J Chem Crystallogr (2008) 38:205–209
DOI 10.1007/s10870-007-9290-x

ORIGINAL PAPER

Synthesis of *E* Isomer and Crystal Structures of *E* and *Z* Isomers of 3-(2,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)acrylonitrile

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Received: 6 March 2007 / Accepted: 16 October 2007 / Published online: 16 November 2007

Abstract Details of the synthesis of the *E* isomer of 3-(2,5-dimethoxyphenyl)-2-(4-methoxyphenyl)acrylonitrile, and the X-ray crystal structures of both the *E* and *Z* isomers of this compound are presented. The *E* isomer crystallizes in the $P2_1/c$ space group with cell parameters, $a = 8.5659(17)$ Å, $b = 16.399(3)$ Å, $c = 11.224(2)$ Å, $\alpha = 90°$, $\beta = 95.27(3)°$, $\gamma = 90°$and $Z = 4$. The *Z* isomer crystallizes in the $Pca2_1$ space group with cell parameters, $a = 4.1223(8)$ Å, $b = 19.113(4)$ Å, $c = 19.453(4)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$ and $Z = 4$.

Keywords *E* and *Z* isomers · Diarylacrylonitrile · X-ray · Single crystal structures

Introduction

Gram-positive bacteria are formidable human pathogens. They display a multitude of surface proteins that serve as an interface between the microbe and its host. Surface proteins often fall into one of four functional categories: microbial adhesion to host tissues, protection from host defense mechanisms, acquisition of nutrients for bacterial growth, and secretion of toxins and invasions. These virulence factors carry out important roles in the infectious process. Sortase A (SrtA), a cysteine transpeptidase, participates in secretion and anchoring many of these surface proteins by a mechanism conserved in almost the entire class of gram-positive bacteria. SrtA, because of its control over the cellular location of multiple virulence factors, is an attractive potential target for the development of antibacterial drugs [1–8]. Based on a hit from random screening, Oh et al. have recently reported a novel small-molecule inhibitor (**1**), a diarylacrylonitrile derivative for *S. aureus* SrtA with IC_{50} value of 9.2 μM in vitro [9]. As a part of our efforts aimed at developing inhibitors of *S. aureus* SrtA, we were interested in making structural modifications to the already identified lead compound **1** (Fig. 1)

Compound **1** has a *Z* diarylacrylonitrile ring system. The aryl ring close to CN group has a methoxy group at the 4-position, and the second aryl ring has two methoxy groups at the 2′- and 5′-positions. In order to compare the activities of geometrical isomers of compound **1**, we were interested in synthesizing its *E* isomer (**2**). We herein describe the synthesis and X-ray crystal structure determination of the *E* isomer (**2**) and the X-ray crystal structure determination of the known *Z* isomer (**1**) of 3-(2,5-dimethoxyphenyl)-2-(4-methoxyphenyl)acrylonitrile.

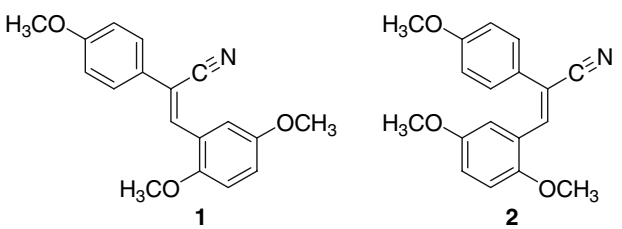

Fig. 1 Geometric isomers of 3-(2,5-dimethoxyphenyl)-2-(4-56-methoxyphenyl)acrylonitrile

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Experimental Section

Synthesis

Melting points were determined using an Electrothermal 9100 apparatus and are uncorrected. IR spectra were taken with Brucker Vector-22 and Bomen MB-104 instruments. All ^{1}H and ^{13}C NMR spectra were recorded on a Brucker 300 MHz spectrometer using TMS as internal standard. The values of chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. Elemental analyses were performed by Atlantic Microlab, Norcross, Georgia and the results are within ±0.3% of theoretical values. Reactions were monitored by TLC (Whatmann, Si gel, UV 254, 25 μM plates). The solvents used for reactions were purchased as anhydrous in Sure-Seal™ bottles from Aldrich chemical company. The chemicals used are purchased from Aldrich, Lancaster or Fisher chemical companies and used as received.

