Synthesis of some new pyridazine, 1,2,4-triazine and 1,3,4-thiadiazole derivatives

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3-(2-Furyl)-3-oxo-propanenitrile (**1**) reacts with some phosphorus ylides to afford new pyridazine and 1,2,4-triazine derivatives. Reaction of **1** with some heterocyclic diazonium salts afforded fused heterocyclic systems with bridgehead nitrogen atoms.

Keywords: 3-oxopropanenitriles, phosphorus ylides, furans, pyridazines, 1,2,4-triazines, thiadiazoles, fused azoles, hydrazonoyl chlorides.

Furans are common substructures in various natural products[1,2] and pharmaceuticals.[3-5] Phosphonium ylides have proved to be useful synthons in the field of preparative organic chemistry.[6,7] In continuation of our research program directed towards the preparation of polysubstituted heterocycles which could be adapted for the synthesis of libraries,[8-19] we have investigated the utility of 3-(2-furyl)-3-oxo-propanenitrile (**1**) as a versatile building block for the synthesis of polysubstituted pyridazines, 1,2,4-triazines, 1,3,4-thiadiazoles.

When ethoxycarbonylmethylenetriphenylphosphorane (**3a**) was treated with 3-(2-furyl)-3-oxo-2-(phenylhydrazono)prop anenitrile (**2**) in dry toluene, it afforded a product identified as 4-(2-furyl)-l-phenyl-6-oxo-pyridazine-3-carbonitrile (**5a**) (Scheme 1). The structure of this product was established on the basis of its elemental analysis and spectroscopic data. Its IR spectrum revealed a nitrile and a carbonyl absorption bands at 2235 and 1682 cm^{-1}, respectively.

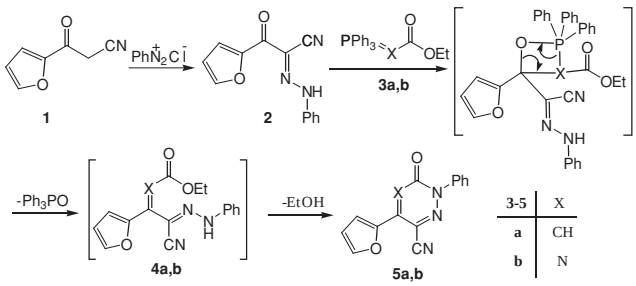
Similarly, compound **2** reacts with *N*-ethoxycarbonyltriphenylphosphimine (**3b**) under the same reaction conditions to afford 4-(2-furyl)-l-phenyl-6-oxo-l,2,4-triazine-3-carbonitrile (**5b**) (Scheme 1). Elemental analysis and spectral data (IR, MS and ^1H NMR spectra) of the isolated product were in accordance with the assigned structure. The formation of the pyridazine **5a** and triazine **5b** derivatives was assumed to take place *via* the elimination of triphenylphosphine oxide and ethanol molecules (Scheme 1).

The reactivity of 2-furoylacetonitrile (**1**) towards some heterocyclic diazonium salts was also investigated. Thus, 2-furoylacetonitrile (**1**) was found to couple smoothly with the diazonium salt of 5-amino-1,2,4-triazole **6** to afford the corresponding hydrazone **9** (Scheme 2). The IR spectrum of the latter showed bands at 3163, 3123, 2220 and 1616 cm^{-1} corresponding to two NH, nitrile and carbonyl functions, respectively.

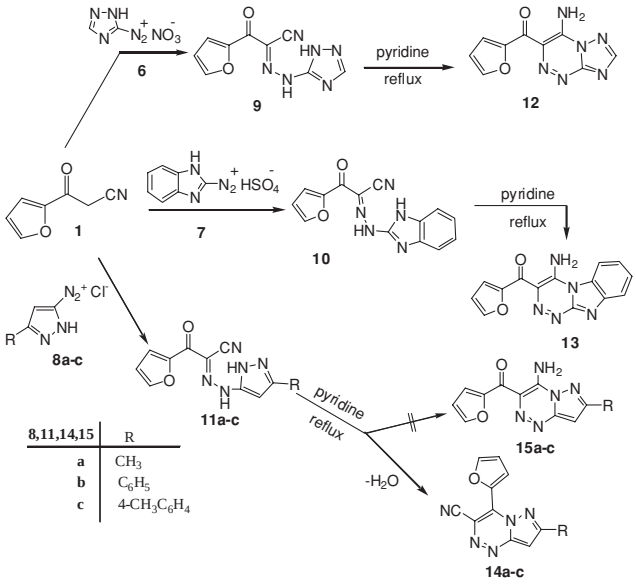
2-Furoylacetonitrile (**1**) was coupled with the diazonium salts of 2-aminobenzimidazole **7** and 3-substituted-5-amino-pyrazoles **8a–b** to afford, in each case, a single product as shown by TLC. The structures of the products were assigned as the hydrazone derivatives **10** and **11a–b** (Scheme 2). The IR spectra of the products showed, in each case, absorption bands corresponding to two NH, nitrile and carbonyl groups.

