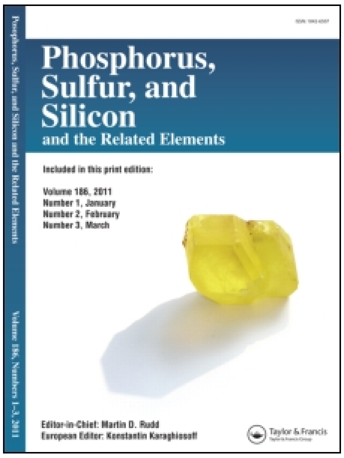

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A Facile Access to Some New Pyrazole, 1,3,4-Thiadiazole, and Thiophene Derivatives via β-Ketosulfones

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A FACILE ACCESS TO SOME NEW PYRAZOLE, 1,3,4-THIADIAZOLE, AND THIOPHENE DERIVATIVES VIA β-KETOSULFONES

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3-Bromoacetyl-1,5-diphenyl-1H-pyrazole-4-carbonitrile (1) reacts with sodium benzenesulfinate to give the corresponding ketosulfone 2. Treatment of 2 with hydrazonoyl chlorides 3a,b gives the 3,3′-bipyrazoles 5a,b. Ketosulfone 2 reacts also with arylidenemalononitriles to give the pyrazolylpyridones 10a,b. The reaction of compound 2 with phenylisothiocyanate and potassium hydroxide and treating intermediate with hydrazonoyl halides and with α-haloketones gives the 1,3,4-thiadiazoles 18a–c and thiophenes 21a–f, respectively.

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

INTRODUCTION

Among sulfur-containing compounds, β-ketosulfones are valuable precursors in organic synthesis.[1–5] Diverse biological activities are associated with ketosulfones. For example, they have been used as antiviral,[6] antitubercular,[7] anti–human renin,[8] and antimicrobial[9] agents. Pyrazole derivatives are also attracting important applications in the field of medicinal chemistry.[10,11] Furthermore, 1,3,4-thiadiazoles were recently reported by us and others as highly anti-inflammatory,[12,13] and anticonvulsant[12,14] agents. In continuation of our work on 1,3,4-thiadiazole derivatives,[15–22] herein we aimed to synthesize some new pyrazole, 1,3,4-thiadiazole, thiophene, and pyridone derivatives through a reactive ketosulfone as key intermediate.

RESULTS AND DISCUSSION

When 3-bromoacetyl-1,5-diphenyl-1H-pyrazole-4-carbonitrile (**1**) reacted with sodium benzenesulfinate in refluxing ethanol. It afforded the novel 1,5-diphenyl-3-(2-(phenylsulfonyl)acetyl)-1H-pyrazole-4-carbonitrile (**2**), as shown in Scheme 1. The structure of compound **2** was established on the basis of its elemental analysis and spectral data. For example, its IR spectrum showed the presence of a strong absorption peak at

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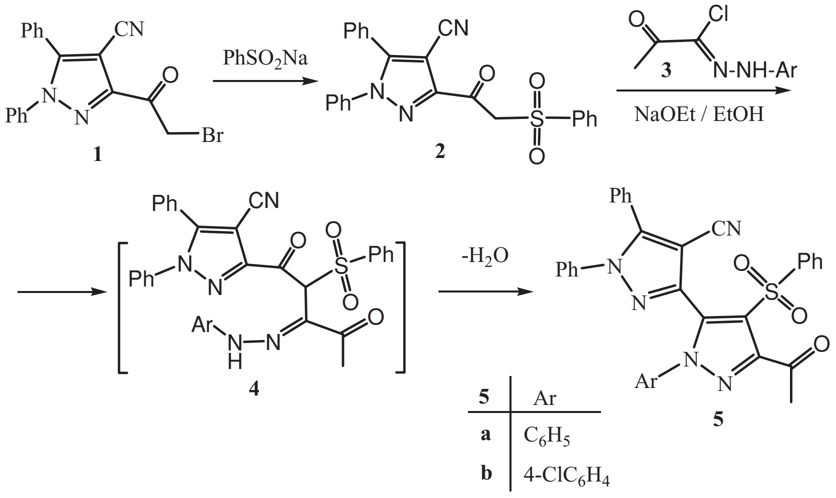
1666 cm^{-1} due to a carbonyl group, and its ^{1}H NMR spectrum revealed a singlet signal at δ 5.25 characteristic for the active methylene protons.

Reaction of the ketosulfone **2** with hydrazonoyl chlorides **3a**,**b** in ethanolic sodium ethoxide solution at room temperature afforded, in each case, a single product (as examined by TLC). The structures of the isolated products were established as 5′-acetyl-1-aryl-2′,5-diphenyl-4′-(phenylsulfonyl)-1H,2′H-3,3′-bipyrazole-4-carbonitriles **5a**,**b** (Scheme 1) on the basis of their elemental and spectral analyses. The ^{1}H NMR spectrum of compound **5a** revealed a singlet signal at δ 2.59 due to $COCH_3$ protons, in addition to an aromatic multiplet in the region δ 7.17–8.23.