Experimental details of the synthesis of *E* isomer (**2**) of 3-(2,5-dimethoxyphenyl)-2-(4-methoxyphenyl)acrylonitrile starting from corresponding *E* carboxylic acid (**3**) are given below. Synthesis of **3** was reported in an earlier communication from our laboratory [10].

(*E*) 3-(2,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)acrylamide (**4**)

To a solution of *E* acid, **3** (0.5 g, 1.59 mmol) in CH_2Cl_2 (85 mL), a solution of $SOCl_2$ (1 mL) in anhydrous DMF

Table 1 Crystal and structure refinement data for **1** and **2**

	1	**2**
CCDC deposit #	633004	633005
Empirical formula	$C_{18}H_{17}NO_3$	$C_{18}H_{17}NO_3$
Formula weight	295.33	295.33
Temperature	293(2) K	293(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Orthorhombic	Monoclinic
Space group	$Pca2_1$	$P2_1/c$
Unit cell dimensions	$a = 19.453(4)$ Å	$a = 8.5659(17)$ Å
	$b = 4.1223(8)$ Å	$b = 16.399(3)$ Å
	$c = 19.113(4)$ Å	$c = 11.224(2)$ Å
	$\alpha = 90°$	$\alpha = 90°$
	$\beta = 90°$	$\beta = 95.27(3)°$
	$\gamma = 90°$	$\gamma = 90°$
Volume	1532.7(5) Å^3	1570.0(5) Å^3
Z	4	4
Density (calculated)	1.280 mg/m^3	1.249 mg/m^3
Absorption coefficient	0.087 mm^{-1}	0.085 mm^{-1}
$F(000)$	624	624
Crystal size	0.15 × 0.3 × 1.0 mm^3	0.2 × 0.8 × 1.0 mm^3
θ range for data collection	2.09–22.49°	2.21–22.48°
Index ranges	$-20 \le h \le 20$, $-1 \le k \le 4$, $0 \le l \le 20$	$-9 \le h \le 9$, $-17 \le k \le 1$, $-12 \le l \le 0$
Reflections collected	2,696	2,345
Independent reflections	1,047 [R(int) = 0.0873]	2,041 [R(int) = 0.0397]
Completeness to $\theta = 22.48°$	99.9%	100.0%
Absorption correction	None	None
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	1047/1/207	2041/0/207
Goodness-of-fit on F^2	0.985	0.973
Final R indices [$I > 2\sigma$(I)]	$R1 = 0.0512$, w$R2 = 0.1086$	$R1 = 0.0836$, w$R2 = 0.2177$
R indices (all data)	$R1 = 0.0947$, w$R2 = 0.1274$	$R1 = 0.1808$, w$R2 = 0.2744$
Absolute structure parameter	2(3)	–
Largest diff. peak and hole	0.196 and −0.214 e Å^{-3}	0.298 and −0.308 e·Å^{-3}

Table 2 Selected bond lengths (Å) and bond angles (°) for **1** and **2**

	1	2
C(3)–C(4)	1.468(8)	1.440(8)
C(1)–N	1.152(8)	1.129(7)
C(1)–C(2)	1.438(10)	1.427(9)
C(2)–C(3)	1.338(9)	1.327(7)
C(2)–C(10)	1.466(8)	1.513(7)
C(3)–C(2)–C(10)	126.3(6)	126.5(5)
N–C(1)–C(2)	177.2(8)	178.8(7)
C(3)–C(2)–C(1)	117.9(7)	118.1(5)
C(10)–C(2)–C(1)	115.7(6)	115.4(5)
C(2)–C(3)–C(4)	127.4(7)	130.2(5)
C(5)–C(4)–C(3)	123.7(6)	120.6(5)
C(11)–C(10)–C(2)	122.1(6)	119.9(5)
C(15)–C(10)–C(2)	122.3(8)	120.7(5)
C(9)–C(4)–C(3)	120.8(6)	121.6(5)

Table 3 Selected dihedral angles (°) for compounds **1** and **2**

	1	2
C(4)–C(9) ring C(10)–C(15) ring	53.52	60.50
C(10)–C(15) ring Alkene[a]	11.93	53.29
C(4)–C(9) ring Alkene[a]	41.73	31.41

