Expeditious Synthesis and Single Crystal Structure of New Pyrazole-Fused 1,4-Oxazine

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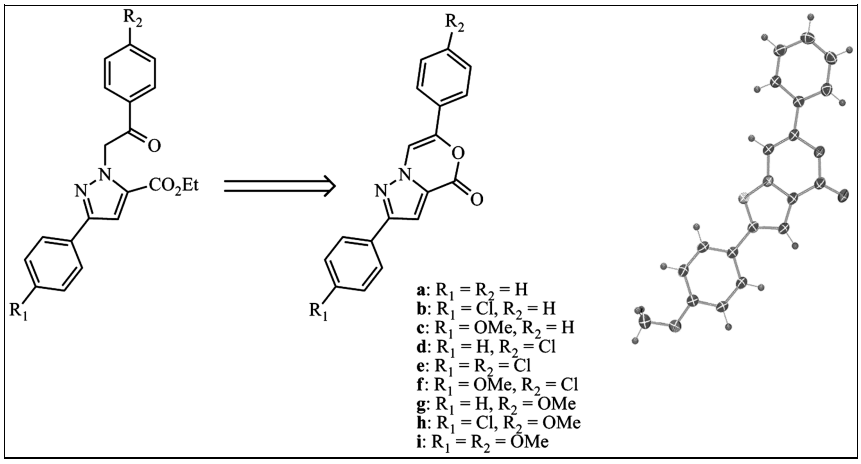

A series of 2,6-diphenyl-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-4-ones has been synthesized *via* a lactonization of 1-(2-oxo-2-phenylethyl)-3-phenyl-1*H*-pyrazole-5-carboxylic acids in the presence of Ac_2O at reflux temperature. The products were isolated by simple filtration in excellent yields and were characterized by IR, ^{1}H-NMR, and HRMS. The molecular structure was confirmed by the X-ray crystal analysis of one compound that was prone to crystallization.

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INTRODUCTION

Convenient routes to aromatic heterocycles are of ongoing interest. In particular, there is an increasing interest in pursuing the study of pyrazole-fused heterocycles, such as pyrazolo-benzotriazine [1], pyrazolo-isoquinoline [2], pyrazolo-indole [3], pyrazolo-naphthyridine [4], pyrazolo-oxazepine [5], pyrazolo-phthalazine [6], pyrazolo-pyrimidine [7], pyrazolo-pyridine [8], pyrazolo-pyridazinone [9], pyrazolo-quinoline [10], pyrazolo-triazine [11], pyrazolo-tetrazine [12], pyrazolo-pyrido-pyrimidine [13], pyrazolo-pyrrolo-pyridine [14], and pyrazolo-triazolo-pyrimidine [15]. Because of their bicyclic or polycyclic nature and conformational constraints, these fused heterocycles may be useful as building blocks in medicinal chemistry such as anti-inflammatory, antifungal, antiplatelets, antituberculosis, antibacterial, antitumor, anticonvulsant, antimalarial, and analgesic agents.

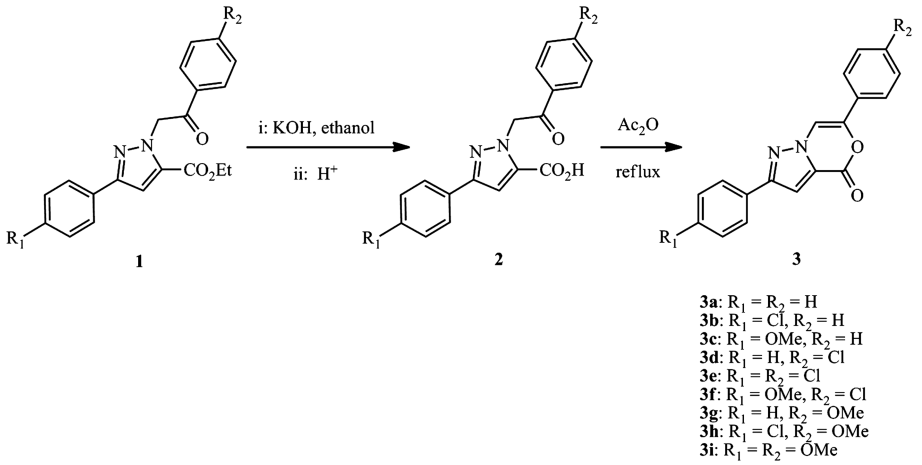
The molecular properties of pyrazolo-oxazine are practically unknown. As part of our ongoing research aiming at the synthesis of new anticancer compounds [16], we are interested in construction of pyrazolo-oxazine skeleton [17]. Although several methods are described for the synthesis of various six-membered lactone moieties [18], many of the established approaches are still severely limited in their use of expensive catalysts, high toxic reagents and solvents involved, low yields, or tedious post-processing required.

