POLYCYCLIC *N*-HETEROCYCLIC COMPOUNDS. 53[1] ONE STEP SYNTHESIS OF IMIDAZO[1,5-*a*]PYRIDINE DERIVATIVES BY THE VILSMEIER REACTION USING *N,N*-DIMETHYLARYLAMIDES

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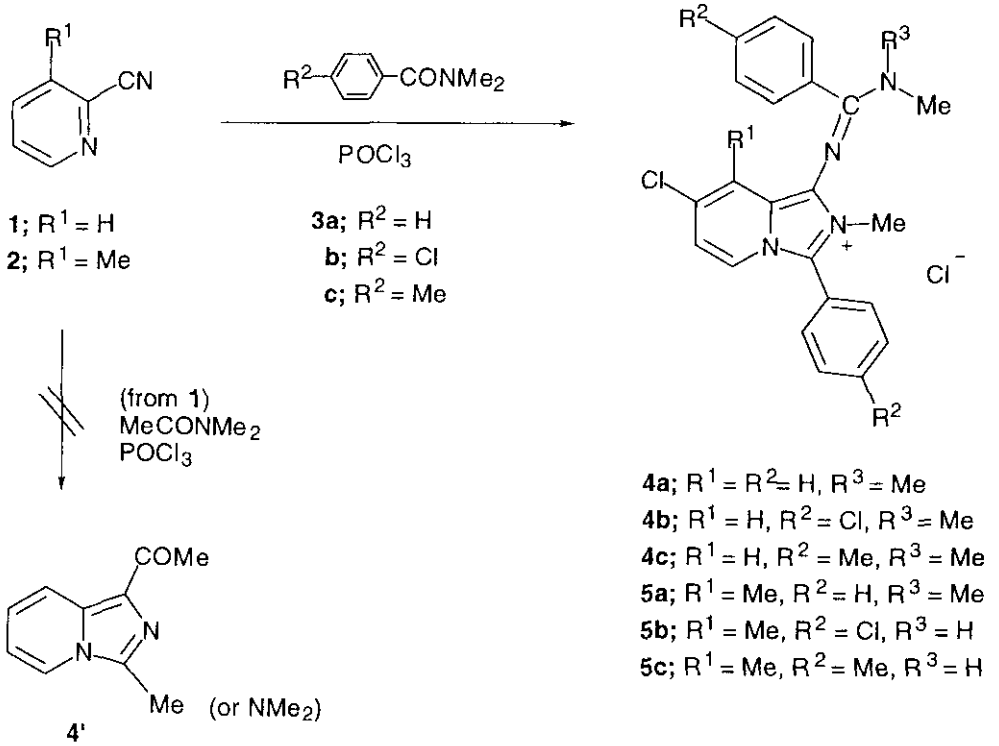
Abstract - The versatile one step synthesis of 3-ary-1-(*C*-aryl-*N,N*-dimethylamino-methyleneamino)-7-chloro-2-methylimidazo[1,5-*a*]pyridin-2-ium chloride and their derivatives by the reaction of 2-pyridinecarbonitriles with *N,N* dimethylaryl-amides and phosphorus oxychloride under the Vilsmeier condition is described. The structures are based upon characteristic spectra and analytical data as well as X-Ray diffraction.

The Vilsmeier reaction is a familiar method for formylation of aromatic and active aliphatic compounds, however, it sometimes gives unexpected cyclization products.[2] We have already reported novel syntheses of isoquinoline, benzofuran, and benzothiophene derivatives by the Vilsmeier reaction of phenylaceto-nitriles,[3] phenoxyacetonitriles,[4] α-phenoxyacetophenones,[5] phenoxyacetaldehyde diethyl acetals,[6] and 3,5-dimethoxyphenylthiomethyl derivatives.[7] Recently the versatile one step synthesis of imidazo[1,5-*a*]-pyridines by the reaction of 2-pyridinecarbonitriles with DMF under the Vilsmeier condition and its application to the formation of imidazo[1,5-*a*]quinolines from 2-quinolinecarbonitriles, and imidazo-[5,1-*a*]isoquinolines from 1-isoquinolinecarbonitriles was also reported.[1] In all these reactions, the Vilsmeier reagent acted as a source of one carbon unit. As the further application of this one step synthesis of imidazo[1,5-*a*]pyridine ring system from 2-pyridinecarbonitrile, we were interested in using arylamide like a *N,N*-dimethylbenzamide instead of alkylamide as an amide component. Because, as shown in Scheme 1, a preliminary attempt of the Vilsmeier reaction of 2-pyridinecarbonitrile (**1**) using *N,N*-dimethylacetamide and phosphorus oxychloride did not afford an expected cyclized product (**4'**). This failure seemed to come from the deactivation of the reagent caused by the dimerization of the amide.[8] So that, *N,N*-dimethylbenzamide (**3a**) which has no α-hydrogen was used instead of *N,N*-dimethylacetamide. Resulted **4a** was the cyclized product of different type from the previous one.[1]

