SYNTHESES OF *PERHYDRO*-1,3,4-THIADIAZIN-5-ONES AND 3-ARYLAMINOTHIAZOLIDIN-4-ONES BY THE REGIOSELECTIVE CYCLOCONDENSATION OF 2-SULFANYLALKANOIC ACIDS OR THEIR SILYL ESTERS WITH METHYL AND ARYL HYDRAZONES

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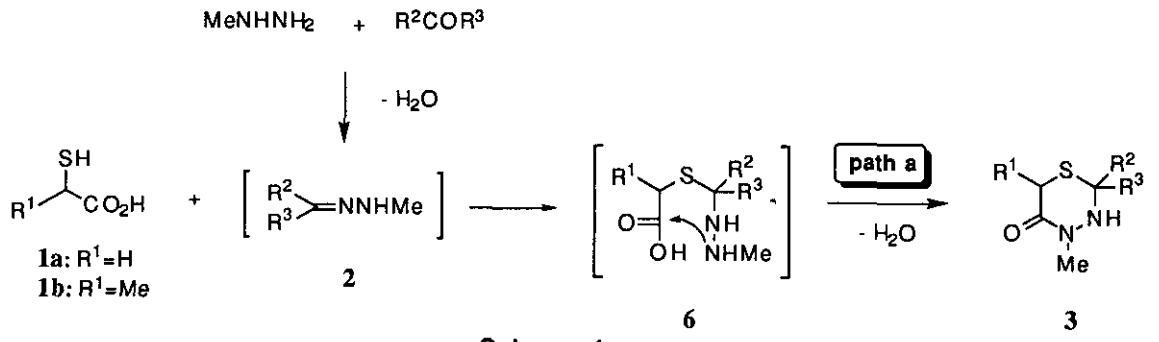
Abstract - *Perhydro*-1,3,4-thiadiazin-5-ones and 3-arylaminothiazolidin-4-ones were prepared by the highly regioselective cyclocondensation of 2-sulfanylalkanoic acids with methyl- and arylhydrazones, respectively. A similar reaction using trimethylsilyl 2-sulfanylalkanoates in the place of the acids proceeded under milder conditions with tetrabutylammonium fluoride catalyst.

The cyclocondensation reactions are recognized as worthwhile synthetic methods for preparing heterocyclic sulfur- and nitrogen-containing compounds.[1] Several cyclocondensation reactions of five-membered thiazoles, benzothiazoles and six-membered thiadiazole are representative. During our continuing synthetic studies on *S*, *N*-containing heterocycles such as thiazoles,[2] benzothiazoles,[3] benzothiadiazoles,[4] thiadiazoles,[2] and mercaptoindoles,[2] we reported the fairly stereoselective synthesis of platelet activating factor (anti-PAF) thiazolidin-4-ones using 2-sulfanylalkanoic acids with arylmethyleneamines.[5]

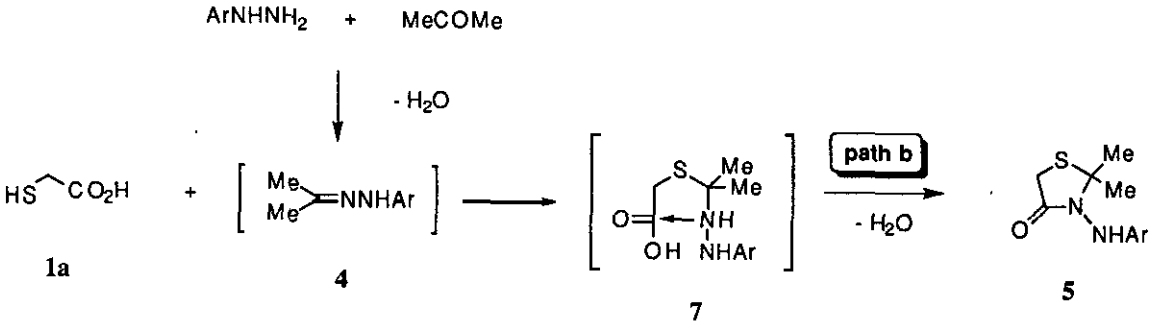
Recently, we have developed a highly stereoselective synthesis of anti-PAF thiazolidin-4-ones using the silyl derivatives of 2-sulfanylalkanoic acids in the place of 2-sulfanylalkanoic acids.[6] This cyclocondensation is effectively catalyzed by metal alkoxides [Ti(O-*i*-Pr)4, Ti(O-*i*-Bu)4, and Al(O-*s*-Bu)3],

