Synthesis of 3,3'-bipyrazole, 5,5'-bi-1,3,4-thiadiazole and fused azole systems *via* bishydrazonoyl chlorides

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A number of novel 3,3'-bi-pyrazole, 5,5'-bi-1,3,4-thiadiazole and azolothiazole derivatives were synthesised *via* cycloadditions of bis-hydrazonoyl chlorides with olefin, active methylene, and thioacetanilide synthons.

Keywords: hydrazonoyl chlorides, benzothiazoles, imidazole-2-thioles, 3,3'-bipyrazoles, 5,5'-bi-1,3,4-thiadiazoles, fused imidazoles, thiazoles, 1,2,4-triazoles

Bipyrazole derivatives are involved in the manufacture of a wide variety of medicinals and pharmacueticals.[1-4] In addition, bi-1,3,4-thiadiazole derivatives are proved to be interesting photoluminescence and electroluminescence and are used as thermotropic liquid crystals.[5,6] In continuation of our ongoing research program investigating the utilisation of hydrazonoyl chlorides as versatile and useful building blocks for the synthesis of a wide variety of fused and bi-heterocyclic systems such as pyrazolo[1,2-*a*]benzimidazoles,[7] pyrrolo[2,1-*b*]benzothiazoles,[8] 1,3,4-thiadiazoles,[9] 2,2'-bi-1,3,4-thiadiazoles,[10] 3,3'-bi-1,2,4-triazoles,[11] 3,3'-bipyrazoles,[12] we report herein a convenient route to some new 3,3'-bipyrazole, 5,5'-bi-1,3,4-thiadiazole and 2,3-bisphenylhydrazono-azolothiazole derivatives.

Reaction of the bis-hydrazonoyl chloride **1a** with fumaronitrile (**2**) in 1:2 molar ratio was performed in refluxing benzene in the presence of triethylamine, to afford only one isolable product that analysed for $C_{20}H_{12}N_6$. The structure of the obtained product was established as 1,1'-diphenyl-3,3'-bipyrazole-4,4'-dicarbonitrile (**4**) (Scheme 1) on the basis of its elemental and spectral analysis. The ^{1}H NMR spectrum showed no aliphatic but only aromatic protons. The IR spectrum of compound **4** exhibited a strong nitrile absorption peak at 2218 cm^{-1}. The molecular weight was confirmed by the presence of the M^+ ion, *m/z* 336, as the base peak. Compound **4** is assumed to be formed through initial formation of the 3,3'-bipyrazoline-4,4',5,5'-tetracarbonitrile cycloadduct **3** followed by elimination of two molecules of hydrogen cyanide under the basic reaction conditions.

When bis-hydrazonoyl chlorides **1a–c** were treated with 3-(benzothiazol-2-yl)-3-oxo-propanenitrile (**5**) in ethanolic sodium ethoxide at ambient temperature they afforded the 3,3'-bipyrazole-4,4'-dicarbonitrile derivatives **6a–c** in good yields. The lack of amino function in both IR and ^{1}H NMR spectra of the reaction products and the presence of a nitrile absorption band around 2235 cm^{-1} in their IR spectra favoured structures **6a–c** and ruled out the alternative structures **7a–c** (Scheme 1). Their mass spectra showed, in each case, a fragment ion corresponding to $M^+/2$ in addition to the molecular ion peak (see Experimental section).

The behaviour of bis-hydrazonoyl chloride **1a** towards the reactive sulfur nucleophiles **9a–d** was also investigated. When compound **1a** was allowed to react with the non-isolable intermediate **9a–d** (formed *in situ* from the reaction of the appropriate active methylene compounds **5** and **8a–c** with phenyl isothiocyanate in the presence of potassium hydroxide), it afforded in each case a 1:2 cyclocondensation product. A fragment ion corresponding to $M^+/2$ was seen in the mass spectrum of the product. This finding provides a good evidence for the 5,5'-bi-1,3,4-thiadiazole structure **12** rather than the alternative criss-cross fused heterocyclic system **13** (Scheme 2).

