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Reactivity of *N*-substituted alkenylidene hydrazinecarbothioamides towards tetraccyanoacetylene and An efficient synthesis stereoselective 1,3-thiazole compounds

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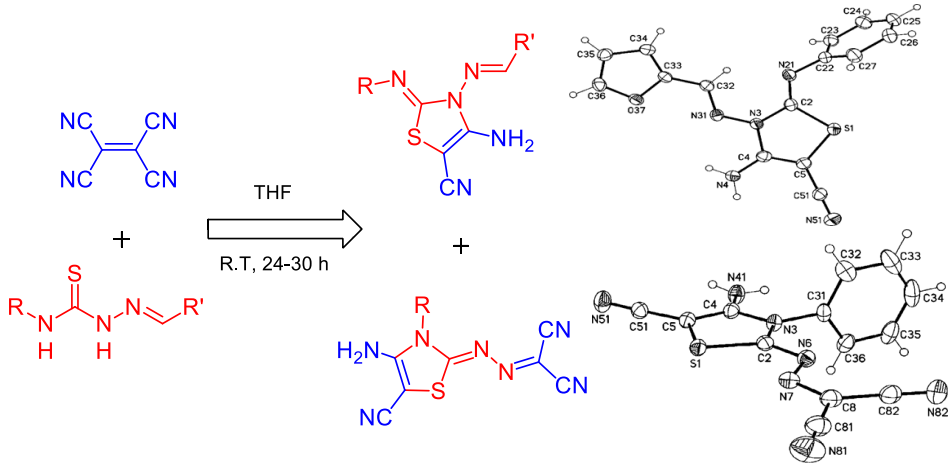
Abstract:

The reaction between *N*-substituted alkenylidene hydrazinecarbothioamides and two molar amounts of ethene-1,1,2,2-tetracarbonitrile (TCNE) in anhydrous THF at room temperature without using any catalyst affords (*Z*)-4-amino-3-(substituted amino)-2-(substituted imino)-2,3-dihydrothiazole-5-carbonitrile and (*Z*)-(4-amino-5-cyano-3-substitued thiazol-2(3*H*)-ylidene)carbonohydrazonoyl dicyanide. Rationales for these transformations are presented. The structures of the obtained products were confirmed *via* single crystal X-ray analyses.

Graphical Abstract



Keywords

N-substituted alkenylidene hydrazinecarbothioamides, ethene-1,1,2,2-tetracarbonitrile; stereoselective 1,3-thiazole derivatives; Donor-acceptor interaction; X-ray crystallography.

Introduction

S, N-containing heterocycles occupy a wide range of organic compounds among them thiazole derivatives which possess versatile biological activities such as anticancer [1, 2] anti-inflammatory [3] antioxidant [4] antimicrobial[5, 6]. Mycobacterium tuberculosis [7] antifungal [8] antiviral [9] and CNS active agents [10]. Besides, thiazole acetamides were synthesized and evaluated for in vitro acetylcholinesterase (AChE) inhibitory showing their usefulness in Alzheimer disease [11] The presence of thiazole nucleus in natural products was reported where it isolated from marine products exhibiting important biological applications [12].

Many synthetic routes were reported in the literature for synthesis, therapeutic and pharmacological importance of thiazole derivatives [13, 14]. Also, the interaction between α-halocarbonyl derivatives with dithiocarbamates afforded 4-substituted-2-(alkylsulfanyl)thiazoles,[15] the condensation of thiourea derivatives with various α-nitroepoxides gave trisubstituted thiazoles [16] and one-pot multi-component reaction of hydrazinecarbothioamide, chlorinated β-keto ester and aldehyde or ketone using anhydrous sodium acetate as catalyst yielded hydrazonothiazoles [17].

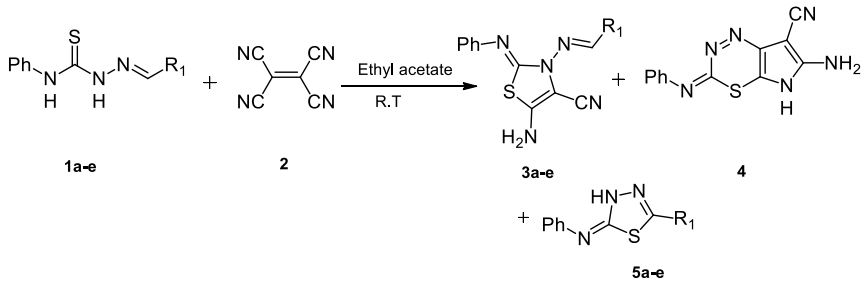
Hassan et al. have prepared several heterocyclic rings e.g. thiadiazole, thiadiazine, thiadiazepine and pyrazolidine derivatives from the reaction of ethene-1,1,2,2-tetracarbonitrile, (TCNE) with 2,4-disubstituted hydrazinecarbothioamides *via* elimination of different fragments [18].

It has been reported that TCNE was used as a useful reagent for the synthesis of (5-amino-2-substituted diazenylthiazollylmethylene)malononitrile derivatives *via* reacting with *N*-substituted hydrazinecarbothioamides [19]. Recently, Freese et al. [20] have investigated reductive 1,3-dipolar cycloaddition reactions of TCNE with (*Z*)-5-(benzoylimino)-3-phenyl-1,2,3-oxadiazolidin-2-ide afforded the corresponding *N*-benzoyl-3,4-dicyano-1-substituted-1*H*-pyrazole-5-carboxamides *via* unusual reaction mechanism. Also, different substituted ketoximes were cyclized to 2-amino-3,4-dicyanopyridines using TCNE and catalyzed by CuI [21].

N-Substituted alkenylidene hydrazinecarbothioamides are one of the best electron rich compounds affording different heterocyclic rings *via* reacting with various reagents e.g. 2,3-diphenylcyclopropen-2-enone [22, 23] dicyanomethylene-1,3-indanedione [24], 2,3-dichloronaphthoquinone [25],and dimethyl acetylenedicarboxylate [26].

