Study on the process of simultaneous oxidation of acyl chloride of novel insecticide tetrachlorantraniliprole using in situ FTIR

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ABSTRACT: The novel insecticide tetrachlorantraniliprole was synthesized utilizing 2,3,5-trichloropyridine as the starting material by a six-step route in 18% yield. The process of simultaneous oxidation and acyl chlorination was studied by in situ FTIR. The molecular structure of tetrachlorantraniliprole was identified by means of NMR, IR, MS, and X-ray diffraction analyses. The single crystal of tetrachlorantraniliprole was formed from toluene solvent, and exhibited monoclinic P\textsubscript{2}/\textsubscript{1} \textsuperscript{n} group with crystal parameters of } a = 15.3316(16) \text{Å, } b = 16.7139(16) \text{Å, } c = 19.6687(19) \text{Å, } V = 4835.2(8) \text{Å}^3, \text{and } Z = 4. \text{Moreover, its density is } 1.605 \text{g/cm}^3, \text{F(000)} = 2328.0, \mu = 2.17 \text{mm}^{-1}, \text{and 26933 reflections were measured (2.992}^\circ < 20 < 51.998^\circ).

KEYWORDS: tetrachlorantraniliprole, synthesis, crystal structure, in situ FTIR

INTRODUCTION

The application of insecticides plays a significant role in the prevention of insect pests to achieve high agricultural productivity [1–3]. Considering the resistance of pests to many current pesticides, the development of innovative insecticides with a new mechanism has been demonstrated as a powerful approach for comprehensive pest management [4–6]. Recently, anthranilic diamide insecticides have gained increasing attention globally due to their unique chemical structure, different mechanism of action and other features [7, 8]. Several new insecticides, such as chlorantraniliprole [9], cyantraniliprole [10, 11], tetrachlorantraniliprole [12], and cyclaniliprole [13] have been subsequently discovered. Among them, chlorantraniliprole was the first insecticide with the structure of anthranilic diamides to appear on the market, and was launched in 2008 by DuPont. Compared with traditional pesticides, it exhibits a new mechanism by activating the ryanodine receptor to imbalances the calcium cation, causing the insects to lose their lives under continuous interaction [14]. Tetra-chlorantraniliprole, another novel anthranilic diamide insecticide, was discovered in 2014 by the Team of Bin Li (Chinese SYRICI) via structural modification of chlorantraniliprole (Fig. 1). Tetrachlorantraniliprole is a low-toxic pesticide with acute oral toxicity of LD\textsubscript{50} > 5000 mg/kg towards female and male rats, acute dermal toxicity of LD\textsubscript{50} > 2000 mg/kg towards female and male rats, and no irritation to rabbit eyes and skin [15, 16].

In general, the conversion of a carboxylic acid to its carbonyl chloride by thionyl chloride is a straightforward procedure. The common preparation method for various anthranilamide insecticides is usually through oxidation of pyrazoline-carboxylate esters to pyrazole-carboxylate esters, followed by hydrolysis, acyl chlorination, and aminolysis [15, 16]. However, there are few reports on the transformations in which thionyl chloride acts both as an oxidant and acyl chlorination reagent, and the process of pyrazoline-carboxylic acids transforming directly to pyrazole-carbonyl chlorides through simultaneous oxidation and acyl chlorination.

In this work, the synthesis of tetrachlorantraniliprole via a six-step route is presented. The process of simultaneous oxidation and acyl chlorination was monitored by in situ FTIR analysis. The single-crystal structure of tetrachlorantraniliprole was also studied.
MATERIALS AND METHODS

Chemistry

The starting material 2,3,5-trichloropyridine (98% purity) was purchased from Xiya Reagent, China. All other related chemicals and reagents were purchased from Sinopharm Chemical Reagent Co., Ltd., China. EasyMax and ReactIR 702L (Mettler Toledo, Switzerland) were used as the PAT analysis systems.

Synthetic procedure for tetrachlorantraniliprole

The procedure for the synthesis of tetrachlorantraniliprole is shown in Fig. 2 [15]. Pyrazoline-carboxylate ester (4, 10.0 mmol) was dissolved in a mixed solution of 15 ml THF and 15 ml water, and then sodium hydroxide (12.0 mmol) was added. The mixture was stirred overnight at 25°C and then concentrated. The residue was redissolved in a mixed solution of 40 ml water and 20 ml ethyl acetate. The aqueous layer was separated, acidified to pH = 2–3, and filtered to give the solid product of pyrazoline-carboxylic acid 5.

