Syntheses and Crystal Structures of a Pair of *Z*-*E* Enaminonitrile Isomerisms①

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ABSTRACT A pair of *Z*-*E* enaminonitrile isomerisms 2-(3,4-dimethoxyphenyl)-3-((3-methoxyphenyl)amino)acrylonitrile ($C_{18}H_{18}N_2O_3$, M_r = 310.34) were synthesized and separated by flash column chromatography, and their structures were determined by IR, ^{1}H NMR, ^{13}C NMR, MS and single-crystal X-ray diffraction. The crystal of compound **2a** belongs to the monoclinic system, space group *C*2/*c* with *a* = 33.805(7), *b* = 5.4496(12), *c* = 18.401(4) Å, β = 112.45(2)°, *V* = 3133.1(12) Å^3, *Z* = 8, μ = 0.091 mm^{-1}, D_c = 1.143 g·cm^{-3}, the final *R* = 0.0491 and *wR* = 0.1439 for 2764 observed reflections ($I > 2\sigma(I)$). The crystal of compound **2b** belongs to the triclinic system, space group *P*1, with *a* = 8.8403(7), *b* = 9.0390(6), *c* = 12.0044(74) Å, α = 72.075(5), β = 86.291(5), γ = 81.216(5)°, *V* = 901.82(10) Å^3, *Z* = 2, *T* = 293(2) K, μ = 0.079 mm^{-1}, D_c = 1.143 g·cm^{-3}, the final *R* = 0.0474 and *wR* = 0.1377 for 3176 observed reflections ($I > 2\sigma(I)$). The crystal packing of **2a** and **2b** is governed by intermolecular N(2)–H(2)···N(1) and N(2)–H(2)···O(2) interactions respectively to stabilize the structure.

Keywords: enaminonitrile, *Z*-*E* isomers, crystal structure, X-ray crystallography;
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1 INTRODUCTION

Enaminonitriles are versatile reagents which are widely used in the fields of medicine, fungicides and biological pesticides[1-3]. The β-enaminonitrile group has been highlighted as a useful building block as precursors for the synthesis of all kinds of heterocycles such as pyrazole, pyridine, pyrimidine, isothiazole and pyrrolinone in biological and pharmaceutical chemistry[4-10], which, in the near future, will become one of the main approaches to the targeted synthesis of heterocycles in the rapidly-rising field of combinatorial chemistry[2]. Despite the importance of β-enaminonitriles, only limited methods such as isomerization, tautomerization, and photochemical reactions so far have been reported for their synthesis[11-13]. In 2015, Hong group developed an efficient synthetic method for N-aryl-β-enaminonitrile using isocyanides as the nitrogen source and CuI as catalyst[11]. As part of our studies on constructing heterocycles to screen their bioactivities, herein we report a novel strategy for the synthesis of β-enaminonitriles under mild conditions without heavy metal catalyst contamination. Interestingly, the desired β-enaminonitrile is a pair of *Z*-*E* isomers with obviously different R_f values, which can be separated by flash column chromatography at room temperature. Their structures were confirmed by spectral analysis and X-ray single crystal diffraction.

2 EXPERIMENTAL

2. 1 Materials and methods

All commercially available reagents and solvents were of analytical grade and used as received without further purification. Flash column chromatography was performed on silica gel (200～300 mesh). Melting points were recorded on WRSIA apparatus without correction. The FT-IR spectrum was recorded on a Bruker VERTEX-70 FT-IR spectrophotometer in the range of 400～4000 cm^{-1} using KBr pellet. NMR spectra were recorded in $CDCl_3$ on a Bruker Advance (500 MHz) with TMS as the internal standard. HRMS were recorded on a Thermo Scientific Exactive LC-MS Spectrometer measured in ESI mode and the mass analyzer was TOF. X-ray diffraction data were collected on a Bruker SMART APEX-CCD diffractometer.

