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Novel Diastereoselective Synthesis and X-Ray Crystallographic Studies of (*E*)-2-cyano-*N*-(4-ethoxyphenyl)-3-methylthio-3-(substituted-amino)Acrylamides

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*Three derivatives of the novel (*E*)-2-cyano-*N*-(4-ethoxyphenyl)-3-methylthio-3-(substituted-amino)acrylamides **3**–**5** were selectively synthesized by the one-pot reaction of 2-cyano-*N*-(4-ethoxyphenyl)acetamide (**2**) with substituted isothiocyanates and methyl iodide in DMF containing potassium hydroxide as a basic catalyst. The stereochemistry and the structures of the synthesized compounds were confirmed by single crystal X-ray diffraction, IR, ^{1}H-NMR, ^{13}C-NMR, mass spectroscopy, and elemental analyses.*

Keywords Crystal structure; cyanoacetylation; diastereoselective; ketene *N*,*S*-acetals; 4-ethoxyaniline

Introduction

The synthesis of α-cyanoketene-*N*,*S*-acetals has been a subject of great interest because of their wide applications. For example, they are important and versatile intermediates in organic synthesis, and have been used particularly for the synthesis of polyfunctionalized heterocycles. A literature survey revealed that there are two possible synthetic routes for α-cyanoketene *N,S*-acetals. These synthetic strategies include (1) a two-step procedure

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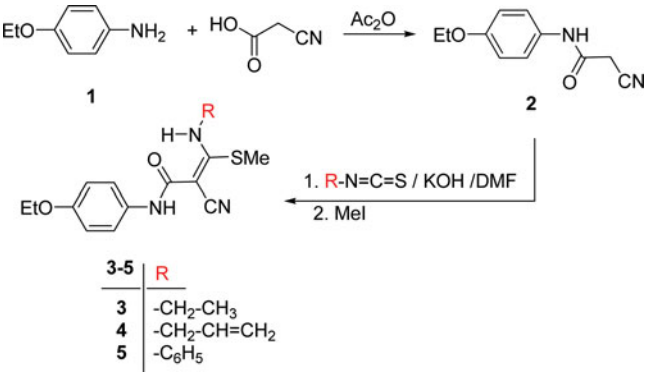
which involves the base promoted nucleophilic addition of cyanoacetanilides to carbon disulfide followed by *in situ* alkylation with methyl iodide or dimethyl sulfate to afford α-cyanoketene *S,S*-acetals; those undergo addition-elimination reactions with strong nucleophiles such as alkylamines or weaker nucleophiles such as arylamines, under gentle or powerful conditions in various solvents [1], and (2) the clean one-pot nucleophilic addition reaction of cyanoacetanilides to alkyl- or aryl- isothiocyantes and subsequent alkylation with methyl iodide or dimethyl sulfate [2,3].

The alkylthio groups at the β carbon in these intermediates are activated by the presence of the electron-withdrawing groups at the α position and can therefore be displaced sequentially by various carbon, nitrogen, and oxygen nucleophiles, creating a variety of applications in C—C, C—N, and C—O bond formation [4,5]. They have been utilized as building blocks for the synthesis of a wide range of heterocyclic system such as pyrroles [6,7], pyrazoles [8,9], thiophenes [10], thieno[2,3-*b*]pyrroles [11], pyrrolo[2,1-*b*]thiazol-6-ones [12], *bis*-2,2-(1,3,4-thiadiazole) and *bis*-3,3-(1,2,4-triazole) derivatives [13], pyridones [14], and tetrahydroisoquinolines [15]. We report herein an easy and efficient (*E*)-diastereoselective synthesis of three derivatives of novel α-cyanoketene-*N*,*S*-acetals and their X-ray crystallographic study.



Scheme 1. Synthesis of (*E*)-2-cyano-*N*-(4-ethoxyphenyl)-3-methylthio-3-(substituted-amino) acry lamides **3**–**5**.

Results and Discussion

The starting material 2-cyano-*N*-(4-ethoxyphenyl)acetamide (**2**) was prepared in a good yield by the reaction of 4-ethoxyaniline (**1**) with cyanoacetic acid in the presence of acetic anhydride following the cyanoaceylation protocol of aromatic amines reported earlier by Slatt et al., [16]. Treatment of **2** with each of ethyl-, allyl-, and phenyl isothiocyanates in DMF containing potassium hydroxide at room temperature for 24 h followed by addition of methyl iodide afforded novel ketene *N*,*S*-acetals **3–5** in high chemical yield (Scheme 1). The structures of the reaction products **3–5** were confirmed by elemental analyses and spectroscopic data. The IR spectrum of compound **5**, as representative example, showed absorption bands at 3319, 3205, 2202, and 1649 cm^{-1} assignable to two NH, CN, and amidic C=O functions, respectively. Its ^{1}HNMR spectrum (DMSO–d_6) showed beside the expected nine aromatic protons, triplet, and quartet signals at δ 1.31 and 3.98 ppm integrated for three and two protons assigned for the ethoxy group, and three singlet signals at δ 2.23, 9.42, and 11.81 ppm specific for thiomethyl, NH, and amidic NH protons, respectively. The ^{13}C-NMR spectrum of **5** revealed 16 carbon types, the most important signals were

displayed at δ 14.6, 16.3, 63.0, 118.4, and 166.5 ppm characteristics for CH_3, SCH_3, OCH_2, CN, and amidic C=O carbons. The mass spectrum showed a molecular ion peak at $m/z = 353$ (M^+), corresponding to a molecular formula $C_{19}H_{19}N_3O_4S$. It is worthwhile to mention that the lower frequency of an amidic carbonyl group in the IR spectrum and the appearance of the amidic NH at downfield in ^{1}H-NMR spectrum is attributed to the formation of intramolecular hydrogen bonding between them as elucidated from single crystal x-ray crystallographic studies.

The formation of compounds **3–5** was assumed to take place *via* the nucleophilic addition of the deprotonated active methylene moiety of **2** to substituted isothiocyanates followed by *in situ* thioalkylation with methyl iodide.

In order to establish unambiguously the structure and stereochemistry of the ketene-*N*,*S*-acetals **3–5**, their crystal structures were determined by X-ray single-crystal crystallography. The X-ray diffraction of compounds **3–5** proves their molecular structures in *trans*-configuration (Figs. 1–3). The crystal data of **3–5** are summarized in Table 1. Bond lengths, angles and torsion angles of **3–5** are listed in Tables 2–4. The hydrogen bonds are listed in Table 5.

