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[4+2] CYCLOADDITION OF DIPHENYLKETENE TO 1-AZA-1,3-DIENES

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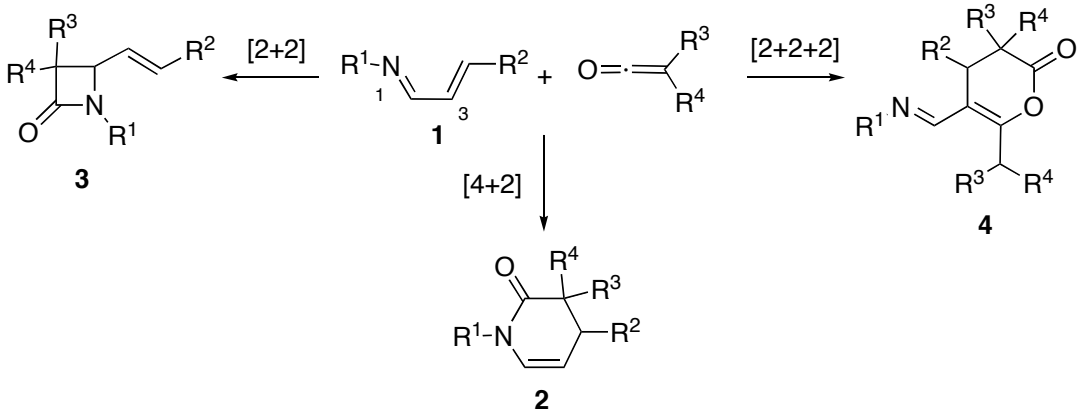
Dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday

Abstract – On heating 3-cyano-1-aza-1,3-dienes **5**, **6** and **9** with diphenylketene, [4+2] cycloaddition took place smoothly to afford the corresponding piperidin-2-one derivatives **7**, **8** and **10** in high yields, respectively.

INTRODUCTION

The Diels-Alder reaction of 1-aza-1,3-dienes **1** with various dienophiles is a useful synthetic tool for six-membered ring systems containing nitrogen atoms.[1] On using ketenes as dienophiles, the Diels-Alder reaction of **1** appears to directly provide piperidin-2-ones **2**; however, this reaction suffers competitive [2+2] cycloaddition of ketenes to imines on **1** to afford β-lactams **3**.[2,3] In general, the [4+2] cycloaddition of **1** is dramatically affected by the substitution pattern at the N1 and C3 positions.[1,4,5] The N1 and/or C3 electron-withdrawing substitution of **1** accelerates its potential [4+2] cycloaddition. In the ketene version, a similar trend is observed. Previously, we disclosed that the [4+2] cycloaddition of diphenylketene to 1-aza-1,3-dienes **1** containing an aromatic C=N bond, competed with [2+2+2] stepwise annulation of ketene (2 eq.) and **1** (1 eq.), giving 2-pyrone derivatives **4**.[6] We also reported [4+2] cycloaddition of diphenylketene to 1,3-diaza-1,3-dienes possessing an aromatic C=N bond to selectively produce piperidin-4-ones.[7] This paper describes the [4+2] cycloaddition of diphenylketene to 1-aza-1,3-dienes **5**, **6** and **9**[8] containing electron withdrawing cyano groups at the C3 position without any competing reactions, to yield piperidin-2-one derivatives **7**, **8** and **10**.



Scheme 1 Cycloaddition of ketenes to 1-aza-1,3-butadienes **1**

RESULTS AND DISCUSSION

The 1-aza-1,3-dienes **5**, **6** and **9** were readily prepared according to the reported method.[5,9,10] When 1-aza-1,3-diene, benzylidene(cyano)methyl-1,3-benzothiazole **5a** was treated with diphenylketene in dry benzene under refluxing conditions for 10 h, [4+2] cycloaddition product **7a** was obtained in quantitative yield (Table 1, entry 1). The structure was assigned on the basis of the analytical and spectral data. The parent peak ion in the mass spectrum appears at *m*/*z* 486, indicating that **7a** is a 1:1 adduct. The infrared spectrum shows absorptions at 2196 (CN) and 1720 cm^{-1} (C=O). In the ^{1}H NMR spectrum, a signal (δ 4.29 ppm) assigned to a vinyl proton is observed. And the ^{13}C NMR spectrum shows a signal of an amide carbonyl at δ 168.8 ppm. These data readily ruled out β-lactam **3** and 2-pyrone **4**. Ultimately the structure of **7a** was determined by X-ray crystal-structure analysis of **7a** (Figure 1).

