Synthesis of 1,3-thiazin-2-ylidene-substituted hydrazides *via* reaction of *N*-substituted-hydrazino-carbothioamides with 1,4-diphenylbut-2-yne-1,4-dione

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1,4-Diphenylbut-2-yne-1,4-dione reacts with *N*-substituted-hydrazino-carbothioamides to form the corresponding *N*'-6-benzoyl-4-phenyl-2*H*-1,3-thiazin-2-ylidene]-substituted-hydrazides.

Keywords: *N*-substituted-hydrazino-carbothioamides, 1,4-diphenylbut-2-yne-1,4-dione, amidine-like addition, cyclisation, 1,3-thiazines

The chemistry of 1,4-diphenylbut-2-yne-1,4-dione (DBD) has been extensively investigated. For example, DBD reacts with benzimidazole-2-thione to produce 2-(acylvinylthio)-benzimidazoles,[1] whilst diarylazines react with DBD to produce pyridazines *via* a Diels–Alder reaction.[2] An effective route to the pyrrol-2-ones involves the reaction of enamines with DBD.[3] Additionally, DBD reacts with enaminocarbonyl compounds to afford pyrrol-2-ol derivatives.[4] Thioamides and their derivatives occupy a special place among the *N*,*S*-containing compounds used in the synthesis of heterocyclic systems due to their accessibility and ability to act as difunctional nucleophiles. Four-, five-, six- and seven-membered heterocyclic compounds have been prepared by reaction of thiosemicarbazide derivatives with α- and β-haloketones.[5-10] Reaction of acetylenecarboxylic acid derivatives with *N*,S-dinucleophiles provides the general approach for construction of 1,3-thiazolidine and 1,3-thiazine systems which are of great interest.[11,12] 1,3-Thiazine compounds have shown wide biological activities such as their potential CNS,[13] analgesic,[14] antiinflammatory[15] and antifungal activities.[15] 1,3-Thiazines are also used as chemotherapeutic agents (i.e. leishmanicides).[16] Recent reports have been indicated that 1,3-thiazines provide as useful control of *M. grisea*[17] and they are also been found as cannabinoid receptor agonists.[18] Aly *et al.* have recently reported the synthesis of thiazinones, during the reaction of *N*-aroyl thioureas with ethyl propiolate, dimethyl but-2-ynedioate and (*E*)-1,4-diphenylbut-2-ene-1,4-dione.[19] Moreover, we have investigated the reaction between 2,3-diphenylcyclopropenone and ylidene-*N*-phenyl-hydrazine-carbothioamides.[20] Various (2*Z*)-2-({(*E*)[arylamino]phenylmethylene}hydrazono)-1,4-diphenylbutan-1,4-diones are obtained during the reaction of amidrazones with DBD.[21] We now report on the reaction of *N*-substituted-hydrazino-carbothioamides **1a–e**[22] with 1,4-diphenylbut-2-yne-1,4-dione (**2**, DBD). That reactions give mainly the corresponding *N*'-[6-benzoyl-4-phenyl-2*H*-1,3-thiazin-2-ylidene]-substituted-hydrazides **3a–e** (Scheme 1). We chose compounds **1a–e** having aryl groups with electron donating and withdrawing substituents on the benzene ring, in order to examine their reactivity. Moreover we chose the benzyl and methyl derivative **1d** and **1e** in order to generalise the idea beyond benzenoid aromatics, to alkyl-substituted starting materials. The structural proof of **3a–e** was based upon the mass, ^{1}H NMR, ^{13}C NMR and IR spectra as well as elemental analyses. The IR and ^{13}C NMR spectra of **3a–e** supported the disappearance of any thione. Mass spectrometry and elemental analysis confirmed the molecular formula of **3a** as $C_{24}H_{17}N_3O_2S$. The ^{1}H NMR spectrum of **3a**, as an example, showed one double-doublets of the aromatic phenyl protons at δ_H = 8.10–8.0 (2 H, J = 8.0, 1.0 Hz). Besides the former three multiplets appeared at δ_H = 7.90–7.40 (m, 7 H), 7.36–7.20 (m, 4 H) and 6.90–6.82 (2 H, ArH). The hydrazine proton resonated in the ^{1}H NMR spectrum of **3a** at δ_H = 6.60. The H-5 proton in the ^{1}H NMR spectrum of **3a** resonated at δ_H = 7.10. The ^{13}C NMR spectrum supported the ^{1}H NMR spectroscopic data by the distinctive appearance of the carbon signals representing the thiazine skeleton at δ_C = 162.8 (C-4), 158.2 (C-2), 132.0 (C-6) and 124.2 (C-5). The carbonyl carbon signals resonated at δ_C = 186.2 and 168.0 assigned to COPh and CONH, respectively (see Experimental).

