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SYNTHESIS OF 4, 6-DIARYL-4,6,7,8-TETRAHYDRO[1,4]OXAZEPINO[4,3-*c*]SYDNONE

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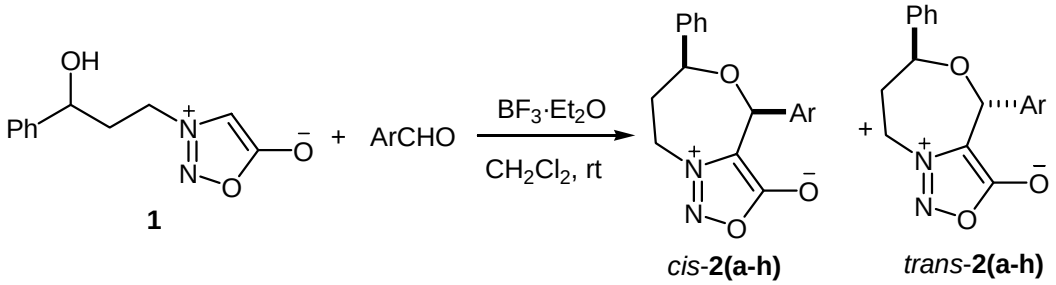
Abstract – Seven-membered ring fused sydnones, 4,6-diaryl-4,6,7,8-tetrahydro-[1,4]oxazepino[4,3-*c*]sydnones (**2**) were prepared *via* oxa-Pictet-Spengler reaction of 3-(3-phenyl-3-hydroxypropyl)sydnone (**1**) with aromatic aldehydes in the presence of Lewis acid. The reactions gave two stereoisomers (*cis*- and *trans*-), and the *cis*- isomers were the major products.

INTRODUCTION

Sydnones are a class of dipolar, mesoionic heteroaromatic compounds.[1] Their unique physical properties, spectral properties and biological activities have attracted researcher's attentions.[2] Efficient syntheses of sydnone derivatives were also developed.[3] These compounds can undergo a variety of reactions including electrophilic aromatic substitution (when unsubstituted at 4-position), 1,3-dipolar cycloaddition (with e.g. alkynes), acid induced cleavage to hydrazines (or products thereform) and metallation at 4-position (when unsubstituted at 4-position) with subsequent electrophilic substitution.[4] As a result they are useful building blocks for heterocycle's preparations (e.g. pyrazole) . In contrast to many reports on single-ring sydnone derivatives, fused-ring sydnones were relatively fewer.[5] This paper reports the oxa-Pictet-Spengler reactions (Scheme 1) of sydnones (**1**), which provides an efficient synthetic approach to seven-membered ring fused sydnones, 4,6-diaryl-4,6,7,8-tetrahydro[1,4]oxazepino[4,3-*c*]sydnones (**2**).



Ar=C_6H_5, 4-BrC_6H_4, 3-BrC_6H_4, 2-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 2,6-$Cl_2C_6H_3$, 2-ClC_6H_4

Scheme 1

RESULTS AND DISCUSSION

In a typical oxa-Pictet-Spengler reaction, 2-arylethanol reacts with an aldehyde or ketone to give a isochromane derivatives.[6] Since sydnones are unstable to both acidic and basic media, we performed the oxa-Pictet-Spengler reaction of 3-(3-phenyl-3-hydroxypropyl)sydnone (**1**) with aromatic aldehydes at room temperature in dioxane or DME. Experiments found that BF_3-Et_2O was a mild and effective catalyst while *p*-TsOH did not work under the same conditions. As listed in Table 1, eight seven-membered ring fused sydnone derivatives were prepared successfully with total yield up to 86%. It was also found that electron-rich aromatic aldehydes such as *p*-anisaldehyde and piperonal were unable to react at the same reaction conditions.