Herein, we would like to report the synthesis of novel pyrazolo-oxazine with excellent yields and a single crystal structure.

RESULTS AND DISCUSSION

In our previous paper [17], we described that ethyl 1-(2-aryl-2-oxoethyl)-3-ferrocenyl-1*H*-pyrazole-5-carboxylate analogues undergo intramolecular esterification reaction *via* soft enolate formation on treatment with $MgBr_2{\cdot}Et_2O$ and *N*,*N*-diisopropylethylamine for 4 h to afford 2-ferrocenyl-6-substituted-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-4-ones in 11–44% yield. Thus, we explored first whether the conditions were suitable for ethyl 3-(4-methoxyphenyl)-1-(2-oxo-2-phenylethyl)-1*H*-pyrazole-5-carboxylate. The result

Scheme 1



showed that target compound **3c** can be obtained under the reaction conditions in toluene refluxed with $MgBr_2 \cdot Et_2O$ and *N*,*N*-diisopropylethylamine for 4 h, but in only 26% yield. Inspired with the result, we searched other reaction conditions for the synthesis of target compounds.

The synthetic strategy we adopted for the synthesis of novel 2,6-diphenyl-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-4-ones **3** are outlined in the Scheme 1. Starting material, ethyl 1-(2-oxo-2-phenylethyl)-3-phenyl-1*H*-pyrazole-5-carboxylate analogue **1** can be easily prepared following the procedure described in our latest paper [19]. Basic hydrolysis of **1** followed by acidic treatment afforded 1-(2-oxo-2-phenylethyl)-3-phenyl-1*H*-pyrazole-5-carboxylic acids **2**. The pyrazolo[5,1-*c*][1,4]oxazin-4-one derivatives **3** were obtained by the lactonization of corresponding the intermediates **2** in the presence of Ac_2O at reflux temperature in excellent yields (70–88%). The structures of the novel pyrazole-fused oxazinone derivatives **3** were determined by IR, ^{1}H-NMR, and HRMS spectroscopy. For example, in compound **3c**, the C=O absorption was found at the region of 1743 cm^{-1}. In the ^{1}H-NMR spectra, two signals for aromatic ortho H-atoms in the methoxybenzene moiety appeared at the range of δ = 7.82 and 6.99 ppm as doublet peaks (J = 8.7 Hz). The methoxy group shows as singlet at δ = 3.86 ppm. In addition, two singlet signals appeared at δ = 7.36 and 7.92 ppm are consistent with protons in pyrazole and oxazine moiety, respectively. In the HRMS, in accordance with the molecular structure of $C_{19}H_{14}N_2O_3$, compound **3c** gave a [M + H]-ion peak at *m/z* 319.1080 (calcd: 319.1083).

In the title molecule of **3c**, two benzene rings are bonded to pyrazolo[5,1-*c*][1,4]oxazin-4-one moiety at C(2) and C(12) as showed in Figure 1. The double bond length of C(2)—C(3) reveals unambiguous proof of the reaction between hydroxyl of enolate and carboxyl group and definitely assigned the structure of pyrazolo[5,1-*c*][1,4]oxazin-4-one. The length of the C(1)—O(2) bond 1.376(3) Å indicates the conjugation between the lone pair of the oxygen atom and π-system of the carbonyl group. The distances of C(2)—C(5), 1.470(3) Å and of C(12)—C(13), 1.470(3) Å are consistent with single bonds between sp^2-hybridized carbon atoms (Table 1).

