Addition–cyclisation of 3-(2-thienyl)acryloyl isothiocyanate with hydrazine derivatives as a source of triazoles and thiadiazoles

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3-(2-Thienyl)acryloyl isothiocyanate reacts additively with hydrazine hydrate, phenylhydrazine, 2-pyridyl hydrazine, (thio) semicarbazides, as well as benzoyl- and ethoxycarbonyl hydrazine. Simultaneous or subsequent cyclisation of the resulting 1:1 adducts in acidic or alkaline media yields substituted 1,3,4-thiadiazoles or 1,2,4-triazoles respectively.

Keywords: 1,2,4-triazole derivatives, hydrazine derivatives, thiourea derivatives, aroyl isothiocyanate

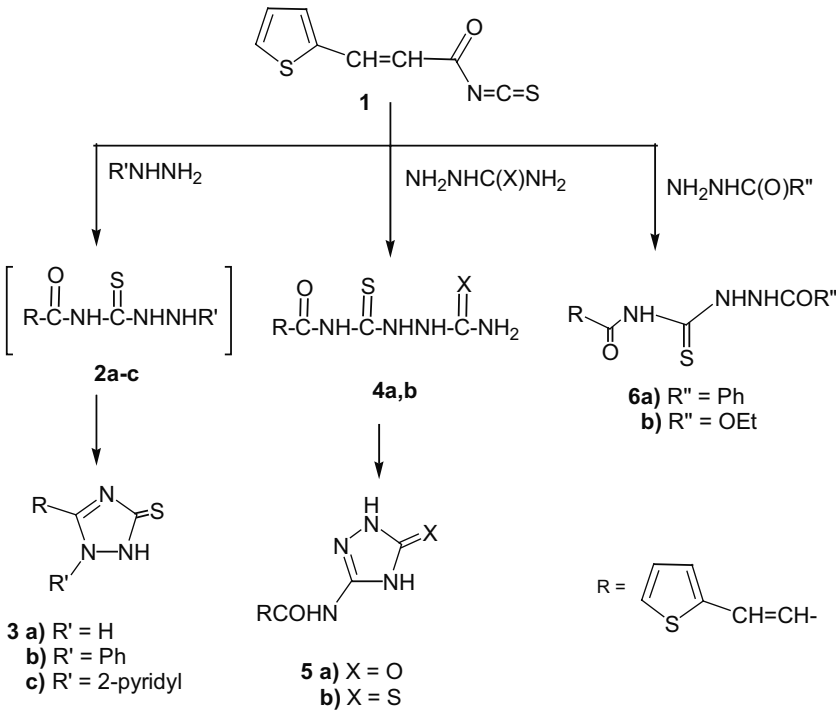
1,2,4-Triazole derivatives exhibit anti-inflammatory,[1] antiviral,[2] analgesic,[3] antimicrobial,[4] anticonvulsant,[5] and antidepressant activities.[6] A series of 1,2,4-triazoles[7] have been patented and extensively employed in agriculture. Our previous investigations on the utilisation of aroyl isothiocyanates[8-10] afforded many different sizes heterocyclic rings. In the present work, we use the prototype hydrazine itself and some of its simple congeners and 3-(2-thienyl)acryloyl isothiocyanate as a source of 1,2,4-triazoles bearing thiophene nucleus aiming to enhance their biological activities.

Results and discussion

The new derivatives of 1,2,4-triazole were prepared following the reaction sequences depicted in scheme 1 and 2. Addition of equimolar amounts of hydrazine derivatives like hydrazine hydrate, phenylhydrazine, or 2-pyridylhydrazine to a solution of 3-(2-thienyl)acryloyl isothiocyanate **(1)** in boiling acetonitrile produced 1,2,4-triazole derivatives **3a–c** in one pot reaction. The triazoles **3a–c** were obtained as *E/Z* mixture in the case of **3a** and exclusively as *E*-isomers for **3b** and **3c**.The formation of 1,2,4-triazoles **3a–c** can be visualised on the basis of cyclocondensation of hydrazines with isothiocyanate **1** via the non isolable thiourea derivatives **2a–c**.