Results and discussion

We have previously demonstrated that substituted thiosemicarbazones **1a-e** reacted with TCNE **2** in ethyl acetate at room temperature with the formation of (*Z*)-5-amino-3-((*E*)-substituted benzylideneamino)-2-(phenylimino)-2,3-dihydrothiazole-4-carbonitrile **3a-e**, (*E*)-6-amino-3-(phenylimino)-3,5-dihydropyrrolo[3,2-*e*][1,3,4]thiadiazine-7-carbonitrile **4** and (*E*)-*N*-(5-substituted-1,3,4-thiadiazol-2(3*H*)-ylidene)aniline **5a-e** (Scheme 1) [27]. Based on the above findings, we decided to investigate the behavior of other hydrazinecarbothioamides, namely *N*-substituted alkenylidene hydrazinecarbothioamides **6a-e** towards TCNE **2**.

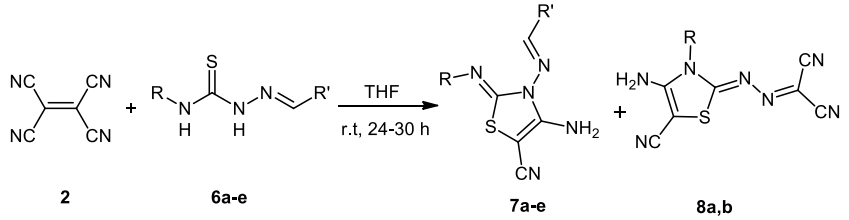


1,3,5: R ; **a** = C_6H_5, **b** = *p*-CH_3O-C_6H_5, **c** = *p*-Cl-C_6H_5, **d** = *p*-$(CH_3)_3$-C_6H_5, **e** = *p*-OH-C_6H_5

Scheme 1. Previous work on substituted thiosemicarbazones **1a-e** reacted with TCNE **2** in ethyl acetate.

Consequently, a solution of *N*-substituted alkenylidene hydrazinecarbothioamides **6a-e** was added to TCNE **2** solution where a red color of the solution was formed first which then readily converted to dark brown color. These changes in colors due to unstable charge transfer (CT) complexation followed by chemical reaction and formation of the products.

Treatment of **6a-e** with two molar equivalents of TCNE in dry tetrahydrofuran (THF at room temperature to afforded (*Z*)-4-amino-3-(substituted amino)-2-(substituted imino)-2,3-dihydrothiazole-5-carbonitrile **7a-e** and (*Z*)-(4-amino-5-cyano-3-substitued thiazol-2(3*H*)-ylidene)carbonohydrazonoyl dicyanide **8a,b** (Scheme 2).



Substrate	R	R'	Product, yield (%)	
6a	Phenyl	Butanyl	**7a** (63 %)	**8a** (33 %)
6b	Phenyl	Furanyl	**7b** (60 %)	**8a** (25 %)
6c	Phenyl	1-Hexenyl	**7c** (57 %)	**8a** (30 %)
6d	Cyclohexyl	Pentanyl	**7d** (58%)	**8b** (26 %)
6e	Cyclohexyl	1-Hexeneyl	**7e** (55%)	**8b** (35 %)

Scheme 2. The reaction of alkenylidene hydrazinecarbothioamides **6a-e** with TCNE **2**.

Therefore, the optimized reaction conditions involved mixing one mole of alkenylidene hydrazinecarbothioamides with two equivalents of TCNE at room temperature in dry THF. The solvent, temperature and molar ratio of the reactants may all play a critical role in the reaction pathway. These variables were investigated. Different solvents such as acetonitrile, 1,2-dichloroethane, 1,4-dioxane were studied, but THF proved to be the best. Increasing the amount of **6a-e** wasn't necessary to obtain high yields of products **7a-e** and **8a,b**.

High product yields were obtained at room temperature and in the presence of air where trace amounts of products were formed when the reactions were performed under nitrogen or argon.

The mixture was stirred at room temperature then left to stand for 24-30 hrs showing consuming all the starting materials and formation of the products. The reaction mixture was concentrated and then subjected to chromatographic separation to give numerous zones among them, (*Z*)-4-amino-3-(substituted amino)-2-(substituted imino)-2,3-dihydrothiazole-5-carbonitrile **7a-e** and (*Z*)-(4-amino-5-cyano-3-substitued thiazol-2(3*H*)-ylidene)carbonhydrazonoyl dicyanide **8a-e** were obtained in 55-63 % and 25-35 % yield, respectively (Scheme 2).

Several nucleophilic sites on *N*-substituted alkenylidene hydrazinecarbothioamides **6a-e** i.e. sulphur atom, ^{1}*N*H, ^{3}*N*H and ^{4}*N*=CH were expected to react with different electrophilic sites in TCNE (C=C and four nitrile groups). All of these nucleophillic sites were participated with different π-electron acceptors to afford the products [22-26] .This was attributed to the nature of electrophilic sites on selected π-electron acceptor with *N*-substituted alkenylidene hydrazinecarbothioamides.

The structure of the obtained products was delineated from their spectroscopic data as follows: The IR spectrum of compound **7b** showed, a broad band at 3345 cm^{-1} relating to the NH_2 group, sharp bands at 2184 and 1650 cm^{-1}, characteristic of nitrile and C=N groups, respectively. Two absorption bands were also observed due to the presence of Ar-CH at 3155 and (Ar-C=C) at 1613 cm^{-1}.

