

**Study of alkylation of deprotonated diphenylacetonitrile with halogeneacetones:
X-ray crystal structure of 3,3-diphenyl-5-methyl-5-acetonylpyrrolidin-2-one – a new cyclization product in acetone co-solvent**

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Dedicated to Professor Sándor Antus on the occasion of his 60th birthday

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Abstract

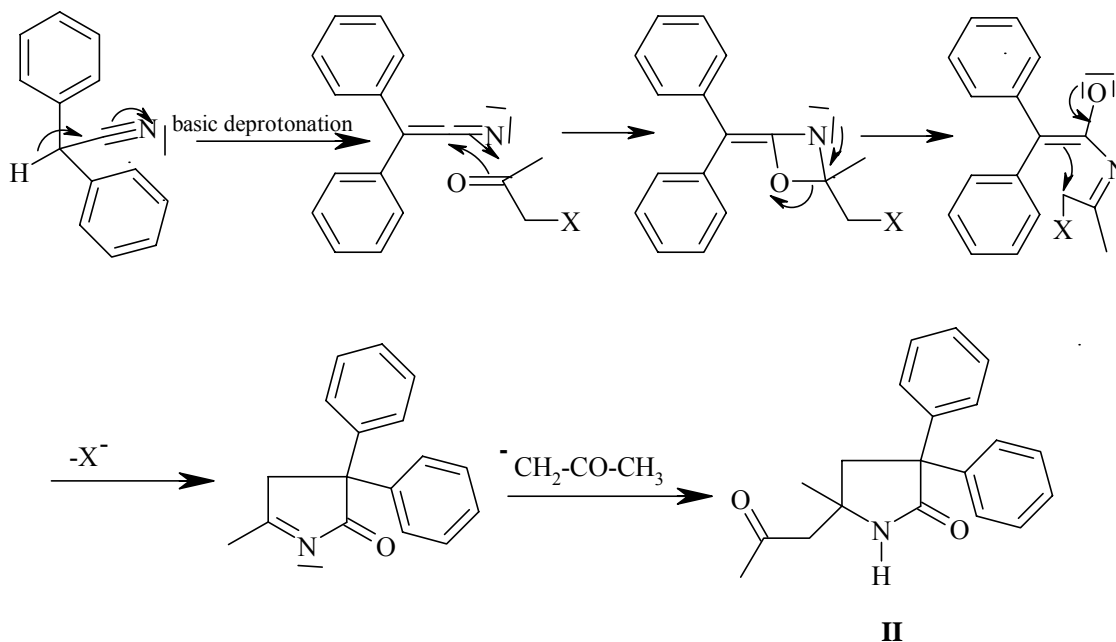
Alkylation of deprotonated diphenylacetonitrile with halogeneacetones (Cl,Br,I) was studied in *N,N*-dimethylformamide (DMF). The differences in yields of the alkylation product, 4-oxo-2,2-diphenylvaleronitrile (**I**), are caused by variations in the haloacetones and solvents. The detailed structure of a new cyclization by-product, 3,3-diphenyl-5-methyl-5-acetonylpyrrolidin-2-one (**II**), in acetone co-solvent was established by X-ray analysis.

Keywords: Diphenylacetonitrile, alkylation, 4-oxo-2,2-diphenylvaleronitrile, 3,3-diphenyl-5-methyl-5-acetonylpyrrolidin-2-one, acetone solvated NaI, X-ray analysis

Introduction

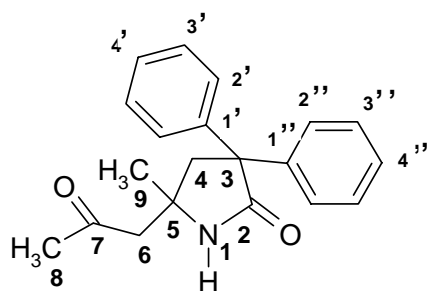
4-Oxo-2,2-diphenylvaleronitrile (**I**) serves as a precursor and useful key substrate for the synthesis of several drugs^{1,2} such as analgetics, antirheumatics, non-peptide neurokinin-3 and angiotensin II receptor antagonists, agents for the treatment of overactive detrusor and novel materials^{3,4} with opto-electronic properties, as well as for dyes and fluorescent compounds. The objective of this study was the design of a scaleable process for the synthesis of 4-oxo-2,2-diphenylvaleronitrile^{1,5,6} (**I**).

