Formation of a benzothiazine via the reaction of *ortho*-halo sulfoximines with copper salts

Aswinkumar Garimallaprabhakaran, Xuechuan Hong[1] and Michael Harmata*

Department of Chemistry, University of Missouri-Columbia, Columbia, Missouri 65211, USA
E-mail: harmatam@missouri.edu

DOI: http://dx.doi.org/10.3998/ark.5550190.0013.611

Abstract

The formation of an interesting benzothiazine from the reaction of *S*-(*o*-halophenyl)-*S*-methyl sulfoximines in the presence of copper salts is reported. The overall yield is 27% over three steps from commercially available 2-halothioanisoles in the best case. The product's structure was confirmed by spectroscopic and X-ray crystal analysis. The benzothiazine shows fluorescent properties.

Keywords: Benzothiazine, sulfoximine, copper catalysis

Introduction

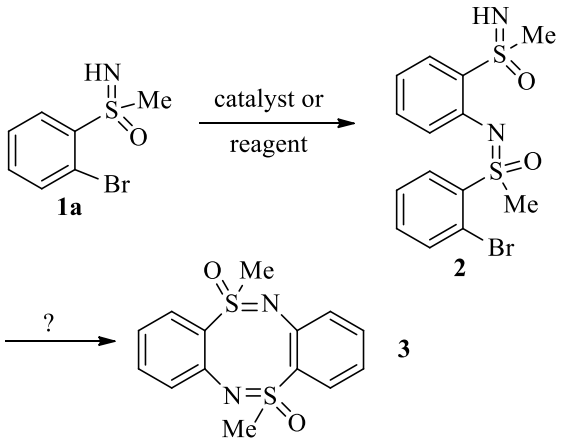
In the course of our continuing work on the preparation of benzothiazines,[2] we have pursued various studies on the *N*-arylation of sulfoximines.[3] The Bolm group has made significant contributions to this area and was the first to establish a palladium-catalyzed N-arylation of sulfoximines.[4] They have also shown that *N*-arylation can be catalyzed or mediated by copper, iron and nickel species and that a variety of electrophilic species besides aryl bromides can be used in the process.[5] More recently, boronic acids[6] and a C-H activation[7] process have been introduced for this *N*-arylation.

Results and Discussion

We became interested in the *N*-arylation of sulfoximine **1a** with itself, a process that might result in the formation of the cyclic bis-sulfoximine **3**, a potentially useful chiral ligand and a progenitor of what could be a family of ligands (Scheme 1).

When treated with a palladium catalyst under conditions that would result in *N*-arylation of the des-bromo analogue of **1a** with bromobenzene,[4] **1a** was unreactive with respect to self-

coupling.[8] It should be noted, however, that we have reported that **1a** undergoes Sonogashira coupling with various alkynes, suggesting that such compounds can readily engage in oxidative addition with Pd(0) species.[9] We have speculated that metallocycles might arise from the



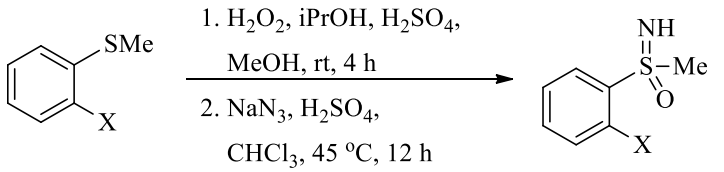
Scheme 1. Proposed formation of the cyclic bis-sulfoximine **3.**

reaction of **1a** with certain metals, but have no definitive evidence as to the existence of such species, much less data about their reactivity. In any case, copper salts were attractive as an alternative catalyst for this process, especially given their cost relative to palladium reagents and their precedented use for the N-arylation of NH sulfoximines.[5a] We thus studied the reaction of **1a** with copper salts. Compound **1a** was treated with 1 equivalent of CuI and 2.5 equivalents of Cs_2CO_3 in DMSO for 12 hours at 110 ^oC. After consumption of the starting material, benzothiazine **4** was isolated in 33% yield. Though other products were obtained, all were complicated mixtures.[10]

This result observed was unexpected, though the benzothiazine **4** is, in fact, known. Hori and coworkers reported its synthesis over 30 years ago, but by a route completely different from that described herein.[11]