piperidine, and a catalytic amount (2 mol%) of tetrabutylammonium fluoride (TBAF). These results prompted us to investigate analogous reactions using hydrazones as the isoster replacement for arylmethyleneamines. We now describe the cyclocondensation of sulfanylacetic acid (**1a**) or 2-sulfanylpropionic acid (**1b**) with isosteric hydrazones (**2**) and (**4**) as the key building block with the azeotropic removal of water in toluene in a one-pot manner (Method A) and, more effectively, the TBAF catalyzed cyclocondensation using the trimethylsilyl (TMS) esters (**8a**) and (**8b**) (Method B) with hydrazones (**2**) and (**4**). We used hydrazones (**2**) and (**4**) being generated *in situ* from the corresponding hydrazines and ketones (or trimethylacetaldehyde) in the case of Method A, whereas freshly prepared hydrazones beforehand were used in the case of Method B.

Methods A involves either of the two highly regioselective pathways **a** and **b**: (1) The use of *N*-methylhydrazones (**2**) gave a new analog of six-membered *perhydro*-1,3,4-thiadiazin-5-ones (**3**) (Scheme 1 and Table 1); and (2) in contrast, the use of *N*-arylhydrazones (**4**) gave a regioisomer of **3**, a five-membered 3-anilinothiazolidin-4-ones (**5**) (Scheme 2 and Table 2).[7,8]



Scheme 1



Scheme 2

A plausible reaction mechanism exemplified for method A is described as follows. The sulfanyl group of acid (**1**) first attacked hydrazone (**2**) and (**4**) to give intermediates (**6**) and (**7**), followed by the regioselective intramolecular cyclization to afford **3** and **5**, respectively. This mechanism is considered to be similar to that of the previous synthesis of thiazolidin-4-ones,[5] however, it is noted that the present reactions proceed in two alternative ways depending on the structures of the hydrazones employed. The difference in the nucleophilicity of adjacent nitrogens of the intermediate (**6**) and (**7**) is thought to cause a profound factor in dictating the regioselectivity; the external nitrogen of **6** and the internal nitrogen of **7** should be more reactive ones (Scheme 1). Matsubara and his co-workers reported a similar cyclocondensation using the methyl phenylhydrazonomethylacetate.[9]

The structures of **3** and **5** were elucidated based on the following spectroscopic and analytical results. In the case of **3a**, for example, mass spectroscopy (M^+, 188) and elementary analyses supported the expected molecular formula $C_8H_{16}N_2OS$ (Table 1). The ^1H nmr spectrum of **3a** exhibited a broad doublet at δ 4.87 due to the proton on *N*(3) coupled with C(2)H, which disappeared by the addition of deuterium oxide.

Table 1. Yields and Analytical Data of *Perhydo*-1,3,4-thiadiazin-5-ones (3a-3a).

Compd (R^1, R^2, R^3)	Yield / %	mp / °C	Formula	Calcd / Found / %			
				C	H	N	S
3a (H, *t*-Bu, H)	23	amorphous[a]	$C_8H_{16}N_2OS$	51.10 51.04	8.57 8.55	14.88 14 78	17.0 16.7
3b (H, Me, Me)	53	100-102[b]	$C_6H_{12}N_2OS$	44.98 44.81	7.55 7.41	17.48 17.43	20.0 19.7
3c (H, Et, Et)	68	55-58[c]	$C_8H_{16}N_2OS$	51.10 51.06	8.57 8.52	14.88 14 85	17.0 16.7
3d (H, -$(CH_2)_4$-)	50	87-89[b]	$C_8H_{14}N_2OS$	51.59 51.61	7.58 7.48	15.04 14.98	17.2 17.2
3e (H, -$(CH_2)_5$-)	63	133-136[b]	$C_9H_{16}N_2OS$	53.97 53.90	8.05 8.03	13.98 13.91	16.0 15.9
3f (Me, Me, Me)	36	67-69[a]	$C_7H_{14}N_2OS$	48.25 48.22	8.10 8.04	16.07 16.04	18.4 18.1

[a] Purified with silica gel column chromatography using chloroform. [b] Recrystallized from diisopropyl ether. [c] Recrystallized from ethyl acetate.