This paper deals with the versatile synthesis of 3-aryl-1-[*C*-aryl-*N,N*-dimethylamino(or *N*-methylamino)-methyleneamino]-7-chloro-2-methylimidazo[1,5-*a*]pyridin-2-ium chloride and its derivatives by the Vilsmeier reaction of 2-pyridinecarbonitriles with *N,N*-dimethylarylamides and phosphorus oxychloride.

As shown in Scheme 1, compound (**1**) was allowed to react with the Vilsmeier reagent which was prepared from **3a** and phosphorus oxychloride. Resulting product (**4a**) had no cyano absorption in its IR spectrum and had fragment peaks at *m/z* 389 and 391 in the intensity ratio of about 3 : 1 in the FAB-MS, which showed the presence of one covalent bonded chloro group. In its ^{1}H-NMR spectrum, three methyl and two phenyl signals were observed, and these observation showed that at least two molecules of **3a** participated in the formation of **4a**. At this stage, the structure of **4a** could not be identified, however, the compound was not an expected product which similarly cyclized as previously reported.[1] So that, the similar reaction using *N,N*-dimethyl-4-chlorobenzamide (**3b**) was attempted for getting additional information on the structure. The resulting product (**4b**) showed the signals at δ 3.02 ppm, 3.31 ppm and 4.17 ppm as each three proton singlet attributed to *N*-methyl groups. Eight protons multiplet which was attributed to the phenyl ring protons was also observed at δ 7.48-8.09 ppm. These result showed the participation of at least two molecules of **3b** in this reaction, and this observation was closely similar to that on compound (**4a**). In FAB-MS, fragment peaks at *m/z* 457, 459, and 461 in the intensity ratio of about 3 : 3 : 1 showed the presence of three chloro groups. However, it was not clear that fragment peak at *m/z* 457 was the molecular ion peak or not at this stage. Fortunately a monohydrate of **4b** was able to be isolated as suitable crystals for X-Ray analysis. The ORTEP drawing of **4b** is shown in Figure 1. It was found that the structure of **4b** was 7-chloro-3-(4-chlorophenyl)-1-(*C*-4-chlorophenyl-*N,N*-dimethyl-



Scheme 1

aminomethyleneamino)-2-methylimidazo[1,5-*a*]pyridin-2-ium chloride which was formed from one molecule of **1** and two molecules of **3b**. It also became clear that the fragment peak at *m/z* 457 was not a molecule ion peak but could be assigned to a fragment peak of $[M\text{-}HCl]H^+$. On the bases of these results, the structure of **4a** could be also identified as 7-chloro-1-(*N,N*-dimethylamino-*C*-phenyl-methyleneamino)-2-methyl-3-phenylimidazo[1,5-*a*]pyridin-2-ium chloride. The reaction of **1** with Vilsmeier reagent using *N,N*-dimethyl-4-methylbenzamide (**3c**) gave a similar cyclized product (**4c**). This product showed the absorptions at δ 2.30 ppm and 2.45 ppm, each of which was attributable to methyl protons of tolyl group in its ^{1}H-NMR spectrum. The FAB-MS spectrum of **4c** showed the fragment peaks at *m/z* 417 and 419 (intensity ratio was about 3 : 1), and the presence of one chloro group was obvious. Therefore, this product could be identified as 7-chloro-1-[*N,N*-dimethylamino-*C*-(4-methylphenyl)methyleneamino]-2-methyl-3-(4-methylphenyl)imidazo[1,5-*a*]pyridin-2-ium chloride similar to the above products **4a,b**.