Intramolecular cyclisation of the hydrazones **9** and **10** was achieved by refluxing in pyridine and resulted in the formation of 1,2,4-triazolo[5,1-c]-1,2,4-triazine **12** and 1,2,4-triazino[4,3-d]benzimidazole **13**, respectively (Scheme 2). The structures of these products were supported by their spectroscopic data. Their IR spectra lacked nitrile absorption and revealed absorption bands characteristic for amino and carbonyl functions (see Experimental).

On the other hand, it was found that the intramolecular cyclisation the hydrazones **11a–b** proceeded with the loss of a water molecule to afford the corresponding pyrazolo[5,1-c]-1,2,4-triazine-3-carbonitrile derivatives **14a–b** rather than the pyrazolo[5,1-c]-1,2,4-triazines **15a–b** (Scheme 2). The IR spectra of the reaction products exhibited nitrile absorption bands near 2230 cm^{-1} (see Experimental).



Scheme 1



Scheme 2

Treatment of compound **1** with phenyl isothiocyanate in dimethylformamide, in the presence of potassium hydroxide, afforded the intermediate potassium salt **16** which was not isolated. Treatment with the α-haloketones **17a–b** furnished the corresponding thiazole derivatives **18a–b**, (Scheme 3). The IR spectra of the isolated products revealed, in each case, two bands in the region 1697–1620 cm^{-1} due to two carbonyl groups in addition to a nitrile absorption band in the region 2197–2195 cm^{-1}.

When the intermediate salt **16** was treated with the hydrazonoyl chlorides **19a–g,** it afforded, in each case, a single

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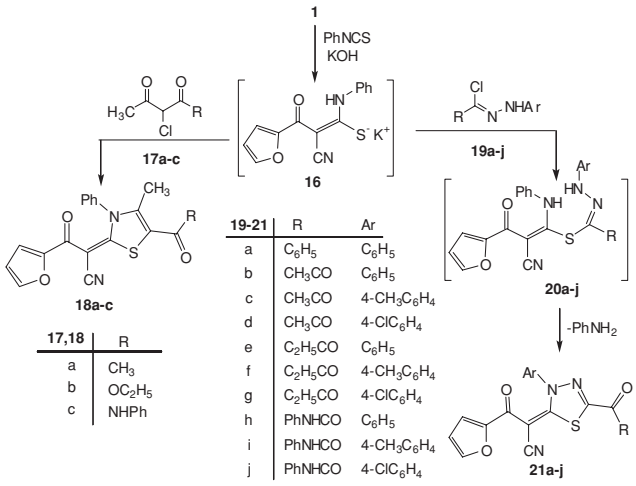

Scheme 3

product (as examined by TLC). Elemental analyses and spectral data were in agreement with the corresponding l,3,4-thiadiazole structures **21a–g** (see Experimental).

Experimental

Melting points were measured with a Gallenkamp apparatus. The IR spectra were recorded on Shimadazu 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.

3-(2-Furyl)-3-oxo-propanenitrile (**1**),[20] 3-(2-furyl)-3-oxo-2-(phenylhydrazono)propanenitrile (**2**),[21] ethoxycarbonylmethylenetriphenylphosphorane(**3a**),[22,23] *N*-ethoxycarbonyltriphenyl-phosphimine (**3b**),[24] heterocyclic diazonium salts **6**,[25] **7**,[26] and **8a–c**,[27] and the hydrazonoyl chlorides **19a**,[28] **19b–d**[29] and **19e–g**[30] were prepared according to the literature procedures.

