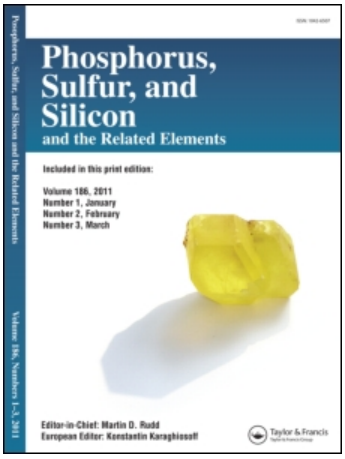

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Facile Synthesis of Thiophene- and 1,3,4-Thiadiazole-Based Heterocycles

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FACILE SYNTHESIS OF THIOPHENE- AND 1,3,4-THIADIAZOLE-BASED HETEROCYCLES

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Treatment of 3-cyanoacetylpyrazole derivative 1 with phenyl isothiocyanate in potassium hydroxide at room temperature followed by α-haloketones 4a–d and hydrazonoyl halides 10a–e gave the corresponding pyrazolylthiophene 6a–d and pyrazolyl-1,3,4-thiadiazole 12a–e derivatives, respectively.

Keywords Hydrazonoyl halides; pyrazoles; 1,3,4-thiadiazoles; thiophenes

INTRODUCTION

Pyrazole derivatives are an interesting class of heterocycles because of their pharmacological importance.[1–3] In addition, 1,3,4-thiadiazoles recently have been reported as highly anti-inflammatory,[4–6] anticonvulsant,[4,7,8] and antimicrobial[9] agents. Furthermore, thiophene derivatives are known to have antiamoebic,[10] molluscicidal,[11] and anti-inflammatory[12,13] activity. Our research work recently has been aimed at the synthesis of various biologically active heterocyclic systems;[14–24] therefore we are concerned here with the synthesis of heterocyclic skeletons having pyrazole, thiophene, and 1,3,4-thiadiazole moieties starting with 3-cyanoacetylpyrazole derivative **1**.

RESULTS AND DISCUSSION

3-Cyanoacetylpyrazole derivative **1** was recently reported by us.[22] Treatment of a solution of the 3-cyanoacetylpyrazole derivative **1** with phenyl isothiocyanate, in dimethylformamide in the presence of potassium hydroxide, at room temperature afforded the intermediate potassium salt **2**, which was converted into the corresponding thioacetanilide derivative **3** upon treatment with dilute hydrochloric acid (Scheme 1). The IR spectrum of compound **3** showed a band at 3242 cm^{-1} due to NH group and two absorption bands at 2233 and 2216 cm^{-1} due to two nitrile functions. Its ^1H NMR spectrum revealed two D_2O-exchangeable singlet signals at δ 4.13 and 14.10 due to SH and NH protons, respectively. Moreover, the mass spectrum of the reaction product **3** exhibited a molecular ion peak at *m/z* 447.

Treatment of compound **3** with chloroacetone (**4a**) in refluxing ethanol and in the presence of a catalytic amount of triethylamine afforded a single product that was identified