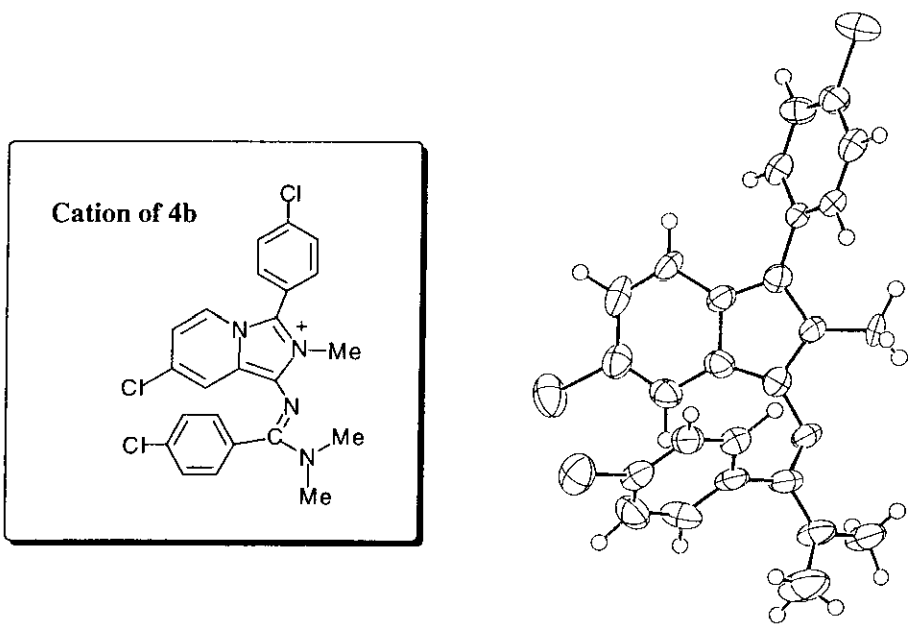
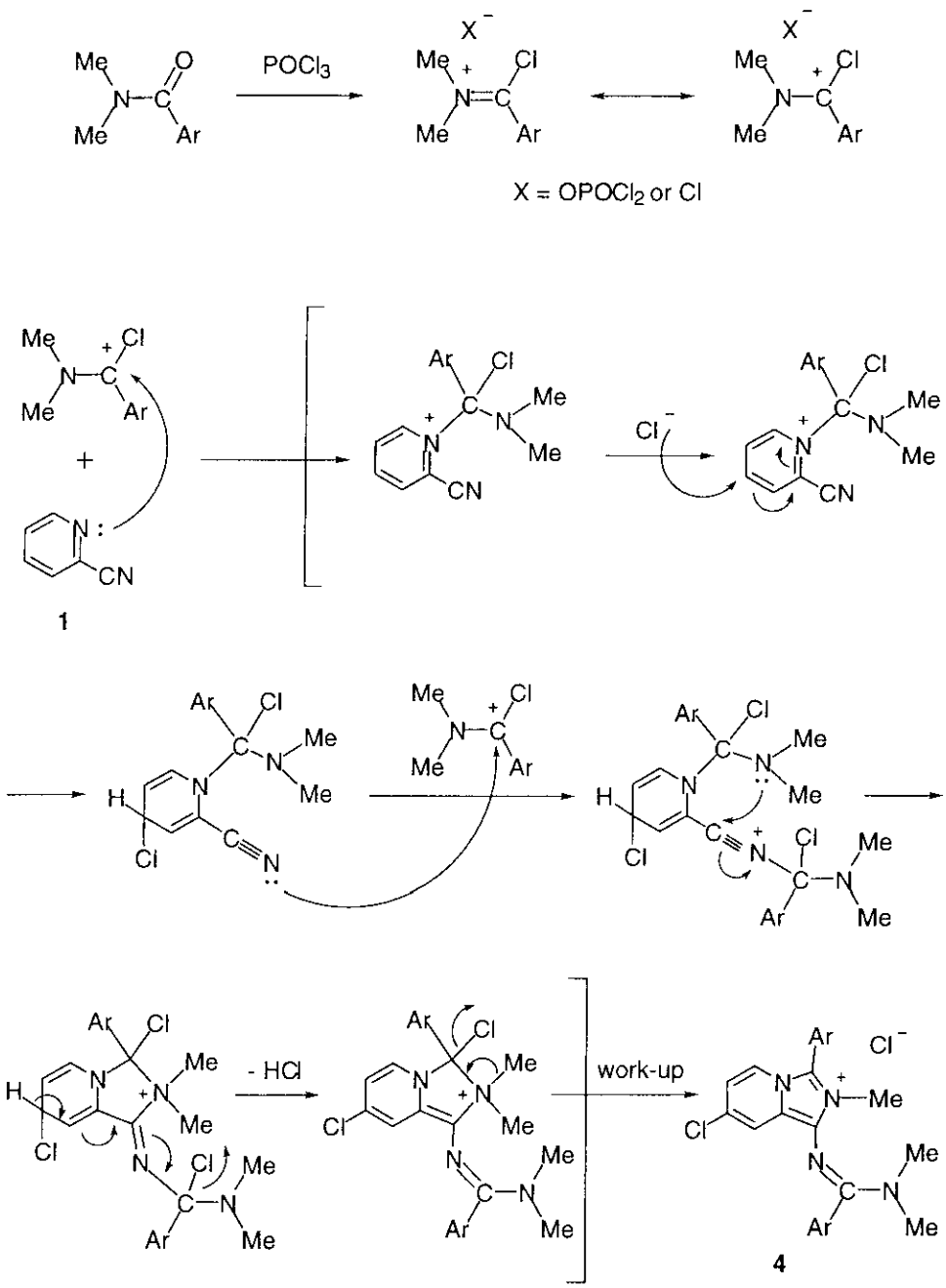