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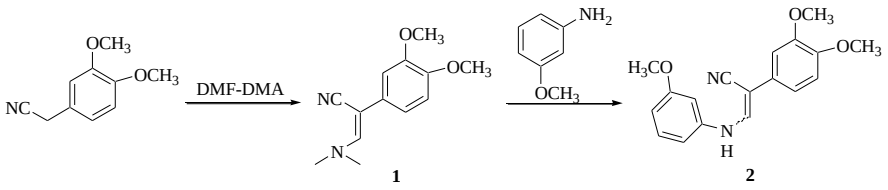
2. 2 Synthesis of compound 2

The *β*-enaminonitrile compound **2** was prepared according to Scheme 1.



1 **2**

Scheme 1. Synthetic route of compound 2

Material 3,4-dimethoxyphenylacetonitrile (3.54 g, 0.02 mol) was mixed with 20 mL N,N-dimethylformamide-dimethylacetal (DMF-DMA) and refluxed for 6 h until the reaction completed (monitored by TLC). Then the excess DMF-DMA was removed under vacuum to obtain compound **1**. Without purification, the next step was carried out directly.

The crude **1** was dissolved in 20 mL toluene. Then 3.80 g (0.02 mol) toluene-*p*-sulfonic acid and 2.46 g (0.02 mol) 1-methoxy-3-amino-benzene were added and the mixture was refluxed for about 3 h (monitored by TLC). After completion, the solvent was removed under vacuum and the crude product was purified by column chromatography on silica gel eluted with ethyl acetate/petroleum ether (V:V = 1:6) to afford a pair of isomers **2** as pale yellow solid, yield 43% for compound **2a** (ethyl acetate/petroleum ether V:V = 1:4, R_f = 0.42) and 28% for compound **2b** (ethyl acetate/petroleum ether V:V = 1:4, R_f = 0.32). (*Z*)-2-(3,4-dimethoxyphenyl)-3-((3-methoxyphenyl)-amino)acrylonitrile (**2a**), m.p. 125～126 ℃, IR (KBr, cm^{-1}): *v* 3262(m), 2199(s), 1651(vs), 1595(vs), 1523(m), 1280(s), 1150(m), 1023(s). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.61(d, *J* = 13.2 Hz, 1H, C=C–H), 7.24(t, *J* = 8.0 Hz, 1H, Ar–H), 7.14(d, *J* = 13.2 Hz,1H, NH), 6.94(dd, *J* = 8.0, 2.3 Hz, 1H, Ar–H), 6.89(d, *J* = 2.2 Hz, 1H, Ar–H), 6.85(d, *J* = 8.5 Hz, 1H, Ar–H), 6.58～6.61 (m, 2H, Ar–H), 6.53～6.54 (m, 1H, Ar–H), 3.92 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 160.97, 149.42, 148.09, 141.39, 139.37, 139.26, 130.74, 126.01, 120.39, 118.21, 116.56, 111.83, 111.76, 111.23, 108.35, 108.11, 107.88, 102.04, 101.60, 85.77, 56.05, 56.02, 55.41. HRMS (ESI): *m*/*z* [M+H$^+$] calcd. for $C_{18}H_{19}N_2O_3$: 311.1396. Found: 311.1382.