A plausible pathway for the formation of **II** is depicted in Scheme 2. The key step in the process involves a [2+2] cycloaddition in which the carbonyl group of the haloacetone adds to a potassium or sodium salt of ketene-imine ($\text{Ph}_2\text{C}=\text{C}=\text{N}^- \text{K}^+$) to form a four membered 1,3-oxazetidíne intermediate. Subsequent ring-opening-ring-closure followed by solvent addition would result in the formation of **II** – a derivative that could easily be isolated by column chromatography on silica gel. The resulting cyclic γ - lactam **II** was obtained in 50 % yield in optically inactive form.



Scheme 2

Standard ^1H and ^{13}C NMR spectra provided information concerning the number and the types of structural fragments present in the studied compound **II**. From DEPT spectra we obtained the proton multiplicity of each individual carbon. In accord with the MS results, we have found from DEPT spectra that in the studied molecule there were the following structural fragments: one keto group, one carboxamide group, two nonequivalent mono substituted phenyl groups, two isolated (from ^1H - ^1H coupling) CH_2 groups and finally two sp^3 hybridized quaternary carbons. As in the proton spectra, the only resolved spin-spin interaction was that observed on geminal CH_2 protons, and all information about the arrangement of individual fragments was obtained from the long-range INEPT spectra. These spectra allow us to correlate the NMR resonances of protons and carbons separated by 2-3 (4) bonds. These long-range correlations are indicated for each individual proton in the last column in Table 1. The observed ^1H - ^{13}C long range correlations (shown in Table 1) are fully consistent with the proposed structure of the molecule.

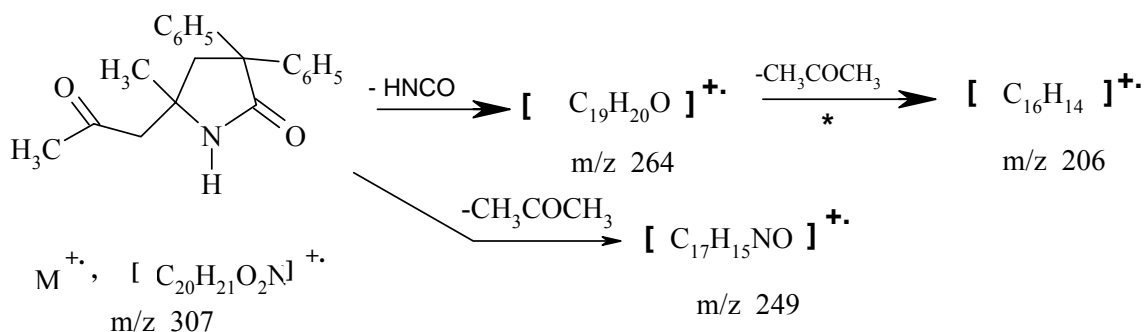
Table 1. NMR spectral parameters of **II**. Chemical shifts are shown in δ scale in ppm

Position	^{13}C Chem. shift	^1H Chem. shift	^1H - ^{13}C Long-range correlations ^a
1	-	6.73	3, 5, 4
2	176.38	-	-
3	57.28	-	-
4	50.46	2.87, 2.86	2, 1', 1'', 3, 5, 9
5	54.03	-	-
6	53.93	2.47, 2.66	7, 5, 9
7	207.13	-	-
8	31.12	2.028	7, 6
9	27.42	1.304	4, 5, 6
1', 1''	143.81, 143.72	-	-
2', 2''	127.84, 127.84	7.2-7.4	-
3', 3''	128.51, 128.35	7.2-7.4	-
4', 4''	126.88, 126.76	7.2-7.4	-

^a Correlations between the protons indicated in the first column and the carbons indicated in the third column.

Mass spectrometry was used extensively as additional confirmation of structural proposals. Thus, the elemental composition $[\text{C}_{20}\text{H}_{21}\text{O}_2\text{N}]^+$ was ascertained from high resolution measurements with 7 ppm precision. The basic decomposition patterns of the molecular ion are depicted in Scheme 3.