Figure 1 ORTEP Drawing of Cation of **4b**

The possible mechanism of the formation of these compounds (**4**) is proposed in Scheme 2. It was assumed that the nitrogen in pyridine ring attacked to carbocation of Vilsmeier reagent at first. After the chlorination of pyridine moiety the similar attack of nitrogen atom in cyano group to another carbocation of Vilsmeier reagent followed by the intramolecular cyclization seemed to occur.

For the further attempt, 3-methyl-2-pyridinecarbonitrile (**2**) was employed as a starting material. As shown in Scheme 1, compound (**2**) was allowed to react with the Vilsmeier reagent prepared from **3a** and



Scheme 2

phosphorus oxychloride. In this case resulting product (**5a**) showed similar characteristic IR, ^{1}H-NMR, and FAB-MS spectra to those described above. Similar treatment of **2** with **3b** and **3c** provided yellow crystalline products (**5b**) and (**5c**), respectively. The structures of **5b** and **5c** were respectively determined as 7-chloro-3-(4-chlorophenyl)-1-[*C*-(4-chlorophenyl)-*N*-methylaminomethyleneamino]-2,8-

dimethylimidazo[1,5-*a*]pyridin-2-ium chloride and 7-chloro-2,8-dimethyl-1-[*N*-methylamino-*C*-(4-methylphenyl)methyleneamino]-3-(4-methylphenyl)imidazo[1,5-*a*]pyridin-2-ium chloride by their analytical and spectral inspections, however, the mechanism on demethylation of *N,N*-dimethylamino-*C*-phenylmethyleneamino group of **5b,c** is not clear and now under consideration.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-melting point apparatus, and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-5 CHN Corder elemental analyzer. The FAB-MS spectra were measured on a VG 70 mass spectrometer and glycerol or *m*-nitrobenzyl alcohol was used as a matrix agent. The IR spectra were recorded on a Japan Spectroscopic IRA-102 diffraction grating infrared spectrophotometer and frequencies are expressed in cm^{-1}. ^{1}H-NMR were recorded on a Varian VXR-200 instrument working at 200 MHz or a Varian VXR-500 instrument working at 500 MHz in $CDCl_3$ with TMS. Chemical shifts are given in ppm (δ) and *J* values in Hz.