(*E*)-2-(3,4-Dimethoxyphenyl)-3-((3-methoxyphenyl)amino) acrylonitrile (**2b**), m.p. 125～126 ℃, IR (KBr, cm^{-1}): *v* 3334(m), 2189(m), 1647(vs), 1597(vs), 1506(m), 1258(m), 1152(m), 1024(m). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.43(d, *J* = 13.2 Hz, 1H, C=C–H), 7.21(t, *J* = 8.1 Hz, 1H, Ar–H), 7.00～7.01 (m, 2H, Ar–H, NH), 6.90～6.92 (m, 2H, Ar–H), 6.58(dd, *J* = 8.5, 2.5 Hz, 1H, Ar–H), 6.51(dd, *J* = 8.0, 2.2 Hz, 1H, Ar–H), 6.45～6.46 (m, 1H, Ar–H), 3.90 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 161.00, 149.84, 148.79, 141.26, 139.29, 139.22, 130.74, 124.10, 121.60, 120.39, 116.56, 111.79, 111.20, 108.34, 108.11, 107.87, 102.01, 101.61, 85.69, 56.05, 55.95, 55.40. HRMS (ESI): *m*/*z* [M+H$^+$] calcd. for $C_{18}H_{19}N_2O_3$: 311.1396. Found: 311.1382.

2. 3 X-ray structure determination

A colourless crystal suitable for X-ray diffraction study for compound **2a** or **2b** was obtained in the test tube from acetate/petroleum ether (V:V = 1:6) by self-volatilization. Single-crystal diffraction data for compounds **2a** and **2b** were collected on a Bruker Smart Apex CCD diffractometer with graphite-monochromated Mo*Kα* radiation (*λ* = 0.71073 Å) at 293(2) K. The structures of **2a** and **2b** were both solved by direct methods and refined by full-matrix least-squares techniques on F^2 with the SHELXTL program[14]. Anisotropic thermal parameters were applied to the non-hydrogen atoms, and all hydrogen atoms were added geometrically and allowed to be put in the idealized calculated positions. Crystallographic parameters and data collection statistics for structure **2a**: $C_{18}H_{18}N_2O_3$, M_r = 310.34 g·mol^{-1}, monoclinic system, space group *C*2/*c*, *a* = 33.805(7), *b* = 5.4496(12), *c* = 18.401(4) Å, *β* = 112.45(2)°, *V* = 3133.1(12) Å^3, *Z* = 8, *μ*(Mo*Kα*) = 0.091 mm^{-1}, D_c = 1.143 g·cm^{-3}, 10890 reflections measured (7.45°≤2*θ*≤49.99°), 2764 unique (R_{int} = 0.0365, R_{sigma} = 0.0285) which were used in all calculations. The final *R* = 0.0491 ($I > 2\sigma(I)$) and *wR* = 0.1439 (all data). Crystal data for structure **2b**: $C_{18}H_{18}N_2O_3$ (M_r = 310.34 g·mol^{-1}), triclinic system, space group $P\bar{1}$, *a* = 8.8403(7), *b* = 9.0390(6), *c* = 12.0044(74) Å, *α* = 72.075(5)°, *β* = 86.291(5)°, *γ* = 81.216(5)°, *V* = 901.82(10) Å^3, *Z* = 2, *T* = 293(2) K, *μ*(Mo*Kα*) = 0.079 mm^{-1}, D_c = 1.143 g·cm^{-3}, 6734 reflections measured (5.82°≤2*θ*≤50.00°), 3176 unique (R_{int} = 0.0159,

R_{sigma} = 0.0258) which were used in all calculations. The final R = 0.0474 ($I > 2\sigma(I)$) and wR = 0.1377 (all data).

3 RESULTS AND DISCUSSION

3. 1 Synthesis and characterization

Enaminonitrile is called an enamine adjacent to a nitrile functional group (N–C=C–CN). Treatment of compound **1** with DMF-DMA in refluxing toluene affords two products which showed obviously different R_f values based on TLC (ethyl acetate/petroleum ether V:V = 1:4, R_f = 0.42 for **2a** and 0.32 for **2b**), and they can be easily separated by flash column chromatography. One product with low polarity is isolated in 43% yield and identified as enaminonitrile derivative **2a**; the other product with high polarity is isolated in 28% yield and identified as enaminonitrile derivative **2b** on the basis of its spectral and X-ray crystal analyses. IR spectrum of compound **2a** exhibits the absorption bands at 3262, 2199 and 1595 cm^{-1} due to amide-NH, a conjugated CN, and C=C groups, respectively. The IR spectrum of compound **2b** exhibits the corresponding absorption bands at 3334, 2189 and 1597 cm^{-1}. The enaminonitrile compound **2** can exist in *E* and *Z* configurations, and the latter is preferred in higher yield as the molecule in this form would experience the least steric interaction. The -C=C–H, -NH protons and the aromatic multiplet are in the region of δ 6.45～7.61 ppm. The mass spectra of compounds **2a** and **2b** showed a molecular ion peak at m/z 311.1382 (M^+), corresponding to a molecular formula $C_{18}H_{18}N_2O_3$.