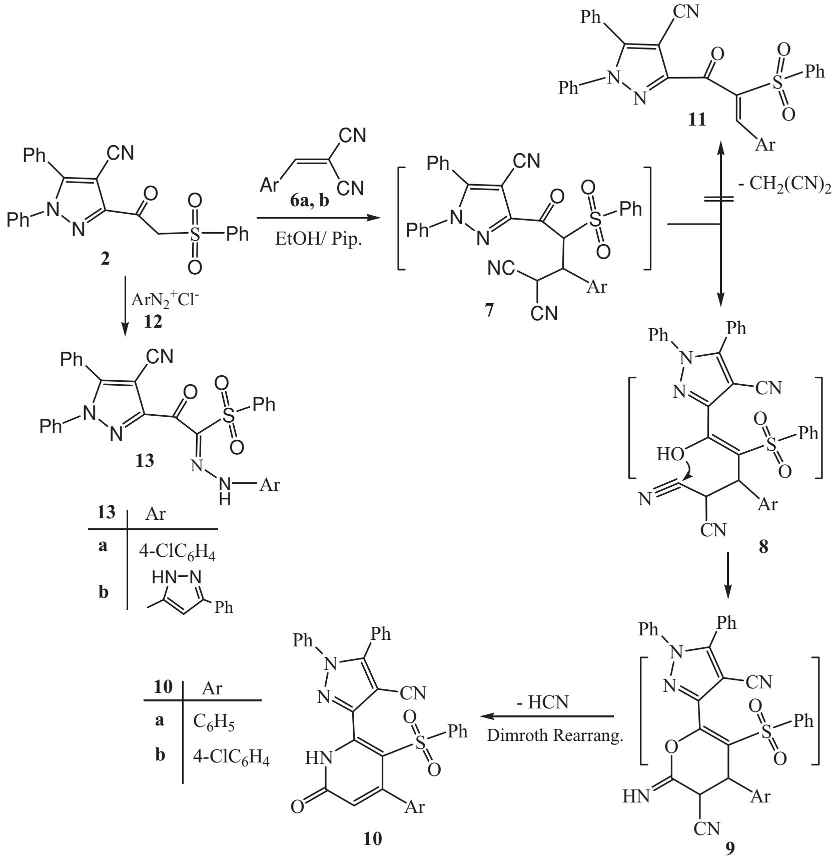


5	Ar
a	C_6H_5
b	4-ClC_6H_4

Scheme 1

The reactivity of the ketosulfone **2** towards arylidenemalononitiriles **6a**,**b** was also investigated. Thus, treatment of compound **2** with benzylidenemalononitrile **6a** in pyridine under reflux conditions gave only one product as examined by TLC. Two possible structures **10** and **11** can be drawn for the reaction product as shown in Scheme 2. However, the elemental analyses and spectroscopic data of the reaction product established its structure as 3-(1,6-dihydro-6-oxo-4-phenyl-3-(phenylsulfonyl)pyridin-2-yl)-1,5-diphenyl-1H-pyrazole-4-carbonitrile (**10a**) and ruled out the expected arylidene exchange adduct **11a**. The IR spectrum of the reaction product showed three absorption peaks at 3322, 2228, and 1640 cm^{-1} corresponding to NH, C≡N, and C=O functions, respectively. In addition, its mass spectrum revealed among other fragments, a fragment at *m/z* 554 due to the molecular ion (M^+) of compound **10a**. Similar treatment of the ketosulfone **2** with *p*-chlorobenzylidene malononitrile **6b** under the same reaction conditions, furnished the corresponding 6-pyridone derivative **10b** as shown in Scheme 2. Formation of the pyridone derivatives **10a**,**b** is suggested to take place via the formation of the intermediate iminopyrane adduct **9** followed by a Dimroth-type rearrangement, then loss of hydrogen cyanide molecule to give the corresponding pyridone derivatives **10a**,**b** as illustrated in Scheme 2.