Refluxing of isothiocyanate **1** with semicarbazide HCl or thiosemicarbazide in acetonitrile was accompanied by release of H_2S gas. The product obtained was formulated as an *E*-isomer of another differently substituted 1,2,4-triazole derivatives **5a,b**. Formation of compounds **5a,b** was based on addition of amino group of semi or thiosemicarbazide to isothiocyanato carbon atom followed by cyclisation of the intermediate thiourea **4a,b** with liberation of H_2S molecule. The release of H_2S gas was detected during the reaction progress by turning wet lead acetate paper black. However, when the reaction of **1** with thiosemicarbazide was carried out at room temperature, the thiourea derivative **4b** was separated.

The structures of compounds **3a–c**, **4b** and **5a,b** were confirmed by their microanalytical and spectral data. Their IR spectra showed absorption bands correlated with υ(NH), υ(C=N), υ(C=C) and υ(C=S), in addition to υ(C=O) for compounds **4b** and **5a,b**. The ^{1}H NMR spectra displayed signals corresponded very well with their structures. ^{1}H NMR spectrum of **3a** found: four NH protons exchangeable with D_2O two of them have integration ratio 72% and the other two a ratio 28%. Moreover, olefinic protons appear as four doublets, two doublets have an integration ratio 72% with coupling constant (*J*) in the range 14–15 Hz and the other two have the ratio 28% with (*J*) in the range 11–12 Hz.



Scheme 1

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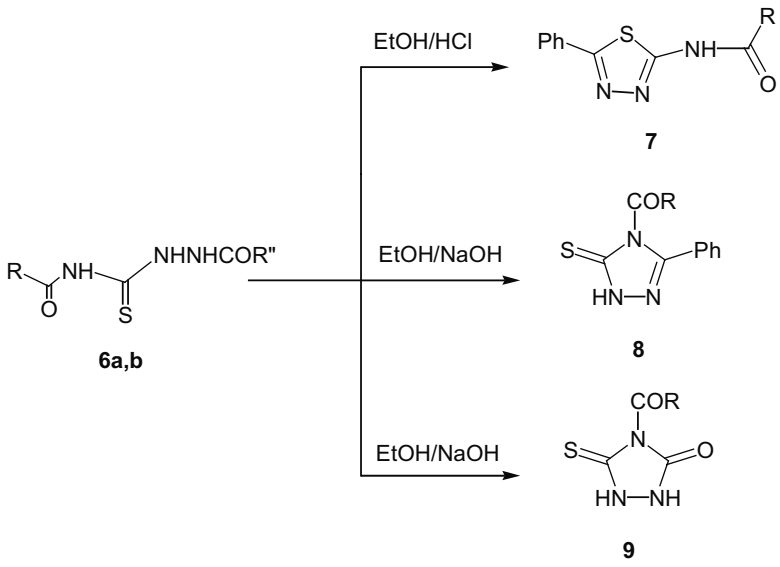

Scheme 2

The former two doublets correspond very well with the *E*-isomer and the latter doublets are in agreement with the *Z*-isomer. This observation is a good evidence for the existence of the compound **3a** as *E/Z* mixture of a ratio 72 : 28. The MS spectra of representative compounds revealed their molecular ions which in accordance with their proposed assignments (see Experimental).

The reaction of equimolar quantities of isothiocyanate **1** with benzoylhydrazine or ethoxycarbonylhydrazine gave good yields of the linear 1 : 1 adducts **6a,b** as shown in Scheme 1. Refluxing of the adduct **6a** in ethanolic hydrochloric acid effected ring closure with elimination of water, to give thiadiazole derivative **7** (compound **7** gave negative spot test characteristics for the C=S group[11]). On the other hand, when a solution of **6a** in ethanol was boiled with a catalytic amount of sodium hydroxide, 1,2,4-triazole derivative **8** was obtained as shown in Scheme 2. Similarly, compound **6b** was cyclised by ethanolic sodium hydroxide to 1,2,4-triazoline derivatives **9** via elimination of ethanol molecule (see Experimental).

