Pyrazole, pyrazolo[1,2-c]-1,3,4-thiadiazole and thia diazepine derivatives from thiosemicarbazides

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Abstract
Thiosemicarbazides 1a–c reacted with tetracyanoethene 2 in ethyl acetate with admission of air to form the 7-amino-2-organylimino-2,3-dihydro-1,3,4-thiadiazepine-5,6-dicarbonitriles 6a,b, 7-amino-1-organylimino-3-oxopyrazolo[1,2-c]-1,3,4-thiadiazole-5,5,6-tricarbonitriles 7a–c, 7-amino-1-organyl-iminopyrazolo[1,2-c]-1,3,4-thiadiazole-3,3,5,5,6-pentacarbonitriles 8a–c and 3-amino-1H-pyrazole-4,5-dicarbonitriles (9) in moderate yields. Rationales for the observed conversations are presented.

Keywords: Substituted thiosemicarbazides, tetracyanoethene, heterocyclic oligonitriles

Introduction
The cyclization of suitable linear compounds is one of the most common and popular methods for preparing heterocyclic compounds. Unsymmetrical ureas have been cyclized to produce several heterocycles such as 1,3,4-thiadiazoles, 1,2,4-triazoles and 1,3,5-triazines.1 2,4-Disubstituted semicarbazones have been proposed as dipeptide isosteres2 and could be a new class of urea peptide mimetics. The possible biological properties of semi- and thiosemicarbazone derivatives make it attractive to study of the reactivity of these compounds.

Chlorocarbonylsulfenyl chloride was allowed to react with alkyl- and arylidene-phenylthiosemicarbazones to give 1,2,4-triazolines and 1,2,4-dithiazolidines.3 2,4-Disubstituted thiosemicarbazides were cyclized to 1,2,4-triazoline-3-thiones and 1,3,4-thiadiazolines when treated with acyl isothiocyanates.4 Oxidative cyclization of substituted aldehyde thiosemicarbazones, induced by different metallic salts, led to 1,2,4-triazoline derivatives.5–9 On the other hand, the interaction of thiosemicarbazide and dithiocarbazate derivatives with some π-acceptors such as tetracyanoethene (2), (1,3-dioxo-2,3-dihydro-1H-inden-2-ylidene)-propanedinitrile, and benzoquinone as well as naphthoquinone affords thiazines, thia diazines, thiadia zoles, indazoles, pyridazines, oxathiadia zoles and various fused heterocyclic compounds possible via a single-electron transfer before the ring-closure step.10–14
Tetracyanoethene 2 has an impressive variety of potential applications.\textsuperscript{15–17} Tetracyanoethene is an established reagent for reacting with ene, diene, and various other rich electron systems in organic and metallo-organic substrates. In addition, 2 is a useful reagent for synthesis of cyanocarbon acids, spiro compounds and novel heterocycles.\textsuperscript{15–21}

Recently, it has been reported that 4-phenyl- and 4-benzylthiosemicarbazides 1a,b reacted with 2 in ethyl acetate with charge-transfer complex (CT) formation, ultimately giving a mixture of thiadiazepine and thiadiazole derivatives 3–5 (Figure 1).\textsuperscript{22}

![Chemical structures](image)

\textbf{Figure 1.} Previous work on the reaction of tetracyanoethene with 4-substituted thiosemicarbazides