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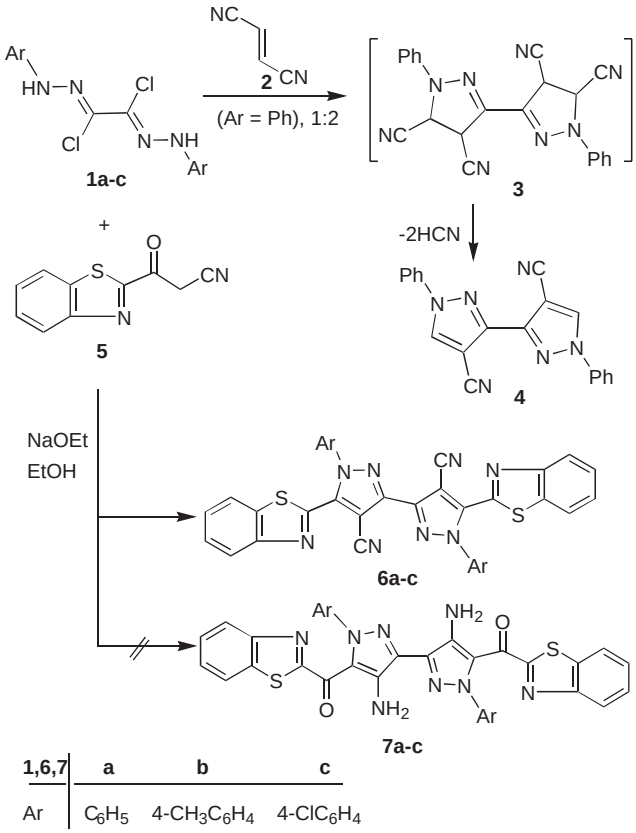
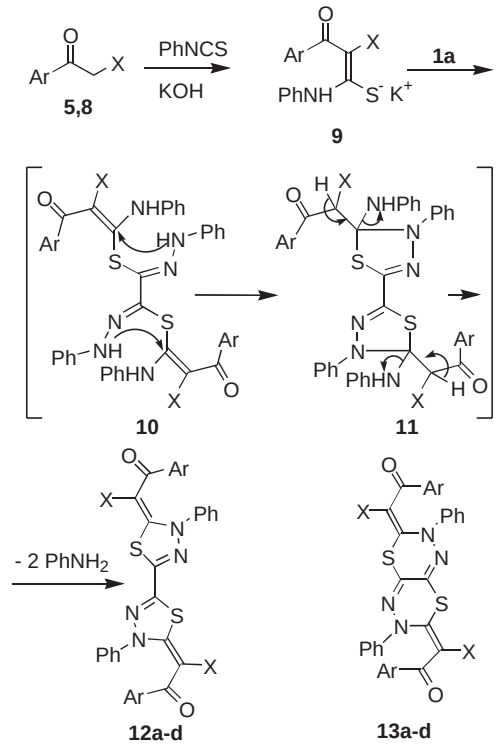


