Synthesis and $E/Z$ Configuration Determination of Novel Derivatives of 3-Aryl-2-(benzothiazol-2'-ylthio) Acrylonitrile, 3-(Benzothiazol-2'-ylthio)-4-(furan-2''-yl)-3-buten-2-one and 2-(1-(Furan-2''-yl)-3'-oxobut-1''-en-2-ylthio)-3-phenylquinazolin-4(3$H$)-one

Fatima Al-Omran $^{1,*}$, Rafat M. Mohareb $^{2,3}$ and Adel Abou El-Khair $^1$

1 Department of Chemistry, Faculty of Science, Kuwait University, P.O. box 12613, safat 13060, Kuwait
2 Department of Chemistry, Faculty of Science, Cairo University, Giza, A.R., Egypt
3 Department of Organic Chemistry, Faculty of Pharmacy, October University for Modern Sciences and Arts, Elwahaat Road, October City, A.R., Egypt

* Author to whom correspondence should be addressed; E-Mail: fatima.alomran@ku.edu.kw.

Received: 21 June 2011; in revised form: 11 July 2011 / Accepted: 14 July 2011 / Published: 20 July 2011

Abstract: Knoevenagel condensation of 2-(benzothiazol-2-ylthio) acetonitrile (2) with either furan-2-carbaldehyde or thiophene-2-carbaldehydes leads to $E$-isomers 4a–b exclusively, while the condensation of the compound 2 with benzaldehyde or para-substituted benzaldehydes with an electron-donating group afforded $E/Z$ mixtures 4c–e with preferentially formation of the $E$-isomer. Condensation of furan-2-carbaldehyde (3a) with either 1-(benzothiazol-2'-ylthio) propan-2-one (5) or 2-(2'-oxo propylthio)-3-phenylquinazolin-4(3$H$)-one (9) leads exclusively to the $Z$-isomers of 6 and 10, respectively. The structures of the newly synthesized compounds were elucidated by elemental analyses, $^1$H-NMR and $^{13}$C-NMR spectra, COSY, HSQC, HMBC, NOE, MS and X-ray crystallographic investigations.

Keywords: benzothiazole; 2-mercaptobenzothiazole; 3-phenylquinazolin-4(3$H$)-one; methyl vinyl ketone; acrylonitrile
1. Introduction

The benzothiazole nucleus is a highly important scaffold for drug development, which has been reported to show good biological activities ranging from anti-microbial [1], anti-inflammatory [1], antibacterial [2], antitumor [3] and anticancer [4,5] to antifungal [6]. On other hand, quinazolin-4-(3H)-ones substituted in the 3-position with a heterocyclic system are attracting the attention of chemists, because of their biological activities ranging from antibacterial, antimicrobial, antifungal, anticonvulsive, sedative, anti-inflammatory, to hypnotic and CNS depression [7-12]. Furthermore, several other publications have pointed out the value of 3-arylacrylonitriles with either triazole [13] or benzimidazole [14] substituents in position 2 of the acrylonitrile also have good cytotoxic activity on human cancer cells and are antibacterial agents [14]. It was recently reported that 2-acetyl-3-(6-methoxybenzothiazol)-2-yl-amino-acrylonitrile (AMBAN) possesses significant anti-proliferative activity and is a potent inducer programmed cell death in human leukemia cells [5].

Based on the abovementioned effects of benzothiazoles, 3-arylacrylonitriles and quinazolin-4-(3H)-ones a series of novel 3-arylacrylonitriles with 2-mercaptobenzothiazoles moiety in the position 2- of the acrylonitrile were synthesized to obtain new potential biologically active agents. On other hand, a series of 4-aryl-3-buten-2-ones with either 2-mercaptobenzothiazole or quinazolin-4-(3H)-one rings in the 3-position of 4-aryl-3-buten-2-one were synthesized. The structures of the newly synthesized compounds have been established by x-ray diffraction studies and on the basis of their spectral data.

2. Result and Discussion

In continuation to our recent research programme dealing with the synthesis of heterocyclic systems, particularly those containing the 2-mercaptobenzothiazole moiety [15,16], 1-(benzothiazol-2-yl-thio)acetonitrile (2) was readily prepared in an excellent yield by treatment of 2-mercaptopbenzothiazole (1) with α-chloroacetonitrile in refluxing acetone containing anhydrous potassium carbonate (cf. Scheme 1). The structure of 2 was unambiguously confirmed by X-ray crystallography [17] as well as on the basis of its spectral data (cf. Figure 1 and Tables 1–3).

Scheme 1. Synthesis of 2.

Figure 1. Perspective view and atom labeling of the X-ray structure of compound 2.
Table 1. Bond lengths (Å) for compound 2.

| atom | atom | distance  | atom | atom | distance  |
|------|------|-----------|------|------|-----------|
| S1   | C1   | 1.730(3)  | S1   | C7   | 1.741(3)  |
| S2   | C7   | 1.747(3)  | S2   | C8   | 1.802(3)  |
| S3   | C10  | 1.732(3)  | S3   | C16  | 1.750(3)  |
| S4   | C16  | 1.745(3)  | S4   | C17  | 1.806(3)  |
| S5   | C19  | 1.731(3)  | S5   | C25  | 1.748(3)  |
| S6   | C25  | 1.747(3)  | S6   | C26  | 1.807(3)  |
| N1   | C6   | 1.400(4)  | N1   | C7   | 1.293(3)  |
| N2   | C9   | 1.136(5)  | N3   | C15  | 1.396(4)  |
| N3   | C16  | 1.292(3)  | N4   | C18  | 1.131(6)  |
| N5   | C24  | 1.402(3)  | N5   | C25  | 1.296(4)  |
| N6   | C27  | 1.136(6)  | C1   | C2   | 1.391(5)  |
| C1   | C6   | 1.404(4)  | C2   | C3   | 1.375(5)  |
| C3   | C4   | 1.388(5)  | C4   | C5   | 1.370(5)  |
| C5   | C6   | 1.384(4)  | C8   | C9   | 1.460(5)  |
| C10  | C11  | 1.392(4)  | C10  | C15  | 1.403(3)  |
| C11  | C12  | 1.366(4)  | C12  | C13  | 1.389(4)  |
| C13  | C14  | 1.373(5)  | C14  | C15  | 1.386(4)  |
| C17  | C18  | 1.447(5)  | C19  | C20  | 1.394(4)  |
| C19  | C24  | 1.400(4)  | C20  | C21  | 1.373(5)  |
| C21  | C22  | 1.391(4)  | C22  | C23  | 1.383(4)  |
| C23  | C24  | 1.386(4)  | C26  | C27  | 1.446(5)  |

Table 2. Bond angles (°) for compound 2.