\textbf{Results and Discussion}

We report here the results of our recent investigations on the reaction of 4-substituted thiosemicarbazides 1a–c with tetracyanoethene 2. These results are compared with those obtained earlier.\textsuperscript{22} Upon addition of doubled molar amounts of 2 to a solution of 1a–c in ethyl acetate, with the admission of air, the green color of a transient charge-transfer complex is observed, which quickly gives way to a brown and finally to a characteristic reddish orange color. The concentrated residue from the filtrate was subjected to vacuum sublimation to remove any unreacted 2. Chromatographic separation of the sublimation residue gave products 6–9 (see Figure 2).
The structural assignments of compounds 6–9 are based on spectroscopic data, on combustion analyses, and on chemical evidence. The thiadiazepine structure 6a has been assigned on the basis of elemental analysis supporting the gross formula C_{12}H_{3}N_{6}S, the mass spectrum, which gave a correct molecular ion at m/z 268 (19 %), and through its $^1$H-NMR, $^{13}$C-NMR, and IR spectra (see Experimental Section). The analytical data of compound 6 would also match for other isomers of products 10–13 (Figure 3). The alternative structures 10–13 could be ruled out on the bases of $^1$H-NMR, $^{13}$C-NMR, and the fragment ions in the mass spectrum of 6a at m/z 150, 135, 118, 91, 77 and 66. As shown from Figure 3, structure 6a fits best to all the spectroscopic data (see Experimental Section).

Compounds 7a–c show a characteristic orange color attributed to the local push–pull systems of conjugated double bonds and lone pairs. The $\lambda_{\text{max}}$ values (486–478 nm) and log $\varepsilon$ (5.435–5.509) are similar owing to their same gross molecular structures and configuration. The IR spectrum of 7a in a KBr disc shows sharp absorptions characteristic of different cyano groups at 2229 and 2202 cm$^{-1}$, of the amino group at 3315, carbonyl at 1655, as well as aryl at 1580 cm$^{-1}$. The $^1$H-NMR spectrum (DMSO-d$_6$, 300 MHz) of 7a clearly shows the presence of phenyl protons and NH$_2$. The $^{13}$C-NMR (DMSO-d$_6$) of 7a shows signals at $\delta$ 47.54 (C-6), 68.93 (C-5), 117.20, 119.23, 119,80 (CN), 153.60 (C-7), 162.87 (C- 1) and 164.34 (C-2), in addition to the aryl carbons. The molecular formulae of compounds 7a–c are supported by elemental analysis and mass spectra which gave the expected molecular ion peaks as base peaks. Several alternative structures based on the same elemental composition and $^1$H-NMR could be eliminated according to the spectral data. Also, structure 21 could be ruled out on the basis of the $^{13}$C-NMR spectrum of 7a.
Figure 3. The alternative structures for compound 6 and the fragment ions in the mass spectrum of 6a

Compounds 8a–c show a characteristic red color. The gross formula, C_{16}H_{7}N_{9}S, of 8a was confirmed by the mass spectrum, which exhibited the molecular ion at m/z 357 (11 %). The IR spectrum showed absorptions at 3365 (NH$_2$), 2227 (CN) and 1638 (Ar-C=C). The $^1$H-NMR spectrum of 8a (DMSO-d$_6$, 300 MHz) displayed one broad singlet at 7.05 ppm for 2H (NH$_2$) in addition to the aromatic protons. In its $^{13}$C-NMR spectrum, C-6 and C-5 resonate at $\delta = 70.63$ and 43.50 ppm respectively; further peaks are at $\delta = 153.60$ (C-7), 162.80 (C-1) and for cyano groups at $\delta = 113.00, 113.40, 114.82, 119.73, 115.80$ ppm. Compound 23 could be ruled out, owing to the absence of C=S signals in the $^{13}$C-NMR spectra.

The results of combustion analysis and spectroscopic data suggested the presence of 3-amino-1H-pyrazole-4,5-dicarbonitrile (9) as a precipitate from the reaction between 1c and 2. The structure of 9 was confirmed by comparison with an authentic sample.$^{23,24}$ When hydrazine hydrate was treated with the doubled molar amount of 2 in ethyl acetate, a product identical in its mp, IR and $^1$H-NMR spectra with the sample of 9 as isolated before$^{23,24}$ was obtained.
Scheme 1. A rationale for the formation of products 6–8
The formation of unusual products such as 6–9 (see Figure 2) is not easily rationalized. Since the reactions require a multitude of steps and are, by necessity, very complex, the moderate yields found (based throughout on the amount of starting material used, see Figure 2) are acceptable, and it will not be possible to clarify every detail. This needs to be taken into account when determining and evaluating yields. A rationale for formation of the products 6–8 is presented in Schemes 1 and 2. The 4-substituted thiosemicarbazides 1a–c and 2 give the neutral adduct 14, which is a tetracyanoethane derivative. Elimination of one molecule of HCN affords the intermediate 15 which cyclizes to the thiadiazepine derivatives 6a,b.