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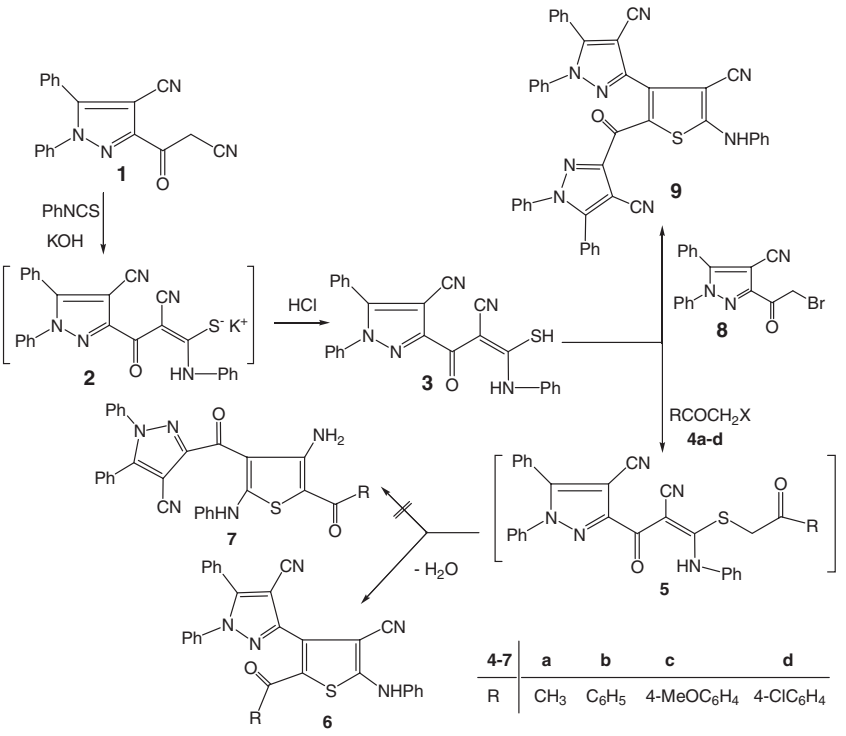


Scheme 1

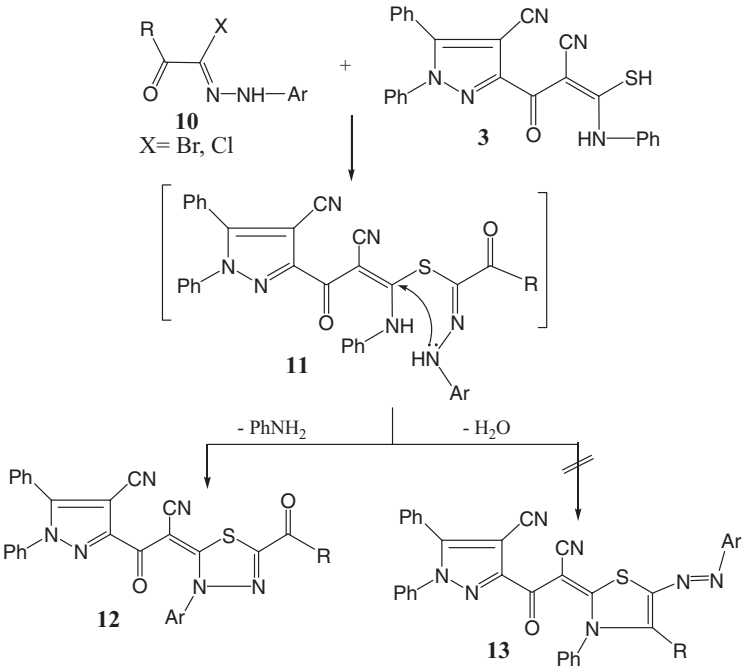
as 2-acetyl-3-(4-cyano-1,5-diphenyl-1H-pyrazol-3-yl)-5-phenylaminothiophene-4-carbonitrile (**6a**), as shown in Scheme 1. Both elemental analysis and spectral data supported the assigned structure **6a** and excluded the other possible structure **7a**. The IR spectrum of the isolated product revealed bands at 2230, 2178, and 1668 cm^{-1}, characteristic for two nitrile and one carbonyl functions, respectively. Its ^1H NMR spectrum revealed a singlet signal at δ 2.25 due to CH_3CO protons and a multiplet at δ 7.27–7.55 due to aromatic protons, in addition to a broad (D_2O exchangeable) signal at δ 10.73 due to NH proton.