Table 2. Yields and Analytical Data of 3-Arylaminothiazolidin-4-ones (5a-5c).

Compd (Ar)	Yield / %	mp / °C	Formula	Calcd / Found / %			
				C	H	N	S
5a (Ph)	20	86-87[a]	$C_{11}H_{14}N_2OS$	59.45 59.35	6.35 6.20	12.60 12.58	14.4 14.4
5b (4-Me-Ph)	21	140-144[a]	$C_{12}H_{16}N_2OS$	61.00 61.05	6.83 6.89	11.86 11.92	13.6 13.7
5c (3-Cl-Ph)	22	amorphous[b]	$C_{11}H_{13}ClN_2OS$	51.46 51.36	5.10 5.08	10.91 10.78	12.5 12.5

[a] Purified with silica gel column chromatography using chloroform followed by recrystallization from 2-propanol. [b] Purified with silica gel column chromatography using chloroform.

Finally, X-ray analysis unambiguously confirmed the structure of **3a**. Accordingly, the possible formation of the isomeric five-membered heterocycle, 2-*tert*-butyl-5,5-dimethyl-3-methylaminothiazolidin-4-one was ruled out. The structure of other *perhydro*-1,3,4-thiadiazin-5-ones (**3b-f**) was similarly determined (Table 1). On the other hand, ^1H nmr spectrum of 3-anilinothiazolidin-4-one (**5a**) showed a broad singlet at δ 6.00 (relatively lower field compared with **3a**) due to the proton on the anilino group. The structure of **5a** was also unambiguously determined by X-ray analysis. Other analogs (**5b**) and (**5c**) were listed in Table 2.

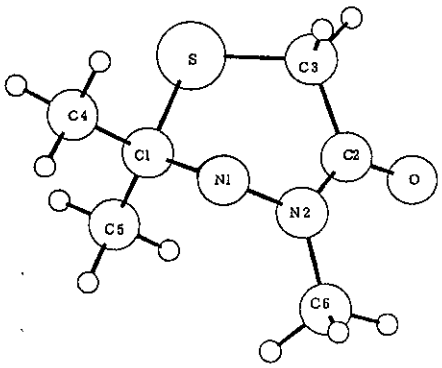


Figure 1 X-Ray structure of 2,2,4-trimethyl-*perhydro*-1,3,4-thiadiazin-5-one (**3b**).

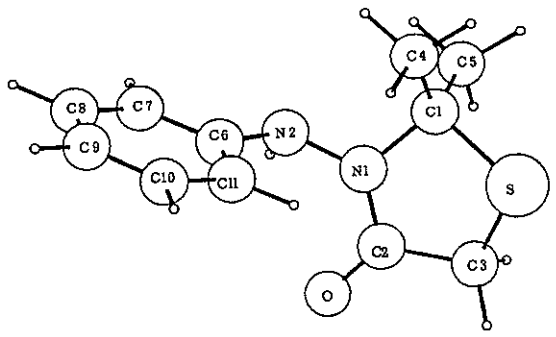
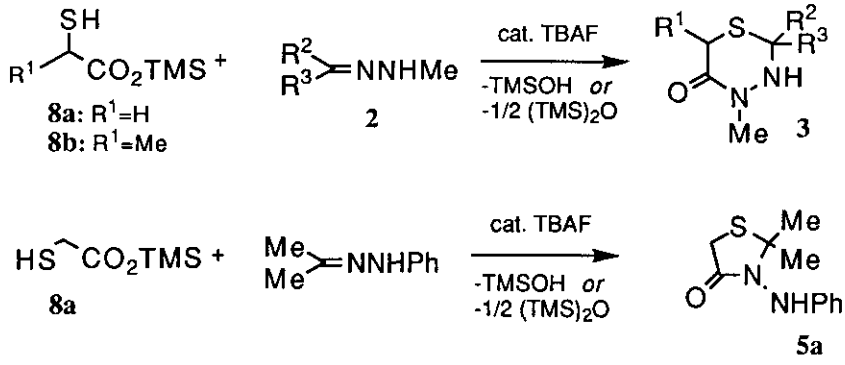


Figure 2 X-Ray structure of 2,2-dimethyl-3-phenylamino-1,3-thiazolidin-4-one (**5a**); Molecules A.