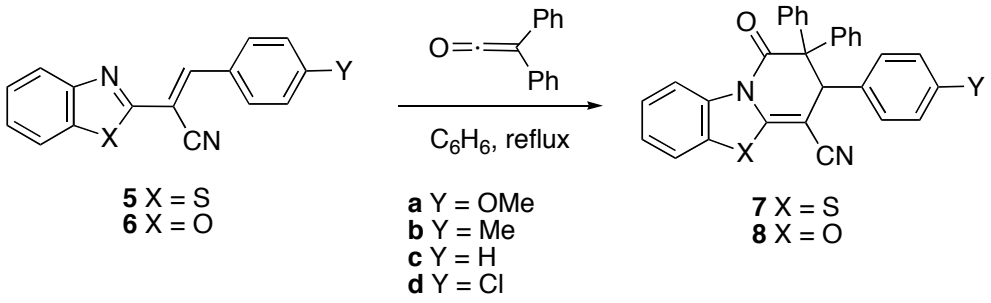


Table 1. Reaction of 1-aza-1,3-dienes **5** and **6** with diphenylketene

entry	**7**	Y	Yield (%)	entry	**8**	Y	Yield (%)
1	**a**	OMe	99	5	**a**	OMe	83
2	**b**	Me	98	6	**b**	Me	88
3	**c**	H	74	7	**c**	H	84
4	**d**	Cl	84	8	**d**	Cl	73

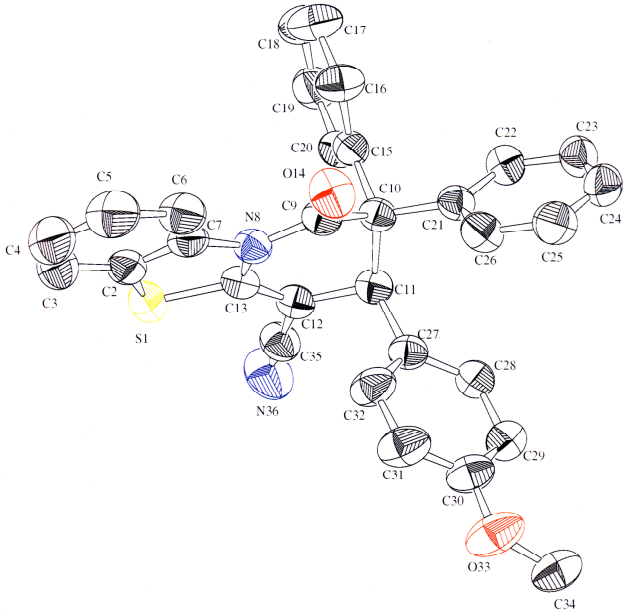
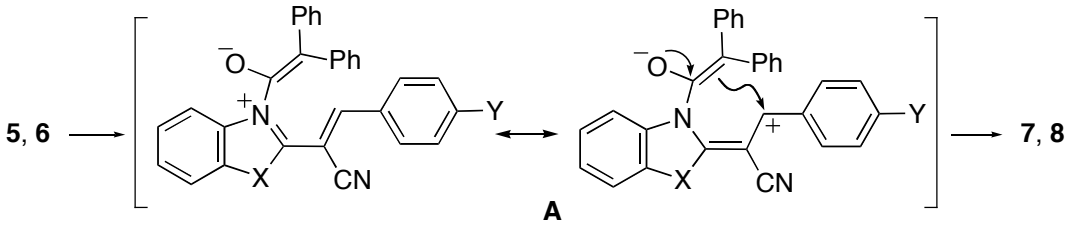