3. 2 X-ray crystal structure

High-quality colourless crystals of compound **2a** or **2b** were obtained in the test tube from acetate/petroleum ether (V:V = 1:6) by self-volatilization. Single-crystal X-ray analyses revealed that the low polar product **2a** adopts the *Z* configuration and the high polar product **2b** exhibits an *E* configuration.

As shown in Fig. 1, the enaminonitrile group (N–C=C–CN) and the two adjacent phenyl rings in compound **2a** shared a common plane. The dihedral angle formed by the two phenyl rings (C(1)–C(2)–C(3)–C(4)–C(5)–C(6) and C(9)–C(10)–C(11)–C(12)–C(13)–C(14)) is ca. 7.24°. In Fig. 2, the enaminonitrile group and the adjacent phenyl ring with a methoxy group in compound **2b** are in a common plane, but they are not coplanar with the adjacent phenyl ring with two methoxy groups. The dihedral angle of the two phenyl rings in **2b** is ca. 70.47°, which is obviously different from that in the planar structure **2a**.

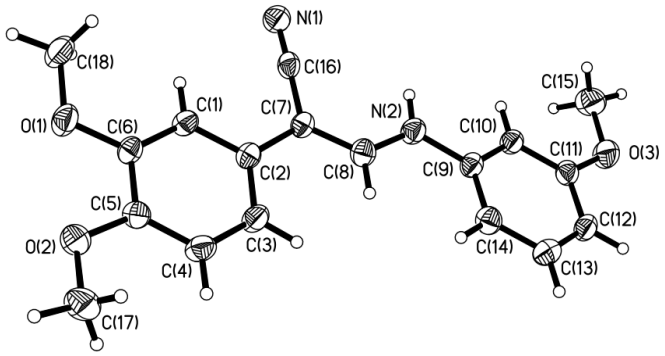


Fig. 1. Molecular structure of 2a, showing the atomic numbering scheme. The displacement ellipsoids are drawn at the 30% probability level

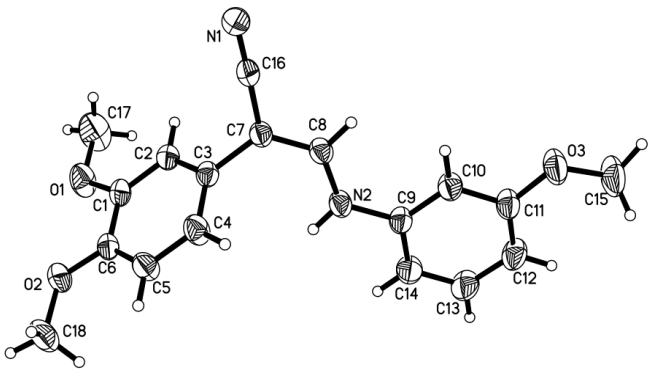


Fig. 2. Molecular structure of 2b with atomic numbering scheme. The displacement ellipsoids are drawn at the 30% probability level