We attempted to optimize the synthesis of **4**, since overall the process we discovered is in principle more efficient than Hori's route. To that end, we decided not only to investigate the chemistry of **1a**,[9] but also of the chlorine and iodine analogues **1b**[12] and **1c**. The synthesis of all 3 congeners is shown in Scheme 2 and followed a standard protocol for the synthesis of sulfoximines of this general type.[13]

As shown in Table 1, variations in the amounts of the copper iodide mediator and the amount of base did not have a significant effect on the yield of the process, the best yield being 40% (Table 1, entry 5). Table 2 shows that of the simple carbonate bases tested, cesium carbonate was the best performer and the dipolar aprotic solvent DMSO was the best solvent for the reaction, though other dipolar aprotic solvents were not examined. It may be that the solubility of the copper salt plays a role in the efficiency of the reaction.

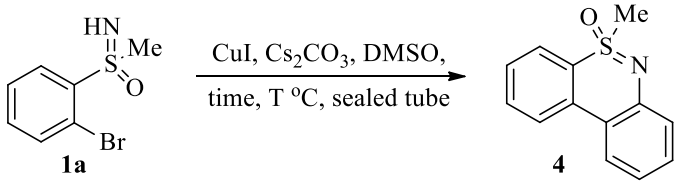


1a, X = Br, 68%
1b, X = Cl, 63%
1c, X = I, 37%

Scheme 2. Synthesis of *o*-halo sulfoximines.

Since neither variation in temperature[14] or time, nor changes in base and solvent, (Tables 1 and 2) resulted in improved yields of the product, we chose those conditions affording the best yield (Table 1, entry 5) as the "optimal" reaction conditions and screened several diamines as additives based on Buchwald's observation that the best performing ligands in copper-catalyzed C-N coupling reactions are 1,2-diamines.[15] However, neither the addition of 2 equivalents of ethylenediamine, *N*,*N*,*N'*,*N'*-tetramethylethylenediamine, *N*,*N*-dimethylethylenediamine, 2,2-bipyridine nor phenanthroline led to any significant changes in the outcome of the reaction.

Table 1. Effect of catalyst and base loading on the copper-mediated self-condensation of sulfoximine **1a**[a]



1a **4**

Entry	CuI, mol%	Cs_2CO_3, equiv	Time, h	T °C	Yield (%)
1	10	1	24	150	0[b]
2	50	1	24	150	2
3	100	1	12	115	10
4	100	2	12	115	15
5	100	2.5	12	115	40
6	100	2.5	24	150	32
7	150	2.5	12	115	35
8	200	2.5	12	115	28

[a]Reaction conditions: **1a** (1 mmol) in DMSO (0.4 M); sealed tube. [b]Recovered starting material.

A survey of copper sources also revealed that CuI was the preferred mediator of the reaction (Table 3). Copper bromide and chloride were poorer promoters of the reaction, but not that much

different from copper iodide. Addition of zinc and copper iodide lowered the yield to zero depending on the amount of zinc added (Table 3, entries 6 and 7). The hope was that formation of an organozinc species[16] would be followed by transmetalation to copper, facilitating the reaction. Since the use of copper acetate and copper oxide has been reported for the *N*-arylation of sulfoximines,[5c,6] we tested these reagents, but the results were inferior to that obtained with copper iodide (Table 3, entries 8 and 9).

Table 2. Effect of solvent and base on the copper-mediated self-condensation of sulfoximine **1a**[a]

Entry	Base	Solvent	Yield (%)
1	Cs_2CO_3	toluene	4
2	Cs_2CO_3	*o*-xylene	10
3	Cs_2CO_3	dioxane	23
4	Cs_2CO_3	DMSO	38
5	K_2CO_3	DMSO	20
6	Na_2CO_3	DMSO	18

[a]Reaction conditions: CuI (1 mmol), base (2.5 mmol), sulfoximine **1a** (1 mmol) in solvent (0.4 M) at 115 ºC for 12 h in a sealed tube.

