STUDIES OF SCHMIDT-TYPE REARRANGEMENTS OF PENTACYCLO-[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]UNDECAN-8-ONE. UNEXPECTED INCURSION OF THE HUISGEN REARRANGEMENT†

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Abstract-Reaction of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (**1**) with H_2NOSO_3H-HCO_2H affords two pentacyclic lactams (**2a**) (15%) and (**2b**) (30%). Reaction of **1** with HN_3-Tf_2O results in the formation of a pentacyclic urea (**3**) (16%) and a tricyclic azidonitrile (**4**) (18%). The unusual "double Schmidt rearrangement" that results in the formation of **3** is rationalized via formation of an intermediate tetrazole (**5**) which undergoes subsequent acylation with concomitant Huisgen rearrangement.

INTRODUCTION

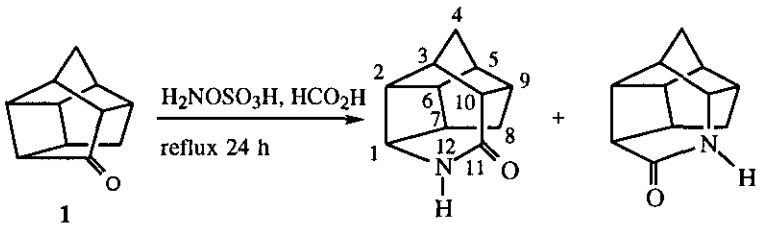
The synthesis and chemistry of novel, substituted pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes (PCUs) have been studied extensively in recent years.[1,2] Compounds of this type are of interest as intermediates in the synthesis of unusual polycyclic cage systems[2] and of triquinane natural products.[3] In particular, ring expansion processes, when performed on PCU-8-one and/or PCU-8,11-dione, provide a convenient entry into a wide variety of unusual pentacyclic C_{12} and C_{13} cage systems. Methods that have been employed for this purpose include: (i) reactions of PCU-ones with N_2CHCO_2Et performed in the presence of F_3B-OEt_2,[4] (ii) Tieffenau-Demjanov *ring expansions,*[5] *and (iii)* Baeyer-Villiger *reactions.*[6] As part of a continuing study of ring expansion reactions of PCU-ones,[4,5] we have examined Schmidt-type rearrangements of PCU-8-one (**1**) under a variety of experimental conditions.

The reaction of **1** with hydroxylamine *O*-sulfonic acid in the presence of formic acid[7] results in Schmidt rearrangement, thereby affording two isomeric lactams (**2a**) and (**2b**) (Scheme 1, product ratio **2a** : **2b** = 1:2). Unequivocal assignment of each of the structures of **2a** (as 12-azapentacyclo[5.5.0.0^{2,6}.0^{3,10}.0^{5,9}]dodecan-11-one) and **2b** (as 11-azapentacyclo[5.5.0.0^{2,6}.0^{3,10}.0^{5,9}]dodecan-12-one) was secured *via* application of X-ray crystallographic methods.

Schmidt reaction of PCU-8,11-dione with NaN_3-MsOH has been reported[8] to be accompanied by extensive skeletal rearrangement of the pentacyclic cage system. In our hands, the corresponding reaction of **1** with HN_3-Tf_2O afforded two products, a substituted polycyclic urea (**3**) (16%) and a tricyclic nitrile (**4**) (18%, Scheme

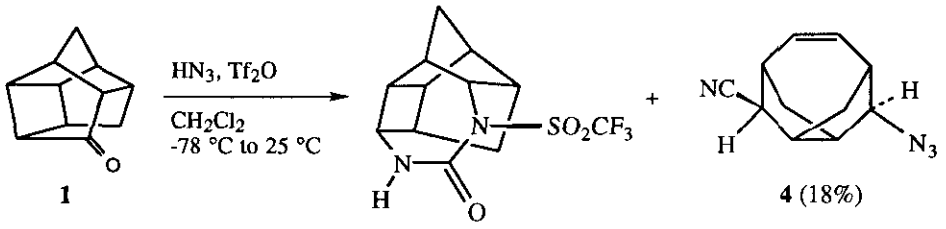
†Dedicated to Professor Rolf Huisgen on the occasion of his 75th birthday.