The structures of compounds **6–9** were elucidated from their microanalytical and spectral data. Thus, their IR spectral data showed absorption correlated with υ(NH), υ(C=C), and υ(C=O), in addition to υ(C=N) for compounds **7,8**. Their ^{1}H NMR spectra displayed signals correspond very well with their structures. Configurational assignments to compounds **6–9** as *E*-isomers was based on the appearance of two doublets of the two olefinic protons with coupling constant (*J*) in the range 15–16 Hz. The MS spectra of compounds **6–9** revealed their molecular ions peaks, as well as some important peaks which are in accord with their proposed structures (see Experimental).

Conclusion

Synthetic utilisation of α,β-unsaturated acy isothiocyanate is based on the different reactivity of both centres against nucleophiles. It is observed from all reactions mentioned that the nucleophilic attach proceeds at the isothiocyanao group rather than the α,β-unsaturated system which reflects the higher reactivity of isothiocyanate group.

Experimental

General

Melting points were determined in open capillary tubes on a Gallenkemp melting point apparatus and are uncorrected. The elemental analyses were carried out at the Micro Analytical Unit, Faculty of Science, Cairo University by using Perkin-Elemer 2400 CHN elemental analyser. The IR spectra were recorded on Perkin–Elmer Spectrum RXIFT-IR systems as KBr discs. The ^{1}H NMR spectra were measured on Varian Gemini 200 MHz instrument with chemical shift (δ) expressed in ppm downfield from TMS as internal standard, in DMSO-d_6. Mass spectra were recorded on Shimadzu GC-MS, QP 1000 EX instrument operating at 70 eV. TLC was carried out to monitor the progress of all reactions and homogeneity of the synthesised compounds. TLC was determined using TLC aluminum sheets silica gel F_{254} (Merck).

3-(2-thienyl)acryloyl isothiocyanate **(1)**: To a solution of 3-(2-thienyl)acryloyl chloride (3 mmole), in dry acetonitrile (30 mL), solid ammonium thiocyanate (4.5 mmole) was added. The reaction mixture was stirred for half an hour at room temperature.[12,13] The precipitated ammonium chloride was filtered off to give a clear yellow solution of isothiocyanate **1**.

Reaction of isothiocyanate **1** *with the hydrazine derivatives: General procedure*

To a solution of isothiocyanate **1** (3 mmole), hydrazine hydrate, phenylhydrazine, 2-pyridyl hydrazine, semicarbazide HCl, thiosemicarbazide, benzoyl hydrazine, or ethyl hydrazine carboxylate, in acetonitrile (50 mL) was added. A few drops of triethylamine were added in the case of the reaction with semicarbazide HCl. The mixture was refluxed for 2–3 hours (TLC), and cooled to room temperature. The precipitated solid was filtered off, washed with ethanol and recrystallised from the suitable solvent.

*5-[(*E,Z*)-2-(Thiophen-2-yl)vinyl]-1*H*-1,2,4-triazole-3(2*H*)-thione* **(3a):** (87% yield); yellow crystals; m.p. > 300 °C (DMF); IR: 3238, 3160 (NH), 1674 (C=N), 1604 (C=C), 1148 (C=S); ^{1}H NMR (DMSO-d6) δ: 7.21–7.78 (m, 3H, ArH), for *Z*-isomer δ: 6.22 (d, 1H, *J* = 11.12 Hz, CH=), 7.91 (d, 1H, *J* = 12.0 Hz, CH=), 12.35, 13.52 (br. s, 2NH exchangeable); for *E*-isomer δ: 6.76 (d, 1H, *J* = 15.4 Hz, CH=), 8.00 (d, 1H, *J* = 14.6 Hz, CH=), 11.95, 14.10 (br. s, 2NH exchangeable), MS *m/z* (%): 209 ($M^{+\cdot}$, 6.8), 153(8.5), 139 (15.4), 137 (100), 122(5), 109 (72); Anal. Calcd for $C_8H_7N_3S_2$ (209.29); C, 45.91; H, 3.37; N, 20.08. Found: C, 45.67; H, 3.51; N, 20.14%.