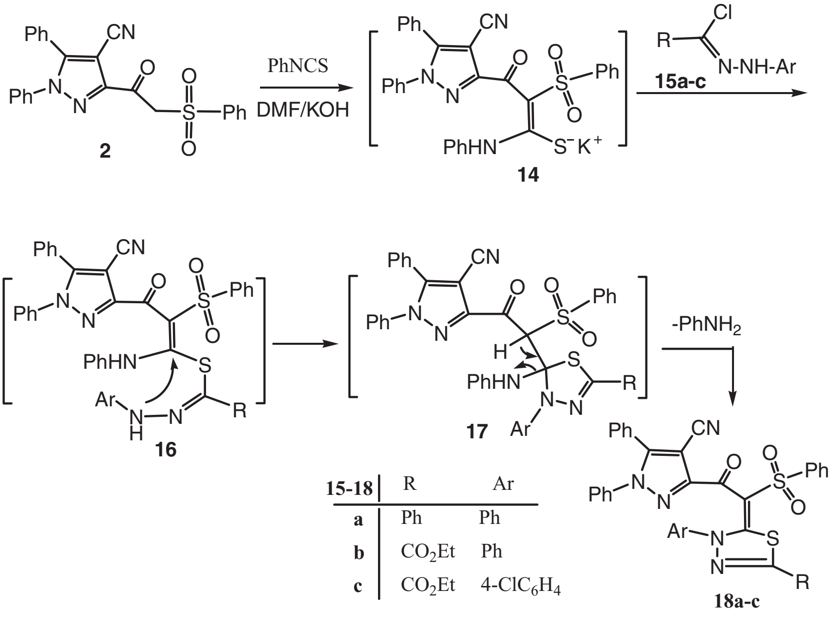
Coupling of the ketosulfone **2** with *p*-chlorobenzenediazonium chloride (**12a**) was also conducted to afford the corresponding hydrazone derivative **13a** (Scheme 2). The IR spectrum of compound **13a** showed two absorption bands at 3210 and 1629 cm^{-1}



Scheme 2

due to hydrazone-NH and carbonyl functions, respectively. The ketosulfone **2** coupled similarly with diazotized 5-amino-3-phenyl-1H-pyrazole (**12b**) to afford the corresponding hydrazone derivative **13b** as shown in Scheme 2.

Treatment of the ketosulfone **2** with phenylisothiocyanate and potassium hydroxide in dimethylformamide at room temperature afforded the potassium salt intermediate **14**, and its reaction with hydrazonoyl halides **15a–c**, as a route to 1,3,4-thiadiazole systems, was also examined. Thus, when the potassium salt **14** was treated with *N*-phenylbenzohydrazonyl chloride **(15a)**, it afforded a single product (based on TLC analysis) that was identified as 3-(2-(3,5-diphenyl-1,3,4-thiadiazol-2(3H)-ylidene)-2-(phenylsulfonyl)acetyl)-1,5-diphenyl-1H-pyrazole-4-carbonitrile **(18a)** (Scheme 3). Elemental analysis and spectral data were in complete accordance with the assigned structure **18a**. Similar treatment of the intermediate **14** with an equimolar amount of hydrazonoyl chlorides **15b**,**c** afforded, in each case, only one isolable product. Elemental analyses and spectral data of the reaction products were compatible with the 1,3,4-thiadiazole structures **18b**,**c**. The IR spectrum of **18b** revealed the presence of three absorption bands at 1756, 1672, and 2232 cm^{-1} due to two carbonyl and one nitrile functions, respectively. The ^1H NMR spectrum of **18b** exhibited a triplet and quartet signals at δ 1.25 and 4.35, respectively, due to ethyl-ester group in addition to aromatic multiplets. A proposed mechanism for the formation of the 1,3,4-thiadiazole structure **18** is depicted in Scheme 3.



15-18	R	Ar
a	Ph	Ph
b	CO_2Et	Ph
c	CO_2Et	4-ClC_6H_4

Scheme 3

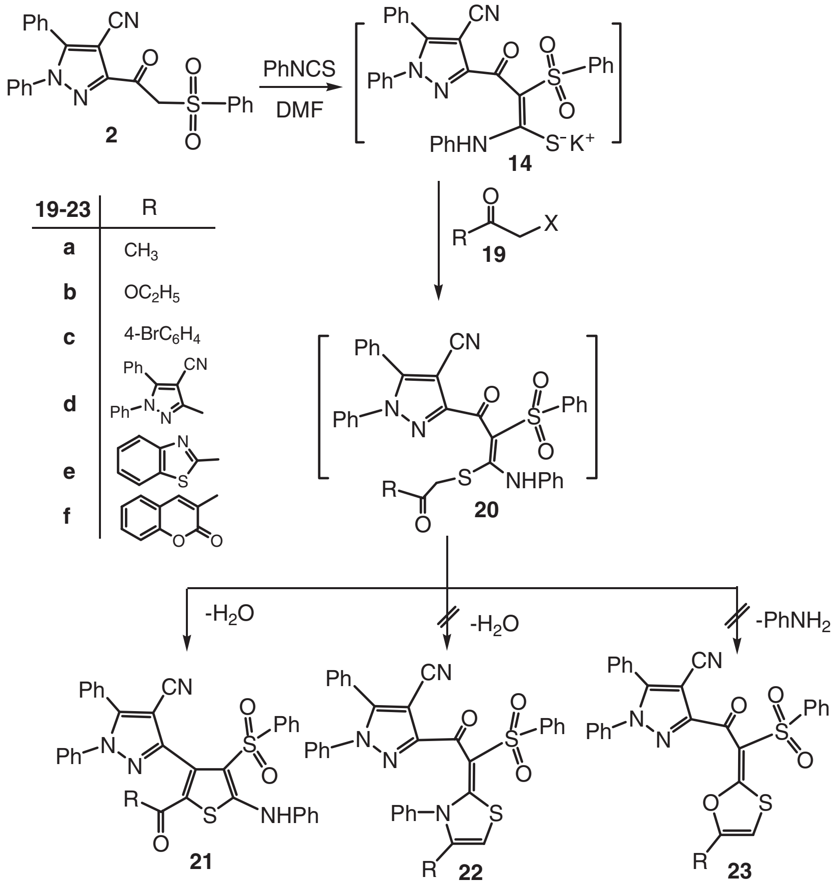
Next, the reactivity of the potassium salt **14** towards various α-haloketones was also investigated. Thus, treatment of **14** with α-chloroacetone gave one product that was identified as 3-(2-acetyl-5-(phenylamino)-4-(phenylsulfonyl)thiophen-3-yl)-1,5-diphenyl-pyrazole-4-carbonitrile (**21a**) as shown in Scheme 4. The other possible structures **22a** and **23a** were ruled out based on the elemental analyses and spectroscopic data of the obtained product. The IR spectrum of the reaction product showed three absorption bands at 3309, 2234, and 1700 cm^{-1} characteristic for NH, C≡N, and C=O functions, respectively. The ^{1}H NMR spectrum of compound **21a** revealed a broad signal at δ 9.69 due to NH proton, in addition to a multiplet at δ 7.24–7.75 due to the aromatic protons.