Scheme 1

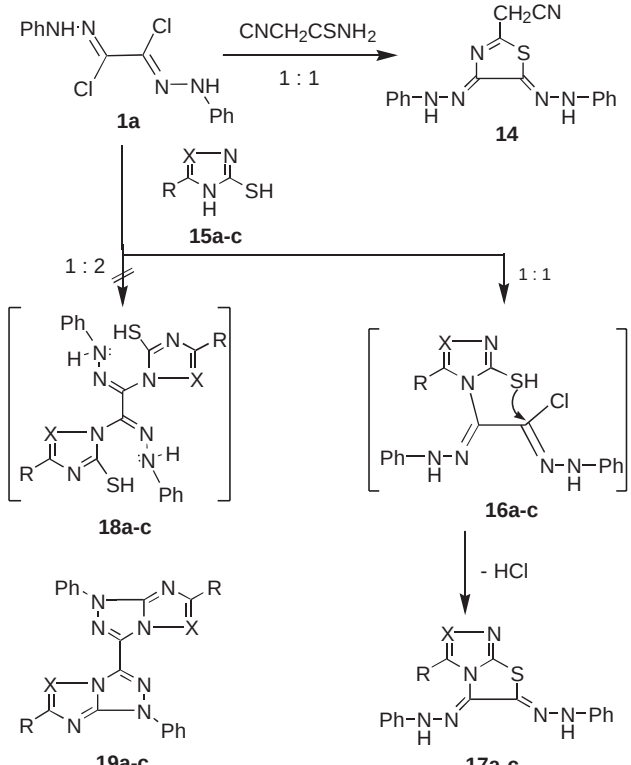
On the other hand, when compound **1a** was treated with cyanothioacetamide either in 1:2 or 1:1 molar ratio in refluxing ethanol, in the presence of triethylamine, only one isolable product was obtained. Elemental analyses and spectral data (IR, ^{1}H NMR and MS) showed that the reaction product is a 1:1 rather than the expected 1:2 cycloadduct. The structure of the isolated product was identified as 2,3-bis-phenylhydrazono-2,3-dihydrothiazole (**14**) (Scheme 3). ^{1}H NMR spectrum of compound **14** revealed singlets at δ 4.78, 10.15 and 11.22 due to methylene and hydrazone-NH protons.

Furthermore, when compound **1a** was treated with imidazole-2-thiol (**15a**) in 1:2 molar ratio, under similar reaction conditions, it afforded a good yield of a brown colored product. Elemental analyses and spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS) showed that the reaction product is 1:1 instead of the expected 1:2 cyclocondensation product. This result was confirmed by conducting the same reaction using 1:1 molar ratio of the starting substrates, where the same product was obtained. The structure of the isolated product was identified as 2,3-bisphenylhydrazono-2,3-dihydroimidazo[2,1-*b*]thiazole (**17a**) (Scheme 3).



8-13	a	b	c	d
Ar	C_6H_5	C_6H_5	2- furyl	2-benzothiazolyl
X	COOEt	CN	CN	CN

Scheme 2



15-19	R	X
a	H	CH
b	C_6H_5	C-C_6H_5
c	H	N

Scheme 3

The expected 1:2 cycloadduct **19a,** which could be formed *via* loss of two molecules of hydrogen chloride and hydrogen sulfide, was not detected in the crude reaction product. Similar results were observed when compound **1a** was treated with 4,5-diphenylimidazole-2-thiol (**15b**) and 1,2,4-triazole-3-thiol (**15c**), respectively to afford the corresponding 1:1 cyclocondensation products **17b,c** (Scheme 3). The IR and ^{1}H NMR spectra of compounds **17a-c** exhibited, in each case, two hydrazone NH peaks (*cf.* Experimental part).

Experimental

Melting points were measured with a Gallenkamp apparatus. IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1}H NMR spectra were determined in DMSO-d_6 at 300 MHz on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 e.V. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

Bis-hydrazonoyl chlorides **1a–c** [11,13], active methylene compounds **5**[14], **8b**[15], and **8c**[16], and cyanothioacetamide[17] were prepared by the literature procedures as referenced.

1,1'-Diphenyl-3,3'-bipyrazole-4,4'-dicarbonitrile (**4**): A mixture of the bis-hydrazonoyl chloride **1a** (0.307 g, 1 mmol) and fumaronitrile (**2**) (0.156 g, 2 mmol) in dry benzene (20 ml),was refluxed for 4h in the presence of triethylamine (0.1 ml), then left to cool to room temperature. The solvent was evaporated under reduced pressure then the residue was treated with methanol to give a solid product. The precipitate was filtered off, washed with methanol and dried. Recrystallisation from acetic acid afforded the 3,3'-bipyrazole-4,4'-dicarbonitrile **4**, yield 59%, grey solid, m.p. 243–244 °C; IR (KBr): ν_{max} 2218 (C≡N), 1604 (C=N) cm^{-1}; ^{1}H NMR [DMSO-d_6]: δ 7.22–7.45 (m, 10H, ArH), 7.88 (s, 2H); ^{13}C NMR [DMSO-d_6]: δ 93.3, 114.7, 120.9, 130.1, 131.6, 137.9, 139.95, 146.5; MS: *m/z* (%) 336 (M$^+$, 100), 310 (13), 233 (4), 169 (6.7), 168 (M$^+$/2, 7.8), 104 (13), 77 (83), 51 (53). Calcd. for $C_{20}H_{12}N_6$: C, 71.42; H, 3.60; N, 24.99. Found: C, 72.73; H, 3.81; N, 24.62 %.