*[(*E*)-1-Phenyl-5-(2-(thiophen-2-yl)vinyl)]-1*H*-1,2,4-triazole-3(2*H*)-thione* **(3b)**: (92% yield); yellow crystals; m.p. 228–231 °C (ethanol); IR: 3120 (NH), 1644 (C=N), 1598 (C=C), 1242 (C=S), 766, 688 δ_{5H}; ^{1}H NMR (DMSO-d6) δ: 6.72 (d, 1H, CH=, *J* = 16.8 Hz), 7.75 (d, 1H, CH=, *J* = 17.6 Hz), 7.15–7.99 (m, 8H, ArH), 13.99 (br. s, NH exchangeable); MS *m/z* (%): 285 ($M^{+\cdot}$, 36), 286 ($M^{+\cdot}$ + 1, 10), 287 ($M^{+\cdot}$ + 2, 5), 284 (20), 252 (18), 143 (45), 109 (12), 91 (100); Anal. Calcd for $C_{14}H_{11}N_3S_2$ (285.39); C, 58.92; H, 3.89; N, 14.72. Found: C, 58.78; H, 3.70; N, 14.59%.

*[(*E*)-1-(Pyridin-2-yl)-5-(2-(thiophen-2-yl)vinyl)]-1*H*-1,2,4-triazole-3(2*H*)-thione* **(3c)**: (88% yield); yellow crystals; m.p. 239–241 °C (ethanol); IR: 3215 (NH), 1637 (C=N), 1594 (C=C), 1213 (C=S); ^{1}H NMR (DMSO-d6) δ: 6.69 (d, 1H, CH=, *J* = 15.6 Hz), 6.73–7.79 (m, 6H, ArH), 7.88 (d, 1H, CH=, *J* = 15.6 Hz), 8.10 (d, 1H, H, *J* = 6.8 Hz), 11.16 (br.s, NH exchangeable); MS *m/z* (%): 286 ($M^{+\cdot}$, 34), 287 ($M^{+\cdot}$ + 1, 7),

288 ($M^{+\cdot}$ + 2, 2), 285 (35), 253 (21), 150 (47), 109 (9), 92 (100); Anal. Calcd for $C_{13}H_{10}N_4S_2$ (286.38); C, 54.52; H, 3.52; N, 19.56. Found: C, 54.39; H, 3.46; N, 19.41%.

*(*E*)-N-[2-(carbamothioyl)hydrazinylcarbonothioyl]-3-(thiophen-2-yl)acrylamide* **(4b)**: (91% yield); pale yellow crystals; m.p. 203–205 °C with decomposition (ethanol); IR: 3406, 3250, 3178, 3076 (NH), 1680 (C=O), 1604 (C=C), 1216, 1134 (C=S); ^{1}H NMR (DMSO-d6) δ: 6.76 (d, 1H, CH=, *J* = 15.4 Hz), 7.20–7.80 (m, 3H, ArH), 7.94 (d, 1H, CH=, *J* = 16.0 Hz), 8.19, 9.74, 10.72, 11.58, 13.60 (br. s, 5NH exchangeables); MS *m/z* (%): 286 ($M^{+\cdot}$, 19), 287 ($M^{+\cdot}$ + 1, 3), 288 ($M^{+\cdot}$ + 2, 2), 253 (14), 252 (29), 152 (43), 137 (100), 109 (23), 100 (3); Anal. Calcd for $C_9H_{10}N_4OS_3$ (286.40); C, 37.74, H, 3.52; N, 19.56. Found: C, 37.38; H, 3.39; N, 19.48%.