Similarly, treatment of the salt **14** with ethyl chloroacetate and *p*-bromophenacyl bromide afforded the corresponding thiophene derivatives **21b**,**c** as outlined in Scheme 4. The thiophene structures **21b**,**c** were confirmed from their elemental analyses and spectral data. For example, the IR spectra of the reaction products showed, in each case, characteristic carbonyl and NH absorptions in the regions 1623–1672 and 3275–3299 cm^{-1}, respectively.

In addition, some 3-bromoacetylheterocycles, namely 3-bromoacetyl-1,5-diphenyl-1H-pyrazole-4-carbonitrile (**1**), 2-bromoacetylbenzothiazole (**19e**), and 3-bromoacetyl coumarin-2-one (**19f**) reacted in a similar fashion with the potassium salt **14**, under the same reaction conditions mentioned above, to afford the corresponding thiophene derivatives **21d–f** (Scheme 4). The assignment of structures **21** was supported by the appearance of NH peak around 3300 cm^{-1} (in IR spectra) and near δ 9.7 (in their ^{1}H NMR spectra).

EXPERIMENTAL

Melting points were measured on a Gallenkamp apparatus. IR spectra were recorded on a Shimadzu FT-IR 8101 PC infrared spectrophotometer. ^{1}H NMR spectra were



Scheme 4

determined in $CDCl_3$ or 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. Arylidenemalonotiriles **6a**,**b**,[23,24] hydrazonoyl halides **3a**,[25] **3b**,[26] **15a**,[27] **15b**,**c**,[28,29] 5-pyrazolediazonium salt **12b**,[30] 4-bromophenacylbromide (**19c**),[31] 3-bromoacetyl-1,5-diphenyl-1H-pyrazole-4-carbonitrile (**1**),[19] 2-bromoacetylbenzothiazole (**19e**),[32] and 3-bromoacetylcoumarin-2-one (**19f**)[33] were prepared according to the procedures in the literature.

1,5-Diphenyl-3-(2-(phenylsulfonyl)acetyl)-1H-pyrazole-4-carbonitrile (2)

To a solution of 3-bromoacetyl-1,5-diphenyl-1H-pyrazole-4-carbonitrile (**1**) (3.66 g, 10 mmol) in absolute ethanol (50 mL), sodium benzenesulfinate (1.64 g, 10 mmol) was added. The mixture was then refluxed for 4 h, then left to cool to room temperature. The solid that formed was filtered off, washed with ethanol, and dried. Recrystallization from ethanol gave the corresponding ketosulfone derivative **2**. Yield (85%), mp 165–167°C. IR (cm^{-1}) 2230 (C≡N), 1666 (C=O), 1596 (C=N). ^1H NMR (DMSO-d_6) δ 5.25 (s, 2H, CH_2), 7.33–7.47 (m, 4H, ArH), 7.49–7.65 (m, 7H, ArH), 7.68–7.95 (m, 4H, ArH); MS *m/z* (%) 427 (M^+, 3.8), 362 (5.5), 286 (11.5), 273 (17.1), 227 (92.3), 135 (64.0), 77 (100). Calcd. for $C_{24}H_{17}N_3O_3S$ (427.42): C, 67.44; H, 4.01; N, 9.83. Found: C, 67.64; H, 3.89; N, 9.92.