[a] Alkene defined by plane through C2–C3–H3

(1.7 mL) was added dropwise. The reaction mixture was stirred at room temperature for 4 h. The solvent was completely removed under reduced pressure in nitrogen atmosphere. The residue obtained was dried under high vacuum to remove the traces of DMF. The resulting residue was dissolved in CH_2Cl_2 (20 mL) and aqueous NH_4OH (50%, 10 mL) was added and the solution was stirred for 45 min at room temperature. TLC analysis (3:2 EtOAc/hexanes) revealed that the reaction was complete. The reaction mixture was then diluted with water (25 mL), and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 25 mL). The combined organic layers were washed with brine (1 × 25 mL) and dried over Na_2SO_4. The drying agent was filtered off, and the filtrate was concentrated under reduced pressure to furnish the crude compound, which was purified by flash column chromatography on silica gel (20 × 3 cm) using EtOAc/hexanes (3:1) as eluent to give *E* amide (**4**) as a white solid (0.378 g, 76%); Mp. 146 °C; ^{1}H NMR ($CDCl_3$) δ 3.33 (s, 3H), 3.82 (s, 6H), 5.50 (bs, 2H), 6.24 (d, 1H, $J = 3.2$ Hz), 6.70–6.79 (m, 2H), 6.94 (d, 2H, $J = 8.8$ Hz), 7.21 (d, 2H, $J = 8.8$ Hz) and 8.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.2, 55.4, 56.1, 111.9, 114.3, 114.8 (2C), 116.4, 124.5, 128.6, 131.3 (2C), 132.2, 133.9, 152.5, 153.0, 159.5 and 170.3; MS (ES^+) *m/z* 314 (M + H); IR ($CHCl_3$) 1,616, 1,673, 3,478, 3,522 cm^{-1}; Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47. Found: C, 68.76; H, 6.10; N, 4.33.

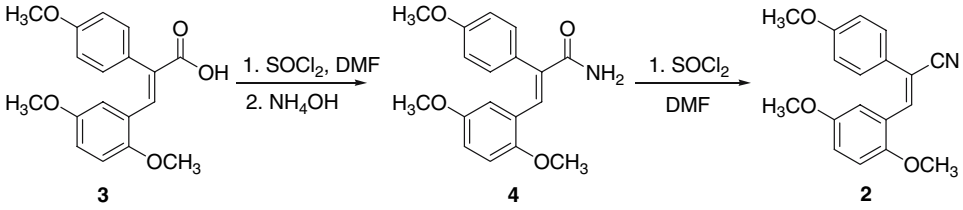
(*E*) 3-(2,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)acrylonitrile (**2**)

To a solution of *E* amide, **4** (0.252 g, 0.80 mmol) in pyridine (7 mL) $SOCl_2$ (3 mL) was added drop wise. The resulting solution was stirred at room temperature for 12 h. TLC analysis (1:1 EtOAc/hexanes) revealed that the reaction was complete. The solvent and excess $SOCl_2$ were completely removed under reduced pressure. The residue was dissolved in EtOAc (75 mL) and washed with 1 N HCl (1 × 50 mL), water (1 × 50 mL) and brine (1 × 50 mL). The organic layer was dried over Na_2SO_4. Drying agent was filtered off and the solvent was removed under reduced pressure to obtain the crude product. The crude compound was purified by flash column chromatography over silica gel (20 × 3 cm) using EtOAc/hexanes (1:5) as eluent to furnish *E* cyanide, 2 as a yellow solid (0.187 g, 79%); Mp. 101 °C; ^{1}H NMR ($CDCl_3$) δ 3.44 (s, 3H), 3.80 (s, 6H), 6.56 (s, 1H), 6.80–6.87 (m, 4H), 7.32 (d, 2H, $J = 6.8$ Hz) and 7.49 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.5, 55.6, 56.2, 112.2, 113.6, 114.3, 114.4 (3C), 117.5, 123.2, 125.2, 130.4 (2C), 138.2, 152.3, 152.9 and 160.2; MS (ES^+) *m/z* 296 (M + H); IR ($CHCl_3$) 1,607, 2,214 cm^{-1}. Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.03; H, 6.02; N, 4.77.