The thioacetanilide derivative **3** reacted also with phenacyl bromides **4b–d** under similar reaction conditions to give the corresponding thiophene derivatives **6b–d** but not **7b–d**, as outlined in Scheme 1. The assignment of the latter structures was based on the elemental analyses and spectral data of the reaction products. For example, the IR spectra of the reaction products showed, in each case, two bands in the region 2200–2230 cm^{-1} characterstic for two nitrile functions and a band in the region 3210–3240 cm^{-1} due to NH group. The ^1H NMR of compound **6c**, for example, revealed a singlet signal at δ 2.89 due to OCH_3 protons, and a multiplet at δ 6.80–7.55 due to aromatic protons, in addition to a broad signal at δ 10.81 due to NH proton. Formation of compounds **6a–d** proves that reaction of the thioacetanilide derivative **3** with α-haloketones **4a–d** proceeded via the loss of hydrogen halide followed by elimination of a water molecule from the non-isolable intermediate **5** (Scheme 1).

Furthermore, the 3-bromoacetylpyrazole **8** reacted with the thioacetanilide derivative **3**, under the same reaction conditions above, to afford a single product that has the thiophene structure **9** as depicted in Scheme 1. The elemental analyses and spectral data of the reaction

product were compatible with structure **9**. This assignment was supported by the appearance of NH and carbonyl absorption bands at 3223 and 1680 cm^{-1}, respectively, in addition to two nitrile functions at 2223 and 2214 cm^{-1}, in the IR spectrum of the isolated product. Moreover, its mass spectrum exhibited a peak at *m/z* 714 corresponding to its molecular ion.

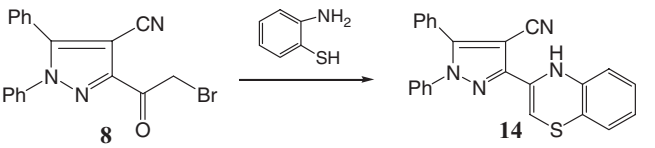
When the thioacetanilide derivative **3** was treated with an equimolar amount of the hydrazonoyl chloride **10a**, it afforded only one isolable product as examined by TLC. Scheme 2 represents the proposed two possible structures **12a** and **13a** for the reaction products. However, the elemental analysis and spectral data are compatible only with the



12	a	b	c	d	e
R	Me	Me	OEt	OEt	NHPh
Ar	4-MePh	4-ClPh	Ph	4-ClPh	4-MePh

Scheme 2

1,3,4-thiadiazole structure **12a**. As outlined in the Experimental section, the IR spectrum of the isolated product **12a** revealed absorption bands at 2240 and 2214 cm^{-1} corresponding to two nitrile functions, in addition to two conjugated carbonyl groups at 1689 and 1670 cm^{-1}. The ^1H NMR spectrum of compound **12a** revealed two singlet signals at δ 2.41 and 2.63 characteristic for 4-tolyl and acetyl protons, respectively, in addition to a multiplet in the region 7.39–7.61 due to aromatic protons. The mass spectrum of compound **12a** exhibited a molecular ion peak at *m/z* 528. These results indicated that the reaction of the thioacetanilide derivative **3** with the hydrazonoyl bromide **10a** proceeded via the loss of hydrogen bromide followed by elimination of aniline molecule from the non-isolable intermediate **11a** (Scheme 2). Further reactions of the thioacetanilide derivative **3** with the



Scheme 3

hydrazonoyl halides **10b–d**, under typical reaction conditions as shown above, resulted in the formation of the 1,3,4-thiadiazole structures **12b–d** as shown in Scheme 2.

Reaction of 3-bromoacetyl-1,5-diphenyl-1H-pyrazole-4-carbonitrile (**8**) with 2-aminothiophenol in refluxing ethanol gave a product identified as 2-(4-cyano-1,5-diphenyl-1H-pyrazol-3-yl)-4H-benzo[1,4]thiazine (**14**) (Scheme 3). Both elemental analyses and spectral data confirmed the assigned structure **14** for the reaction product.