Reaction of the Ketosulfone 2 with Hydrazonoyl Halides 3a,b

1,5-Diphenyl-3-(2-(phenylsulfonyl)acetyl)-1H-pyrazole-4-carbonitrile (**2**) (0.854 g, 2 mmol) was added to an ethanolic sodium ethoxide solution [prepared from sodium metal (0.046 g, 2 mmol) and absolute ethanol (25 mL)]. After stirring for 10 min, the appropriate hydrazonoyl chloride **3a**,**b** (2 mmol) was added, and stirring was continued for an additional 30 min. The reaction mixture was then left to stir at room temperature for 12 h. The solid product that formed was collected by filtration, washed with water, and dried. Recrystallization from ethanol gave the corresponding pyrazole derivatives **5a**,**b**.

5′-Acetyl-1,2′,5-triphenyl-4′-(phenylsulfonyl)-1H,2′H-3,3′-bipyrazole-4-carbonitrile (5a). Yield (78%), mp > 300°C. IR (cm^{-1}) 2230 (C≡N), 1695 (C=O), 1592 (C=N). ^1H NMR (DMSO-d_6) δ 2.59 (s, 3H, CH_3), 7.17–7.44 (m, 11H, ArH), 7.46–7.78 (m, 6H, ArH), 7.81–8.23 (m, 3H, ArH); MS *m/z* (%) 569 (M^+, 9.8), 554 (100), 325 (25), 244 (11.8), 143 (35.7), 78 (22.2), 65 (40.2). Calcd. for $C_{33}H_{23}N_5O_3S$ (569.65): C, 69.55; H, 4.07; N, 12.29. Found: C, 69.79; H, 4.20; N, 12.04.

5′-Acetyl-1,5-diphenyl-2′-(4-chlorophenyl)-4′-(phenylsulfonyl)-1H,2′H-3,3′-bipyrazole-4-carbonitrile (5b). Yield (76%), mp > 300°C. IR (cm^{-1}) 2235 (C≡N), 1700 (C=O), 1592 (C=N). ^1H NMR (DMSO-d_6) δ 2.64 (s, 3H, CH_3), 7.25–7.29 (m, 7H, ArH), 7.31–7.60 (m, 10H, ArH), 8.32 (d, 2H, $J = 8.1$ Hz, ArH); MS *m/z* (%) 604 (M^+, 15.8), 589 (29.9), 510 (16.1), 405 (100), 364 (25.3), 261 (12.6), 171 (31.0), 116 (17.2). Calcd. for $C_{33}H_{22}N_5O_3SCl$ (604.09): C, 65.61; H, 3.67; N, 11.59. Found: C, 65.76; H, 3.85; N, 11.38.

3-(4-Aryl-1,6-dihydro-6-oxo-3-(phenylsulfonyl)pyridin-2-yl)-1,5-diphenyl-1H-pyrazole-4-carbonitrile Derivatives (10a,b)

A mixture of the 1,5-diphenyl-3-(2-(phenylsulfonyl)acetyl)-1H-pyrazole-4-carbonitrile (**2**) (0.427 g, 1 mmol) and the appropriate arylidenemalononitrile **6a,b** (1 mmol) in ethanol (20 mL) was refluxed for 5 h then cooled. The reaction mixture was poured onto ice-cold water and neutralized with 10% hydrochloric acid until its pH was 7. The solid product was collected, washed with water, dried, and finally recrystallized from EtOH:DMF (3:1) to afford the corresponding pyridine derivatives **10a**,**b** in 76% and 70% yields, respectively.

3-(1,6-Dihydro-6-oxo-4-phenyl-3-(phenylsulfonyl)pyridin-2-yl)-1,5-diphenyl-1H-pyrazole-4-carbonitrile (10a). Yield (76%), mp. 270–271°C. IR (cm^{-1}) 3322 (NH), 2228 (C≡N), 1640 (C=O). ^1H NMR (DMSO-d_6) δ 7.39–7.49 (m, 13H, ArH), 7.50–7.57 (m, 4H, ArH), 7.59–7.71 (m, 3H, ArH), 7.8 (s, 1H, CH); MS *m/z* (%) 554 (M^+, 12.4), 550 (38.2), 466 (90.2), 452 (54.9), 194 (13.7), 113 (22.5), 77 (100). Calcd. for $C_{33}H_{22}N_4O_3S$ (554.63): C, 71.46; H, 4.00; N, 10.10. Found: C, 71.32; H, 3.91; N, 10.22.

