Reaction of 3-Nitro- and 3-Diethylphosphonocoumarin with Phenacyl Bromide. X-Ray Molecular Structure of 3-Nitro-3,4-phenacylidenecoumarin

Nestor A. Rodios*

Laboratory of Organic Chemistry, University of Thessaloniki, GR-54006 Thessaloniki, Greece

Anka Bojilova

Department of Organic Chemistry, University of Sofia, Anton Ivanov 1, 1126 Sofia, Bulgaria

A. Terzis and C. P. Raptopoulou

NCR Demokritos, Institute of Material Sciences, Athens, Greece

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3-Nitro- and 3-diethylphosphonocoumarins **4a,b** react with phenacyl bromide stereoselectively under phase-transfer conditions, in the presence of a base and of a transfer agent, to give the cyclopropyl derivatives **6** and **7** in good yields. A mechanistic explanation is given for the stereoselectivity of the reaction. The X-ray molecular structure of compound **6a** is also presented.

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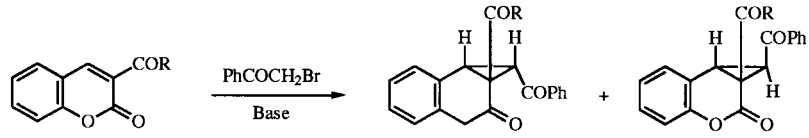
Recently [1] we have reported the results of a study on the reaction of 3-acyl substituted coumarins, **1**, with phenacyl bromide in the presence of a base, from which the cyclopropane derivatives **2** and **3** have been isolated.



1 **2** **3**

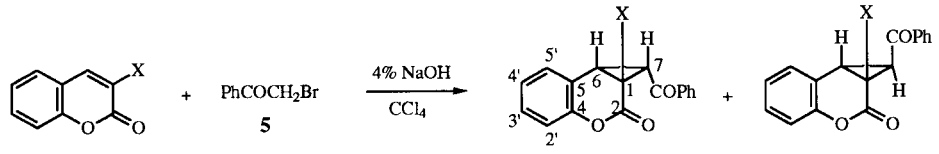
In that study it was revealed that the best results, concerning the yields of the cyclopropane derivatives **2** and **3**, were obtained when the reaction was carried out under two phase system conditions and in the presence of a transfer agent. It was also observed that the stereoselectivity of the reaction depended on the reaction conditions and on the nature of the 3-acyl group of the substituted coumarin **1**. Thus, with the less bulky substituents, such as the 3-acetyl or 3-ethoxycarbonyl groups, the *endo*-isomer, **2**, predominated over the *exo*-isomer, **3**, in the reaction products. However, in the cases of coumarins with bulky 3-acyl-substituents, such as 3-isobutyryl and 3-pivaloyl groups, the reaction gave the products **2** and **3** but with the reverse stereoselectivity, *i.e.* with the *exo*-isomer **3** predominating over the *endo*- isomer **2**.

The stereoselectivity of these reactions and, especially in the case of the bulky 3-acyl substituents the formation predominantly of the less favored *exo*-isomer, **3**, was explained [1] by considering the relative orientation and the interactions between the 3-acyl and the phenacyl groups in the Michael addition intermediate. It was concluded that, besides the reaction conditions, steric factors as well as dipolar interactions in the intermediate govern the stereochemistry of the reaction products.

In the context of the above work, and in order to explore further the influence of the substituents on the yield and the stereoselectivity of these reactions, the 3-nitro-, **4a**, and 3-diethylphosphono-, **4b**, coumarins were reacted with phenacyl bromide under the same [1] conditions and the reaction products were examined. In order to ascertain the structure of these products, the X-ray molecular structure of compound **6a** was also examined.

Results and Discussion.