Preparation of Imidazo[1,5-*a*]pyridine Derivatives

General Method: A mixture of dry *N,N*-dimethylarylamide (15 mmol) and phosphorus oxychloride (4.6 g, 30 mmol) was stirred under ice-cooling for 30 min. After addition of **1** or **2** (5 mmol) to the mixture, the resulting mixture was further stirred at 80 °C until the material was completely disappeared (TLC monitoring, for 2.5 days—one week). The resulting mixture was basified with sodium carbonate, and extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was recrystallized from ethyl acetate-acetonitrile to provide the corresponding imidazo[1,5-*a*]pyridines (**4**) or (**5**) as yellow needles or yellow plates.

Some data of **4** or **5** are as follows:

7-Chloro-1-[*N,N*-dimethylamino-*C*-phenylmethyleneamino]-2-methyl-3-phenylimidazo[1,5-*a*]-pyridin-2-ium Chloride (4a)

Stirred for one week; 57% (from **1** and **3a**) as yellow needles, mp 246—247 °C; ^{1}H-NMR (200 MHz): 3.02 and 3.32 (each 3H, each s, 2 x NMe), 4.13 (3H, s, 2-Me), 6.52 (1H, br d, J = 8, 6-H), 6.62 (1H, br s, 8-H), 7.36—7.50 (3H, m, phenyl-H and 5-H), 7.57—7.68 (6H, m, phenyl-H), 7.92—7.97 (2H, m, phenyl-H); FAB-MS: *m/z* 389 (MH^+ - HCl, intensity ratio of 389 : 391 was about 3 : 1); *Anal.* Calcd for $C_{23}H_{22}N_4Cl_2 \cdot 1/2H_2O$: C, 63.60; H, 5.34; N, 12.90. Found: C, 63.76; H, 5.22; N, 13.08.

7-Chloro-3-(4-chlorophenyl)-1-[*C*-(4-chlorophenyl)-*N,N*-dimethylaminomethyleneamino]-2-methylimidazo[1,5-*a*]pyridin-2-ium Chloride (4b)

Stirred for 2.5 days; 57% (from **1** and **3b**) as yellow needles, mp 180—183 °C; ^{1}H-NMR (500 MHz): 3.02 and 3.31 (each 3H, each s, 2 x NMe), 4.17 (3H, s, 2-Me), 6.57 (1H, dd, J = 8 and 2, 6-H), 6.64 (1H, br s, 8-H), 7.48—8.90 (9H, m, phenyl-H and 5-H); FAB-MS: *m/z* 457 (MH^+ - HCl, intensity ratio of 457 : 459 : 461 was about 3 : 3 : 1); *Anal.* Calcd for $C_{23}H_{20}N_4Cl_4 \cdot H_2O$: C, 53.93; H, 4.33; N, 10.94. Found: C, 53.71; H, 4.48; N, 10.93.

7-Chloro-1-[*N,N*-dimethylamino-*C*-(4-methylphenyl)methyleneamino]-2-methyl-3-(4-methylphenyl)imidazo[1,5-*a*]pyridin-2-ium Chloride (4c)

Stirred for 4 days; 50% (from **1** and **3c**) as yellow needles, mp 230—232 °C; ^{1}H-NMR (200 MHz): 2.30 and 2.45 (each 3H, each s, 2 x phenyl-Me), 3.01 and 3.30 (each 3H, each s, 2 x NMe), 4.05 (3H, s, 2-Me), 6.55 (1H, br d, J = 7.4, 6-H), 6.61 (1H, br s, 8-H), 7.23—7.77 (9H, m, phenyl-H and 5-H); FAB-MS: m/z 417 (MH^+ - HCl, intensity ratio of 417 : 419 was about 3 : 1); *Anal.* Calcd for $C_{25}H_{26}N_4Cl_2$: C, 66.23; H, 5.78; N, 13.36. Found: C, 66.46; H, 5.62; N, 13.21.