All aromatic rings in the structure are planar within 0.005(2) Å deviation. The oxazine ring is planar with a maximum deviation of −0.012(3) Å for the atom C(1) though without aromatic property. It seems that the presence of the conjugated conformation enforces planarity of the oxazine ring system. The methoxyl group is coplanar to the benzene ring [the C(19)—O(3)—C(16)—C(15) torsion angle is 1.7(3)°]. Moreover, it is also observed that the whole molecule is planar with the torsion angle: N(2)—C(12)—C(13)—C(14) −1.6(3)°, O(2)—C(2)—C(5)—C(6)−2.9(3)°. The dihedral angles formed by substituted benzene and unsubstituted benzene ring with pyrazole are 1.91(7)° and 6.54(10)°, respectively.

The molecules of **3c** are mutually parallel and disposed in a herringbone fashion. Two intramolecular H-bonds resulting from O(2) in oxazine moiety and N(2) in pyrazole moiety are contributed for planar conformation (Fig. 2).

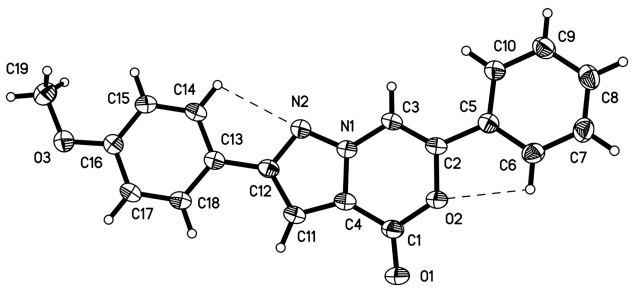


Figure 1. Molecular structure and atomic numbering showing 30% probability displacement ellipsoids in structure **3c**.

Table 1

Selected bond lengths (Å) and angles (°) for the compound **3c**.

O(1)—C(1)	1.210 (2)	C(1)—O(2)—C(2)	122.96 (16)
O(2)—C(1)	1.376 (3)	N(2)—N(1)—C(4)	112.48 (15)
O(2)—C(2)	1.396 (2)	N(2)—N(1)—C(3)	124.46 (16)
N(1)—N(2)	1.346 (2)	C(4)—N(1)—C(3)	123.03 (16)
N(1)—C(4)	1.372 (2)	N(1)—N(2)—C(12)	104.63 (16)
N(1)—C(3)	1.388 (2)	O(1)—C(1)—O(2)	117.8 (2)
N(2)—C(12)	1.349 (3)	O(1)—C(1)—C(4)	126.0 (2)
C(1)—C(4)	1.440 (3)	O(2)—C(1)—C(4)	116.23 (18)
C(2)—C(3)	1.334 (3)	C(3)—C(2)—O(2)	120.42 (17)
C(2)—C(5)	1.470 (3)	C(2)—C(3)—N(1)	118.67 (18)
C(4)—C(11)	1.373 (3)	N(1)—C(4)—C(1)	118.64 (17)
C(11)—C(12)	1.410 (3)	N(1)—C(4)—C(11)	106.44 (17)
C(12)—C(13)	1.470 (3)	C(4)—C(11)—C(12)	105.29 (18)

There are two C—H$\cdots\pi$ contacts between H atoms and the π-electrons of the rings (Table 2). The contact from phenylic atom H(9) to the centre of the benzene ring [C(5)—C(6)—C(7)—C(8)—C(9)—C(10)] has a distance of 2.78 Å, and the angle at the H atom is 137°. The second, slightly longer, contact links methylic atom H_A at a distance of 2.79 Å to the centre of the oxazine ring and the angle at the H atom is 148°. Furthermore, in this structure, a C—O$\cdots\pi$ contact to the centre of the core oxazine can be observed. The distance from O(1) to the centre of the oxazine ring is 2.994(2) Å and the angle at O(1) is 136.97(18)°. It is interesting to note that there is no π-π stacking interaction between aromatic rings.

CONCLUSIONS

An expeditious method for preparing 2,6-diphenyl-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-4-one derivatives was described, and the structure of synthesized compounds was determined by IR, ^{1}H-NMR, and HRMS. Moreover, the molecular structure was confirmed by the X-ray crystal analysis. Currently, investigations are underway to elucidate the bioactivity of these pyrazole-fused oxazinone and the results will be reported in due course.