Pyrazoline-carboxylic acid 5 (1.0 mmol) was suspended in 25 ml toluene, and thiocarbonyl chloride (5.0 mmol) was added. The mixture was heated to reflux temperature for 2 h and then concentrated. The residue, pyrazole-carbonyl chloride 6, was diluted with 5 ml of acetonitrile and added dropwise into a mixture of 2-amino-3,5-dichloroanilinamide (1.1 mmol) in 10 ml acetonitrile. The reaction mixture was heated to reflux temperature for 2 h and then filtered. The precipitate was washed with 15 ml water and dried to afford the final product tetrachlorantraniliprole 7. Then, it was cultured from toluene to afford a single crystal. White solid; m.p. 189–191°C; 

\[
\begin{align*}
\text{H NMR} & \text{ (600MHz, DMSO)}\; \delta \text{ (ppm):} & 10.55 & \text{(s, 1H, NH)}, \\
\text{C NMR} & \text{ (150MHZ, DMSO)}\; \delta & 167.33, & 156.65, 147.41, 145.57, 137.97, 137.94, 134.95, 132.97, 132.35, 130.53, 129.28, 129.09, 128.55, 126.30, 112.26, 26.93; \; \text{IR (KBr, cm}^{-1}) & 3417 \text{ (m, NH), 3250 (m), 3144 (w), 2922 (w), 1673 \text{ (s, CO), 1589 (m), 1566 (m), 1530 (s), 1463 (s), 1414 (m), 1346 (m), 1301 (m), 1170 (s), 1121 (m), 1095 (s), 1021 (s), 840 (s); HRMS (ESI)} \\
\text{calcd for C}_{18}H_{10}BrCl_{4}N_{2}O_{2}^{+}, (M+H)^{+} & 535.8850, \text{found 534.8844.}
\end{align*}
\]

X-ray crystallographic analysis

XRD patterns were recorded utilizing a single-crystal X-ray diffractometer on a SuperNova CCD, operated at 0.8 mA and 50 kV employing Mo Kα radiation at 296.15 K. The constructions were resolved through a direct approach applying SHELXS and polished on F2 through full-matrix least-squares employing SHELXL [17]. Refinement details and crystallographic parameters are listed in Table S1. The data of selected bond lengths are provided in Table S2 and bond angles in Table S3, respectively. CCDC reference number 2049913 corresponds to tetrachlorantraniliprole.

RESULTS AND DISCUSSION

Synthesis of tetrachlorantraniliprole

Fig. 2 shows the synthesis of tetrachlorantraniliprole via a six-step route. First, 2,3,5-trichloropyridine 1 was selected as the starting material to obtain the substituted hydrazine 2 in 72% yield. The reaction of substituted hydrazine with diethylmaleate in the presence of sodium ethoxide afforded pyrazolone 3 in 47% yield, which subsequently gave bromopyrazoline 4 in 67% yield after treatment with phosphoryl chloride at reflux temperature (of acetonitrile). The esters were hydrolyzed to pyrazoline-carboxylic acid 5 in 90% yield. Then, pyrazoline-carboxylic acid 5 was reacted with thionyl chloride to obtain pyrazole-carbonyl chloride 6 in 98% yield. Condensation of acyl chloride 6 with anthranilamide afforded tetrachlorantraniliprole 7 in 90% yield.

Process analytical technologies (PAT) are widely utilized in the pharmaceutical and pesticide fields [18]. Measurements of parameters difficult to survey with standard off-line approaches can be achieved by PAT technology. In this case, during traditional HPLC analysis with water as mobile phase, it is difficult to accurately monitor acyl chloride 6 as it is unstable in the aqueous phase. To investigate the process of acyl chlorination reaction with simultaneous oxidation between pyrazoline-carboxylic acids and thionyl chloride, a powerful PAT tool, ReactIR, was carried out and the results are shown in Fig. 3 and Fig. 4.

As shown in Fig. 3, there are three groups of peaks at 1235 cm$^{-1}$, 828 cm$^{-1}$, and 859 cm$^{-1}$. The peak at wavenumber of 1235 cm$^{-1}$ corresponds to the S=O stretching vibration of SOCl$_2$, the C−Cl stretching vibration peak is located at 828 cm$^{-1}$ which is regarded as the characteristic peak indicating acyl chlorination reaction, and the stretching vibration peak of C=C of pyrazole ring appears at 859 cm$^{-1}$ which is regarded as indicator of oxidation reaction, respectively.