X-ray Data Collection and Solution

For each compound, a suitable single crystal of the compound was glued on a glass fiber with epoxy and aligned

Scheme 1



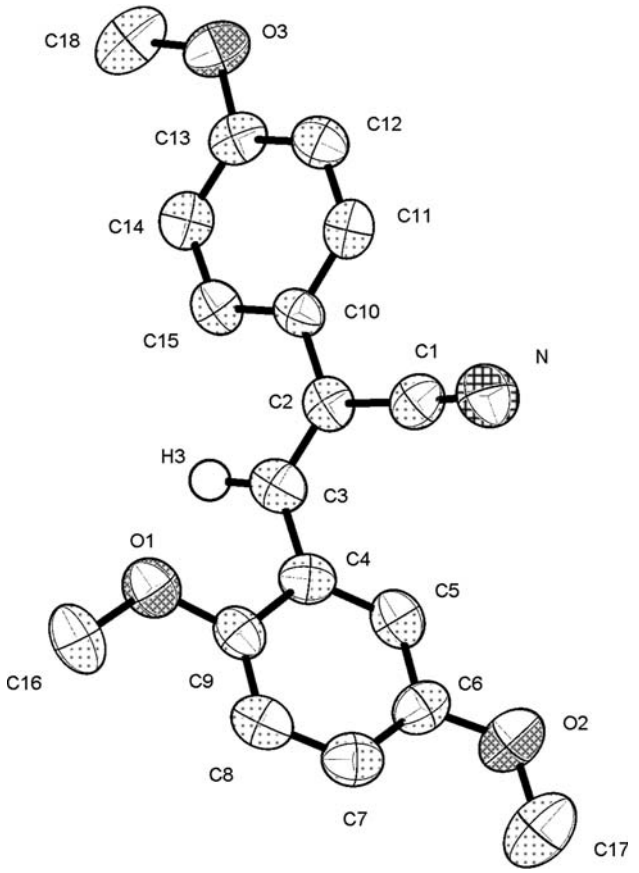


Fig. 2 ORTEP [14] drawing of the molecular structure of the *Z* Isomer, **1**. Thermal ellipsoids are drawn at 50% and nonspecific hydrogens are omitted for clarity

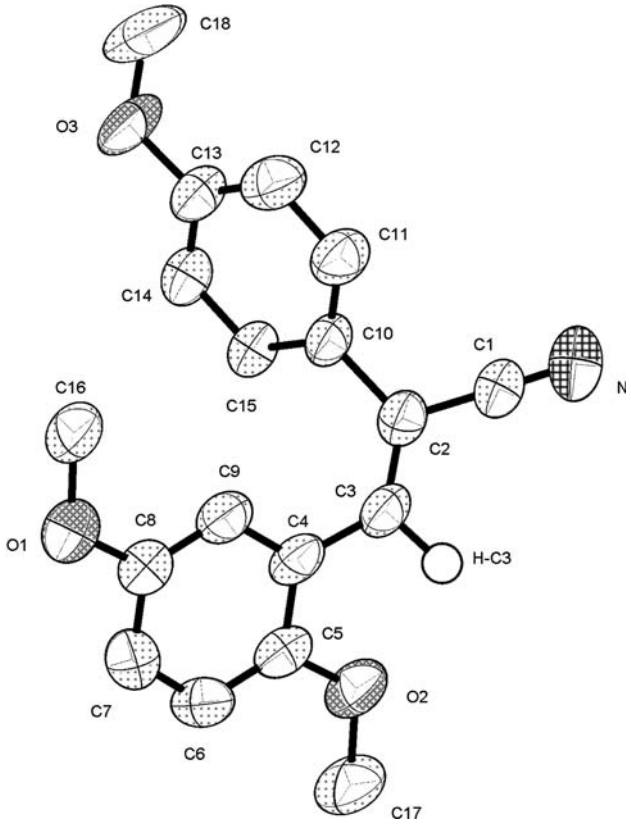


Fig. 3 ORTEP [14] drawing of the molecular structure of the *E* Isomer, **2**. Thermal ellipsoids are drawn at 50% and nonspecific hydrogens are omitted for clarity

upon an Enraf Nonius CAD4 single crystal diffractometer under aerobic conditions. Standard peak search and automatic indexing routines followed by least squares fits of 25 accurately centered reflections resulted in accurate unit cell parameters. The space groups were assigned on the basis of systematic absences and intensity statistics. All data collection was carried out using the CAD4-PC software [11], and details of the data collections are given in Table 1. The analytical scattering factors of the complex were corrected for both $\Delta f'$ and $i\Delta f''$ components of anomalous dispersion. All data were corrected for the effects of absorption and for Lorentz and polarization effects.