*[(*E*)-N-(5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-3-(thiophen-2-yl)]acrylamide* **(5a)**: (77% yield); yellow crystals; m.p. 219–221 °C (ethanol); IR: 3314, 3234, 3160 (NH), 1682 (C=O), 1588 (C=N), 1544 (C=C), 1254 (C=S); ^{1}H NMR (DMSO-d6) δ: 6.76 (d, 1H, CH=, *J* = 15.8 Hz), 7.18–7.76 (m, 3H, ArH), 7.88 (d, 1H, CH=, *J* = 15.8 Hz), 9.47, 9.82 11.12 (br. s, 3NH exchangeables); MS *m/z* (%): 236 ($M^{+\cdot}$, 5), 237 ($M^{+\cdot}$ + 1, 1), 152 (61), 137 (100), 109 (52); Anal. Calcd for $C_9H_8N_4O_2S$ (236.25); C, 45.75; H, 3.41; N, 23.72. Found: C, 45.58; H, 3.23; N, 23.49%.

*[*E*-N-(5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-3-(thiophen-2-yl)]acrylamide* **(5b)**: (86% yield); yellow crystals; m.p. 246–248 °C (toluene); IR: 3356, 3182, 3102 (NH), 1666 (C=O), 1610 (C=N), 1510 (C=C), 1192 (C=S); ^{1}H NMR (DMSO-d6) δ: 6.63 (d, 1H, CH=, *J* = 15.4 Hz), 6.82 (br. s, 2NH exchangeable), 7.17–7.74 (m, 3H, ArH), 7.85 (d, 1H, CH=, *J* = 15.8 Hz), 12.04 (br. s, NH exchangeable); MS *m/z* (%): 252 ($M^{+\cdot}$, 65), 253 ($M^{+\cdot}$ + 1, 11), 254 ($M^{+\cdot}$ + 2, 5), 219 (23), 152 (33), 137 (100), 109 (19), 100 (11); Anal. Calcd for $C_9H_8N_4OS_2$ (252.32); C, 42.84, H, 3.20; N, 22.21. Found: C, 42.68; H, 3.03; N, 21.96%.

*(*E*)-*N*-[2-(benzoyl)hydrazinylcarbonothioyl]-3-(thiophen-2-yl) acrylamide* **(6a)**: (88% yield); pale yellow crystals; m.p. 203–204 °C (ethanol); IR: 3320, 3182, 3160 (NH), 1680, (C=O), 1628 (C=C), 1228 (C=S); ^{1}H NMR (DMSO) δ: 6.23 (d, 1H, CH=, *J* = 14.6 Hz), 7.31 (d, 1H, CH=, *J* = 18.6 Hz), 7.11–8.03 (m, 8H, ArH), 8.54, 9.92, 13.50 (br. s, 3NH exchangeable); MS *m/z* (%): 331 ($M^{+\cdot}$, 5.4), 332 ($M^{+\cdot}$ + 1, 1.4), 333 ($M^{+\cdot}$ + 2, 1.1), 194 (2.5), 137 (77), 109 (47.4), 105 (98), 77 (100), 76 (12); Anal. Calcd for $C_{15}H_{13}N_3O_2S_2$ (331.41); C, 54.36; H, 3.95; N, 12.68. Found: C, 53.98; H, 3.76; N, 12.55%.

*(*E*)-Ethyl 2-(3-(thiophen-2-yl)acryloylcarbamothioyl) hydrazine carboxylate* **(6b)**: (96% yield); yellow crystals; m.p. 150–152 °C (ethanol); IR: 3320, 3200 (NH), 1738, 1684 (C=O), 1614 (C=C), 1140 (C=S); ^{1}H NMR (DMSO-d6) δ: 1.22 (m, 3H, $\underline{CH_3}CH_2$–), 4.11 (d, 2H, *J* = 6.8 Hz, $CH_3\underline{CH_2}$–), 6.78 (d, 1H, CH=, *J* = 15.4 Hz), 7.20–7.78 (m, 3H, ArH), 7.92 (d, 1H, CH=, *J* = 15 Hz), 9.78, 11.61, 11.79 (br. s, 3NH exchangeables); MS *m/z* (%): 299 ($M^{+\cdot}$, 3), 254 (12), 226 (4), 195 (27), 152 (42), 137 (100), 109 (18); Anal. Calcd for $C_{11}H_{13}N_3O_3S_2$ (299.37); C, 44.13; H, 4.38; N, 14.04. Found: C, 43.87; H, 4.17; N, 14.22%.

