Facile synthesis of 4-phenyl-6-[(*Z*)phenylimino]-3,6-dihydro-1,3,5-thiadiazine-2,2-dicarbonitriles

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N-Imidoylthioureas **2a–e** reacted with 1,1,2,2-tetracyanoethylene (**1**) to form the thiadiazines **3a–e**. In the case of **1e**, tricyanovinylation of a phenyl substituent accompanied formation of the thiadiazine ring.

Keywords: *N*-Imidoylthioureas, 1,1,2,2,-tetracyanoethylene, thiadiazines

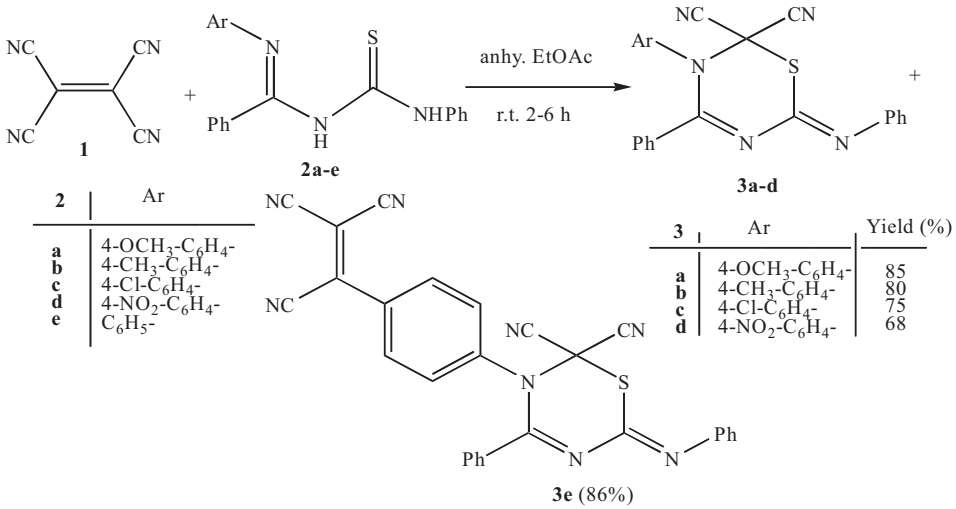
N-Imidoylthioureas having four nucleophilic centres, have been the subject of few studies in heterocyclic synthesis.[1,2] Cyanovinylated products resulting from the reactions of aromatic amines with 1,1,2,2-tetracyanoethylene (TCNE) are known as second-order optically non-linear compounds.[3,4] The rationale is that chromophores comprising an electron donor (D) linked to an electron acceptor (A) by means of a conjugated π-electron system have nonlinear optical activities. Some time ago, we reported anomalous behaviour of 4-amino [2.2]paracyclophane and its *N*-methyl derivative towards TCNE and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), that gave unexpected products such as 2-(4-[2.2]-paracyclophanyl)-3,3-dicyanoaziridine, 4-(*N*-carbonitrile-*N*-ethyl)-amino[2.2]-paracyclophane, and 2,3-dichloro-5-cyano-6-([2.2]-paracyclophanyl)-amino-1,4-benzoquinone.[5] We also isolated cyanovinylated products during the reaction of TCNE with 1,8-diaminonaphthalene.[6] Moreover, we succeeded in the syntheses of many heterophanes,[7,8] in addition to our synthesis of 1,4-benzoxazepines from 4-arylidene-2-phenyl-1,3-oxazol-5(4*H*)-ones and benzyne *via* [2π + 2π] cycloaddition.[9] Subsequently, we synthesised heterocycles, which have proved anticancer activities.[10] Synthesis of heterocycles containing sulfur and nitrogen heteroatoms has shed still more light in heterocyclic chemistry.[11-13] Rees reported that 4-dicyanomethylene-1,2,6-thiadiazine was obtained from the reaction of tetracyanoethylene with SCl_2.[14] In literature, four classes of TCNE-derivative heterocycles can be identified: (i) reaction products obtained by nucleophilic attack on tetracyanocyclopropenes which, in turn, are formed from the reaction of TCNE with aliphatic monobromides; (ii) products resulting from interconversion of unstable charge-transfer compounds of TCNE and an electron-donor; (iii) Diels–Alder cycloadducts between TCNE and a diene; and (iv) products derived from previously unknown reactions of TCNE. Since we have long experience in the synthesis of heterocycles *via* donor–acceptor interactions,[5-7] we were encouraged to investigate the reaction of *N*-imidoyl–thioureas **2a–e** with tetracyanoethylene (TCNE, **1**; Scheme 1).

