Pyrazole, pyrazolo[1,2-c]-1,3,4-thiadiazole and thiadiazepine 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-1*H*-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 isosteres[2] 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-1*H*-inden-2-ylidene)-propanedinitrile, and benzoquinone as well as naphthoquinone affords thiazines, thiadiazines, thiadiazoles, indazoles, pyridazines, oxathiadiazoles 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.[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.[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).[22]

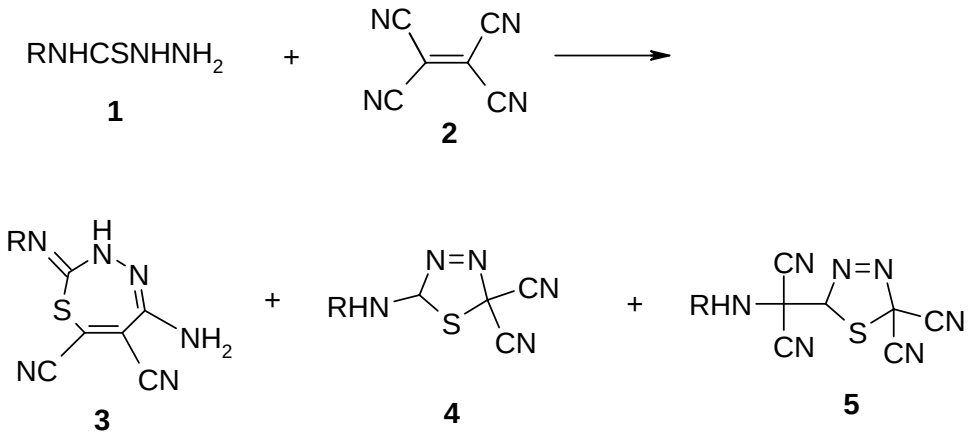
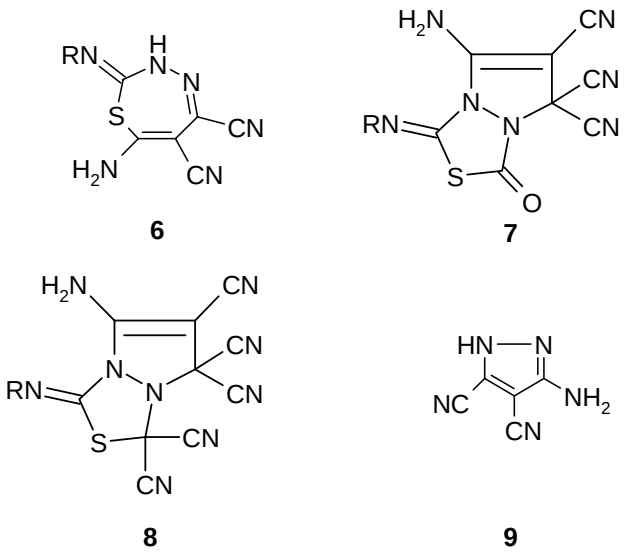


Figure 1. Previous work on the reaction of tetracyanoethene with 4-substituted thiosemicarbazides

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.[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).



6-8 : **a**, R = Phenyl; **b**, R = Benzyl; **c**, R = Allyl

Figure 2. New products formed during the reaction of 4-substituted thiosemicarbazides **1a–c** and tetracyanoethene (**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 $C_{12}H_3N_6S$, 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 λ_{max} values (486–478 nm) and log ε (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 δ 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**.