In **3b**, mass spectrometry and elemental analysis proved the molecular formula as $C_{24}H_{17}N_3O_3S$. The IR spectrum did not reveal any absorption due to C=S group, whereas the spectrum revealed absorption bands at ν = 3490, 3330, 1700 and 1680 cm^{-1} assigned to the OH, NH, COPh and CONH stretching, respectively. In the ^{1}H NMR spectrum of **3b**, the OH and the NH protons resonated at δ_H = 9.10 and 6.80 respectively. Distinctive ^{13}C NMR signals of **3b** appeared at δ_C = 186.6 (COPh), 168.4 (CONH), 163.0 (C-4), 158.4 (C-2), 148.8 (OH-Ar-C), 132.4 (C-6), 134.0 (OH-Ph-C), 134.4, 133.0 (Ph-C), 128.6, 127.2, 127.0 (*ortho*-2Ar CH), 126.2, 125.4 (*meta*-Ar 2CH), 125.0, 124.6 (*para*-Ar 2CH), 124.0 (CH-5), 120.6 (*ortho*-Ar 2CH). The NMR of compound **3d,** showed the benzyl protons as a singlet at δ_H = 5.10, whereas its carbon signal absorbed at δ_C = 42.0. Whilst the ^{1}H NMR spectrum of **3e** showed the methyl moiety as a singlet at δ_H = 2.10, and its carbon signal appeared at δ_C = 20.0.

The reaction of **1e** with **2** took the most time of refluxing (48 h) compared with the other substituents. Note that the yield percentages of the obtained products increase in case of presence of electron donating groups of the aromatic moiety such as hydroxyl and methoxy in **1b** and **1c**. However, here and in (4-bromophenylaceto)thiosemicarbazide **1d**, the yield percentage decreases. On the other hand, the methyl derivative, as in case of **1e**, shows less yield percentage and the reaction requires more time compared with the other derivatives of **1a–d**. The reaction mechanism depends on the presence of a tautomerism between the NH and the C=S into the N=C–SH groups in **1a–e** (Scheme 1). It is logical to assume that any nucleophilic centre of **1a–e** has to attack firstly the triple bond in **2**. Additionally it is believed that attachment by the SH group proceeds faster compared to the aromatic amine (Scheme 1).[19,20] Therefore we excluded the possibility of the formation of any other regio-isomers as in compounds **4a–e** (Scheme 1). Accordingly, the reaction of **1a–e** with **2** can be described as being due to nucleophilic attack of the thiol group to the triple bond carbon to form the intermediate **5**. Thereafter another nucleophilic attack from the terminal NH *via* amidine-like addition to the carbonyl carbon in **5** has occurred to form the salt **6**. Neutralisation of **6** gives **7**, which is accompanied by water elimination to afford compounds **3a–e** (Scheme 1). In conclusion *N*-substituted-hydrazino-carbothioamides react with 1,4-diphenylbut-2-yne-1,4-dione by way of an initial thiol addition followed by another cyclisation process.