The reactions were carried out under different experimental conditions as described previously [1]. However, the isolation of the desired cyclopropane derivatives was possible only when the reaction was performed under phase transfer conditions, with carbon tetrachloride as a solvent and by using equimolecular or a small excess of a base and tricaprylmethylammonium chloride (aliquat 336) as the transfer agent.



4a,b **6a,b** **7b**

a) X = NO_2 b) X = $PO(OCH_2CH_3)_2$

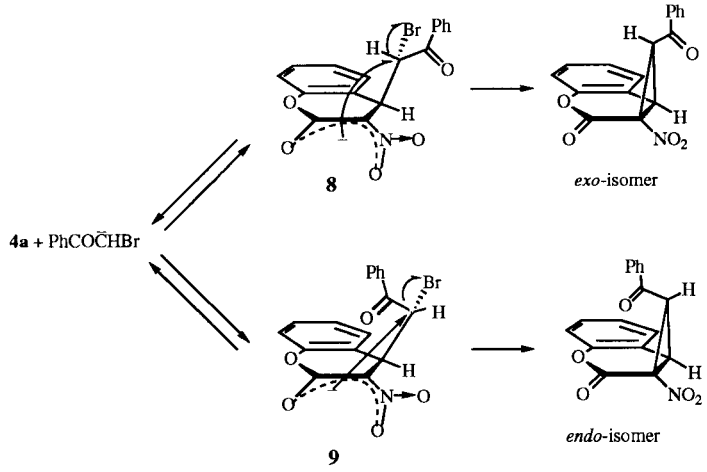
From the reaction of **6a** with phenacyl bromide only one, the *endo*-isomer, **6a**, was isolated in 50% yield, whereas from the reaction of **4b** both, the *endo*-, **6b**, and the *exo*-, **7b**, isomers were isolated in yields of 75% and 15% respectively.

The stereoselectivity of the reaction and the preference in the formation of the *endo*-isomer is similar to that observed in the same reactions of the 3-acylcoumarins [1] and could be explained analogously. Thus for the nitro derivative **4a**, from the two possible Michael addition intermediates (Scheme 1), **8**, which would lead to the formation of the *exo*-isomer, is destabilized due to steric interactions between the benzoyl- and nitro-group, whereas **9**, although suffering from steric interactions, more probably is stabilized by interactions between the π-systems of the benzoyl and the benzopyranone groups and by the possibility of the benzoyl carbonyl to be aligned over the pyranone plane and towards the C=O and N=O bonds, thus leading to the formation predominantly of the *endo*-isomer. An analogous explanation could be given for the 3-diethoxyphosphonate derivative, where also the *endo*-isomer **6b** was the main reaction product.

Differentiation between *endo*-, **6**, and *exo*-, **7**, isomers was based on their ^1H nmr spectra and particularly on the coupling constants between the cyclopropane protons 6-H and 7-H (for numbering see **6**). Thus the coupling constants between these protons were found in the range of 9.5-10.5 Hz in **6a,b**, suggesting their *cis* disposition in respect to the cyclopropane ring, whereas in **7b** the smaller coupling value of 6.3 Hz suggests their *trans* configuration [1,2]. In compound **6b** and **7b** there was a further splitting of the peaks of these protons due to the hydrogen-phosphorus coupling. Thus in compound **6b**, where both 6-H and 7-H stay *cis* to the phosphorus atom, there were two large coupling values $^3J_{HP}$ = 14.3 Hz and $^3J_{HP}$ = 14.7 Hz for the protons at δ = 3.69 and δ = 3.90 respectively. In compound **7b** there was a large coupling $^3J_{HP}$ = 13.7 for the proton at δ = 3.87, indicating that this proton should stay *cis* to the phosphorus atom and thus was assigned to 6-H, whereas the proton at δ = 3.02, with a smaller coupling value, $^3J_{HP}$ = 9.1 Hz, should stay *trans* to the phosphorus atom, and therefore was assigned to 7-H [4].