Table 3. Screening of copper sources for the reaction of **1a**[a]

Entry	Reactant	Cu source	Yield **4** (%)
1	**1a**	CuI	40
2	**1b**	CuCl	22
3	**1c**	CuBr	20
4	**1a**	CuCl	30
5	**1a**	CuBr	29
6	**1a**	Zn/CuI (1:10)	24
7	**1a**	Zn/CuI (1:1)	0[b]
8	**1a**	Cu_2O	10
9	**1a**	$Cu(OAc)_2$	12

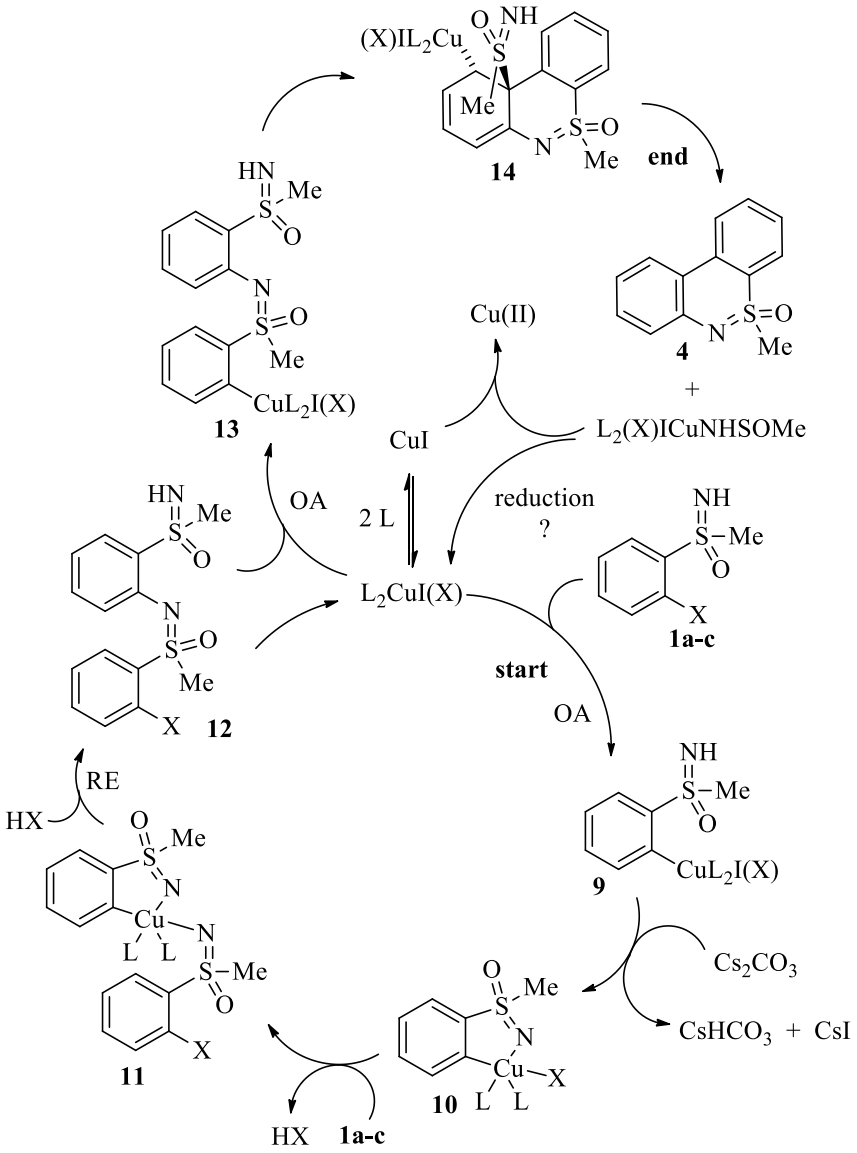
[a]Reaction conditions: Copper source (1 mmol), base (2.5 mmol), sulfoximine **1** (1 mmol) in DMSO (0.4 M) at 115 ºC for 12 h. [b]Recovered starting material.

As the "best" conditions for the process seemed unchanged by these studies, we examined the reaction of **1b** and **1c** to assess the effect of the *ortho*-halogen on the sulfoximine on the course of the reaction. The results are shown in Table 4. Although one might expect a more considerable difference in yields, neither the chloride **1b** or the iodide **1c** was significantly worse as a substrate in the reaction than **1a**, although we were surprised to find that **1c** was not better.

