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ORIGINAL ARTICLE

Convenient synthesis of azolopyrimidine, azolotriazine, azinobenzimidazole and 1,3,4-thiadiazole derivatives

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KEYWORDS

Pyrazolo[1,5-*a*]pyrimidine;
Triazolo[1,5-*a*]pyrimidine;
Pyrimido[1,2-*a*]benzimidazole;
Pyrazolo[5,1-*c*]triazine;
Triazino[4,3-*a*]benzimidazole;
1,3,4-Thiadiazole

Abstract Several pyrazolo[1,5-*a*]pyrimidine, triazolo[1,5-*a*]pyrimidine, pyrido[1,2-*a*]-benzimidazole, pyrimido[1,2-*a*]benzimidazole, pyrazolo[5,1-*c*]triazine, triazolo[5,1-*c*]-triazine, triazino[4,3-*a*] benzimidazole and 1,3,4-thiadiazole derivatives were synthesized *via* the reactions of (*E*)-3-oxo-5-phenylpent-4-enenitrile and the versatile, *hitherto* unreported (*E*)-2-(*N*,*N*-dimethylaminomethylene)-3-oxo-5-phenyl-4-pentenenitrile with the appropriate nitrogen and sulfur nucleophiles.

1. Introduction

α,β-Unsaturated nitriles are versatile intermediates and were utilized for the synthesis of carbocycles and heterocycles (Zoretic et al., 1998; Sharanin et al., 1998; Fleming et al., 1999; Lattanzi et al., 2003; Fleming and Wang 2003). Also, heterocyclic hydrazones have remarkable applications in the synthesis of fused heterocycles (Ciesielski et al., 2005). On the other hand, pyrazole derivatives have also important applications in the field of medicinal chemistry (Shaaban et al., 2012; Manna et al., 1992; Stauffer et al., 2000), whereas 1,3,4-thiadiazoles were reported as highly anti-inflammatory (Labanauskas et al., 2001; Schenone et al., 2001), antimicrobial (Dogan et al., 2002) and anticonvulsant (Archana et al., 2002; Ilies et al., 2004) agents.

In continuation of our recent work concerned with the synthesis of a variety of heterocyclic systems for biological evaluation (Farag et al., 2007, 2008a,b, 2011; Dawood et al., 2007, 2009, 2013; Darweesh et al., 2010; Shaaban et al., 2011; Hegazi et al., 2013; Dawood, 2013; Mabkhot et al., 2013), we report here on the reactivity of (*E*)-3-oxo-5-phenylpent-4-enenitrile (**1**) and the *hitherto* unreported (*E*)-2-(*N*,*N*-dimethylaminomethylene)-3-oxo-5-phenyl-4-pentenenitrile (**2**) as versatile building blocks for the synthesis of the title compounds.

2. Experimental

2.1. Materials and methods

All melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded in potassium bromide disks on pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. The NMR spectra

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were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in deuterated chloroform ($CDCl_3$) or dimethyl sulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 e.V. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. The heterocyclic diazonium salts **19a–c** (Butler, 1975; Elnagdi et al., 1976; Farag, 1995) and hydrazonoyl chlorides **26a–d** (Dieckmann and Platz, 1906; Shawali and Osman, 1971) were prepared following the reported literature procedures.

*2.2. (E)-2-(N,N-dimethylaminomethylene)-3-oxo-5-phenyl-4-pentenenitrile (**2**)*

To a solution of 3-oxo-5-phenyl-4-pentenenitrile (**1**) (1.71 g, l0 mmol) in dry xylene (50 ml) was added dimethylformamide-dimethylacetal (DMF-DMA) (1.34 g, 10 mmol) and the mixture was refluxed for 3 h. Then, the solvent was distilled off under reduced pressure and the residual reddish brown viscous liquid was taken in ether and the resulting brown crystals were collected by filtration, washed thoroughly with ether, dried and finally recrystallized from EtOH to afford compound **2** in 65% yield; mp. 193–195 °C; IR (KBr) ν_{max}/cm^{-1} 2219 (C≡N), 1644 (C=O); ^{1}H NMR ($CDCl_3$) δ 3.44 (s, 6H, $2CH_3$), 7.35–7.36 (m, 3H, ArH), 7.40 (d, 1H, –CH=CH–, J = 15.6 Hz), 7.57–7.62 (m, 2H, ArH), 7.69 (d, 1H, –CH=CH–, J = 15.6 Hz), 7.99 (s, 1H, =CH–N); MS m/z (%) 226 (M$^+$, 96.3), 197 (24.4), 149 (100), 131 (88.3), 103 (89.7), 77 (57.7). For $C_{14}H_{14}N_2O$ Calcd: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.54; H, 6.01; N, 12.16%.