Table 1. Synthesis of 4,6-diaryl-4,6,7,8-tetrahedro[1,4]oxazepino[4,3-*c*]sydnones

Entry	Ar	Product	Yield (%)[a]			δ (H-4)	
			cis-	*trans*-	total	*cis*-	*trans*-
1	C_6H_5	**2a**	52	21.4	73.4	5.83	6.32
2	4-BrC_6H_4	**2b**	46.5	20.5	67	5.74	6.19
3	3-BrC_6H_4	**2c**	54.2	10.4	64.6	5.79	6.20
4	2-$O_2NC_6H_4$	**2d**	45.2	0[b]	45.2	6.45	-
5	4-$O_2NC_6H_4$	**2e**	79	7	86	5.87	6.18
6	3-$O_2NC_6H_4$	**2f**	77.6	6.8	84.4	5.87	6.15
7	2,6-$Cl_2C_6H_3$	**2g**	67	9	76	6.48	6.60
8	2-ClC_6H_4	**2h**	56	0[b]	56	6.01	-
9	4-$MeOC_6H_4$	**2i**	0[c]	0	0	-	-

[a] Isolated yields, after silica gel column chromatography (eluent: petroleum ether-EtOAc).
[b] No *trans*-isomer was isolated.
[c] No cyclization product was observed at room temperature after 5 days.

High *cis*-selectivity for isochromans has been previously observed in the oxa-Pictet-Spengler reaction.[7] In our experiments, reactions of **1** with aromatic aldehydes are also stereoselective, giving the *cis*-stereoisomer as major product. In the reactions of **1** with *o*-nitrobenzaldehyde and *o*-chlorobenzaldehyde, only the *cis*-stereoisomers are isolated.

The definitive assignments of the *cis*-stereochemical relationship between the substituents at C-4 and C-6 was made by the nuclear NOE difference spectroscopy. For example, H-6 of *cis*-**2f** showed 6% signal enhancement when H-4 was irradiated, while H-6 of *trans*-**2f** showed only 0.2% signal enhancement when H-4 was irradiated, and H at the Ph group showed 1.2% signal enhancement. Since the chemical shift of H-4 of *cis*-**2** is smaller than that of *trans*-**2**, we can easily distinguish the *cis*- and *trans*-isomers by the chemical shifts of H-4.

The solid state structure of *cis*-**2g** was determined by X-Ray diffraction (Figure 1), which shows that the *cis*-configuration of the substituents Ph and Ar in tetrahydro[1,4]oxazepine ring and the two substituents were at equatorial positions.