The elemental analysis and mass spectrum of **7b** suggested a gross formula of $C_{15}H_{11}N_5OS$, which was corresponding to a molecular ion peak at *m/z* = 309 (25%). Thus, the proposed structure is in agreement with the addition of one molecule of **2** to one molecule of **6b** with the elimination of a molecule of malononitrile ($CH_2(CN)_2$). The proton spectrum of **7b** consists of a mono substituted phenyl system, another three-spin system, and a sharp singlet downfield at δ_H 10.06. The phenyl 2H doublet, 2H triplet, and 1H triplet are distinctive at δ_H 7.03 (H-*o*), 7.39 (H-*m*), and 7.15 (H-*p*) respectively, their attached carbons appear at δ_C 120.71 (C-*o*), 129.64 (C-*m*), and 124.49 (C-*p*) (Table 1). H-*o* gives HMBC correlation with one of the two carbons at δ_C 148.94 and 148.66, and one of the two at δ_C 151.39 and 151.25; these are assigned as C-2 (downfield) and C-*i* (upfield). Also, H-*o* correlates with nitrogen at δ_N 247.1, assigned as N-2a. N-2a also gives HMBC correlation with the proton singlet at δ_H 10.06, H-3b; this is a five-bond correlation, which is surprising to observe. Five-bond N-H coupling constants are normally very small. H-3b gives HSQC correlation with a carbon at δ_C 145.17. HSQC correlation of H-3b with a carbon, and not with nitrogen, requires the compound be an imine not a secondary amide. H-3b also gives HMBC correlation with two other nitrogens, at δ_N 301.1 and 173.4. The more upfield nitrogen also gives HMBC correlation with the broad amino protons at δ_H 7.47, H-4a. H-4a also gives HSQC correlation with the sp^3 nitrogen at δ_N 70.2, assigned as N-4a. H-4a also gives HMBC correlation with the other of the two carbons at δ_C 151.39 and 151.25, assigned as C-4,

and with a carbon at δ_C 45.71, assigned as C-5. The upfield shift of this carbon stems from its position in a push-pull system. The nitrile carbon, C-5a at δ_C 115.62 gives no correlations. The nitrile nitrogen is five bonds from the nearest protons and is not observed. H-3b gives HMBC correlation with either C-2 or C-4 and with the other of the carbons at δ_C 148.94 and 148.66. Since this carbon is non-protonated, it is assigned as C-3c. H-3b also gives HMBC correlation with a carbon at δ_C 116.46, assigned as C-3d; its attached proton appears at δ_H 7.40. H-3d gives COSY correlation with a double-doublet, H-3e at δ_H = 6.74, besides its attached carbon appears at δ_C 112.80. Finally, H-3e also gives COSY correlation with a broad singlet, H-3f at δ_H 7.40 and its attached carbon appears at δ_C 116.46 (Table 1). The small coupling constants within this three-spin system are typical of furan (Fig. 1).

Table. **1**. NMR data of **7b.**

^{1}H NMR:	**^{1}H-^{1}H COSY:**	**Assignment:**
10.06 (s; 1H)		H-3b
7.99 (bs; 1H)	6.74	H-3f
7.47 (b; 2H)		H-4a
7.40 (bs; 1H)	6.74	H-3d
7.39 ("t", *J* = 7.7; 2H)	7.15, 7.03	H-*m*
7.15 (t, *J* = 7.4; 1H)	7.39, 7.03	H-*p*
7.03 (d, *J* = 8.0; 2H)	7.39, 7.15	H-*o*
6.74 (dd, *J* = 3.2, 1.6; 1H)	7.99, 7.40	H-3e

^{13}C NMR:	**HSQC:**	**HMBC:**	**Assignment:**
151.39, 151.25		10.06, 7.47, 7.03	C-2, 4
148.94, 148.66		10.06, 7.99, 7.40, 7.15, 7.03, 6.74	C-*i*, 3c
146.82	7.99	7.40, 6.74	C-3f
145.17	10.06	7.40	C-3b
129.64	7.39	7.39, 7.15	C-*m*
124.49	7.15	7.40, 7.03	C-*p*
120.71	7.03	7.40, 7.15, 7.03	C-*o*
116.46	7.40	10.06, 7.99, 6.74	C-3d
115.62			C-5a
112.80	6.74	7.99, 7.40	C-3e
45.71		7.47	C-5

^{15}N NMR:	**HSQC:**	**HMBC:**	**Assignment:**
301.1		10.06	N-3a
247.1		10.06, 7.03	N-2a
173.4		10.06, 7.47	N-3
70.2	7.47		N-4a

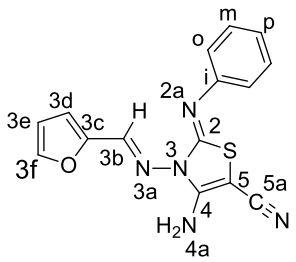


Fig. 1. Distinctive structure of **7b**.

Therefore, various mechanisms were discussed. ^{1}H-NMR and ^{13}C-NMR were used as an efficient tool for excluding some structures. Moreover, the correct structure of **7b** was resolved from single crystal X-ray analysis (Fig. 2). Specifically, compound (**7b**) crystallizes in the monoclinic space group $P2_1/c$ (no.14). The bond distance for C2-S1, C2-N3, N3-N31, C4-N4 and C5-C51 = 1.7727 (14) Å, 1.4016 (18) Å, 1.3833 (17) Å, 1.3350 (19) Å, 1.404 (2) Å, respectively; suggests that they have single bond characters but shorter than found for C-S, C-N, N-N and C-C; 1.82, 1.43 Å, 1.47 Å, 1.54 Å (literature value for the bond distances). The bond length of C4-C5 = 1.364 (2) Å is longer than literature value for the value for C=C (1.34 Å) bond distance and C2-N21, N31-C32 = 1.2703 (19) Å, 1.2876 (18) Å are shorter than corresponding literature value for the C=N (1.38 Å) bond distance. The bond length C51-N51 = 1.150 (2) Å and has C≡N (literature value for the 1.16 Å) triple bond character. The difference in bond length between some atoms in this molecule is due to high resonance in **7b**. ~~It was also observed that the sums of the angles around carbons of benzene ring are less or more than 360° showing the restrain of benzene ring.~~

