

# Solar Thermochemical Reactions IV: Unusual Reaction of Nitrones with Acetonitrile Derivatives Induced by Solar Thermal Energy

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## Abstract

The behaviour of cyanothioacetamide **1** and the acetonitrile derivatives **6** and **10**, respectively, towards the nitrones **2a-i** induced by free solar thermal energy is reported. Structures and reaction mechanisms are also discussed.

**Keywords:** Nitrones, Cyanothioacetamide, 2-(Hetaryl)Acetonitrile Derivatives, Synthesis, Solar Thermal Energy

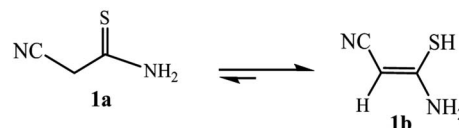
## 1. Introduction

Nitrones are used as useful reagents or intermediates in the synthesis of a variety of nitrogen-containing compounds which find application as agro-chemicals and/or pharmaceuticals [1]. Generally, nitrones easily undergo 1,3-dipolar cycloaddition reactions with a large variety of substituted alkenes including both electron-rich and electron-poor dipolarophiles [2,3]. The resulting five-membered isoxazolidine derivatives may be converted into amino alcohols, precursors to biologically important amino acids, alkaloids or  $\beta$ -lactams [4-8]. In addition to the well-known cycloaddition chemistry of nitrones, there are several reports on nucleophilic additions to nitrones promoted and/or catalyzed by Lewis acids [9-11].

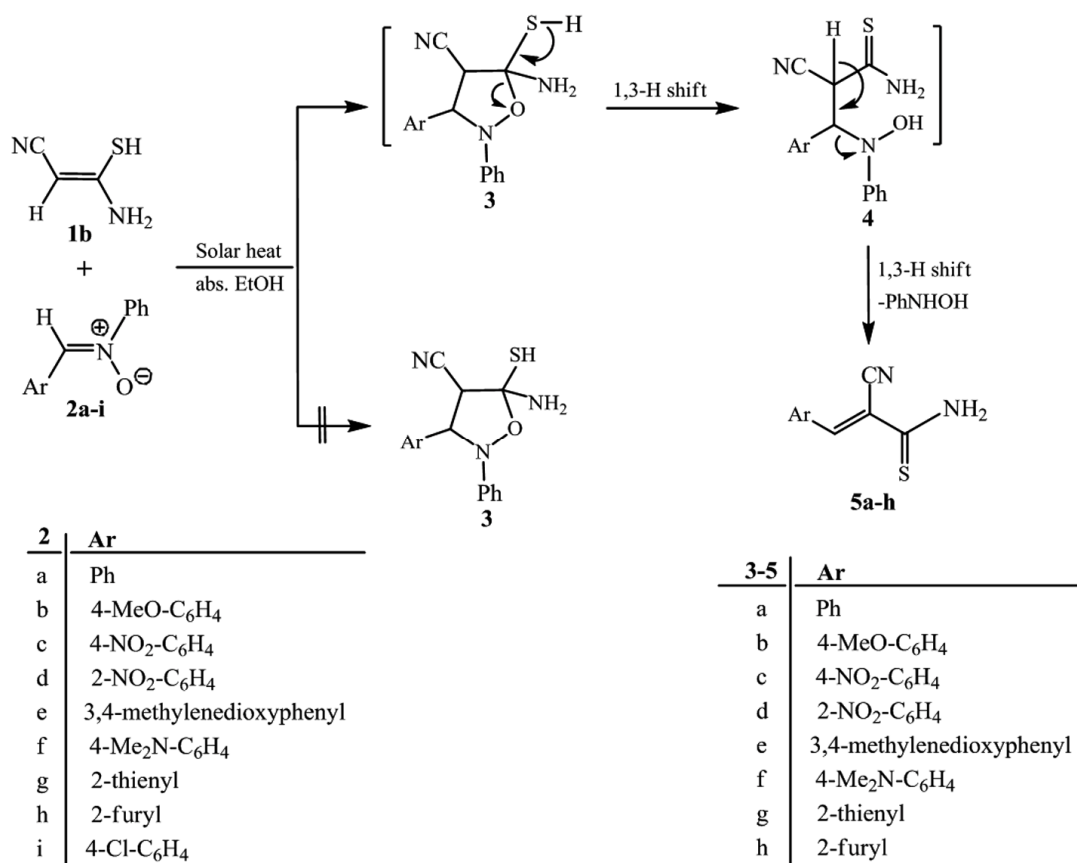
Recently, we have designed a new strategy aiming at the synthesis of pharmacologically interesting heterocyclic systems using solar energy as eco-friendly energy source [12-14]. In continuation of this work, we report herein the behaviour of some acetonitrile derivatives towards differently substituted open-chain C-aryl(or hetaryl)-N-phenylnitrones under the effect of solar thermal energy. To the best of our knowledge, the use of free solar thermal energy to accomplish such study has not so far been reported in the literature.