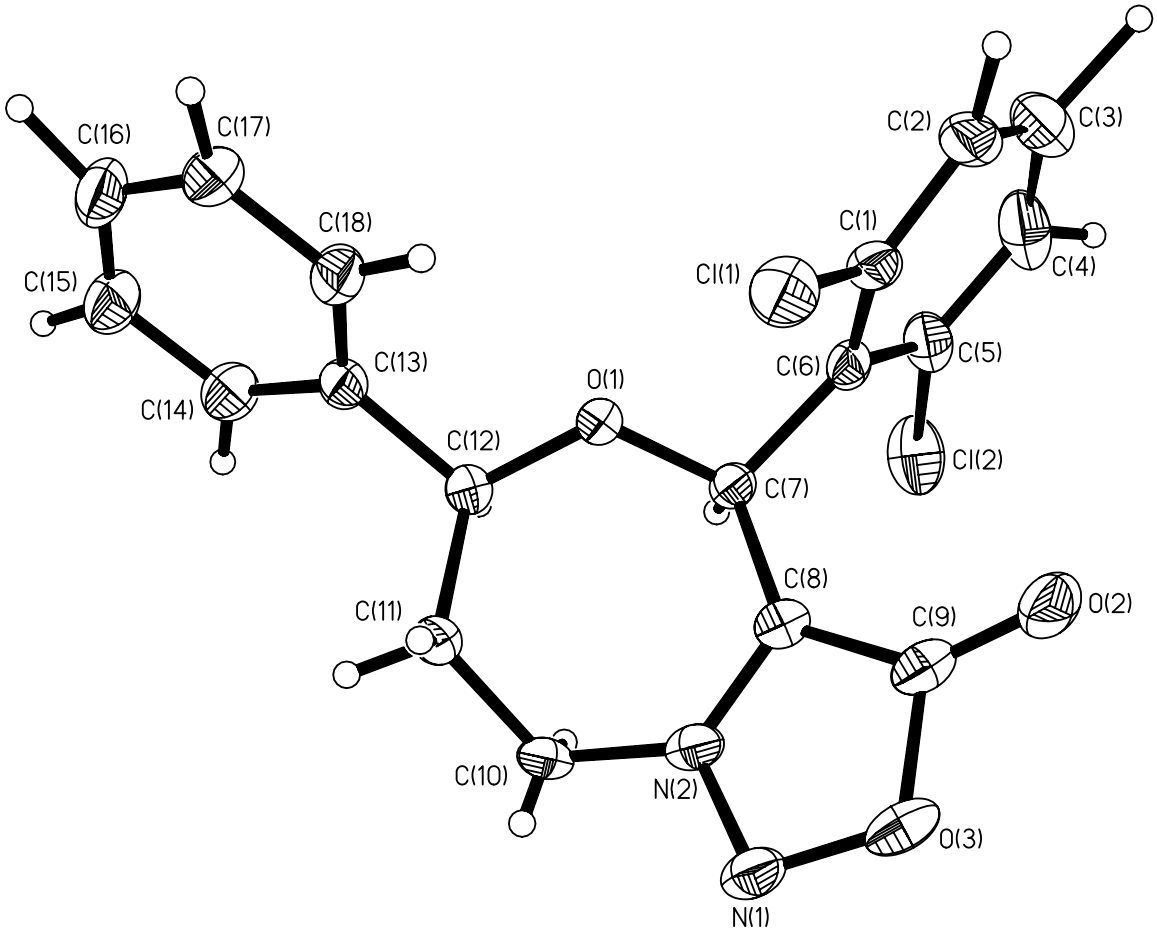


Figure 1. Molecular structure of *cis*-**2g**

In summary, we have successfully established an efficient synthetic method for the preparation of tetrahedro[1,4]oxazepino[4,3-*c*]sydnones by the oxa-Pictet-Spengler cyclization. Manipulation of the sydnone ring is valuable in organic syntheses, and tetrohydro[1,4]oxazepino[4,3-*c*]sydnone is a useful precursor for the synthesis of fused pyrazole derivatives by the [3+2] cycloaddition with alkene or alkyne.

EXPERIMENTAL

Melting points were measured on a RY-1 apparatus and are uncorrected. Elemental analyses were carried out on an Elementar Vario El instrument. FT-IR spectra were measured on a Nicolet Avatar 360 spectrometer. ^{1}HNMR (500MHz) spectra were recorded on Bruker Avance 500 NMR spectrometer with TMS as internal reference. Mass spectra (EI, 70eV) were taken on a Finigan GC2000/TRACE^{TM}MS mass spectrometer. Starting material (**1**) was prepared by literature produces.[8] All other chemicals were commercially available and were used as received.

General Procedure for the Reaction of 3-(3-Phenyl-3-hydroxypropyl)sydnone with Aromatic Aldehyde.

To a solution of compound (**1**) (440 mg, 2 mmol) in dioxane (15 mL) were added aromatic aldehyde (24 mmol) and boron trifluoride etherate (568 mg, 4 mmol) with stirring at rt. After the mixture was stirred at rt for 3 d, saturated aqueous $NaHCO_3$ solution (20 mL) was added, and the mixture was extracted with ethyl acetate (2×20 mL). The combined extracts were dried (Na_2SO_4) and the solvent was removed in vacuo. The crude mixture was separated by column chromatography over silica gel (petroleum ether/EtOAc=3:1) to yield *trans*-**2** (minor) and *cis*-**2** (major).

4,6,7,8-Tetrahydro-4,6-diphenyl[1,4]oxazepino[4,3-*c*]sydnone (*cis*-2a)

colorless crystals; mp 161-162°C (recrystallized from AcOEt/hexane); IR(KBr, cm^{-1}) *v* 1746, 1491, 1199, 1091, 1062, 755, 698; ^1H NMR ($CDCl_3$) δ 7.28-7.53 (m, 10H, Ar-H), 5.83 (s, 1H), 4.95 (dd, *J*=9.9, 3.9 Hz, 1H), 4.82-4.87 (m, 1H), 4.63 (ddd, *J*=13.7, 6.9, 3.4 Hz, 1H), 2.55-2.62 (m, 1H), 2.32-2.40 (m, 1H); Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.01; H, 5.50; N, 8.87. MS: 308 (M^+), 309 $(M+H)^+$.

