Reactivity of 2-substituted hydrazinecarbothioamides towards tetracyanoethylene and convenient synthesis of (5-amino-2-diazenylthiazolylmethylene)malononitrile derivatives

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Abstract
2-{Amino-[5-amino-2-(substituted diazenyl)thiazol-4-yl]methylene}malononitriles were synthesized from the reaction of 2-substituted hydrazinecarbothioamides with tetracyanoethylene (TCNE) to give tetracyanoethane adduct, followed by heterocyclization afforded the target compounds. The structure of (E)-2-{amino-[5-amino-2-(phenyldiazenyl)thiazol-4-yl]methylene}malononitrile was supported by single crystal X-ray crystallography.

Keywords: Malononitrile, thiazoles, thiosemicarbazides, tetracyanoethylene, X-ray crystallography

Introduction
Recently, thiazole derivatives have attracted a great deal of interest due to their low toxicity and broad biological activity. For example, naturally occurring and synthetic thiazoles find applications as antibiotics and anti-inflammatory agents, while selected aminothiazoles act as inhibitors of human cancer and Alzheimer’s disease.

The syntheses of thiazoles and 2-aminothiazoles have been studied extensively, however, the preparation of 5-aminothiazoles has not been so widely reported. Despite this, 5-aminothiazoles have received attention in a range of applications from antibiotics to photosensitizers.
A convenient route to 5-amino-4-phenylthiazoles has been developed from N-acylated-glycinamides and Lawesson’s reagent via trifluoroacetamides.12 A flexible route to 5-amino-thiazoles has been developed based on cyclization of diamide adducts, prepared using the Ugi reaction,16-18 in presence of Lawesson’s reagent.19 5-Amino-3-(substituted benzylidenamino)-2-phenylmino-2,3-dihydrothiazole-4-carbonitrile is one of the products which have been isolated from the reaction of aldehyde thiosemicarbazones with tetracyanoethylenes (TCNE).20

Mesoionic 1,2,4-triazolium-3-thiolate derivatives were synthesized from the reaction of N-substituted 2-phenylhydrazinecarbothioamides with TCNE.21

Herein, we report our investigation on the reaction of 2-substituted hydrazinecarbothioamides 1a-e with TCNE 2 (Fig. 1) and compared with the products isolated from the reaction of N-substituted 2-phenylhydrazinecarbothioamides with TCNE 2.

**Results and Discussion**

Treatment of the hydrazinecarbothioamides 1a-e with TCNE 2 (1.1 equiv) in dry ethyl acetate at room temperature resulted in a pink coloration of the reaction solution which quickly turned reddish orange. Tentatively, the color change observed may be owed to the formation of unstable charge-transfer (CT) complexes. The mixture was stirred and then left to stand for 24 hours at room temperature, resulting in the formation of single products 3a-e in 81-88% yields (Scheme 1).

![Scheme 1. Reactions of 2-substituted hydrazinecarbothioamides 1a-e with TCNE 2.](image)

<table>
<thead>
<tr>
<th>1a-e</th>
<th>Yields 3a-e, (%)</th>
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<tbody>
<tr>
<td>a: Ph</td>
<td>88</td>
</tr>
<tr>
<td>b: p-TolSO₂</td>
<td>84</td>
</tr>
<tr>
<td>c: Bn</td>
<td>83</td>
</tr>
<tr>
<td>d: CH₂=CH-CH₂</td>
<td>81</td>
</tr>
<tr>
<td>e: m-Cl-C₆H₄</td>
<td>86</td>
</tr>
</tbody>
</table>