The ^{13}C nmr spectra of **6a,b** and **7b** gave the expected peaks for the various carbon atoms and were assigned by

Scheme 1



Analytical and spectral data of the compounds **6a,b** were in agreement with the proposed structure and with those found in other analogous compounds [1-3]. The structure of **6a** was also confirmed by X-ray analysis.

analogy to the similar 1-acyl substituted derivatives [1,5]. In **6b**, **7b** the $^1J_{CP}$ were equal to 187-189 Hz for C-1. It is of interest to note the 4 ppm downfield shift of C-1 and the 5 ppm downfield shift of C-5 in going from the *endo*-,

6b, to the *exo-*, **7b**, isomer. These differences, that have been also found in the analogous 1-acyl derivatives [1], can be used to distinguish between the *endo* and *exo* isomers of these compounds. In particular a shift value of 113.5-114.0 ppm for C-5 is indicative of the *endo* isomer, whereas in the *exo* isomer the C-5 should show a shift value of 118.5-119.0 ppm.

X-Ray Crystallographic Study of Compound **6a**.

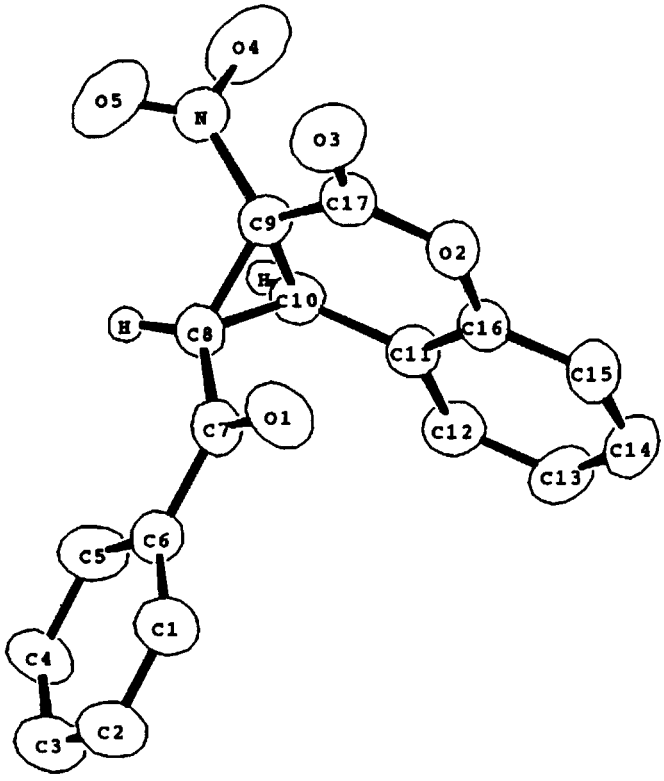


Figure 1. Molecular structure of **6a**.

The molecular structure of compound **6a**, as derived from the X-ray analysis, is given in Figure 1, whereas Tables 1 and 2 contain the positional parameters and selected bond lengths and angles respectively. From these data is clearly evident the stereochemistry of **6a** *i.e.* the *endo* character of the benzoyl group and the *cis* disposition of 6-H and 7-H in respect to the cyclopropane ring. In this structure the benzopyranone ring system is almost planar, as indicated by the torsional angles C9C10C11C16 and C11C16O2C17 (Figure 1), being equal to -2.39 and 3.48 respectively, and C11C10C9C17, C10C9C17O3 and C10C9C17O2, being equal to 0.82,178.80 and 2.82 respectively. The C=O bond of the benzoyl group stays eclipsed to the C(8)-C(9) bond and directed slightly outside of the cyclopropane ring and toward the pyranone-C=O bond, the corresponding planes O1C7C8-C7C8C9

Table 1

Positional and Equivalent Thermal Parameters (x10^4) of the non-H Atoms. E.s.d.'s in Parentheses.
$Ueq = 1/3\ (U_{11} + U_{22} + U_{33})$