Results and discussion

We chose *N*-imidoylthioureas **2a–e** having aryl groups with electron donating and withdrawing substituents on the benzene ring, in order to examine their effect on the course of reaction. The reaction of **2a–e** with **1** was carried out in dry ethyl acetate at room temperature. Addition of **2a–e** as electron donors to electron acceptor **1** in dichloromethane at room temperature led to complex formation characterised by CT-bands in the visible region (Table 1). These CT-complexes gradually disappeared to give the precipitated reaction products. Presumably, the CT-complexes are transient intermediates. The reaction time and the λ_{max} of the CT-complexes of **2a–e** with **1** are given in Table 1. Treatment of compounds **2a–e** with **1**, under the conditions just described, afforded compounds **3a–e** in 85–68% yields

Table 1 Reaction time and absorption maxim for the CT-complexes of **1** towards **2a–e** in dichloromethane at 25°C

Donor	λ_{max}/nm	Reaction time/h
2a	500	2
2b	470	3
2c	430	5
2d	400	6
2e	482	4.5



Scheme 1 Reaction of TCNE **1** with N-imidoylthioureas **2a–e**.

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(Scheme 1). The assigned structures of **3a–e** are supported by mass, ^{1}H NMR, ^{13}C NMR and IR spectra as well as elemental analyses. For example, compound **3a** was obtained as deep red plates with a strong UV absorption band (λ_{max} 450 nm, log ε 4.00). Mass spectroscopy and elemental analysis proved the molecular formula of **3a** as $C_{24}H_{17}N_5OS$. The IR spectrum of **3a–e** did not show any absorptions due to NH– or C=S groups, whereas a strong band appeared at ν_{max} 2225–2210 cm^{-1} assigned to the nitrile group. The aromatic protons resonated in the ^{1}H NMR spectrum of **3a** as two double-doublets and four multiplets, assigned to the *p*-methoxyphenyl group and the two unsubstituted phenyl groups respectively. The ^{13}C NMR spectrum of **3a** supported the ^{1}H NMR spectroscopic data by the appearance only 12-carbon signals. Distinctive signals appeared at δ_C 50.1, 55.0, 138.9, 148.6, 150.0, 160.0, and 162.1 corresponding to *C*-2, *C*-29, *C*-9, *C*-22, *C*-12, *C*-4 and *C*-6, respectively. The COSY H–H and C–H spectra of **3a–e** indicated several distinctive δ's values, given in Fig. 1. Surprisingly on reaction of **1** with **2e**, the reaction proceeded completely to give the thiadiazine **3e** (Scheme 2), presumably formed by reaction of excess **1** with **2e**. The IR spectrum of compound **3e** showed nitrile absorption bands at ν_{max} 2220–2210 and 2228 cm^{-1}. The mass spectrum revealed a molecular ion peak at *m/z* 494 [M$^+$]. Moreover, the ^{13}C NMR spectrum revealed signals at δ_C 48.9, 97.4, 121.2, 140.6, 145.0, 149.6, 162.3, and 163.0 corresponding to *C*-2, [*C*(CN)$_2$ =], *C*-12, *C*-9, [*C*(CN) =], *C*-22, *C*-4 and *C*-6, respectively. More details are shown in Fig. 1. In the ^{1}H NMR spectrum of **3d,** the *p*-nitrophenyl group gave two double-doublets at δ_H 6.70 and 8.00 (J = 8.2, 1.2 Hz) related to H-10,12 and H-13,14, respectively. The reaction mechanism can be simply described as due to the existence of **2a–e** in three possible tautomeric forms that enhance the nucleophilicity of the SH and NH groups. Thus, nucleophilic attack of the SH group on the C-1 in **1** would form the intermediate **4a–e** (Scheme 2). Subsequently, further nucleophilic attack by the terminal NH functional group to the C-2 of the branched tetracyano-intermediate **4a–e,** was followed by elimination of a molecule of malononitrile (Scheme 2) to form **3a**–**d** and **5e**. Therefore, this step is described as an S_N2 at a highly congested centre. In case of the reaction between **1** and **2e,** another molecule of **1** was added to **5e** to give **3e**.