Other ions, identified by high resolution measurements were the following: m/z 167 $[\text{C}_{13}\text{H}_{11}]^+$, m/z 165 $[\text{C}_{13}\text{H}_9]^+$, m/z 91 $[\text{C}_7\text{H}_7]^+$, m/z 77 $[\text{C}_6\text{H}_5]^+$, m/z 43 $[\text{C}_2\text{H}_3\text{O}]^+$ and m/z 42 $[\text{C}_2\text{H}_4\text{N}]^+$.



Scheme 3

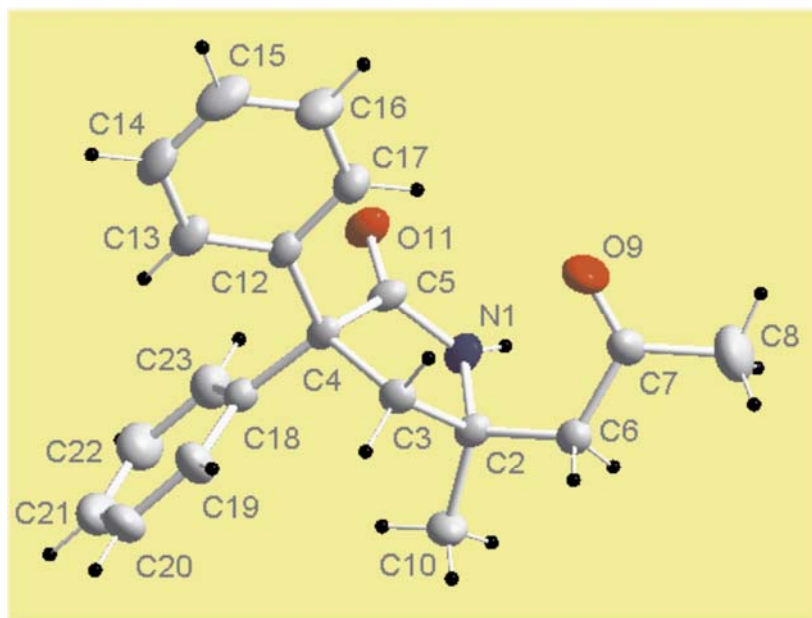
Table 2. Mass spectral fragments (EI) of **II**, m/z (%)^a

307, M⁺ (7), 264(17), 250(7), 249(21), 234(8), 220(10), 207(22), 206(48), 191(7), 180(7), 179(8), 178(9), 167(28), 165(13), 143(9), 129(11), 128(7), 126(7), 105(5), 103(13), 91(28), 77(7), 58(30), 44(5), 43(100), 42(18), 39(6).

^a Only ions with relative intensity above 5 %.

X-ray Analysis

Suitable crystals of **II** were obtained by slow crystallization from a mixture of methyl *tert*-butyl ether at room temperature. The relevant crystallographic data¹¹ and structure refinement are given in Table 3. The bond length and bond angles are listed in Table 4. A list of selected torsion angles is given in Table 5. The final positional parameters are summarized in Table 6. A perspective view¹² and the numbering of the atoms are depicted in Figure 1. The hydrogen atoms were refined isotropically in idealized positions riding on the atom to which they are attached.

Figure 1. ORTEP plot and atomic numbering of compound **II**.

Experimental Section

General Procedures. All reagents - diphenylacetonitrile (99+% Avocado), chloroacetone (96% Acros) potassium tert-butoxide (98+%, Merck), sodium hydride, 60% dispersion in mineral oil, in toluene and DMF soluble bags (Acros), *N,N*-dimethylformamide (99% Acros) were commercial products and were used without purification. Column chromatography was performed on silica gel 100-200 mesh, Merck. Thin-layer chromatography (TLC, on aluminum plates coated with silica gel 60F₂₅₄, 0.25 mm thickness, Merck) was used for monitoring the reactions, eluant CHCl₃ : methanol (99:1). Melting points were determined on a Kofler hot-stage microscope. NMR spectra were measured at ambient temperature on Varian VXR-300 spectrometer equipped with 5 mm broad-band probe operating at 300 MHz for protons and 75 MHz for carbons, respectively. The ¹H and ¹³C chemical shifts were extracted from standard proton and carbon NMR spectra. To achieve unambiguous signal assignment and identification additional NMR experiments were performed: HECTOR (H,C one-bond correlation)⁷, DEPT⁸ and long-range INEPT⁹ HECTOR and DEPT spectra were recorded with the standard pulse sequences provided by the spectrometer manufacturer. The long-range INEPT experiment was performed according to the literature.¹⁰