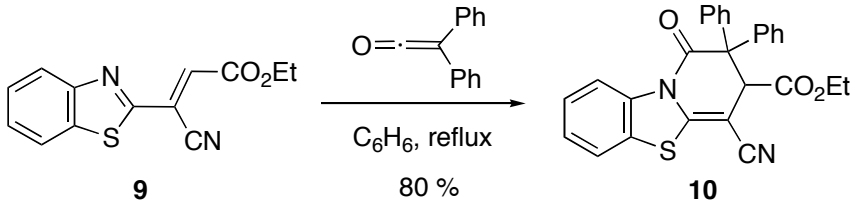
Figure 1 X-Ray crystal structure analysis of **7a**

Similar reactions of azadienes **5b**-**e** with diphenylketene proceeded with [4+2] cycloaddition to give the corresponding piperidin-2-ones **7b**-**f** in good yields (entries 2-4), respectively. 1,3-Benzoxazoles **6a**-**d**, *O*-analogues to **5,** were allowed to react with diphenylketene under the same conditions to afford [4+2] cycloadducts **8a-d** in good yields (entries 5-8). However, the reaction of benzoxazoles **6** required prolonged heating in comparison with that of the corresponding benzothiazoles **5**. The effect of the C4 substituent (Y) on azadienes **5** and **6** affects their reactivity, *i.e.*, **5a**-**b** and **6a**-**b** with electron-donating groups react smoothly relative to **5d** and **6d** with electron-withdrawing groups (entries 1,2 vs. entry 4 and entries 5,6 vs. entry 8). This tendency is inversely related to the effect of the C4 substituent on **1** in a Diels-Alder reaction of **1** with dienophiles, *N*-methylmaleimide or anethol.[1,5] The reaction path is explained in terms of stepwise addition-cyclization (Scheme 2), as the previously discussed mechanism for the reaction of **1** with diphenylketene.[2] In the case of **1** having an amino or alkoxy group at the C4 position, the cycloaddition of diphenylketene proceeds smoothly owing to stabilization of an intermediary cation.[2a,c] A similar tendency for the reactions of **5** and **6** may be dependent on the stabilization of an ionic intermediate **A** by the substituent Y.



Scheme 2 Stepwise pathway of cycloaddition

Finally, we tried a reaction of diphenylketene with 4-ethoxycarbonyl-1-aza-1,3-diene **9**. This azadiene **9** shows higher reactivity toward electron-donating dienophiles, such as vinyl ethers and, on the contrary, lower reactivity toward ethyl acrylate as an electron-poor dienophile.[10] Surprisingly, azadiene **9** reacted smoothly with diphenylketene in a similar manner to give piperidin-2-one **10** in 80% yield (Scheme 3).



Scheme 3 Reaction of 1-aza-1,3-diene **9** with diphenylketene

In summary, we developed the reaction of diphenylketene to 1-aza-1,3-dienes **5**, **6** and **9** holding electron-withdrawing cyano groups at the C3 position, which proceeded selectively with [4+2] cycloaddition to provide piperidin-2-one derivatives **7**, **8** and **10** in good yield.

EXPERIMENTAL

All mps were measured on a Yanagimoto micromelting point apparatus, and are uncorrected. IR spectra were recorded with a Hitachi 270-30 spectrophotometer. NMR spectra were determined with a JEOL JNM-GX 270 spectrometer with tetramethylsilane as an internal standard. *J*-Values are given in Hz. Mass spectra were obtained with a JEOL JMS 700 instrument with a direct system. Column chromatography was carried out on silica gel (Merck, 400 mesh). 1-Aza-1,3-dienes **5**, **6** and **9** were prepared according to the reported procedures.[5,9,10]

General procedure for reaction of dienes with diphenylketene

A mixture of diene **5**, **6** or **9** (1.0 mmol) and diphenylketene (1.1 mmol) in dry benzene (20 mL) was heated under reflux. After consuming the starting diene (monitored by TLC, 10-47 h), the reaction mixture was condensed *in vacuo* to give a residue. The residue was purified by column chromatography on silica gel with *n*-hexane-acetone (10:1) to afford the corresponding adducts **7**, **8** or **10**.