4,6,7,8-Tetrahydro-4,6-diphenyl[1,4]oxazepino[4,3-*c*]sydnone (*trans*-2a)

colorless crystals; mp 128-130°C (recrystallized from AcOEt/hexane); IR(KBr, cm^{-1}) *v* 1732, 1512, 1492, 1453, 1186, 1065, 1004, 764, 744, 701; ^1H NMR ($CDCl_3$) δ 7.24-7.46 (m, 10H, Ar-H), 6.32 (s, 1H), 4.89 (d, *J*=9.5 Hz, 1H), 4.67 (m, 1H), 4.45 (t, *J*=12.9 Hz, 1H), 2.28 (m, 2H); Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.11; H, 5.45; N, 8.91. MS: 308(M^+), 309$(M+H)^+$.

4-(4-Bromophenyl)-4,6,7,8-tetrahydro-6-phenyl[1,4]oxazepino[4,3-*c*]sydnone (*cis*-2b)

colorless crystals; mp 176-178°C (recrystallized from AcOEt/hexane); IR(KBr, cm^{-1}) *v* 1750, 1500 1080, 1020 780, 710; ^1H NMR($CDCl_3$) δ 7.35-7.54 (m, 9H, Ar-H), 4.93 (dd, *J*=9.9, 3.3 Hz, 1H, CH-Ph), 5.74 (s, 1H, CH-Syd), 4.80, 4.60 (2m, 2H, CH_2-Syd), 2.55, 2.34 (2m, 2H, CH_2); Anal. Calcd for $C_{18}H_{15}N_2O_3Br$: C, 55.83; H, 3.90; N, 7.23. Found: C, 55.42; H,3.98; N, 7.61. MS(FAB): 387$(M+H)^+$.

4-(4-Bromophenyl)-4,6,7,8-tetrahydro-6-phenyl[1,4]oxazepino[4,3-*c*]sydnone (*trans*-2b)

colorless crystals; mp 174-176°C (recrystallized from AcOEt/hexane); IR(KBr, cm^{-1}) *v* 1750, 1520, 1490, 1070, 1010, 765, 705; ^1H NMR ($CDCl_3$) δ 7.10-7.58 (m, 9H, Ar-H), 4.84 (dd, *J*=8.7, 3.3 Hz, 1H, CH-Ph), 6.19 (s, 1H, CH-Syd), 4.67, 4.41 (2m, 2H, CH_2-Syd), 2.33 (m, 2H, CH_2); Anal. Calcd for $C_{18}H_{15}N_2O_3Br$: C, 55.83; H, 3.90; N, 7.23. Found: C, 56.03; H, 3.85; N, 7.27. MS(FAB): 387$(M+H)^+$.

4-(3-Bromophenyl)-4,6,7,8-tetrahydro-6-phenyl[1,4]oxazepino[4,3-*c*]sydnone (*cis*-2c)

colorless crystals; mp 160-162°C (recrystallized from AcOEt/hexane); IR(KBr, cm^{-1}) *v* 1747, 1496, 1188, 1074, 1057, 761, 700; ^1H NMR ($CDCl_3$) δ 7.27-7.66 (m, 9H), 5.79 (s, 1H), 4.94 (dd, *J*=9.9, 3.8 Hz, 1H),

4.83 (ddd, *J*=13.3, 8.6, 3.5 Hz, 1H), 4.63 (ddd, *J*=13.8, 7.2, 3.4 Hz, 1H), 2.58 (m, 1H), 2.37 (m, 1H); Anal. Calcd for $C_{18}H_{15}N_2O_3Br$: C, 55.83; H, 3.90; N, 7.23. Found: C, 55.67; H, 3.81; N, 7.35. MS: 387 $(M+H)^+$.

4-(3-Bromophenyl)-4,6,7,8-tetrahydro-6-phenyl[1,4]oxazepino[4,3-*c*]sydnone (*trans*-2c)

colorless crystals; mp 112-113°C (recrystallized from AcOEt/hexane); IR(KBr, cm^{-1}) *v* 1750, 1500, 1180, 1080, 1020, 780, 760, 720; ^1H NMR ($CDCl_3$) δ 7.17-7.55 (m, 9H, Ar-H), 6.20 (s, 1H, CH-Syd), 4.86 (m, 1H, CH-Ph), 4.42, 4.66 (2m, 2H, CH_2-Syd), 2.30 (m, 2H, CH_2); Anal. Calcd for $C_{18}H_{15}N_2O_3Br$: C, 55.83; H, 3.90; N, 7.23. Found: C, 55.51; H, 3.88; N, 7.49. MS: 387 $(M+H)^+$.