1,1'-Diaryl-5,5'-(dibenzothiazol-2-yl)-3,3'-bipyrazole-4,4'-dicarbonitriles (**6a–c**): 3-Oxo-3-(benzothiazol-2-yl)propanenitrile (**5**) (0.404 g, 2 mmol) was added to ethanolic sodium ethoxide [prepared from sodium metal (0.046 g, 2 mmol) and absolute ethanol (20 ml)] with stirring. After stirring for 15 min, the appropriate bishydrazonoyl chloride **1a–c** (1 mmol) was added portionwise over a period of 30 min and the reaction mixture was stirred for further 12h at room temperature. The solid that formed was filtered off, washed with water and dried. Recrystallisation from dimethylformamide (DMF) afforded the 3,3'-bipyrazole derivatives **6a–c** in 73-87% yields.

Diphenyl derivative **6a:** yield 85%, pale yellow solid, m.p. >300 °C; IR (KBr): ν_{max} 2235 (C≡N), 1565 (C=N) cm^{-1}; ^{1}H NMR [DMSO-d_6]: δ 7.21–7.84 (m, ArH); MS: *m/z* (%) 602 (M$^+$, 81), 569 (4.5), 441 (4), 302 (11.5), 301 (M$^+$/2, 39), 275 (49), 248 (22), 223 (12.5), 108 (17), 77 (100). Calcd. for $C_{34}H_{18}N_8S_2$: C, 67.76; H, 3.01; N, 18.59; S, 10.64. Found: C, 67.61; H, 3.25; N, 18.42; S, 10.47 %.

Di-p-tolyl derivative **6b**: yield 73%, pale yellow solid, m.p. >300 °C; IR (KBr) ν_{max} 2241 (C≡N), 1564 (C=N) cm^{-1}; ^{1}H NMR [DMSO-d_6] δ 2.40 (s, 6H), 7.43–7.64 (m, 12H, ArH), 8.11–8.20 (m, 4H, ArH); MS: *m/z* (%) 630 (M$^+$, 100), 340 (25), 316 (52), 315 (M$^+$/2, 37), 289 (53), 236 (24), 108 (20), 91 (52), 77 (19), 65 (63). Calcd. for $C_{36}H_{22}N_8S_2$: C, 68.55; H, 3.52; N, 17.77; S, 10.17. Found: C, 68.63; H, 3.45; N, 17.32; S, 10.33 %.

Di-p-chlorophenyl derivative **6c**: yield 87%, pale yellow solid, m.p. >300 °C; IR (KBr): ν_{max} 2237 (C≡N), 1556 (C=N) cm^{-1}; ^{1}H NMR insoluble in the common NMR solvents; MS, *m/z* (%) 670 (M$^+$, 100), 336 (66), 335 (M$^+$/2, 70), 309 (84), 273 (54), 257 (41), 134 (26), 111 (95), 75 (90), 69 (85). Calcd. for $C_{34}H_{16}Cl_2N_8S_2$: C, 60.81; H, 2.40; N, 16.69; S, 9.55. Found: C, 60.65; H, 2.43; N, 16.31; S, 9.48 %.

