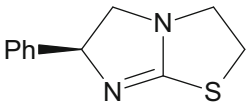


8 (levamisole)

The most illustrious molecule sporting this architecture is the drug levamisole (8), a phenyl tetrahydro derivative.[7] Levamisole (8) is an approved antiparasitic drug but is also known for its immunomodulating properties. Reportedly it has also antidepressant properties. A recent review by Leoni *et al.*,[8] on (7) along with contributions of their own groups over the years touches upon compounds having the ring system (7).

In this paper, we report a novel reaction of 2-phenacyl mercaptoimidazole with acetic anhydride that results in an unexpected imidazothiazole with the loss of a phenyl group in the product. In addition to the possible reaction mechanism, we also describe crystal structure analysis of the product and an unusual S…Br intermolecular chalcogen bonding motif.

2. Experimental

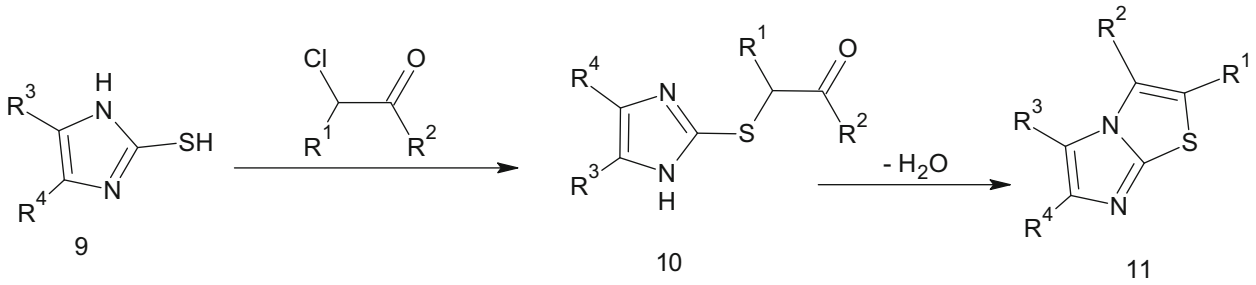
Melting points of the compounds were recorded by an open capillary method and are uncorrected. ^{1}H NMR spectra were recorded (in DMSO-d_6/$CDCl_3$) on a 400MHz NMR spectrometer using TMS as an internal standard. Mass spectra were recorded on Agilent mass spectrometer operating at 70ev. Progress of the reactions and the purity of the products were monitored by TLC. Appropriate solvent systems were used as eluents.

2.1 *1-(3-methylimidazo[2,1-b][1,3]thiazol-2-yl)ethanonehydrobromide (14)*

A mixture of 2-imidazolylthioacetophenone hydrobromide (**12**) (5.0 g, 16.7 mmol) and acetic anhydride 50 mL was heated to reflux for two hours. After the completion of the reaction, acetic anhydride was distilled off completely. To the residue, diethyl ether was added and the resulting solid was collected by filtration and dried (4.14 g, 95%. yield). M.p. 276–279 °C. ^{1}H NMR (400 MHz, DMSO-D_6): δ 8.27 (d, J = 1.87 Hz, 1H, imidazole), 7.77(d, J = 1.99 Hz, 1H, imidazole), 2.84 (s, 3H, acetyl), 2.63 (s, 3H, methyl); ^{13}C NMR (100.6 MHz, DMSO-d6); δ 191.39, 145.49, 136.22, 130.07, 127.18, 114.80, 29.35, 13.36; mass spectrum: MF $C_8H_8N_2OS$.HBr, calculated m/z 261.22, observed m/z 180.9 $(m+1)^+$ corresponding to the free base.