4,6,7,8-Tetrahydro-4-(2-nitrophenyl)-6-phenyl[1,4]oxazepino[4,3-*c*]sydnone (*cis*-2d)

yellow crystals; mp 193-195°C (recrystallized from AcOEt/hexane); IR(KBr, cm^{-1}) *v* 1734, 1525, 1345, 1072, 1057, 762, 732; ^1H NMR ($CDCl_3$) δ 7.30-8.30 (m, 9H, Ar-H), 6.45 (s, 1H, CH-Syd), 5.04 (dd, *J*=10.2, 1.8 Hz,1H), 4.80, 4.83 (2m, 2H, CH_2-Syd), 2.33, 2.51(2m, 2H, CH_2); Anal. Calcd for $C_{18}H_{15}N_3O_5$: C, 61.19; H, 4.28; N, 11.89. Found: C, 61.32; H, 4.48; N, 11.62. MS: 354 $(M+H)^+$.

4,6,7,8-Tetrahydro-4-(4-nitrophenyl)-6-phenyl[1,4]oxazepino[4,3-*c*]sydnone (*cis*-2e)

yellow crystals; mp 182-183°C (recrystallized from AcOEt/hexane); IR(cm^{-1}) *v* 1740, 1515, 1505, 1340, 1080, 1060, 1020, 850, 760, 740,700; ^1H NMR($CDCl_3$) δ 7.38-8.25 (m, 9H, Ar-H), 5.88 (s, 1H, CH-Syd), 4.98 (dd, *J*=9.9, 2.7 Hz, 1H, CH-Ph), 4.83, 4.69 (2m, 2H, CH_2-Syd), 2.53,2.36 (2m, 2H, CH_2); Anal. Calcd for $C_{18}H_{15}N_3O_5$: C, 61.19; H, 4.28; N, 11.89. Found: C, 61.24; H, 4.17; N, 12.02.

4,6,7,8-Tetrahydro-4-(4-nitrophenyl)-6-phenyl[1,4]oxazepino[4,3-*c*]sydnone (*trans*-2e)

yellow crystals; mp 172-174°C (recrystallized from AcOEt/hexane); IR(KBr, cm^{-1}) *v* 1750, 1515, 1340, 1080, 1020, 770, 705; ^1H NMR ($CDCl_3$) δ 7.26-7.8.29 (m, 9H, Ar-H), 6.18 (s, 1H, CH-Syd), 4.88 (dd, *J*=8.7, 3.6 Hz, 1H, CH-Ph), 4.73, 4.45 (2m, 2H, CH_2-Syd), 2.39 (m, 2H, CH_2); Anal. Calcd for $C_{18}H_{15}N_3O_5$: C, 61.19; H, 4.28; N, 11.89. Found: C, 61.01; H, 4.20; N, 11.88. MS: 353(M^+), 354$(M+H)^+$.

4,6,7,8-Tetrahydro-4-(3-nitrophenyl)-6-phenyl[1,4]oxazepino[4,3-*c*]sydnone (*cis*-2f)

yellow crystals; mp 199-201°C (recrystallized from AcOEt/hexane); IR(KBr, cm^{-1}) *v* 1740, 1530, 1350, 1080, 1060, 765, 735, 700; ^1H NMR ($CDCl_3$) δ 7.34-8.35 (m, 9H, Ar-H), 5.87 (s, 1H, CH-Syd), 4.98 (dd, *J*=9.6, 3.3 Hz, 1H, CH-Ph), 4.83, 4.69 (2m, 2H, CH_2-Syd), 2.54,2.37 (2m, 2H, CH_2); Anal. Calcd for $C_{18}H_{15}N_3O_5$: C, 61.19; H, 4.28; N, 11.89. Found: C, 61.24; H, 4.19; N, 11.94. MS: 353(M^+), 354$(M+H)^+$

4,6,7,8-Tetrahydro-4-(3-nitrophenyl)-6-phenyl[1,4]oxazepino[4,3-*c*]sydnone (*trans*-2f)

yellow crystals; mp 161-163°C (recrystallized from AcOEt/hexane); IR(KBr, cm^{-1}) *v* 1760,1545, 1360, 1080, 1030, 760, 720; ^1H NMR ($CDCl_3$) δ 7.28-8.29 (m, 9H, Ar-H), 6.15 (s, 1H, CH-Syd), 4.91 (dd, *J*=8.1, 4.5 Hz, 1H, CH-Ph), 4.74, 4.49 (2m, 2H, CH_2-Syd), 2.45 (m, 2H, CH_2); Anal. Calcd for $C_{18}H_{15}N_3O_5$: C, 61.19; H, 4.28; N, 11.89. Found: C, 61.05; H, 4.20; N, 12.12. MS: 353(M^+), 354$(M+H)^+$.