Scheme 1



2). X-Ray structure drawings of **3** and **4** are shown in Figures 1 and 2, respectively. The latter compound is closely analogous to the kinds of rearranged polycyclic ketonitriles that were reported previously for the reaction of PCU-8,11-dione with NaN_3-MsOH.[8]

Scheme 2



Compound(**3**)appears to have been produced from **1** *via* a "double Schmidt rearrangement". The formation of a cyclic urea by double ring-homologation of a cyclic ketone is highly unusual but not entirely unprecedented.[9] Thomas[10] has reported that tetrazoles can be prepared conveniently via reaction of aliphatic secondary amides with NaN_3-Tf_2O. In addition, when treated with acyl halides, 5-substituted tetrazoles are known to undergo *N*-acylation accompanied by fragmentation of the tetrazole ring with concomitant loss of N_2. This procedure has been employed extensively to synthesize 1,3,4-oxadiazoles[11] and is an example of the familiar "Huisgen rearrangement".[12]

The formation of cyclic urea (**3**) as a product of the reaction of **1** with HN_3-Tf_2O can be rationalized in terms of the mechanism postulated in Scheme 3. Here, Schmidt rearrangement leads initially to **2a** and **2b**. Further reaction with HN_3-Tf_2O appears to occur selectively with **2b**, thereby resulting in formation of the corresponding tetrazole (**5**). *N*-acylation of **5** can occur subsequently via reaction with Tf_2O, ultimately affording the corresponding triflyl enol ether (**8**).[13] Finally, hydrolysis of trflyl enol ether, which occurs during aqueous workup, leads to the observed reaction product (**3**).

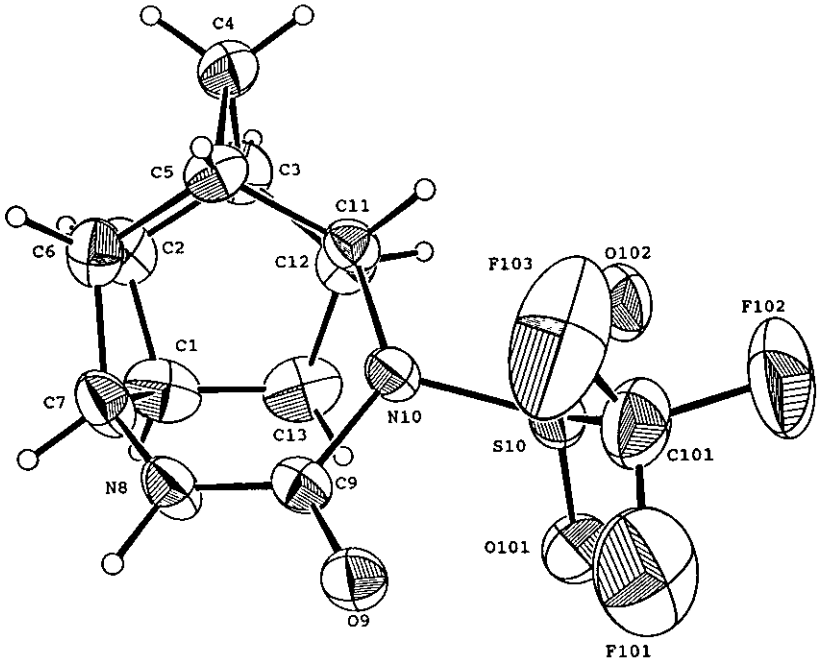


Figure 1. X-ray structure drawing of **3**.