2.2 *1-(3-methyl[1,3]thiazolo[3,2-a]benzimidazol-2-yl)ethanone (18)*

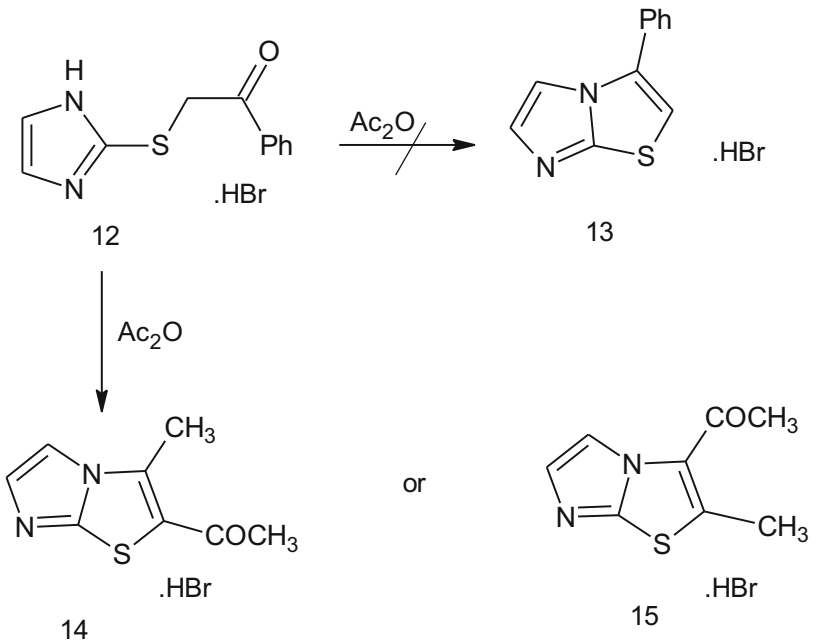
A mixture of 2-phenacylmercapto benzimidazole hydrobromide (**17**) (5.0 g, 14.3 mmol) and acetic anhydride 50 mL was heated to reflux for two hours. After the completion of the reaction, acetic anhydride was distilled off completely. To the residue obtained diethylether was added and the resulting solid was collected by filtration, and dried (2.47g, 75%, yield), M.p. 125–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, 1H, J = 7.24 Hz, benzimidazole), 7.81 (d, 1H, J = 8.12Hz, benzimidazole), 7.43 (t, 1H, J = 7.56Hz, benzimidazole), 7.30 (t, 1H, J = 7.76Hz, benzimidazole), 3.14 (s, 3H, acetyl), 2.57 (s, 3H, methyl); mass spectrum: MF $C_{12}H_{10}N_2OS$, calculated m/z 230.28, observed m/z 231 $(m+1)^+$.



Scheme 1. Synthesis of imidazo[2,1-b] thiazole derivatives.

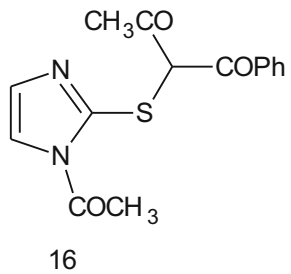
2.3 *Crystal structure experimental*

A suitable crystal of (**14**) was selected and mounted on a Xcalibur, Eos, Nova diffractometer. The structure was solved with the structure solution program SHELXS and the refinement package SHELXL[9] using Olex2[10] CCDC 1950502 contain the supplementary crystallographic data for this paper.