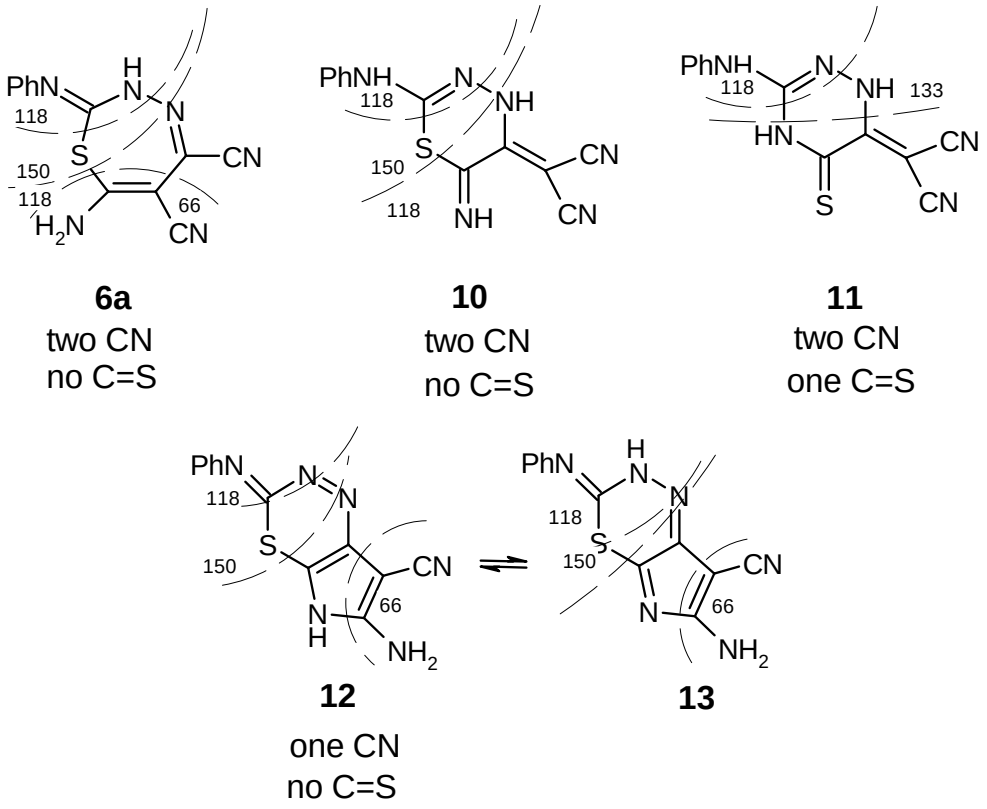