Crystal Structure Description of Compound 3

The molecular structure of **3** is depicted in Fig. 1a. There are two crystallographic independent molecules, *A* and *B*, in the asymmetric unit of **3**. The molecule exists in *trans* configuration with respect to the C3=C5 double bond and the torsion angle S1—C3—C5—C7 = 176.3 (7)° in molecule *A* and −179.3 (6)° in molecule *B*. The ethoxy group is co-planar with the attached benzene ring with the torsion angle C11—O2—C14—C15 = −179.6 (9)° in molecule *A* and −177.6 (6) in molecule *B*. The acrylamide is essentially co-planar with the phenyl ring with the torsion angle C8—N3—C7—C5 = 176.9(8)° in molecule *A* and −179.5 (8)° in molecule *B*. The bond angles around C3 [111.9 (5)–128.2(4)°] (Table 2) indicate sp^2 hybridization. The orientation of the methylthio unit can be indicated by the torsion angle C4—S1—C3—C5 = −38.5 (10) in molecule *A* and −5.8 (11)° in molecule *B*. Moreover, the ethylamino moiety is deviated from the mean plane of the molecule as indicated by the torsion angle C3—N1—C2—C1 = −173.2 (10)° in molecule *A* and 174.8 (11)° in molecule *B*. In both molecules of *A* and *B*, intramolecular N—H . . . O hydrogen bond between the ethylamino and carbonyl groups generates a R(6) ring motif [17] (Fig. 1a). Bond lengths [18] and angles are within normal ranges. In the crystal structure of **3** (Fig. 1b), the adjacent molecules are linked into dimers by two related inversion N—H . . . .N_{cyano} hydrogen bonds generating a $R^2_2(12)$ ring motif [17]. These dimers are further connected by C—H . . . $O_{carbonyl}$ weak interactions into ribbons parallel to [001] (Fig. 1b). The crystal is stabilized by intermolecular N—H . . . N_{cyano} hydrogen bond, C—H . . . $O_{carbonyl}$ and C—H . . . π weak interactions (Table 5); Cg_2 is the centroid of C8B—C13B phenyl ring.

Crystal Structure Description of Compound 4

The molecular structure of **4** is shown in Fig. 2a. There are two crystallographic independent molecules *A* and *B* in the asymmetric unit of **4**. The molecule exists in *trans* configuration with respect to the C4=C6 double bond and the torsion angle S1—C4—C6—C8 = 172.21 (17)° in molecule *A* and −171.44 (16)° in molecule *B*. The molecular structure of **4**, which contains the allylamino substituent, is more twisted when compared to the

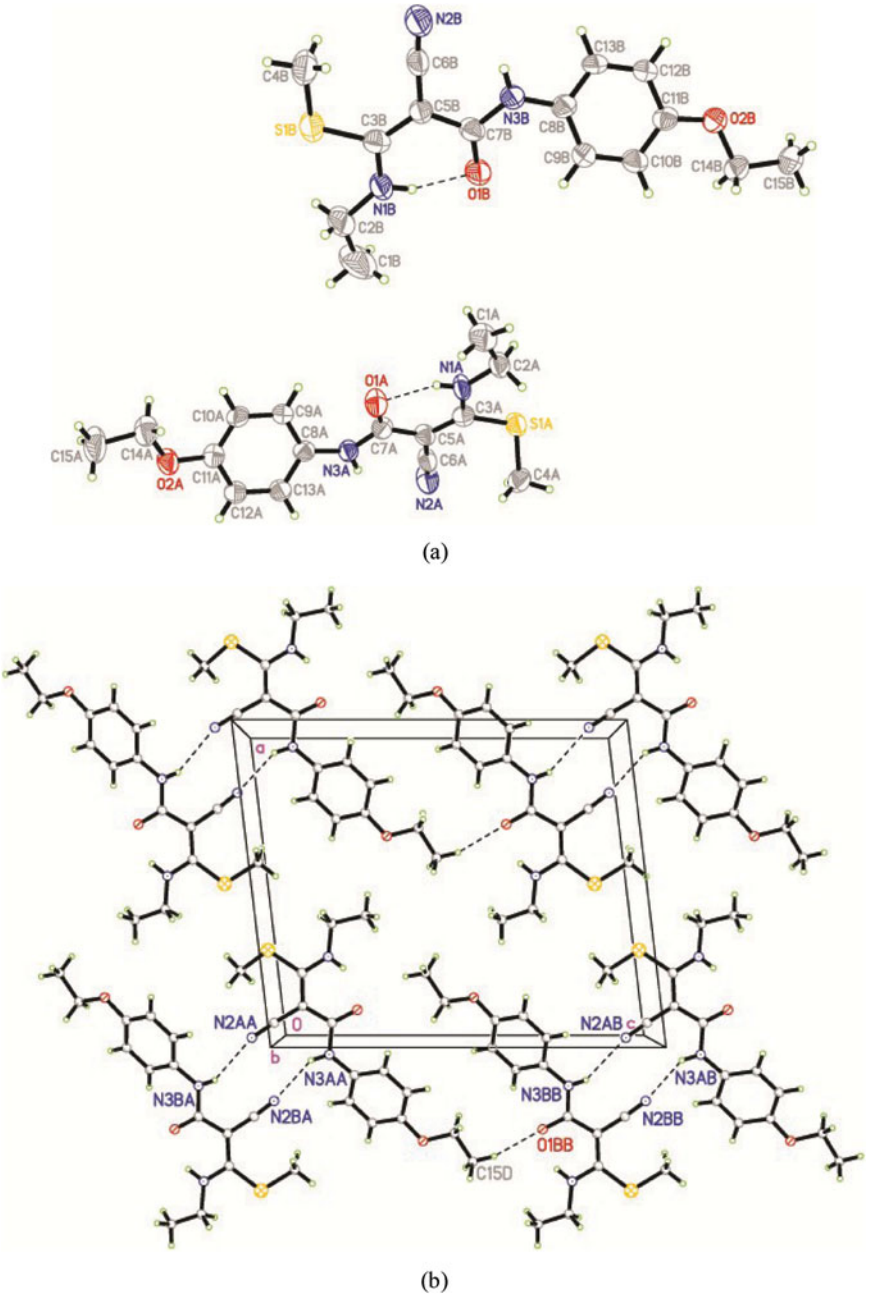
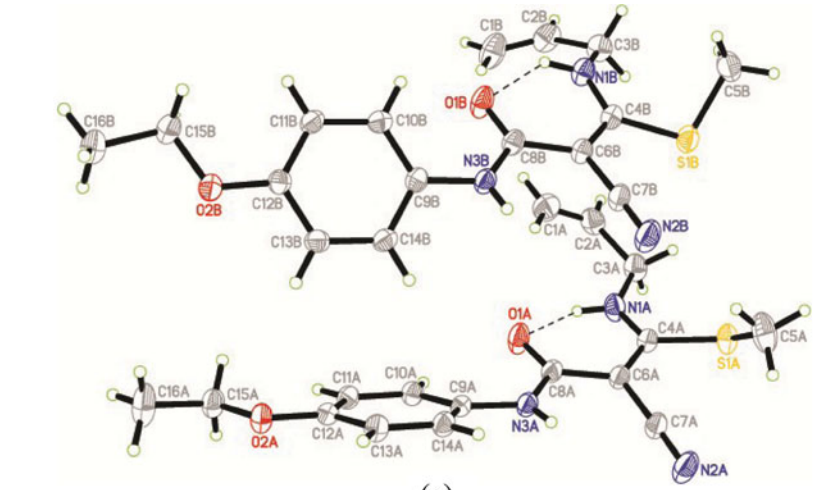
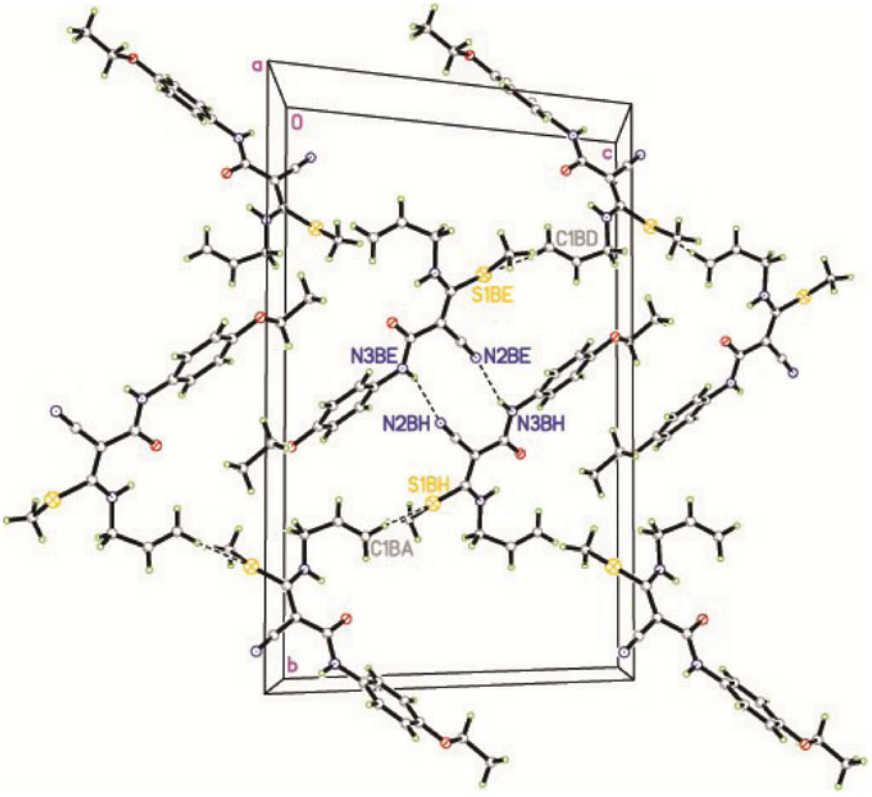