Experimental

All m.p.s were recorded on a Gallenkamp apparatus. ^{1}H NMR and ^{13}C NMR spectra (Bruker AM 400, ^{1}H: 400.13 MHz, ^{13}C: 100.6 MHz); s = singlet, d = doublet, dd = double-doublet and m = multiplet. The NMR samples were dissolved in DMSO-d_6 solutions. Coupling constants were expressed in Hz. Elemental analyses were carried at the Assiut Microanalysis Centre of Assiut University. Mass spectroscopy was performed with a Finnigan MAT 8430 spectrometer at 70 eV, Institute of Organic Chemistry, Technical University-Braunschweig, Germany. IR spectra were run on a Shimadzu 470 spectrometer using KBr pellets.

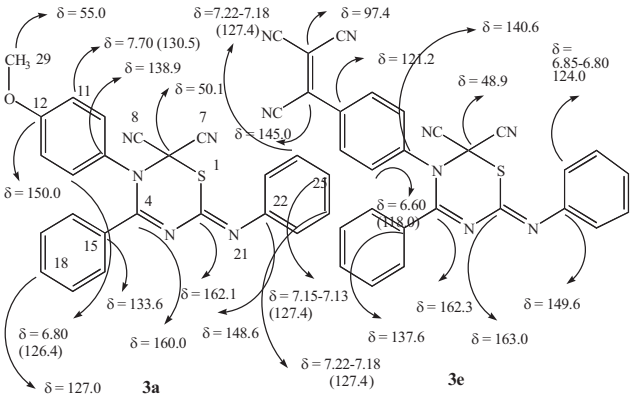


Figure 1 Distinctive δs values of compounds **3a** and **3e.**

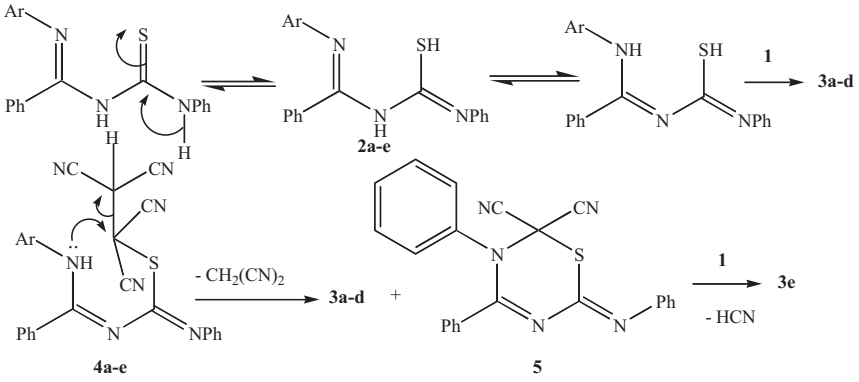
Starting materials: N-Imidoylthioureas **2a–e** were prepared according to ref 1.

General procedure

Into a 250 cm^3 two-necked round bottom flask containing a solution of **2a–e** (2 mmol) in ethyl acetate (50 ml), a solution of 4 mmol of **1** in ethyl acetate (20 ml) was added dropwise with stirring. The mixture was stirred at room temperature for 2–6 h (the reaction was monitored by TLC analyses). The solvent was evaporated under vacuum and the formed solid products were purified by dissolving in dry acetone (30 ml) and was subjected to preparative plate chromatography (silica gel), toluene:ethyl acetate (10:1). The obtained products were recrystallised from the stated solvents.