Reaction of compound **2** *with phosphonium ylides* **3a,b**: To a solution of 3-(2-furyl)-3-oxo-2-(phenylhydrazono)propanenitrile (**2**) (0.48 g, 2 mmol) in dry toluene (20 ml), was added the phosphonium ylide **3a** or **3b** (2 mmol) and the reaction mixture was refluxed for 12h. After the reaction was complete, the solvent was removed under reduced pressure and the residue was triturated with ethanol. The product was filtered off, washed with ethanol, dried and finally recrystallised from DMF/H_2O to afford the corresponding pyridazine **5a** and 1,2,4-triazine **5b** derivatives, respectively.

4-(2-Furyl)-l-phenyl-6-oxo-pyridazine-3-carbonitrile (**5a**): Yield (76%); m.p. 220–221˚C (DMF/H_2O); IR (KBr) ν_{max}/cm^{-1} 2235 (C≡N), 1682 (C=O); ^{1}H NMR ($CDCl_3$) δ 6.67 (dd, 1H, *J*=3.4, 1.8 Hz), 7.34 (dd, 1H, *J*=3.4, 0.8 Hz), 7.46–7.64 (m, 6H), 7.70 (dd, 1H, *J*=1.8, 0.7 Hz); MS (*m/z*) 264 (M^++1), 263 (M^+), 235, 206, 130, 77, 55. For Calcd: $C_{15}H_9N_3O_2$ C, 68.18; H, 3.81; N, 15.90%. Found: C, 68.34; H, 3.53; N, 16.18%.

4-(2-Furyl)-l-phenyl-6-oxo-1,2,4-triazine-3-carbonitrile (**5b**): Yield (64%); m.p. 203–205˚C (DMF/H_2O); IR (KBr) ν_{max}/cm^{-1} 2233 (C≡N), 1699 (C=O); ^{1}H NMR ($CDCl_3$) δ 6.66 (dd, 1H, *J*=3.5, 1.7 Hz), 7.34 (dd, 1H, *J*=3.4, 0.8 Hz), 7.46–7.63 (m, 5H), 7.71 (dd, 1H, *J*=1.9, 0.8 Hz); MS (*m/z*) 265 (M^++1), 264 (M^+), 233, 204, 127, 77, 55. Calcd: For $C_{14}H_8N_4O_2$ C, 63.39; H, 3.42; N, 21.12%. Found: C, 63.52; H, 3.20; N, 21.33%.

Reactions of 2-furoylacetonitrile (1) with heterocyclic diazonium salts
General procedure
To a cold solution of 2-furoylacetonitrile (**1**) (0.27 g, 2 mmol) and sodium acetate trihydrate (3.0 g) in ethanol (50 ml), was added the heterocyclic diazonium salt **6**, **7** or **8a–b** (2 mmol). The addition was carried out portion-wise with stirring at 0–5°C over a period of 30 min. After complete addition, the reaction mixture was stirred for further 4h, then kept in an ice-chest for 12h and finally diluted with water. The product was filtered off, washed with water, dried and recrystallised from EtOH/DMF to give the corresponding hydrazones **9**, **10** and **11a–b**, respectively.

3-(2-Furyl)-3-oxo-2-(1H-1,2,4-triazol-5-ylhydrazono)propanenitrile **(9)**: Yield (78%); m.p.270–271˚C (EtOH/DMF); IR (KBr) ν_{max}/cm^{-1} 3163, 3123 (2NH), 2220 (C≡N), 1616 (C=O); ^{1}H NMR (DMSO-d_6) δ 6.80 (dd, 1H, *J*=3.3, 1.6 Hz), 7.89 (dd, 1H, *J*=3.4, 0.8 Hz), 8.18 (dd, 1H, *J*=1.8, 0.8 Hz), 8.80 (s, 1H), 9.47 (s, 1H, D_2O-exchangeable), 9.86 (s, 1H, D_2O-exchangeable); MS (*m/z*) 231 (M^++1), 230 (M^+), 200, 95, 77, 51. Calcd.: For $C_9H_6N_6O_2$ C, 46.96; H, 2.63; N, 36.51%. Found: C, 46.81; H, 2.85; N, 36.28%.