EXPERIMENTAL

Melting points were measured with a Gallenkamp apparatus. The IR spectra were recorded on a 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 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. Cyanoacetylpyrazole **1**,[22] phenacyl bromides **4b–d**,[25] bromoacetylpyrazole **8**,[21] and hydrazonoyl bromides **10a**,**b**,[26] **10c**,**d**,[27,28] and **10e**[29] were prepared according to the procedures in the literature.

Synthesis of the Thioacetanilide Derivative 3

To a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in dimethylformamide (20 mL), the cyanoacetylpyrazole **1** (0.6 g, 2 mmol) was added. After stirring for 30 min, phenyl isothiocyanate (0.27 g, 2 mmol) was added to the resulting mixture. Stirring was continued for 6 h, then poured over crushed ice containing hydrochloric acid. The solid product that formed was filtered off, washed with water, dried, and finally recrystallized from acetic acid to afford 0.81 g (90%) of compound **3**; mp 202–204°C; IR (KBr) ν 3442 (NH), 2233, 2216 (2 C≡N), 1710 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d$_6$) δ 4.13 (br.s, 1H, SH), 7.13–7.17 (m, 1H, ArH), 7.33–7.52 (m, 12H, ArH), 7.83–7.88 (m, 2H, ArH), 14.10 (br.s, 1H, D$_2$O-exchangable, NH); MS *m/z* (%) 447 (M$^+$, 4), 414 (8.2), 273 (98), 180 (12.9), 141 (20.8), 77 (100). Calcd. for $C_{26}H_{17}N_5OS$: C, 69.78; H, 3.83; N, 15.65; S, 7.17. Found C, 69.70; H, 3.90; N, 15.76; S, 7.01%.

Reaction of Thioacetanilide Derivative 3 with α-Haloketones

To a solution of **3** (0.89 g, 2 mmol) in ethanol (20 mL), the appropriate α-bromoketone **4a–d** or **8** (2 mmol) was added followed by few drops of triethylamine. The mixture was refluxed for 2 h, then allowed to cool to room temperature. The formed solid was filtered off, washed with ethanol, and recrystallized from EtOH/DMF to afford the corresponding thiophene derivatives **6a–d** and **9**, respectively.

2-Acetyl-3-(4-cyano-1,5-diphenylpyrazol-3-yl)-5-phenylaminothiophene-4-carbonitrile (6a)

Yield (70%); mp 236–238°C; IR (KBr) ν 3315 (NH), 2230, 2178 (2 C≡N), 1668 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.25 (s, 3H, $COCH_3$), 7.27–7.55 (m, 15H, ArH), 10.73 (br.s, 1H, NH); MS *m/z* (%) 485 (M^+, 33.1), 244 (90.5), 198 (12.6), 144 (22.1), 77 (100). Calcd for $C_{29}H_{19}N_5OS$: C, 71.73; H, 3.94; N, 14.42; S, 6.60. Found: C, 71.85; H, 4.08; N, 14.33; S, 6.87%.

2-Benzoyl-3-(4-cyano-1,5-diphenylpyrazol-3-yl)-5-phenylaminothiophene-4-carbonitrile (6b). Yield (69%); mp 254–256°C; IR (KBr) ν 3219 (NH), 2226 (C≡N), 1688 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.30–7.68 (m, 20H, ArH), 11.03 (br.s, 1H, NH); MS *m/z* (%) 547 (M^+, 32.2), 470 (16.3), 443 (3.8), 295 (8), 180 (9.2), 105 (52.6), 77 (100). Calcd. for $C_{34}H_{21}N_5OS$: C, 74.57; H, 3.87; N, 12.79; S, 5.86. Found: C, 74.79; H, 3.96; N, 12.94; S, 5.70%.