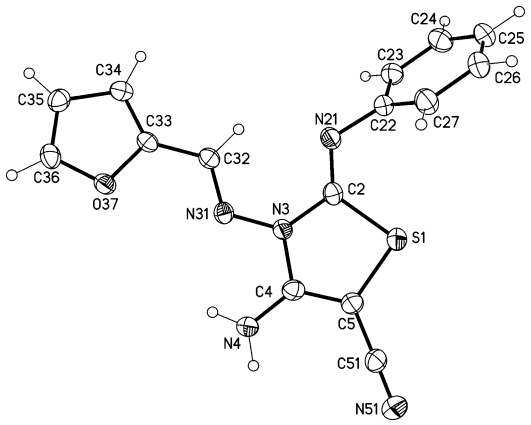


Fig. 2. Molecular structure of **7b** (displacement parameters are drawn at 50% probability level).

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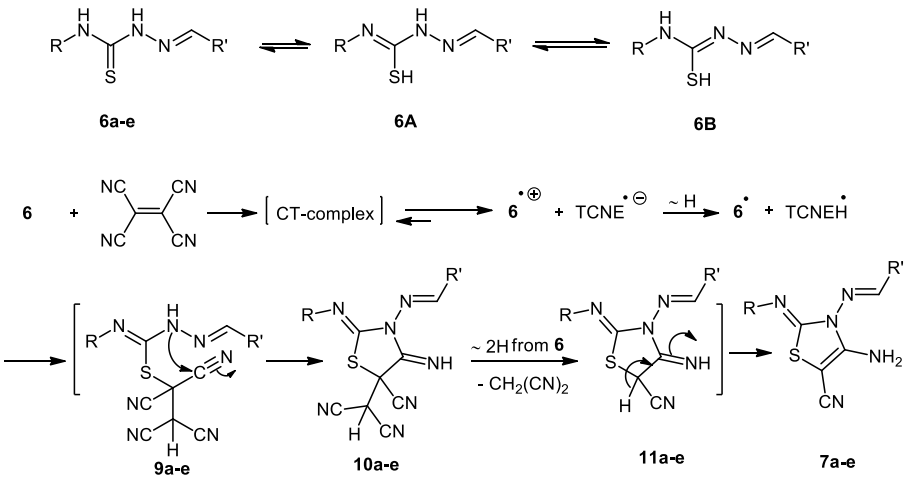
The formation of (*Z*)-4-amino-3-(substituted amino)-2-(substituted imino)-2,3-dihydrothiazole-5-carbonitrile **7a-e** was discussed as depicted in scheme 3. The attack of the SH group of **6a-e** on the C=C double bond of TCNE affords the intermediate **9a-e** which followed by another nucleophilic attack from ^{2}*N*H gives intermediate **10a-e**. The product (*Z*)-4-amino-3-(substituted amino)-2-(substituted imino)-2,3-dihydrothiazole-5-carbonitrile, **7a-e** was obtained *via* loss of a molecule of malononitrile from **10a-e** (Scheme 3).



Scheme 3. Mechanism displaying the formation of compound **7a-e**.

Interestingly, in addition to compounds **7a-e**, the result of combustion analysis, spectroscopic data as well as single crystal X-ray analysis suggests the presence of another novel compound, which was detected and identified as (*Z*)-(4-amino-5-cyano-3-substitued thiazol-2(3*H*)-ylidene)carbonohydrazonoyl dicyanide **8a,b**. The most significant spectroscopic properties of this compound are as follows: the IR spectra (KBr) of **8a** shows characteristic absorptions at 3310, 3177, 2228 and 2201, 1640 and 1578 cm^{-1} relating to NH_2, Ar-CH, CN, C=N and Ar-C=C, respectively. ^{1}H NMR also supports the presence of broad band at 7.45 ppm due to NH_2. The downfield shift of the NH_2 group may be due to intermolecular H-bonding between the NH_2 and the oxygen of 1,4-dioxane (the solvent of crystallization) (Fig. 3), as well as aromatic protons resonated from 7.54 to 7.61 ppm. ^{13}C NMR spectrum of this compound shows its characteristic bands where thiazole C4 and C5 resonated at 58.12 and 175.46 ppm were corresponding to carbon atoms in push-pull alkene system. Three cyano groups were observed, one resonated upfield at 113.09 and two symmetric resonated downfield at 113.29 ppm, and the carbon of <u>*C*</u>-$(CN)_2$ was observed at 98.98 ppm. The elemental analysis and mass spectrum of compound **8a** displayed $C_{13}H_7N_7S$ molecular formula and the molecular ion peak at *m/z* 293. However, the structure of **8a** was unambiguously confirmed from single crystal X-ray structure analysis (Fig 4). The bond length of C81-N81, C82-N82 and C51-N51 = 1.149 (3) Å, 1.143 (2) Å and 1.149 (2) Å, has C≡N (1.16 Å) a triple bond character. The bond length of C2-N6, C8-N7 = 1.329 (2) Å, 1.305 (2) Å which are shorter than the literature value for the C=N bond distance (1.38 Å). The bond length of C4-

C5 = 1.379 (2) and is longer than the literature value for the C=C bond distance (1.34 Å). The bond length of C-N varies from shorter in case of C4-N3 = 1.396 (2) Å and C2-N3 = 1.360 (2) Å to longer in case of C31-N3 = 1.454 (2) Å than the literature value for the C-N bond distance (1.43 Å). ~~The restrain of benzene and thiazole ring were observed at C31, C32, C34, C36 and C2, N3, C4 respectively.~~

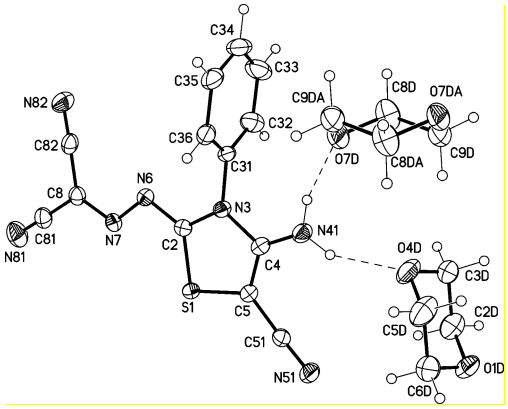


Fig.3. Structure of **8a** showing intermolecular H-bonding between the NH_2 and the oxygen of 1,4-dioxane (displacement parameters are drawn at 50% probability level).