The relative concentrations of SOCl$_2$ and acyl chloride 6 during the process of acyl chlorination and oxidation are shown in Fig. 4. Furthermore, the endpoint of reaction could be accurately judged by the concentration trends of the feed reactant SOCl$_2$. When SOCl$_2$ was added into the reaction solution, the concentration maintained the initial maximum value and the relative concentration of the peak at 1235 cm$^{-1}$ decreased continuously. After 30 min, the concentration of SOCl$_2$ hardly changed, indicating the end of the reaction. At the endpoint, there was still a large amount of residual SOCl$_2$, which indicates that SOCl$_2$ was excessive and its amount may be accurately reduced in the process optimization.
acyl chloride 6 at 828 cm\(^{-1}\) and 859 cm\(^{-1}\) increased simultaneously, indicating that the acylation reaction (at 828 cm\(^{-1}\)) and oxidation reaction (at 859 cm\(^{-1}\)) occurred at the same time.

**Single crystal structure**

The single crystal was in monoclinic \(P2_1/n\) space group (Table S1) with formula of \(C_{41}H_{28}Br_2Cl_8N_{10}O_4\). The simplified unit cell structure is shown in Fig. 5a, which displays the asymmetric unit comprised of two tetrachlorantraniliprole molecules and one toluene molecule (solvent). Fig. 5b shows the crystal structure of one molecule of tetrachlorantraniliprole. The bond lengths of N8-C23 and N6-C22 are 1.31 and 1.32 Å, similar to the typical C–N bond (1.32 Å). This result indicated that the N8-C23, N6-C22, N6-C18 and N7-C25 bonds of the target compound exhibited a partial double bond character due to large \(\pi\)-electron conjugation. The bond lengths of C27-C28, C29-C30, and C31-C32 are 1.370, 1.385, and 1.383 Å, similar to the typical C–C bond on the benzene ring (1.39 Å). The bond lengths of N6-C22 and C20-C21 are 1.325 and 1.375 Å, which correspond to the distances of C=N and C=C of the pyridine ring. The bond lengths of O3-C26 and O4-C33 are 1.222 and 1.223 Å, which correspond to the distance of the carbonyl group. The bond angles of C26-N9-C27, C26-N9-H9 and C27-N9-H9 are 125°, 117.5°, and 117.5°. Accordingly, the pyrazole carbonyl

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**Fig. 2** Synthetic route of tetrachlorantraniliprole. Reaction conditions: (a) hydrazine hydrate, dioxane, reflux; (b) diethyl maleate, sodium ethoxide, alcohol, 50 °C; (c) POBr\(_3\), CH\(_3\)CN, reflux; (d) NaOH, THF, H\(_2\)O; (e) SOCl\(_2\), toluene, reflux; (f) anthranilamide, CH\(_3\)CN, reflux.

**Fig. 3** In situ IR three-dimensional spectrum of acyl chlorination with oxidation.

**Fig. 4** Relative concentration profiles of sulfoxide chloride (at 1235 cm\(^{-1}\)) and compound 6 (chlorination at 828 cm\(^{-1}\), oxidation at 859 cm\(^{-1}\)).
chloride and anthranilamide moieties were coplanar. All of these coordination atoms result in a supramolecular structure for tetrachlorantraniliprole. Fig. 6 shows different view directions of tetrachlorantraniliprole. There are many pores among the molecules in all directions. The bond distances and bond angles of Br–C, Cl–C, N–C, and ON for tetrachlorantraniliprole are within the typical range [17, 19–21]. The results of bond distances and bond angles of Br–C, Cl–C, N–C, and O–N are listed in Table S2 and Table S3.

**CONCLUSION**

In this work, a novel insecticide tetrachlorantraniliprole was successfully prepared through a successive six-step path including hydrazine substitution, cyclization, bromination, hydrolysis, simultaneous oxidation and acyl chlorination, and amidation. Following the simultaneous oxidation and acyl chlorination, anthranilamide insecticides could be prepared more conveniently and with less discharge of waste sulfuric acid. Moreover, the application of in situ FTIR enhanced the efficiency of process optimization and provided the parameters of the kinetic process in real-time. In addition, the single crystal displayed an asymmetric unit comprised of two tetrachlorantraniliprole molecules and one toluene molecule. Tetrachlorantraniliprole is worthy of attention with the advantages of broad-spectrum activity, high efficiency, low toxicity, low manufacturing costs, and excellent market potential.
At present, tetrachlorantraniliprole is hardly used in overseas markets except China, but it is likely to expand to markets in Southeast Asia in the future.