## 2. Results and Discussion

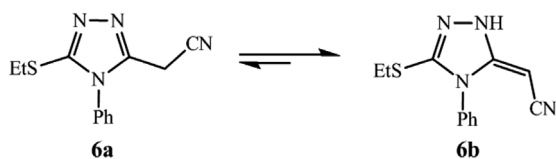
The reactions between cyanothioacetamide **1** with the nitrones **2** were first investigated. Thus, the reaction of cyanothioacetamide **1a**, which is completely enthiolized in liquid phase (**Figure 1**), with the diphenylnitron **2a** in absolute ethanol under solar heating for 2h (TLC control) did not afford 5-amino-5-mercapto-2,3-diphenylisoxazolidine-4-carbonitrile **3a**, as a final product, but furnished instead the unexpected 2-cyano-3-phenylprop-2-enethioamide **5a**, in good yield (**Scheme 1**). Although the synthesis of arylmethylenecyanothioacetamide derivatives has been reported [15-18], compound **5a** was not previously isolated as a solid and always generated *in situ*. Therefore, it seems to be very interesting to report the first isolation of 2-cyano-3-phenylprop-2-enethioamide **5a**. The structure of **5a** was assigned on the basis of consistent elemental and spectral data. Thus, the IR spectrum showed the presence of absorption bands at



**Figure 1.** The equilibrium between cyanothioacetamide (**1a**) and 3-amino-3-mercapto-acrylonitrile (**1b**).



**Scheme 1.** Synthetic route used for preparing the 3-aryl-2-cyanothio-acrylamides **5a-h** from nitrones and cyanothioacetamide and proposed mechanism for their synthesis.



**Figure 2.** The equilibrium between 2-(5-ethylthio-4-phenyl-4H-1,2,4-triazol-3-yl)acetonitrile (**6a**) and 2-(3-ethylthio-4-phenyl-1H-1,2,4-triazol-5(4H)-ylidene)acetonitrile (**6b**).

3400  $\text{cm}^{-1}$ , 3300  $\text{cm}^{-1}$ , 3200  $\text{cm}^{-1}$  and 2220  $\text{cm}^{-1}$  assignable to  $\text{NH}_2$  and  $\text{CN}$  functions, while the  $^1\text{H}$  NMR spectrum contained two singlet signals at 7.95 ppm and 9.57 ppm, attributable to the olefinic proton and the thioamide protons respectively, in addition to five aromatic protons at 7.43 ppm - 7.61 ppm. Furthermore, its structure was supported by  $^{13}\text{C}$  NMR, MS and analytical data analysis which confirmed the proposed structure. Formation of **5a** could be achieved by an initial 1,3-dipolar cycloaddition of the nitronium salt **2a** and compound **1b** giving the isoxazolidine intermediate **3**. This adduct undergoes an internal proton shift and ring-opening to yield a further intermediate **4** which then undergoes a proton shift and carbon-nitrogen fission to afford the final product **5a**

**(Scheme 1).**

The generality of the method is demonstrated by using different C-aryl (or hetaryl)-N-phenylnitrones. Thus, reaction of **1b** with **2b-h** under the same reaction conditions gave the corresponding 3-aryl-2-cyanothio-acrylamides **5b-h**. Their structures were confirmed by comparison of their physical properties (mp, mixed mp, IR,  $^1\text{H}$  NMR) with those of authentic samples prepared as previously described [15].