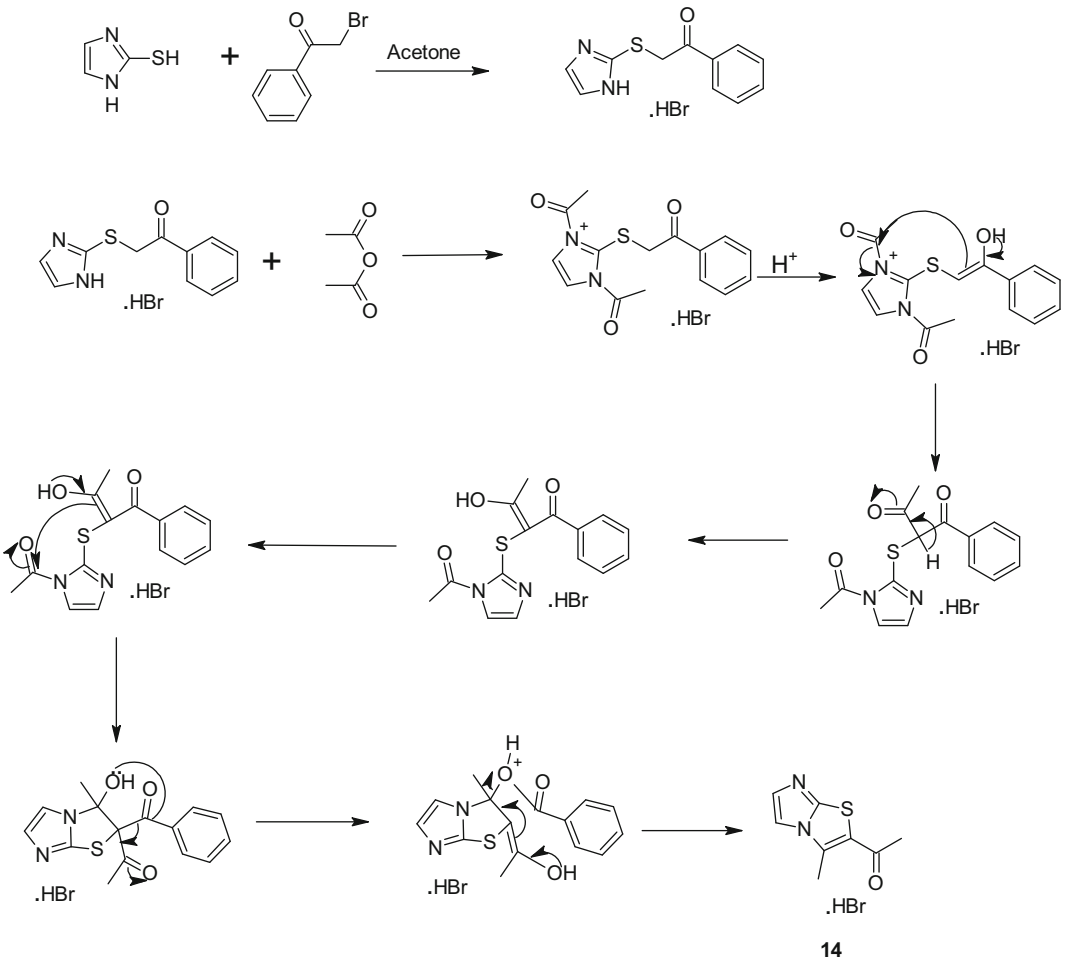


Single crystal X-Ray studies identified the novel structure as (14).

We wish to offer a speculative pathway (Scheme 3) for its formation involving the bis-acetyl derivative (16) as a likely intermediate.



Scheme 2. Synthesis of 1-(3-methylimidazo[2,1-*b*][1,3]thiazol-2-yl)ethanone hydrobromide (14).



Scheme 3. Speculative pathway for the formation compound 14.

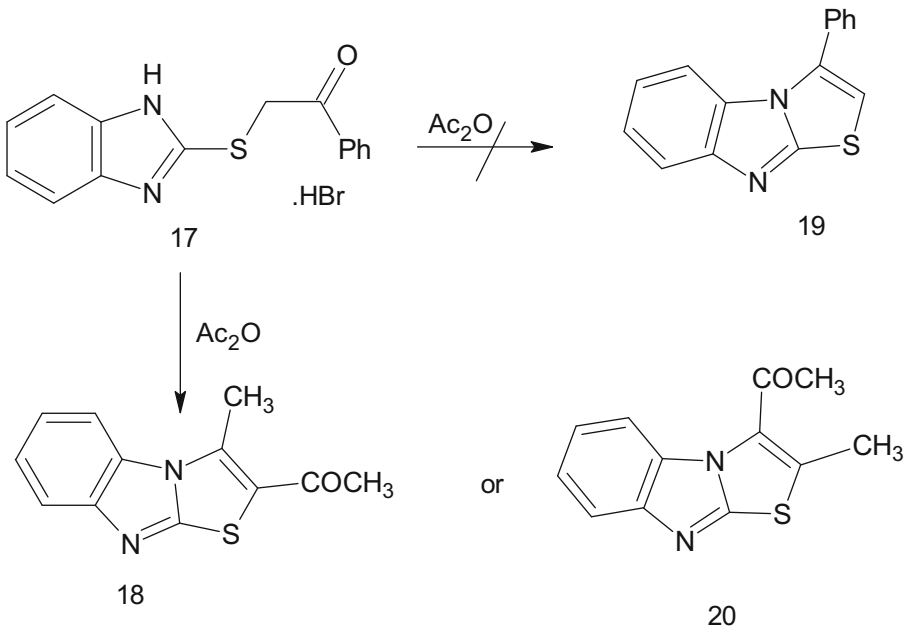
3. Result and Discussion

3.1 *Chemistry*

A classical synthesis of imidazo[2,1-b] thiazole derivatives starts with 2-mercaptoimidazoles (9) and alkylation with α-haloketones to afford (10) which are cyclodehydrated to (11). The dehydration is generally brought about using water abstracting agents like phosphorous oxychloride (Scheme 1).