3-(4-(4-Chlorophenyl)-1,6-dihydro-6-oxo-3-(phenylsulfonyl)pyridin-2-yl)-1,5-diphenyl-1H-pyrazole-4-carbonitrile (10b). Yield (70%), mp > 300°C. IR (cm^{-1}) 3325 (NH), 2333 (C≡N), 1624 (C=O). ^1H NMR (DMSO-d_6) δ 7.26 (s, 1H, CH), 7.42–7.51 (m, 11H, ArH), 7.65–7.75 (m, 6H, ArH), 7.95 (d, 2H, $J = 7.8$ Hz, ArH); MS *m/z* (%) 591 (M^++2, 74.7), 590 (M^++1, 64.7), 589 (M^+, 55.2), 511 (44.6), 169 (88.1), 91 (100). Calcd. for $C_{33}H_{21}N_4O_3SCl$ (589.08): C, 67.29; H, 3.59; N, 9.51. Found: C, 67.17; H, 3.33; N, 9.41.

1,5-Diphenyl-3-(2-arylhydrazono-2-phenylsulfonyl)acetyl-1H-pyrazol-4-carbonitriles 13a,b

To a cold solution of the ketosulfone **2** (0.854 g, 2 mmol) in ethanol (50 mL), sodium acetate trihydrate (3 g) was added, then the appropriate diazonium salt **12a**,**b** (2 mmol) (prepared by diazotization of the appropriate amine with nitrous acid) were added portionwise with stirring at 0–5°C over a period of 30 min. After complete addition, the reaction mixture was stirred for additional 4 h, then kept in an ice chest overnight. The reaction mixture was then diluted with water, dried, and finally recrystallized from acetic acid to afford the corresponding hydrazones **13a**,**b** in 69% and 64% yields, respectively.

1,5-Diphenyl-3-(2-(4-chlorophenyl)hydrazono)-2-(phenylsulfonyl)acetyl)-1H-pyrazole-4-carbonitrile (13a). Yield (64%), mp 208°C. IR (cm^{-1}) 3210 (NH), 2230 (C≡N), 1629 (C=O). ^{1}H NMR (DMSO-d_6) δ 7.24–7.35 (m, 6H, ArH), 7.37–7.46 (m, 8H, ArH), 7.57–7.69 (m, 3H, ArH), 8.22 (d, 2H, J = 8.1Hz, ArH), 12.58 (br.s, 1H, NH); MS *m/z* (%) 566 (M^+, 7.2), 561 (21.7), 533 (61.3), 442 (29.2), 381 (100), 272 (58.5), 180 (68.9), 104 (52.8). Calcd. for $C_{30}H_{20}N_5O_3SCl$ (566.98): C, 63.55; H, 3.56; N, 12.35. Found: C, 63.27; H, 3.48; N, 12.33.

1,5-Diphenyl-3-(2-(3-phenyl-1H-pyrazol-5-yl)hydrazono)-2-(phenylsulfonyl)-acetyl)-1H-pyrazol-4-carbonitrile (13b). Yield (69%), mp 181–183°C. IR (cm^{-1}) 3345, 3276 (2NH), 2230 (C≡N), 1695 (C=O). ^{1}H NMR (DMSO-d_6) δ 7.41–7.72 (m, 10H, ArH), 7.74–7.90 (m, 10H, ArH), 8.16 (s, 1H, CH), 8.62 (br.s, 1H, NH), 9.15 (br.s, 1H, D_2O-exchangable, NH). Calcd. for $C_{33}H_{23}N_7O_3S$ (597.66): C, 66.32; H, 3.88; N, 16.41. Found: C, 66.27; H, 3.82; N, 16.50.

Synthesis of 1,3,4-Thiadiazole Derivatives 18a–c

To a stirred solution of potassium hydroxide (60 mg, 1 mmol) in dimethylformamide (15 mL), 1,5-diphenyl-3-(2-(phenylsulfonyl)acetyl)-1H-pyrazole-4-carbonitrile (**2**) (0.427 g, 1 mmol) was added. After stirring for 30 min, phenylisothiocyanate (0.135 g, 1 mmol) was added to the resulting mixture. The stirring was continued for a further 6 h, then the appropriate hydrazonoyl halide **15a–c** (1 mmol) and the reaction mixture was further stirred overnight then diluted with water (5 mL). The solid product was filtered off, washed with water, dried, and finally recrystallized from DMF/EtOH to afford the corresponding 1,3,4-thiadiazole derivatives **18a–c**.

3-(2-(3,5-Diphenyl-1,3,4-thiadiazol-2(3H)-ylidene)-2-(phenylsulfonyl)acetyl)-1,5-diphenyl-1H-pyrazole-4-carbonitrile (18a). Yield (63%), mp 290°C. IR (cm^{-1}) 2233 (C≡N), 1675 (C=O), 1594 (C=N); ^{1}H NMR (DMSO-d_6) δ 6.87–7.99 (m, ArH). Calcd. for $C_{38}H_{25}N_5O_3S_2$ (663.77): C, 68.76; H, 3.80; N, 10.55; S, 9.66. Found: C, 66.87; H, 3.85; N, 10.65; S, 9.34.