The gross formula C₁₃H₉N₇S represents a product from one molecule of 1a and one molecule of TCNE 2 without elimination of any atoms. Two NH₂ groups are present in ¹H NMR (exchangeable with D₂O) as broad signals, the downfield at 10.22 ppm due to NH₂ attached to
vinyl group in 3a, the other NH2 resonate at 7.94 because of NH2 attached to thiazole C5. The aromatic protons observed at 7.83-7.10 ppm. In its 13C NMR spectrum, thiazole C2, C4 and C5 resonate at 161.2, 150.4 and 152.6, respectively. In the (aminomethylene)malononitrile fragment, of 3a, the dicyanovinyl carbons C2 and C1 resonated at 164.4 and 61.6 ppm, respectively, and were in accord with the observed trends in the δ values for C-atoms in push-pull alkenes.22,23 Further peaks at 115.6 (CN), besides the aromatic carbons support the assigned structure.

Absorption bands around 3373-3320 cm\(^{-1}\) relating to NH2 groups appeared in IR spectra of 3a-d. The IR spectra of 3a-e showed two sharp absorption bands at 2220-2210 cm\(^{-1}\) (CN) and 1623-1612 cm\(^{-1}\) that assigned to C=N vibration. The absence of C=S signal in IR and 13C NMR, also support the structures 3a-e. Moreover, the structure of (E)-2-[aminomethylene]malononitrile 3a has been strongly supported by a single crystal X-ray structure analysis (Figure 1 and Tables S1-S7 in the supplementary data). The asymmetric unit of (E)-2-[aminomethylene]malononitrile 3a (C\(_{13}\)H\(_9\)N\(_7\)S), confirms two independent molecules whose conformations differ primarily in the orientations of phenyl and substituted vinyl groups with respect to the thiazole ring. The X-ray structure analysis confirms a transoid geometry of thiazole and substituted groups with respect to the N=N double bond.

![Figure 1](TIF file) Molecular structure of 3a in the crystal. The crystallographic numbering does not reflect the systematic IUPAC numbering.

All bond lengths and angles in compound 3a are normal. The thiazole ring is planar; mean deviation from the S1/C2/N3/C4/C5 plane 0.019 Å. The amino group and the planar phenyldiazenyl substituent are coplanar to the thiazole moiety, while the planar aminomethyl(enemalononitrile is twisted by 43° to the thiazole plane.

A rationale for the formation of compounds 3a-d given in Scheme 2. Nucleophilic attack from the terminal NH2 of 1a-d on the C=C double bond of 2 to give the tetracyanoethane derivatives 4; charge-transfer complexes may, but do not necessarily have to,24 play an intermediate role. Intramolecular nucleophilic attack of SH of 4 on the C≡N triple bond and cyclization to give the intermediate 5 followed by the formation of bicyclic 6 that can open due to the proton transfer.
from thiazole ring. Compound 6 can then rearrange to form 7 and 8 and finally the highly stable [amino-(5-amino-2-substituted diazenylthiazolyl)methylene]malono-nitriles 3a-e.

Scheme 2: Mechanistic rationale for the formation of compounds 3a-e.
Conclusions

In conclusion, novel (diazenylthiazolyl)methylene]malononitriles have been synthesized from the nucleophilic addition reactions of 2-substituted hydrazinecarbothioamides on TCNE. The products were synthesized from readily accessible starting materials using a simple experimental procedure.

Experimental Section

General. Gallenkamp melting point apparatus was used for determining the melting points; the results are uncorrected. The IR spectra (KBr discs technique) were recorded on Alpha, Bruker FT-IR and Shimadzu 408 instruments. The \(^{1}\)H-NMR (400.13 MHz) and \(^{13}\)C-NMR (100.6 MHz) spectra were determined on a Bruker AM 400 spectrometer; s = singlet, m = multiplet, b = broad. The \(^{13}\)C NMR signals were assigned based on DEPT 135/90 spectra. Chemical shifts are expressed as \(\delta\) in parts per million (ppm). The mass spectra (70 eV, electron impact mode) were recorded on a Finnigan MAT 312 instrument. The elemental analyses for C, H, N and S were carried out at the Microanalytical Centre, Cairo University, Egypt using an Elmyer 306. Preparative layer chromatography (PLC) used air-dried 1.0 mm thick layers of slurry-applied silica gel (Merck P254) on glass plates 48 × 20 cm using the solvents listed.