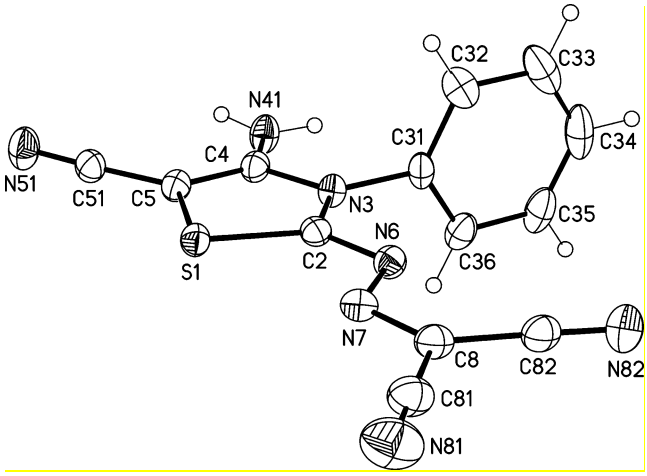


Fig.4. Molecular structure for **8a** (displacement parameters are drawn at 50% probability level).

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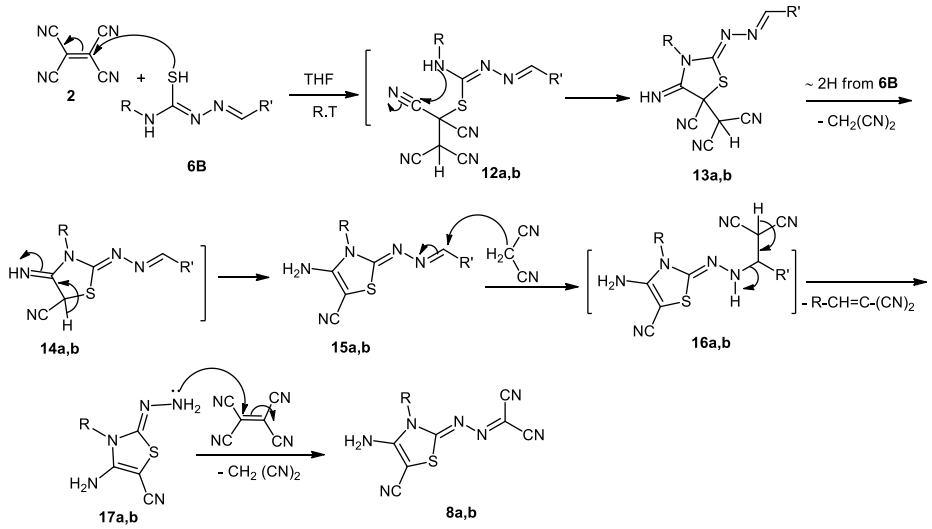
The mechanism describing the formation of compounds **8a,b** was discussed in scheme 4. Nucleophillic attack of SH of **6a-e** on C=C of **2** gives the intermediate **12a,b** which cyclizes *via* attack of ^{1}*N*H on cyano group to form **13a,b**. Loss of a molecule of malononitrile ($CH_2(CN)_2$) affords compounds **15a,b**. Reaction of **15a,b** with ($CH_2(CN)_2$) gives **16a,b** that converted to **17a,b** upon loss of substituted ylidene malononitrile (R-CH=C$(CN)_2$).

Another molecule of TCNE **2** reacted with lone pair of electron of NH_2 of **17a,b** and followed by elimination of malononitrile to afford the final product **8a,b** (Scheme 4).



Scheme 4. Plausible mechanism describing the formation of compound **8a,b**.

Experimental

Melting points (mp's) were recorded on a Gallenkamp melting point apparatus (Gallenkamp, UK), by using open capillaries and are uncorrected. NMR data were recorded on a Bruker AM 400 spectrophotometer (Germany), The ^{1}H-NMR (400.13 MHz) and ^{13}C-NMR (100.6 MHz). Chemical shifts were reported in ppm from tetramethylsilane using solvent resonance in $CDCl_3$ or DMSO-d_6 solutions as the internal standard. The ^{13}C-NMR signals were assigned based on DEPT 135/90 spectra. The mass spectra were obtained on Finnigan MAT 312) (Germany) instrument using electron impact ionization (70 eV). Elemental analyses were determined by using an Elemenatar 306. In addition, IR spectra were recorded on Bruker Alpha FT-IR instrument with samples prepared as potassium bromide pellets. Preparative layer chromatography (Plc) was made on 1.0 mm thick air-dried layers of slurry applied (Merck Pf_{254}) on 48 cm wide and 20 cm high glass plates, zones were visualized by ultraviolet (UV) light.

Starting materials

Various substituted alkenylidene hydrazinecarbothioamides **6a-e** were prepared by the reaction of 4-substituted hydrazinecarbothioamides with the proper aldehyde according to the published procedures in literature; **6b** [28] **6c** [29] and **6e** [24].

(*E*)-2-butylidene-*N*-phenylhydrazinecarbothioamide 6a

Yield: 1.19 g (86 %); colorless crystals (EtOH); mp: … °C.