Figure 1. (a) ORTEP diagram drawn at 40% ellipsoids for nonhydrogen atoms and (b) the crystal packing of **3**.

structure of **3**, which contains the ethylamino substituted group. In the structure of **4**, the ethoxy group is almost co-planar with the attached benzene ring with the torsion angle C12—O2—C15—C16 = −175.2 (2)° in molecule *A* and 178.42 (18)° in molecule *B*. The acrylamide unit is essentially co-planar with the phenyl ring with the torsion angle



(a)



(b)

Figure 2. (a) ORTEP diagram drawn at 40% ellipsoids for nonhydrogen atoms and (b) the crystal packing of **4**.

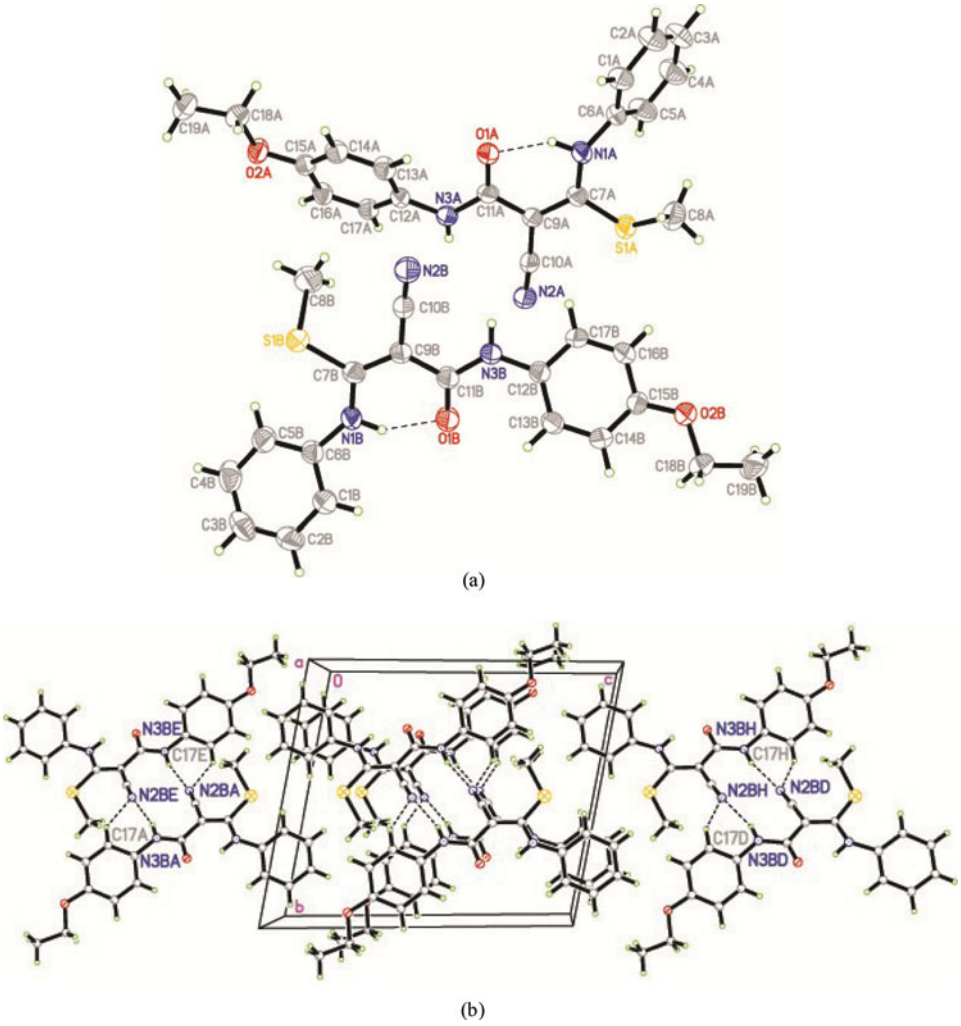


Figure 3. (a) ORTEP diagram drawn at 40% ellipsoids for nonhydrogen atoms and (b) the crystal packing of **5**.