2,3-Dihydro-2,2-diphenyl-3-(4-methoxyphenyl)-1-oxo-1*H*-pyrido[2,1-*b*]benzothiazol-4-carbonitrile (7a): Mp 240-242 ºC (EtOH); IR (KBr) 2196, 1720, 1616, 1582, 1512 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 3.72 (3H, s), 4.29 (1H, s), 6.55 (2H, d, *J* = 6.9 Hz), 6.61(4H, s), 6.95-7.10 (3H, m), 7.18-7.43 (6H, m), 7.54 (2H, d, *J* = 6.6 Hz), 8.47 (1H, d, *J* = 7.9 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 168.8, 159.4, 151.0, 139.9, 138.5, 138.0, 130.2(2), 129.5(2), 129.0(2), 128.6, 128.2(2), 127.6, 127.1(2), 127.0, 126.7, 126.0,

123.9, 121.8, 118.1, 117.6, 114.0(2), 83.5, 62.4, 55.2, 50.3; MS (FAB) *m/z* (%) 487 (M^+ + H, 62), 194 (100); HRMS (FAB) *m/z* calcd for $C_{31}H_{22}N_2O_2S$ + H 487.1480, found 487.1476.

2,3-Dihydro-2,2-diphenyl-1-oxo-1*H*-3-(*p*-tolyl)-pyrido[2,1-*b*]benzothiazol-4-carbonitrile (7b): Mp 247-248 ºC (EtOH); IR (KBr) 2196, 1720, 1616, 1582, 1512 cm^{-1}; ^1H NMR ($CDCl_3$ 270 MHz) δ 2.24 (3H, s), 4.30 (1H, s), 6.56 (2H, d, *J* = 10.2 Hz), 6.59 (2H, d, *J* = 9.9 Hz), 6.90 (2H, d, *J* = 7.6 Hz), 6.94-7.08 (3H, m), 7.17-7.42 (6H, m), 7.54 (2H, d, *J* = 6.6 Hz), 8.47 (1H, d, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 168.8, 151.1, 139.8, 138.5, 138.0, 137.8, 132.6, 130.2 (2), 129.3 (2), 128.9 (2), 128.6, 128.2 (2), 128.1 (2), 127.1, 126.9 (2), 126.6, 126.0, 123.8, 121.7, 118.0, 117.6, 83.3, 62.2, 50.7, 21.0 MS (FAB) *m/z* (%) 471 (M^+ + H, 61), 194 (100); HRMS (FAB) *m/z* calcd for $C_{31}H_{22}N_2OS$ + H 471.1531, found 471.1528.

2,3-Dihydro-2,2-diphenyl-1-oxo-1*H*-3-phenyl-pyrido[2,1-*b*]benzothiazol-4-carbonitrile (7c): Mp 249-250 ºC (EtOH); IR (KBr) 2196, 1710, 1616, 1582 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 4.33 (1H, s), 6.54 (2H, d, *J* = 7.6 Hz), 6.72 (2H, d, *J* = 7.1 Hz), 6.93-7.46 (12H, m), 7.55 (2H, d, *J* = 7.6 Hz), 8.46 (1H, d, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 168.7, 151.4, 139.7, 138.5, 138.0, 135.8, 130.1 (2), 128.9 (2), 128.7, 128.6 (2), 128.4 (2), 128.1 (2), 128.0, 127.1, 127.0 (2), 126.7, 126.0, 123.8, 121.8, 118.0, 117.6, 83.0, 62.2, 51.1; MS (FAB) *m/z* (%) 457 (M^+ + H, 67), 194 (100); HRMS (FAB) *m/z* calcd for $C_{30}H_{20}N_2OS$ + H 457.1375, found 457.1371.

3-(4-Chrolophenyl)-2,3-dihydro-2,2-diphenyl-1-oxo-1*H*-pyrido[2,1-*b*]benzothiazol-4-carbonitrile (7d): Mp 246-247 ºC (EtOH); IR (KBr) 2196, 1720, 1614, 1582 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 4.32 (1H, s), 6.58 (2H, d, *J* = 7.3 Hz), 6.63 (2H, d, *J* = 8.6 Hz), 6.99-7.09 (5H, m), 7.23-7.44 (6H, m), 7.53 (2H, d, *J* = 6.6 Hz), 8.47 (1H, d, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 168.4, 151.8, 139.6, 138.3, 138.0, 134.5, 134.0, 130.1 (2), 129.7 (2), 129.1 (2), 128.8 (2), 128.1 (2), 127.2 (2), 126.9, 126.2, 123.7, 121.8, 117.8, 117.7, 82.4, 62.0, 50.5; MS (FAB) *m/z* (%) 491 (M^+ + H, 48), 194 (100); HRMS (FAB) *m/z* calcd for $C_{30}H_{19}N_2OSCl$ + H 491.0985, found 491.0982.