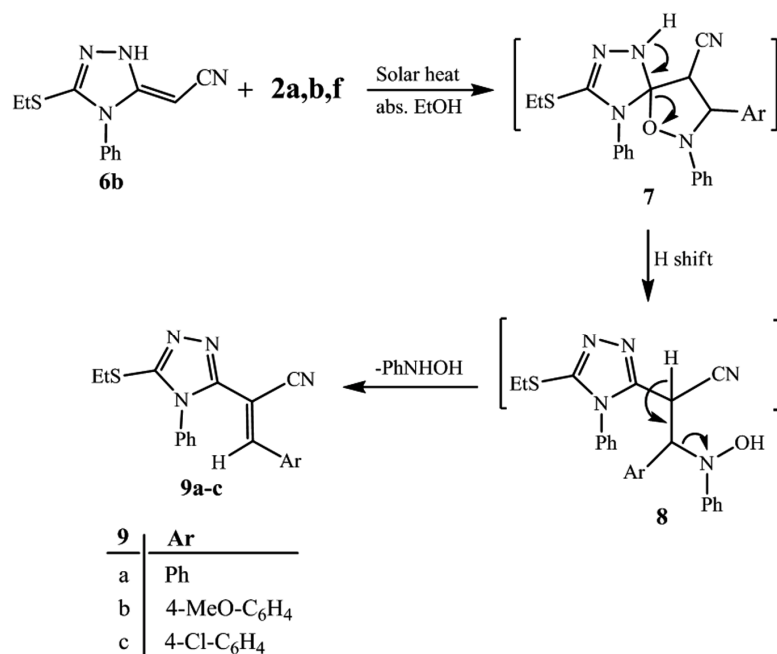
To develop this reaction into a more general method, other acetonitrile derivatives, containing a heterocyclic sub-structure at position 2, were also tried. Thus, the reaction of 2-(5-ethylthio-4-phenyl-4H-1,2,4-triazol-3-yl)acetonitrile **6b** (Figure 2), with the nitrones **2a,b,i** gave the corresponding derivatives **9a-c** (Scheme 2). The compound **9a** thus obtained was identical in all respects (mp, mixed mp, IR,  $^1\text{H}$  NMR) with that previously prepared by Mekheimer *et al.* [19]. The structures of **9b,c** were deduced from their IR, NMR and correct elemental analyses as well as mass spectra. Thus, the IR spectra of **9b,c** revealed the presence of absorption band at 2220  $\text{cm}^{-1}$  due to cyano function. The  $^1\text{H}$  NMR spectra contained a singlet signal at 7.88 ppm and 8.45 ppm assign-

able to the olefinic proton in **9b** and **9c**, respectively, in addition to signals due to ethyl, phenyl and aryl protons. Additionally, their structures were supported by  $^{13}\text{C}$  NMR and correct mass spectra and analytical data, which were all compatible with the assigned structures (see Experimental). The formation of **9a-c** may take place through an initial 1,3-dipolar cycloaddition of **2** to the olefinic  $\pi$  bond of **6b** to yield the spiro intermediate **7** which was converted to **9** by a similar mechanism to that discussed above for the formation of **5** (see **Scheme 2**).

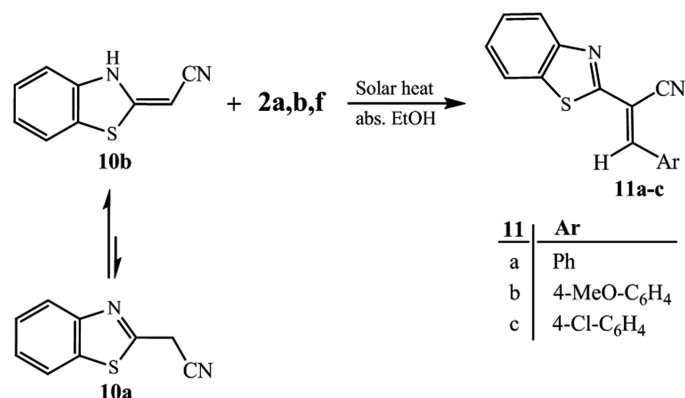
Other acetonitriles derivatives in which the 2-position is substituted with benzothiazole moiety were also used. Thus, the nitrones **2a,b,i** reacted with 2-(benzo-thiazol-

2(3*H*)-ylidene)acetonitrile **10b**, under the same reaction conditions, to afford 3-aryl-2-(benzothiazol-2-yl)acrylonitrile derivatives **11a-c** (**Scheme 3**), presumably by a mechanism similar to that discussed above for the formation of **9**. The structures of the benzothiazole derivatives **11a-c** were established by comparison with authentic samples (mp, mixed mp, IR,  $^1\text{H}$  NMR) prepared as previously reported [20].

In order to investigate the exact effect of solar energy in accelerating the reaction whether it is a thermal or a photochemical one, we carried out the reaction in dark under conventional heating and for the same reaction time. It afforded the same products obtained under solar



**Scheme 2.** Synthetic route used for preparing the 3-aryl-2-(5-ethylthio-4-phenyl-4*H*-1,2,4-triazol-3-yl)acrylonitrile **9a-c** from nitrones **2a,b,f** and 2-(3-ethylthio-4-phenyl-1*H*-1,2,4-triazol-5(4*H*)-ylidene)acetonitrile (**6b**) and proposed mechanism for their synthesis.