*2.3. Synthesis of 5-Amino-4-cinnamoylisoxazole (**3**)*

A mixture of *trans* 2-(*N,N*-dimethylaminomethylene)-3-oxo-5-phenyl-4-pentenenitrile (**2**) (2.26 g, 10 mmol), hydroxylaminehydrochloride (10 mmol) and anhydrous potassium carbonate (0.5 g) in absolute EtOH (25 ml) was refluxed for 5 h then left to cool. The reaction mixture was poured into cold water and the solid product filtered off, washed with water, dried and finally recrystallized from EtOH to afford 5-amino-4-cinnamoylisoxazole (**3**). Yield, 73%; mp. 215–217 °C; IR (KBr) ν_{max}/cm^{-1} 3250, 3142 (NH_2), 1640 (C=O), 1608 (C=N); ^{1}H NMR (DMSO) δ 7.30–7.38 (m, 5H, ArH), 7.42 (d, 1H, –CH=CH–, J = 15.6 Hz), 7.67 (d, 1H, –CH=CH–, J = 15.6 Hz), 8.2 (s, 1H), 8.83 (s, 2H, NH_2); MS m/z (%) 214 (M$^+$, 17.2), 196 (5.5), 17 (35.8), 131 (100), 103 (71.9), 77 (47.3), 51 (50.6); For $C_{12}H_{10}N_2O_2$ Calcd: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.42; H, 4.58; N, 12.89%.

*2.4. 2-Amino-4-styrylpyrimidine-5-carbonitrile (**5**)*

A mixture of 2-(*N,N*-dimethylaminomethylene)-3-oxo-5-phenyl-4-pentenenitrile (**2**) (2.26 g, 10 mmol), guanidine nitrate (10 mmol) and anhydrous potassium carbonate (0.5 g), in absolute EtOH (25 ml), was refluxed for 5 h then left to cool. The reaction mixture was poured into cold water and the solid product was filtered off, washed with water, dried and finally recrystallized from EtOH to afford 2-amino-4-styrylpyrimidine-5-carbonitrile (**5**). Yield, 77%; mp. 223–225 °C; IR (KBr) ν_{max}/cm^{-1}: 3333, 3179 (NH_2), 2214 (C≡N), 1610 (C=N); MS m/z (%) 222 (M$^+$, 100), 179 (15.3), 102 (11.8), 77 (29.2), 51 (35.9); For $C_{13}H_{10}N_4$ Calcd: C, 70.26; H, 4.54; N, 25.21. Found: C, 70.03; H, 4.65; N, 5.42%.

*2.5. Reaction of the enaminone **2** with heterocyclic amines*

2.5.1. General procedure

A mixture of **2** (2.26 g, 10 mmol) and the appropriate heterocyclic amine [5-amino-3-1*H*-phenylylpyrazole (**11**) or 3-amino-l,2,4-triazole (**12**)] (10 mmol) in absolute EtOH (25 ml) and a few drops of piperidine was refluxed for 3 h then allowed to cool. The formed solid product was filtered off, washed with EtOH, dried and finally recrystallized from EtOH to afford the corresponding pyrazolo[1,5-*a*]pyrimidine derivative **13** or triazolo[1,5-*a*]pyrimidine derivative **14**, respectively.

*2.5.1.1. 2-Phenyl-5-styrylpyrazolo[1,5-a]pyrimidine-6-carbonitrile (**13**).* Yield, 66%; mp. 102–104 °C; IR (KBr) ν_{max}/cm^{-1} 2213 (C≡N), 1608 (C=N); MS m/z (%) 322 (M$^+$, 100%), 245 (62.4), 219 (10.7), 77 (18.3), 51 (14.8); For $C_{21}H_{14}N_4$ Calcd: C, 78.24; H, 4.38; N, 17.38. Found: C, 78.54; H, 4.26; N, 17.54%.