Ethyl 5-(2-(4-Cyano-1,5-diphenyl-1H-pyrazol-3yl)-2-oxo-1-(phenylsulfonyl) ethylidene)-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-carboxylate (18b). Yield (62%), mp 245–247°C. IR (cm^{-1}) 2232 (C≡N) 1756, 1672 (2 C=O), 1590 (C=N); ^{1}H NMR (DMSO-d_6) δ 1.25 (t, 3H, J = 7.2 Hz, $\underline{CH_3}CH_2$), 4.35 (q, 2H, J = 7.2 Hz, $CH_3\underline{CH_2}$), 6.81–7.02 (m, 4H, ArH), 7.19–7.32 (m, 6H, ArH), 7.34–7.53 (m, 7H, ArH), 7.54–7.71 (m, 3H, ArH); MS *m/z* (%) 659 (M^+, 7.3), 644 (9.1), 518 (12.1), 464 (9.1), 364 (8.1), 272

(54.4), 228 (2.0), 181 (8.1), 141 (10.1), 77 (100). Calcd. for $C_{35}H_{25}N_5O_5S_2$ (659.75): C, 63.72; H, 3.82; N, 10.62; S, 9.72. Found: C, 63.44; H, 4.67; N, 10.82; S, 9.65.

Ethyl 5-(2-(4-Cyano-1,5-diphenyl-1H-pyrazol-3yl)-2-oxo-1-(phenylsulfonyl) ethylidene)-4-(4-chlorophenyl)-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (18c). Yield (68%), mp 260°C. IR (cm^{-1}) 2233 (C≡N), 1757, 1674 (2C=O), 1592 (C=N); ^{1}H NMR (DMSO-d$_6$) δ 1.26 (t, 3H, $J = 7.2$ Hz, $\underline{CH_3}CH_2$), 4.38 (q, 2H, $J = 7.2$ Hz, $CH_3\underline{CH_2}$), 6.98–7.24 (m, 6H, ArH), 7.29–7.42 (m, 10H, ArH), 7.44–7.63 (m, 3H, ArH); MS *m/z* (%) 694 (M$^+$, 18.7), 687 (18), 497 (9.0), 463 (14.4), 411 (4.5), 272 (29.7), 180 (15.3), 154 (18.0), 118 (42.3), 77 (100). Calcd. for $C_{35}H_{24}N_5O_5S_2Cl$ (694.19): C, 60.56; H, 3.48; N, 10.09; S, 9.24. Found: C, 60.87; H, 3.35; N, 9.99; S, 9.15.

Synthesis of Thiophene Derivatives 21a–f

A similar procedure to the one that was used for the synthesis of 1,3,4-thiadiazole is applied here using the appropriate α-haloketone [chloroacetone (**19a**), ethyl chloroacetate (**19b**), p-bromophenacyl bromide (**19c**), bromoacetylpyrazole (**1**), 2-(bromoacetyl) benzothiazole (**19e**), and bromoacetylcoumarine (**19f**)] (2 mmol each) instead of the hydrazonoyl halides **15a–c**. The formed solid product was filtered off, washed with ethanol, dried, and finally recrystallized from DMF/EtOH to afford the corresponding thiophene derivatives **21a–f**, respectively.

3-(2-Acetyl-5-(phenylamino)-4-(phenylsulfonyl)thiophen-3-yl)-1,5-diphenyl-1H-pyrazole-4-carbonitrile (21a). Yield (65%), mp 281–283°C. IR (cm^{-1}) 3309 (NH), 2234 (C≡N), 1640 (C=O); ^{1}H NMR (DMSO-d$_6$) δ 2.07 (s, 3H, CH$_3$), 7.24–7.28 (m, 4H, ArH), 7.32–7.49 (m, 10H, ArH), 7.73–7.76 (m, 6H, ArH), 9.69 (s, 1H, NH, D$_2$O-exchangeable); MS m/z (%) 600 (M$^+$, 100), 522 (34.3), 422 (27.4), 272 (15.8), 180 (19.5), 77 (87.5). Calcd. for $C_{34}H_{24}N_4O_3S_2$ (600.72): C, 67.98; H, 4.03; N, 9.33; S, 10.68. Found: C, 67.72; H, 4.11; N, 9.01; S, 10.59.

Ethyl 3-(4-Cyano-1,5-diphenyl-1H-pyrazol-3-yl)-5-(phenylamino)-4-(phenylsulfonyl)-thiophene-2-carboxylate (21b). Yield (63%), mp 211–213°C. IR (cm^{-1}) 3299 (NH), 2234 (C≡N), 1623 (C=O); ^{1}H NMR (DMSO-d$_6$) δ 1.15 (t, 3H, $J =$ 7.2 Hz, $\underline{CH_3}CH_2$), 4.14 (q, 2H, $J = 7.2$ Hz, $CH_3\underline{CH_2}$), 7.26–7.37 (m, 8H, ArH), 7.38–7.5 (m, 7H, ArH), 7.74–7.77 (m, 5H, ArH), 9.6 (s, 1H, NH); MS *m/z* (%) 631 (M$^+$+1, 65.2), 630 (M$^+$, 77.9), 520 (19.3), 494 (28.3), 371 (24.5), 272 (39.0), 180 (14.7), 77 (100). Calcd. for $C_{35}H_{26}N_4O_4S_2$ (630.75): C, 66.65; H, 4.15; N, 8.88; S, 10.17. Found: C, 66.86; H, 4.27; N, 8.71; S, 10.30.