Appendix A. Supplementary data

Supplementary data associated with this article can be found at http://dx.doi.org/10.2306/scienceasia1513-1874.2022.052.

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REFERENCES

1. Jeschke P (2016) Progress of modern agricultural chemistry and future prospects. Pest Manag Sci 72, 433–455.
2. Lamberg C, Jeanmart S, Luksch T, Plant A (2013) Current challenges and trends in the discovery of agrochemicals. Science 341, 742–746.
3. Guo H, Zhang X, Sun J, Zheng X, Zhao G, Li G, Qian H (2021) Effects of pyriproxyfen exposure on damage to midgut and related gene expressions in the Bombyx mori silkworm. ScienceAsia 47, 733–740.
4. Jeschke P (2021) Status and outlook for acaricide and insecticide discovery. Pest Manag Sci 77, 64–76.
5. Jeschke P (2017) Latest generation of halogen-containing pesticides. Pest Manag Sci 73, 1053–1066.
6. Jeanmart S, Edmunds AJF, Lamberg C, Pouliot M (2016) Synthetic approaches to the 2010–2014 new agrochemicals. Bioorganic Med Chem 24, 317–341.
7. Lahn GP, Cordova D, Barry JD (2009) New and selective ryanodine receptor activators for insect control. Bioorganic Med Chem 17, 4127–4133.
8. Selby TP, Lahn GP, Stevenson TM (2017) A retrospective look at anthranilic diamide insecticides: discovery and lead optimization to chlorantraniliprole and cyantraniliprole. Pest Manag Sci 73, 658–665.
9. Lahn GP, Selby TP, Freudenberg JH, Stevenson TM, Myers BJ, Seburyamo G, Smith BK, Flexner L, et al (2005) Insecticidal anthranilic diamides: a new class of potent ryanodine receptor activators. Bioorganic Med Chem Lett 15, 4898–4906.
10. Selby TP, Lahn GP, Stevenson TM, Hughes KA, Cordova D, Annan IB, Barry JD, Benner EA, et al (2013) Discovery of cyantraniliprole, a potent and selective anthranilic diamide ryanodine receptor activator with cross-spectrum insecticidal activity. Bioorganic Med Chem Lett 23, 6341–6345.
11. Caballero R, Cyma S, Schuster DJ, Portillo HE, Slater R (2013) Baseline susceptibility of Bemisia tabaci (Genn.) biotype B in southern Florida to cyantraniliprole. Crop Prot 44, 104–108.
12. Kambrekar DN, Jahagirdar S, Aruna J (2017) Tetranipliprol-new diamide insecticide molecule featuring novel mode of action against soybean insect pests. Biochem Cell Arch 17, 801–804.
13. Lu Z, Pan H (2021) Preparative isolation of the major metabolite NK-1375 of diamide insecticide cyclaniliprole and its application to pertinent residue analysis in plant-origin foods using UHPLC–MS/MS. Biomed Chromatogr 35, e5056.
14. Liu SW, Chang XH, Ban LF, Song YQ, Li B (2017) Research on biological activity of four ryanodine receptor insecticides. Modern Agrochemicals 16, 51–53.
15. Bin L, Hui-bin Y, Jun-feng W, Yu-quan S (2014) Synthesis and insecticidal activity of Si Lv Chong Xian'an. Mod Agrochem 13, 17–20.
16. Cong YB, Wei ZY, Ma XH, Li ZL, Li QG, Ming X, Cheng CS (2021) Determination of SADT and TMRad of 3-bromo-1-(3,5-dichloropyridin-2-yl)-4,5-dihydro-1H-pyrazole-5-carboxylic acid: Applying thermal decomposition kinetics. Results Chem 3, ID 100112.
17. Li Z, Cong Y, Ma X, Wei Z, Cheng C, Shi F, Li S (2020) Absolute configuration of four chiral isomers of pyrsoxa-zole and their bioactivity. Pest Manag Sci 76, 3780–3784.
18. Graciano-Verdugo AZ, Peralta E, González-Ríos H, Soto-Valdez H (2006) Determination of α-tocopherol in low-density polyethylene (LDPE) films by diffuse reflectance Fourier transform infrared (DRIFT-IR) spectroscopy compared to high performance liquid chromatography (HPLC). Anal Chim Acta 557, 367–372.
19. Sun PP, Zhang YH, Yu X, Shi Q, Tian B, Gao J, Shi FN (2020) Cu powder decorated 3D Mn-MOF with excellent electrochemical properties for supercapacitors. Inorganica Chim Acta 508, ID 119629.
20. Sigala PA, Ruben EA, Liu CW, Piccoli PMB, Hohenstein EG, Martinez TJ, Schultz AJ, Herschlag D (2015) Determination of hydrogen bond structure in water versus aprotic environments to test the relationship between length and stability. J Am Chem Soc 137, 5730–5740.
21. Jia L-L, Ji Y-C, Yangk K, Wang Z-J, Chen H-B, Pan F (2020) Interface reconstruction study by functional scanning probe microscope in Li-ion battery research. Chin J Struct Chem 39, 200–205.
Appendix A. Supplementary data