3-(2-Furyl)-3-oxo-2-(1H-benzimidazol-2-ylhydrazono)propanenitrile (**10**): Yield (70%); m.p.>300˚C (EtOH/DMF); IR (KBr) ν_{max}/cm^{-1} 3261, 3140 (2NH), 2204 (C≡N), 1620 (C=O); ^{1}H NMR (DMSO-d_6) δ 6.76 (dd, 1H, *J*=3.5, 1.5 Hz), 7.18–7.57 (m, 4H), 7.82 (dd, 1H, *J*=3.4, 0.8 Hz), 8.16 (dd, 1H, *J*=1.7, 0.8 Hz), 8.97 (s, 1H, D_2O–exchangeable), 11.15 (s, 1H, D_2O-exchangeable); MS (*m/z*) 279 (M^+), 255, 129, 95, 51. Calcd.: For $C_{14}H_9N_5O_2$ C, 60.21; H, 3.25; N, 25.08%. Found: C, 60.03; H, 3.44; N, 24.86%.

3-(2-Furyl)-3-oxo-2-(3-methyl-1H-pyrazol-5-ylhydrazono)propane nitrile (**11a**): Yield (73%); m.p. 188–189˚C (EtOH/DMF); IR (KBr) ν_{max}/cm^{-1} 3294, 3204 (2NH), 2220 (C≡N), 1683 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.47 (s, 3H), 6.83 (dd, 1H, *J*=3.5, 1.5 Hz), 7.85 (dd, 1H, *J*=3.4, 0.8 Hz), 8.15 (dd, 1H, *J*=1.8, 0.7 Hz), 8.65 (s, 1H), 9.44 (s, 1H, D_2O-exchangeable), 10.65 (s, 1H, D_2O-exchangeable); MS (*m/z*) 243 (M^+), 214, 148, 95, 54. Calcd.: For $C_{11}H_9N_5O_2$ C, 54.32; H, 3.73; N, 28.79%. Found: C, 54.48; H, 3.56; N, 29.02%.

3-(2-Furyl)-3-oxo-2-(3-phenyl-IH-pyrazol-5-ylhydrazono)propane nitrile (**11b**): Yield (77%); m.p. 198–200˚C (EtOH/DMF); IR (KBr) ν_{max}/cm^{-1} 3311, 3192 (2NH), 2222 (C≡N), 1635 (C=O); ^{1}H NMR (DMSO-d_6) δ 6.77 (dd, 1H, *J*=3.5, 1.6 Hz), 7.22–7.60 (m, 5H), 7.89 (dd, 1H, *J*=3.4, 0.7 Hz), 8.14 (dd, 1H, *J*=1.7, 0.8 Hz), 8.68 (s, 1H), 9.21 (s, 1H, D_2O-exchangeable), 10.47 (s, 1H, D_2O-exchangeable); MS (*m/z*) 305 (M^+), 289, 142, 77, 51. Calcd.: For $C_{16}H_{11}N_5O_2$ C, 62.95; H, 3.63; N, 22.94%. Found: C, 63.11; H, 3.48; N, 23.22%.

Synthesis of the fused heterocyclic systems **12, 13** *and* **14a–b**
General procedure
A solution of the hydrazone **9, 10** or **11a–b** (1 mmol) in pyridine (10 ml) was refluxed for 3h, then left to cool to room temperature. The precipitate was filtered off, washed with ethanol, dried and then recrystallised from ethanol/DMF to afford the corresponding fused heterocyclic systems **12, 13** and **14a–b**, respectively.

4-Amino-3-(2-furoyl)-1,2,4-triazolo[5,1-c]-1,2,4-triazine (**12**): Yield (72%); m.p.>300˚C (EtOH/DMF); IR (KBr) ν_{max}/cm^{-1} 3344, 3203 (NH_2), 1650 (C=O); ^{1}H NMR (DMSO-d_6) δ 6.82 (dd, 1H, *J*=3.5, 1.9 Hz), 7.53 (s, 2H, D_2O-exchangeable), 7.95 (dd, 1H, *J*=3.4, 0.9 Hz), 8.16 (dd, 1H, *J*=1.9, 0.7 Hz), 8.98 (s, 1H); MS (*m/z*) 230 (M^+), 202, 95, 77, 53. Calcd.: For $C_9H_6N_6O_2$ C, 46.96; H, 2.63; N, 36.51%. Found: C, 47.16; H, 2.53; N, 36.22%.