Both the products 6 and 7 require the intermediate formation of 15. Cyclization of the latter and elimination of a molecule of HCN forms intermediate 18 which, in turn, reacts with another molecule of 2 affording 7a–c via oxidation of 19. The formation of 8a–c can be rationalized by elimination of a molecule of malononitrile from 14 followed by further reaction with another molecule of 2, and cyclization.

Scheme 2. The theoretically proposed TCV-products A–C and 15
Next, we have to accept that 2 may effect tricyanovinylation (TCV) theoretically at four positions of 1 (the three nitrogen atoms and the sulfur), thus giving rise to the TCV- products A–C and 15 (Scheme 2). A and B could be ruled out on the basis of the structures formed and the spectroscopic data. It has been reported recently, that the –SH group is the reactive center, but the formation of compound 9 supports our suggested rationalization (Scheme 1). As shown in Scheme 3, the NH$_2$ group first attacks the double bond of 2, forming the substituted pyrazole 9 via steps 11c $\rightarrow$ 24 $\rightarrow$ 25.

Scheme 3. A rationale for the formation of compound 9

**Experimental Section**

**General Procedures.** Melting points (uncorrected) were determined with a Reichert Thermovar hot-stage microscope. IR spectra were recorded using KBr disks on Shimadzu 408 or Bruker Vector 22 FT-IR instruments. NMR spectra were obtained for $^1$H at 300 MHz, and for $^{13}$C at 75 MHz, using a Bruker WM 300 instrument with tetramethylsilane as internal reference; s=singlet, m=multiplet. The mass spectra (70 eV, electron-impact mode) were obtained on an AMD 604 instrument. The UV–Vis spectra were recorded on a Perkin-Elmer Lambda 2 spectrophotometer. Combustion analyses were carried out with a Carlo Erba Model 1106 CHN analyzer. Preparative-layer chromatography was carried out using air-dried 1.0-mm thick layers of slurry-
applied silica gel, Merck PF_{254}, on 48 cm wide x 20-cm high glass plates. Zones were detected by their color or by quenching of indicator fluorescence upon exposure to 254-nm light.

**Materials.** The 4-substituted thiosemicarbazides 1a–c were prepared according to the literature,^{25-28} as were 4-phenylthiosemicarbazide (1a),^{25,26} 4-benzylthiosemicarbazide (1b),^{26,27} and 4-(2-propenyl)-thiosemicarbazide (1c).^{27,28} Tetracyanoethene (ethenetetracarbonitrile, 2, Merck) was recrystallized from chlorobenzene and sublimed.

**General procedure. Reaction of 4-substituted thiosemicarbazides 1a–c with 2**

To 2 mmol of 2b in dry ethyl acetate (10 ml), 1 mmol of 1a–c in 15 ml of dry ethyl acetate was added with stirring within 2h. The mixture was left standing for 48h at room temperature, during which time a crystalline colorless product separated. The resulting solid material was filtered and the precipitate was washed with ethyl acetate, dried and recrystallized from ethanol to give the thiadiazepine derivatives 6a,b (in the reaction of 1a,b with 2) or pyrazole derivative 9 (in the reaction of 1c with 2). The filtrate was concentrated to dryness and the residue sublimed at 80°C under vacuum to remove any unreacted 2. The residue was then separated by preparative layer chromatography (100 mg per plate) using the suitable eluent (cyclohexane/ethyl acetate, 3:1, for the reactions of 2 with 1a and 1b; cyclohexane/ethyl acetate, 5:1, for the reaction of 2 with 1c) to give numerous colored zones, two of which (with high intensity) were removed and extracted. The faster-migrating one, R_f = 0.135 (which is always characterized by its orange color) contained the thiadiazole derivatives 7a–c, and the second zone, R_f = 0.096 (characterized by its deep red color) contained pyrazole[1,2-c]-1,3,4-thiadiazole derivatives 8a–c. Extraction of the zones with acetone, and concentration, gave a residue which was re-chromatographed to separate the pure compounds.