Mass spectra (AEI) were measured with a GC/MS 25 RFA instrument (Kratos Analytical, Manchester), equipped with a direct inlet system at a ionizing electron energy 70 eV, trap current 100 μA at temperature of the ion source 200 C°. The precise measurements of the masses was done at static resolution about 4 000 (10% valley definition) using perfluorokerosene as standard and scan speed 10 s/decade.

Crystal and experimental data for compound **II** are given in Table 3 and hydrogen-bonds for **II** in Table 4. The structure was solved by direct methods¹³ and refined by anisotropic full-matrix least-squares technique.¹⁴ Because of the small anomalous scattering power of one nitrogen and two oxygen atoms to twenty carbon atoms, the absolute structure was not determined.

Table 3. Crystal and experimental data for compound **II**

Empirical formula	C ₂₀ H ₂₁ NO ₂
Formula weight	307.38
Temperature, <i>T</i> (K)	301(2) K
Wavelength, λ (Å)	0.71093
Crystal system	Orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
Unit cell dimensions (Å)	$a = 7.597(1)$ $\alpha = \beta = \gamma = 90^\circ$ $b = 12.918(3)$ $c = 16.762(3)$
Unit-cell volume, <i>V</i> (Å ³)	1645.0(5)
Formula units per unit cell, <i>Z</i>	4

Table 3. Continued

Calculated density, D_x (g cm ⁻³)	1.241
Absorption coefficient, μ (mm ⁻¹)	0.080
F(000)	656
Crystal size (mm)	0.17 x 0.17 x 0.13
Diffractometer	Enraf-Nonius CAD4
Theta range for data collection, (°)	1.99 - 23.98
Index ranges	-8 ≤ h ≤ 2, -14 ≤ k ≤ 0, -19 ≤ l ≤ 0
Reflections collected	1959
Independent reflections [$I > 2\sigma(I)$]	1897 (Rint = 0.083)
Absorption correction	Empirical Psi-scan
Max. and min. transmission	0.9899 and 0.9363
Refinement method	Full-matrix least-squares on F ²
Data / parameters	1897 / 209
Goodness-of-fit (all)	0.977
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0439, wR2 = 0.0937
R indices (all data)	R1 = 0.1658, wR2 = 0.1222
Absolute structure parameter	-3(4)
Extinction coefficient	0.012(3)
Largest diff. peak and hole	0.165 and -0.192 (e Å ⁻³)

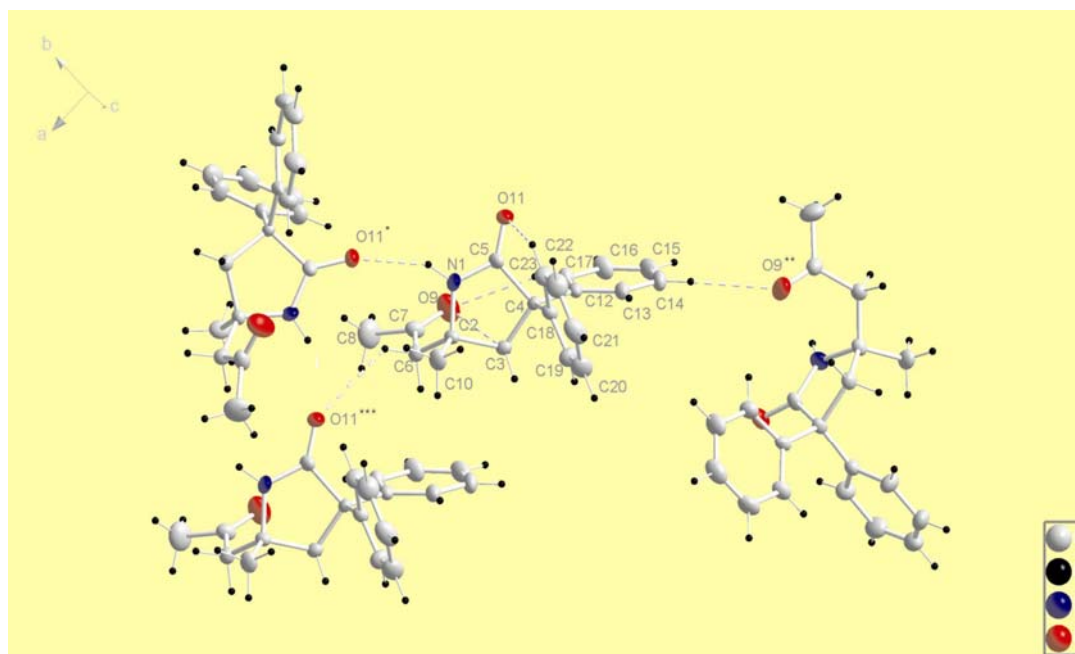
**Figure 2.** Crystal packing and hydrogen bonds for compound **II**.