IR (KBr): 3370 (NH), 3099 (Ar-CH), 2947 (Ali-CH), 1628 (C=N), 1605 (Ar-C=C), 1350, 975 (C=S and C–N str.) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (*t*, *J* = 7.63 Hz, 3H, CH_3), 1.49-1.53 (m, 2H, pentyl-CH_2), 1.65-1.69 (m. 2H, pentyl-CH_2), 7.17-7.18 (m,1H, Ar-H), 7.36-7.38 (m,2H, Ar-H), 7.60-7.63 (m,2H, Ar-H), 7.7 (s, 1H, CH=N), 8.4 (s, 1 H, phenyl-NH), 9.22 (br, 1H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.58 (CH_3), 22.15 (CH_2), 28.22 (CH_2), 124.10, 126.31, 129.22 (Ar-CH), 138.11 (Ar-C), 149.50 (CH=N), 179.00 (C=S).

Anal. Calcd for $C_{11}H_{15}N_3S$ (221.32): C, 59.69; H, 6.83; N, 18.99; S, 14.49. Found: C, 59.60; H, 9.89; N, 19.05; S, 14.57.

(*E*)-*N*-cyclohexyl-2-pentylidenehydrazinecarbothioamide 6d

Yield: 2.169 g (90 %); colorless crystals (EtOH); mp: 76-77 °C.

IR (KBr): 3352 (NH), 3062 (Ar-CH), 2957 (Ali-CH), 1637 (C=N), 1607 (Ar-C=C), 1358, 970 (C=S and C–N str.) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.61 Hz, 3H, CH_3), 1.20-1.25 (m, 2H, pentyl-CH_2), 1.36-1.39 (m. 2H, cyclohexyl-CH_2), 1.44-1. 46 (m, 2H, pentyl-CH_2), 1.65-1.67 (m. 4H, cyclohexyl-CH_2), 1.76-1.78 (m. 4H, cyclohexyl -CH_2), 2.10-2.12 (m, 2H, pentyl-CH_2), 2.25-2.28 (m. 2H, cyclohexyl -CH_2), 7.24 (s, 1H, CH=N), 7.64 (s, 1 H, cyclohexyl-NH), 9.98 (br, 1H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.58 (CH_3), 22.15 (CH_2), 27.50 (cyclohexyl-CH_2), 28.22 (CH_2), 30.71 (cyclohexyl-CH_2), 33.02 (CH_2), 34.33 (cyclohexyl-CH_2), 57.82 (cyclohexyl-CH), 146.98 (CH=N), 176.99 (C=S).

Anal. Calcd for $C_{12}H_{13}N_3S$ (241.40): C, 59.71; H, 9.60; N, 17.41; S, 13.28. Found: C, 59.61; H, 9.69; N, 17.48; S, 13.35.

Reaction of *N*-substituted alkenylidene hydrazinecarbothioamides with TCNE

General procedure: To a stirred solution of TCNE (ethene-1,1,2,2-tetracarbonitrile), (**2**, 2.0 mmol) in dry THF (20 mL) at room temperature, different *N*-alkenylidene hydrazinecarbothioamide derivatives (**6a-e**, 1.0 mmol) in dry THF (25 mL) were added to the former solution. The mixture was stirred for 6 hrs. The red color of the mixture was changed to a reddish brown after standing for 24-30 hrs at room temperature. TLC analysis showed consuming all the starting materials then the reaction mixture was concentrated to dryness and sublimed to remove any excess of TCNE then subjected to plc (chromatographic plates) where two different zones were separated using toluene/ EtOAc (10:8). The fast migrating zone containing compounds **8a,b** and the slowest migrating zone containing compound **7a-e**. Recrystallization of the products were achieved using different solvents such as 1,4-dioxane and ethanol.

(*Z*)-4-amino-3-((*E*)-butylideneamino)-2-(phenylimino)-2,3-dihydrothiazole-5-carbonitrile 7a

Yield: (0.179 g, 63 %); yellow crystals (ethanol); m.p: 180-181 °C.

IR (KBr): 3307 (NH_2), 3117 (Ar-CH), 2188 (CN), 1625 (C=N), 1600 (Ar-C=C) cm^{-1}.

^{1}H NMR & ^{13}C NMR (see table 1 and fig.1)

MS: *m/z* (%) = 285 (M^+, 17), 217 (5), 176 (21), 153 (100), 136 (65), 107 (18).

Anal. Calcd. for $C_{14}H_{15}N_5S$ (285.37): C, 58.92; H, 5.30; N, 24.54; S, 11.24. Found: C, 58.98; H, 5.22; N, 24.60; S, 11.32.

(*Z*)-4-amino-3-((*E*)-(furan-2-ylmethylene)amino)-2-(phenylimino)-2,3-dihydrothiazole-5-carbonitrile 7b

Yield: (0.185g, 60 %); yellow crystals (ethanol); m.p.: 199-200 °C.

IR (KBr): 3345 (NH_2), 3121 (Ar-CH), 2184 (CN), 1650 (C=N), 1613 (Ar-C=C) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ_H = 6.74 (*dd*, 1H, furan-H4, *J* = 3.2), 7.03 (*d*, 2H, Ar-H, *J* = 8.0), 7.15 (*t*, 1H, Ar-H, *J* = 7.4), 7.39 (*t*, 2H, Ar-H, *J* = 7.7), 7.40 (bs, 1H, furan-H3), 7.47 (br, 2H, NH_2), 7.99 (s, 1H, furan-H5),10.06 (s,1H, CH=N).

^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 45.71 (thiazole-C5), 112.80 (furan-C4), 116.46 (furan-C3), 116.62 (CN), 120.71, 124.49, 129.64 (Ar-CH), 145.17 (CH=N), 148.62 (furan-C5), 148.66, 148.94 (Ar-C), 151.39 (thiazole-C_2), 151.25 (thiazole-C4).