| atom | atom | atom | angle  | atom | atom | atom | angle  |
|------|------|------|--------|------|------|------|--------|
| C1   | S1   | C7   | 88.34(12) | C7   | S2   | C8   | 98.36(13) |
| C10  | S3   | C16  | 88.53(12) | C16  | S4   | C17  | 98.83(13) |
| C19  | S5   | C25  | 88.36(12) | C25  | S6   | C26  | 99.08(12) |
| C6   | N1   | C7   | 109.3(2)  | C15  | N3   | C16  | 109.99(19) |
| C24  | N5   | C25  | 109.60(18) | S1   | C1   | C2   | 129.17(19) |
| S1   | C1   | C6   | 109.9(2)  | C2   | C1   | C6   | 121.0(3)  |
| C1   | C2   | C3   | 117.7(3)  | C2   | C3   | C4   | 121.5(4)  |
| C3   | C4   | C5   | 120.9(3)  | C4   | C5   | C6   | 118.9(3)  |
| N1   | C6   | C1   | 114.9(2)  | N1   | C6   | C5   | 125.1(3)  |
| C1   | C6   | C5   | 120.0(3)  | S1   | C7   | S2   | 117.68(14) |
| S1   | C7   | N1   | 117.6(2)  | S2   | C7   | N1   | 124.7(2)  |
| S2   | C8   | C9   | 112.7(3)  | N2   | C9   | C8   | 179.6(3)  |
| S3   | C10  | C11  | 129.56(18) | S3   | C10  | C15  | 109.71(19) |
| C11  | C10  | C15  | 120.7(3)  | C10  | C11  | C12  | 118.5(3)  |
| C11  | C12  | C13  | 121.1(3)  | C12  | C13  | C14  | 121.0(3)  |
| C13  | C14  | C15  | 119.0(3)  | N3   | C15  | C10  | 115.0(3)  |
| N3   | C15  | C14  | 125.2(2)  | C10  | C15  | C14  | 119.8(3)  |
| S3   | C16  | S4   | 118.30(13) | S3   | C16  | N3   | 116.8(2)  |
Table 2. Cont.

| atom | atom | atom | angle   | atom | atom | atom | angle   |
|------|------|------|---------|------|------|------|---------|
| S4   | C16  | N3   | 124.92(18) | S4   | C17  | C18  | 112.2(3) |
| N4   | C18  | C17  | 178.8(4)  | S5   | C19  | C20  | 128.9(2) |
| S5   | C19  | C24  | 110.11(16) | C20  | C19  | C24  | 121.0(3) |
| C19  | C20  | C21  | 117.9(3)  | C20  | C21  | C22  | 121.5(3) |
| C21  | C22  | C23  | 120.9(3)  | C22  | C23  | C24  | 118.4(3) |
| N5   | C24  | C19  | 114.8(2)  | N5   | C24  | C23  | 124.9(2) |
| C19  | C24  | C23  | 120.3(2)  | S5   | C25  | S6   | 117.87(15) |
| S5   | C25  | N5   | 117.12(16) | S6   | C25  | N5   | 125.00(16) |
| S6   | C26  | C27  | 112.65(17) | N6   | C27  | C26  | 178.8(3) |

Table 3. Bond lengths involving hydrogen’s (Å) for compound 2.

| atom | atom | distance | atom | atom | distance |
|------|------|----------|------|------|----------|
| C2   | H2   | 0.930    | C3   | H3   | 0.930    |
| C4   | H4   | 0.930    | C5   | H5   | 0.930    |
| C8   | H8A  | 0.970    | C8   | H8B  | 0.970    |
| C11  | H11  | 0.930    | C12  | H12  | 0.930    |
| C13  | H13  | 0.930    | C14  | H14  | 0.930    |
| C17  | H17A | 0.970    | C17  | H17B | 0.970    |
| C20  | H20  | 0.930    | C21  | H21  | 0.930    |
| C22  | H22  | 0.930    | C23  | H23  | 0.930    |
| C26  | H26A | 0.970    | C26  | H26B | 0.970    |

Knoevenagel condensation of the ethanolic solution of 1-(benzothiazol-2-yl-thio) acetonitrile (2) with either hetero-2-carbaldehydes 3a–b or benzaldehyde or para-substituted benzaldehydes 3c–e with an electron-donating group at the para-position, as depicted in Scheme 2. The reactions were carried out in the presence of a catalytic amount of piperidine at the reflux temperature leading to novel 3-aryl-2-(benzothiazol-2′-ylthio)acrylonitriles 4a–e (cf. Scheme 2).

Scheme 2. Syntheses of 4.
The new 3-aryl-2-(benzothiazol-2'-ylthio)acrylonitrile derivatives 4a–e which were formed are highly conjugated systems containing heteroaromatic or phenyl rings, or para-substituted phenyl rings with an electron-donating group in the para- position such as –OCH₃ or –OH. One the other hand, all systems are linked to the benzothiazole nuclei through an S linkage at the α-vinylic carbon. The formation of a carbon-carbon double bond usually lead to the creation of acrylonitriles with either E or Z configuration or a mixture of E and Z isomers (cf. Scheme 2). The yields are based on isolated products and the E/Z ratio was affected by the kind of substitution of the aryl aldehydes 3a–e. The E/Z ratio was determined on the basis of the ¹H-NMR spectra of the products. The structures of isolated S-alkylated acrylonitrile products 4a–e were confirmed on the basis of elemental analysis and spectral data. The mass spectrum of 4a revealed a molecular ion peak (M⁺) with \( m/z \) 284. The chemical shifts of protons for 4a were assigned using the COSY (correlation spectroscopy) measurement which provided the proton-proton couplings. The ¹H-NMR revealed in addition to an aromatic multiplet, a singlet signal for a vinylic proton (H-3), that appears at \( \delta_H \) 8.06 ppm. Moreover, the chemical shifts of carbons for compound 4a were assigned using HSQC (Heteronuclear Single Quantum Coherence) and HMBC (Heteronuclear Multiple Bond Coherence) measurements. The ¹³C-NMR spectrum for 4a is characterized by two signals at \( \delta_C \) 142.2 and \( \delta_C \) 91.9 ppm for the carbon-carbon double bond group. The ¹³C signal of the β carbon at the higher frequency coupled with a proton, while the ¹³C signal of the α-carbon appears at lower frequency (cf. Figure 2).

**Figure 2.** The complete assignment of H¹ and ¹³C chemical shift for 4a based on the COSY, HSQC and HMBC experiments.

Nuclear Overhauser Effect (NOE) experiments were run to establish the stereo-orientation for acrylonitrile derivatives 4 as either E or Z isomers. NOE experiments for 4a showed an enhanced triplet signal (H-4") at \( \delta_H \) 6.84 ppm upon irradiating the doublet signal (H-5") at \( \delta_H \) 8.15 ppm. On irradiating the doublet signal (H-3") at \( \delta_H \) 7.30 ppm both the triplet signal (H-4") and the singlet signal (H-3) at \( \delta_H \) 6.84 and 8.06 ppm, respectively, were enhanced, while the benzothiazole protons showed no effect, confirming that the benzothiazol-2-ylthio moiety and 2'-furyl groups are on opposite sides of the double bond as required by the E-form. The structure of 4a was unambiguously confirmed by X-ray crystallography [18] (cf. Figure 3 and Tables 4–6).
Figure 3. Perspective view and atom labeling of the X-ray structure of 4a.

