Reaction of *N*-imidoylthioureas with dimethyl acetylenedicarboxylate: synthesis of new 1,3,5-thiadiazepines

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The reaction of *N*-imidoylthioureas **2a–e** with dimethyl acetylenedicarboxylate (DMAD, **1**) led unexpectedly to the 1,3,5-thiadiazepines **6a–e**. The mechanism of the reaction is discussed.

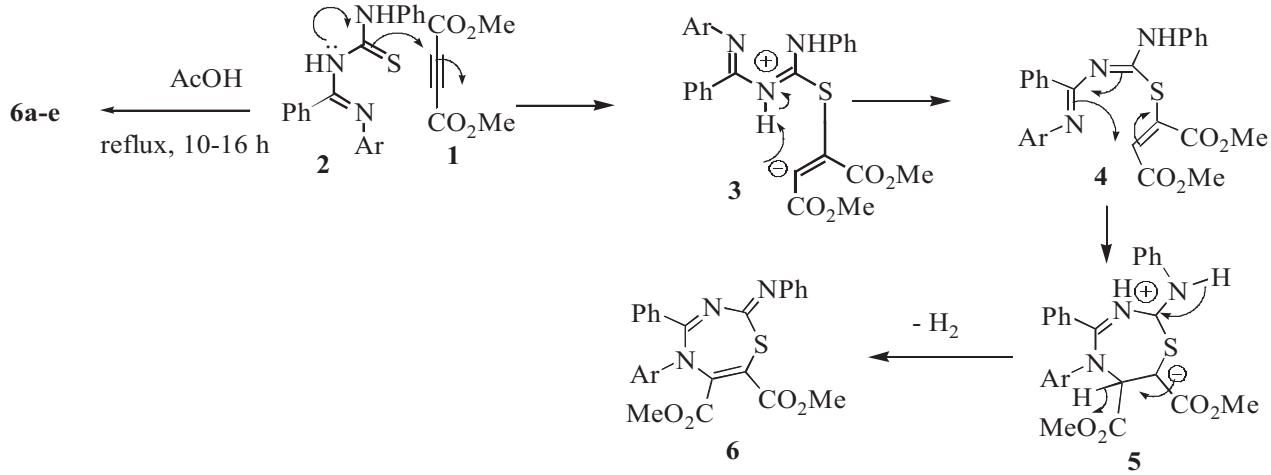
Keywords: imidoylthioureas, DMAD, stepwise mechanism, cyclisation, 1,3,5-thiadiazepines

The cyclisation of compounds having an extended urea-like chain has been shown to be an excellent method for the synthesis of several heterocycles like 1,3,4-thiadiazoles, 1,2,4-triazoles and 1,3,5-triazines. 1-Substituted benzoyl thiosemicarbazide on irradiation with microwaves in aqueous alkali is reported to form 3-aryl-1,2,4-triazoline-5-thiones.[1] *N*-Imidoylthioureas have been shown attention in the field of thiadiazole synthesis.[2,3] Oxidation of *N*-imidoylthioureas with bromine yielded 2,3,5-substituted-1,2,4-thiadiazoles as their hydrobromide salts.[3] We have recently investigated the chemistry of *N*-imidoylthioureas towards π-deficient compounds. In this point of view, we isolated pyrimidin-4(3*H*)-ones from the reaction of 2,3-diphenylcyclopropenone with *N*-imidoylthioureas.[4] Aly *et al*. also demonstrated that *N*-imidoylthioureas reacted with 1,1,2,2-tetracyanoethylene to form the corresponding thiadiazines.[5] Also, syntheses of various diastereomeric 1,2,4-thiadiazole-5-carbonitriles were reported. Their successful synthesis depends on the reaction of *N*-imidoylthioureas with 2-(1,3-dioxoindan-2-ylidene)-malononitrile.[6] Synthetic potential and biological activity of benzodiazepines has been explored to the maximum extent.[7-9] Owing to their well-established role as psychotherapeutics,[10] benzodiazepines have been the object of intense investigation in medicinal chemistry. The area of biological interest of this family of compounds has been extended recently to various diseases such as cancer,[11] viral infections (HIV)[12] and cardiovascular disorders.[13,14] To the best of our knowledge only a few reports are available for the synthesis, and pharmacological activity of 1,3,5-thiadiazepines, 1,2,7-thiadiazepines, 1,3,4-thiadiazepines, and 1,4,5-thiadiazepines.[15,16] Renewed interest in the chemistry of organosulfur systems,[17-21] prompted us to explore the chemistry of *N*-imidoyl-thioureas **2a–e** towards dimethyl acetylenedicarboxylate (DMAD, **1**) aiming to shed more light on the selectivity of the reaction pathway.