2,3-Dihydro-2,2-diphenyl-1-oxo-1*H*-3-(4-methoxyphenyl)-pyrido[2,1-*b*]benzoxazol-4-carbonitrile (8a): Mp 270-271.5 ºC (EtOH); IR (KBr) 2208, 1708, 1612, 1512 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 3.71 (3H, s), 4.34 (1H, s), 6.55-6.61 (6H, m), 6.96-7.05 (3H, m), 7.20-7.26 (3H, m), 7.35-7.43 (3H, m), 7.59 (2H, d, *J* = 8.3 Hz), 8.00-8.03 (1H, m); ^{13}C NMR ($CDCl_3$, 67.8 Hz) δ 167.1, 159.3, 155.9, 146.8, 139.7, 138.4, 130.1 (2), 129.3 (2), 129.0 (2), 128.7, 128.4 (2), 128.0, 127.5, 127.1 (2), 126.7, 125.8, 125.0,

116.1, 114.7, 114.0 (2), 110.3, 65.7, 62.6, 55.2, 48.8; MS (FAB) *m/z* (%) 471 (M^+ + H, 75), 194 (100); HRMS (FAB) *m/z* calcd for $C_{31}H_{22}N_2O_3$ + H 471.1709, found 471.1715.

2,3-Dihydro-2,2-diphenyl-1-oxo-1*H*-3-(*p*-tolyl)-pyrido[2,1-*b*]benzoxazol-4-carbonitrile (8b): Mp 224-226.5 ºC (EtOH); IR (KBr) 2204, 1708, 1626, 1582, 1512 cm^{-1}; ^1H NMR ($CDCl_3$, 270M Hz) δ 2.23 (3H, s), 4.35 (1H, s), 6.58 (4H, dd, *J* = 7.9, 2.0 Hz), 6.85 (2H, d, *J* = 7.9 Hz), 6.94-7.08 (3H, m), 7.20-7.26 (3H, m), 7.32-7.43 (3H, m), 7.59-7.61 (2H, m), 7.99-8.03 (1H, m); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 167.1, 156.0, 146.8, 139.6, 138.5, 137.7, 133.0, 130.1 (2), 129.2 (2), 128.9 (2), 128.7, 128.4 (2), 128.0 (2), 127.5, 127.1 (2), 126.7, 125.8, 125.0, 116.1, 114.7, 110.3, 65.6, 62.4, 49.1, 21.0; MS (FAB) *m/z* (%) 455 (M^+ + H, 72), 194 (100); HRMS (FAB) *m/z* calcd for $C_{31}H_{22}N_2O_2$ + H 455.1760, found 455.1767.

2,3-Dihydro-2,2-diphenyl-1-oxo-1*H*-3-phenyl-pyrido[2,1-*b*]benzoxazol-4-carbonitrile (8c): Mp 247-249 ºC (EtOH); IR (KBr) 2200, 1682, 1634, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 4.38 (1H, s), 6.56 (2H, d, *J* = 7.3 Hz), 6.71 (2H, d, *J* = 7.3 Hz), 6.96 (2H, t, *J* = 6.9 Hz), 7.05 (3H, t, *J* = 6.9 Hz), 7.13 (1H, d, *J* = 7.3 Hz), 7.18-7.27 (3H, m), 7.33-7.44 (3H, m), 7.61 (2H, d, *J* = 7.6 Hz), 8.02 (1H, m); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 167.0, 156.1, 146.8, 139.6, 138.4, 136.3, 130.0 (2), 128.9 (2), 128.8, 128.5 (2), 128.3 (2), 128.2 (2), 127.9, 127.5, 127.1 (2), 126.7, 125.8, 125.0, 116.0, 114.7, 110.3, 65.4, 62.4, 49.5.; MS (FAB) *m/z* (%) 441 (M^+ + H, 86), 194 (100); HRMS (FAB) *m/z* calcd for $C_{30}H_{20}N_2O_2$ + H: 441.1603, Found 441.1596.