4-(2,6-Dichlorophenyl)-4,6,7,8-tetrahydro-6-phenyl[1,4]oxazepino[4,3-*c*]sydnone (*cis*-2g)

colorless crystals; mp 201-203°C (recrystallized from AcOEt/hexane); IR(KBr, cm^{-1}) ν 1740, 1500, 1440, 1100, 790, 770, 700; ^1H NMR ($CDCl_3$) δ 7.22-7.50 (m, 8H, Ar-H), 6.48 (s, 1H, CH-Syd), 5.11 ((dd, *J*=7.3, 4.0 Hz, 1H), 4.85 (ddd, 1H, *J*=14.1, 8.1, 1.8 Hz), 4.60 (ddd, *J*=14.1, 9.2, 1.5 Hz, 1H), 2.67, 2.45 (2m, 2H, CH_2); Anal. Calcd for $C_{18}H_{14}N_2O_3Cl_2$: C, 57.31; H, 3.74; N, 7.43. Found: C, 57.51; H, 3.90; N, 7.17. MS: 376(M^+), 377$(M+H)^+$.

4-(2,6-Dichlorophenyl)-4,6,7,8-tetrahydro-6-phenyl[1,4]oxazepino[4,3-*c*]sydnone (*trans*-2g)

colorless crystals; mp 150-152°C (recrystallized from AcOEt/hexane); IR(KBr, cm^{-1}) ν 1760, 1510, 1455, 1220, 1120, 1080, 805, 790, 720; ^1H NMR($CDCl_3$) δ 7.25-7.50 (m, 8H, Ar-H), 6.60 (s, 1H, CH-Syd), 5.30 (m, 1H, CH-Ph), 5.04, 4.90 (2m, 2H, CH_2-Syd), 2.72-2.39 (2m, 2H, CH_2); Anal. Calcd for $C_{18}H_{14}N_2O_3Cl_2$: C, 57.31; H, 3.74; N, 7.43. Found: C, 57.10; H, 3.65; N, 6.85. MS: 377$(M+H)^+$.

4-(2-Chlorophenyl)-4,6,7,8-tetrahydro-6-phenyl[1,4]oxazepino[4,3-*c*]sydnone (*cis*-2h)

colorless crystals; mp 197-199°C (recrystallized from AcOEt/hexane); IR(KBr, cm^{-1}) ν 1749, 1492, 1209, 1199, 1046, 1017, 760, 698; ^1H NMR($CDCl_3$) δ 7.25-7.50 (m, 9H, Ar-H), 6.01 (s, 1H, CH-Syd), 5.03 (dd, *J*=10.2, 2.1 Hz, 1H), 4.79 (m, 2H), 2.48 (m, 1H), 2.32 (m, 1H); Anal. Calcd for $C_{18}H_{15}N_2O_3Cl$: C, 63.39; H, 4.73; N, 8.19. Found: C, 63.07; H, 4.41; N, 8.17. MS: 343$(M+H)^+$.

X-Ray Structural Analysis of *cis*-2g

Molecular formula $C_{18}H_{14}N_2O_3Cl_2$, formula weight 377.21, crystal description colorless prism, crystal size 0.40 x 0.40 x 0.20 mm, monoclinic, space group P2(1)/n, T=293(2) K, a = 12.397(2)Å, b = 11.032(2)Å, c = 14.528(3)Å, α=90°, β=100.44(2)°, γ=90°, V=1954.0(6) $Å^3$, *Z*=4, λ(MoK α)=0.71073 Å, Dc=1.282Mg/cm^3, μ=0.350mm^{-1}, F(000)=776, collected 1.99°< θ < 27.99°, Limiting indices, -1<=h<=16, -1<=k<=14, -19<=l<=19, Goodness-of-fit on F^2 0.929, Final R indices [I>2σ(I)] R1 =0.0839, wR2 = 0.2638, R indices (all data) R1 = 0.1435, wR2 =0.2973.

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