*5,5'-Di-(aroylmethylene)-4,4'-diphenyl-4,4',5,5'-tetrahydro-2,2'-bi-(1,3,4-thiadiazole)*s (**12a-d**): To a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in DMF (20 ml) was added the appropriate active methylene substrate (2 mmol). The mixture was stirred for 30 min., then phenylisothiocyanate (0.27 g, 2 mmol) was added, and the stirring was continued for 6h. The bis-hydrazonoyl chloride **1a** (1 mmol) was added portion wise, and the resulting reaction mixture was stirred for further 12h, during which the bis-hydrazonoyl chlorides **1a** was dissolved and a brown-coloured product was precipitated. The solid product was filtered off, washed with water and ethanol, dried and finally recrystallised from DMF to

afford the corresponding 5,5'-bi-1,3,4-thiadiazole derivatives **12a–d** in 62–77% yields.

Dibenzoyl diester **12a**: yield 66%, greenish solid, m.p. 290 °C; IR (KBr): ν_{max} 1712 (C=O), 1651 (C=O), 1595 (C=N) cm^{-1}; ^1H NMR [DMSO-d_6] δ 1.2 (t, 6H, *J* = 7 Hz), 3.95 (q, 4H, *J* = 7 Hz), 7.33–7.64 (m, 20H, ArH); MS, *m/z* (%) 702 (M^+, 2.5), 603 (38), 530 (6.3), 351 (M^+/2, 1.1), 270 (2.3), 211 (2.4), 135 (6.5), 115 (20.0), 93 (9.4), 73 (100); Calcd. for $C_{38}H_{30}N_4O_6S_2$: C, 64.94; H, 4.30; N, 7.97; S, 9.13. Found: C, 64.59; H, 4.66; N, 7.63; S, 9.27 %.

Dibenzoyl dicarbonitrile **12b**: yield 74%, yellowish-brown solid, m.p. >300 °C; IR (KBr) ν_{max} 2207 (C≡N), 1652 (C=O), 1594 (C=N) cm^{-1}; ^1H NMR [DMSO-d_6] δ 7.31–7.74 (m, ArH); MS, *m/z* (%) 608 (M^+, 12), 531 (5), 327 (2.0), 304 (M^+/2, 0.7), 239 (6), 92 (100), 77 (66); Calcd. for $C_{34}H_{20}N_6O_2S_2$: C, 67.09; H, 3.31; N, 13.81; S, 10.54. Found: C, 67.42; H, 3.26; N, 13.97; S, 10.28 %.

Di-2-furoyl dicarbonitrile **12c**: yield 62%, yellowish-green solid, m.p. >300 °C; IR (KBr) ν_{max} 2195 (C≡N), 1642 (C=O), 1574 (C=N) cm^{-1}; ^1H NMR, insoluble in the common NMR solvents; MS, *m/z* (%) 588 (M^+, 13), 570 (8), 495 (10), 303 (4), 294 (M^+/2, 2.4), 253 (5), 225 (8), 95 (100), 77 (20); Calcd. for $C_{30}H_{16}N_6O_4S_2$: C, 61.21; H, 2.74; N, 14.28; S, 10.90. Found: C, 61.38; H, 3.02; N, 14.22; S, 10.73 %.

Di-2-benzothiazolylcarbonyl dicarbonitrile **12d**: yield 77%, yellow solid, m.p. >300 °C; IR (KBr) ν_{max} 2215 (C≡N), 1658 (C=O), 1600 (C=N) cm^{-1}; ^1H NMR, insoluble in the common NMR solvents; MS, *m/z* (%) 722 (M^+, 12), 613 (72), 569 (25), 361 (M^+/2, 2.1), 345 (14), 336 (20), 233 (23), 181 (27), 91 (100), 64 (35); Calcd. for $C_{36}H_{18}N_8O_2S_4$: C, 59.82; H, 2.51; N, 15.50; S, 17.74. Found: C, 59.45; H, 2.36; N, 15.67; S, 17.72 %.

2,3-Bis-phenylhydrazono-2,3-dihydro-thiazole 14, -imidazo[2,1-b] thiazoles **17a,b**, *and -1,2,4-triazolo[3,4-b]thiazole derivative* **17c**: A mixture of the bis-hydrazonoyl chloride **1a** (0.307 g, 1 mmol) and cyanothioacetamide or imidazole-2-thioles **15a,b** or 1,2,4-triazol-3-thiole (**15c**) (1 mmol) in ethanol (20 ml), in the presence of triethylamine (0.1 ml), was refluxed for 1h, then left to cool to room temperature. The precipitated product was filtered off, washed with water followed by ethanol and then dried. Recrystallisation from dimethylformamide (DMF) or acetic acid afforded the corresponding 2,3-dihydrothiazole **14**, imidazo[2,1-*b*]thiazoles **17a,b** and triazolo [3,4-*b*]thiazole **17c**, respectively, in 52-76% yields.