Results and discussion

In the light of the aforementioned promising results, our attention turned to the reactions of DMAD (**1**) with *N*-imidoylthioureas **2a–e** (Scheme 1).

We chose *N*-imidoylthioureas **2a–e** having aryl groups with electron donating and withdrawing substituents on the benzene ring, in order to examine their reactivity and effect on the course of reaction. The reactions of **2a–e** with **1** were carried out in acetic acid at reflux temperature, and afforded the thiadiazepines **6a–e** in 65–84% yields (Scheme 1). The structures **6a–e** were characterised on the basis of mass, ^{1}H NMR, ^{13}C NMR and IR spectra as well as elemental analyses. For example, reaction of compound **1** with **2a**, for 10 h, furnished yellow crystals of **6a** in 84% yield (Scheme 1). Mass spectrometry and elemental analysis proved the molecular formula of **6a** as $C_{27}H_{23}N_3O_5S$. The IR spectrum did not reveal any absorption assigned to the presence of NH, CS, or OH groups. Moreover, the structure feature of 1,3,5-thiadiazepines **6a–e** could be ruled out, owing to the absence of C=S signals in the ^{13}C NMR spectra. However, a broad band appeared at ν = 1725–1716 cm^{-1} due to the presence of a carbonyl ester group. The aromatic protons resonated in the ^{1}H NMR spectrum of **6a** as two double-doublets and two multiplets, respectively corresponding to the *p*-methoxyphenyl group and the other two phenyl groups. The ^{13}C DEPT 135/90 spectrum of **6a** supported the ^{1}H NMR spectroscopic data by the appearance with positive amplitude of only eight aromatic-



Scheme 1 Synthesis of 1,3,5-thiadiazepines **6**.
a: Ar = 4-$CH_3OC_6H_4$ (84%); **b**: Ar = 4-$CH_3C_6H_4$ (80%); **c**: Ar = 4-ClC_6H_4 (75%); **d**: 4-$O_2NC_6H_4$ (65%); **e**: Ar = Ph (82%).

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CH signals In the case of **6d**, the ^{1}H NMR spectrum revealed the most deshielded aromatic protons as double-doublets at δ = 7.95 and 6.80 ppm (*J* = 8.0, 1.2 Hz) corresponding to the *p*-nitrophenyl group. NOE experiments for compounds **6a–e** proved their proposed structure (Fig. 1). For example, irradiation of the methyl–ester protons (δ = 3.95 ppm), in **6a** moderately enhances the *ortho*-protons of the neighbouring phenyl group (δ = 6.60 ppm), and strongly enhances the other methyl-ester (δ = 3.92 ppm)**.** Besides, irradiation of the *ortho*-protons (δ = 6.60 ppm) of substituted phenyl group causes moderately enhancement of the neighbour phenyl group (δ = 7.30 ppm) and strong enhancement to the methyl-ester (Fig. 1). The same tendency of NOE experiments was noted in the case of **6d** (Fig. 1). The fragment ions in the mass spectrum of **6a** appeared at *m/z* = 396, 140, 134 and 77. The same aforesaid fragmentation patterns are also appeared in compounds **6b–e** (see Experimental). As shown from Fig. 2, consequently, the structure **6a** fits best to all the spectroscopic data (see Experimental). The reaction mechanism can be simply described as due to sulfur atoms attacking the triple bond of DMAD in conjugate fashion, followed by proton transfer and nucleophilic attack of the amidine group on the double bond in **3** to form the intermediates **4** (Scheme 1). Nucleophilic attack of the amidine-like on the ethylenic-ester would form the salt **5** (Scheme 1). Aromatisation of **5** is accompanied by the extrusion of a hydrogen molecule to produce the stable compounds **6a-e** (Scheme 1). Similar observation was reported by Alajarín and his group.[22] It was also reported that compound 4,5-dihydrodibenzo-1,4,5-thiadiazepine *S,S*-dioxides can be oxidised to give the corresponding dibenzo-1,4,5-thiadiazepines,[23] which is isoelectronic with compound **6**, so it is also logically to accept oxidation as the last step. It is notable that aromatic rings on the imidoyl moiety, which bear electron-donating substituents at the 4-position, accelerate the reactions (entries **2a** and **2b** versus **2c** and **2d**).