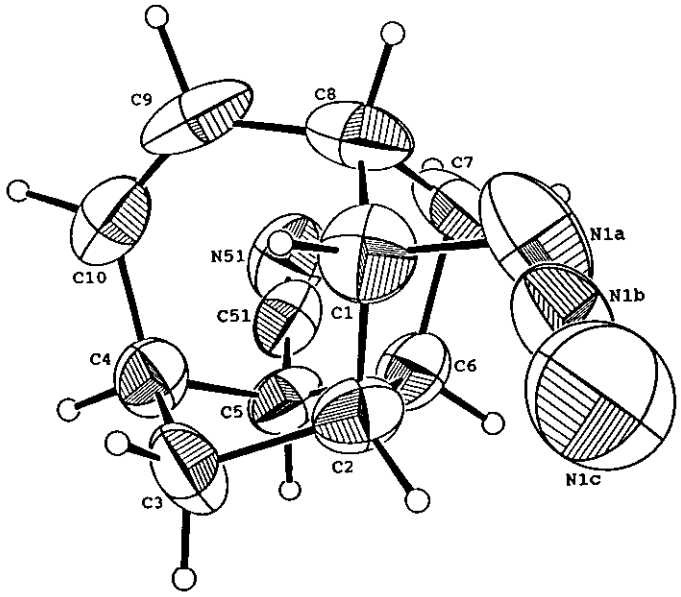
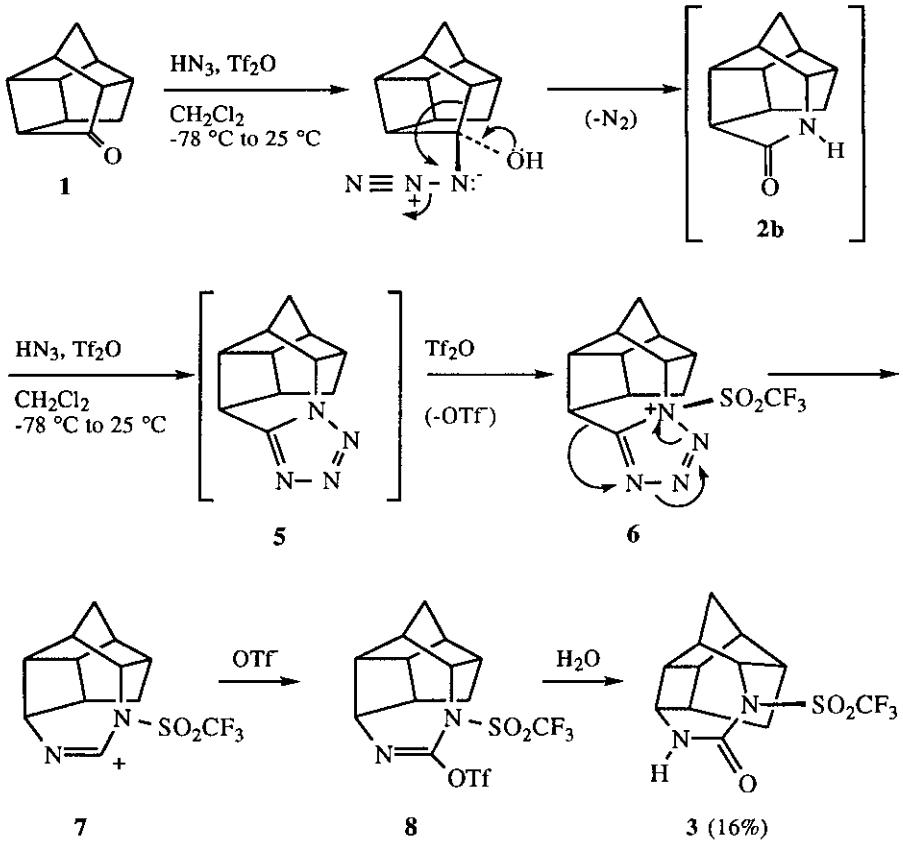


Figure 2. X-ray structure drawing of **4**.

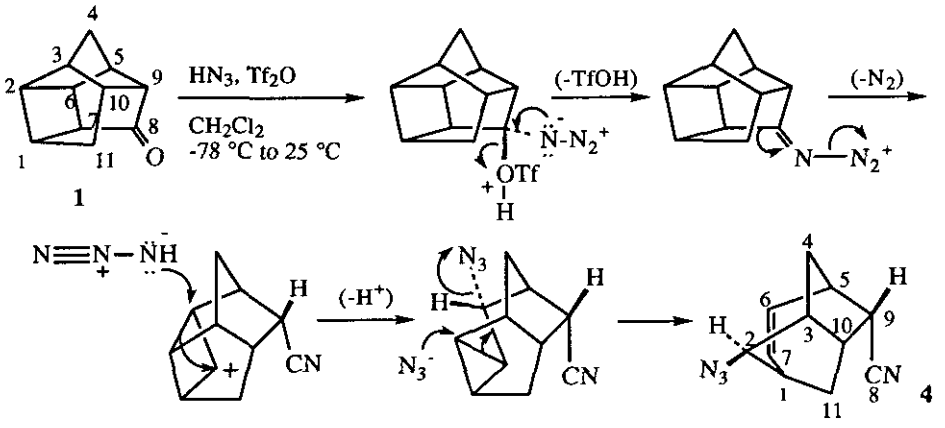
Our suggestion that **2b** (rather than **2a**) is the key intermediate in the reaction of **1** with HN_3-Tf_2O which is transformed selectively into **3** has been verified by the results of a control experiment. Thus, a 1:2 mixture of **2a** and **2b** was subjected to the reaction conditions which are identical to those shown in Scheme 2. Unreacted starting material was recovered, and the composition of this material was subjected subseqeuently to ^1H nmr spectroscopic analysis. Integration of the ^1H nmr spectrum of the mixture of recovered **2a** and **2b** indicated that the ratio of **2a** : **2b** had dropped to 1:1.3, a result that is consistent with the mechanism shown in Scheme 3 (see the Experimental Section).