Table 4. Bond lengths (Å) for compound 4a.

| atom | atom | distance  | atom | atom | distance |
|------|------|-----------|------|------|----------|
| S1   | C1   | 1.727(3)  | S1   | C7   | 1.747(3) |
| S2   | C7   | 1.762(3)  | S2   | C8   | 1.770(3) |
| O1   | C10  | 1.381(3)  | O1   | C13  | 1.352(4) |
| N1   | C6   | 1.391(4)  | N1   | C7   | 1.298(4) |
| N2   | C14  | 1.136(4)  | C1   | C2   | 1.406(5) |
| C1   | C6   | 1.403(4)  | C2   | C3   | 1.363(5) |
| C3   | C4   | 1.382(6)  | C4   | C5   | 1.355(7) |
| C5   | C6   | 1.387(5)  | C8   | C9   | 1.349(4) |
| C8   | C14  | 1.438(4)  | C9   | C10  | 1.401(4) |
| C10  | C11  | 1.356(4)  | C12  | C13  | 1.403(4) |
| C12  | C13  | 1.322(4)  |      |      |          |

Table 5. Bond lengths involving hydrogen's (Å) for compound 4a.

| atom | atom | distance |
|------|------|----------|
| C2   | H2   | 0.93     |
| C4   | H4   | 0.93     |
| C9   | H9   | 0.93     |
| C12  | H12  | 0.93     |

The condensation of 2 with thiophene-2-carbaldehyde (3b) afforded a mixture of (E)- and (Z)-2-(benzothiazol-2'-ylthio)-3-(2''-thienyl) acrylonitriles in a ratio of 6:0.5 based on the $^1$H-NMR spectrum, which revealed, in addition to the expected aromatic signals, two downfield signals at $\delta_H$ 8.52 and 8.70 ppm assignable to the E and Z-vinyllic protons. Upon recrystallization of the crude product from a mixture of ethanol and diethyl ether in a ratio of 3:2 one isomer 4b was obtained. The $^1$H-NMR spectrum of the crystallized product showed the vinylic proton resonance at $\delta_H$ 8.52 ppm. In order to determine the configuration of the obtained isomer, different NMR experiments have been carried out such as COSY, HSQC and NOE experiments. The NOE experiments showed a strong NOE coupling between H-3 and (vinyllic-H) and the thiophene protons H-3'' and H-4'' and no coupling between the benzothiazole and the thienyl ring protons, indicating that the benzothiazole and the thienyl rings are on opposite sides of the double bond, confirming that compound 4b exists in the E-configuration.
Table 6. Bond angles (°) for compound 4a.

| atom | atom | atom | angle | atom | atom | atom | angle |
|------|------|------|-------|------|------|------|-------|
| C1   | S1   | C7   | 88.04(14) | C7   | S2   | C8   | 101.83(13) |
| C10  | O1   | C13  | 106.66(19) | C6   | N1   | C7   | 109.2(3)   |
| S1   | C1   | C2   | 128.6(3)  | S1   | C1   | C6   | 110.1(3)   |
| C2   | C1   | C6   | 121.3(3)  | C1   | C2   | C3   | 118.6(4)   |
| C2   | C3   | C4   | 119.6(4)  | C3   | C4   | C5   | 122.5(4)   |
| C4   | C5   | C6   | 119.9(4)  | N1   | C6   | C1   | 115.2(3)   |
| N1   | C6   | C5   | 126.9(3)  | C1   | C6   | C5   | 118.0(3)   |
| S1   | C7   | S2   | 121.46(15) | S1   | C7   | N1   | 117.5(3)   |
| S2   | C7   | N1   | 121.0(3)  | S2   | C8   | C9   | 120.82(19) |
| S2   | C8   | C14  | 114.9(2)  | C9   | C8   | C14  | 123.9(3)   |
| C8   | C9   | C10  | 129.9(3)  | O1   | C10  | C9   | 119.7(3)   |
| O1   | C10  | C11  | 107.9(2)  | C9   | C10  | C11  | 132.4(3)   |
| C10  | C11  | C12  | 107.7(3)  | C11  | C12  | C13  | 106.6(3)   |
| O1   | C13  | C12  | 111.2(3)  | N2   | C14  | C8   | 174.9(3)F |

On the other hand, condensation of 2 with either benzaldehyde or para-substituted benzaldehydes 3c–e in refluxing ethanol containing a catalytic amount of piperidine, afforded a mixture of E and Z isomers of 3-aryl-2-(benzothiazol-2'-ylthio) acrylonitriles 3c–e in a ratio of 7:2 based on the 1H-NMR spectra of the crude products. The chemical shifts of the 1H- and 13C- spectra were assigned on the basis of the proton-proton and the carbon-proton coupling patterns observed in the COSY and HSQC spectra. The 1H-NMR spectra display vinylic proton singlets in the δH 8.12–8.29 ppm region. The chemical shifts for the carbon-carbon double bond are observed at δC 91–97 and at δC 157–158 ppm for the α- and β carbon, respectively. Moreover, Nuclear Overhauser Effect (NOE) experiments were run to establish the stereo-orientation for either the E or Z isomers of 2-(benzothiazol-2'-ylthio)-3-(4''-methoxyphenyl)acrylonitrile 4d. On irradiating the singlet of the vinylic proton at δH 8.17 ppm the doublet of H-2'' of phenyl ring at δH 8.00 ppm was enhanced. On irradiating the doublet signal of the phenyl ring H-3'' at δH 7.15 ppm both the doublet of the phenyl ring H-2'' and the para-methoxy group protons at δH 8.00 and 3.87 ppm, respectively, were enhanced, while the benzothiazole protons showed no effect, indicating that the benzothiazole and the 4-methoxyphenyl rings are on opposite sides of the double bond, as required by an E-form.

In a similar manner, the 1-(benzothiazol-2'-ylthio)propan-2-one (5) used in our experiments has been recently prepared in an excellent yield by treatment of 2-mercaptobenzothiazole (1) with α-chloroacetone in refluxing acetone containing anhydrous potassium carbonate [15]. The structure of 5 was unambiguously confirmed by X-ray crystallography [19] (cf. Scheme 3, Figure 4 and Tables 7–9). Condensation of 5 with the furan-2-carbaldehyde in refluxing ethanol containing a catalytic amount of piperidine afforded 3-(benzothiazol-2'-ylthio)-4-(furan-2''yl)-3-buten-2-one in excellent yield (cf. Scheme 3). The structure of the isolated product was confirmed on the basis of its elemental analysis and spectral data (see Experimental section).
Scheme 3. Synthesis of compound 6.

![Scheme 3](image)

Figure 4. Perspective view and atom labeling of the X-ray structure of 5.

![Figure 4](image)

Table 7. Bond lengths (Å) for compound 5.

| atom | atom | distance | atom | atom | distance |
|------|------|----------|------|------|----------|
| S1   | C1   | 1.758(3) | S1   | C2   | 1.730(4) |
| S2   | C1   | 1.738(3) | S2   | C8   | 1.785(3) |
| O1   | C9   | 1.206(4) | N1   | C1   | 1.289(4) |
| N1   | C7   | 1.392(4) | C2   | C3   | 1.387(5) |
| C2   | C7   | 1.410(4) | C3   | C4   | 1.369(6) |
| C4   | C5   | 1.393(7) | C5   | C6   | 1.371(5) |
| C6   | C7   | 1.389(5) | C8   | C9   | 1.501(4) |
| C9   | C10  | 1.494(5) |      |      |          |
Table 8. Bond lengths involving hydrogen's (Å) for compound 5.