**7-Amino-5,6-dicyano-2-phenylimino-2,3-dihydro-1,3,4-thiadiazepine (6a).** Colorless crystals (ethanol) (110 mg, 41%), mp 249–251°C. IR; ν_{max} (KBr) cm\(^{-1}\) 3350–3280 (NH, NH\(_2\)), 2230 (CN), 1625 (C=O), 1585 (aryl). \(^1\)H-NMR (DMSO-d\(_6\)); δ 7.00–7.90 (m, 7H, NH\(_2\) and aryl), 10.96 (s, 1H, thiadiazepine-NH). \(^13\)C-NMR (DMSO-d\(_6\)); δ 109.82 (C-6), 117.93, 118.11 (CN), 123.50, 127.22, 128.24, 129,14 (aryl-C), 129.86 (C-7), 132.83 (aryl-C), 165.81 (C-5), 166.24 (C-2). MS; m/z (%) 268 (M\(^+\), 19), 150 (22), 135 (81), 118 (100), 91 (92), 77 (91), 66 (58). Anal. Calcd. for C\(_{12}\)H\(_8\)N\(_6\)S: C, 53.72; H, 3.00; N, 31.32; S, 11.92. Found: C, 53.89; H, 2.91; N, 31.26; S, 12.06%.

**7-Amino-2-benzylimino-5,6-dicyano-2,3-dihydro-1,3,4-thiadiazepine (6b).** Colorless crystals (ethanol) (125 mg, 44%), mp 192–194°C. IR; ν_{max} (KBr) cm\(^{-1}\) 3330–3290 (NH, NH\(_2\)), 2960 (CH\(_2\)), 2234 (CN), 1630 (C = C), 1585 (aryl). \(^1\)H-NMR (DMSO-d\(_6\)); δ 7.00–7.90 (m, 7H, NH\(_2\) and aryl), 10.96 (s, 1H, thiadiazepine-NH). \(^13\)C-NMR (DMSO-d\(_6\)); δ 4.90 (s, 2H, CH\(_2\)), 7.00 (s, 2H, NH\(_2\)), 7.20–7.45 (m, 5H, aryl), 11.20 (s, 1H, thiadiazepine-NH). \(^13\)C-NMR (DMSO-d\(_6\)); δ 48.55 (CH\(_2\)), 112.44 (C-6), 118.23, 118.73 (CN), 121.70, 125.42, 127.62, 128,30 (aryl-C), 129.60 (C-7), 129.80 (aryl-C), 163.40 (C-2), 165.20 (C-5). MS; m/z (%) 282 (M\(^+\), 2), 149 (34), 133 (30), 91 (100), 78 (14), 65 (22). Anal. Calcd. for C\(_{13}\)H\(_{10}\)N\(_6\)S: C, 55.30; H, 3.57; N, 29.77; S, 11.36. Found: C, 55.41; H, 3.63; N, 29.69; S, 11.27%.
7-Amino-4-phenylimino-3-oxopyrazolo[1,2-c]-1,3,4-thiadiazole-5,5,6-tricarbonitrile (7a). Orange crystals (ethanol) (102 mg, 32%), mp 228–230 °C. UV–Vis; \(\lambda_{\text{max}}\) (acetonitrile) 486 nm, \(\log \varepsilon = 5.494\). IR; \(v_{\text{max}}\) (KBr) cm\(^{-1}\) 3315 (NH\(_2\)), 2229, 2202 (CN), 1655 (CO), 1580 (aryl). \(^1\)H-NMR (DMSO-d\(_6\)); \(\delta\) 7.25 (s, 2H, NH\(_2\)), 7.45–7.65 (m, 5H, aryl); \(^{13}\)C-NMR (DMSO-d\(_6\)); \(\delta\) 47.54 (C-6), 68.93 (C-5), 117.20, 119.23, 119,80 (CN), 131.12, 118.00, 129.43, 144.50 (aryl-C), 153.60 (C-7), 162.87 (C-1), 164.34 (C-3). MS; \(m/z\) (%) 321 (M\(^+\), 7), 293 (6), 231 (100), 216 (37), 118 (47), 119 (19), 104 (89), 77 (76), 66 (9). Anal. Calcd. for C\(_{14}\)H\(_7\)N\(_2\)S: C, 52.33; H, 2.20; N, 30.51; S, 9.98. Found: C, 52.46; H, 2.29; N, 30.38; S, 10.11%.