Table 4. Reactivity of *o*-halo sulfoximines **1a-c** in presence of copper iodide[a]

Entry	Sulfoximine	Yield **4** (%)
1	**1a**	40
2	**1b**	28
3	**1c**	32

[a]Reaction conditions: CuI (1 mmol), Cs_2CO_3 (2.5 mmol), sulfoximine (1 mmol) in DMSO (0.4 M) at 115 °C for 12 h.



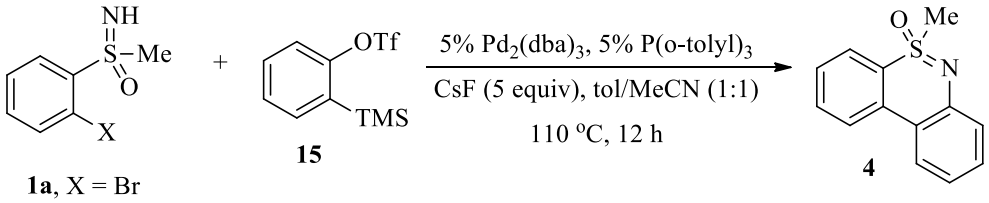
Scheme 3. Proposed mechanism for the formation of **4** from **1.**

The mechanism for this reaction is not known, but we speculate based on literature precedent that a reasonable pathway for the reaction is that shown in Scheme 3.[17] Thus, oxidative addition (OA) of CuI to **1** results in the formation of **9**.[18] In the presence of base, it seems likely that metallocycle formation would proceed to give **10**. Substitution of a labile ligand on copper, either iodide originating from CuI or "X" originating from **1**, by additional **1**, would result in the formation of **11**. Reductive elimination (RE) would afford **12** and regenerate a copper (I) species. So, in principle, this cycle is catalytic.

Another oxidative addition into the C-X bond of **12** would give the intermediate **13**. An intramolecular carbometalation would lead to the cyclic intermediate **14**. Though this temporarily disrupts aromaticity, it provides a good rationalization for the loss of one of the sulfur groups through β-elimination, which leads directly to **4**. A copper (III) species remains, which could disproportionate with copper (I) compounds, rendering the process non-catalytic.

In cogitating our proposed mechanism, we thought it might be possible to take advantage of chemistry based on the interception of benzynes by organopalladium species, as in the annulation of *ortho*-halobenzaldehydes as reported by Larock.[19] We thus decided to apply this chemistry to the synthesis of **4**. The results are shown in Table 5. Thus, treatment of **1a-c** with **15** in the presence of $Pd_2(dba)_3$, P(o-tolyl)$_3$ and excess CsF resulted in the formation of **4** in low yield. Changes to the catalyst loading (10%, 15%, 20% Pd) and ligand (10%, 15%, 20%) did not improve the yield of the reaction. Similarly, changes to the amount of base (5, 10 equiv) and elevated temperatures (135 °C, 150 °C) did not result in improved yields. It is interesting, however, that the iodide **1c** performed the best in this particular reaction sequence. Unfortunately, no clean side products in this process could be isolated, save recovered starting material (ca. 20%).

Table 5. Palladium-catalyzed of **1a-c** with **15** to form **4**



1a, X = Br
1b, X = Cl
1c, X = I

15

4

Entry	Sulfoximine	Yield **4** (%)
1	**1a**	24
2	**1b**	20
3	**1c**	30

Conclusions

In summary, a copper-mediated and palladium-catalyzed method for the synthesis of a benzo-fused benzothiazine from *o*-halo sulfoximines has been described. The low yields are attributed to unidentified side reactions of the *o*-halo sulfoximines. This chemistry is not yet synthetically useful, yet it compares well to the known synthesis of **4**. Hori produced **4** in 21% overall yield in 4 steps.[11] We obtained **4** in 27% yield over three steps from *o*-bromothioanisole. Finally, it is worth noting that **4** is fluorescent and members of this class of compound may be useful in the development of fluorescent sensors.[20]

Experimental Section

General. All reactions were carried out under argon atmosphere in a flame dried sealed tube. CuI was used as purchased from Acros organics. DMSO was purchased from Drysolv® Acros organics and distilled over CaH_2. Toluene and acetonitrile are distilled over CaH_2. The synthesis of all 3 congeners is shown in Scheme 3 and followed a standard protocol for the synthesis of sulfoximines of this general type.[21] The reaction mixture was concentrated by using a rotary evaporator attached to a water aspirator. Residual solvents were usually removed under reduced pressure using vacuum pump (approximately 1 mmHg).