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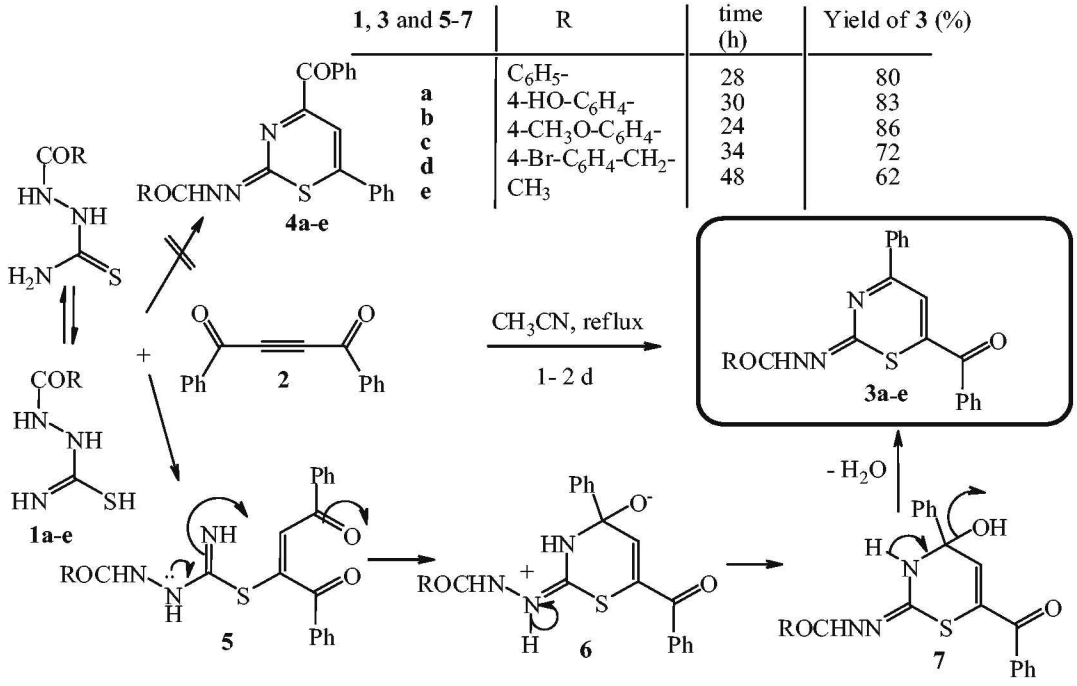

Scheme 1 Reaction of *N*-substituted-hydrazino-carbothioimides **1a-e** with 1,4-diphenylbut-2-yne-1,4-dione (**2**).

Experimental

All melting points 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 and/or $CDCl_3$ solutions. Coupling constants were expressed in Hz. Elemental analyses were carried at the Cairo Microanalysis Centre of Cairo 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.

Starting materials: *N*-Substituted-hydrazino-carbothioamides **1a–e** and 1,4-diphenylbut-2-yne-1,4-dione (DBA, **2**) were prepared according to references 22 and 23, respectively.

General procedure: To a 250 cm^3 two-necked round bottom flask containing a solution of **1a–e** (1 mmol) in acetonitrile (100 ml) and a solution of **2** (0.468 g, 1 mmol) in acetonitrile (30 ml) was refluxed for 1–2 days (the reaction was monitored by TLC). The solvent was evaporated under vacuum and the solid residue was dissolved in dry acetone (20 ml) and the solution was chromatographed on thin layer plates (silica gel) using toluene. The mobile phases containing products **3a–e** were extracted by acetone. The obtained products were recrystallised from the stated solvents.

N'-(6-Benzoyl-4-phenyl-2H-1,3-thiazin-2-ylidene)-benzohydrazide **(3a):** Yellow crystals (0.66 g, 80%), m.p. 310 °C (ethanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.10–8.0 (dd, 2 H, J = 8.0, 1.0 Hz, ArH), 7.90–7.40 (m, 7 H, ArH), 7.36–7.20 (m, 4 H, ArH), 7.10 (s, 1 H, H-5), 6.90–6.82 (m, 2 H, ArH), 6.60 (s, 1 H, NH–N). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 186.2 (COPh), 168.0 (CONH), 162.8 (C-4), 158.2 (C-2), 132.0 (C-6), 135.2, 133.8, 130.0 (Ph-C), 127.2, 127.0, 126.8 (*ortho*-2Ar CH), 126.4, 126.2, 126.0 (*meta*-Ar 2CH), 125.6, 125.0, 124.8 (*para*-Ar CH), 124.2 (CH-5). IR (KBr): ν_{max} = 3320 (m, NH), 3090–3010 (w, Ar-CH), 1700 (s, COPh), 1680 (s, CONH), 1612–1600 (br, s, C=N), 1590 (m, C=C), 1120 (m, C-S) cm^{-1}. λ_{max} (CH_3CN, lg ε, nm): 360 (3.4). MS (EI): *m/z* (%) = 411 [M$^+$] (100), 335 (22), 306 (24), 292 (18), 286 (14), 278 (14), 202 (34), 128 (24), 126 (26), 105 (62), 77 (24). $C_{24}H_{17}N_3O_2S$ (411.49): Calcd C, 70.06; H, 4.16; N, 10.21; S, 7.79%. Found C, 70.20; H, 4.08; N, 10.16; S, 7.71%.