**Table S1** Crystallographic parameters for tetrachlorantraniliprole.

| Parameter                  | Value                                      |
|----------------------------|--------------------------------------------|
| Empirical formula          | C_{41}H_{28}N_{10}O_{4}Cl_{8}Br_{2}         |
| Formula weight             | 1168.15                                    |
| Temperature (K)            | 296.15                                     |
| Crystal system             | monoclinic                                 |
| Space group                | P2\_1/n                                    |
| a (Å)                      | 15.3311(16)                                |
| b (Å)                      | 16.7139(16)                                |
| c (Å)                      | 19.6687(19)                                |
| α (°)                      | 90                                         |
| β (°)                      | 106.38                                     |
| γ (°)                      | 90                                         |
| Volume (Å³)                | 4835.2(8)                                  |
| Z                          | 4                                          |
| Density (g/cm³)            | 1.605                                      |
| \( \mu \) (mm⁻¹)          | 2.17                                       |
| F(000)                     | 2328.0                                     |
| Crystal size (mm³)         | 0.28 \times 0.22 \times 0.2               |
| 2θ range for data collection (°) | 2.992 to 51.998                           |
| Index ranges               | \(-14 \leq h \leq 18, -20 \leq k \leq 15, -24 \leq l \leq 22\) |
| Reflections collected      | 26933                                      |
| Independent reflections    | 9492 [R_{int} = 0.0370, R_{sigma} = 0.0484] |
| Data/restraints/parameters | 9492/0/589                                 |
| Goodness-of-fit on \( F^2 \) | 1.013                                      |
| Final R indexes \([I \geq 2\sigma(I)]\) | \( R_1 = 0.0468, wR_2 = 0.1065 \)         |
| Final R indexes [all data] | \( R_1 = 0.0866, wR_2 = 0.1236 \)         |
| CCDC number                | 2049913                                    |
| Bond      | Bond length  | Bond      | Bond length  |
|-----------|--------------|-----------|--------------|
| Br(1)-C(6)| 1.853(4)     | N(10)-C(34)| 1.447(5)     |
| Br(2)-C(23)| 1.868(3)   | N(10)-H(10)| 0.8600       |
| Cl(1)-C(2)| 1.726(4)     | C(1)-C(2)| 1.348(6)     |
| Cl(2)-C(4)| 1.712(4)     | C(1)-H(1)| 0.9300       |
| Cl(3)-C(11)| 1.727(4)    | C(2)-C(3)| 1.368(6)     |
| Cl(4)-C(13)| 1.726(4)    | C(3)-C(4)| 1.379(6)     |
| Cl(5)-C(19)| 1.724(4)    | C(3)-H(3)| 0.9300       |
| Cl(6)-C(21)| 1.717(4)    | C(4)-C(5)| 1.370(6)     |
| Cl(7)-C(28)| 1.728(4)    | C(6)-C(7)| 1.379(5)     |