Atom	X	Y	Z	Ueq
C(1)	1702(3)	8953(2)	4503(3)	513
C(2)	-2025(4)	9592(2)	5248(4)	630
C(3)	-1053(4)	9770(2)	6559(4)	670
C(4)	240(4)	9316(2)	7154(4)	667
C(5)	583(4)	8676(2)	6425(3)	535
C(6)	-384(3)	8490(1)	5101(3)	406
C(7)	-64(3)	7812(2)	4276(3)	391
O(1)	-847(2)	7675(1)	3062(2)	551
C(8)	1309(3)	7304(1)	4967(3)	380
C(9)	1802(3)	6651(1)	4171(3)	377
C(10)	2832(3)	7351(1)	4501(3)	362
C(11)	2931(3)	7828(1)	3271(3)	368
C(12)	3841(3)	8511(2)	3424(3)	439
C(13)	3930(3)	8932(2)	2249(3)	515
C(14)	3116(3)	8684(2)	897(3)	529
C(15)	2207(3)	8015(2)	717(3)	460
C(16)	2140(3)	7596(1)	1914(2)	377
O(2)	1220(2)	6923(1)	1629(2)	417
C(17)	956(3)	6460(2)	2660(3)	423
O(3)	132(3)	5901(1)	2324(2)	632
N	2359(3)	5926(1)	4992(2)	483
O(4)	3514(4)	5628(2)	4857(4)	1529
O(5)	1625(4)	5647(2)	691(4)	1412

Table 2

Bond [a] Lengths (Å) and Angles ( ) of **6a**

Length	(Å)	Angle	( )
C(6)-C(7)	1.484(3)	C(1)C(6)C(7)	118.5(2)
C(7)-O(1)	1.221(3)	C(5)C(6)C(7)	122.1(2)
C(7)-C(8)	1.493(3)	C(6)C(7)O(1)	122.5(2)
C(8)-C(9)	1.493(3)	C(6)C(7)C(8)	117.4(2)
C(8)-C(10)	1.528(3)	O(1)C(7)C(8)	120.0(2)
C(9)-C(10)	1.484(3)	C(7)C(8)C(9)	121.0(2)
C(9)-C(17)	1.497(3)	C(7)C(8)C(10)	120.1(2)
C(9)-N	1.487(3)	C(9)C(8)C(10)	58.8(1)
C(10)-C(11)	1.476(3)	C(8)C(9)C(10)	61.8(2)
C(11)-C(12)	1.402(3)	C(8)C(9)C(17)	122.7(2)
C(11)-C(16)	1.377(3)	C(10)C(9)C(17)	120.0(2)
C(12)-C(13)	1.377(4)	C(8)C(9)N	116.4(2)
C(13)-C(14)	1.386(4)	C(10)C(9)N	117.8(2)
C(14)-C(15)	1.381(4)	C(17)C(9)N	110.6(2)
C(15)-C(16)	1.386(3)	C(8)C(10)C(9)	59.4(2)
C(16)-O(2)	1.392(3)	C(8)C(10)C(11)	121.4(2)
O(2)-C(17)	1.351(3)	C(9)C(10)C(11)	116.0(2)
C(17)-O(3)	1.192(3)	C(10)C(11)C(12)	122.3(2)
N-O(4)	1.175(3)	C(10)C(11)C(16)	119.9(2)
N-O(5)	1.162(3)	C(11)C(16)O(2)	123.0(2)
		C(15)C(16)O(2)	114.6(2)
		C(16)O(2)C(17)	123.1(2)
		C(9)C(17)O(2)	117.8(2)
		C(9)C(17)O(3)	123.2(2)
		0(2)C(17)O(3)	118.8(2)
		C(9)NO(4)	118.0(2)
		C(9)NO(5)	120.5(2)
		C(4)NO(5)	121.4(3)