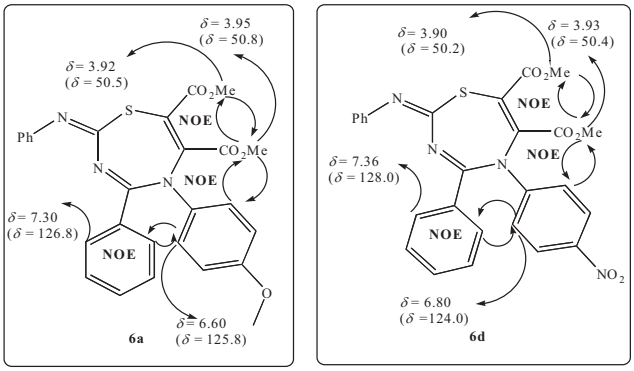

Fig. 1 NOE experiments for compounds **6a** and **6d**.

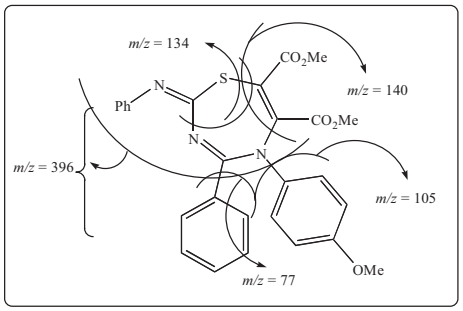

Fig. 2 Possible fragmentation ions in compound **6a**.

Experimental

General

All melting points were recorded on a Gallenkamp apparatus. The IR spectra were obtained on a Shimadzu 470 spectrophotometer using potassium bromide pellets. The ^{1}H NMR (400.134 MHz) and ^{13}C NMR (100.6 MHz) spectra were measured in DMSO-d_6 using a Bruker AM 400 Spectrometer. Coupling constants are expressed in Hz. Mass spectra were recorded on a Finnigan MAT 8430 instrument at 70 eV. Elemental analyses were carried out in the Microanalysis Centre of Cairo University. For preparative TLC (plc), glass plates (20 × 48 cm) were covered with a slurry of silica gel Merck PF_{254} and air-dried using the solvents listed for development. Zones were detected by quenching of indicator fluorescence upon exposure to 254 nm light; elution of the different bands with toluene afforded the pure products.

Starting materials

N-Imidoylthioureas **2a–e** were prepared according to ref.2.

General procedure

Into a 250 cm^3 two-necked round bottom flask containing a solution of **2a–e** (2 mmol) in glacial acetic (100 ml), a solution of **1** (0.284 g, 2 mmol) in glacial acetic acid (30 ml) was added dropwise with stirring. The mixture was stirred at room temperature for 1 h, and at reflux for 10–16 h (the reaction was monitored by TLC analyses). The solvent was evaporated under vacuum and the formed solid products were purified by dissolving them in dry acetone (30 ml) and then subjected to preparative plate chromatography (silica gel), toluene: ethyl acetate (10:1). The obtained products **6a-e** were recrystallised from the stated solvents.

Dimethyl ester 5-(4-methoxyphenyl)-4-phenyl-2-phenylimino-2,5-dihydro-1,3,5-thiadiazepine-6,7-dicarboxylate (**6a**): Compound **6a** was obtained as yellow crystals (0.84 g, 84%), m.p. 220ºC (ethanol). ^{1}H NMR (DMSO-d_6): δ = 7.80 (dd, 2 H, *J* = 8.0, 1.2 Hz, ArH), 7.50–7.33 (m, 6 H, PhH), 7.30 (dd, 2 H, *J* = 8.0, 1.2 Hz, PhH), 6.76–6.66 (m, 2 H, PhH), 6.60 (dd, 2 H, *J* = 8.0, 1.2 Hz, ArH), 3.98 (s, 3 H, OCH_3), 3.95 (s, 3 H, CH_3–ester), 3.92 (s, 3 H, CH_3–ester). ^{13}C NMR: (DMSO-d_6): δ = 166.8 (*C*O–ester), 165.8 (*C*O–ester), 160.0 (*C*-2), 158.0 (*C*-4), 150.5 (OCH_3-Ph *C*), 143.2 (NAr *C*), 142.0 (N-Ph *C*), 132.0 (*C*-6), 131.8 (Ph *C*), 128.0 (CH_3O–Ph 2*C*H), 127.6, 127.3, 127.0 (Ph 2*C*H), 126.8 (C-4, Ph 2*C*H), 125.8 (CH_3O–Ph 2*C*H), 125.6, 125.2 (*para*-Ph *C*H), 125.0 (*C*-7), 54.5 (OCH_3), 50.8 (CH_3-ester), 50.5 (CH_3-ester). IR (KBr): 3070–3018 (w, ArCH), 2960–2860 (m, aliph-CH), 1725–1716 (s, CO), 1612 (s, C=N), 1580 (m, C=C), 1450 (s), 918 (m) cm^{-1}. λ_{max} (CH_3CN, lg ε, nm): 380 (3.6). MS (*m/z*,%): 501 [M$^+$] (100), 406 (18), 396 (24), 378 (24), 360 (34), 354 (10), 316 (24), 275 (26), 248 (14), 222 (36), 197 (12), 140 (26), 134 (26), 105 (60), 77 (28), 51 (22). $C_{27}H_{23}N_3O_5S$ (501.57): Calcd: C, 64.66; H, 4.62; N, 8.38; S, 6.39. Found: C, 64.50; H, 4.60; N, 8.30; S, 6.34.