Next, we examined the cyclocondensation of the silyl derivatives of sulfanylacetic acid (**1a**) with hydrazones (**2**) and (**4**; Ar=Ph), since these analogous reactions of **1a** with arylmethyleneamines for the

synthesis of thiazolidin-4-ones smoothly proceeded.[6] Several attempts using trimethylsilyl sulfanylalkanoates (**8a**) and (**8b**) with the addition of catalyst such as metal alkoxides [Ti(O-*i*-Pr)4, Ti(O-*i*-Bu)4, and Al(O-*s*-Bu)3] and piperidine gave unfruitful results. However, use of TBAF as the catalyst effectively promoted this reaction under mild conditions (room temperature) as shown in Table 3 and Scheme 3. In the absence of the TBAF catalyst, the cyclocondensation only slightly proceeded. Dichloromethane was a better solvent than toluene. In the case of the synthesis of **3a**, Method B provided higher yields than Method A. The use of trimethylsilyl trimethylsilylthioacetate (**9**) in the place of **8a** with hydrazone (**2**) resulted in a lower yield (7%); such decrease in yield was not observed in the case of using arylmethyleneamines.[6]



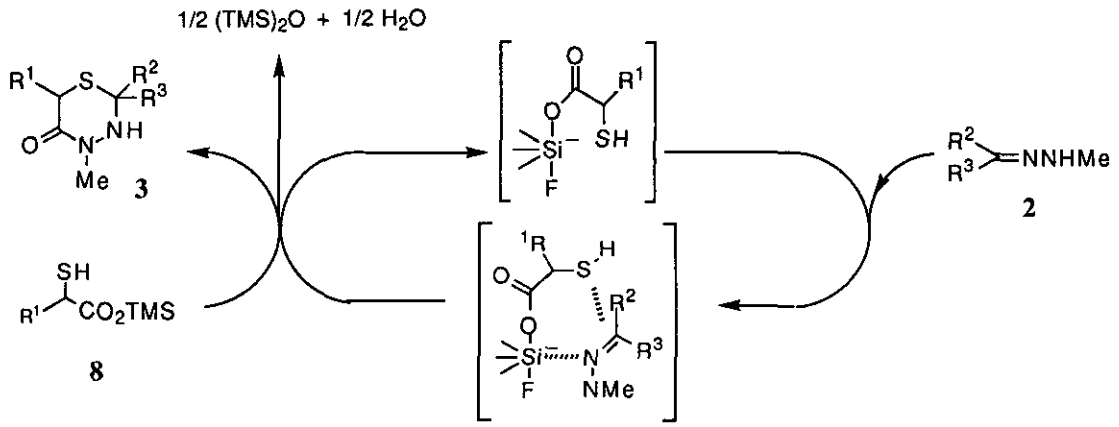
Scheme 3

Table 3. TBAF Catalyzed Cyclocondensation Reactions of TMS Esters (8a and 8b) with Hydrazones (2).[a]

Entry	TMS ester (8)	Hydrazone (2)		Solvent	Product	Yield / %
	R^1	R^2	R^3			
1	H	*t*-Bu	H	Toluene	**3a**	23
2	H	*t*-Bu	H	CH_2Cl_2	**3a**	52
3	H	-$(CH_2)_5$-		Toluene	**3e**	50
4	H	-$(CH_2)_5$-		CH_2Cl_2	**3e**	67
5	Me	Me	Me	CH_2Cl_2	**3f**	33

[a] The reactions were carried out at room temperature for 10 h. Molar ratio of **8** : **2** : TBAF = 1: 1: 0.02.

A plausible catalytic cycle is proposed as follows. The TBAF catalyst first attacks the silyl ester (**8**) to form the reactive pentavalent fluorosilicate. The silicate catch an hydrazone (**2**) to produces the *perhydro*-1,3,4-thiadiazin-5-ones (**3**) with eliminating 1/2(TMS)$_2$O and H_2O. The fluoride anion is transferred from the fluorosilicate to the remaining silyl ester to release the silyl ether (**8**) and to reform the acyloxy(fluoro)-silicate.



In summary, *perhydro*-1,3,4-thiadiazin-5-ones (**3**) and 3-arylaminothiazolidin-4-ones (**5**) were obtained by the regioselective cyclocondensation of 2–sulfanylalkanoic acids with methyl- and arylhydrazones, respectively. In addition, a similar reaction using trimethylsilyl 2–sulfanylalkanoates in the place of the acids proceeded under milder conditions. This is an example of reactions utilizing the effective activation of the silicon-heteroatom bond.[10]

EXPERIMENTAL

All melting points were determined on a hot stage microscope apparatus (Yanagimoto) and are uncorrected. ^{1}H Nmr spectra were recorded on a Hitachi R-24 B or JEOL EX-90 (90MHz) spectrometer using TMS as an internal standard in $CDCl_3$. Mass spectra were obtained on a Hitachi M-80 spectrometer.