C9—N3—C8—C6 = 179.81 (19)° in molecule *A* and −179.75 (18)° in molecule *B*. The bond angles around atom C4 [117.49 (17)–122.95 (16)°] (Table 3) indicated sp^2 hybridization. The methylthio moiety is twisted from the mean plane through the acrylamide unit as indicated by the torsion angle C5—S1—C4—C6 = −44.8 (2)° in molecule *A* and −135.39 (19)° in molecule *B*. Moreover, the allylamino moiety is also deviated from the mean plane of the acrylamide with the torsion angle C4—N1—C3—C2 = −150.7 (2)° and C1—C2—C3—N1 = 10.5 (4)° in molecule *A* and the corresponding values are 139.3 (2)° and −6.8 (4)° in molecule *B*. In both molecules of *A* and *B*, intramolecular N—H . . . O between the allylamino and carbonyl groups generates a R(6) ring motif [17] (Fig. 2a). Bond lengths [18] and angles are within normal ranges and comparable to compound **3**. In the crystal structure of **4** (Fig. 2b), the molecules are linked into screw chains along the *c*-axis by C—H . . . S weak interactions and the adjacent screw chains are interconnected

Table 1. Crystal data and parameters for structure refinement of **3**, **4**, and **5**

Compound	**3**	**4**	**5**
CCDC deposition numbers	932122	932121	932120
Molecular formula	$C_{15}H_{19}N_3O_2S$	$C_{16}H_{19}N_3O_2S$	$C_{19}H_{19}N_3O_2S$
Molecular weight	305.40	317.41	353.44
Crystal system	Monoclinic	monoclinic	triclinic
Space group	$P2_1$	$P2_1/c$	P-1
a/Å	13.3022 (5)	9.5879 (3)	9.7424 (4)
b/Å	7.4418 (4)	23.6868 (6)	12.7919 (5)
c/Å	15.9314 (6)	16.8275 (5)	14.9537 (5)
α /°	90	90	100.311 (3)
β/°	96.785 (3)	121.821 (2)	100.136 (3)
γ/°	90	90	91.743 (3)
V/ Å^3	1566.04 (12)	3247.24 (18)	1801.18 (12)
Z	4	8	4
D_{calc} (g cm^{-3})	1.295	1.298	1.303
Crystal Dimensions (mm)	0.07 × 0.41 × 0.55	0.08 × 0.52 × 0.57	0.08 × 0.12 × 0.58
μ/mm^{-1}	1.905	1.860	1.736
Radiation λ (Å)	1.54178	1.54178	1.54178
T_{min}/T_{max}	0.4200/ 0.8782	0.4165/0.8655	0.4320/0.8736
Reflections measured	10,260	19,905	20,693
Ranges/indices (h, k, l)	−15, 15; −8, 7; −18, 18	−7, 10; −26, 26; −18, 18	−10, 9; −14, 14; −16, 16
θ limit (°)	2.79–64.96	3.61–60.00	3.06–60.00
Unique reflections	2889	4772	4340
Observed reflections ($I > 2\sigma(I)$)	1745	3718	3706
Parameters	401	401	472
Goodness of fit on F^2	1.031	1.061	1.058
R_1, wR_2 [$I \geq 2\sigma(I)$]	0.0570, 0.1422	0.0422, 0.1162	0.0456, 0.1196

by N—H . . . .N_{cyano} hydrogen bonds forming sheets parallel to the *bc* plane with $R^2_2(12)$ ring motifs (Fig. 2b). The crystal is stabilized by intermolecular N—H . . . N_{cyano} hydrogen bond, C—H . . . S, and C—H . . . π weak interactions (Table 5); Cg_1 and Cg_2 are the centroids of C10A—C14A and C10B—C14B phenyl rings, respectively.

Crystal Structure Description of Compound 5

The molecular structure of **5** is shown in Fig. 3a. There are also two crystallographic independent molecules *A* and *B* in the asymmetric unit of **5**. The molecule exists in *trans* configuration respected to the C7 = C9 double bond and the torsion angle S1—C7—C9—C11 = −177.96 (19)° in molecule *A* and −178.90 (19)° in molecule *B*. The molecular structure of **5**, which contains the phenylamino substituent, is more twisted than compounds **3** and