The selected bond lengths and bond angles or torsion angles are listed in Table 1. The bond length of N(2)–C(8) is 1.336(2) Å for **2a** and 1.339(2) Å for **2b**, which is obviously shorter than that of N(2)–C(9) (1.418(2) Å for **2a** and 1.414(2) Å for **2b**), so there is enamination among C(7)=C(8)–N(2)–H(2). The bond lengths of C(2)–C(7) for **2a** and C(3)–C(7) for **2b** are 1.475(2) and 1.490(2) Å respectively, which showed the conjugation system in C(8)=C(7)–C(2)=C(1) for **2a** and C(8)=C(7)–C(3)=C(2) for **2b**. The torsion angles of N(2)–C(8)–C(7)–C(16) of **2a** and corresponding N(2)–C(8)–C(7)–C(16) of **2b** are 0.1(3)° and –178.80(18)°, respectively, which is consistent with the *Z-E* configuration. The other bond lengths and bond angles of compound **2a** or **2b** are similar to those presented in the analogous compound[5].

Table 1. Selected Bond Lengths (Å) and Bond Angles (°) or Torsion Angles (°) of Compound 2

2a					
Bond	Dist.	Bond	Dist.	Bond	Dist.
C(2)–C(7)	1.475(3)	C(8)–N(2)	1.336(2)	O(1)–C(6)	1.369(2)
C(7)–C(16)	1.424(3)	N(2)–C(9)	1.418(2)	C(18)–O(1)	1.418(2)
N(1)–C(16)	1.146(2)	O(2)–C(17)	1.417(3)	O(3)–C(11)	1.367(2)
C(7)–C(8)	1.360(3)	O(2)–C(5)	1.362(2)	O(3)–C(15)	1.413(3)
Angle	(°)	Angle	(°)	Angle	(°)
C(5)–O(2)–C(17)	116.88(16)	C(8)–C(7)–C(2)	122.19(17)	N(2)–C(8)–C(7)	129.12(19)
C(6)–O(1)–C(18)	116.89(16)	C(8)–C(7)–C(16)	120.01(17)	C(8)–N(2)–C(9)	124.05(17)
C(11)–O(3)–C(15)	118.02(16)	C(16)–C(7)–C(2)	117.79(15)	N(1)–C(16)–C(7)	178.6(2)
Torsion angle	(°)	Torsion angle	(°)	Torsion angle	(°)
N(2)–C(8)–C(7)–C(16)	0.1(3)	N(2)–C(8)–C(7)–C(2)	–178.96(18)	C(16)–C(7)–C(2)–C(1)	–1.3(2)
2b					
Bond	Dist.	Bond	Dist.	Bond	Dist.
C(3)–C(7)	1.490(2)	C(8)–N(2)	1.339(2)	O(2)–C(6)	1.363(2)
C(7)–C(16)	1.422(3)	N(2)–C(9)	1.414(2)	C(18)–O(2)	1.424(3)
N(1)–C(16)	1.150(2)	O(1)–C(17)	1.419(3)	O(3)–C(11)	1.363(2)
C(7)–C(8)	1.360(2)	O(1)–C(1)	1.373(2)	O(3)–C(15)	1.429(3)
Angle	(°)	Angle	(°)	Angle	(°)
C(1)–O(1)–C(17)	117.92(17)	C(3)–C(7)–C(8)	125.54(16)	N(2)–C(8)–C(7)	125.71(16)
C(6)–O(2)–C(18)	117.32(16)	C(8)–C(7)–C(16)	117.18(15)	C(9)–N(2)–C(8)	126.39(15)
C(11)–O(3)–C(15)	118.09(18)	C(16)–C(7)–C(3)	117.20(15)	N(1)–C(16)–C(7)	178.50(19)
Torsion angle	(°)	Torsion angle	(°)	Torsion angle	(°)
N(2)–C(8)–C(7)–C(16)	–178.80(18)	N(2)–C(8)–C(7)–C(3)	4.5(3)	C(16)–C(7)–C(3)–C(2)	63.6(2)

The hydrogen bond parameters are shown in Table 2. The packing diagram of compound **2a** is depicted in Fig. 3. The crystal packing of **2a** is governed by intermolecular N(2)–H(2)···N(1) interactions. There are not intermolecular π-π stacking interactions between the phenyl rings. The packing diagram of compound **2b** is depicted in Fig. 4. The crystal packing of **2b** is governed by intermolecular N(2)–H(2)···O(2) interactions to stabilize the structure.