General Procedure of Method A

To a stirred solution of carbonyl compound (20 mmol) in toluene (10 ml) was added methylhydrazine or arylhydrazine (20 mmol) at room temperature. After half an hour, 2-sulfanylalkanoic acid **1** (20 mmol) was added to the mixture. The resultant solution was heated under reflux with azeotropic removal of water.

After cooling the mixture, sat. aqueous $NaHCO_3$ solution (20 ml) was added to the mixture, which was extracted with chloroform (50 ml x 2). The organic phase was washed with water, brine, dried (Na_2SO_4), concentrated. The crude residue was purified by silica gel column chromatography (chloroform and/or hexane/ethyl acetate = 5:1) to give the corresponding *perhydro*-1,3,4-thiadiazin-5-ones (**3**) or 3-anilinothiazolidin-4-one (**5**).

2-(*t*-Butyl)-4-methyl-*perhydro*-1,3,4-thiadiazin-5-one (3a).

^{1}H Nmr δ=1.02 (9H, s), 3.03 (1H, d, *Jgem* = 15 Hz), 3.04 (3H, s), 3.45 (1H, d, *Jgem* = 15 Hz), 4.25 (1H, d, *J* = 12 Hz), 4.87 (1H, br d, *J* = 12 Hz); ms *m/z* 188 (M^+, 12).

2,2,4-Trimethyl-*perhydro*-1,3,4-thiadiazin-5-one (3b).

^{1}H Nmr δ=1.52 (6H, s), 3.13 (3H, s), 3.29 (2H, s), 4.98 (1H, br s); ms *m/z* 160 (M^+, 100).

2,2-Diethyl-4-methyl-*perhydro*-1,3,4-thiadiazin-5-one (3c).

^{1}H Nmr δ=0.93 (3H, t, *J* = 7 Hz), 1.50-2.00 (4H, m), 3.07 (3H, s), 3.21 (2H, s), 5.05 (1H, br s); ms *m/z* 188 (M^+, 100).

***Perhydro*-1,3,4-thiadiazin-5-one-2-spiro-1'-cyclopentane (3d).**

^{1}H Nmr δ=1.40-2.20 (8H, m), 3.08 (3H, s), 3.28 (2H, s), 4.47 (1H, br s); ms *m/z* 186 (M^+, 100).

***Perhydro*-1,3,4-thiadiazin-5-one-2-spiro-1'-cyclohexane (3e).**

^{1}H Nmr δ=1.00-2.10 (10H, m), 3.13 (3H, s), 3.25 (2H, s), 4.53 (1H, br s); ms *m/z* 200 (M^+, 100).

2,2,4,5-Tetramethyl-*perhydro*-1,3,4-thiadiazin-5-one (3f).

^{1}H Nmr δ=1.35 (3H, d, *J* = 7 Hz), 1.46 (3H, s), 1.56 (3H, s), 3.16 (3H, s), 3.67 (1H, q, *J* = 7 Hz), 4.79 (1H, br s); ms *m/z* 174 (M^+, 100).

3-Anilinothiazolidin-4-one (5a).

^{1}H Nmr δ=1.55 (6H, s), 3.55 (2H, s), 6.40-6.00 (1H, br s), 6.60-7.35 (5H, m); ms *m/z* 222 (M^+, 100).

3-(*p*-Tolylamino)thiazolidin-4-one (5b).

^{1}H Nmr δ=1.55 (6H, s), 2.55 (3H, s), 3.55 (2H, s), 6.05-6.35 (1H, br s), 6.50-7.20 (4H, m); ms *m/z* 236 (M^+, 100).

3-(3-Chlorophenylamino)thiazolidin-4-one (5c).

^{1}H Nmr δ=1.55 (6H, s), 3.55 (2H, s), 6.10-6.30 (1H, br s), 6.55-7.35 (4H, m); ms *m/z* 256 (M^+, 100).

Trimethylsilyl Sulfanylacetate (8a).