3-(4-Cyano-1,5-diphenylpyrazol-3-yl)-2-(4-methoxybenzoyl)-5-phenylaminothiophene-4-carbonitrile (6c). Yield (76%); mp 220–222°C; IR (KBr) ν 3211 (NH), 2229, 2219 (2C≡N), 1670 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.71 (s, 3H, OCH_3), 6.79–6.89 (m, 2H, ArH), 7.05–7.27 (m, 3H, ArH), 7.37–7.55 (m, 14H, ArH), 10.81 (br.s, 1H, D_2O-exchangable, NH); MS *m/z* 577 (M^+), 337, 244, 139, 98, 77. Calcd. for $C_{35}H_{23}N_5O_2S$ (577.65): C, 72.77; H, 4.01; N, 12.12; S, 5.55. Found: C, 72.89; H, 3.84; N, 12.34; S, 5.78%.

3-(4-Cyano-1,5-diphenylpyrazol-3-yl)-2-(4-chlorobenzoyl)-5-phenylaminothiophene-4-carbonitrile (6d). Yield (75%); mp 233–235°C; IR (KBr) ν 3240 (NH), 2220, 2198 (2 C≡N), 1635 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.25–7.66 (m, 19H, ArH), 10.95 (br.s, 1H, D_2O-exchangable, NH); MS *m/z* 582 (M^+), 337, 244, 139, 98, 77. Calcd for $C_{34}H_{20}ClN_5OS$ (582.07): C, 70.16; H, 3.46; N, 12.03; S, 5.50. Found: C, 70.27; H, 3.40; N, 11.94; S, 5.74%.

2-(4-Cyano-1,5-diphenylpyrazol-3-carbonyl)-3-(4-cyano-1,5-diphenylpyrazol-3-yl)-5-phenylaminothiophene-4-carbonitrile (9). Yield (74%); mp 278–280°C; IR (KBr) ν 3223 (NH), 2223, 2214 (2 C≡N), 1680 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.15–7.27 (m, 10H, ArH), 7.30–7.57 (m, 15H, ArH), 10.85 (s, 1H, NH); MS *m/z* 714 (M^+), 444, 273, 180, 141, 77. Calcd. for $C_{44}H_{26}N_8OS$ (714.8): C, 73.93; H, 3.67; N, 15.68; S, 4.49. Found: C, 74.06; H, 3.73; N, 15.74; S, 4.63%.

Synthesis of 1,3,4-Thiadiazole Derivatives 12a–e

To a solution of **3** (0.89 g, 2 mmol) in ethanol (20 mL), the appropriate hydrazonoyl halide **10** (2 mmol) and few drops of triethylamine were added. The mixture was refluxed for 1 h then allowed to cool. The solid product that formed was filtered off, washed with ethanol, and recrystallized from DMF to afford the corresponding 1,3,4-thiadiazole derivatives **12a–e**.

5-Acetyl-2-(4-cyano-1,5-diphenylpyrazol-3-carbonyl)-3-(4-tolyl) cyanomethylene-2,3-dihydro-1,3,4-thiadiazole (12a). Yield 74%; mp 277–279°C; IR (KBr) ν 2240, 2214 (2 C≡N), 1689, 1670 (2 C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.41 (s, 3H, CH_3), 2.63 (s, 3H, $COCH_3$), 7.39–7.48 (m, 12H, ArH), 7.61 (d, 2H, ArH, J = 7.4 Hz); MS *m/z* 528 (M^+), 311, 272, 144, 91, 77. Calcd. for $C_{30}H_{20}N_6O_2S$ (528.54): C, 68.17; H, 3.81; N, 15.90; S, 6.07. Found: C, 68.29; H, 3.72; N, 16.01; S, 6.02%.

5-Acetyl-2-(4-cyano-1,5-diphenylpyrazol-3-carbonyl)-3-(4-chlorophenyl) cyanomethylene-2,3-dihydro-1,3,4-thiadiazole (12b). Yield 75%; mp 298–300°C; IR (KBr) ν 2281, 2208 (2 C≡N), 1687, 1668 (2 C=O) cm^{-1}; MS, *m/z* 550 (M^+ +2), 548 (M^+), 505, 276, 272, 244, 233, 77. Calcd. for $C_{29}H_{17}N_6O_2SCl$ (549.01): C, 63.44; H, 3.12; N, 15.31; S, 5.84. Found: C, 63.56; H, 3.25; N, 15.41; S, 5.91%.