N'-(6-Benzoyl-4-phenyl-2H-1,3-thiazin-2-ylidene)-(4'-hydroxyphenyl)hydrazide **(3b):** Yellow plates (0.71 g, 83%), m.p. 234 °C (ethanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 9.10 (s, 1 H, OH), 7.90–7.75 (dd, 2 H, J = 8.0, 1.2 Hz, ArH), 7.60–7.42 (m, 6 H, ArH), 7.30–7.12 (m, 6 H, ArH), 6.98 (s, 1 H, H-5), 6.80 (s, 1 H, NH–N). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 186.6 (COPh), 168.4 (CONH), 163.0 (C-4), 158.4 (C-2), 148.8 (OH-Ar-C), 132.4 (C-6), 133.8, 133.6, 133.0 (Ph-C), 128.6, 127.2, 127.0 (*ortho*-2Ar CH), 126.2, 126.0 (*meta*-Ar 2CH), 125.2 (CH-5), 125.0, 124.8 (*para*-Ar CH), 120.6 (*meta*-Ar 2CH). IR (KBr): ν_{max} = 3490 (s, OH), 3330 (m, NH), 3096-3012 (m, Ar–CH), 1700 (s, COPh), 1680 (s, CONH–), 1610 (s, C=N), 1596 (m, C=C), 1450 (s), 1118 (m, C–S), cm^{-1}. λ_{max} (CH_3CN, lg ε, nm): 375 (3.6). MS (EI): *m/z* (%) = 428 [M + 1] (38), 427 [M$^+$] (100), 411 (18), 335 (22), 322 (28), 246 (18), 220 (34), 216 (26), 208 (30), 120 (34), 104 (44), 76 (32). $C_{24}H_{17}N_3O_3S$ (427.49): Calcd C, 67.43; H, 4.01; N, 9.83; S, 7.50%. Found C, 67.28; H, 3.94; N, 9.80; S, 7.46%.

N'-(6-Benzoyl-4-phenyl-2H-1,3-thiazin-2-ylidene)-(4'-methoxyphenyl)hydrazide **(3c):** Yellow crystals (0.76 g, 86%), m.p. 210 °C (acetonitrile). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.17–8.10 (dd, 2 H, J = 7.8, 1.0 Hz, ArH), 7.68–7.48 (m, 5 H, ArH), 7.36–7.22 (m, 5 H, ArH), 7.10 (s, 1 H, H-5), 6.80–6.75 (dd, 2 H, J = 8.0, 1.0 Hz, ArH), 6.70 (s, 1 H, NH–N), 3.95 (s, 3 H, OCH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 186.4 (COPh), 168.0 (CONH), 163.2 (C-4), 158.6 (C-2), 153.8 (H_3CO-Ar-C), 134.0 (Ph-C), 132.4 (C-6), 132.4, 132.0 (Ph-C), 128.6, 127.2, 127.0 (*ortho*-2Ar CH), 126.2, 125.4 (*meta*-Ar 2CH), 125.3 (C-5), 124.6, 124.2 (*para*-Ar CH), 122.6 (*meta*-Ar 2CH), 52.0 (OCH_3). IR (KBr): ν_{max} = 3330 (m, NH), 3070–3010 (w, Ar-CH), 2996–2880 (m, aliph.–CH), 1700 (s, COPh), 1700 (s, CONH), 1612 (s, C=N), 1590 (s, C=C), 1452 (s), 1122 (m, C-S) cm^{-1}. λ_{max} (CH_3CN, lg ε, nm): 382 (4.1). MS (EI): *m/z* (%) = 441 [M$^+$] (100), 426 (24), 410 (24), 365 (28), 336 (42), 286 (32), 254 (24), 222 (34), 190 (26), 135 (42), 104 (56), 77 (26). $C_{25}H_{19}N_3O_3S$ (441.51): Calcd C, 68.01; H, 4.34; N, 9.52; S, 7.26%. Found C, 68.11; H, 4.28; N, 9.62; S, 7.12%.