Table 2. Hydrogen Bond Lengths (Å) and Bond Angles (°)

D–H···A	d(D–H)	d(H···A)	d(D···A)	∠DHA
2a				
N(2)–H(2)···N(1)	0.86	2.31	3.157(2)	169
2b				
N(2)–H(2)···O(2)	0.86	2.47	2.970(2)	118

Symmetry codes: for **2a**, 1–*x*, 2–*y*, 1–*z*; for **2b**, 1–*x*, 1–*y*, 1–*z*

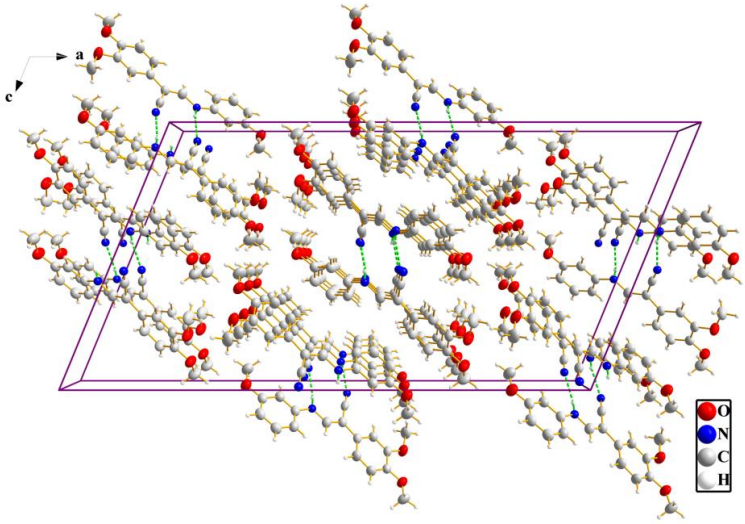


Fig. 3. Packing diagram of compound 2a connected through intermolecular hydrogen bonds

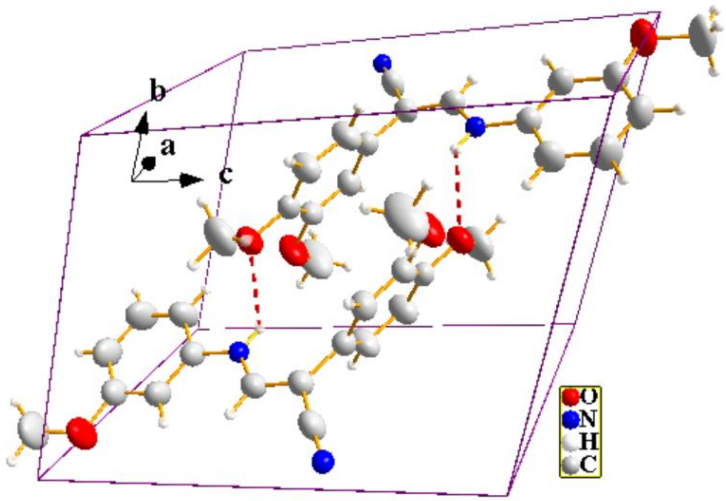


Fig. 4. Packing diagram of compound 2b connected through intermolecular hydrogen bonds

4 CONCLUSION

In summary, we have described a facile, safe and efficient new method to synthesize enaminonitrile derivatives. A pair of *Z*-*E* enaminonitrile isomerisms were determined by IR, ^{1}H NMR, ^{13}C NMR, MS analysis and single-crystal X-ray diffraction. Further studies used in the heterocyclic synthesis and about activities are in progress in our laboratory.

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