Starting materials
The starting materials 1a-e were prepared following published methods: \(1a^{25}, 1b^{26}, 1c^{27}, 1d^{28}\) and 1e\(^{29}\). Tetracyanoethylene (TCNE, 2) was bought from Fluka (USA), recrystallized from chlorobenzene and sublimed before used. Ethyl acetate and toluene were purified according to Vogel\(^{30}\) and Organikum,\(^{31}\) dried and distilled. Acetonitrile (Merck) was used without further purification.

Reaction of 2-substituted hydrazinecarbothioamides 1a-e with tetracyanoethylene (2). General procedure. A solution of TCNE 2 (141 mg, 1.1 mmol) in dry EtOAc (10 mL), was added dropwise to a solution of 1a-e (1.0 mmol) in dry EtOAc (15 mL), which causes a spontaneous change of color from yellow to pink and finally to reddish orange. The mixture was stirred for 2 h, then left to stand for 24 h at room temperature. A red-orange precipitate was formed, filtered and recrystallized from acetonitrile to give pure crystals 3a-e. In case of the reaction between 1d and TCNE 2, the mixture of the reaction was subjected to PLC and using toluene/ethyl acetate (5:1) as eluent to give an intense red-orange zone from 3d. The zone was separated by using acetone and recrystallized from acetonitrile.

\((E)\)-2-\{Amino-5-\{amino-2-(phenyldiazenyl)thiazol-4-yl\}methylene\}malononitrile (3a). Red crystals (0.259 g, 88%), mp 231-233 °C (MeCN), IR: \(\nu_{\text{max}}\) (KBr)/cm\(^{-1}\) 3373-3342 (NH\(_2\)), 2215 (CN), 1620 (C=N), 1595 (Ar-C=C), 1571, 1455 (N=N) cm\(^{-1}\). NMR: \(\delta_{H}\) (400 MHz, DMSO-\(d_6\)) 7.10-7.12 (m, 1H, Ar-H), 7.60-7.62 (m, 2H, Ar-H), 7.80-7.83 (m, 2H, Ar-H), 7.95 (br, s, 2H, NH\(_2\))
attached to thiazole), 10.22 (br, s, 2H, NH₂). δ<sub>H</sub> (100 MHz, DMSO-<em>d</em><sub>6</sub>) 61.6 (C-C=N), 115.6 (CN), 124.1, 128.6, 129.7 (Ar-CH), 133.0 (Ar-C), 150.5 (thiazole-C4), 152.6 (thiazole-C5), 161.2 (thiazole-C2), 164.4 (=C-NH₂). <em>m/z</em> (%): 295 (M<sup>+</sup>, 76), 268 (14), 190 (16), 105 (37), 77 (100). Anal. Caled for C<sub>13</sub>H<sub>9</sub>N<sub>7</sub>S (295.32) C, 52.87; H, 3.07; N, 33.20; S, 10.86. Found: C, 53.02; H, 2.94; N, 33.33; S, 10.71%.

**E)**-2-[Amino-5-[amino-2-(4-toluenesulfonlyldiazenyl)thiazol-4-yl]methylene]malononitrile (3b). Red crystals (0.313 g, 84%). mp 255-257 °C (MeCN). IR: <em>v</em> <em>max</em> (KBr)/cm<sup>-1</sup> 3360-3320 (NH₂), 2210 (CN), 1617 (C=N), 1580 (Ar-C=C), 1565, 1446 (N≡N) cm<sup>-1</sup>. δ<sub>H</sub> (400 MHz, DMSO-<em>d</em><sub>6</sub>) 2.42 (s, 3H, CH₃), 7.52-7.55 (m, 2H, Ar-H), 7.72-7.75 (m, 2H, Ar-H), 7.99 (br, s, 2H, NH₂ attached to thiazole), 10.31 (br, s, 2H, NH₂). δ<sub>C</sub> (100 MHz, DMSO-<em>d</em><sub>6</sub>) 21.2 (CH₃), 61.4 (C-C≡N), 115.8 (CN), 125.2, 129.5 (Ar-CH), 135.7, 140.1 (Ar-C). Anal. Caled for C<sub>14</sub>H<sub>11</sub>N<sub>7</sub>S (373.41) C, 45.03; H, 2.97; N, 26.26; S, 17.17. Found: C, 44.89; H, 3.06; N, 26.12; S, 17.33%.