N'-(6-Benzoyl-4-phenyl-2H-1,3-thiazin-2-ylidene)-(4'-bromobenzyl) hydrazide **(3d):** Orange crystals (0.71 g, 72%), m.p. 320 °C (ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 7.72 (dd, dd, 2 H, J = 8.0, 1.0 Hz, ArH), 7.68–7.46 (m, 6 H, ArH), 7.36–7.28 (m, 4 H, ArH), 7.00 (s, 1 H, H-5), 6.80–6.65 (dd, 2 H, J = 8.0, 1.2 Hz, ArH), 6.62 (s, 1 H, NH–N), 5.10 (s, 2 H, CH_2). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C = 186.3 (COPh), 168.0 (CONH), 162.8 (C-4), 158.6 (C-2), 134.2 (C-6), 133.4 (*ortho*-2Ar CH), 134.0 (Ph-C), 132.0 (Br-Ar-C4'), 131.6 (Ph-C), 128.0 (Br-Ar-C), 127.6, 127.4 (*ortho*-2Ar CH), 126.0, 125.6 (*meta*-Ar 2CH), 125.2 (C-5), 125.0, 124.8 (*para*-Ar CH), 118.8 (*meta*-Ar 2CH), 42.0 (CH_2). IR (KBr): ν_{max} = 3334 (m, NH), 3050-3012 (w, Ar–CH), 2980–2860 (aliph.–CH), 1702 (s, COPh), 1684 (s, $CONH_2$), 1610 (s, C=N), 1592 (s, C=C), 1450 (s), 1120 (m, C–S) cm^{-1}. λ_{max} (CH_3CN, lg ε, nm): 382 (4.1). MS (EI): *m/z* (%) = 506 [M + 2] (96), 504 [M$^+$] (100), 412 (22), 429 (40), 427 (42), 426 (34), 402 (60), 400 (42), 337 (26), 335 (36), 309 (18), 307 (26), 302 (22), 300 (24), 272 (22), 270 (26), 226 (34), 224 (36), 186 (28), 186 (34), 184 (38), 106 (40), 104 (44), 78 (34), 76 (36). $C_{25}H_{18}BrN_3O_2S$ (504.41): Calcd C, 59.53; H, 3.60; Br, 15.84; N, 8.33; S, 6.36. Found C, 59.68; H, 3.50; Br, 15.90; N, 8.40; S, 6.40%.

N'-(6-Benzoyl-4-phenyl-2H-1,3-thiazin-2-ylidene)-methylhydrazide (**3e**): Pale yellow crystals (0.43 g, 62%), m.p. 198°C (methanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.80–7.70 (dd, 2 H, J = 8.0, 1.2 Hz, ArH), 7.60–7.48 (m, 3 H, ArH), 7.30–7.16 (m, 3 H, ArH), 7.00 (s, 1 H, H-5), 6.88–6.66 (m, 3 H, ArH, NH–N), 2.10 (s, 3 H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 186.0 (COPh), 167.6 (CONH), 162.3 (C-4), 158.5 (C-2), 134.0 (C-6), 133.4, 132.6 (Ph–C), 127.2, 126.8 (*ortho*-2Ar CH), 126.6, 126.2 (*meta*-Ar 2CH), 125.2, 125.0 (*para*-Ar CH), 124.6 (CH-5), 20.0 (CH_3). IR (KBr): ν_{max} = 33325 (m, NH), 3080–3006 (w, Ar–CH), 2987–2880 (m, aliph.–CH), 1700 (COPh), 1700 (s, CONH), 1610 (s, C=N), 1590 (s, C=C), 1120 (m, C-S) cm^{-1}. λ_{max} (CH_3CN, lg ε, nm): 360 (3.4). MS (EI): *m/z* = 349 [M^+] (100), 334 (24), 273 (26), 244 (40), 216 (32), 194 (24), 166 (24), 151 (18), 130 (24), 105 (62), 77 (26), 72 (24). $C_{19}H_{15}N_3O_2S$ (349.41): Calcd C, 65.31; H, 4.33; N, 12.03; S, 9.18%. Found C, 65.24; H, 4.30; N, 12.10; S, 9.10%.

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