Scheme 3



The formation of **4** as a product of the reaction of **1** with HN_3-Tf_2O is rationalized by the mechanism shown in Scheme 4. This mechanism is consistent with that which was forwarded previously to account for the course of the corresponding reaction of PCU-8,11-dione with NaN_3-MsOH.[8]

Scheme 4



EXPERIMENTAL

Melting points are uncorrected. Elemental microanalyses were performed by M-H-W Laboratories, Phoenix, AZ.

Schmidt Rearrangement of 1. A solution of **1** (1.6 g, 10 mmol) and hydroxylamine *O*-sulfonic acid (H_2NOSO_3H, 1.5 g, 15 mmol) in HCO_2H (15 ml) was refluxed for 24 h. The reaction mixture was concentrated *in vacuo* to remove formic acid, and water (50 ml) was added to the residue. The resulting suspension was extracted with $CHCl_3$ (3 x 15 ml). The combined organic layers were washed sequentially with 10% aqueous $NaHCO_3$ (20 ml), water (20 ml), and brine (20 ml). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified *via* column chromatography on silica gel by using a gradient elution scheme (10-50% EtOAc-hexane mixed solvent). The first chromatography fraction afforded an oil (0.5 g) which was not identified. The second fraction afforded a mixture of lactams (**2a**) and (**2b**) (800 mg, 46%, product ratio **2a**:**2b** = 1:2). Individual pure isomers were obtained by fractional recrystallization of this product mixture from EtOAc. Pure **2a** was thereby obtained as a colorless microcrystalline solid: mp 251 °C (decomp.); ir (KBr) 3186 (m), 2941 (s), 1656 (vs), 1463 (w), 1401 cm^{-1} (w); ^1H nmr ($CDCl_3$) δ 1.39 (*AB*, J_{AB} = 10.5 Hz, 1 H), 1.60 (*AB*, J_{AB} = 10.5 Hz, 1 H), 1.55 (s, 2 H), 2.30 (br s, 1 H), 2.50 (s, 3 H), 2.55-2.70 (m, 1 H), 2.70-2.95 (m, 2 H), 3.86 (dt, *J* = 6.2, 8.5 Hz, 1 H), 7.12 (br s, 1 H); ^{13}C nmr ($CDCl_3$) δ 30.09 (t), 36.35 (t), 38.65 (d), 39.12 (d), 40.61 (d), 41.98 (d), 42.88 (d), 45.83 (d), 47.85 (d), 50.00 (d), 177.2 (s). Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48. Found: C, 75.34; H, 7.32.

Compound (**2b**) was obtained as a colorless microcrystalline solid, mp 237 °C; ir (KBr) 3187 (m), 3071 (m), 2928 (s), 1671 (s), 1470 (w), 1402 cm^{-1} (w); ^1H nmr ($CDCl_3$) δ 1.41 (*AB*, J_{AB} =10.5 Hz, 1 H), 1.62 (*AB*, J_{AB} =10.5 Hz, 1 H), 1.55 (s, 2 H), 2.13 (t, *J* = 3.9 Hz, 1 H), 2.40 (m, 1 H), 2.47-2.68 (m, 2 H), 2.75-2.95 (m, 2 H), 3.10 (m, 1 H), 3.63 (m, 1 H), 7.26 (br s, 1 H); ^{13}C nmr ($CDCl_3$) δ 31.05 (t), 33.09 (t), 35.06 (d), 37.11 (d), 38.42 (d), 38.68 (d), 42.49 (d), 44.15 (d), 48.14 (d), 56.30 (d), 173.8 (s). Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48. Found: C, 75.15; H, 7.53.