4-Amino-3-(2-furoyl)-1,2,4-triazino[4,3-a]benzimidazole (**13**): Yield (67%); m.p.>300˚C (EtOH/DMF); IR (KBr) ν_{max}/cm^{-1} 3393, 3258 (NH_2), 1624 (C=O); ^{1}H NMR (DMSO-d_6) δ 6.79 (dd, 1H, *J*=3.5, 1.8 Hz), 7.43–7.61 (m, 4H), 7.76 (s, 2H, D_2O-exchangeable), 7.96 (dd, 1H, *J*=3.4, 0.7 Hz), 8.09 (dd, 1H, *J*=1.7, 0.8 Hz); MS (*m/z*) 280 (M^++1), 279 (M^+), 252, 132, 95, 51. Calcd: For $C_{14}H_9N_5O_2$ C, 60.21; H, 3.25; N, 25.08%. Found: C, 59.96; H, 3.38, N, 25.30%.

4-(2-Furyl)-7-methylpyrazolo[5,l-c]-l,2,4-triazine-3-carbonitrile (14a): Yield (73%); m.p. 218–219˚C (EtOH/DMF); IR (KBr) ν_{max}/cm^{-1} 2229 (C≡N); ^{1}H NMR ($CDCl_3$) δ 2.71 (s, 3H), 6.93 (dd, 1H, *J*=3.6, 1.7 Hz), 7.91 (dd, 1H, *J*=3.5, 0.8 Hz), 8.11 (dd, 1H, *J*=1.9, 0.7 Hz), 8.71 (s, 1H); MS (*m/z*) 226 (M^++1), 225 (M^+), 211, 175, 51. Calcd.: For $C_{11}H_7N_5O$ C, 58.67; H, 3.13; N, 31.10%. Found: C, 58.52; H, 3.25; N, 31.32%.

4-(2-Furyl)-7-phenylpyrazolo[5,1-c]-1,2,4-triazine-3-carbonitrile (**14b**): Yield (76%); m.p. 225–227˚C (EtOH/DMF); IR (KBr) ν_{max}/cm^{-1} 2233 (C≡N); ^{1}H NMR ($CDCl_3$) δ 6.92 (dd, 1H, *J*=3.4, 1.9 Hz), 7.89 (dd, 1H, *J*=3.4, 1.7 Hz), 7.52–7.61 (m, 5H), 8.03 (dd, 1H, *J*=1.7, 0.7 Hz), 8.07 (s, 1H); MS (*m/z*) 288 (M^++1), 287 (M^+), 142, 77, 51. Calcd.: For $C_{16}H_9N_5O$ C, 66.90; H, 3.16; N, 24.38%. Found: C, 67.17; H, 3.35; N, 24.21%.

Synthesis of 2,3-dihydrothiazoles **18a–b** *and 2,3-dihydro-1,3,4-thiadiazoles* **21a–g**
General procedure
To a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in dimethylformamide (20 ml), 2-furoylacetonitrile (**1**) (0.27g, 2 mmol) was added. After stirring for 30 min, phenyl isothiocyanate (0.27g, 2 mmol) was added to the reaction mixture. Stirring was continued for 6h, then the appropriate α-haloketones **17a–b** or hydrazonoyl chlorides **19a–g** (2 mmol), was added to the reaction mixture. The stirring was continued overnight. The precipitate was filtered off,

washed with ethanol and recrystallised to afford the corresponding products **18a–b** and **21a–g**.

5-Acetyl-2-(2-furoylcyanomethyelene)-4-methyl-3-phenyl-2,3-dihydro-1,3,4-thiadiazole (**18a):** Yield (75%); m.p.>300˚C (EtOH/DMF); IR (KBr) ν_{max}/cm^{-1} 2195 (C≡N), 1672, 1620 (2C=O); ^{1}H NMR (DMSO-d$_6$) δ 2.27 (s, 3H), 2.57 (s, 3H), 6.62 (dd, 1H, *J*=3.4, 1.9 Hz), 7.27 (dd, 1H, *J*=3.5, 0.8 Hz), 7.50–7.65 (m, 5H), 7.89 (dd, 1H, *J*=1.8, 0.8 Hz); MS (*m/z*) 351 (M$^+$+1), 350 (M$^+$), 273, 95, 77, 56. Calcd.: For $C_{19}H_{14}N_2O_3S$ C, 65.13; H, 4.03; N, 7.99; S, 9.15%. Found: C, 65.49; H, 4.08; N, 8.17; S, 9.06%.