Table 2. Selected bond lengths (Å), angles, and torsion angles (°) for **3**

Bond lengths					
1S1A-C3A	1.756 (6)	C4A-H4AB	0.9600	C1B-C2B	1.413 (9)
S1A-C4A	1.790 (7)	C4A-H4AC	0.9600	C1B-H1BA	0.9600
O1A-C7A	1.218 (6)	C14A-C15A	1.521 (10)	C1B-H1BB	0.9600
O2A-C11A	1.381 (7)	C14A-H14A	0.9700	C1B-H1BC	0.9600
O2A-C14A	1.405 (7)	C14A-H14B	0.9700	C2B-H2BA	0.9700
N1A-C3A	1.322 (7)	C15A-H15A	0.9600	C2B-H2BB	0.9700
N1A-C2A	1.449 (7)	C15A-H15B	0.9600	C3B-C5B	1.412 (8)
N1A-H1N1	0.80 (5)	C15A-H15C	0.9600	C4B-H4BA	0.9600
N2A-C6A	1.138 (8)	S1B-C4B	1.730 (7)	C4B-H4BB	0.9600
N3A-C7A	1.373 (7)	S1B-C3B	1.745 (7)	C4B-H4BC	0.9600
N3A-C8A	1.405 (7)	O1B-C7B	1.234 (7)	C14B-C15B	1.512 (8)
N3A-H1N3	0.84 (5)	O2B-C11B	1.367 (7)	C14B-H14C	0.9700
C1A-C2A	1.518 (8)	O2B-C14B	1.435 (7)	C14B-H14D	0.9700
C1A-H1AA	0.9600	N1B-C3B	1.328 (8)	C15B-H15D	0.9600
C1A-H1AB	0.9600	N1B-C2B	1.458 (8)	C15B-H15E	0.9600
C1A-H1AC	0.9600	N1B-H1NB	0.85 (5)	C15B-H15F	0.9600
C2A-H2AA	0.9700	N2B-C6B	1.127 (7)	C1B-C2B	1.413 (9)
C2A-H2AB	0.9700	N3B-C7B	1.356 (7)	C1B-H1BA	0.9600
C3A-C5A	1.412 (8)	N3B-C8B	1.415 (7)	C1B-H1BB	0.9600
C4A-H4AA	0.9600	N3B-H1NC	0.80 (5)	C1B-H1BC	0.9600
Bond angles					
C3A-S1A-C4A	107.4 (3)	C5A-C3A-S1A	125.0 (4)	C7B-N3B-C8B	127.3 (5)
C11A-O2A-C14A	118.3(5)	C12A-C11A-O2A	116.2 (6)	N1B-C3B-C5B	119.9 (6)
C3A-N1A-C2A	127.6 (5)	O2A-C11A-C10A	125.0 (5)	N1B-C3B-S1B	111.9 (5)
C7A-N3A-C8A	125.0 (4)	C4B-S1B-C3B	111.7 (3)	C5B-C3B-S1B	128.2 (4)
N1A-C3A-C5A	120.4 (5)	C11B-O2B-C14B	119.0 (5)	O2B-C11B-C12B	116.5 (6)
N1A-C3A-S1A	114.6 (5)	C3B-N1B-C2B	127.5 (6)	O2B-C11B-C10B	124.7 (5)
Torsion angles					
S1A-C3A-C5A-C7A	–176.3 (7)	C3A-C5A-C7A-N3A	–175.5 (9)	C4B-S1B-C3B-C5B	–5.8 (11)
C3A-N1A-C2A-C1A	–173.2 (10)	C11A-O2A-C14A-C15A	–179.6 (9)	C8B-N3B-C7B-C5B	–179.5(8)
C4A-S1A-C3A-C5A	–38.5 (10)	S1B-C3B-C5B-C7B	–179.3 (6)	C3B-C5B-C7B-N3B	177.8 (8)
C8A-N3A-C7A-C5A	176.9 (8)	C3B-N1B-C2B-C1B	174.8 (11)	C11B-O2B-C14B-C15B	–177.6 (6)

Table 3. Selected bond lengths (Å), angles, and torsion angles (°) for **4**

		Bond lengths			
S1A-C4A	1.761 (2)	C9A-C14A	1.391 (3)	C1B-C2B	1.283 (4)
S1A-C5A	1.791 (2)	C10A-C11A	1.389 (3)	C2B-C3B	1.489 (3)
O1A-C8A	1.240 (2)	C11A-C12A	1.380 (3)	C3B-H12	0.9700
O2A-C12A	1.371 (2)	C12A-C13A	1.386 (3)	C3B-H13	0.9700
O2A-C15A	1.433 (2)	C13A-C14A	1.374 (3)	C4B-C6B	1.392 (3)
N1A-C4A	1.329 (3)	C15A-C16A	1.488 (3)	C5B-H14	0.9600
N1A-C3A	1.443 (3)	C15A-H15A	0.9700	C5B-H15	0.9600
N1A-H19	0.8486	C15A-H15B	0.9700	C5B-H16	0.9600
N2A-C7A	1.140 (3)	C16A-H16A	0.9600	C6B-C7B	1.422 (3)
N3A-C8A	1.349 (3)	C16A-H16B	0.9600	C6B-C8B	1.467 (3)
N3A-C9A	1.416 (2)	C16A-H16C	0.9600	C9B-C10B	1.379 (3)
N3A-H17	0.7553	S1B-C4B	1.756 (2)	C9B-C14B	1.391 (3)
C1A-C2A	1.274 (4)	S1B-C5B	1.802 (3)	C10B-C11B	1.384 (3)
C2A-C3A	1.480 (3)	O1B-C8B	1.240 (2)	C11B-C12B	1.383 (3)
C3A-H4	0.9700	O2B-C12B	1.376 (2)	C12B-C13B	1.381 (3)
C3A-H5	0.9700	O2B-C15B	1.422 (2)	C13B-C14B	1.375 (3)
C4A-C6A	1.394 (3)	N1B-C4B	1.332 (3)	C15B-C16B	1.500 (3)
C5A-H6	0.9600	N1B-C3B	1.450 (3)	C15B-H15C	0.9700
C5A-H7	0.9600	N1B-H20	0.9019	C15B-H15D	0.9700
C5A-H8	0.9600	N2B-C7B	1.141 (3)	C16B-H16D	0.9600
C6A-C7A	1.415 (3)	N3B-C8B	1.348 (3)	C16B-H16E	0.9600
C6A-C8A	1.465 (3)	N3B-C9B	1.420 (2)	C16B-H16F	0.9600
C9A-C10A	1.381 (3)	N3B-H18	0.8056		
		Bond angles			
C4A-S1A-C5A	104.25 (11)	9N2A-C7A-C6A	178.3 (3)	N1B-C3B-C2B	112.1 (2)
C12A-O2A-C15A	117.84 (16)	O1A-C8A-N3A	121.4 (2)	N1B-C4B-C6B	122.0 (2)
C4A-N1A-C3A	128.6 (2)	O1A-C8A-C6A	121.31 (19)	N1B-C4B-S1B	120.49 (16)
C8A-N3A-C9A	126.87 (18)	N3A-C8A-C6A	117.25 (19)	C6B-C4B-S1B	117.49 (17)
N1A-C3A-C2A	112.1 (2)	C4B-S1B-C5B	104.10 (12)	N2B-C7B-C6B	176.8 (2)
N1A-C4A-C6A	121.7 (2)	C12B-O2B-C15B	117.68 (16)	O1B-C8B-N3B	121.5(2)
N1A-C4A-S1A	115.35 (15)	C4B-N1B-C3B	127.7 (2)	O1B-C8B-C6B	121.19 (19)
C6A-C4A-S1A	122.95 (16)	16C8B-N3B-C9B	125.40 (18)	N3B-C8B-C6B	117.33 (18)
		Torsion angles			
S1A-C4A-C6A-C8A	172.21 (17)	C9A-N3A-C8A-C6A	179.81 (19)	C4B-N1B-C3B-C2B	139.3(2)
C1A-C2A-C3A-N1A	10.5 (4)	C12A-O2A-C15A-C16A	–175.2 (2)	C9B-N3B-C8B-O1B	0.2 (3)
C5A-S1A-C4A-N1A	137.4 (2)	S1B-C4B-C6B-C8B	–171.44 (16)	C9B-N3B-C8B-C6B	–179.75 (18)
C4A-N1A-C3A-C2A	–150.7 (2)	C1B-C2B-C3B-N1B	–6.8 (4)	C12B-O2B-C15B-C16B	178.42 (18)
C9A-N3A-C8A-O1A	0.3 (4)	C5B-S1B-C4B-N1B	46.3 (2)		