Thiazole derivative **14**: yield 69%, brown solid, m.p. 170–172 °C (DMF); IR (KBr) ν_{max} 3374, 3216 (2NH), 2192 (C≡N) cm^{-1}; ^1H NMR [DMSO-d_6] δ 4.78 (s, 2H, CH_2), 6.83–7.60 (m, 10H, ArH), 10.15 (s, 1H, NH), 11.22 (s, 1H, NH); MS, *m/z* (%) 335 (M^++1, 4.5), 334 (M^+, 11), 303 (19), 226 (4), 174 (7), 142 (11), 104 (15), 93 (22), 77 (100), 65 (26). Calcd. for $C_{17}H_{14}N_6S$: C, 61.06; H, 4.22; N, 25.13; S, 9.59. Found: C, 61.38; H, 4.08; N, 25.29; S, 9.61 %.

Imidazo-thiazole derivative **17a**: yield 65%, greenish-yellow solid, m.p. 258–260 °C; IR (KBr): ν_{max} 3362, 3217 (2NH), 1593 (C=N) cm^{-1}; ^1H NMR [DMSO-d_6] δ 6.89–7.03 (m, 2H), 7.20–7.44 (m, 10H), 10.38 (s, 1H, NH), 11.01 (s, 1H, NH); ^{13}C NMR [DMSO-d_6] δ 113.0, 120.7, 121.4, 129.2, 133.2 (C), 126.1, 128.9, 139.7, 139.9, 140.0, 143.2, 143.3 (CH); MS, *m/z* (%) 335 (M^++1, 4.9), 334 (M^+, 23), 242 (10), 229 (3.9), 136 (2.8), 105 (24), 93 (26), 77 (100), 65 (38). Calcd. for $C_{17}H_{14}N_6S$: C, 61.06; H, 4.22; N, 25.13; S, 9.59. Found: C, 61.23; H, 4.18; N, 25.48; S, 9.46 %.

Imidazo-thiazole derivative **17b**: yield 76%, orange solid, m.p. 194–196 °C; IR (KBr): ν_{max} 3407, 3325 (2NH), 1597 (C=N) cm^{-1}; ^1H NMR [DMSO-d_6] δ 6.71–6.74 (m, 2H, ArH), 7.41–7.63 (m, 18H, ArH), 10.63 (s, 1H, NH), 12.89 (s, 1H, NH); MS, *m/z* (%) 487 (M^++1, 3.6), 486 (M^+, 8), 396 (18), 277 (51), 165 (58), 103 (12.5), 77 (100); Calcd. for $C_{29}H_{22}N_6S$: C, 71.58; H, 4.56; N, 17.27; S, 6.59. Found: C, 71.72; H, 4.15; N, 17.19; S, 6.55 %.

Triazolo-thiazole derivative **17c**: yield 52%, yellow solid, m.p. 225–226 °C (EtOH/DMF); IR (KBr) ν_{max} 3317, 3271 (2NH), 1604 (C=N) cm^{-1}; ^1H NMR [DMSO-d_6] δ 7.22–7.67 (m, 10H, ArH), 7.98 (s, 1H), 10.45 (s, 1H, NH), 12.61 (s, 1H, NH); MS, *m/z* (%) 335 (M^+, 3.2), 261 (6.0), 244 (8), 217 (3),160 (27), 118 (13), 77 (100), 51 (55). Calcd. for $C_{16}H_{13}N_7S$: C, 57.30; H, 3.91; N, 29.23; S, 9.56. Found: C, 57.52; H, 4.15; N, 29.49; S, 9.34 %.

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