| Cl(8)-C(30)| 1.725(3)    | C(7)-C(8)| 1.361(5)     |
| O(1)-C(9)| 1.214(4)     | C(7)-H(7)| 0.9300       |
| O(2)-C(16)| 1.234(4)     | C(8)-C(9)| 1.474(5)     |
| O(3)-C(26)| 1.222(4)     | C(10)-C(15)| 1.383(5)   |
| O(4)-C(33)| 1.233(4)     | C(10)-C(11)| 1.389(5)    |
| N(1)-C(5)| 1.310(5)     | C(11)-C(12)| 1.374(5)    |
| N(1)-C(1)| 1.333(5)     | C(12)-C(13)| 1.356(6)    |
| N(2)-N(3)| 1.355(4)     | C(12)-H(12)| 0.9300       |
| N(2)-C(8)| 1.362(4)     | C(13)-C(14)| 1.378(5)     |
| N(2)-C(5)| 1.428(5)     | C(14)-C(15)| 1.383(5)     |
| N(3)-C(6)| 1.306(5)     | C(14)-H(14)| 0.9300       |
| N(4)-C(9)| 1.350(4)     | C(15)-C(16)| 1.492(5)     |
| N(4)-C(10)| 1.421(4)    | C(17)-H(17A)| 0.9600   |
| N(4)-H(4)| 0.8600       | C(17)-H(17B)| 0.9600      |
| N(5)-C(16)| 1.316(4)    | C(17)-H(17C)| 0.9600      |
| N(5)-C(17)| 1.448(5)    | C(18)-C(19)| 1.368(5)     |
| N(5)-H(5)| 0.8600       | C(18)-H(18)| 0.9300       |
| N(6)-C(22)| 1.325(4)    | C(19)-C(20)| 1.374(5)     |
| N(6)-C(18)| 1.332(4)    | C(20)-C(21)| 1.375(5)     |
| N(7)-N(8)| 1.361(4)     | C(20)-H(20)| 0.9300       |
| N(7)-C(25)| 1.363(4)    | C(21)-C(22)| 1.383(5)     |
| N(7)-C(22)| 1.420(4)    | C(23)-C(24)| 1.383(5)     |
| N(8)-C(23)| 1.310(5)    | C(24)-C(25)| 1.364(5)     |
| N(9)-C(26)| 1.333(4)    | C(24)-H(24)| 0.9300       |
| N(9)-C(27)| 1.412(4)    | C(25)-C(26)| 1.485(4)     |
| N(9)-H(9)| 0.8600       | N(10)-C(33)| 1.320(4)     |
| Bond Angles | Angle (°) | Bond Angles | Angle (°) |
|------------|----------|------------|----------|
| C(5)-N(1)-C(1) | 117.2(4) | N(3)-C(6)-C(7) | 113.4(4) |
| N(3)-N(2)-C(8) | 111.7(3) | N(3)-C(6)-Br(1) | 119.8(3) |
| N(3)-N(2)-C(5) | 116.7(3) | C(7)-C(6)-Br(1) | 120.6(3) |
| C(8)-N(2)-C(5) | 131.5(3) | C(8)-C(7)-C(6) | 104.9(3) |
| C(6)-N(3)-N(2) | 103.8(3) | C(8)-C(7)-H(7) | 127.6 |
| C(9)-N(4)-C(10) | 123.2(3) | C(6)-C(7)-H(7) | 127.6 |
| C(9)-N(4)-H(4) | 118.4 | C(7)-C(8)-N(2) | 106.2(3) |
| C(10)-N(4)-H(4) | 118.4 | C(7)-C(8)-C(9) | 129.8(3) |
| C(16)-N(5)-C(17) | 122.2(3) | N(2)-C(8)-C(9) | 124.0(3) |
| C(16)-N(5)-H(5) | 118.9 | O(1)-C(9)-N(4) | 122.1(3) |
| C(17)-N(5)-H(5) | 118.9 | O(1)-C(9)-C(8) | 113.8(3) |
| C(22)-C(6)-H(6) | 118.3 | N(4)-C(9)-C(8) | 113.8(3) |
| C(9)-N(4)-H(4) | 118.4 | C(8)-C(7)-C(6) | 104.9(3) |
| C(10)-N(4)-H(4) | 118.4 | C(8)-C(7)-H(7) | 127.6 |
| C(16)-N(5)-C(17) | 122.2(3) | N(2)-C(8)-C(9) | 124.0(3) |
| C(16)-N(5)-H(5) | 118.9 | O(1)-C(9)-N(4) | 122.1(3) |
| C(17)-N(5)-H(5) | 118.9 | O(1)-C(9)-C(8) | 113.8(3) |
| C(22)-N(6)-C(18) | 118.3 | N(4)-C(9)-C(8) | 113.8(3) |
| C(9)-N(4)-H(4) | 118.4 | C(8)-C(7)-C(6) | 104.9(3) |
| C(10)-N(4)-H(4) | 118.4 | C(8)-C(7)-H(7) | 127.6 |
| C(16)-N(5)-C(17) | 122.2(3) | N(2)-C(8)-C(9) | 124.0(3) |
| C(16)-N(5)-H(5) | 118.9 | O(1)-C(9)-N(4) | 122.1(3) |
| C(17)-N(5)-H(5) | 118.9 | O(1)-C(9)-C(8) | 113.8(3) |