*2.5.1.2. 5-Styryl-1,2,4-triazolo[1,5-a]pyrimidine-6-carbonitrile (**14**).* Yield, 75%; mp. 255–257 °C; IR (KBr) ν_{max}/cm^{-1} 2218 (C≡N), 1612 (C=N); ^{1}H NMR (DMSO) δ 7.29–7.52 (m, 6H, ArH and 1H, –CH=CH–), 7.63 (d, 1H, –CH=CH–, J = 15.6 Hz), 7.89 (s, 1H); MS m/z (%) 247 (M$^+$, 20.4), 230 (38.2), 131 (40.9), 103 (100), 77 (68.3), 51 (88.6); For $C_{14}H_9N_5$ Calcd: C, 68.01; H, 3.67; N, 28.32. Found: C, 67.82; H, 3.84; N, 28.43%.

*2.6. Reaction of **2** with 1H-benzimidazole-2-acetonitrile (**7**) and 2-aminobenzimidazole (**17**).*

2.6.1. General procedure

To a mixture of **2** (2.26 g, 10 mmol) and 1*H*-benzimidazole-2-acetonitrile (**7**) or 2-aminobenzimidazole (**17**) (10 mmol) in absolute EtOH (25 ml) were added few drops of piperidine and the reaction mixture was refluxed for 7 h then left to cool. The solid product that formed was filtered off, washed with EtOH and dried. Recrystallization from EtOH afforded the corresponding products **9** and **18**, respectively.

*2.6.1.1. 3-Amino-2-cinnamoylpyrido[1,2-a]benzimidazole-4-carbonitrile (**9**).* Yield, 62%; mp. > 300 °C; IR (KBr) ν_{max}/cm^{-1} 3338, 3176 (NH_2), 2214 (C≡N), 1654 (C=O), 1618 (C=N); ^{1}H NMR (DMSO) **δ** 7.21–7.69 (m, 9H, ArH and 1H, –CH=CH–), 7.82 (d, 1H, –CH=CH–, J = 15.4 Hz), 8.10 (s, 2H, NH_2), 8.41 (s, 1H); MS m/z (%) 338 (M$^+$, 23.9), 320 (12.4), 261 (54.9), 235 (25.9), 103 (90.0), 77 (100), 51 (70.1). For $C_{21}H_{14}N_4O$ Calcd: C, 74.54; H, 4.17; N, 16.56. Found: C, 74.79; H; 4.34 N, 16.55%

*2.6.1.2. 2-Styrylpyrimido[1,2-a]benzimidazole-3-carbonitrile (**18**).* Yield, 65%; mp. 303–305 °C; IR (KBr) ν_{max}/cm^{-1} 2189 (C≡N), 1618 (C=N); ^{1}H NMR (DMSO) **δ** 7.21–7.69 (m, 11H, ArH and 2H, CH=CH–), 8.1 (s, 1H); MS m/z (%) 296 (M$^+$, 100), 270 (34.95), 236 (23.8), 140 (11.8), 77 (47.1), 51 (38.0). For $C_{19}H_{12}N_4$ Calcd: C, 77.01; H, 4.08; N, 18.91. Found: C, 77.27; H, 4.21; N, 18.68%.

2.7. Reaction of pentenenitrile **1** with diazonium salts of heterocyclic amines

2.7.1. General procedure

To a cold solution of 3-oxo-5-phenyl-4-pentenenitrile (**1**) (1.71 g, l0 mmol) in pyridine (20 ml) was added the appropriate diazonium salt of heterocyclic amine [5-amino-3-phenylpyrazole (**19a**), 3-amino-l,2,4-triazole (**19b**) or 2-aminobenzimidazole (**19c**)] (10 mmol). The addition was carried out portionwise with stirring at 0–5 °C over a period of 30 min. After complete addition, the reaction mixture was stirred for further 4 h, then kept in an ice-chest for 12 h, and finally diluted with water. The precipitated solid was collected by filtration, washed with water and dried. Recrystallization from EtOH afforded the corresponding hydrazones **20a**,**b** and **23**, respectively.