Flash chromatographic separations were carried out on Silicyle ultra-pure silica gel (230-400 mesh) with ACS reagent grade solvents. Analytical thin chromatography was performed on EM reagent 0.25 nm silicagel 60-F plates with F-254 indicator. Compounds were visualized under UV light. Melting points were determined with a Fisher-Johns Hot stage melting point apparatus and were not corrected.

^{1}H NMR spectra were recorded on a Bruker DRX-500 at 500 MHz as $CDCl_3$ solutions with tetramethylsilane (δ = 0 ppm) as the internal standard. ^{13}C NMR spectra were recorded on the same instrument at 125 MHz with $CDCl_3$ (δ = 77.0 ppm) as the internal reference. Chemical shifts are reported in ppm from tetramethylsilane (0.0 ppm). Multiplicities are reported as s (singlet), b (broad), d (doublet), t (triplet) , q (quartet), m (multiplet) and dd (doublet of doublet), etc. All the reaction yields were reported based on the best result, if not stated otherwise.

A round-bottomed flask was charged with (2-bromophenyl)methyl sulfide (8.9 g, 43.9 3mmol), MeOH (125 mL) and a mixture of sulfuric acid and 2-propanol (12.7 g, 4.4% w/w H_2SO_4/2-propanol). 3.5 M H_2O_2 (15.4 mL, 15.38 mmol, 1 equiv) was added at once to the stirred mixture. After 4 h, the reaction was complete, and water (500 mL) was added to the reaction mixture. The aqueous layer was saturated with NaCl and extracted with $CHCl_3$ (3 × 150 mL). The combined organic layers were dried over $MgSO_4$, and evaporated to give the pure sulfoxide for the next step reaction. To a round-bottomed flask equipped with a condenser, an addition funnel, and a magnetic stir bar, a mixture of the above sulfoxide, sodium azide (4.89 g, 75.2 mmol), and 100 mL of chloroform (0.5 M) were added and mixture was cooled in an ice bath. To this slurry,

13.44 mL of concentrated sulfuric acid was added over 15 min with stirring. The mixture was then carefully warmed to 45 ºC and heated for 12 h. After cooling, 100 mL of ice water was added. After all of the salts were dissolved, the $CHCl_3$ layer was separated and the aqueous layer was reextracted with 100 mL of $CHCl_3$. The aqueous layer was made slightly alkaline with a 20% sodium hydroxide solution and extracted twice with 3 × 100 mL of $CHCl_3$. The combined extracts were dried over magnesium sulfate and evaporation of the solvent yielded 6.8 g (68%, two steps) of the sulfoximine **1a** as a pale white solid. NMR data matched that published in the literature.[9]

S-(2-Chlorophenyl)-S-methyl sulfoximine (1b). (63% in two steps following the above procedure from commercially available S-(2-chlorophenyl)-S-methyl sulfide) white solid from 50% ethyl acetate/hexanes, mp 97-99 ºC; R_f = 0.2 (50% ethyl acetate/hexanes); IR (KBr) ν 3267, 3123, 2925, 1573, 1450, 1230, 1016, 952, 755 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 8.0, 1.5 Hz, 1H), δ 7.55-7.53 (m, 2H), δ 7.46 (dt, *J* = 8.0, 1.5 Hz, 1H), 3.32 (s, 3H), 2.91 (b, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 140.9, 133.9, 132.2, 131.9, 130.5, 127.3, 43.3; HRMS calculated for $(C_7H_8ClNOS)_2Na^+$: 400.9922, found: 400.9922.