[a] Average values for CO-phenyl C-C 1.380(4), internal angle 120.0(3) and for coumarin-phenyl C-C 1.381(4), internal angle 120.0(3).

and OlC7C8-C7C8C10 forming dihedral angles equal to 3.22 and 72.75 respectively. The nitro goup is directed outside of the cyclopropane ring as indicated by the torsional angles C8C9NO5 and C8C9NO4, with values 48.86 and -134.84 respectively and C10C9NO5 and C10C9NO4 with values 119.25 and -64.44 respectively, whereas the two hydrogens of the cyclopropane ring show almost equal interatomic distances from the two oxygen atoms of the nitro group, H(10)-0(4) 2.897 Å and H(8)-O(5) 2.722 Å

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus. The ir spectra were recorded with a Specord 71 IR spectrometer. The ^{1}H nmr spectra were obtained with a Bruker WM 250 (250 MHz) or a Varian XL 200 (200 MHz) instrument. The ^{13}C nmr spectra were obtained with a Bruker WM 250 instrument. All nmr spectra were obtained by using tetramethylsilane (TMS) as the internal standard in deuteriochloroform solutions. The mass spectra were recorded at 70 eV with a Jeol JMS-D 300 or a VG TS-250 spectrometer. Column chromatography was carried out on silica gel (Merk 60; 0.063-0.2 mm), using *n*-hexane/ethyl acetate mixtures of increasing polarity as the eluent.

Preparation of Starting Compounds **4**.

3-Nitrocoumarin (**4a**).

This compound was prepared according to the literature [6], yield 76% (ethanol), mp 142-143 (lit [7] 142).

Diethyl Coumarin-3-phosphonate (**4b**).

This compound was prepared from the reaction of salicylaldehyde and ethyl diethylphosphonoacetate under condition of the Knoevenagel reaction [8,9], yield 70%, mp 72-74 (lit [10] 64-66).

4,5-Benzo-*endo*-7-benzoyl-1-nitro-3-oxa-*cis*-bicyclo[4.1.0]-hept-4-en-2-one (**6a**).

To a solution of **4a** (0.191 g, 1 mmole), phenacyl bromide (0.2 g, 1 mmole) and a small amount of tricaprylmethylammonium chloride (aliquat 336) (0.01 g) in carbon tetrachloride (3 mm) a solution of 4% sodium hydroxide (1 ml, 1 mmole) was added dropwise and the reaction mixture was stirred for 1 hour at 25°. The reaction mixture was then worked up as described previously [1] and after it was chromatographed gave **6a**, 0.15 g (50%), mp 200-202° (ethanol); ir (nujol): 1780 (lactone C=O), 1670 (benzoyl C=O), 1560 (NO_2) cm^{-1}; ^{1}H nmr (200 MHz): δ = 3.92 (d, J = 10.9 Hz, 1H, H-6), 4.71 (d, J = 10.9 Hz, 1H, 7-H), 7.04-7.18 (m, 2H), 7.27-7.38 (m, 2H), 7.42-7.52 (m 2H), 7.57-7.66 (m, 1H), 7.84-7.96 (m, 2H); ^{13}C nmr: δ = 34.5, 37.4 (C-6/C-7), 68.2 (C-1), 113.6 (C-5), 116.5 (C-2'), 125.2 (C-4'), 129.2, 130.0 (C-3'/C-5'), 149.6 (C-4), 157.4 (C-2, C=O); PhCO: 128.6, 129.0 (C-2, C-6/C-3, C-5), 134.6 (C-4), 134.7 (C-1), 190.0 (C=O); ms: m/z (%), 309 (0.3) [M$^+$], 264 (24), 263 (77), 262 (10), 236 (13), 235 (53), 219 (17), 218 (10), 207 (18), 201 (15), 191 (52), 190 (10), 189 (10), 179 (18), 178 (37), 165 (12), 155 (6), 130 (11), 117 (7), 115 (6), 106 (9), 105 (100), 102 (16), 78 (22), 77 (84).