**E)**-2-[Amino-5-[benzylidiazonil]thiazol-4-yl]methylene]malononitrile (3c). Red-orange crystals (0.256 g, 83%). mp 242-244 °C (MeCN). IR: <em>v</em> <em>max</em> (KBr)/cm<sup>-1</sup> 3366-3346 (NH₂), 2212 (CN), 1612 (C≡N), 1589 (Ar-C=C), 1561, 1440 (N≡N) cm<sup>-1</sup>. δ<sub>H</sub> (400 MHz, DMSO-<em>d</em><sub>6</sub>) 4.66 (s, 2H, CH₂Ph), 7.04-7.08 (m, 1H, Ar-H), 7.54-7.58 (m, 2H, Ar-H), 7.71-7.76 (m, 2H, Ar-H), 7.98 (br, s, 2H, NH₂ attached to thiazole), 10.29 (br, s, 2H, NH₂). δ<sub>C</sub> (100 MHz, DMSO-<em>d</em><sub>6</sub>) 52.1 (CH₂Ph), 61.6 (C-C≡N), 116.0 (CN), 124.3, 128.5, 129.1 (Ar-CH), 133.6 (Ar-C), 149.7 (thiazole-C4), 152.5 (thiazole-C5), 161.2 (thiazole-C2), 164.4 (=C-NH₂). <em>m/z</em> (%): 373 (M<sup>+</sup>, 12), 346 (18), 281 (100), 191 (19), 156 (16), 91 (46). Anal. Caled for C<sub>14</sub>H<sub>11</sub>N<sub>7</sub>S (309.35) C, 54.36; H, 3.58; N, 31.69; S, 10.37. Found: C, 54.22; H, 3.66; N, 31.81; S, 10.23%.

**E)**-2-[[2-(Allyldiazenyl)-5-aminothiazol-4-yl](amino)methylene]malononitrile (3d). Red-orange crystals (0.209 g, 81%), mp 167-169 °C (MeCN). <em>v</em> <em>max</em> (KBr)/cm<sup>-1</sup> 3358-3326 (NH₂), 2210 (CN), 1615 (C≡N), 1558, 1438 (N≡N) cm<sup>-1</sup>. δ<sub>H</sub> (DMSO-<em>d</em><sub>6</sub>) 4.05-4.08 (m, 2H, allyl-CH₂N), 5.11-5.13 (m, 2H, allyl-CH₂), 5.91-5.94 (m, 1H, allyl-CH=), 7.94 (br, s, 2H, NH₂ attached to thiazole), 10.16 (br, s, 2H, NH₂). δ<sub>C</sub> (DMSO-<em>d</em><sub>6</sub>) 49.3 (allyl-CH₂N), 60.9 (C≡N), 115.0 (CN), 116.2 (allyl-CH=), 135.4 (allyl-CH=), 149.8 (thiazole-C4), 152.6 (thiazole-C5), 161.9 (thiazole-C2), 164.0 (=C-NH₂). <em>m/z</em> (%): 259 (M<sup>+</sup>, 21), 232 (26), 154 (46), 69 (37), 41 (100). Anal. Caled for C<sub>10</sub>H<sub>9</sub>N<sub>7</sub>S (259.29) C, 46.32; H, 3.50; N, 37.81; S, 12.37. Found: C, 46.45; H, 3.57; N, 37.93; S, 12.40%.