| atom | atom | distance | atom | atom | distance |
|------|------|----------|------|------|----------|
| C3   | H3   | 0.930    | C4   | H4   | 0.930    |
| C5   | H5   | 0.930    | C6   | H6   | 0.930    |
| C8   | H8A  | 0.970    | C8   | H8B  | 0.970    |
| C10  | H10A | 0.960    | C10  | H10B | 0.960    |
| C10  | H10C | 0.960    |      |      |          |

Table 9. Bond angles (°) for compound 5.

| atom | atom | atom | angle  | atom | atom | atom | angle  |
|------|------|------|--------|------|------|------|--------|
| C1   | S1   | C2   | 88.71(14) | C1   | S2   | C8   | 101.10(14) |
| C1   | N1   | C7   | 110.6(3)  | S1   | C1   | S2   | 116.94(16) |
| S1   | C1   | N1   | 116.3(3)  | S2   | C1   | N1   | 126.8(2)   |
| S1   | C2   | C3   | 129.9(3)  | S1   | C2   | C7   | 109.6(3)   |
| C3   | C2   | C7   | 120.5(3)  | C2   | C3   | C4   | 118.8(4)   |
| C3   | C4   | C5   | 120.8(4)  | C4   | C5   | C6   | 121.3(4)   |
| C5   | C6   | C7   | 118.8(4)  | N1   | C7   | C2   | 114.8(3)   |
| N1   | C7   | C6   | 125.4(3)  | C2   | C7   | C6   | 119.8(3)   |
| S2   | C8   | C9   | 116.2(3)  | O1   | C9   | C8   | 122.8(3)   |
| O1   | C9   | C10  | 122.3(3)  | C8   | C9   | C10  | 114.9(3)   |

The mass spectrum of 6 revealed a molecular ion peak [M+]. with m/z 301. The effect of the conjugation of the carbonyl group with the carbon-carbon double bond reduces the frequency of the absorption at $\nu_{\text{max}}$ 1662 cm$^{-1}$. It is considered lower than the isolated carbonyl group in compound 5, which revealed a carbonyl stretching band at $\nu_{\text{max}}$ 1720 cm$^{-1}$ [15]. The chemical shift of protons for 6 were assigned using COSY (correlation spectroscopy) measurements which provided the proton-proton coupling. The $^1$H-NMR spectrum showed a resonance at $\delta_{\text{H}}$ 8.25 ppm corresponding to H-4 of the vinylic proton. Moreover, the $^{13}$C-NMR chemical shift assignments were straightforward using HSQC (Heteronuclear Quantum Coherence) measurements (cf. Figure 5). The $^{13}$C-NMR spectrum of the reaction product revealed a low field signal at $\delta_{\text{C}}$ 194.8 that corresponds to the carbonyl carbon. Also were revealed two low field signals at ca. $\delta_{\text{C}}$ 148 and 136 ppm corresponding to a carbon coupled with a proton. As in the furan ring system, the carbon resonating at ca. $\delta_{\text{C}}$ 148 ppm corresponds to C-5'', while the carbon resonating at ca. $\delta_{\text{C}}$ 136 ppm corresponds to the vinylic carbon C-4. The complete assignment of $^1$H and $^{13}$C chemical shifts for 6 are presented in Figure 6.

Moreover, the configuration of the product 6 was assigned as the Z-isomer based on Nuclear Overhauser Effect (NOE) experiments; on irradiating the methyl proton at $\delta_{\text{H}}$ 2.54 ppm only the signal at $\delta_{\text{H}}$ 8.25 ppm for the vinylic proton was enhanced and there is no effect on the benzothiazole protons or furyl protons, which indicate that acetyl group and the vinylic proton are on the same side of the carbon 3,4 double bond as numbered, therefore it has the Z configuration. On irradiating the vinylic H-4 at $\delta_{\text{H}}$ 8.25 ppm both the singlet and doublet signals at $\delta_{\text{H}}$ 2.54 and 7.47 ppm, respectively, were enhanced. The signal at $\delta_{\text{H}}$ 2.54 ppm corresponds to the acetyl group, while the doublet signal at $\delta_{\text{H}}$ 7.47 ppm corresponds to the furyl system H-3''. On other hand, on irradiating the doublet signal of the H-4' proton at $\delta_{\text{H}}$ 7.92 ppm only the triplet signal at $\delta_{\text{H}}$ 7.32 ppm was enhanced. These two signals
correspond to the benzothiazole H-4' and H-5' protons. On irradiating the triplet signal H-4" at δH 6.74 ppm both the H-5" and H-3" signals at δH 8.05 and 7.47 ppm, respectively, were enhanced. The NOE experiments show that the Z-isomer of compound 6 was preferred over the E-isomer indicating that the furyl and 2-benzothiazol-2-thio nuclei are on the same sides of the double bond, but away from each other in space.

**Figure 5.** 13C-HSQC spectra for the compound 6 in DMSO-d6.

Thus it can be concluded that Knoevenagel condensation of 2-(benzothiazol-2-ylthio) acetonitrile with furan-2-carbaldehyde leads preferentially to (E)-2-(benzothiazol-2'-ylthio)-3-(furan-2''-yl) acrylonitrile (4a). In this conformation the lone pair electrons of the sulfur atom can conjugated with the π orbital of the double bond, and thereby stabilize the molecule. That is why this conformation is the most stable conformer. On the other hand, the Knoevenagel condensation of 3-(benzothiazl-2'-ylthio) propan-2-one with furan-2-carbaldehyde lead preferentially to (Z)-3-(benzothiazol-2'-ylthio)-4-(furan-2''-yl)-3-buten-2-one. By changing the size and the geometry of the group attached to the α-carbon from a cyano group to an acetyl group, the conformation changes from E to Z. One may
therefore conclude that under these circumstances the most $E$-isomer is unlikely to be the most stable conformer, because of the steric strain between the acetyl group and furan ring. The steric strain makes this conformation energetically highly unfavorable in the $E$-isomer so the conformer changes from $E$ to $Z$. On the other hand, 2-(2'-oxopropylthio)-3-phenylquinazolin-4(3$H$)-one (9) was readily prepared in good yield by the treatment of 2-mercapto-3-phenylquinazolin-4(3$H$)-one (8) [20] with $\alpha$-chloroacetone in refluxing acetone containing potassium carbonate. The structure was established on the basis of its spectral data. The mass spectrum of the reaction product showed a molecular ion peak at $m/z$ 310. The $^1$H-NMR spectrum revealed, in addition to aromatic signals, two upfield singlets at $\delta_H$ 2.33 and 4.06 ppm, assignable to methyl and methylene protons, respectively. Moreover, the $^{13}$C-NMR spectrum showed two downfield signals at $\delta_C$ 202.5 and 161.1 ppm. The signal at $\delta_C$ 202.5 ppm corresponds to the ketone carbonyl carbon, while that at $\delta_C$ 161.1 ppm corresponds to the cyclic amide carbon. The data are therefore consistent with structure 9 (cf. Scheme 4).

Scheme 4. Synthesis of 9 and 10.