7-Amino-4-benzylimino-3-oxopyrazolo[1,2-c]-1,3,4-thiadiazole-5,5,6-tricarbonitrile (7b). Orange crystals (acetonitrile) (105 mg, 31%), mp 205–207 °C. UV–Vis; \(\lambda_{\text{max}}\) (acetonitrile) 482 nm, \(\log \varepsilon = 5.509\). IR; \(v_{\text{max}}\) (KBr) cm\(^{-1}\) 3320 (NH\(_2\)), 2890 (CH\(_2\)), 2210 (CN), 1658 (CO), 1583 (aryl). \(^1\)H-NMR (DMSO-d\(_6\)); \(\delta\) 4.92 (s, 2H, CH\(_2\)), 7.20 (s, 2H, NH\(_2\)), 7.35–7.68 (m, 5H, aryl). MS; \(m/z\) (%) 335 (M\(^+\), 6), 307 (9), 91 (100), 65 (23). Anal. Calcd. for C\(_{15}\)H\(_8\)N\(_2\)S: C, 53.73; H, 2.71; N, 29.24; S, 9.56. Found: C, 53.89; H, 2.64; N, 29.16; S, 9.49%.

7-Amino-4-allylimino-3-oxopyrazolo[1,2-c]-1,3,4-thiadiazole-5,5,6-tricarbonitrile (7c). Orange crystals (acetonitrile) (110 mg, 39%), mp 202–204 °C. UV–Vis; \(\lambda_{\text{max}}\) (acetonitrile) 478 nm, \(\log \varepsilon = 5.435\). IR; \(v_{\text{max}}\) (KBr) cm\(^{-1}\) 3325 (NH\(_2\)), 2220, (CN), 1660 (CO). \(^1\)H-NMR (DMSO-d\(_6\)); \(\delta\) 4.70 (s, 2H, CH\(_2\)N), 5.25 (s, 2H, = CH\(_2\)), 5.90 (m, 1H, CH), 7.50 (s, 2H, NH\(_2\)). MS; \(m/z\) (%) 285 (M\(^+\), 6), 257 (13), 190 (6), 173 (8), 160 (27), 133 (46), 77 (21), 66 (15), 41 (100). Anal. Calcd. for C\(_{11}\)H\(_5\)N\(_2\)S: C, 46.34; H, 2.47; N, 34.37; S, 11.24. Found: C, 46.22; H, 2.61; N, 34.51; S, 11.16%.