All crystallographic calculations were performed with the Siemens SHELXTL-PC program package [12]. All heavy atom positions were located using Direct Methods with the vinyl hydrogen atoms located in difference Fourier maps. Full matrix refinement of the positional and anisotropic thermal parameters for all these atoms versus F^2 was carried out. All other hydrogen atoms were placed in calculated positions with the appropriate molecular geometry and the d(C–H) = 0.96 Å. The isotropic thermal parameter associated with each hydrogen atom was fixed equal to 1.2 times the U_{eq} of the atom to which it was bound. Selected bond lengths and angles for complexes **1** and **2** are given in Table 2; selected dihedral angles and torsion angles are given in Table 3.

Results and Discussion

Synthesis

Compound **1** was prepared according to the reported procedure [9]. Isomerization of compound **1** to its geometric isomer **2** was first attempted by irradiation with UV light (λ = 254 nM, Rayonet RPR-2000 reactor). This resulted in the formation of a 1:1 mixture of both *E* and *Z* isomers. However, the separation of these two isomers by normal chromatographic methods did not work as they had same R_f values on TLC. So, the *E* isomer of this compound was prepared by a different route starting from the *E* carboxylic acid derivative, **3** as outlined in Scheme 1.

The acid, **3** was first converted to *E* amide (**4**) by treatment with $SOCl_2$ followed by treatment with aqueous NH_4OH in 76% yield. No isomerization was observed

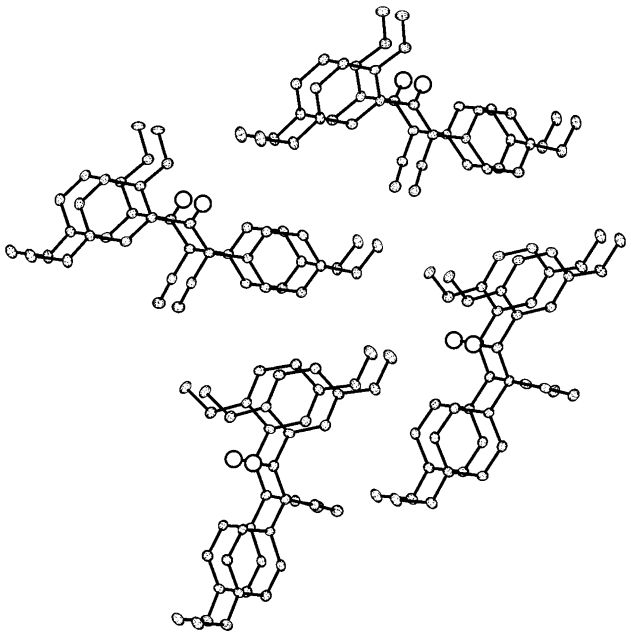


Fig. 4 ORTEP [14] drawing of the π–π stacking in the molecular structure of the *Z* Isomer, **1**. Thermal ellipsoids are drawn at 5% and nonspecific hydrogens are omitted for clarity

during this step, and the product obtained was pure *E* amide. The *E* amide (**4**) was converted to *E* nitrile (**2**) by treatment with $SOCl_2$ in anhydrous DMF in 79% yield.

X-ray Crystal Structures

The crystal structures of **1** and **2** are shown in Figs. 2 and 3 and exhibit a number of features which differ from one another. The selected dihedral angles, given in Table 3, indicate that the *E* isomer (**2**) is considerably more sterically hindered by the interaction between the two aromatic rings causing them to twist out of plane with one another. This is demonstrated by the 53.29° dihedral angle between the least squares planes through the C(10)–C(15) ring and the least squares plane through the alkene bond. This interaction between the two rings would lessen the amount of conjugation in the molecule as the rings are now twisted out of plane relative to the alkene bond. In contrast, the dihedral angle between these least squares planes in the *Z* isomer (**1**) is much smaller (11.93°) and would allow an increased amount of conjugation in this molecule.

One final point of interest is the manner in which these compounds stack in the crystal lattice with respect to the two rings. The *Z* isomer (**1**) exhibits π–π stacking (Fig. 4) between adjacent molecules in the unit cell whereas this is not seen in the *E* isomer (**2**). The interplanar distance between interacting rings of 3.462 Å is consistent with previous work done on purine rings by Bugg et al., who found the distances of interacting rings in stacked structures to be 3.879 Å [13]. The presence of this interaction in the *Z* isomer (**1**) is likely due to the increased planarity of the molecule, which allows for the rings to orient themselves on one another to stack throughout the lattice. The *E* isomer (**2**) has the rings twisted much more out of plane relative to the alkene bond preventing adjacent molecules from π–π stacking.

Supplementary Material

CCDC 633004 and 633005 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via (please use the link below) by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, Fax: +44(0)1223-336033.

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