MS: *m/z* (%) = 309 (M^+, 25), 215 (8), 152 (100), 136 (68), 135 (62), 106 (17).

Anal. Calcd. for $C_{15}H_{11}N_5OS$ (309.35): C, 58.24; H, 3.58; N, 22.64; S, 10.37. Found: C, 58.28; H, 3.64; N, 22.60; S, 10.31.

(*Z*)-4-amino-3-((*E*)-((*E*)-hex-2-en-1-ylidene)amino)-2-(phenylimino)-2,3-dihydrothiazole-5-carbonitrile 7c

Yield: (0.177g, 57 %); yellow crystals (ethanol); mp: 205-207 °C.

IR (KBr): 3329 (NH_2), 3111 (Ar-CH), 2963 (Ali-CH), 2195 (CN), 1635 (C=N), 1604 (Ar-C=C) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ_H = 0.96 (*t*, 3H, CH_3, *J* = 7.65), 1.50 (m, 2H, CH_2), 2.24 (m, 2H, CH_2), 6.34 (*d*, 1H, CH=CH, *J* = 15.9), 6.64 (d, 1H, CH=CH, *J* = 15.7), 7.02 (m, 1H, Ar-CH), 7.36 (m, 2H, Ar-CH), 7.64 (m, 2H, Ar-CH), 7.55 (br, 2H, NH_2), 10.44 (s,1H, CH=N).

^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 13.54 (CH_3), 21.31 (CH_2), 34.29 (CH_2), 47.51 (thiazole-C5), 111.90, 117.42 (CH=CH), 116.42 (CN), 121.07, 121.91, 129.05 (Ar-CH), 139.68 (Ar-C), 146.32 (CH=N), 153.56 (thiazole-C_2), 162.48 (thiazole-C4).

MS: *m/z* (%) = 311 (M^+, 5), 246 (5), 174 (10), 153 (100), 136 (67), 107 (22).

Anal. Calcd. for $C_{16}H_{17}N_5S$ (311.40): C, 61.71; H, 5.50; N, 22.49; S, 10.30. Found: C, 61.68; H, 5.48; N, 22.54; S, 10.35.

(Z)-4-amino-2-(cyclohexylimino)-3-((*E*)-pentylideneamino)-2,3-dihydrothiazole-5-carbonitrile 7d

Yield: (0.176g, 58 %); yellow crystals (ethanol); m.p.: 244-246°C.

IR (KBr): 3320 (NH_2), 3130 (Ar-CH), 2950 (Ali-CH), 2018 (CN), 1640 (C=N), 1606 (Ar-C=C) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ_H = 0.93 (*t*, 3H, CH_3), 1.23 (m, 2H, CH_2), 1.21 (m, 2H, CH_2), 1.39 (m, 2H, cyclic-CH_2), 1.56 (m, 2H, CH_2), 1.74 (m, 4H, cyclic-CH_2), 2.0 (m, 4H, cyclic-CH_2), 2.33 (m, 1H, cyclic-CH), 7.50 (br, 2H, NH_2), 10.23 (s,1H, CH=N).

^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 13.44 (CH_3), 21.11 (CH_2), 24.12 (CH_2), 24.32, 28.95, 29.40 (cyclic-CH_2), 30.46 (CH_2), 48.00 (thiazole-C5), 62.81 (cyclic-CH), 115.10 (CN), 145.05 (CH=N), 151.96 (thiazole-C_2), 165.12 (thiazole-C4).

MS: *m/z* (%) = 305 (M^+, 25), 290 (25), 155 (28), 152 (100), 136 (70), 138 (30), 107 (21).

Anal. Calcd. for $C_{16}H_{23}N_5S$ (305.44): C, 58.98; H, 7.59; N, 22.93; S, 10.50. Found: C, 58.94; H, 7.55; N, 23.00; S, 10.57.

(*Z*)-4-amino-2-(cyclohexylimino)-3-((*E*)-((*E*)-hex-2-en-1-ylidene)amino)-2,3-dihydrothia-zole-5-carbonitrile 7e

Yield: (0.174g, 55 %); yellow crystals (ethanol); m.p.: 225-227 °C.

IR (KBr): 3315 (NH_2), 3143 (Ar-CH), 2970 (Ali-CH), 2193 (CN), 1620 (C=N), 1610 (Ar-C=C) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ_H = 0.94 (*t*, 3H, CH_3, *J* = 7.63), 1.41 (m, 2H, cyclic-CH_2), 1.57 (m, 2H, CH_2), 1.79 (m, 4H, cyclic-CH_2), 1.90 (m, 4H, cyclic-CH_2), 2.26 (m, 2H, CH_2), 2.35 (m, 1H, CH_2, cyclic-CH), 6.43 (m, 2H, CH=CH), 7.60 (br, 2H, NH_2), 10.30 (s,1H, CH=N).

^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 14.20 (CH_3), 22.42 (CH_2), 25.5, 28.6, 29.55 (cyclic-CH_2), 33.50 (CH_2), 46.58 (thiazole-C5), 60.95 (cyclic-CH), 111.90, 117.33 (CH=CH), 116.22 (CN), 147.11 (CH=N), 152.70 (thiazole-C_2), 163.55 (thiazole-C4).

MS: *m/z* (%) = 317 (M^+, 9), 179 (15), 153 (100), 141 (25), 138 (30), 107 (22).

Anal. Calcd. for $C_{16}H_{23}N_5S$ (317.45): C, 60.54; H, 7.30; N, 22.06; S, 10.10.. Found: C, 60.60; H, 7.28; N, 22.00; S, 10.17.

(*Z*)-(4-amino-5-cyano-3-phenylthiazol-2(3*H*)-ylidene)carbonohydrazonoyldicyanide 8a

Yield: (0.096 g, 33%); orange crystals (1,4-dioxane); m.p.: 167-168 °C.