3-(4-Methoxyphenyl)-4-phenyl-6-[(Z)-phenylimino]-3,6-dihydro-1,3,5-thiadiazine-2,2-dicarbonitrile (**3a**): Compound **3a** was obtained as red crystals (0.72 g, 85%), m.p. 180°C (ethanol). ^{1}H NMR (DMSO-d_6): δ = 7.70 (dd, 2 H, J = 8.0, 1.2 Hz, H-11,13), 7.45–7.30 (m, 5 H, Ph-H), 7.22–7.18 (m, 2 H, H-24,26), 7.15–7.13 (m, 1 H, H-25), 6.80 (dd, 2 H, J = 8.0, 1.2 Hz, H-10,14), 7.11–7.08 (m, 2 H, H-23,27), 3.90 (s, 3 H, H-29). ^{13}C NMR: δ = 162.1 (*C*-6), 160.0 (*C*-4), 150.0 (*C*-12), 148.6 (*C*-22), 138.9 (*C*-9), 133.6 (*C*-15), 130.4 (*C*H-11,13), 129.2, 128.9, 127.8, (*C*H-17,19; 18; 23,27), 127.4 (*C*H-24,26), 127.0 (*C*H-16,20), 126.4 (*C*H-10,14), 113.9 (2 *C*N), 55.0 (*C*-29), 50.1 (*C*-2). IR (KBr): 3090–2996 (w, Ar–CH), 2950–2880 (m, aliph.-CH), 2220–2215 (CN), 1600 (s, C=N), 1490 (m, C=C), 1450 (s), 920 (m) cm^{-1}. λ_{max} (CH_3CN, lg ε, nm): 450 (4.0). MS (*m/z,%*): 424 [M + 1] (18), 423 [M$^+$] (100), 408 (12), 396 (18), 392 (24), 371 (22), 346 (30), 282 (24), 205 (28), 128 (24), 109 (22), 77 (34). $C_{24}H_{17}N_5OS$ (423.50): Calcd: C, 68.07; H, 4.05; N, 16.54; S, 7.57. Found: C, 67.91; H, 4.00; N, 16.42; S, 7.39.

3-(4-Methyphenyl)-4-phenyl-6-[(Z)-phenylimino]-3,6-dihydro-1,3,5-thiadiazine-2,2-dicarbonitrile (**3b**): Compound **3b** was obtained as red crystals (0.65 g, 80%), m.p. 220°C (ethanol). ^{1}H NMR (DMSO-d_6): δ = 7.50–7.30 (m, 8 H, Ph-H), 7.15–7.00 (m, 2 H, H-24,26), 6.80 (dd, 2 H, J = 8.0, 1.2 Hz, H-10,14), 6.60 (dd, 2 H, J = 8.0, 1.2 Hz, H-10,14), 2.35 (s, 3 H, CH_3). ^{13}C NMR: δ = 160.9 (*C*-6), 159.2 (*C*-4), 146.0 (*C*-22), 138.0 (*C*-9), 136.8



Scheme 2 Rational formation of 1,3,5-thiadiazines **3a–e.**

(*C*-12), 133.0 (C-15), 128.9 (*C*H-10,14), 128.5, 128.0, 127.0 (Ar 2 *C*H), 127.0 (*C*H-23,27), 127.2 (*C*H-16,18), 119.6 (*C*H-11,13), 114.5 (2 *C*N), 51.4 (*C*-2), 34.0 (CH_3). IR (KBr): 3090–2990 (w, Ar–CH), 2940–2870 (m, aliph.-CH), 2220–2210 (CN), 1608 (s, C=N), 1492 (m, C=C), 920 (m) cm^{-1}. λ_{max} (CH_3CN, lg ε, nm): 430 (3.8). MS (*m/z,%*): 407 [M^+] (100), 392 (24), 315 (20), 289 (26), 262 (18), 250 (20), 205 (24), 128 (28), 109 (20), 77 (32). $C_{24}H_{17}N_5S$ (407.50): Calcd: C, 70.74; H, 4.21; N, 17.19; S, 7.87. Found: C, 70.57; H, 4.15; N, 17.02; S, 7.69.

3-(4-Chlorophenyl)-4-phenyl-6-[(Z)-phenylimino]-3,6-dihydro-1,3,5-thiadiazine-2,2-dicarbonitrile (**3c**): Compound **3c** was obtained as pale red crystals (0.64 g, 75%), m.p. 192°C (ethanol). ^{1}H NMR: δ = 7.60–7.56 (m, 2 H, H-16,20), 7.50–7.32 (m, 8 H, Ph-H), 7.66 (d, 2 H, *J* = 8.0, 1.2 Hz, H-13,15), 6.60–6.55 (dd, 2 H, *J* = 8.2, 1.2 Hz, H-10,14). ^{13}C NMR: δ = 164.0 (*C*-4), 163.0 (*C*-6), 149.0 (*C*-22), 141.0 (*C*-9), 132.6 (*C*-15), 130.2 (*C*H-10,13), 129.0 (*C*H-23,26), 127.6, 127.0, 126.2 (Ar*C*H), 124.6 (*C*H-23,27), 123.0 (*C*-12), 120.0 (*C*H-10,14), 114.5, 113.6 (*C*N), 49.8. (*C*-2). IR (KBr): 3080–2996 (m, Ar–CH), 2220–2212 (CN), 1610 (s, C=N), 1580 (s, C=C), 916 (m) cm^{-1}. λ_{max} (CH_3CN, lg ε, nm): 410 (3.9). MS (*m/z,%*): 428 [M + 1] (22), 427 [M^+] (100), 426 (30), 392 (24), 376 (28), 374 (32), 290 (20), 288 (26), 278 (18), 188 (22), 186 (24), 180 (30) 114 (24), 112 (26), 77 (36). $C_{23}H_{14}ClN_5S$ (427.92): Calcd; C, 64.56; H, 3.30; Cl, 8.28; N, 16.37; S, 7.49. Found; C, 64.37; H, 3.20; Cl, 8.11; N, 16.19; S, 7.37.