7-Amino-4-phenyliminopyrazolo[1,2-c]-1,3,4-thiadiazole-3,3,5,5,6-pentacarbonitrile (8a). Red crystals (acetonitrile) (87 mg, 22%), mp 347–349 °C. UV/Vis; \(\lambda_{\text{max}}\) (acetonitrile) 536 nm, \(\log \varepsilon = 5.583\). IR; \(v_{\text{max}}\) cm\(^{-1}\) 3365 (NH\(_2\)), 2227, (CN), 1638 (aryl). \(^1\)H-NMR (DMSO-d\(_6\)); \(\delta\) 7.05 (s, 2H, NH\(_2\)), 7.25–7.70 (m, 5H, aryl). \(^{13}\)C-NMR (DMSO-d\(_6\)); \(\delta\) 43.50 (C-5), 70.63 (C-6), 113.00, 113.40, 114.82, 119.73, 125.80 (CN), 128.44, 128.61, 129.00, 129.60, 130.55, 143.62 (aryl-C), 153.60 (C-7), 162.80 (C-1). MS; \(m/z\) (%) 357 (M\(^+\), 11), 293 (81), 267 (66), 240 (82), 224 (31), 133 (80), 93 (55), 77 (100). Anal. Calcd. for C\(_{16}\)H\(_7\)N\(_5\)S: C, 53.78; H, 1.97; N, 35.28; S, 8.97. Found: C, 53.62; H, 2.11; N, 35.14; S, 9.11%.

7-Amino-4-benzyliminopyrazolo[1,2-c]-1,3,4-thiadiazole-3,3,5,5,6-pentacarbonitrile (8b). Red crystals (acetonitrile) (80 mg, 22%), mp 338–340 °C. UV–Vis; \(\lambda_{\text{max}}\) (acetonitrile) 531 nm, \(\log \varepsilon = 5.596\). IR; \(v_{\text{max}}\) cm\(^{-1}\) 3360 (NH\(_2\)), 2966 (CH\(_2\)), 2220, (CN), 1635 (aryl). \(^1\)H-NMR (DMSO-d\(_6\)); \(\delta\) 5.10 (s, 2H, CH\(_2\)), 7.19 (s, 2H, NH\(_2\)), 7.35–7.75 (m, 5H, aryl). MS; \(m/z\) (%) 371 (M\(^+\), 7), 307 (72), 281 (41), 255 (53), 239 (37), 91 (100), 67 (77). Anal. Calcd. for C\(_{17}\)H\(_8\)N\(_5\)S: C, 54.98; H, 2.44; N, 33.94; S, 8.63. Found: C, 55.16; H, 2.36; N, 33.79; S, 8.58.

7-Amino-4-(2-propenyl)iminopyrazolo[1,2-c]-1,3,4-thiadiazole-3,3,5,5,6-pentacarbonitrile (8c). Red crystals (acetonitrile) (105 mg, 33%), mp 318–320 °C. UV–Vis; \(\lambda_{\text{max}}\) (acetonitrile) 524 nm, \(\log \varepsilon = 5.524\). IR; \(v_{\text{max}}\) cm\(^{-1}\) 3335 (NH\(_2\)), 2207, (CN), 1635 (aryl). \(^1\)H-NMR (DMSO-d\(_6\)); \(\delta\) 4.60 (m, 2H, CH\(_2\)N), 5.25 (m, 2H, = CH\(_2\)), 5.90 (m, 1H, CH), 7.55 (s, 2H, NH\(_2\)). \(^{13}\)C-NMR (DMSO-d\(_6\)); \(\delta\) 54.40 (CH\(_2\)N), 69.66 (C-6), 43.12 (C-5), 90.62, 91.14, 91.70, 93.25 (CN), 117.70
(=CH₂), 128.82 (CN), 133.26 (CH), 149.35 (C-7), 160.12 (C-1); MS; m/z (%) 321(M⁺, 12), 257 (26), 231 (41), 205 (52), 189 (31), 66 (62), 41 (100). Anal. Calcd. for C₁₃H₇N₉S; C, 48.59; H, 2.20; N, 39.23; S, 9.98. Found; C, 48.48; H, 2.36; N, 39.37; S, 10.14.

3-Amino-1H-pyrazole-4,5-dicarbonitrile (9). Yield 32 mg (24 %) mp 250–252°C (dec.) (lit.²⁴ 250°C).

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References