3-(4-Chrolophenyl)-2,3-dihydro-2,2-diphenyl-1-oxo-1*H*-pyrido[2,1-*b*]benzoxazol-4-carbonitrile (8d): Mp 252-254 ºC (EtOH); IR (KBr) 2208, 1702, 1626, 1600 cm^{-1}: ^1H NMR ($CDCl_3$, 270 MHz) δ 4.37 (1H, s), 6.59 (2H, d, *J* = 7.3 Hz), 6.63 (2H, d, *J* = 8.6 Hz), 6.98-7.11 (5H, m), 7.22-7.27 (3H, m), 7.33-7.44 (3H, m), 7.58 (2H, d, *J* = 8.3 Hz), 8.00-8.04 (1H, m); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 166.8, 156.2, 146.8, 139.4, 138.2, 135.0, 133.9, 130.0 (2), 129.5 (2), 129.0 (2), 128.9, 128.7, 128.3 (2), 127.4, 127.4 (2), 127.0, 125.1, 115.8, 114.8, 110.4, 64.9, 62.2, 49.0; *m/z* (%) 475 (M^+ + H, 60), 194 (100); HRMS (FAB) *m/z* calcd for $C_{30}H_{19}N_2O_2Cl$ + H 475.1213, found 475.1207.

Ethyl 4-Cyano-2,3-dihydro-3,3-diphenyl-1-oxo-1*H*-pyrido[2,1-*b*]benzothiazol-3-carboxylate (10): Mp 202-206 ºC (EtOH); IR (KBr) 2200, 1728, 1604, 1580 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.00 (3H, t, *J* = 7.3 Hz), 3.94 (1H, dq, *J* = 10.6, 6.9 Hz), 3.97 (H, dq, *J* = 10.9, 7.3 Hz), 4.12 (1H, s), 7.16-7.42 (13H, m), 8.51 (1H, d, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 169.7, 168.0, 155.3, 139.5, 138.2, 137.2, 129.6 (2), 129.2 (2), 129.0, 128.8, 127.9 (2), 127.7 (2), 127.5, 127.3, 125.9, 123.6, 121.7, 117.8, 117.4,

62.0, 57.6, 51.6, 13.7; MS (FAB) *m/z* (%) 453 (M^+ + H, 100), 194 (69); HRMS (FAB) *m/z* calcd for $C_{27}H_{20}N_2O_3S$ + H 453.1273, found 453.1276.

X-Ray structure analysis of compound 7a

Crystal data: $C_{31}H_{22}N_2O_2S$, M = 486.59, T = 298 K, Monoclinic, a = 11.512(2) Å, b = 12.496(2) Å, c = 17.336(1) Å, β = 100.946(10)°, V = 2448.3(5) Å^3 (from setting angles of 25 centered reflections with 59.1 < 2θ < 60.0; λ = 1.54178 Å), space group $P2_1/n$ (#14), Z = 4, D_{cal} = 1.320 g cm^{-3}, 0.60 x 0.50 x 0.20 mm, μ(Cu-Kα) = 14.3 cm^{-1}.

Data collection and processing: Rigaku AFC7R four-circle diffractometer with fine-focused 8.3 kW rotating anode generator, ω/2θ scans with ω scan width (1.84 + 0.30 tan θ)°, graphite monochromated Cu-Kα radiation; 5055 reflections measured to $2\theta_{max}$ = 136.2, giving 4675 with $I > 3\sigma(I)$ which were retained in all calculations. No decay correction was observed and no corrections were applied for absorption.

Structure solution and refinement: The structure was solved by direct methods using SIR92 and expanded using Fourier techniques DIRDIF94 and refined by the full matrix least-squares method with all non-H atoms anisotropic. All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation. The weighting scheme $w = 1/\sigma^2(Fo)$ gave satisfactory agreement analyses. Final R-value was 0.036, R_w = 0.056. The maximum and minimumu peaks on the final ΔF map corresponded to 0.12 and -0.16 e^-/Å^3, respectively.

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