*2.7.1.1. 2-Cyano-4-(3-phenyl-1H-pyrazol-5-ylhydrazono)-5-phenyl-3-oxo-4-pentenenitrile (**20a**).* Yield (78%); mp. 158–160 °C; IR (KBr) ν_{max}/cm^{-1} 3382, 3206 (2NH), 2205 (C≡N), 1666 (C=O), 1605 (C=N); MS *m/z* (%) 341 (M^+, 27.3), 225 (44.1), 77 (100), 51 (76.2). For $C_{20}H_{15}N_5O$ Calcd: C, 70.37 H, 4.43 N, 20.52. Found: C, 70.50 H, 4.27 N, 20.64%

*2.7.1.2. 2-Cyano-4-(1H-1,2,4-triazol-5-ylhydrazono)-5-phenyl-3-oxo-4-pentenenitrile (**20b**).* Yield (76%); mp. 145–147 °C; IR (KBr) ν_{max}/cm^{-1} 3360, 3146 (2NH), 2215 (C≡N), 1665 (C=O), 1609 (C=N); MS *m/z* (%) 266 (M^+, 78.9), 189 (13.7), 136 (20.5), 103 (81.3), 77 (100), 51 (59.6). For $C_{13}H_{10}N_6O$ Calcd: C, 58.64; H, 3.79; N, 31.56. Found: C, 58.46; H, 3.65; N, 31.71%.

*2.7.1.3. 2-Cyano-4-(benzimidazol-2-ylhydrazono)-5-phenyl-3-oxo-4-pentenenitrile (**23**).* Yield (60%); mp.175–177 °C; IR (KBr) ν_{max}/cm^{-1} 3410, 3216 (2NH), 2221 (C≡N), 1658 (C=O), 1613 (C=N). MS *m/z* (%) 315 (M^+, 55.6), 298 (40.4), 103 (10.2), 77 (100), 51 (75.9). For $C_{18}H_{13}N_5O$ Calcd: C, 68.56; H, 4.16; N, 22.21. Found: C, 68.43; H, 4.13; N, 22.06%.

2.8. Cyclization of the heterocyclic hydrazones

2.8.1. General procedure

A solution of the appropriate hydrazone **20a**,**b** or **23** (2 mmol) in pyridine (10 ml) was refluxed for 3 h, then left to cool. The formed solid was filtered off, washed with EtOH and dried. Recrystallization from EtOH and DMF afforded the corresponding fused heterocyclic systems **22a**,**b** and **25**, respectively.

*2.8.1.1. 4-Amino-3-cinnamoyl-7-phenylpyrazolo[5,1-c][1,2,4]triazine-3-carbonitrile (**22a**).* Yield (64%); mp. 250–252 °C; IR (KBr) ν_{max}/cm^{-1} 3420, 3185 (NH_2), 1665 (C=O), 1610 (C=N); MS *m/z* (%) 341 (M^+, 45.2), 312 (10.5), 180 (54), 77 (100); For $C_{20}H_{15}N_5O$ Calcd: C, 70.37; H, 4.43; N, 20.52. Found: C, 70.16; H, 4.33; N, 20.37%.

*2.8.1.2. 4-Amino-3-cinnamoyl-1,2,4-triazolo[5,1-c][1,2,4]triazine (**22b**).* Yield (70%); mp. 235–237 °C; IR (KBr) ν_{max}/cm^{-1} 3415, 3182 (NH_2), 1665 (C=O), 1615 (C=N); MS *m/z* (%) 266 (M^+, 56.8), 189 (15), 77 (100), 51 (60.8). For $C_{13}H_{10}N_6O$ Calcd: C, 58.64; H, 3.79; N, 31.56. Found: C, 58.49 H, 3.84 N, 31.65%.

*2.8.1.3. 4-Amino-3-cinnamoyl-1,2,4-triazino[4,3-a]benzimidazole (**25**).* Yield (58%); mp. 265–267 °C; IR (KBr) ν_{max}/cm^{-1} 3385, 3168 (NH_2), 1668 (C=O), 1609 (C=N); MS *m/z* (%) 315 (M^+, 15.6), 77 (100), 51 (42.6). For $C_{18}H_{13}N_5O$ Calcd: C, 68.56; H, 4.16; N, 22.21. Found: C, 68.68; H, 4.17; N, 22.35%.