Impelled by curiosity, we wanted to try out acetic anhydride for dehydration. Accordingly, we synthesized 2-phenacyl mercaptoimidazole hydrobromide (12) from 2-mercaptoimidazole and phenacyl bromide[3] and subjected it to react with acetic anhydride at 90 °C. The reagent was distilled off and the product isolated by addition of ether. The crystalline product obtained in very high yield surprisingly was not the HBr salt of known 2-phenylimidazo[2,1-*b*][1,3]thiazole (13). The ^{1}H NMR spectrum showed no aryl protons at all other than signals due to C=C–CH_3 and $COCH_3$ in addition to imidazole protons. The mass spectrum showed a molecular weight of 181 mass units in the positive mode. These data allowed us to speculate that the structure of the novel unexpected product could be (14) or (15) Scheme 2. Detailed ^{13}C spectral studies were not helpful in providing a choice.

The selective cleavage of the benzoyl group (which leaves as benzoic acid) over the acetyl group is seen in the above mechanism. The benzoyl and acetyl groups are sterically close to each other and the bulkier group benzoyl may leave better than acetyl group. Limited studies of this unusual reaction seem to indicate it to be restricted in scope. The reaction of propionic anhydride with (12) gave a mixture of unidentified products while trifluoroacetic anhydride gave only (13). The action of acetic anhydride on the free base of



Scheme 4. Synthesis of 1-(3-methyl[1,3]thiazolo[3,2-a]benzimidazol-2-yl)ethanone 18.

(12) gave a mixture of known (13) and novel (14) as their bases (Scheme 4).

On the other hand, the reaction of acetic anhydride with 2-phenacylmercapto benzimidazole hydrobromide[6] (17) gave a product (18) similar to (14) in good yield, lacking phenyl protons in ^{1}H NMR, ruling out the formation of (19), but showing CO and CH_3 groups; structure (20) is not excluded. It is likely that because of the weaker basicity of the aniline nitrogens in benzimidazole (18) compared imidazole the product is the base as shown and not the HBr salt.

3.2 *Crystal structure analysis*

In order to confirm the molecular structure of the product (14), single-crystal X-ray diffraction was performed. The analysis of the data confirmed the structure of (8). The crystal structure showed 2 molecules of (14) with bromide anions in the asymmetric unit. An ORTEP showing the asymmetric unit is given in Figure 1a. The crystallographic data table is given below (Table 1).

3.2a *Unusual S…Br chalcogen bonding interactions in the crystal structure*: In recent years there is an increased interest in unusual intermolecular interactions such as halogen bonding and chalcogen bonding, which are essentially weak electrostatic interactions between halogen/chalcogen atoms such as I, Br, Cl or Te, Se, S with electronegative atoms such as O, N, F, Cl, etc.[11] These weak interactions form supramolecular motifs like hydrogen bonds. Chalcogen bonding[12] has gained special attention for their ability to control molecular conformations (*via* intramolecular chalcogen bonding,[13] and specific supramolecular ring motifs. In the crystal structure of (14), we find similar chalcogen bonding motif with S…Br interactions, in addition to hydrogen bonds. Given the sum of van der Waals radii of S and Br is 3.65 Å, the S…Br distances of 3.23 Å and 3.19 Å observed in the crystal structure of (8) indeed represent short chalcogen bonding interactions (Figure 1b). The linear Br….S-C angle close to 180° further satisfies the geometric criteria for such chalcogen interactions.