Ethyl 2-(4-cyano-1,5-diphenylpyrazol-3-carbonyl)-3-phenylcyano-methylene-2,3-dihydro-1,3,4-thiadiazole-5-carboxylate (12c). Yield 69%; mp 254–256°C; IR (KBr) ν 2233, 2200 (2 C≡N), 1718, 1686 (2 C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.36–1.41 (t, 3H, CH_3, $J = 7.2$ Hz), 4.47–4.52 (q, 2H, CH_2, $J = 7.2$ Hz), 7.27–7.78 (m, 15H, ArH); MS *m/z* 544 (M^+), 311, 272, 245, 131, 77. Calcd. for $C_{30}H_{20}N_6O_3S$ (544.595): C, 66.17; H, 3.70; N, 15.43; S, 5.89. Found: C, 66.00; H, 3.50; N, 15.31; S, 5.74%.

Ethyl 2-(4-cyano-1,5-diphenylpyrazol-3-carbonyl)-3-(4-chlorophenyl)cyanomethylene-2,3-dihydro-1,3,4-thiadiazole-5-carboxylate (12d). Yield 73%; mp 261–263°C; IR (KBr) ν cm^{-1} 2232, 2205 (2 C≡N), 1740, 1689 (2 C=O); MS, *m/z* 579 (%) (M^+, 44.7), 549 (13.5), 306 (15), 272 (100), 180 (30.2), 141 (44), 77 (72). Calcd. for $C_{30}H_{19}N_6O_3SCl$ (579.04): C, 62.23; H, 3.31; N, 14.51; S, 5.54. Found: C, 62.05; H, 3.20; N, 14.33; S, 5.46%.

2-(4-Cyano-1,5-diphenylpyrazol-3-carbonyl)-3-(4-tolyl)-5-(carboxamido-*N*-phenyl)cyano-methylene-2,3-dihydro-1,3,4-thiadiazole (12e). Yield 78%; mp 282–284°C; IR (KBr) ν 3180 (NH), 2239, 2208 (2 C≡N), 1665, 1679 (2 C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.42 (s, 3H, CH_3), 7.17–7.49 (m, 15H, ArH), 7.67–7.80 (m, 4H, ArH), 11.08 (br, s, 1H, D_2O exchangable, NH); MS *m/z* (%) 605 (M^+, 41.3), 500 (21.7), 334 (49.1), 191 (16.2), 141 (18.1), 77 (61). Calcd. for $C_{35}H_{23}N_7O_2S$ (605.68): C, 69.41; H, 3.83; N, 16.19; S, 5.30. Found: C, 69.32; H, 4.03; N, 16.35; S, 5.13%.

Synthesis of the Benzothiazine Derivative 14

A mixture of bromoacetylpyrazole **8** (0.73 g, 2 mmol) and 2-aminothiophenol (2.2 mmol) in ethanol (20 mL) was refluxed for 2 h, then allowed to cool. The precipitated product was filtered off, washed with water, and dried. Recrystallization from dimethylformamide afforded 2-(4-cyano-1,5-diphenylpyrazol-3-yl)-4H-benzo[1,4]thiazine (**14**). Yield (81%); mp > 300°C; IR (KBr) ν 3310 (NH), 2230 (C≡N) cm^{-1}; MS *m/z* (%) 392 (M^+, 100), 359 (5.7), 229 (2.6), 121 (6.5), 77 (34.8). Calcd. for $C_{24}H_{16}N_4S$: C, 73.45; H, 4.11; N, 14.28; S, 8.17. Found: C, 73.48; H, 4.02; N, 14.47; S, 8.37%.

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