Table 4. Selected bond lengths (Å), angles, and torsion angles (°) for **5**

Bond lengths					
S1A-C7A	1.747 (3)	C9A-C10A	1.418 (3)	N2B-C10B	1.148 (3)
S1A-C8A	1.792 (3)	C9A-C11A	1.474 (4)	N3B-C11B	1.349 (3)
O1A-C11A	1.238 (3)	C18A-C19A	1.497 (4)	N3B-C12B	1.414 (3)
O2A-C15A	1.370 (3)	C18A-H18A	0.9700	N3B-H3NB	0.83 (3)
O2A-C18A	1.418 (3)	C18A-H18B	0.9700	C7B-C9B	1.385 (4)
N1A-C7A	1.345 (3)	C19A-H19A	0.9600	C8B-H8BA	0.9600
N1A-C6A	1.418 (3)	C19A-H19B	0.9600	C8B-H8BB	0.9600
N1A-H1N1	0.94 (3)	C19A-H19C	0.9600	C8B-H8BC	0.9600
N2A-C10A	1.145 (3)	S1B-C7B	1.752 (3)	C9B-C10B	1.419 (3)
N3A-C11A	1.348 (3)	S1B-C8B	1.786 (3)	C9B-C11B	1.474 (4)
N3A-C12A	1.415 (3)	O1B-C11B	1.240 (3)	C18B-C19B	1.481 (4)
N3A-H1N3	0.70 (3)	O2B-C15B	1.365 (3)	C18B-H18C	0.9700
C7A-C9A	1.393 (4)	O2B-C18B	1.435 (3)	C18B-H18D	0.9700
C8A-H8AA	0.9600	N1B-C7B	1.350 (3)	C19B-H19D	0.9600
C8A-H8AB	0.9600	N1B-C6B	1.415 (3)	C19B-H19E	0.9600
C8A-H8AC	0.9600	N1B-H1NB	0.89 (3)	C19B-H19F	0.9600
Bond angles					
C7A-S1A-C8A	103.27 (14)	C7A-C9A-C10A	118.9 (2)	N1B-C7B-C9B	119.0 (2)
C15A-O2A-C18A	118.7 (2)	C7A-C9A-C11A	122.1 (2)	N1B-C7B-S1B	119.3 (2)
C7A-N1A-C6A	131.2 (2)	C10A-C9A-C11A	119.1 (2)	C9B-C7B-S1B	121.6 (2)
C11A-N3A-C12A	126.4 (2)	C7B-S1B-C8B	103.83 (15)	C7B-C9B-C10B	118.6 (2)
N1A-C7A-C9A	119.7 (2)	C15B-O2B-C18B	118.9 (2)	C7B-C9B-C11B	123.3 (2)
N1A-C7A-S1A	122.6 (2)	C7B-N1B-C6B	133.6 (2)	C10B-C9B-C11B	117.9 (2)
C9A-C7A-S1A	117.7 (2)	C11B-N3B-C12B	126.7 (2)		
Torsion angles					
S1A-C7A-C9A-C11A	–177.96 (19)	C12A-N3A-C11A-O1A	5.6 (4)	C8B-S1B-C7B-C9B	50.7 (3)
C6A-N1A-C7A-C9A	–153.9 (3)	C15A-O2A-C18A-C19A	178.7 (2)	C12B-N3B-C11B-C9B	175.3 (2)
C8A-S1A-C7A-C9A	–140.7 (2)	S1B-C7B-C9B-C11B	–178.90(19)	C12B-N3B-C11B-O1B	–3.5 (5)
C12A-N3A-C11A-C9A	–174.4 (2)	C6B-N1B-C7B-C9B	166.4 (3)	C15B-O2B-C18B-C19B	179.2 (3)

4 which are the compounds containing the ethylamino and allylamino substituents, respectively. In the structure of **5**, the ethoxy group is co-planar with the attached benzene ring with the torsion angle C15—O2—C18—C19 = 178.7 (2)° in molecule *A* and 179.2 (3)° in molecule *B*. The acrylamide unit is essentially co-planar with the phenyl ring with the torsion angle C12—N3—C11—C9 = −174.4 (2)° in molecule *A* and 175.3 (2)° in

Table 5. Hydrogen bond geometries for compounds **3**, **4**, and **5**

D–H···*A*	*d*(*D*–H) (Å)	*d*(H···*A*) (Å)	*d*(*D*···*A*) (Å)	*Angle* (*D*–H···*A*) (°)
		(**3**)		
N3B–H1NC···N2A [i]	0.79 (5)	2.57 (5)	3.298 (7)	153 (5)
N3A–H1N3···N2B [ii]	0.84 (5)	2.34 (5)	3.089 (7)	149 (5)
N1B–H1NB···O1B	0.85 (5)	1.82 (5)	2.580 (7)	147 (5)
N1A–H1N1···O1A	0.80 (5)	1.90 (5)	2.606 (6)	146 (5)
C4A–H4AB···N2A	0.96	2.61	3.238 (10)	124
C15A–H15A···O1B [iii]	0.96	2.44	3.355 (7)	159
C9A–H9AA···Cg2 [iv]	0.93	2.83	3.567 (9)	137
C14B–H14D···Cg2 [v]	0.97	2.84	3.585 (9)	134
		(**4**)		
N3A–H17···N2A [vi]	0.76	2.41	3.119 (3)	157
N3B–H18···N2B [vii]	0.81	2.37	3.124 (3)	155
N1A–H19···O1A	0.85	1.90	2.607 (2)	141
N1B–H20···O1B	0.90	1.90	2.617 (2)	135
C1B–H10···S1B [viii]	0.93	2.76	3.638 (3)	159
C10A–H10A···O1A	0.93	2.30	2.834 (3)	116
C11B–H11B···Cg1 [ix]	0.93	2.78	3.564 (3)	142
C14B–H14B···Cg1	0.93	2.74	3.522 (3)	142
C15A–H15A···Cg2 [x]	0.97	2.96	3.723 (2)	137
		(**5**)		
N3B–H3NB···N2B [xi]	0.83 (3)	2.23 (3)	3.044 (3)	165 (3)
N1B–H1NB···O1B	0.88 (3)	1.80 (3)	2.599 (3)	149 (3)
N1A–H1N1···O1A	0.93 (3)	1.80 (3)	2.591 (3)	141 (3)
N3A–H1N3···N2A [xii]	0.70 (3)	2.44 (3)	3.075 (4)	152 (3)
C5A–H5AA···S1A	0.93	2.82	3.317 (3)	115
C5B–H5BA···S1B	0.93	2.62	3.173 (3)	118
C13B–H13B···O1B	0.93	2.41	2.896 (3)	112
C8B–H8BC···N2B	0.96	2.61	3.315 (4)	131
C17B–H17B···N2B [xi]	0.93	2.61	3.274 (4)	129
C2A–H2AA···Cg3 [xi]	0.93	2.93	3.654 (3)	136
C5A–H5AA···Cg3 [xii]	0.93	2.85	3.644 (3)	144
C14A–H14A···Cg4 [xi]	0.93	2.94	3.721 (3)	142
C14B–H14B···Cg2 [xiii]	0.93	2.89	3.700 (3)	146
C17A–H17A···Cg4 [xii]	0.93	2.73	3.514 (3)	143