Reaction of 1 with HN_3 - Tf_2O. A solution of **1** (2.00 g, 12.5 mmol) and HN_3 (37 ml of a 1.7 M solution in CH_2Cl_2, 2.69 g, 62.8 mmol) under argon was cooled externally to -78 °C (dry ice-acetone bath). To this cold solution was added Tf_2O (3.55 g, 12.6 mmol) dropwise with stirring. After the addition of Tf_2O had been completed, the cold bath was removed, and the stirred reaction mixture was allowed to warm gradually to room temperature during 3 h. A solid, which precipitated during the course of the reaction, was removed by filtration.The filtrate was extracted with 10% aqueous $NaHCO_3$ (100 ml). The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (3 x 25 ml). The combined organic layers were washed sequentially with water (100 ml) and brine (100 ml). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue, a pale yellow oil, was dissolved in EtOAc (4 ml). The resulting solution was concentrated slowly *via* evaporation under ambient conditions, during which time crystals gradually formed and precipitated from solution. After several days, the precipitated solid was collected by suction filtration, thereby affording **3** (647 mg, 16%) as a colorless microcrystalline solid: mp 196-197 °C; ir (KBr) 3223 (m), 3110 (m), 2973 (s), 1683 (s), 1445 (m), 1382 (s), 1194 (vs), 1088 cm^{-1} (s); ^1H nmr ($CDCl_3$) δ 1.41 (*A*B, J_{AB} = 11.3 Hz, 1 H), 1.66 (A*B*, J_{AB} = 11.3 Hz, 1 H), 1.60-2.05 (m, 2 H), 2.65 (m, 4 H), 2.94 (m, 1 H), 3.12 (m, 1 H), 3.82, (dd, *J* = 17.6, 8.7 Hz, 1 H), 4.45 (dd, *J* = 9.1, 2.7 Hz, 1 H), 6.28 (d, *J* = 7.8 Hz, 1 H); ^{13}C nmr ($CDCl_3$) δ 29.10 (t); 37.69 (t), 40.55 (d), 41.31 (d), 42.58 (d), 44.39 (d), 46.12 (d), 46.48 (d), 46.93 (d), 63.83 (d), 119.7 (q, $^1J_{CF}$ = 322 Hz), 154.3 (s); ^{19}F nmr ($CDCl_3$; $CFCl_3$ internal standard) -70.72 (d). Anal. Calcd for $C_{12}H_{13}N_2O_3F_3S$: C, 44.72; H, 4.06, N 8.69. Found: C, 44.91; H, 4.07; N, 8.57.

The mother liquor which remained after removal of **3** was concentrated *in vacuo*. The residual yellow oil was purified *via* column chromatography on silica gel by eluting with 20% EtOAc-hexane. The initial chromatography fractions afforded an oil (180 mg), which was not characterized. Continued elution of the chromatography column with 50% EtOAc-hexane afforded pure **4** (450 mg, 18%) as a colorless microcrystalline solid: mp 85-86 °C; ir (KBr) 2950 (s), 2876 (m), 2226 (m), 2088 (vs), 1650 (m), 1444 (m), 1243 cm^{-1} (m); ^1H nmr ($CDCl_3$) δ 1.60-2.20 (m, 4 H), 2.60 (m, 1 H), 2.85 (m, 3 H), 3.12 (m, 1 H), 3.75 (s, 1 H), 6.08 (m, 2 H); ^{13}C nmr ($CDCl_3$) δ 34.39 (t), 39.68 (d), 40.43 (t), 40.92 (d), 44.08 (d, 2 C), 49.53 (d), 73.35 (d), 120.1 (s), 133.5 (d), 134.8 (d). Anal. Calcd for $C_{11}H_{12}N_4$: C, 65.98; H, 6.04; N, 27.98. Found: C, 65.86; H, 6.00; N, 27.84.