Condensation of 2-(2'-oxopropylthio)-3-phenylquinazolin-4(3$H$)-one (9) with furan-2-carbaldehyde (3a) afforded a product which could have been either $E$ or $Z$-isomer of $\alpha,\beta$-unsaturated ketone 10 (cf. Scheme 4). The structure of $\alpha,\beta$-unsaturated ketone 10 was deduced from its elementanal analysis and spectra data. The mass spectrum revealed a molecular ion peak (M$^+$) with $m/z$ 388. The chemical shifts of the protons for 10 were assigned using COSY (correlation spectroscopy) measurements which provided the proton-proton coupling. The $^1$H-NMR revealed in addition to an aromatic multiplet, a singlet for a vinylic proton (H-1') which appears at low field at ca. $\delta_H$ 7.88 ppm. Moreover, the $^{13}$C-NMR chemical shift assignments were straightforward using HSQC (Heteronuclear Single Quantum Coherence) measurements (cf. Figure 7). The $^{13}$C-NMR spectrum for 10 is characterized by two signals at $\delta_C$ 132.0 and $\delta_C$ 119.7 ppm for the $\alpha,\beta$-unsaturated ketone group. The vinylic carbons at
the higher frequency is the one coupled with a proton, while the other one is a disubstituted sp² carbon. The complete assignment of H¹ and ¹³C chemical shift for 10 are presented in Figure 8.

**Figure 7.** ¹³C-HSQC spectra for the compound 10 in DMSO-d₆.

![13C-HSQC spectra for the compound 10 in DMSO-d₆.](image)

**Figure 8.** The complete assignment of H¹ and ¹³C chemical shifts for 10 based on the COSY and HSQC experiments.

![The complete assignment of H¹ and ¹³C chemical shifts for 10 based on the COSY and HSQC experiments.](image)

Moreover, the configuration of the product 10 was assigned as the Z-isomer based on Nuclear Overhauser Effect (NOE) experiments; on irradiating the methyl proton at δ_H 2.48 ppm the vinylic proton signal at δ_H 7.88 ppm was enhanced. There is no effect on the 3-phenylquinazolin-4(3H)-one or furan protons, which indicates that the acetyl group and the vinylic proton are on the same side of the C1',2' double bond as numbered, which therefore has Z configuration. On irradiating the vinylic H'-1 at δ_H 7.88 ppm the methyl signal at δ_H 2.48 ppm was enhanced.

On the other hand irradiation of the H-8 proton at δ_H 8.08 ppm has no effect, confirming that the 3-phenylquinazolin-4(3H)-one moiety and 2'-furyl groups are on same sides of the double bondas required by a Z-form. The structure of 10 was also confirmed by X-ray crystallography [21] (cf. Figure 9 and Tables 10–12).
Figure 9. Perspective view and atom labeling of the X-ray structure of 10.

Table 10. Bond lengths (Å) for compound 10.

| atom | atom | distance  | atom | atom | distance |
|------|------|-----------|------|------|----------|
| S1   | C8   | 1.7609(19)| S1   | C15  | 1.7687(19) |
| O1   | C7   | 1.219(3)  | O2   | C17  | 1.350(3)  |
| O2   | C20  | 1.398(4)  | O3   | C21  | 1.216(3)  |
| N1   | C7   | 1.402(3)  | N1   | C8   | 1.400(3)  |
| N1   | C9   | 1.440(3)  | N2   | C1   | 1.389(3)  |
| N2   | C8   | 1.285(3)  | C1   | C2   | 1.404(3)  |
| C1   | C6   | 1.397(3)  | C2   | C3   | 1.382(4)  |
| C3   | C4   | 1.388(4)  | C4   | C5   | 1.365(4)  |
| C5   | C6   | 1.399(4)  | C6   | C7   | 1.456(3)  |
| C9   | C10  | 1.378(4)  | C9   | C14  | 1.382(4)  |
| C10  | C11  | 1.393(5)  | C11  | C12  | 1.374(6)  |
| C12  | C13  | 1.354(6)  | C13  | C14  | 1.384(5)  |
| C15  | C16  | 1.354(3)  | C15  | C21  | 1.483(3)  |
| C16  | C17  | 1.424(3)  | C17  | C18  | 1.345(4)  |
| C18  | C19  | 1.385(4)  | C19  | C20  | 1.324(5)  |
| C21  | C22  | 1.499(4)  |      |      |          |

Table 11. Bond lengths involving hydrogen's (Å) for compound 10.

| atom | atom | distance |
|------|------|----------|
| C2   | H2   | 0.930    |
| C4   | H4   | 0.930    |
| C10  | H10  | 0.930    |
| C12  | H12  | 0.930    |
| C14  | H14  | 0.930    |
| C18  | H18  | 0.930    |
| C20  | H20  | 0.930    |
| C22  | H22B | 0.960    |
| C22  | H22B | 0.960    |
|      |      | 0.960    |
In particular, we were interested in the reasons for the predominance of the s-cis conformation of the Z configuration and the E/Z determination of the prepared novel derivatives of 2-(benzothiazol-2'-ylthio)-3-arylacrylonitrile, 3-(benzothiazol-2'-ylthio)-4-(furan-2''-yl)-3-buten-2-one and 2-(1-(furan-2''-yl)-3-oxobut-1-en-2-ylthio)3-phenylquinazolin-4(3H)-one in accordance with expectations, it was ascertained that s-trans conformations were more stable than s-cis conformations for both the E and Z molecular configurations. Thus the disparity displayed here where s-cis conformations in case of compound 6 dominated over the s-trans conformation was of interest and one supposition was that electronic interactions could be responsible, e.g., by delocalization of a sulfur lone electron pair with the unsaturated segments residing in the newly formed heterocyclic ring and attendant side-chains or through hyperconjugation. The s-cis conformational preference over s-trans in a structurally similar system has been reported previously [22] and an electronic cause was also postulated, though that system differed significantly in the distribution of unsaturation. It is obvious to note that compounds 4c–e are predominantly in the E/Z form and this is due to the large range of mesomeric effects due to large conjugations in the phenyl group present in such compounds. However, the existence of compounds 4a and 4b in the E form is due to the existence of the heterocyclic, furan and thiophene rings, respectively, where less conjugation occurs in such compounds.
3. Experimental

General

Melting points are reported uncorrected and were determined on a Gallenkamp apparatus. The Infrared spectra were recorded on a Jasco FT/IR-6300 FT-IR using KBr disks. $^1$H-NMR and $^{13}$C-NMR spectra were measured on a Bruker DPX 400 MHz and Bruker AVANCE II 600 MHz spectrometers, with DMSO-d$_6$ or CDCl$_3$ as solvent using TMS as an internal standard. The methods used for the purpose of NMR assignment were COSY, HSQC and HMBC. The chemical shifts are expressed as $\delta$ unit in parts per million (ppm) and TMS = 0.00 ppm. The following abbreviation are used: s = singlet, d = doublet, t = triplet; q = quartet; m = multiple; br. = broad. Mass spectra were measured on GC/MS DFS, THERMO instrument. Microanalyses were performed on a CHNS-Vario Micro Cube analyzer, Single crystal X-ray crystallography was perfomed using a Rigaku Rapid II located at the Chemistry Department of Kuwait University. Compound 5 was prepared according to our recent reference [15] and its X-ray data was reported in reference [19].