[i] $-1+x, y, -1+z$; [ii] $1+x, y, 1+z$; [iii] $1+x, y, z$; [iv] $1-$ x, $1/2+y, 1-z$; [v] $-x, -1/2+y, 1-z$; [vi] $2-x, 2-y, -z$; [vii] $1-x, 2-y, -z$; [viii] $x, 3/2-y, 1/2+z$; [ix] $-1+x, y, z$; [x] $2-x, 2-y, 1-z$; [xi] $-x, 1-y, 1-z$; [xii] $1-x, 1-y, 1-z$; [xiii] $x, 1+y, z$.

molecule *B*. The bond angles around atom C7 [117.7 (2)–122.6 (2)°] (Table 4) reflected sp^2 hybridization. The methylthio moiety is deviated from the mean plane through the acrylamide unit as indicated by the torsion angle C8—S1—C7—C9 = −140.7 (2)° in molecule *A* and 50.7 (3)° in molecule *B*. The orientation of the phenylamino moiety respected to the acrylamide unit can be indicated by the torsion angle C6—N1—C7—C9 = −153.9 (3)° and the dihedral angle between the C1—C6 phenyl ring and the mean plane through the N1/C7/C9/C11/O1 unit is 45.57 (14)° in molecule *A* and the corresponding values are

166.4 (3) and 27.63 (14)° in molecule *B*. Intramolecular N—H . . . O between the amide of phenylamino and carbonyl groups generates R(6) ring motif [17] in both molecules *A* and *B* (Fig. 3a). Bond lengths [18] and angles are within normal ranges and comparable to those in compound **3** and **4**. In the crystal structure of **5** (Fig. 3b), the two inversion related molecules are linked into a dimer by N—H . . . $.N_{cyano}$ hydrogen bonds and C—H . . . $.N_{cyano}$ weak interactions generating two $R^2{}_1(6)$ ring motifs [17]. These dimers are arranged into sheets parallel to the *bc* plane (Fig. 3b). The crystal is stabilized by intermolecular N—H . . . N_{cyano} hydrogen bond, C—H . . . S and C—H . . . π weak interactions (Table 5); Cg_2, Cg_3, and Cg_4 are the centroids of C12A—C17A, C1B—C6B, and C12B—C17B phenyl rings, respectively.

Experimental

General Method

Melting points were determined on digital Gallen-Kamp MFB-595 instrument using open capillary tubes and are uncorrected. IR spectra were recorded on Perkin-Elmer FT-IR Spectrum BX Spectrometer at cm-1 scale using KBr pellets. NMR spectra were recorded at 500 MHz for ^{1}H and ^{13}C, respectively on a BRUKER AC NMR spectrometer in DMSO-d6; chemical shifts are reported as δ ppm units. Mass spectra were performed on Shimadzu Qp-2010 plus mass spectrometer at 70 eV. The elemental analyses were carried out at the Microanalytical Center, Cairo University, Cairo, Egypt. TLC was carried out on Fluka silica gel/ TLC-cards 91835. All the chemicals and solvents used were obtained from Merck.

Synthesis of 2-cyano-N-(4-ethoxyphenyl)acetamide (2)

To a warm solution of cyanoacetic (50 mmol) and acetic anhydride (50 mmol) at 50°C, was added (50 mmol) of 4-ethoxyaniline. The mixture was heated to 85°C for 25 min, where upon the product started to crystallize. After a further 5 min, the mixture was allowed to cool to room temperature, and the resulting solid product was collected by filtration, washed with methanol, dried in air and recrystallized from dioxane. Grey crystals, yield (78%), mp 178–180°C; IR (KBr) νmax/cm^{-1}: 3297 (NH), 3096 (CH-Ar), 2973 (CH– sp^3), 2254 (CN), 1662 (CO); ^{1}H-NMR (DMSO-d$_6$): $\delta_{ppm} = 1.31$ (t, $J = 7$ Hz, 3H, CH_3), 3.85 (s, 2H, $COCH_2$), 3.98 (q, $J = 7$ Hz, 2H, CH_2), 6.89 (d, $J = 9$ Hz, 2H, CH_{Ar}), 7.45 (d, $J = 9$ Hz, 2H, CH_{Ar}), 10.13 (s, 1H, NH); ^{13}C-NMR (DMSO-d$_6$): $\delta_{ppm} = 14.6$, 26.4, 63.1, 114.5 (2C), 115.9, 120.8 (2C), 131.3, 154.8, 160.3; MS *m/z* (%): 204 (M^+, 86), 176 (45), 135 (29), 108 (100), 80 (7), 68 (11); Anal. Calcd. for $C_{11}H_{12}N_2O_2$ (204): C, 64.69; H, 5.92; N, 13.72%, Found: C, 64.65; H, 5.95; N, 13.76%.

General Procedure for the Synthesis of Ketene N,S-acetals 3–5

To an empty 100 mL round-bottom flask equipped with a magnetic stirrer and septum was added a solution of 2-cyano-*N*-(4-ethoxyphenyl)acetamide (**2**) (10.0 mmol) in DMF (30 mL). Potassium hydroxide (10.0 mmol) was added and the mixture was stirred for 1 hr at room temperature. Substituted isothiocyanates (10.0 mmol) was then added dropwise and the mixture was stirred for 24 hr at room temperature, followed by the addition of methyl iodide (10.0 mmol). The reaction mixture was allowed to stir for a further

2 hr. The reaction was then quenched with 100 mL of cold water and the crude product precipitated was purified by filtration followed by crystallization from ethanol and charcoal.