EXPERIMENTAL

General. Analytical TLC was carried out with Merck silica gel (60 F_{254}). Melting points were determined with an XD-4 digital micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker Avance 400 (400 MHz) spectrometer, using $CDCl_3$ as solvent and TMS as internal standard. The chemical shifts (δ) were measured in ppm with respect to the solvent ($CDCl_3$: ^{1}H: δ = 7.26 ppm). IR spectra were measured as KBr plates with an IR spectrophotometer Avtar 370 FTIR (Termo Nicolet). HRMS spectra were recorded with a LTQ Orbitrap Hybrid mass spectrograph. Reagents and solvents used were commercially available analytical grade materials used as supplied, without further purification.

General procedure for the synthesis of 2,6-diphenyl-4H-pyrazolo[5,1-c][1,4]oxazin-4-ones. To a mixture of **1** (2.5 mmol) in 50 mL of EtOH/H_2O (v/v = 4:1), KOH (566 mg, 10.1 mmol) was added at ambient temperature. The reaction mixture was stirred and heated to reflux for 1–2 h, until TLC indicated the end of reaction. Solvent was removed under reduced pressure, and the residue was distilled in 100-mL H_2O. The mixture was neutralized (pH = 5) using aqueous HCl (10%). The crude product was filtered from the formed suspension and washed with water. Product **2** was obtained without further purification.

A mixture of 1-(2-oxo-2-phenylethyl)-3-phenyl-1*H*-pyrazole-5-carboxylic acid **2** (2.0 mmol) and acetic anhydride (10–15 mL) was stirred and heated under nitrogen atmosphere. The reaction mixture was maintained under reflux for 4 h, until TLC indicated the end of reaction. After this time, the reaction mixture stood over night and the solid formed was collected by filtration and washed with ethanol and water to afford crystals. As a result of this process, the compounds **3** were prepared in total yield of 70–88%.

2,6-Diphenyl-4H-pyrazolo[5,1-c][1,4]oxazin-4-one (3a). White solid, yield: 72%, mp. 216–217°C; IR (KBr): 1745 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.41 (t, 1H, *J* = 7.2, Ar—H), 7.46 (s, 1H, pyrazole-H), 7.47–7.51 (m, 5H, Ar—H), 7.76 (d, 2H, *J* = 7.6, Ar—H), 7.89 (d, 2H, *J* = 7.2, Ar—H), 7.95 (s, 1H, oxazine-H); HRMS ($C_{18}H_{13}N_2O_2$): calcd. for $[M + H]^+$ 289.0977, found 289.0978.

2-(4-Chlorophenyl)-6-phenyl-4H-pyrazolo[5,1-c][1,4]oxazin-4-one(3b). White solid, yield: 71%, mp. 265–266°C; IR (KBr): 1737 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.43–7.44 (m, 2H, Ar—H), 7.46 (s, 1H, pyrazole-H), 7.48–7.51 (m, 3H, Ar—H), 7.76 (d, 2H, *J* = 7.0, Ar—H), 7.83 (d, 2H, *J* = 8.3, Ar—H), 7.94 (s, 1H, oxazine-H); HRMS ($C_{18}H_{12}ClN_2O_2$): calcd. for $[M + H]^+$ 323.0587, found 323.0570.

2-(4-Methoxyphenyl)-6-phenyl-4H-pyrazolo[5,1-c][1,4]oxazin-4-one (3c). Yellow solid, yield: 76%, mp. 207–209°C; IR (KBr): 1743 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.86 (s, 3H, OCH_3), 6.99 (d, 2H, *J* = 8.7, Ar—H), 7.36 (s, 1H, pyrazole-H), 7.45 (t, 1H, *J* = 7.6, Ar—H), 7.47 (t, 2H, *J* = 7.6, Ar—H), 7.75 (d, 2H, *J* = 7.6, Ar—H), 7.82 (d, 2H, *J* = 8.7, Ar—H), 7.92 (s, 1H, oxazine-H); HRMS ($C_{19}H_{15}N_2O_3$): calcd. for $[M + H]^+$ 319.1083; found 319.1080.