S-(2-Iodophenyl)-S-methyl sulfoximine (1c). (37% in two steps following the above procedure from commercially available (2-iodophenyl)methyl sulfide, brown oil, R_f = 0.2 (50% ethyl acetate/hexanes), IR ($CHCl_3$) ν 3250, 3140, 2925, 1567, 1440, 1226, 1016, 999, 749 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 8.0, 1.5 Hz, 1H), δ 8.13 (dd, *J* = 8.0, 1.5 Hz, 1H), δ 7.55 (dt, *J* = 8.0, 1.5 Hz , 1H), δ 7.22 (dt, *J* = 8.0, 1.5 Hz, 1H), 3.29 (s, 3H), 2.76 (b, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 145.3, 142.9, 133.6, 130.3, 128.8, 93.0, 42.3; HRMS calculated for $(C_7H_8INOS)_2Na^+$: 584.8634, found: 584.8631.

General procedure for the reaction of (1a-c) with copper salts

A flame-dried, 50 mL sealed tube fitted with a screw cap and a stir bar was charged with sulfoximine **1a** (2.5 g, 10 mmol) in dimethyl sulfoxide (25 mL, 0.4 M). Copper iodide (1.97 g, 10 mmol) and cesium carbonate, (8.68 g, 26 mmol) were added under an argon atmosphere, and the mixture was degassed by bubbling with argon for 15 min with stirring. The tube was sealed and heated to 115 ºC in an oil bath. The greenish solution changed to light blue at around 80 ºC. This solution was further heated to 115 ºC for 12 h. After cooling to room temperature, the reaction mixture was neutralized with hydrochloric acid solution (125 mL, 1M) and extracted with ethyl acetate (3 × 125 mL). The organic layers were collected, dried with magnesium sulfate, filtered and the solvent was removed under vacuum. The crude product was then purified by flash column chromatography using 50% ethyl acetate/hexanes to afford 480 mg of pure **4**.

General procedure for the palladium-catalyzed annulation of *o*-halo sulfoximines

A flame-dried, 10 mL sealed tube fitted with a screw cap and a stir bar was charged with sulfoximine **1a** (100 mg, 0.43 mmol), Pd_2dba_3 (19.7 mg, 0.022 mmol), P(*o*-tolyl)$_3$ (6.5 mg, 0.022 mmol), 2-(trimethylsilyl)phenyltrifluoromethanesulfonate (640 mg, 2.15 mmol), cesium fluoride (324 mg, 2.15 mmol), and toluene/acetonitrile (1:1, 5.8 mL, 0.075 M) under an argon

atmosphere. The mixture was degassed by bubbling with argon for 15 min with stirring. The tube was sealed and heated at 110 ºC for 16 h. After cooling to room temperature, the reaction mixture was washed with brine (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried with magnesium sulfate. Filtration and removal of solvent afforded crude product. This was purified by flash column chromatography using 50% ethyl acetate/hexanes to afford 14.2 mg (24%) of **4**.

5-Methyl-4a,10b-dihydro-5λ^4-dibenzo[c,e][1,2]thiazine 5-oxide (4). Dull white solid from 50% ethyl acetate/hexanes, mp 132-33 ºC; R_f = 0.33 (50% ethyl acetate/hexanes); IR (KBr) ν 3060, 3029, 2918, 1599, 1473, 1190, 1016, 801 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.5 Hz, 1H), 8.00 (d, *J* = 8.5 Hz , 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 3.53 (s, 3H) ; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 142.7, 133.9, 132.8, 130.6, 127.8, 124.78, 123.8, 123.4, 120.7, 117.3 44.0; HRMS calculated for $(C_{13}H_{11}NOS)Na^+$: 252.0453, found: 252.0450.

Crystal Structure of compound (4). $C_{13}H_{11}NOS$, *M* = 229.29; a block crystal (0.35 x 0.25 x 0.15mm), *T* = 173(2) K, λ = 0.71073 Å, monoclinic, space group: P21/n, *a* = 8.3878(5) Å, *b* = 11.6377(7) Å, *c* = 10.9212(7)Å, *V* = 1065.89(11) A^3, 7503 total reflections, 2346 unique, *R*int = 0.0287 *R*1 = 0.0448(I > 2s), w*R*2 = 0.0897, Flack parameter: 0.06 (10). Please see CCDC 822212.

Acknowledgements

We are grateful to the Petroleum Research Fund, administered by the American Chemical Society, and to the National Science Foundation for support of this work. We thank Dr. Charles L. Barnes for the acquisition of X-ray data.

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