2-(Benzothiazol-2-ylthio) acetonitrile (2): A mixture of 1 (1.67 g, 10.0 mmol), chloroacetonitrile (0.63 g, 10.0 mmol), and anhydrous potassium carbonate (1.38 g, 10.0 mmol) in acetone (100 mL), were heated in water bath for 2 h. The solvent was then evaporated under reduced pressure. The solid product, so formed, was collected by filtration and crystallized from ethanol as brown crystals. Yield: 1.85 g (90%), mp. 70–72 °C; FT-IR: $\nu_{\text{max/cm}^{-1}}$: 2243 (CN); $^1$H-NMR (DMSO-d$_6$): $\delta$H 4.58 (s, 2H, CH$_2$), 7.43 (t, 1H, $J$ = 8.0 Hz, H-5'), 7.52 (t, 1H, $J$ = 8.0 Hz , H-6'), 7.95 (d, 1H, $J$ = 8.0 Hz, H-7'), 8.08 (d, 1H, $J$ = 8.0 Hz, H-4'); $^{13}$C-NMR (DMSO-d$_6$): $\delta$C 163.8 (C-2'), 152.7 (C-3a'), 135.6 (C-7a'), 127.1 (C-6'), 125.5 (C-5'), 122.6 (C-4'), 117.9 (CN), 18.6 (CH$_2$) ppm; MS m/z (%) 206 [M +, 100%].

Anal. Calcd. for C$_9$H$_6$N$_2$S$_2$ (206.28): C, 52.40; H, 2.93; N, 13.57%. Found: C, 52.29; H, 3.19; N, 13.45%.

2-(Benzothiazol-2-ylthio)-3-(furan-2"-yl) acrylonitrile (4a): This compound was crystallized from ethanol as brown crystals. Yield: 2.24g (79%) yield, mp. 134–136 °C; FT-IR: $\nu_{\text{max/cm}^{-1}}$: 2209 (CN); $^1$H-NMR (DMSO-d$_6$): 6.84 (dd, 1H, $J$ = 3.6 & 1.2 Hz, H-4"), 7.30 (d, 1H, $J$ = 3.6 Hz, H-3"), 7.43 (t, $J$ = 8.2 Hz, H-5"), 7.51 (t, 1H, $J$ = 8.0 Hz, H-6"), 7.94 (d, 1H, $J$ = 8.2 Hz, H-7"), 8.06 (s, 1H, H-3), 8.07 (d, 1H, $J$ = 8.0 Hz, H-4"), 8.15 (d, 1H, $J$ = 1.2 Hz, H-5"); $^{13}$C-NMR (DMSO-d$_6$): $\delta$C 164.6 (C-2"), 153.1 (3a"), 148.8 (C-5"), 148.2 (C-2"), 142.2 (C-3), 135.3 (C-7a"), 126.8 (C-6"), 125.2 (C-5"), 122.1 (C-4"), 121.9 (C-7"), 121.6 (C-3"), 116.9 (CN), 113.8 (C-4"), 91.9 (C-2) ppm. MS m/z (%) 284 [M$^+$, 18%].

Anal. Calcd. for C$_{14}$H$_8$N$_2$OS$_2$ (284.36): C, 59.13; H, 2.84; N, 9.85; S, 22.55%. Found: C, 58.95; H, 2.81; N, 10.07; S, 22.56%.
(E)-2-(Benzothiazol-2'-ylthio)-3-(thiophen-2''-yl) acrylonitrile (4b). This compound was crystallized from a 3:2 mixture of ethanol/diethyl ether as yellow crystals. Yield: 2.4 g (88%), mp. 98–100 °C; FT-IR: ν_{max/cm}^{-1}: 2210 (CN); ^1H-NMR (DMSO-d_6): δ_H 7.35 (dd, 1H, J = 4.8 & 3.5 Hz, H-4''), 7.43 (t, 1H, J = 7.6 Hz, H-5''), 7.52 (t, 1H, J = 7.6 Hz, H-6''), 7.89 (d, 1H, J = 3.5 Hz, H-3''), 7.95 (d, 1H, J = 8.0 Hz, H-7''), 8.09 (d, 1H, J = 8.0 Hz, H-4''), 8.14 (d, 1H, J = 4.8 Hz, H-5''), 8.52 ppm (s, 1H, H-3); ^13C-NMR (DMSO-d_6): δ_C 164.8 (C-2''), 153.2 (C-3a''), 150.4 (C-3), 137.5 (C-3''), 135.9 (C-2''), 135.3 (C-7a''), 135.1 (C-5''), 128.6 (C-4''), 126.8 (C-6''), 125.2 (C-5''), 121.1 (C-4''), 117.1 (CN), 92.3 (C-3) ppm; MS m/z (%): 300 [M+, 14%]. Anal. Calcd. for C_{14}H_{8}N_{2}S_{3} (300.42): C, 55.97; H, 2.68; N, 9.32; S, 32.01%. Found: C, 56.04; H, 2.52; N, 9.54; S, 32.08%.

(E)-2-(Benzothiazol-2'-ylthio)-3-phenyl acrylonitrile (4c). This compound was crystallized from a 2:1 mixture of ethanol/diethyl ether as yellow crystals. Yield: 2.08 g (71%), mp. 103–105 °C; FT-IR: ν_{max/cm}^{-1}: 2206 (CN); ^1H-NMR (DMSO-d_6): δ_H 7.38 (t, 1H, J = 7.8 Hz, H-5''), 7.49 (t, 1H, J = 8.4 Hz, H-6''); 7.58–7.63 (m, 3H, H-3'', H-4'' & H-5''), 7.96 (d, 1H, J = 8.4 Hz, H-7), 7.97 (d, 2H, J = 8.4 Hz, H-2'' & H-6''), 8.10 (d, 1H, J = 8.0 Hz, H-4''), 8.29 ppm (s, 1H vinylic-H); ^13C-NMR (DMSO-d_6): δ_C 163.7 (C-2''), 157.0 (C-3), 153.1 (C-3a''), 135.4 (C-7a''), 132.6 (C-4''), 130.8 (C-1''), 129.5 (C-2'' & C-6''), 128.9 (C-3'' & C-5''), 126.8 (C-6''), 125.5 (C-5''), 126.7 (C-4''), 122.2 (C-7'), 116.8 ppm (CN), 97.5 (C-2) ppm. MS m/z (%): 294 [M+, 83%]. Anal. Calcd. for C_{16}H_{10}N_{2}S_{2} (294.39) requires: C, 65.28; H, 3.42; N, 9.52; S, 21.78%. Found: C, 64.98; H, 3.25; N, 9.73; S, 22.03%.

(E)-2-(Benzothiazol-2'-ylthio)-3-(4''-methoxyphenyl) acrylonitrile (4d). This compound was crystallized from ethanol as brown crystals. Yield: 2.62 g (81%), mp. 95–97 °C. FT-IR: ν_{max/cm}^{-1}: 3417 (OH), 2200 (CN); ^1H-NMR (DMSO-d_6): δ_H 6.97 (d, 2H, J = 8.4 Hz, H-3'' & H-5''), 7.39 (t, 1H, J = 8.4 Hz, H-6''), 7.93 (d, 1H, J = 8.4 Hz, H-7'), 8.06 (d, 2H, J = 8.4 Hz, H-2'' & H-6''), 8.06 (d, 1H, J = 8.4 Hz, H-4''), 8.17 ppm (s, 1H, H-3); ^13C-NMR (DMSO-d_6): δ_C 165.6 (C-2''), 158.0 (C-3), 153.3 (C-3a''), 135.2 (C-7a''), 132.1 (C-2'', C-6''), 126.7 (C-6''), 125.1 (C-5''), 124.9 (C-1''), 122.1 (C-4''), 117.5 (CN), 114.8 (C-3'' & C-5''); 117.8 (CN), 116.3 (OCH_3) ppm; MS m/z (%): 324 [M^+, 20%]. Anal. Calcd. for C_{17}H_{12}N_{2}OS_2 (324.42): C, 62.94; H, 3.73; N, 8.63; S, 19.76%. Found: C, 63.06; H, 3.63; N, 8.87; S, 20.06%.