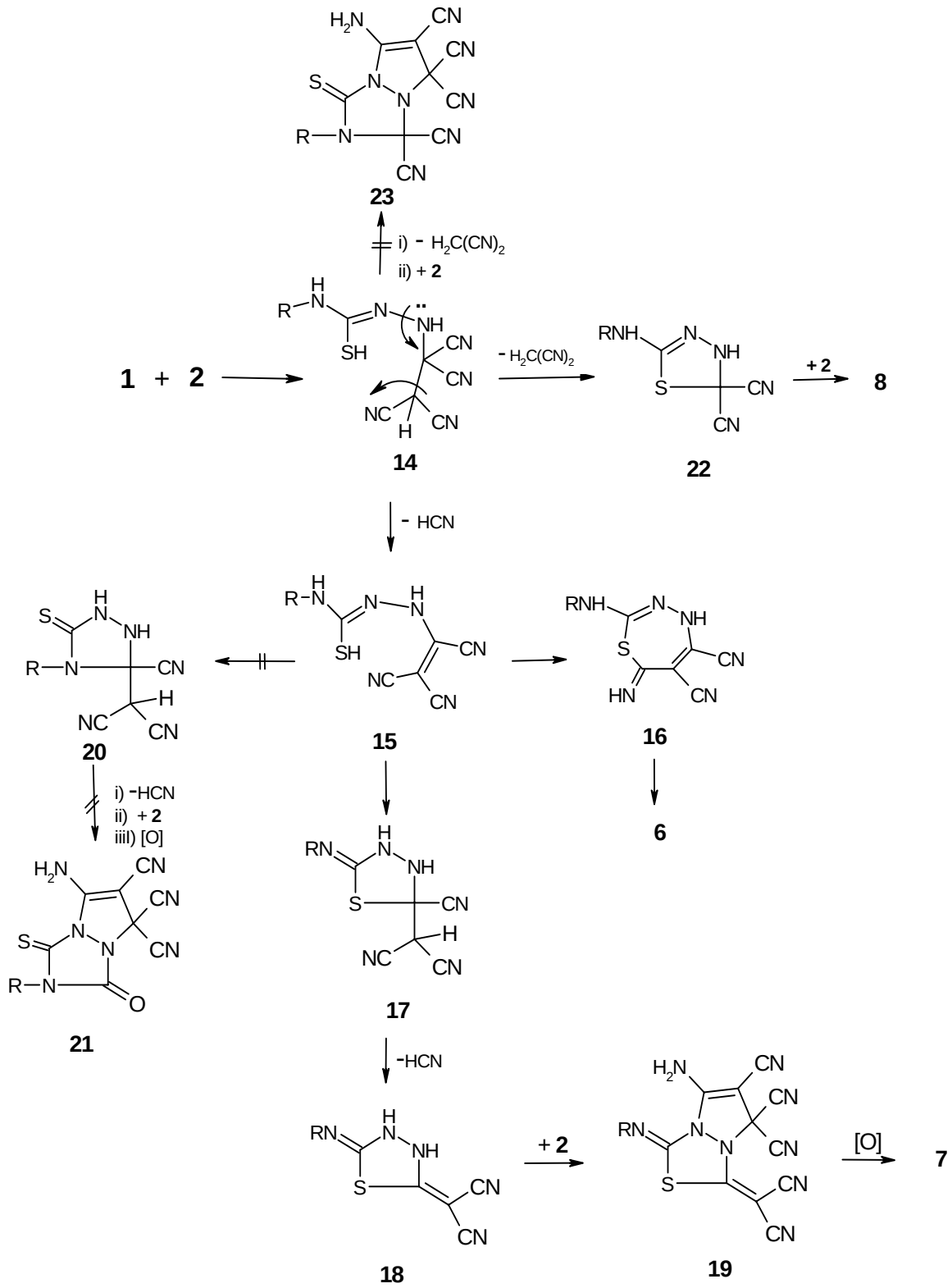