2.9. Reaction of the pentenenitrile 1 with hydrazonoyl chlorides 26a-d

2.9.1. General Procedure

3-Oxo-5-phenyl-4-pentenenitrile (**1**) (1.71 g, 10 mmol) was added to an EtOHic sodium ethoxide solution [prepared from sodium metal (0.23 g, 10 mmol) and 50 ml of absolute EtOH]. After stirring for 10 min, the appropriate hydrazonoyl chloride **26a**–**d** (10 mmol) was added and stirring was continued for further 30 min. The reaction mixture was then left at room temperature with stirring for 12 h. The solid product that formed was collected by filtration, washed with water and dried. Crystallization from EtOH afforded the corresponding pyrazole derivatives **28a**–**d**

*2.9.1.1. 3-Acetyl-5-(β-styryl)-1-phenylpyrazole-4-carbonitrile (**28a**).* Yield (76%); mp. 200–202 °C; IR (KBr) ν_{max}/cm^{-1} 2227 (C≡N), 1690 (C=O), 1595 (C=N); ^1H NMR ($CDCl_3$) δ 2.65 (s, 3H, $COCH_3$), 6.76 (d, 1H, CH=CH, J = 16.6 Hz), 7.34–7.67 (m, 10H, ArH), 7.82 (d, 1H, CH=CH, J = 16.6 Hz); MS *m/z* (%) 313 (M^+ , 61.6), 270 (28.4), 236 (21.4), 77 (100), 51 (79.5). For $C_{20}H_{15}N_3O$ Calcd: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.84; H, 5.01; N, 13.57%.

*2.9.1.2. 3-Acetyl-5-(β-styryl)-1-(4-tolyl)pyrazole-4-carbonitrile (**28b**).* Yield (72%); mp. 210–212 °C; IR (KBr) ν_{max}/cm^{-1}: 2227 (C≡N), 1686 (C=O), 1605 (C=N); ^1H NMR ($CDCl_3$) δ 2.36 (s, 3H, CH_3), 2.66 (s, 3H, $COCH_3$), 6.74 (d, 1H, CH=CH, J = 16.6 Hz), 7.32–7.72 (m, 9H, ArH), 7.82 (d, 1H, CH=CH, J = 16.6 Hz); MS *m/z* (%) 327 (M^+, 44.1), 180 (55.4), 164 (22.8), 77 (100), 51 (72.7); For $C_{21}H_{17}N_3O$ Calcd: C, 77.04; H, 5.23; N, 12.83. Found: C, 76.82; H, 5.41; N, 13.04%.

*2.9.1.3. 3-(N-Phenylcarboxamido)-5 - β-styryl)-1-phenylpyrazole-4-carbonitrile (**28c**).* Yield (77%); mp.201–203 °C; IR (KBr) ν_{max}/cm^{-1} 3385 (NH), 2233 (C≡N), 1690 (C=O), 1606 (C=N); MS *m/z* (%) 390 (M^+, 25.3), 330 (40.2), 131 (100), 103 (97.5), 77 (65.4). For $C_{25}H_{18}N_4O$ Calcd: C, 76.91; H, 4.65; N, 14.35. Found: C, 77.01; H, 4.49; N, 14.54%.

*2.9.1.4. 3-(N-Phenylcarboxamido)-5-(β-styryl)-1-(4-tolyl)pyrazole-4-carbonitrile (**28d**).* Yield (68%); mp. 208–210 °C; IR (KBr) ν_{max}/cm^{-1} 3398 (NH), 2228 (C≡N), 1886 (C=O), 1597 (C=N); ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H, CH_3), 6.77 (d, 1H, CH=CH, J = 16.6 Hz), 7.29–7.66 (m, 14H, ArH), 7.78 (d, 1H, CH=CH, J = 16.6 Hz), 8.64 (br.s, 1H, NH, D_2O-exchangeable); MS *m/z* (%) 403 (M^+), 131 (100), 103 (64.8), 77 (34.8), 51 (42.6); For $C_{26}H_{20}N_4O$ Calcd: C, 77.21; H, 4.98; N, 13.85. Found: C, 77.43; H, 4.73; N, 13.94%.

2.10. Synthesis of 1,3,4-thiadiazole derivatives **31a–d**

2.10.1. General procedure

To a stirred solution of potassium hydroxide (0.56 g, 10 mmol) in DMF (30 ml), 3-oxo-5-phenyl-4-pentenenitrile (**1**) (1.71 g, 10 mmol) was added. After stirring for 30 min phenyl isothiocyanate (1.38 g, 10 mmol) was added to the resulting mixture. Stirring was continued for 6 h, and then the appropriate hydrazonoyl chloride **26a–d** (10 mmol) was added portion-wise over a period of 30 min. After the addition was complete, the reaction mixture was stirred for 12 h during which the hydrazonoyl chloride dissolved and a yellowish colored product precipitated. The solid product was filtered off, washed with water, dried and finally recrystallized from EtOH/DMF to afford the corresponding 1,3,4-thiadiazole derivatives **31a–d**, respectively.