(E)-2-(Benzothiazol-2'-ylthio)-3-(4''-hydroxyphenyl) acrylonitrile (4e). This compound was crystallized from a 2:1 mixture of ethanol/diethyl ether as yellow crystals. Yield: 2.32 g (81%), mp. 95–97 °C. FT-IR: ν_{max/cm}^{-1}: 3417 (OH); ^1H-NMR (DMSO-d_6): δ_H 6.97 (d, 2H, J = 8.4 Hz, H-3'' & H-5''), 7.39 (t, 1H, J = 8.4 Hz, H-6''), 7.93 (d, 1H, J = 8.4 Hz, H-7'), 8.06 (d, 1H, J = 8.4 Hz, H-4''), 8.12 (s, 1H, H-3); 9.05 (bs., 1H ,OH, D_2O exchangeable); ^13C-NMR (DMSO-d_6): δ_C 165.6 (C-2''), 162.2 (C-3), 153.3 (C-3a''), 135.2 (C-7a''), 126.7 (C-6''), 125.0 (C-5''), 123.0 (C-1''), 122.1 (C-4''), 117.8 (CN), 116.3 (C-3'' & C-5''), 91.2 (C-2) ppm; MS m/z (%): 310 [M^+, 44%]. Anal. Calcd. for C_{17}H_{12}N_{2}OS_2 (310.39): C, 61.91; H, 3.25 ; N, 9.03; S, 20.66%. Found: C, 61.63; H, 3.40; N, 9.27; S, 20.92%.

(Z)-3-(Benzothiazol-2'-ylthio)-4-(furan-2''-yl)-3-buten-2-one (6): A mixture of 5 (2.33 g, 10.0 mmol) and furan-2-carbaldehyde 3a (10.0 mmol) in ethanol (20 mL) containing a few drops of piperidine was
refluxed to 4 h. The reaction was allowed to cool to room temperature for 24 h. The solid product so formed was collected by filtration and crystallized from the ethanol as yellow crystals. Yield: 2.16 g (72%) yield, mp. 85–87 °C; FT-IR: \( \nu_{\text{max}} \text{cm}^{-1} \): 1662 (CO); \( ^1\text{H-NMR} \) (DMSO-d6): 2.54 (s, 3H, CH3), 6.74 (dd, 1H, \( J = 3.6 \) & 1.2 Hz, H-4"), 7.32 (t, 1H, \( J = 8.0 \) Hz, H-5"), 7.47 (d, 1H, \( J = 3.6 \) Hz, H-3"), 7.82 (d, 1H, \( J = 8.0 \) Hz, H-7"), 7.92 (d, 1H, \( J = 8.0 \) Hz, H-4"), 8.05 (d, 1H, \( J = 1.6 \) Hz, H-5"), 8.25 (s, 1H, H-4); \( ^{13}\text{C-NMR} \) (DMSO-d6): \( \delta \text{C} 194.8 \) (C-2), 166.3 (C-2"), 153.2 (C-3a"), 149.2 (C-2"'), 148.4 (C-5"'), 136.0 (C-4), 135.8 (C-7a''), 126.4 (C-6'), 124.5 (C-5'), 123.9 (C-3), 121.7 (C-4"'), 121.4 (C-3"'), 121.3 (C-7''), 113.7 (C-4''), 26.6 (CH3) ppm; MS \( m/z \) (%): 301 [M+ 30%].

**Analytical.** Calcd. for C15H11NO2S2 (301.38): C, 59.78; H, 3.67; N, 4.64%. Found: C, 59.41; H, 3.68; N, 4.80%.

3-(2'-Oxopropylthio)-3-phenylquinazolin-4(3H)-one (9): A mixture 8 (2.54 g, 10.0 mmol), chloroacetone (0.79 g, 10.0 mmol), and anhydrous potassium carbonate (1.38 g, 10.0 mmol) in acetone (100 mL) were heated in water bath for 2 h. The solvent was then evaporated under reduced pressure. The solid product, so formed, was collected by filtration and crystallized from ethanol as yellow crystals. Yield: 2.4 g (79%), mp. 140–142 °C; FT-IR: \( \nu_{\text{max}} \text{cm}^{-1} \): 1725 (CO ketone), 1683 (CO amide); \( ^1\text{H-NMR} \) (DMSO-d6): \( \delta \text{H} 2.33 \) (s, 3H, CH3), 4.06 (s, 2H, CH2), 7.29 (d, 1Hz, \( J = 7.6 \) Hz, H-5), 7.35 (t, 1H, \( J = 7.6 \) Hz, H-7), 7.63–7.41 (m, 5H, phenyl–H), 7.81 (t, 1H, \( J = 8.0 \) Hz, H-8); \( ^{13}\text{C-NMR} \) (DMSO-d6): \( \delta \text{C} 202.5 \) (C-2''), 161.1 (C-4), 157.3 (C-2), 147.5 (C-8a), 136.4 (C-6), 135.4 (C-1''), 130.4, 129.8, 129.5 (phenyl carbons), 127.1 (C-8), 126.5 (C-7), 123.9 (C-4a), 42.6 (C-1''), 28.7 (CH3) ppm; MS \( m/z \) (%): 310 [M+, 12%].

**Analytical.** Calcd. for C17H14N2O2S (310.37): C, 65.79; H, 4.55; N, 9.03%. Found: C, 65.65, H, 4.30, N, 9.06%.

\((Z)-2-(1'-(Furan-2''-yl)-3'-oxobut-1''-en-2-ylthio)-3-phenylquinazolin-4(3H)-one \) (10): A mixture of 9 (3.10 g, 10 mmol) and 3a (0.83 g, 10 mmol) in ethanol (20 mL) containing a few drops of piperidine was refluxed for 4 h. The reaction was allowed to cool to room temperature for 24 h. The solid product so formed was collected by filtration and crystallized from ethanol as brown crystals. Yield: 2.83 g (73%) yield, mp. 190–192 °C; FT-IR: \( \nu_{\text{max}} \text{cm}^{-1} \): 1675 (CO ketone), 1610 (CO amide); \( ^1\text{H-NMR} \) (DMSO-d6): \( \delta \text{H} 2.48 \) (s, 3H, CH3), 6.68 (dd, 1H, \( J = 3.6 \) Hz & 1.8 Hz, H-4''), 7.42 (d, 1H, \( J = 8.0 \) Hz, H-5'), 7.46 (t, 1H, \( J = 8.0 \) Hz, H-7'), 7.67–7.59 (m, 5H, phenyl–H), 7.77 (t, 1H, \( J = 8.0 \) Hz, H-6'), 7.88 (s, 1H, H-1'), 7.92 (d, 1H, \( J = 1.8 \) Hz, H-5''), 8.08 (d, 1H, \( J = 8.0 \) Hz, H-8) ppm; \( ^{13}\text{C-NMR} \) (DMSO-d6): \( \delta \text{C} 195.5 \) (C-3'), 160.7 (C-4), 155.9 (C-2), 149.2 (C-8a), 147.0 (C-5''), 146.8 (C-2''), 136.2 (C-1''), 134.9 (C-6), 132.0 (C-1', vinylic–H), 130.1, 129.7, 129.2 (phenyl carbons), 127.1 (C-8), 126.5 (C-7), 126.4 (C-5), 123.9 (C-4a), 42.6 (C-1''), 28.7 (CH3) ppm; MS \( m/z \) (%): 388 [M+, 82%].