5-(Ethoxycarbonyl)-2-(2-furoylcyanomethyelene)-4-methyl-3-phenyl-2,3-dihydro-1,3,4-thiadiazole (**18b**): Yield (72%); m.p.>300˚C (EtOH/DMF); IR (KBr) ν_{max}/cm^{-1} 2197 (C≡N), 1697, 1621 (2C=O); ^{1}H NMR (DMSO-d$_6$) δ 1.26 (t, 3H), 2.23 (s, 3H), 4.31(q, 2H), 6.57 (dd, 1H, *J*=3.5, 1.8 Hz), 7.29 (dd, 1H, *J*=3.5, 0.7 Hz), 7.43–7.63 (m, 5H), 7.85 (dd, 1H, *J*=1.7, 0.8 Hz); MS (*m/z*) 381 (M$^+$+1), 380 (M$^+$), 367, 349, 274, 95, 77, 51. Calcd.: For $C_{20}H_{16}N_2O_4S$ C, 63.15; H, 4.24; N, 7.36; S, 8.43%. Found: C, 62.94; H, 4.14; N, 7.55; S, 8.52%.

2-(Furoyl)cyanomethylene-3,5-diphenyl-2,3-dihydro-1,3,4-thiadiazole (**21a**): Yield (84%); m.p.>300˚C (DMF/H_2O); IR (KBr) ν_{max}/cm^{-1} 2193 (C≡N), 1612 (C=O), 1574 (C=N);^{1}H NMR ($CDCl_3$) δ 5.16 (dd, 1H, *J*=3.5, 1.7 Hz), 7.12–7.44 (m, 10H), 7.56 (dd, 1H, *J*=3.5, 0.9 Hz), 7.62 (dd, 1H, *J*=1.7, 0.9 Hz); MS (*m/z*) 371 (M$^+$), 294, 217, 77, 65, 51. Calcd.: For $C_{21}H_{13}N_3O_2S$ C, 67.91; H, 3.53; N, 11.31; S, 8.63%. Found: C, 68.16; H, 3.42; N, 11.50; S, 8.79%.

2-(2-Furoyl)cyanomethylene-3-phenyl-5-acetyl-2,3-dihydro-1,3,4-thiadiazole (**21b**): Yield (80%); m.p.>300˚C (DMF/H_2O); IR (KBr) ν_{max}/cm^{-1} 2205 (C≡N), 1693, 1651 (2C=O), 1580 (C=N); ^{1}H NMR ($CDCl_3$) δ 2.54 (s, 3H), 6.58 (dd, 1H, *J*=3.6, 1.9 Hz), 7.29–7.51 (m, 4H), 7.59 (dd, 1H, *J*=3.5, 0.7 Hz), 7.67 (dd, 1H, *J*=1.8, 0.9 Hz); MS (*m/z*) 337 (M$^+$), 241, 199, 95, 71, 55. Calcd.: For $C_{17}H_{11}N_3O_3S$ C, 60.53; H, 3.29; N, 12.46; S, 9.50%. Found: C, 60.33; H, 3.42; N, 12.60; S, 9.35%.

2-(2-Furoyl)cyanomethylene-3-(4-tolyl)-5-acetyl-2,3-dihydro-l,3,4-thiadiazole (**21c**): Yield (77%); m.p.>300˚C (DMF/H_2O); IR (KBr) ν_{max}/cm^{-1} 2101 (C≡N), 1695, 1655 (2C=O); ^{1}H NMR ($CDCl_3$) δ 2.51 (s, 3H), 2.66 (s, 3H), 6.51 (dd, 1H, *J*=3.4, 1.7 Hz), 7.26–7.61 (m, 4H), 7.55 (dd, 1H, *J*=3.5, 0.9 Hz), 7.61 (dd, 1H, *J*=1.9, 0.7 Hz); MS (*m/z*): 351 (M$^+$), 323, 308, 258, 216, 95, 55. Calcd.: For $C_{18}H_{13}N_3O_3S$ C, 61.53; H, 3.70; N, 11.96; S, 9.12%. Found: C, 61.72; H, 3.76; N, 12.13; S, 8.97%.