3-(2-(4-Bromobenzoyl)-5-(phenylamino)-4-(phenylsulfonyl)thiophen-3-yl)-1,5-diphenyl-1H-pyrazole-4-carbonitrile (21c). Yield (72%), mp 253–255°C. IR (cm^{-1}) 3275 (NH), 2230 (C≡N), 1672 (C=O); ^{1}H NMR (DMSO-d$_6$) δ 6.97–7.13 (m, 4H, ArH), 7.27–7.41 (m, 8H, ArH), 7.43–7.69 (m, 10H, ArH), 7.72 (d, 2H, $J = 8.1$ Hz, ArH), 9.82 (s, 1H, NH, D$_2$O-exchangeable); MS *m/z* (%) 742 (M$^+$, 66.0), 741 (35.9), 676 (19.4), 645 (24.6), 493 (23.0), 371 (11.7), 183 (52.9), 195 (10.2), 77 (100). Calcd. for $C_{39}H_{25}N_4O_3S_2Br$ (741.69): C, 63.16; H, 4.40; N, 7.55; S, 8.65. Found: C, 63.24; H, 4.37; N, 7.32; S, 8.57.

3-(3-(4-Cyano-1,5-diphenyl-1H-pyrazol-3-yl)-5-phenylamino-4-(phenylsulfonyl)-(thiophene-2-carbonyl))-1,5-diphenyl-1H-pyrazole-4-carbonitrile (21d). Yield (65%), mp > 300°C. IR (cm^{-1}) 3282 (NH), 2232 (C≡N), 1631 (C=O); ^{1}H NMR (DMSO-d$_6$) δ 7.22–7.38 (m, 10H, ArH), 7.39–7.46 (m, 10H, ArH), 7.48–7.50 (m, 8H, ArH), 7.73–7.76 (d, 2H, $J = 7.8$ Hz, ArH), 9.78 (s, 1H, NH, D$_2$O-exchangeable). Calcd.

for $C_{49}H_{31}N_7O_3S_2$ (829.945): C, 70.91; H, 3.76; N, 11.81; S, 7.73. Found: C, 70.72; H, 4.03; N, 12.10; S, 7.67.

3-(2-(Benzothiazol-2-yl)carbonyl)-5-(phenylamino)-4-(phenylsulfonyl) thiophen-3-yl)-1,5-diphenyl-1H-pyrazole-4-carbonitrile (21e). Yield (67%), mp 251–253°C. IR (cm^{-1}) 3252 (NH), 2236 (C≡N), 1672 (C=O); ^1H NMR (DMSO-d_6) δ 6.97–7.40 (m, 10H, ArH), 7.41–7.69 (m, 10H, ArH), 7.71–7.72 (m, 4H, ArH), 9.79 (s, 1H, NH, D_2O-exchangeable); MS *m/z* (%) 720 (M^++1, 27.4), 719 (M^+, 63.3), 579 (13.8), 493 (33.7), 443 (27.7), 312 (15.7), 180 (21.2), 162 (29.2), 134 (19.5), 77 (100). Calcd. for $C_{40}H_{25}N_5O_3S_3$ (719.87): C, 66.74; H, 3.05; N, 9.73; S, 13.36. Found: C, 66.83; H, 2.98; N, 9.59; S, 13.54.

3-(2-(2-Oxo-2H-chromene-3-carbonyl)-5-phenylamino-4-(phenylsulfonyl)-(thiophen-3-yl)-1,5-diphenyl-1H-pyrazole-4-carbonitrile (21f). Yield (70%), mp > 300°C. IR (cm^{-1}) 3289 (NH), 2232 (C≡N), 1729, 1669 (2C=O); ^1H NMR (DMSO-d_6) δ 6.72–6.75 (m, 2H, ArH), 6.94–7.20 (m, 7H, ArH), 7.23–7.39 (m, 8H, ArH), 7.42–7.52 (m, 5H, ArH), 7.65–7.69 (m, 2H, ArH), 8.2 (s, 1H, CH), 9.80 (s, 1H, NH, D_2O-exchangeable). Calcd. for $C_{42}H_{26}N_4O_5S_2$ (730.83): C, 69.03; H, 3.59; N, 7.69 S, 8.78. Found: C, 68.92; H, 3.71; N, 7.62; S, 8.69.

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