Table 4. Hydrogen-bonds for **II** [Å and deg.]

D-H...A		d(D-H)	d(H...A)	d(D...A)	<(DHA)
C3-H3A...O9	(0)	0.970(5)	2.504(4)	3.106(6)	120.1(3)
C17-H17...O9	(0)	0.930(5)	2.608(5)	3.486(7)	157.7(3)
C23-H23...O11	(0)	0.930(5)	2.423(3)	3.085(6)	128.1(3)
C6-H6B...O11	(*)	0.970(5)	2.758(4)	3.456(6)	129.4(3)
C14-H14...O9	(**)	0.930(6)	2.562(5)	3.463(7)	163.4(3)
N1-H1...O11	(***)	0.860(4)	2.170(3)	2.952(5)	151.0(3)

EQUIVALENT POSITIONS:

(0)	X,Y,Z	(**)	-X,+Y-1/2,-Z+1/2
(*)	+X+1,+Y,+Z	(***)	+X+1/2,-Y+1/2,-Z

Table 5. Alkylation of diphenylacetonitrile with X-CH₂-CO-CH₃

Entry	X	procedure	Base	Solvent	Product (%)	
					I	II
1.	Cl	a)	KOt-Bu	DMF	16	-
2.	Br	a)	KOt-Bu	DMF	70	-
3.	Cl +NaI	b)	KOt-Bu	DMF+Acetone	28	50
4.	Cl +NaI	c)	KOt-Bu	DMF	71	-
5.	Cl+NaI	d)	NaH	DMF	62	-
6.	Br+NaI	d)	NaH	DMF	73	-
7.	Cl+NaI	e)	NaH	DMF	55	-

Yields analyzed by gas chromatography.

Alkylation of diphenylacetonitrile

a) Potassium tert.-butylate in DMF.

A flame dried flask was charged with a solution of diphenylacetonitrile 19.2g (0.1 mole) in 200 mL DMF, and under vigorous stirring 0.12 mol of potassium tert.-butylate powder was added at 25 °C, while a flow of dry argon was maintained through the apparatus. The resulting mixture was stirred 30 min at 25 °C. A solution of 0.12 mol haloacetone in 50 mL of DMF was added at 20 min and thereafter the reaction temperature rose steadily, but was not allowed to exceed 45 °C. The reaction mixture was stirred at 50 °C for 3-5 h and the solvent was evaporated at the same temperature under reduced pressure. Cold water (200 mL) containing 5g NaCl was added and the product was extracted into CH₂Cl₃. The extract was washed well with water, dried over

sodium sulfate, and the solvent was removed *in vacuo* at 40 °C leaving crystalline material, analyzed by gas chromatography. For the yields see Table 5.

4-Oxo-2,2-diphenylvaleronitrile (I) purified by column chromatography and recrystallized from n-heptane-toluene, m.p. 105-107 °C. Lit.¹ m.p. 105-107 °C (n-hexane/ethyl acetate). IR, Mass, ¹H and ¹³C NMR identical to those given in the lit.¹

b) Potassium tert.-butylate in DMF and NaI in acetone and DMF.