3-(4-Nitrophenyl)-4-phenyl-6-[(Z)-phenylimino]-3,6-dihydro-1,3,5-thiadiazine-2,2-dicarbonitrile (**3d**): Compound **3d** was obtained as orange crystals (0.6 g, 68%), m.p. 250°C (ethanol). IR (KBr): ^{1}H NMR: δ = 8.00 (d, 2 H, *J* = 8.2, 1.2 Hz, H-10,12), 7.40–7.20 (m, 8 H, Ar–H), 7.60 (m, 2 H, H-16,20), 6.70 (d, 2 H, *J* = 8.2, 1.2 Hz, H-10,14). ^{13}C NMR: δ = 164.0 (*C*-4), 163.0 (*C*-6), 149.6 (*C*-9), 148.0 (*C*-22), 137.0 (*C*-12), 132.5 (C-15), 129.4 (*C*H-24,26), 128.6 (*C*H-16,18), 128.2, 127.4, 127.0 (Ar *C*H), 126.0 (2 *C*H-11,13), 114.2, 113.9 (*C*N), 112.0 (*C*H-10,14), 47.8 (*C*-2). IR (KBr): 3050–2990 (w, Ar–CH), 2220–2210 (s, CN), 1590 (s, C=N), 1496 (s, C=C), 920 (s) cm^{-1}. λ_{max} (CH_3CN, lg ε, nm): 410 (3.7). MS (*m/z,%*): 438 [M + 1] (20), 437 [M^+] (100), 390 (22), 360 (26), 340 (28), 314 (14), 288 (14), 262 (16), 250 (22), 186 (18), 122 (28), 77 (40). $C_{23}H_{14}N_6O_2S$ (438.47) Calcd; C, 63.00; H, 3.22; N, 19.17; S, 7.31. Found; C, 63.17; H, 3.20; N, 19.19; S, 7.30.

4-Phenyl-6-[(Z)-phenylimino]-3-[4-(1,2,2-tricyanovinyl)phenyl]-3,6-dihydro-1,3,5-thiadiazine-2,2-dicarbonitrile (**3e**): Compound **3e** was obtained as reddish brown crystals (0.85 g, 86%), m.p. 122°C (ethyl acetate). ^{1}H NMR: δ = 7.32–7.20 (m, 7 H, Ar–H), 7.11–6.95 (m, 3 H, Ar–H), 6.85–6.80 (m, 2 H, H-23,27), 6.60 (dd, 2 H, *J* = 8.0, 1.2 Hz, H-10,14). ^{13}C NMR: δ = 163.0 (*C*-6), 162.3 (*C*-4), 149.6 (*C*-22), 145.0 [*C*(CN) =], 140.6 (*C*-9), 137.6 (*C*-15), 128.0, 127.6, 127.2, 126.8, 126.4 (Ar 2 *C*H), 124.0 (2 *C*-23,27), 121.2 (*C*-12), 118.0 (2 *C*-10,14), 117.7, 117.4, 116.9, 116.2, 115.8 (*C*N), 97.4 [$C(CN)_2$ =], 48.9 (*C*-2). IR (KBr): 2960-2870 (m, aliph.-CH), 2228, 2220-2210, (CN), 1596 (s, C=N), 1492 (m, C=C), 918 (m) cm^{-1}. λ_{max} (CH_3CN, lg ε, nm): 440 (3.8). MS (*m/z,%*): 494 [M^+] (100), 468 (30), 442 (26), 430 (22), 417 (40), 366 (34), 340 (18), 326 (22), 250 (24), 186 (16), 179 (36) 109 (18), 77 (30). $C_{28}H_{14}N_8S$ (494.54) Calcd; C, 68.00; H, 2.85; N, 22.66; S, 6.48. Found; C, 67.80; H, 2.83; N, 22.59; S, 6.44.

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