Dimethyl ester 5-(4-methylphenyl)-4-phenyl-2-phenylimino-2,5-dihydro-1,3,5-thia-diazepine-6,7-dicarboxylate (**6b**): Compound **6b** was obtained as yellow crystals (0.78 g, 80%), m.p. 260ºC (methanol). ^{1}H NMR (DMSO-d_6): δ = 7.56–7.34 (m, 10 H, PhH), 6.80–6.62 (m, 4 H, PhH), 3.94 (s, 3 H, CH_3–ester), 3.92 (s, 3 H, CH_3–ester), 2.34 (s, 3 H, CH_3). ^{13}C NMR: (DMSO-d_6): δ = 166.2 (*C*O–ester), 165.8 (*C*O–ester), 158.8 (*C*-2), 157.6 (*C*-4), 143.2 (NAr *C*), 142.0 (NPh *C*), 134.0 (CH_3Ph *C*), 132.4 (*C*-6), 131.6 (Ph *C*), 130.0, 128.0, 127.6, 127.4, 127.0 (Ph 2*C*H), 126.4, 126.0 (*para*-Ph-*C*H), 124.8 (*C*-7), 120.2 (NPh 2*C*H), 50.2 (CH_3–ester), 50.0 (CH_3–ester), 34.6 (*C*H_3–Ph) . IR (KBr): 3070–3010 (w, ArCH), 2950-2870 (m, aliph.–CH), 1725–1715 (s, CO), 1610 (s, C=N), 1588 (m, C=C), 1450 (s), 920 (m) cm^{-1}. λ_{max} (CH_3CN, lg ε, nm): 366 (3.5). MS (*m/z*,%): 485 [M$^+$] (100), 470 (18), 420 (22), 406 (30), 396 (22), 378 (24), 348 (34), 354 (10), 275 (30), 265 (26), 248 (14), 206 (32), 197 (12), 140 (24), 134 (24), 105 (60), 77 (28), 51 (20). $C_{27}H_{23}N_3O_4S$ (485.57): Calcd: C, 66.79; H, 4.77; N, 8.65; S, 6.60. Found: C, 66.60; H, 4.70; N, 8.60; S, 6.54.

Dimethyl ester 5-(4-chlorophenyl)-4-phenyl-2-phenylimino-2,5-dihydro-1,3,5-thia-diazepine-6,7-dicarboxylate (**6c**): Compound **6c** was obtained as pale yellow crystals (0.76 g, 75%), m.p. 186ºC (ethyl acetate). ^{1}H NMR (DMSO-d_6): δ = 7.40–7.24 (m, 5 H, PhH), 7.16–7.00 (m, 5 H, PhH), 6.80–6.62 (m, 4 H, PhH), 3.94 (s, 3 H, CH_3–ester), 3.90 (s, 3 H, CH_3–ester). ^{13}C NMR: (DMSO-d_6): δ = 166.6 (*C*O-ester), 165.6 (*C*O–ester), 159.6 (*C*-2), 157.8 (*C*-4), 142.6 (NAr *C*), 141.7 (NPh *C*), 132.2 (*C*-6), 131.6 (Ph *C*), 127.8, 127.6, 127.2 (Ph 2*C*H), 127.0 (ClPh *C*), 126.6 (C-4, Ph 2*C*H), 126.0, 125.8 (ClPh 2*C*H), 125.4, 125.0 (*para*-Ph *C*H), 124.8 (*C*-7), 51.0 (*C*H_3–ester),

50.6 (*C*H_3–ester). IR (KBr): 3068–3008 (w, ArCH), 1722–1710 (s, CO), 1600 (s, C=N), 1590 (m, C=C), 1450 (s), 922 (m) cm^{-1}. λ_{max} (CH_3CN, lg ε, nm): 354 (3.4). MS (*m/z,%*): 507 [M + 2] (28), 505 [M^+] (100), 490 (12), 472 (22), 470 (34), 396 (24), 392 (22), 426 (24), 282 (60), 252 (34), 236 (24), 234 (26), 194 (24), 192 (28), 140 (26), 134 (24), 115 (30), 113 (34), 77 (38). $C_{26}H_{20}ClN_3O_4S$ (505.98): Calcd: C, 61.72; H, 3.98; Cl, 7.01; N, 8.30; S, 6.34. Found: C, 61.62; H, 4.00; Cl, 7.00; N, 8.20; S, 6.40.