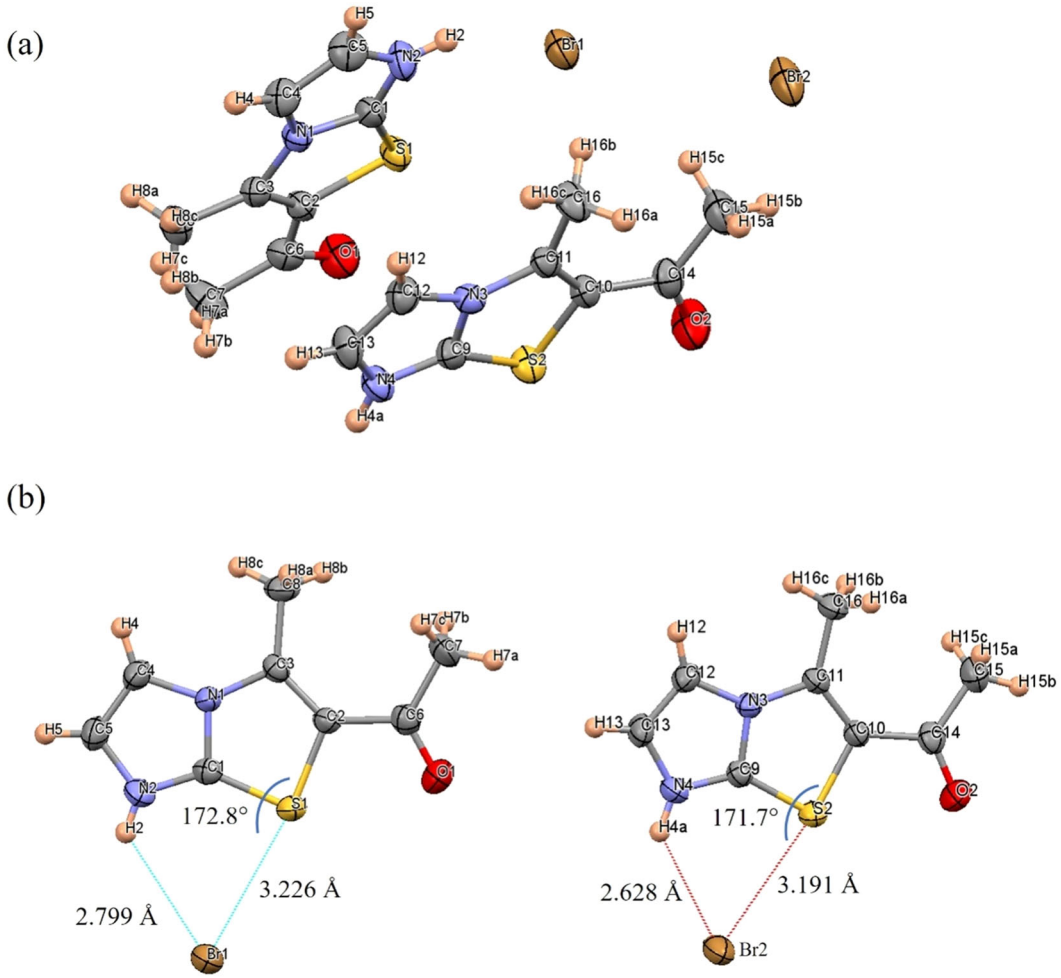


Figure 1. **a** ORTEP of (14) with 50% probability ellipsoids with two molecules in the asymmetric unit; **b** S…Br intermolecular interaction motif observed in the crystal structure.

4. Conclusions

The cyclization reaction of 2-phenacylmercaptoimidazole hydrobromide (12), carried out using acetic anhydride, afforded an unexpected imidazothiazole (14) lacking a phenyl ring. Single crystal X-ray studies confirmed the molecular structure of the product. The crystal structure also revealed a short S…Br chalcogen bonding intermolecular interactions. Further confirming the generality of the reaction, a similar reaction was carried out with phenacylmercaptobenzimidazole (17) to afford (18).

Table 1. Crystal data and structure refinement for (14).

Empirical formula	$C_8H_9N_4OSBr$
Formula weight	261.13
Temperature/K	100
Crystal system	Monoclinic
Space group	$P2_1/n$
a/Å	15.5548(9)
b/Å	7.7188(3)
c/Å	17.7074(13)
α/°	90
β/°	114.484(8)
γ/°	90
Volume/Å^3	1934.8(2)
Z	8
ρ_{calc}g/cm^3	1.985
μ/mm^{-1}	4.42
F(000)	1152.0
Crystal size/mm^3	0.21 × 0.16 × 0.13
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.056 to 65.886
Index ranges	$-22 \leq h \leq 23$, $-11 \leq k \leq 11$, $-26 \leq l \leq 26$
Reflections collected	32191
Independent reflections	6683 [R_{int} = 0.0834, R_{sigma} = 0.1186]
Data/restraints/parameters	6683/0/247
Goodness-of-fit on F^2	0.775
Final R indexes [I ≥ 2σ (I)]	R_1 = 0.0352, wR_2 = 0.0594
Final R indexes [all data]	R_1 = 0.1149, wR_2 = 0.0662
Largest diff. peak/hole/e Å^{-3}	0.40/− 0.64

Supplementary Information (SI)

Supplementary figures 1-17 are available at www.ias.ac.in/chemsci.

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