A flame dried flask was charged with a solution of diphenyl acetonitrile 19.2g (0.1 mole) in 200 mL DMF, and under vigorous stirring 0.12 mol of potassium tert.-butylate powder was added at 25 °C, while a flow of dry argon was maintained through the apparatus. The resulting mixture was stirred 30 min at 25 °C. A solution of 0.12 mol *in situ* prepared iodoacetone in 60 mL acetone and 30 mL DMF was added (prepared separately from 0.12 mol chloroacetone and 18g dried NaI in 60 mL acetone and 30 mL DMF at 15 °C, 30 min) at 20 min and thereafter the reaction temperature rose steadily, but was not allowed to exceed 40 °C. The reaction mixture was stirred at 40 °C for 8 h and at the same temperature the solvent was evaporated under reduced pressure. Cold water (200 mL) containing 5g NaCl and Na₂S₂O₃ was added and the product was extracted into ether. The extract was washed well with water, dried over sodium sulfate, and the solvent was removed *in vacuo* at 40 °C leaving crystalline material, analyzed by gas chromatography. Yields of **I** and **II** see Table 5.

3,3-Diphenyl-5-methyl-5-acetonylpyrrolidin-2-one (II) purified by column chromatography and recrystallized from n-heptane-toluene, m.p. 97-99 °C. ¹H and ¹³C NMR see Table 1, and mass spectra see Table 2.

c) Potassium tert.-butylate in DMF and NaI in DMF.

The preparation is identical to b) but without acetone as co-solvent for dissolution of NaI in DMF.

d) Sodium hydride, 60% dispersion in mineral oil in DMF and NaI in DMF.

A flame dried flask was charged with 0.12 mol of a sodium hydride 60% dispersion in mineral oil while a flow of dry argon was maintained through the apparatus. The sodium hydride was freed of the carrier by washing with three portions of 50 mL n-heptane, and then it was layered with 50 mL of dry DMF.

To this vigorously stirred suspension, a solution of diphenylacetonitrile 19.2g (0.1 mole) in 150 mL DMF was added at 25 °C. Hydrogen evolution commenced and thereafter the reaction temperature rose steadily, but was not allowed to exceed 45 °C. When the evolution of gas had become slow (after app. 30 min) a solution of 0.12 mol of the *in situ* prepared iodoacetone in 50 mL DMF (prepared separately from 0.12 mol chloro- or bromoacetone and 18g dried NaI in 50 mL DMF at 15 °C, 30 min) was added over 20 min. The reaction mixture was stirred at 40 °C

for 8 h and at the same temperature the solvent was evaporated under reduced pressure. Cold water (200 mL) containing 5g NaCl and Na₂S₂O₃ was added and the product was extracted into diethyl ether. The extract was washed well with water, dried over sodium sulfate, and the solvent was removed *in vacuo* at 40 °C leaving crystalline material, analyzed by gas chromatography. Yield of **I** see Table 5.

e) Diphenyl acetonitrile, chloroacetone, NaI in DMF and sodium hydride, 60% dispersion in mineral oil in DMF.

A flame dried flask was charged with a solution of diphenyl acetonitrile 57.2 g (0.3 mole) in 250 mL DMF, and under vigorous stirring 0.3 mol of NaI and 0.33 mol chloroacetone in 50 mL of DMF at 25 °C, were added while a flow of dry argon was maintained through the apparatus. The resulting mixture was stirred 30 min. A suspension of 0.33 mol of sodium hydride as a 60% dispersion in mineral oil was freed of the carrier by washing with three portions of 50 mL n-heptane, and then it was layered with 50 mL of dry DMF and added during 20 min at 0 °C; thereafter the reaction temperature rose steadily, but was not allowed to exceed 25 °C. The reaction mixture was stirred at 25 °C for 3-5 h and at the same temperature the solvent was evaporated under reduced pressure. Cold water (500 mL) containing 50g NaCl and 50g Na₂S₂O₃ was added and the product was extracted into diethyl ether. The extract was washed well with water, dried over sodium sulfate, and the solvent was removed *in vacuo* at 40 °C leaving crystalline material. 4-Oxo-2,2-diphenylvaleronitrile (**I**) (55 % isolated yield) was purified by column chromatography and recrystallized from n-heptane-toluene, m.p. 105-107 °C.

Acknowledgements

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Supporting Information Available

Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. The corresponding deposition number is CCDC 227633. Copies of the data can be obtained free of charge on request to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Tel.: +44-1223-336408, Fax: +44-1223 336-033).

Samples Availability: Available from the authors.

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