**Scheme 3.** Synthetic route used for preparing the 3-aryl-2-(benzothiazol-2-yl)acrylonitrile derivatives **11a-c** from nitrones **2a,b,f** and 2-(benzothiazol-2(3*H*)-ylidene)acetonitrile (**10b**).

energy. At the same time, we performed the same reaction at a low temperature (10°C) under the effect of artificial visible light and the reactants were recovered, unchanged even when exposure was performed for a longer reaction time. This rules out the possibility of a photochemical reaction.

### 3. Conclusions

In this fourth-generation version of our strategy, we have shown that the reaction between nitrones and some acetonitrile derivatives under solar heating efficiently leads the unexpected 3-aryl-2-cyanothioacrylamide and 3-aryl-2-(hetaryl)acrylonitrile derivatives. The significant advantages of this procedure are green, high yields, a simple work-up procedure. Further studies in our laboratory aimed at the synthesis of new heterocyclic ring systems induced by solar thermal energy are now in progress and will be published in due course.

## 4. Experimental

### 4.1. General

Melting points were measured on a Gallenkamp apparatus and were not corrected. IR spectra were recorded with a Nicolet Magna 520FT IR spectrophotometer.

Peaks are reported in  $\text{cm}^{-1}$ .  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker DPX (600 MHz for  $^1\text{H}$  NMR and 150 MHz for  $^{13}\text{C}$  NMR) spectrometer in  $\text{DMSO}-d_6$  using TMS as an internal standard; the chemical shifts are given in  $\delta$  units (ppm). Mass spectra were measured on a GCMS-QP1000EX mass spectrometer. Analytical thin-layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60F-254). Visualization was accomplished by UV light. Micro-analyses were performed at the Microanalytical Data Unit at Cairo University.

### 4.2. Synthesis of 3-Aryl-2-cyanothioacrylamides 5a-h, General Procedure

To a solution of cyanothioacetamide (**1**) (2.5 mmole) in absolute EtOH (10 mL), nitrones **2a-h** (2.5 mmole) were added. Then, the reaction mixture was exposed to direct sunlight for 1-3 h, until the TLC showed the disappearance of the starting materials. The maximum temperature of the reaction mixture was determined and cited in **Table 1**. The excess of solvent was removed in *vacuo*. The resulting solid product was collected by filtration and recrystallized from EtOH to yield **5a-h**. The products **5b-h** were characterized by IR, NMR and through comparison of their physical properties with those reported in literature.

**Table 1.** Solar thermal energy synthesis of 3-aryl-2-cyanothioacrylamides **5a-h** and 3-aryl-2-(hetaryl)acrylonitrile derivatives **9a-c** and **11a-c**.

Product	Ar	Time (h)	Yield (%)	M. P. (°C)	Lit. M. P. (°C)	Maximum reaction temperature (°C)
<b>5a</b>	Ph	2	63	145 - 147	—	53
<b>5b</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	2	73	189 - 190	190 - 191 <sup>15</sup>	48
<b>5c</b>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	3	69	187 - 188	188 - 189 <sup>15</sup>	58
<b>5d</b>	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	5	66	179 - 180	180 - 181 <sup>15</sup>	58
<b>5e</b>	3,4-methylenedioxyphenyl	2	67	216 - 217	215 - 216 <sup>15</sup>	55
<b>5f</b>	4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	1	65	229 - 231	231 - 232 <sup>15</sup>	57
<b>5g</b>	2-thienyl	3	54	168 - 169	169 - 170 <sup>15</sup>	57
<b>5h</b>	2-furyl	3	52	156 - 157	158 <sup>15</sup>	51
<b>9a</b>	Ph	14	98	149 - 150	149 - 150 <sup>19</sup>	56
<b>9b</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	5	67	172 - 173	—	58
<b>9c</b>	4-ClC <sub>6</sub> H <sub>4</sub>	11	66	169 - 170	—	59
<b>11a</b>	Ph	6	64	121 - 122	121 - 123 <sup>20</sup>	56
<b>11b</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	4	81	142 - 143	143 - 144 <sup>20</sup>	59
<b>11c</b>	4-ClC <sub>6</sub> H <sub>4</sub>	4	73	148 - 150	148 - 150 <sup>20</sup>	56