Anal. Calcd. for $C_{17}H_{11}NO_5$ (309.232): C, 66.02; H, 3.58; N, 4.53. Found: C, 65.93; H, 3.89; N, 4.51.

Diethyl 4,5-Benzo-*endo*-7-benzoyl-3-oxa-2-oxo-*cis*-bicyclo[4.1.0]hept-4-en-1-phosphonate (**6b**).

To a solution of **4b** (0.282 g, 1 mmole), phenacyl bromide (0.2 g, 1 mmole) and aliquat 336 (0.01 g) in carbon tetrachloride (3 ml) a solution of 4% sodium hydroxide (2 ml 2 mmoles) was added dropwise and the solution was stirred for 1 hour at 25°. The reaction mixture was worked up as described previously [1] and after it was chromatographed gave **6b**, 0.30 g (75%), mp 156-157° (*n*-hexane/ether); ir (chloroform): 1750 (lactone C=O), 1675 (benzoyl C=O) cm^{-1}; ^{1}H nmr (250 MHz): δ = 1.33 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.41 (t, J = 7.1 Hz, 3H, CH_2CH_3), 3.69 (dd, J = 9.5 and 14.3 Hz, 1H, H-6), 3.90 (dd, J = 9.5 and 14.7 Hz, 1H, H-7), 4.18-4.30 (m, 2H, CH_2CH_3), 4.30-4.41 (m, 2H, CH_2CH_3), 6.99-7.10 (m, 2H), 7.21-7.32 (m, 2H), 7.41-7.47 (m, 2H), 7.54-7.60 (m, 1H), 7.88-7.92 (m, 2H); ^{13}C nmr: δ = 16.2 and 16.3 (two d, $^3J_{CCOP}$ = 5.7 Hz, CH_3), 27.2 (d, $^1J_{CP}$ = 187.4 Hz, C-1), 30.7, 33.1 (C-6/C-7), 64.1 and 64.3 (two d, $^2J_{COP}$ = 6.1 Hz, CH_2), 113.7 (C-5), 116.6 (C-2'), 124.3 (C-4'), 128.3, 129.4 (C-3'/C-5'), 151.1 (C-4), 161.5 (C-2, C=O); PhCO: 128.3, 128.8 (C-2, C-6/C-3, C-5), 133.8 (C-4), 136.0 (C-1), 191.0 (C=O); ms: m/z (%), 401 (4), 400 [M$^+$] (10), 372 (1), 281 (6), 267 (4), 264 (9), 263 (15), 262 (55), 247 (22) 246 (29), 235 (8), 218 (24), 191 (4), 190 (6), 189 (8), 178 (11), 165 (2), 131 (4), 130 (5), 115 (3), 106 (4), 105 (100), 102 (11), 89 (3), 81 (7), 78 (10), 77 (41).

Anal. Calcd. for $C_{21}H_{21}O_6P$ (400.35): C, 63.00; H, 5.29; P, 7.74. Found: C, 63.01; H, 5.32; P, 7.37.

Diethyl 4,5-Benzo-*exo*-7-benzoyl-3-oxa-2-oxo-*cis*-bicyclo-[4.1.0]hept-4-en-1-phosphonate (**7b**).