Dimethyl ester 5-(4-nitrophenyl)-4-phenyl-2-phenylimino-2,5-dihydro-1,3,5-thiadiazepine-6,7-dicarboxylate (**6d**): Compound **6d** was obtained as pale orange crystals (0.67 g, 65%), m.p. 250ºC (methanol). ^{1}H NMR: δ = 7.95 (dd, 2 H, *J* = 8.0, 1.2 Hz, NO_2Ph), 7.60–7.40 (m, 5 H, PhH), 7.10–6.90 (m, 5 H, PhH). 6.80 (dd, 2 H, *J* = 8.0, 1.2 Hz, NO_2Ph), 3.93 (s, 3 H, CH_3–ester), 3.90 (s, 3 H, CH_3–ester). δ = ^{13}C NMR (DMSO-d_6): δ = 166.8 (*C*O–ester), 166.0 (*C*O–ester), 158.8 (*C*-2), 157.6 (*C*-4), 143.8 (O_2NPh *C*), 136.0 (NPh *C*), 132.8 (*C*-6), 131.6 (Ph *C*), 128.8 (O_2NPh 2*C*H), 127.6, 127.4, 127.0 (Ph 2*C*H), 126.8 (C-4, Ph 2*C*H), 126.0 (*C*-7), 125.8, 125.5 (*para*-Ph *C*H), 126.0 (*C*-7), 124.0 (O_2NPh 2*C*H), 50.4 (*C*H_3–ester), 50.2 (*C*H_3–ester). IR (KBr): 3090–2998 (w, ArCH), 1720–1710 (CO), 1610 (s, C=N), 1500 (s, C=C), 920 (s) cm^{-1}. λ_{max} (CH_3CN, lg ε, nm): 340 (3.3). MS (*m/z,%*): 516 [M^+] (100), 501 (18), 485 (20), 440 (22), 396 (28), 362 (34), 322 (30), 276 (24), 246 (30), 238 (36), 192 (30), 140 (30), 134 (28), 122 (34), 88 (32), 77 (40). $C_{26}H_{20}N_4O_6S$ (516.54): Calcd; C, 60.46; H, 3.90; N, 10.85; S, 6.21. Found; C, 60.30; H, 3.80; N, 10.90; S, 6.18.

Dimethyl ester 4,5-diphenyl-2-phenylimino-2,5-dihydro-1,3,5-thiadiazepine-6,7-dicarboxylate (**6e**): Compound **6e** was obtained as pale yellow plates (0.77 g, 82%), m.p. 160ºC (acetonitrile). ^{1}H NMR: δ = 7.50–7.20 (m, 10 H, PhH), 7.10–6.90 (m, 3 H, PhH), 6.60 (m, 2 H, PhH), 3.95 (s, 3 H, CH_3–ester), 3.92 (s, 3 H, CH_3–ester). ^{13}C NMR (DMSO-d_6): δ = 166.6 (*C*O–ester), 166.0 (*C*O–ester), 159.6 (*C*-2), 158.2 (*C*-4), 143.0 (NAr *C*), 142.2 (NPh *C*), 131.8 (*C*-6), 131.5 (Ph *C*), 128.0, 127.6, 127.3, 127.0, 126.8 (Ph 2*C*H), 126.6 (C-4, Ph 2*C*H), 126, 125.6, 125.4 (*para*-Ph *C*H), 125.0 (*C*-7), 51.2 (CH_3–ester), 50.8 (CH_3–ester). IR (KBr): 3072–3010 (w, ArCH), 1725–1718 (s, CO), 1610 (s, C=N), 1588 (m, C=C), 1450 (s), 920 (m) cm^{-1}. λ_{max} (CH_3CN, lg ε, nm): 365 (3.5). MS (*m/z,%*): 471 [M^+] (100), 456 (28), 440 (24), 396 (30), 274 (56), 252 (34), 225 (24), 192 (48), 178 (30), 140 (20), 134 (24), 116 (22), 77 (34). $C_{26}H_{21}N_3O_4S$ (471.54): Calcd: C, 66.23; H, 4.49; N, 8.91; S, 6.80. Found: C, 66.10; H, 4.40; N, 8.80; S, 6.70.

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