A mixture of sulfanylacetatic acid (3.00 g, 32.5 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (5.78 g, 32.5 mmol) was stirred at room temperature for 2 h. Evaporation and distillation of the residue gave 3.17 g (59%) of **8a**. Colorless liquid; bp 65-68 °C/18 mmHg; ir (film) 2970, 1725, 1065 cm^{-1}; ^1H nmr ($CDCl_3$) δ=0.30 (9H, s), 2.00 (1H, d, *J* = 9.0 Hz), 3.30 (2H, d, *J* = 9.0 Hz). *Anal.* Calcd for $C_5H_{12}O_2SSi$: C, 36.55; H, 7.36. Found: C, 36.78; H, 7.65.

Trimethylsilyl 2-Sulfanylpropionate (8b) and **Trimethylsilyl 2-(Trimethylsilylthio)propionate (9).** These silyl compounds are prepared by the reported procedure.[6]

A Typical Procedure of Method B (TBAF-Catalyzed Cyclocondensation).

To a stirred solution of **8a** (164 mg, 1.0 mmol) in CH_2Cl_2 (2.0 ml) was added successively TBAF (1M-THF solution, 20 μl) and cyclohexanone methylhydrazone (126 mg, 1.0 mmol) at room temperature with stirring and allowed to stand at room temperature for 10 h. Then the reaction mixture was quenched by water and extracted with CH_2Cl_2; the organic phase was then washed with water, brine, dried (Na_2SO_4), and concentrated. The crude oil obtained was purified by silica gel column chromatography (hexane/ethyl acetate = 3:1) to give *perhydro*-1,3,4-thiadiazin-5-one-2-spiro-1'-cyclohexane (**3e**; 134 mg) in 67% yield. In a similar manner, 3-anilinothiazolidin-4-one (**5a**) was obtained from **8a** and acetone phenylhydrazone in 21 % yield.

X-Ray Crystallography of 2,2,4-Trimethyl-*Perhydro*-1,3,4-thiadiazin-5-one (3b).

A single crystal of **3b** was obtained by recrystallization from 2-propanol-ether. Intensity data were collected on an Enraf-Nonius CAD4 diffractometer using graphite-monochromated CuKα radiation (λ=1.5418 Å). Crystal data are as follows: $C_6H_{12}N_2OS$, *M* 160.24, monoclinic, space group P2/c, a = 12.378(2) Å, b = 6.379(1) Å, c = 10.458(2) Å, β = 105.36(1)°, V = 796.3 $Å^3$, Z = 4, F(000) = 344, D_X = 1.336 gcm^{-3}, μ(CuKα) = 7.037 cm^{-1}. A total of 1681 reflections with 1°<θ<70° were collected by ω-2θ scan technique. The structure was solved by direct methods using MITHRIL and refined by full-matrix least-squares. Non-hydrogen atoms were refined with anisotropic thermal parameters. The final R and Rw factors were 0.066 and 0.075, respectively, for 430 observed reflections [I>3σ (I)]. All calculations were

carried out on a micro VAX II using SDP package. Bond distances, bond angles, torsional angles, final positional parameters, anisotropic thermal parameters are available on any current masthead page.

X-Ray Crystallography of 2,2-Dimethyl-3-phenylamino-1,3-thiazolidin-4-one (5a).

A single crystal of **5a** was obtained by recrystallization from 2-propanol. Intensity data were collected similarly with the case of **3b**. Crystal data are as follows: $C_{11}H_{14}N_2OS$, *M* 222.33, monoclinic, space group $P2_1/n$, a = 21.266(2) Å, b = 6.658(1) Å, c = 17.015(2) Å, β = 103.94(1)°, V = 2338.2 Å^3, Z = 8, F(000) = 94.4, D_X = 1.263 gcm^{-3}, μ(CuKα) = 7.037 cm^{-1}. A total of 4766 reflections with 1°<θ<70° were collected by ω-2θ scan technique. The structure was solved by direct methods using MULTAN and refined by full-matrix least-squares. Non-hydrogen atoms were refined with anisotropic thermal parameters. The final R and Rw factors were 0.046 and 0.064, respectively, for 2880 observed reflections [I>3σ (I)]. All calculations were carried out on a micro VAX II using SDP package. Bond distances, bond angles, torsional angles, final positional parameters, anisotropic thermal parameters are available on any current masthead page. There were two crystallographically independent molecules A and B.

ACKNOWLEDGMENT

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