6-(4-Chlorophenyl)-2-phenyl-4H-pyrazolo[5,1-c][1,4]oxazin-4-one (3d). Yellow solid, yield: 81%, mp. 222–223°C; IR (KBr): 1757 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.41 (t, 1H, *J* = 7.2, Ar—H), 7.45 (s, 1H, pyrazole-H), 7.46

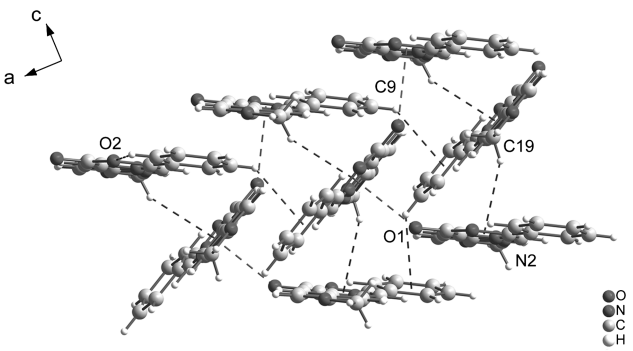


Figure 2. Packing diagram of the structure **3c**, C—H(O)$\cdots\pi$ interactions were showed with dashed lines.

Table 2

C—H/O···π interaction geometry for compound **3c**.

C—H/O···π	C—H/O (Å)	H/O···Cg[a] (Å)	C···Cg (Å)	C—H/O···Cg (°)
C(9)—H(9)···Cg(1)[b]	0.93	2.78	3.513 (3)	137
C(19)—H(19)$_A$···Cg(2)[c]	0.96	2.79	3.647 (3)	148
C(1)—O(1)···Cg(2)[d]	1.210 (2)	2.994 (2)	3.965 (3)	136.97 (18)

[a]Cg(1) and Cg(2) are centroids of the unsubstituted benzene ring and oxazine ring, respectively.
[b]Symmetry code: $-1/2 - x, y, -1/2 + z$.
[c]$-x, 1 - y, -1/2 + z$.
[d]$1/2 - x, y, 1/2 + z$.

(d, 2H, J = 8.6, Ar—H), 7.47 (t, 2H, J = 7.2, Ar—H), 7.69 (d, 2H, J = 8.6, Ar—H), 7.89 (d, 2H, J = 7.2, Ar—H), 7.93 (s, 1H, oxazine-H); HRMS ($C_{18}H_{12}ClN_2O_2$): calcd. for $[M + H]^+$ 323.0587, found 323.0587.

2,6-Bis(4-chlorophenyl)-4H-pyrazolo[5,1-c][1,4]oxazin-4-one (3e). Yellow solid, yield: 84%, mp. 284–285°C; IR (KBr): 1756 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.42 (d, 2H, J = 8.6, Ar—H), 7.45 (s, 1H, pyrazole-H), 7.47 (d, 2H, J = 8.4, Ar—H), 7.69 (d, 2H, J = 8.6, Ar—H), 7.82 (d, 2H, J = 8.4, Ar—H), 7.90 (s, 1H, oxazine-H); HRMS ($C_{18}H_{11}Cl_2N_2O_2$): calcd. for $[M + H]^+$ 357.0198, found 357.0199.

6-(4-Chlorophenyl)-2-(4-methoxyphenyl)-4H-pyrazolo[5,1-c][1,4]oxazin-4-one (3f). Yellow solid, yield: 88%, mp. 255–256°C; IR (KBr): 1754 (C=O) cm^{-1}; ^{1}H-NMR (DMSO, 400 MHz) δ: 3.81 (s, 3H, OCH_3), 7.05 (d, 2H, J = 8.8, Ar—H), 7.58 (d, 2H, J = 8.8, Ar—H), 7.77 (s, 1H, pyrazole-H), 7.89 (d, 2H, J = 8.8, Ar—H), 7.93 (d, 2H, J = 8.8, Ar—H), 8.85 (s, 1H, oxazine-H); HRMS ($C_{19}H_{14}ClN_2O_3$): calcd. for $[M + H]^+$ 353.0693, found 353.0693.