Control Experiment: Reaction of 2a + 2b with HN_3 - Tf_2O. A solution of **2a** and **2b** (ratio **2a** : **2b** = 1:2, 1.0 g, 5.7 mmol) and HN_3 (20 ml of a 1.7 M solution in CH_2Cl_2, 1.46 g, 34 mmol) under argon was cooled externally to -78 °C (dry ice-acetone bath). To this cold solution was added Tf_2O (1.6 g, 5.7 mmol) dropwise with stirring. After the addition of Tf_2O had been completed, the cold bath was removed, and the stirred reaction mixture was allowed to warm gradually to room temperature during 3.5 h. A pale yellow oil separated from solution during the course of the reaction. The supernatant liquid was decanted and then was washed sequentially with water (50 ml), 10% aqueous $NaHCO_3$ (50 ml), and brine (25 ml). The organic leayer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residual solid was recrystallized from EtOAc, thereby affording **3** (280 mg, 15%). The ^1H and ^{13}C nmr spectra of this material were identical in

all respects with the corresponding spectra of **3** that had been obtained perviously from the reaction of **1** with HN_3 - Tf_2O (*vide supra*).

The remaining mother liquor was concentrated *in vacuo*, and the residue was purified *via* column chromatography on silica gel by eluting with 50% EtOAc-hexane.The initial chromatography fractions afforded an oil (160 mg) which was not further characterized. Continued elution of the chromatography column gave a mixture of **2a** and **2b** (ratio **2a** : **2b** = 1:1.3). These results suggest that **2a** and **2b** are formed via reaction of **1** with HN_3 - Tf_2O, and that **3** is formed selectively by subsequent *in situ* reaction of **2b** with HN_3 - Tf_2O.

X-Ray Structures of 2a, 2b, 3, and 4. All data were collected on an Enraf-Nonius CAD-4 diffrac-tometer by using the ω–2θ scan technique, Mo Kα radiation (λ = 0.71073 Å) and a graphite monochromator. Standard procedures used in our laboratory for this purpose have been described previously.[14] Pertinent X-ray data are given in Table 1.[15] Data were corrected for Lorentz and polarization effects but not for absorption. The structures were solved by direct methods [i.e., SIR[16] (**2a**, **2b**, and **4**) and SHELXS-86[17] (**3**)], and the model was refined by using full-matrix least-squares techniques. Anisotropic parameters were incorporated for all non-hydrogen atoms. Hydrogen atoms were located on difference maps and then were included in the model in idealized positions {$U(H) = 1.3\ B_{eq}(C)$}. All computations other than those specified were performed by using MolEN.[18] Scattering factors were taken from the usual sources.[19]

Table 1. X-ray structure data for **2a**, **2b**, **3**, and **4**.

Compound	**2a**	**2b**	**3**	**4**
Formula	$C_{11}H_{13}NO$	$C_{11}H_{13}NO$	$C_{12}H_{13}F_3N_2O_3S$	$C_{11}H_{12}N_4$
Size (mm)	.08 x .22 x .24	.21 x .23 x .27	.42 x .44 x .48	.48 x .49 x .52
Space Group	P1	$P2_1/c$	$P2_1/c$	$P2_12_12_1$
a (Å)	6.4423 (5)	10.964 (4)	12.795 (1)	8.0082 (7)
b (Å)	6.5451 (5)	6.629 (1)	8.990 (1)	9.443 (1)
c (Å)	11.0543 (6)	12.817 (2)	12.306 (2)	13.515 (2)
α (°)	95.175 (6)			
β (°)	94.450 (6)	115.21 (2)	115.60 (1)	
γ (°)	114.105 (6)			
V (Å^3)	420.27 (6)	842.8 (4)	1276.6 (3)	1022.2 (2)
Z	2	4	4	4
D_c (g-cm^{-3})	1.385	1.381	1.677	1.301
μ (cm^{-1})	0.83	0.83	2.90	0.78
ω–2θ ($2\theta_{max}$)	44	44	44	44
Total refl.	1027	1204	1756	1442
Unique refl.	1027	1156	1679	1260
R_{int}	- -	0.027	0.019	0.026
$I \geq 3\sigma(I)$	734	771	1295	834
Parameters	118	118	190	136
R, wR	.0450, .0461	.0454, .0453	.0464, .0463	.0621, .0663
$(\Delta/\sigma)_{max}$	<0.01	<0.01	<0.01	<0.01
ρ_{min}; ρ_{max}	0.19; -0.21	0.15; -0.12	0.64; -0.42	0.30; -0.25

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