*(*E*)-N-[(5-phenyl-1,3,4-thiadiazol-2-yl)-3-(thiophen-2-yl)]acrylamide* **(7)**: A suspension of **6a** (0.5 g) in ethanol (30 mL), 3M hydrochloric acid (5 mL) was refluxed for 2 h. The solution was vacuum-evaporated to a small volume. A solution of sodium carbonate (0.1 N) was added until effervescence ceased. The yellow precipitate obtained was filtered off and recrystallised from ethanol to give (83% yield); pale yellow crystals; m.p. 244–246 °C (toluene); IR: 3120 (NH), 1684, (C=O), 1610 (C=N), 1564 (C=C), 784, 694 δ_{5H}; ^{1}H NMR (DMSO) δ: 6.20 (d, 1H, CH=, *J* = 15.0 Hz), 7.76 (d, 1H, CH=, *J* = 13.8 Hz), 7.16–7.94 (m, 8H, ArH), 13.66 (br. s, NH exchangeable); MS *m/z* (%): 313 ($M^{+\cdot}$, 28), 314 ($M^{+\cdot}$ + 1, 5), 315 ($M^{+\cdot}$ + 2, 1), 161 (2), 152 (33), 137 (100), 109 (44), 103 (7), 89 (13), 77 (76), 76 (52); Anal. Calcd for $C_{15}H_{11}N_3OS_2$ (313.40); C, 57.49; H, 3.54; N, 13.41. Found: C, 57.32; H, 3.37; N, 13.23%.

Reaction of **6a** *and* **6b** *with ethanolic sodium hydroxide: general procedure* A solution of **6a** or **6b** in ethanol (30 mL), 3M sodium hydroxide (10 mL) was refluxed for 1 h, vacuum-distilled to *ca* half-volume and acidified with 3M hydrochloric acid. The precipitate was collected and crystallised from ethanol to give compounds **8** or **9**.

*[(*E*)-1-(3-phenyl-5-thioxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-3-(thiophen-2-yl)]prop-2-en-1-one* **(8)**: A pale yellow crystals; (79% yield); m.p. 295–297 °C; IR: 3180 (NH), 1682, (C=O), 1618 (C=N), 1556 (C=C), 1172 (C=S), 744, 688 δ_{5H}; ^{1}H NMR (DMSO) δ: 6.72 (d, 1H, CH=, *J* = 15.4 Hz), 7.16–8.04 (m, 9H, 8ArH + 1CH=), 12.84 (br. s, NH exchangeable); MS *m/z* (%): 313 ($M^{+\cdot}$, 8.0), 314 ($M^{+\cdot}$ + 1, 0.6), 182 (6.5), 176 (3.5), 151 (2), 137 (100), 109 (39), 103 (11), 89 (7), 77 (25), 76 (10); Anal. Calcd for $C_{15}H_{11}N_3OS_2$ (313.40); C, 57.49; H, 3.54; N, 13.41. Found: C, 57.28; H, 3.43; N, 13.54%.

*(*E*)-4-(3-(thiophen-2-yl)acryloyl)-5-thioxo-1,2,4-triazolidin-3-one* **(9)**: (68% yield); pale yellow crystals; m.p. 260–262 °C; IR: 3315, 3220 (NH), 1681, 1665 (C=O), 1574 (C=C), 1196 (C=S); ^{1}H NMR (DMSO) δ: 6.22 (d, 1H, CH=, *J* = 16.6 Hz), 7.12–7.61 (m, 3H, ArH), 7.60 (d, 1H, CH=, *J* = 14 Hz), 9.42, 13.53 (br. s, 2NH exchangeable); MS *m/z* (%): 253 ($M^{+\cdot}$, 12), 254 ($M^{+\cdot}$ + 1, 3), 255 ($M^{+\cdot}$ + 2, 1.7), 116 (2), 151 (21), 137 (100), 109 (36); Anal. Calcd for $C_9H_7N_3O_2S_2$ (253.30); C, 42.68; H, 2.79; N, 16.59. Found: C, 42.37; H, 2.56; N, 16.22%.

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