**Analytical.** Calcd. for C22H16N2O3S (388.44): C, 68.02; H, 4.15; N, 7.21; S, 8.25%. Found: C, 67.78; H, 4.26; N, 7.16, S, 8.32%.

**4. Conclusions**

Knoevenagel condensation of 2-(benzothiazol-2'-ylthio) acrylonitrile (2) with aromatic benzaldehydes 3a–e leads preferentially to \( E \)-isomers. The 3-aryl-2-(benzothiazol-2'-ylthio) acrylonitriles 4a–e were characterized by spectroscopic measurements. Condensation of furan-2-carbaldehyde with either 1-(benzothiazol-2'-ylthio)propan-2-one or with 2-(2'-oxopropylthio)-3-
phenylquinazolin-4(3H)-one afforded compounds 6 and 10 respectively. The condensation products 6 and 10 were characterized by spectroscopic measurements and were shown to be the Z-isomers.

Acknowledgements

This work was financed by the University of Kuwait research grant SC02/08. We are grateful to the Faculty of Science, Chemistry Department, SAF facility for the spectral and analytical data (Project GS01/01, GS03/08, GS01/03).

References and Notes

1. Prabhu, P.P; Pande, S.; Shastry, C.S. Synthesis and Biological evaluation of of Schiff's bases of some new benzothiazole derivatives as antimicrobial agents. Int. J. Chem. Tech. Res. 2011, 3, 185-191.

2. Alang, G.; kaur, R.; Kaur, G.; Singh, A.; Singla, P. Synthesis and antibacterial activity of some new benzothiazole derivatives. Acta Pharm. Sci. 2010, 52, 213-218.

3. Well, G.; Lowe, R.P.; Malcolm, F.; Steven, G. Antitumor benzothiazoles. 13. (Diacetyloxy)-iodobenzene (DAIB) oxidation of 2-(4-hydroxy-3-methoxyphenyl)benzothiazole and related compounds in the presence of dienophiles. ARKIVOC 2000, 779-797.

4. Devmurari, V.P.; Shivanand, P.; Goyani, M.B.; Nandanwar, R.R.; Jivani, N.P.; Perumal, P. Synthesis and anticancer activity of some novel 2-substituted benzothiazole derivatives. Int. J. Chem. Tech. Res. 2010, 2, 681-689.

5. Repicky, A.; Jantova, S.; Cipak, L. Apoptosis induced by 2-acetyl-3-(6-methoxybenzothiao)-2-yl-aminoacylonitrile in human leukemia cell involves ROS- mitochondrial mediated death signaling and activation of p38 MAPK. Cancer Lett. 2009, 277, 55-63.

6. Armenise, D.; Laurentis, N.D.; Reho, A.; Rosato, A.; Morlacchi, F. Synthesis and antifungal activity against of candida albicans of 6-fluoro-4(5 or 7)chloro-2-(difluorobenzoyl) amino-benzothioazoles. J. Heterocyclic Chem. 2004, 41, 771-775.

7. Wasfy, A.A.F. Studies on quinazolines: Part II—Synthesis and antimicrobial evaluation of some 2,2-disubstituted -3,3-biquinazolin-4(3H)-ones. Ind. J. Chem. 2003, 42B, 3102-3107.

8. Kidwai, M.; Misra, P.; Dave, B.; Bhushan, K.R.; Saxena, R.K.; Singh, M. Microwave activated solid support synthesis of new antibacterial quinolones. Monat. für Chemie. 2000, 131, 1207-1212.

9. Saksena, R.K; Khan, A. Synthesis of some new bis(4-oxo-3-phenyl-6,8-disubstituted -quinazolin-2-yl) disulfides, sulphides, sulphones & alkylenedisulphides & their CNS activities. Ind. J. Chem. 1988, 27B, 295-297.

10. El-Nagady, S.I.; El-Hashash, M.A.; El-Badaway, A.S. Synthesis of some new 4(3H)-quinazolinone derivatives. Egypt. J. Chem. 2006, 46, 721-730.

11. El-Brollosy, E.N.; Abdel-Megeed, M.; Genady, A.R. A facile and efficient synthesis of novel 1,2,4-triazolo[5,1-b]quinazolin-9-one derivatives. Monat. für Chemie. 2001, 132, 1063-1073.

12. Jatav, V.; Mishra, P.; Kashaw, S.; Stables, J.P. CNS depressant and anticonvulsant activities of some novel 3-[5-substituted 1,3,4-thiadiazole -2-yl]-2-styrylquinazoline-4(3H)-ones. Eur. J. Med. Chem. 2008, 43, 1945-1954.
13. Brzozowski, Z.; Saczewski, F. Synthesis and antitumor activity of novel 2-amino-4-(3,5,5-trimethyl-2-pyrazolino)-1,3,5-triazine derivatives. *Eur. J. Med. Chem.* **2002**, *37*, 709-720.

14. Saczewski, F.; stencel, A.; Bienczak, A.M.; Langowska, K.A.; Michaelis, M.; Werel, W.; Halasa, R.; Reszka, P.; Bednarski, P.J. Structure -activity relationships of novel heteroaryl-acrylonitriles as cytotoxic and antibacterial agents. *Eur. J. Med. Chem.*** **2008**, *43*, 1847-1857.

15. Al-Omran, F.; El-Khair, A.A. Studies with 2-(acetonylthio)benzothiazole. New rout to isoxazoles, isoxazole[3,4-b]pyridines, pyrazolo[1,5-a]pyrimidines, pyridines and quinolizines. *J. Chem. Res.* **2009**, *433-436*.

16. Al-Omran, F.; El-Khair, A.A. Studies with 2-(acetonylthio)benzothiazole: novel synthesis of pyridazin-6-(1H)-one, pyridazin-6 (1H)-imine, and phthalazine derivatives of antimicrobial and antifungal activities. *J. Heterocyclic. Chem.* **2011**, *48*, 241-248.

17. CCDC 818581 contains the supplementary crystallographic data for compound 2 in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk.

18. CCDC 819585 contains the supplementary crystallographic data for compound 4a in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk.

19. CCDC 819585 contains the supplementary crystallographic data for compound 5 in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk.

20. Wheeler, A.S.; Qates, W.M. The bromination of anthranilic acid. *J. Am. Chem. Soc.* **1910**, *32*, 770-773.

21. CCDC 822086 contains the supplementary crystallographic data for compound 10 in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk.

22. Matthias, K.E.; Kleinpeter, E.M.; Pulst, M.; Borsdorf, R. Combined dynamic -NMR and lanthanide induced shift studies on the conformational behavior of formylmethylenethiopyran. *Monatsh. Chem.* **1984**, *289-302*.

Sample Availability: Not available.

© 2011 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0/).