From the same reaction as above and from the column compound **7b** was isolated 0.06 g (15%), mp 102-104° (*n*-hexane/ether); ir (chloroform): 1750 (lactone C=O), 1690 (benzoyl C=O) cm^{-1}; ^{1}H nmr (250 MHz): δ = 1.16 (td, J = 2.52, 7.04 Hz, 6H, CH_2CH_3), 3.02 (dd, J = 6.3, 9.1 Hz, 1H, H-7), 3.87 (dd, J = 6.3, 13.7 Hz, 1H, H-6), 3.92-4.20 (m, 4H, CH_2CH_3), 7.07 (m as d, 1H), 7.16-7.22 (m as td, 1H), 7.27-7.34 (m, 1H), 7.47-7.54 (m, 3H), 7.58-7.64 (m, 1H), 8.01-8.04 (m, 2H); ^{13}C nmr: δ = 16.0 (d, $^3J_{CCOP}$ = 5.3 Hz, CH_3), 24.8 (C-6 or C-7), 31.1 (d, $^1J_{CP}$ = 189.0 Hz, C-l), 36.4 (d, $^2J_{CCP}$= 3.3 Hz, C-7 or C-6), 63.6 (d, $^2J_{COP}$= 5.4, CH_2), 117.2 (C-2'), 118.1 (C-5), 125.1 (C-4'), 128.4, 128.9 (C-3'/C-5'), 149.9 (C-4), 161.7 (C-2, C=O); PhCO: 128.7, 129.1 (C-2, C-6/C-3, C-5), 133.9 (C-4), 136.2 (C-1), 189.6 (C=O); ms: m/z (%), 401 (13) [M+1], 400 (12) [M$^+$], 372 (4), 355 (5), 327 (5), 298 (4), 281 (10), 264 (19), 263 (58), 262 (100), 247 (53), 246 (56), 236 (11), 235 (18), 219 (24), 218 (74), 207 (6), 191 (24), 190 (10), 189 (38), 179 (8), 178 (26), 165 (8), 159 (7), 152 (9), 131 (19), 122 (7), 118 (15), 115 (18), 109 (17), 106 (24), 105 (35), 102 (24), 91 (9), 89 (13), 77 (86), 76 (10).

Anal. Calcd. for $C_{21}H_{21}O_6P$ (400.35): C, 63.00; H, 5.29; P, 7.74. Found: C, 62.66; H, 5.21; P, 7.78.

X-Ray Analysis of Compound **6a**.

Compound **6a**, $C_{17}H_{11}NO_5$, M = 309.23 crystallizes (from ethanol) as light yellow prismatic crystals; space group $P2_1/n$, z = 4, a = 8.7838(6), b = 17.139(1), c = 9.7686(7) Å, β = 105.797(2) Å, V = 1415.07 Å^3, D_m = 1.44 g cm^{-3}, Mo-Kα, Zr

filtered radiation, $\lambda = 0.7107$ Å, $\mu = 1.00$ cm^{-1}.

Data were collected using a crystal with ca 0.18 x 0.22 x 0.30 mm dimensions mounted on a Nicolet $P2_1$ refractometer upgraded by Crystal Logic using Zr-filtered Mo radiation. Unit cell dimensions were determined and refined by using the angular settings of 25 automatically centered reflections in the range $11<2\theta<24$. Intensity data were recorded using a θ-2θ scan to $2\theta_{max} = 54$ with scan speed 3.0 deg/min and scan range 2.5 plus $\alpha_1\alpha_2$ separation. Three standard reflections monitored every 97 reflections showed less than 3% variation and no decay. Lorentz and polarization correction were applied using Crystal Logic software.

Symmetry equivalent data were averaged with R = 0.0581 to give 3081 independent reflections from a total of 3375 collected. The structure was solved by direct methods using SHELXS-86 [11] program and refined by full-matrix leastsquares techniques with SHELX-76 [12] program using only 2093 reflections with $F>5\sigma$ (F) and refining 252 parameters. All hydrogen atoms were located by difference maps and their positions were refined isotropically. All non-hydrogen atoms were refined anisotropically. Final for all data R, R_w and GOF values are 0.0814, 0.0795 and 2.18 respectively. The maximum and minimum residual peaks in the final difference map were 0.497 and -0.329 e/Å^3. The largest shift/esd in the final cycle was 0.003. Positional and U(equiv) thermal parameters are given in Table 1 and selected bond distances and angles in Table 2.

Acknowledgement.

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