**E)**-2-(Amino-5-amino-2-[(3-chlorophenyl)diazenyl]thiazol-4-yl)methylene]malononitrile (3e). Red-orange crystals (0.282 g, 86%), mp 248-250 °C (MeCN). IR: <em>v</em> <em>max</em> (KBr)/cm<sup>-1</sup> 3365-3338 (NH₂), 2220 (CN), 1623 (C≡N), 1583 (Ar-C=C), 1569, 1450 (N≡N) cm<sup>-1</sup>. NMR: δ<sub>H</sub> (400 MHz, DMSO-<em>d</em><sub>6</sub>) 7.55-7.59 (m, 1H, Ar-H), 7.63-7.66 (m, 1H, Ar-H), 7.69-7.80 (m, 2H, Ar-H), 8.01 (br, s, 2H, NH₂ attached to thiazole), 10.28 (br, s, 2H, NH₂). δ<sub>C</sub> (100 MHz, DMSO-<em>d</em><sub>6</sub>) 61.6 (C-C≡N), 115.8 (CN), 125.2, 126.3, 129.6, 130.1 (Ar-CH), 135.1, 141.2 (Ar-C), 149.7 (thiazole-C4), 153.1 (thiazole-C5), 161.2 (thiazole-C2), 164.5 (=C-NH₂). <em>m/z</em> (%): 329 (M<sup>+</sup>, 36), 218 (28), 190 (61), 139 (43), 111 (100). Anal. Caled for C<sub>13</sub>H<sub>8</sub>CIN<sub>7</sub>S (329.77) C, 47.35; H, 2.45; N, 29.73; S, 9.72. Found: C, 47.42; H, 2.36; N, 29.61; S, 9.83%. 
Single crystal X-ray structure determination of 3a

Single crystals were obtained by recrystallization from acetonitrile. The single crystal X-ray diffraction study was carried out on a Bruker D8 Venture diffractometer with Photon100 detector at 123 K using CuKα radiation (λ = 1.54178 Å) 3a. Direct Methods (SHELXS-97)\textsuperscript{32} were used for structure solution and refinement was carried out using SHELXL-2014\textsuperscript{33} (full-matrix least-squares on F\textsuperscript{2}). Hydrogen atoms were localized by difference electron density determination and refined using a riding model (H (N) free). A semi-empirical absorption correction was applied.

Compound 3a: C\textsubscript{13}H\textsubscript{9}N\textsubscript{7}S, M = 295.32 g mol\textsuperscript{-1}, red plates, crystal size 0.12 × 0.08 × 0.02 mm, triclinic space group, P-1 (no. 2), a = 7.3780 (4) Å, b = 7.9678 (5) Å, c = 11.9389 (7) Å, α = 99.249 (2)°, β = 104.589 (2)°, γ = 100.386 (2)°, V = 652.23 (7) Å\textsuperscript{3}, Z = 2, D\textsubscript{calc} = 1.504 Mg m\textsuperscript{-3}, F(000) = 304, μ = 2.256 mm\textsuperscript{-1}, T = 123 K, 11384 measured reflections (2θ\textsubscript{max} = 144°), 2540 independent reflections [R\textsubscript{int} = 0.030], 202 parameters, 4 restraints, R1 [for 2405 reflections with I > 2σ (I)] = 0.028, wR\textsuperscript{2} (for all data) = 0.068, S = 1.06, largest diff. peak and hole = 0.266 eÅ\textsuperscript{-3}/-0.245 eÅ\textsuperscript{-3}. Crystallographic data (excluding structure factors) for structure reported in this work have been deposited with Cambridge Crystallographic Data center as supplementary publication no 1048447 (3a) Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223) 336 033: e-mail: deposit@ccdc.cam.ac.uk.

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