Figure 3. The alternative structures for compound **6** and the fragment ions in the mass spectrum of **6a**

Compounds **8a–c** show a characteristic red color. The gross formula, $C_{16}H_7N_9S$, 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 δ = 70.63 and 43.50 ppm respectively; further peaks are at δ = 153.60 (C-7), 162.80 (C-1) and for cyano groups at δ = 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.

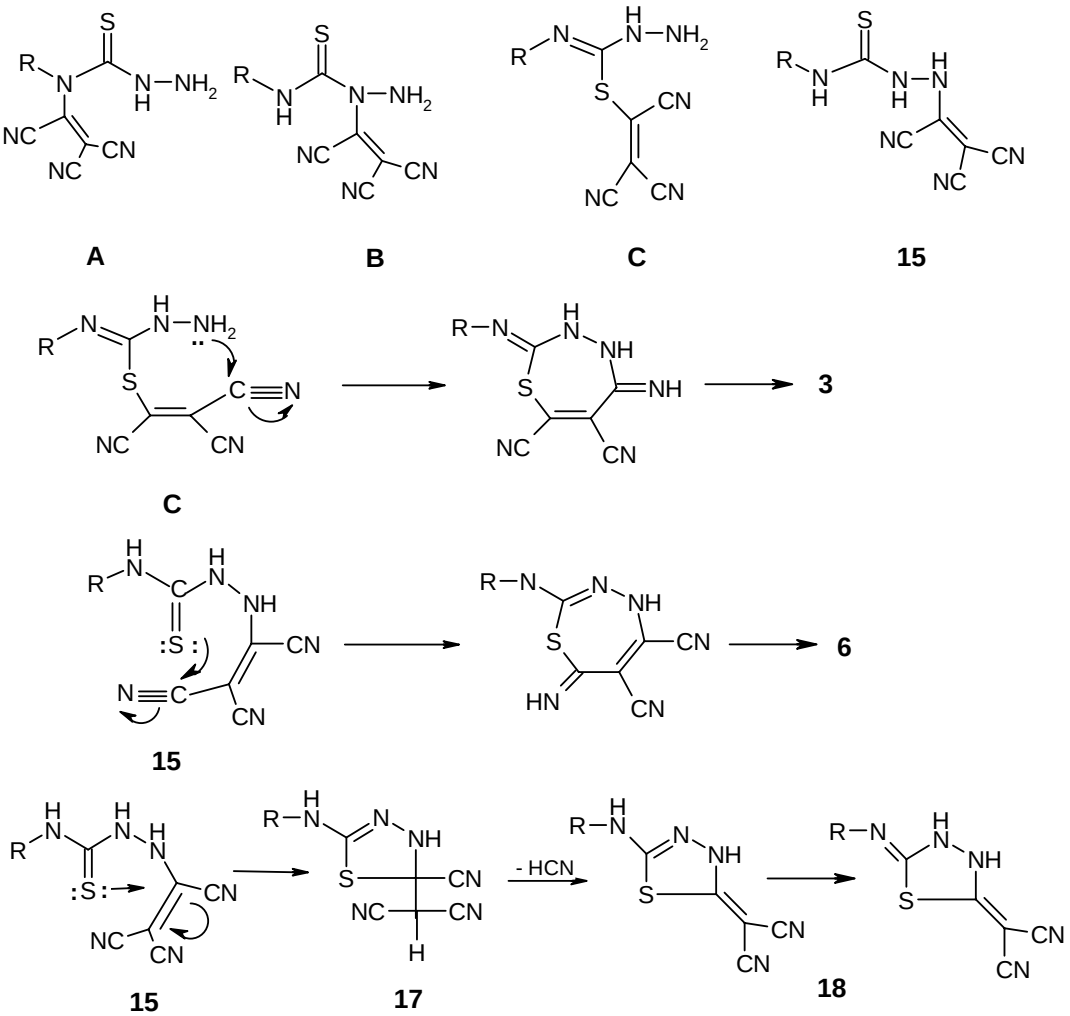
The results of combustion analysis and spectroscopic data suggested the presence of 3-amino-1*H*-pyrazole-4,5-dicarbonitrile (**9**) as a precipitate from the reaction between **1c** and **2**. The structure of **9** was confirmed by comparison with an authentic sample.[23,24] When hydrazine hydrate 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**