IR (KBr): 3310 (NH_2), 3150 (Ar-CH), 2228, 2201 (CN), 1640 (C=N), 1578 (Ar-C=C) cm^{-1}.

^1H NMR (400 MHz, DMSO-d6): δH = 7.54-7.56 (m, 3H, Ar-H), 7.59-7.61 (m, 2H, Ar-H), 7.45 (br, 2H, NH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 58.12 (thiazole-C5), 98.98 (*C*-$(CN)_2$), 113.09, 113.29 (CN), 128.23, 129.92, 130.66 (Ar-CH), 132.84 (Ar-C), 153.66 (thiazole-C2), 175.46 (thiazole-C4).

MS: *m/z* (%) = 293 (M^+, 8), 231 (34), 216 (13), 154 (34), 149 (100), 136 (32), 107 (15).

Anal. Calcd. for $C_{13}H_7N_7S$ (293.31): C, 53.23; H, 2.41; N, 33.43; S, 10.93. Found: C, 53.31; H, 2.50; N, 33.32; S, 10.84.

(Z)-(4-amino-5-cyano-3-cyclohexylthiazol-2(3*H*)-ylidene)carbonohydrazonoyl dicyanide 8b

Yield: (0.077 g, 26 %); 0.104 g, 35%); reddish brown crystals (1,4-dioxane); m.p.: 189-190 °C.

IR (KBr): 3340 (NH_2), 2928 (Ar-CH), 2244, 2225 (CN), 1630 (C=N), 1561 (Ar-C=C) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ_H = 1.30-1.32 (m, 2H, cyclic-CH_2), 1.74-1.76 (m, 4H, cyclic-CH_2), 1.90-1.92 (m, 4H, cyclic-CH_2), 2.25-2.26 (m, 1H, cyclic-CH), 7.60 (br, 2H, NH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 27.81, 31.15, 36.09 (cyclic-CH_2), 57.62 (thiazole-C5), 60.11 (cyclic-CH), 99.01 (*C*-$(CN)_2$), 114.51, 115.86 (CN), 155.50 (thiazole-C4), 173.40 (thiazole-C_2).

MS: *m/z* (%) = 299 (M^+, 6), 273 (44), 216 (32), 177 (49), 154 (21), 149 (100), 136 (19), 107 (13).

Anal. Calcd. for $C_{13}H_{13}N_7S$ (299.35): C, 52.16; H, 4.38; N, 32.75; S, 10.71. Found: C, 52.29; H, 4.48; N, 32.84; S, 10.83.

Single Crystal X-ray Structure Determination of 7b and 8a

A single crystal of **7b** was obtained by recrystallization from ethanol, a single crystal of **8a** was obtained by recrystallization from 1,4-dioxane. The single-crystal X-ray analyses were carried out on a Bruker D8 Venture diffractometer with Photon II CPAD detector at 123K using Cu-Kα radiation (λ = 1.54178 Å). Dual Space Methods (SHELXT [30]) were used for structure solution and refinement was carried out using SHELXL-2014 (full-matrix

least-squares on F^2) [31]. Hydrogen atoms were localized by difference electron density synthesis and refined using a riding model (H (N) free). Semi-empirical absorption corrections were applied.

Compound 7b: $C_{15}H_{11}N_5OS$, Mr = 309.35 g mol^{-1}, yellow plates, size 0.20 × 0.06 × 0.02 mm, monoclinic, space group $P2_1/c$ (no.14), a = 14.9554 (6) Å, b = 4.2289 (2) Å, c = 22.4278 (9) Å, β = 92.996 (2)°, V = 1416.50 (10) $Å^3$, Z = 4, D_{calcd} = 1.451 Mg m^{-3}, F (000) = 640, μ (Cu-Kα) = 2.12 mm^{-1}, T = 123 K, 23888 measured reflections ($2\theta_{max}$ = 144.6 °), 2785 independent reflections [R_{int} = 0.034], 205 parameters, 2 restraints, R_1 [for 2601 I › 2σ (I)] = 0.033, wR^2 (for all data) = 0.089, S = 1.03, largest diff. peak and hole = 0.38 e $Å^{-3}$/- 0.24 e $Å^{-3}$.

Compound 8a: $C_{13}H_7N_7S \cdot 1.5(C_4H_8O_2)$, Mr = 425.47 g mol^{-1}, red plates, size 0.10 × 0.04 × 0.02 mm, monoclinic, space group $P2_1/n$ (no.14), a = 6.7850 (3) Å, b = 14.6393 (7) Å, c = 21.0620 (10) Å, β = 91.147 (2)°, V = 2091.62 (17) $Å^3$, Z = 4, D_{calcd} = 1.351 Mg m^{-3}, F (000) = 888, μ (Cu-Kα) = 1.69 mm^{-1}, T = 123 K, 21063 measured reflections ($2\theta_{max}$= 144.8 °), 4075 independent reflections [R_{int} = 0.055], 277 parameters, 2 restraints R_1 [for 3366 I › 2σ (I)] = 0.039, wR^2 (for all data) = 0.091, S = 1.03, largest diff. peak and hole = 0.32 e $Å^{-3}$/- 0.26 e $Å^{-3}$.

CCDC 1951940 (**7b**), and 1951941 (**8a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Conclusion

In conclusion, novel (*Z*)-4-amino-3-(substituted amino)-2-(substituted imino)-2,3-dihydrothiazole-5-carbonitrile and (*Z*)-(4-amino-5-cyano-3-substitued thiazol-2(3*H*)-ylidene)carbonohydrazonoyl dicyanide have been synthesized through the nucleophillic addition reactions of *N*-substituted alkenylidene hydrazinecarbothioamides on ethene-1,1,2,2-tetracarbonitrile. TCNE reacting as building block gave the obtained products in good yields without any prior activation. Different nucleophillic sites on hydrazinecarbothioamides were expected to participate in heterocyclization and formation of the products.

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