2-(2-Furoyl)cyanomethylene-3-(4-chlorophenyl)-5-acetyl-2,3-dihydro-1,3,4-thiadiazole (**21d**): Yield (81%); m.p.>300˚C (DMF/H_2O); IR (KBr) ν_{max}/cm^{-1} 2205 (C≡N), 1672, 1655 (2C=O), 1578 (C=N); ^{1}H NMR (DMSO-d$_6$) δ 2.48 (s, 3H), 6.54 (dd, 1H, *J*=3.6, 1.9 Hz), 7.24–7.59 (m, 4H), 7.56 (dd, 1H, *J*=3.5, 0.8 Hz), 7.63 (dd, 1H, *J*=1.8, 0.8 Hz); MS (*m/z*) 372 (M$^+$+1), 371 (M$^+$), 241, 210, 145, 75, 53. Calcd.: For $C_{17}H_{10}ClN_3O_3S$ C, 54.92; H, 2.71; N, 11.30; S, 8.62%. Found: C, 54.83; H, 2.78; N, 11.21; S, 8.78%.

2-(2-Furoyl)cyanomethylene-3-phenyl-5-(ethylcarboxylate)-2,3-dihydro-l,3,4-thiadiazole (21e): Yield (75%); m.p. 245–246˚C (DMF/H_2O); IR (KBr) ν_{max}/cm^{-1} 2195 (C≡N), 1724, 1675 (2C=O), 1582 (C=N); ^{1}H NMR (DMSO-d$_6$) δ 1.26 (t, 3H), 4.34 (q, 2H), 6.53 (dd, 1H, *J*=3.6, 1.8 Hz), 7.23–7.55 (m, 5H), 7.62 (dd, 1H, *J*=3.7, 0.8 Hz), 7.72 (dd, 1H, *J*=1.9, 0.7 Hz); MS (*m/z*) 367 (M$^+$), 292, 250, 117, 73, 53. Calcd.: For $C_{18}H_{13}N_3O_4S$ C, 58.85; H, 3.57; N, 11.44; S, 8.73%. Found: C, 59.06; H, 3.78; N, 11.42; S, 8.56%.

2-(2-Furoyl)cyanomethylene-3-(4-tolyl)-5-(ethylcarboxylate)-2,3-dihydro-1,3,4-thiadiazole (**21f**): Yield (73%); m.p.>249–251˚C (DMF/H_2O); IR (KBr) ν_{max}/cm^{-1} 2199 (C≡N), 1720, 1678 (2C=O), 1582 (C=N); ^{1}H NMR (DMSO-d$_6$) δ 1.37 (t, 3H), 2.49 (s, 3H), 4.32 (q, 2H), 6.55 (dd, 1H, *J*=3.5, 1.7 Hz), 7.19–7.55 (m, 4H), 7.60 (dd, 1H, *J*=3.5, 0.8 Hz), 7.68 (dd, 1H, *J*=1.9, 0.9 Hz); MS (*m/z*) 382 (M$^+$+1), 381 (M$^+$), 306, 270, 194, 129, 75, 55. Calcd.: For $C_{19}H_{15}N_3O_4S$ C 59.83; H, 3.96; N, 11.02; S, 8.41%. Found: C, 60.04; H, 4.25; N, 11.25; S, 8.34%.

2-(2-Furoyl)cyanomethylene-3-(4-chlorophenyl)-5-(ethylcarboxylate)-2,3-dihydro-1,3,4-thiadiazole (**21g**): Yield (78%); m.p. 279–280˚C (DMF/H_2O); IR (KBr) ν_{max}/cm^{-1} 2203 (C≡N), 1726, 1683 (2C=O), 1582 (C=N); ^{1}H NMR (DMSO-d$_6$) δ 1.29 (t, 3H), 4.31 (q, 2H), 6.52 (dd, 1H, *J*=3.4, 1.9 Hz), 7.23–7.57 (m, 4H), 7.69 (dd, 1H, *J*=3.4, 0.9 Hz), 7.82 (dd, 1H, *J*=1.8, 0.8 Hz); MS (*m/z*) 402 (M$^+$+1), 401 (M$^+$), 328, 286, 113, 73, 55. Calcd.: For $C_{18}H_{12}ClN_3O_4S$ C, 53.80; H, 3.01; N, 10.46; S, 7.98%. Found: C, 53.55; H, 2.86; N, 10.27; S, 7.80%.

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