7-Chloro-2,8-dimethyl-1-(*N*,*N*-dimethylamino-*C*-phenylmethyleneamino)-3-phenylimidazo[1,5-*a*]-pyridin-2-ium Chloride (5a)

Stirred for 2.5 days; 53% (from **2** and **3a**) as yellow needles, mp 240—242 °C; ^{1}H-NMR (200 MHz): 2.50 (3H, s, 8-Me), 2.94 and 3.31 (each 3H, each s, 2 x NMe), 3.68 (3H, s, 2-Me), 6.68 (1H, d, J = 7.0, 6-H), 7.25—7.49 (7H, m, phenyl-H and 5-H), 7.54—7.59 (4H, m, phenyl-H); FAB-MS: m/z 403 (MH^+ - HCl, intensity ratio of 403 : 405 was about 3 : 1); *Anal.* Calcd for $C_{24}H_{24}N_4Cl_2 \cdot 2H_2O$: C, 60.63; H, 5.94; N, 11.79. Found: C, 60.69; H, 5.84; N, 11.68.

7-Chloro-3-(4-chlorophenyl)-1-[*C*-(4-chlorophenyl)-*N*-methylaminomethyleneamino]-2,8-dimethyl-imidazo[1,5-*a*]pyridin-2-ium Chloride (5b)

Stirred for 4 days; 56% (from **2** and **3b**) as yellow plates, mp 274—276 °C; IR: cm^{-1} 3160 (N-H); ^{1}H-NMR (200 MHz): 2.62 (3H, s, 8-Me), 2.89 (3H, d, J = 4.8, changed to singlet after addition of D_2O, NMe), 3.71 (3H, s, 2-Me), 6.72 (1H, d, J = 7.4, 6-H), 7.43—7.66 (9H, m, phenyl-H and 5-H), 8.95 (1H, br, exchangeable with D_2O, NH); FAB-MS: m/z 457 (MH^+ - HCl, intensity ratio of 457 : 459 : 461 was about 3 : 3 : 1); *Anal.* Calcd for $C_{23}H_{20}N_4Cl_4$: C, 53.89; H, 4.08; N, 11.34. Found: C, 53.62; H, 4.25; N, 11.16.

7-Chloro-2,8-dimethyl-1-[*N*-methylamino-*C*-(4-methylphenyl)methyleneamino]-3-(4-methyl-phenyl)imidazo[1,5-*a*]pyridin-2-ium Chloride (5c)

Stirred for 3 days; 42% (from **2** and **3c**) as yellow plates, mp 250—252 °C; IR: cm^{-1} 3160 (N-H); ^{1}H-NMR (200 MHz): 2.42 and 2.61 (each 3H, each s, 2 x phenyl-Me), 2.47 (3H, s, 8-Me), 2.90 (3H, d, J = 4.8, changed to singlet after addition of D_2O, NMe), 3.71 (3H, s, 2-Me), 6.65 (1H, d, J = 7.5, 6-H), 7.30 (2H, d, J = 8, phenyl-H), 7.42—7.51 (7H, m, phenyl-H and 5-H), 8.83 (1H, br d, J = 4.8, exchangeable with D_2O, NH); FAB-MS: m/z 417 (MH^+ - HCl, intensity ratio of 417 : 419 was about 3 : 1); *Anal.* Calcd for $C_{25}H_{26}N_4Cl_2 \cdot H_2O$: C, 63.70; H, 5.99; N, 11.88. Found: C, 63.91; H, 5.84; N, 11.90.

Crystallography of 7-Chloro-3-(4-chlorophenyl)-1-[*C*-(4-chlorophenyl)-*N*,*N*-dimethylamino-methyleneamino]-2-methylimidazo[1,5-*a*]pyridin-2-ium Chloride (4b) Monohydrate

A yellow prismatic crystal having approximate dimensions of 0.50 x 0.40 x 0.40 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC5R diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å). Crystal data: $[C_{23}H_{22}N_4Cl_4O]^+Cl^- \cdot H_2O$; M_r = 512.27; monoclinic, space group $C2/c$, Z = 8 with a = 18.860 (5) Å, b = 16.193 (7) Å, c = 15.969 (4) Å, β = 91.04 (2)°, V = 4876 (5) Å^3, D_{calc} = 1.395 g/cm^3, and μ = 0.51 mm^{-1}. Calculations were performed using the TEXSAN program.[9] The structure was solved by a direct method. The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement was based on 1676 observed reflections [$I > 3.00\sigma(I)$] and 289 variable parameters and converged (largest parameter shift was 0.08 times of its esd) with unweighted and weighted residual factors of R = 0.064 and R_w = 0.062.

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