### 4.3. 2-Cyano-3-phenylprop-2-enethioamide (5a)

<sup>1</sup>H NMR (600 MHz, DMSO-d<sub>6</sub>): δ = 7.43 - 7.61 (m, 5H), 7.95 (s, 1H), 9.57 (br s, 2H). <sup>13</sup>C NMR (150 MHz, DMSO-d<sub>6</sub>): δ = 102.2, 118.0, 128.0, 128.4, 129.0, 129.2, 129.6, 130.4, 136.5, 195.5. IR (KBr): ν = 3410, 3295, 3200, 2185, 1619 cm<sup>-1</sup>. Found: C, 63.67; H, 4.37; N, 15.0; S, 16.85; anal. calcd for C<sub>10</sub>H<sub>8</sub>N<sub>2</sub>S: C, 63.80; H, 4.28; N, 14.88; S, 17.03. MS: *m/z* = 188 (M<sup>+</sup>, 60), 187 (M<sup>+</sup>-1, 100), 172 (3), 162 (4), 161 (4), 160 (7), 155 (12), 128 (14), 102 (20), 101 (11), 100 (7), 78 (8), 77 (24), 76 (14), 75 (13), 74 (11), 60 (49), 51 (42), 50 (29).

### 4.4. Synthesis of 3-Aryl-2-(hetaryl)acrylonitriles 9a-c and 11a-c; General Procedure

To a solution of compounds **6** or **10** (2.5 mmole) in absolute EtOH (12 mL), nitrones **2a,b,i** (2.5 mmole) were added. The flask was exposed to direct sunlight for a period determined by TLC control (see **Table 1**). The maximum temperature of the reaction mixture was determined and cited in **Table 1**. Then, the reaction mixture was worked up as described above for **5a-h** to give the products **9a-c** and **11a-c**, respectively.

### 4.5. 2-(5-Ethylthio-4-phenyl-4H-1,2,4-triazol-3-yl)-3-(4-methoxyphenyl)acrylonitrile (9b)

<sup>1</sup>H NMR (600 MHz, DMSO-d<sub>6</sub>): δ = 1.43 (t, <sup>3</sup>J = 7.2 Hz, 3H), 3.28 (q, <sup>3</sup>J = 7.2 Hz, 2H), 3.86 (s, 3H), 6.93 (d, <sup>3</sup>J = 7.8 Hz, 2H), 6.97 (m, 1H), 7.33 (m, 2H), 7.53 (m, 1H), 7.58 (m, 1H), 7.82 (d, <sup>3</sup>J = 7.8 Hz, 2H), 7.88 (s, 1H). <sup>13</sup>C NMR (150 MHz, DMSO-d<sub>6</sub>): δ = 14.7, 29.7, 55.5, 93.6, 114.5, 115.1, 121.3, 127.4, 129.0, 130.1, 132.3, 132.7, 146.3, 149.3, 153.9, 157.6. IR (KBr): ν = 2922, 2200 cm<sup>-1</sup>. MS: *m/z* = 362 (M<sup>+</sup>, 12), 361 (45), 333 (7), 118 (12), 115 (7), 114 (14), 108 (2), 88 (7), 78 (11), 77 (100), 65 (11), 64 (15), 63 (21), 61 (7), 60 (12), 51 (72), 50 (20). Found: C, 66.41; H, 4.89; N, 15.29; S 9.07; anal. calcd for C<sub>20</sub>H<sub>18</sub>N<sub>4</sub>OS: C, 66.28; H, 5.01; N, 15.46; S, 8.85.

### 4.6. 3-(4-Chlorophenyl)-2-(5-ethylthio-4-phenyl-4H-1,2,4-triazol-3-yl)acrylonitrile (9c)

<sup>1</sup>H NMR (600 MHz, DMSO-d<sub>6</sub>): δ = 1.43 (t, <sup>3</sup>J = 7.2 Hz, 3H), 4.06 (q, <sup>3</sup>J = 7.2 Hz, 2H), 6.93 (m, 2H), 7.23 (m, 3H), 7.44 (d, <sup>3</sup>J = 8.4 Hz, 2H), 7.82 (d, <sup>3</sup>J = 8.4 Hz, 2H), 8.45 (s, 1H). IR: (KBr): ν = 3050, 2970, 2200. MS: *m/z* = 368 (M<sup>+</sup>, 4), 366 (M<sup>+</sup>, 8), 337 (9), 255 (3), 244 (2), 230 (2), 189 (3), 161 (5), 137 (7), 126 (9), 118 (10), 113 (3), 112 (3), 105 (9), 100 (5), 99 (9), 91 (12), 77 (99), 65 (22), 64 (12), 63 (17), 61 (10), 60 (19), 59 (24), 51 (100), 50 (28). Found: C, 62.01; H, 4.25; Cl, 9.59; N, 15.38; S,

8.68; anal. calcd for C<sub>19</sub>H<sub>15</sub>ClN<sub>4</sub>S: C, 62.20; H, 4.12; Cl, 9.66; N, 15.27; S, 8.74.

## 5. Acknowledgements

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