6-(4-Methoxyphenyl)-2-phenyl-4H-pyrazolo[5,1-c][1,4]oxazin-4-one (3g). Yellow solid, yield: 70%, mp. 189–190°C; IR (KBr): 1742 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.87 (s, 3H, OCH_3), 7.00 (d, 2H, J = 8.7, Ar—H), 7.41 (t, 1H, J = 7.5, Ar—H), 7.44 (s, 1H, pyrazole-H), 7.47 (t, 2H, J = 7.5, Ar—H), 7.69 (d, 2H, J = 8.7, Ar—H), 7.85 (s, 1H, oxazine-H), 7.89 (d, 2H, J = 7.5, Ar—H); HRMS ($C_{19}H_{15}N_2O_3$): calcd. for $[M + H]^+$ 319.1083, found 319.1084.

2-(4-Chlorophenyl)-6-(4-methoxyphenyl)-4H-pyrazolo[5,1-c][1,4]oxazin-4-one (3h). Yellow solid, yield: 80%, mp. 254–256°C; IR (KBr): 1759 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.88 (s, 3H, OCH_3), 7.00 (d, 2H, J = 8.8, Ar—H), 7.40 (s, 1H, pyrazole-H), 7.44 (d, 2H, J = 8.4, Ar—H), 7.69 (d, 2H, J = 8.8, Ar—H), 7.82 (d, 2H, J = 8.4, Ar—H), 7.83 (s, 1H, oxazine-H); HRMS ($C_{19}H_{14}ClN_2O_3$): calcd. for $[M + H]^+$ 353.0693, found 353.0691.

2,6-Bis(4-methoxyphenyl)-4H-pyrazolo[5,1-c][1,4]oxazin-4-one (3i). Yellow solid, yield: 86%, mp. 247–250°C; IR (KBr): 1750 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.98 (d, 2H, J = 8.8, Ar—H), 7.00 (d, 2H, J = 8.2, Ar—H), 7.34 (s, 1H, pyrazole-H), 7.68 (d, 2H, J = 8.8, Ar—H), 7.80 (s, 1H, oxazine-H), 7.81 (d, 2H, J = 8.4, Ar—H); HRMS ($C_{20}H_{17}N_2O_4$): calcd. for $[M + H]^+$ 349.1188, found 349.1184.

X-ray crystal-structure analysis. Crystal suitable for X-ray analysis was grown by slow evaporation from ethyl acetate solution. The diffraction measurement was carried out by graphite monochromated Mo Kα radiation with λ = 0.71073 Å on a Bruker SMART CCD diffractometer at room temperature. The structure was solved with direct methods using the SHELXS-97 program, and refined on F^2 by full-matrix least-squares with the SHELXL-97 package [20]. All data were corrected by multiscan method using SADABS program. The hydrogen atoms were placed at calculated positions with 0.96 Å (methyl CH_3) and 0.93 Å (aromatic CH) using a riding model. Molecular graphics were designed by using XP and DIAMOND 3.2 [21]. PLATON program was also used for structure analysis

Table 3

Summary of crystal data and structure refinement.

Compound	**3c**
Empirical formula	$C_{19}H_{14}N_2O_3$
Formula weight	318.32
Crystal system	Orthorhombic
Space group	$Pca2_1$
a (Å)	11.361 (3)
b (Å)	17.813 (5)
c (Å)	7.517 (2)
α (°)	90
β (°)	90
γ (°)	90
Z	4
D_x (g/cm^3)	1.390
Crystal size (mm)	0.16 × 0.14 × 0.10
μ (mm^{-1})	0.096
F(000)	664
Reflection collected	7659
Unique reflection	1465
Data/restraints/parameters	1465/0/218
θ Range for data collection (°)	2.13 − 25.04
R(int)	0.0225
Ranges of indices h, k, l	$-13 \le h \le 12$, $-21 \le k \le 21$, $-8 \le l \le 7$
Absorption correction	Multiscan (T_{min} = 0.985, T_{max} = 0.990)
Refinement method	Full-matrix least-squares on F^2
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0269, ωR_2 = 0.0651[a]
Goodness of fit on F^2	1.060
Δρ (max./min) (e Å^{-3})	0.104; −0.099
CCDC No.	784,526

[a]Weighting scheme: $\omega = 1/[\sigma^2(F_o)^2 + (0.0386P)^2 + 0.1142P]$ where $P = (F_o^2 + 2F_c)^2/3$.

[22]. The crystal data and details concerning data collection and structural refinement are given in Table 3.

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