***(E)-2-Cyano-N-(4-ethoxyphenyl)-3-(ethylamino)-3-(methylthio)acrylamide* (3)**. Yellow crystals, yield (83%), mp 87–88°C, IR (KBr) νmax/cm^{-1}: 3325, 3189 (2NH), 3041 (CH-Ar), 2974 (CH– sp^3), 2196 (CN), 1632 (CO); ^{1}H-NMR (DMSO-d$_6$): $\delta_{ppm} = 1.18$ (t, $J = 7$ Hz, 3H, CH_3), 1.31 (t, $J = 7$ Hz, 3H, CH_3), 2.62 (s, 3H, SCH_3), 3.54–3.56 (m, 2H,CH_2N), 3.98 (q, $J = 7$ Hz, 2H, CH_2O), 6.85 (d, $J = 9$ Hz, 2H, CH_{Ar}), 7.41 (d, $J = 9$ Hz, 2H, CH_{Ar}), 9.03 (s, 1H, NH), 10.7 (s, 1H, NH); ^{13}C-NMR (DMSO-d$_6$): $\delta_{ppm} = 14.6$, 15.3, 17.5, 40.5, 63.0, 74.8, 114.0, 119.4, 122.9, 131.1, 154.8, 165.5, 169.3; MS *m/z* (%): 305 (M$^+$, 53), 169 (31), 137 (93), 108 (100), 93 (34); Anal. Calcd. for $C_{15}H_{19}N_3O_2S$ (305): C, 58.99; H, 6.27; N, 13.76%, Found: C, 58.94; H, 6.23; N, 13.72%.

***(E)-3-(Allylamino)-2-cyano-N-(4-ethoxyphenyl)-3-(methylthio)acrylamide* (4)**. Yellowish grey crystals, yield (81%), mp 75–77°C; IR (KBr) νmax/cm^{-1}: 3320, 3195 (2NH), 3012 (CH-Ar), 2969 (CH– sp^3), 2199 (CN), 1647 (CO); ^{1}H-NMR (DMSO-d$_6$): $\delta_{ppm} = 1.31$ (t, $J = 7$ Hz, 3H, CH_3), 2.61 (s, 3H, SCH_3), 3.99 (q, $J = 7$ Hz, 2H, CH_2), 4.19–4.20 (m, 2H, CH_2N), 5.17–5.21 (m, 2H, CH_2=), 5.90–6.00 (m, 1H, CH=), 6.84 (d, $J = 9.5$ Hz, 2H, CH_{Ar}), 7.42 (d, $J = 9$ Hz, 2H, CH_{Ar}), 9.09 (s, 1H, NH), 10.80 (s, 1H, NH); ^{13}C-NMR (DMSO-d$_6$): $\delta_{ppm} = 14.6$, 17.7, 47.5, 63.0, 75.8, 114.0 (2C), 116.3, 119.2, 122.9 (2C), 131.0, 134.3, 154.8, 165.5, 169.9; MS *m/z* (%): 317 (M$^+$, 42), 181 (11), 137 (100), 108 (38); Anal. Calcd. for $C_{16}H_{19}N_3O_2S$ (317): C, 60.54; H, 6.03; N, 13.24%, Found: C, 60.59; H, 6.06; N, 13.26%.

***(E)-2-Cyano-N-(4-ethoxyphenyl)-3-(methylthio)-3-(phenylamino)acrylamide* (5)**. Yellow crystals, yield (92%), mp 109–110 °C; IR (KBr) νmax/cm^{-1}: 3319, 3205 (2NH), 3287 (NH), 3049 (CH-Ar), 2972 (CH- sp^3), 2202 (CN), 1649 (CO); ^{1}H-NMR (DMSO-d$_6$): $\delta_{ppm} = 1.31$ (t, $J = 7$ Hz, 3H, CH_3), 2.23 (s, 3H, SCH_3), 3.98 (q, $J = 7$ Hz, 2H, CH_2), 6.83 (d, $J = 9$ Hz, 2H, CH_{Ar}), 7.22–7.40 (m, 7H, CH_{Ar}), 9.42 (s, 1H, NH), 11.81 (s, 1H, NH); ^{13}C-NMR (DMSO-d$_6$): $\delta_{ppm} = 14.6$, 16.3, 63.0, 79.5, 114.0 (2C), 118.4, 122.9 (2C), 123.6 (2C), 125.9, 129.2 (2C), 130.8, 138.5, 155.0, 164.1, 166.5; MS *m/z* (%): 353 (M$^+$, 100), 327 (3), 189 (4); Anal. Calcd. for $C_{19}H_{19}N_3O_2S$ (353): C, 64.57; H, 5.42; N, 11.89%, Found: C, 64.54; H, 5.47; N, 11.93%.

X-Ray Crystallography Analysis

Selected crystals were mounted on glass fibers and intensity data were collected using a Bruker SMART Apex II diffractometer. The data for these compounds were processed with *SAINT* [19] and corrected for absorption using *SADABS* [19]. The structures of the compounds were solved by direct method using the program *SHELXTL* [18], and were refined by full-matrix least squares technique on F^2 using anisotropic displacement parameters. The nonhydrogen atoms were refined anisotropically. Amide H atoms of **3** and **5** were located in difference maps and refined isotropically. The remaining H atoms were placed in calculated positions with N−H=0.76–0.90 Å, C−H = 0.93 Å for aromatic, 0.97 Å for CH_2 and 0.96 Å for CH_3. The U_{iso}(H) values were constrained to be $1.5U_{eq}$ of the carrier atoms for methyl H atoms and $1.2U_{eq}$ for amide and the other H atoms. A rotating group model was applied to the methyl groups. The final refinement converged well. Materials for publication were prepared using *SHELXTL* [20] and *PLATON* [21]. CCDC 932122 for (**3**), 933121 for (**4**) and 933120 for (**5**) contain the supplementary crystallographic data for this article. These data can be obtained free of charge at http://www.ccdc.cam.ac.uk/data_request/cif, or 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 1223 336033; email: deposit@ccdc.cam.ac.uk.

4. Conclusions

In summary, we reported the success of an easy and efficient (*E*)-diastereoselective synthesis of three novel ketene-*N*,*S*-acetal derivatives which are (*E*)-2-cyano-*N*-(4-ethoxyphenyl)-3-(ethylamino)-3-(methylthio)acrylamide (**3**), (*E*)-3-(allylamino)-2-cyano-*N*-(4-ethoxyphenyl)-3-(methylthio) acrylamide (**4**), and (*E*)-2-cyano-*N*-(4-ethoxyphenyl)-3-(methylthio)-3-(phenylamino)acrylamide (**5**). The 3D molecular and crystal structures of **3–5** were confirmed by X-ray single-crystal crystallography.

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