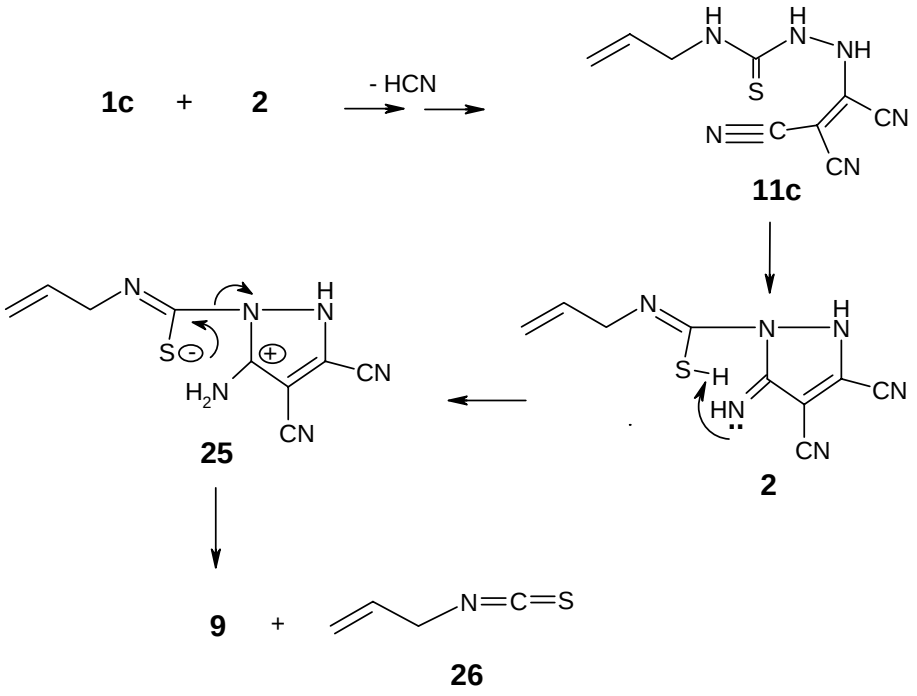
The formation of unusual products such as **6–9** (see Figure 2) is not easily rationalized. Since the reactions require a multitude of steps and are, by necessity, very complex, the moderate yields found (based throughout on the amount of starting material used, see Figure 2) are acceptable, and it 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,[22] 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** →**24** →**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 mmoles 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 ^{o}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^{o} C. IR; ν_{max} (KBr) cm^{-1} 3350–3280 (NH, NH_2), 2230 (CN), 1625 (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 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-2), 166.24 (C-5). MS; *m/z* (%) 268 (M^+, 19), 150 (22), 135 (81), 118 (100), 91 (92), 77 (91), 66 (58). Anal. Calcd. for $C_{12}H_8N_6S$: 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 ^{o}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 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 $C_{13}H_{10}N_6S$: 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 ^{o}C. UV–Vis; λ_{max} (acetonitrile) 486 nm, log ε = 5.494. IR; ν_{max} (KBr) cm^{-1} 3315 (NH_2), 2229, 2202 (CN), 1655 (CO), 1580 (aryl). ^{1}H-NMR (DMSO-d_6): δ 7.25 (s, 2H, NH_2), 7.45–7.65 (m, 5H, aryl); ^{13}C-NMR (DMSO-d_6): δ 47.54 (C-6), 68.93 (C-5), 117.20, 119.23, 119,80 (CN), 113.12, 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 $C_{14}H_7N_7SO$: 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 ^{o}C. UV–Vis; λ_{max} (acetonitrile) 482 nm, log ε= 5.509. IR; ν_{max} (KBr) cm^{-1} 3320 (NH_2), 2890 (CH_2), 2210 (CN), 1658 (CO), 1583 (aryl). ^{1}H-NMR (DMSO-d_6); δ 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 $C_{15}H_9N_7SO$: 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 ^{o}C. UV–Vis; λ_{max} (acetonitrile) 478 nm, log ε= 5.435. IR; ν_{max} (KBr) cm^{-1} 3325 (NH_2), 2220, (CN), 1660 (CO). ^{1}H-NMR (DMSO-d_6); δ 4.70 (s, 2H, CH_2N), 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 $C_{11}H_7N_7SO$: 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, 24%), mp 347–349 ^{o}C. UV/Vis; λ_{max} (acetonitrile) 536 nm, log ε = 5.583. IR; ν_{max} cm^{-1} 3365 (NH_2), 2227, (CN), 1638 (aryl). ^{1}H-NMR (DMSO-d_6); δ 7.05 (s, 2H, NH_2), 7.25–7.70 (m, 5H, aryl). ^{13}C-NMR (DMSO-d_6); δ 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 $C_{16}H_7N_9S$: 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 ^{o}C. UV–Vis; λ_{max} (acetonitrile) 531 nm, log ε = 5.596; IR; ν_{max} cm^{-1} 3360 (NH_2), 2966 (CH_2), 2220, (CN), 1635 (aryl). ^{1}H-NMR (DMSO-d_6); δ 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 $C_{17}H_9N_9S$; 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 ^{o}C. UV–Vis; λ_{max} (acetonitrile) 524 nm, log ε = 5.524. IR; ν_{max} cm^{-1} 3335 (NH_2), 2207, (CN), 1635 (aryl). ^{1}H-NMR (DMSO-d_6); δ 4.60 (m, 2H, CH_2N), 5.25 (m, 2H, = CH_2), 5.90 (m, 1H, CH), 7.55 (s, 2H, NH_2).^{13}C-NMR (DMSO-d_6); δ 54.40 (CH_2N), 69.66 (C-6), 43.12 (C-5), 90.62, 91.14, 91.70, 93.25 (CN), 117.70

(=CH_2), 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 $C_{13}H_7N_9S$; 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- 1*H*-pyrazole-4,5-dicarbonitrile (9). Yield 32 mg (24 %) mp 250–252 ^oC (dec.) (lit.[24] 250 ^oC).

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