*2.10.1.1. 5-Acetyl-2-(cinnamoyl)cyanomethylene-3-phenyl-2,3-dihydro-1,3,4-thiadiazole (**31a**).* Yield (66%); mp. 225–227 °C; IR (KBr) ν_{max}/cm^{-1} 2199 (C≡N), 1700, 1685 (2C=O), 1612 (C=N); ^{1}H NMR ($CDCl_3$) δ 2.62 (s, 3H, $COCH_3$), 7.31 (d, 1H, CH=CH, J = 15.6 Hz), 7.33–7.68 (m, 10H, ArH), 7.76 (d, 1H, CH=CH, J = 15.6 Hz); ^{13}C NMR (DMSO-d_6) δ 26, 77.9, 114.9, 120.9, 127.8, 128.2, 128.8, 129.5, 130.5, 131.4, 134.3, 137.9, 142.7, 156.4, 165.1, 180.8, 190.5; MS m/z (%) 373 (M^+, 33.5), 296 (53.9), 103 (100), 77 (66.5). For $C_{21}H_{15}N_3O_2S$ Calcd: C, 67.54; H, 4.05; N, 11.25; S, 8.59. Found: C, 67.72; H, 3.89; N, 11.19; S, 8.74%.

*2.10.1.2. 5-Acetyl-2-(cinnamoyl)cyanomethylene-3-(4-tolyl)-2,3-dihydro-l,3,4-thiadiazole (**31b**).* Yield (60%); mp.279–281 °C; IR (KBr) ν_{max}/cm^{-1} 2203 (C≡N), 1700, 1691 (2C=O), 1619 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.44 (s, 3H, CH_3), 2.58 (s, 3H, $COCH_3$), 7.28 (d, 1H, CH=CH, J = 15.6 Hz), 7.39–7.64 (m, 9H, ArH), 7.71 (d, 1H, CH=CH, J = 15.6 Hz); ^{13}C NMR (DMSO-d_6) δ 20.9, 25.9, 77.8, 115, 121, 127.5, 128.2, 129, 129.7, 130.5, 134.3, 135.5, 141.2, 142.6, 156.4, 165.1, 180.8, 190.4; MS m/z (%) 387 (M^+, 29.5), 294 (46), 147 (74.2), 103 (91.3), 77 (100). For $C_{22}H_{17}N_3O_2S$ Calcd: C, 68.20; H, 4.42; N, 10.84; S, 8.28. Found: C, 68.03; H, 4.61; N, 10.66; S, 8.01%.

*2.10.1.3. 2-(Cinnamoyl)cyanomethylene-3-phenyl-5-(N-phenylcarboxamido)-2,3-dihydro-1,3,4-thiadiazole (**31c**).* Yield (66%); mp. 254–256 °C; IR (KBr) ν_{max}/cm^{-1} 3292 (NH), 2210 (C≡N), 1655, 1624 (2C=O), 1593 (C=N); ^{1}H NMR ($CDCl_3$) δ 7.29 (d, 1H, CH=CH, J = 15.4 Hz), 7.35–7.71 (m, 15H, ArH), 7.76 (d, 1H, CH=CH, J = 15.4 Hz), 8.94 (br.s, D_2O exchangeable, 1H, NH); MS m/z (%) 450 (M^+, 21.9), 373 (42.6), 131 (72.4), 103 (94), 77 (100). For $C_{26}H_{18}N_4O_2S$ Calcd: C, 69.32; H, 4.03; N, 12.44; S, 7.12. Found: C, 69.47; H, 3.87; N, 12.61; S, 7.00%.

*2.10.1.4. 2-(Cinnamoyl)cyanomethylene-3-(4-tolyl)-5-(N-phenylcarboxamido)-2,3-dihydro-1,3,4-thiadiazole (**31d**).* Yield (63%); mp.230–232 °C; IR (KBr) ν_{max}/cm^{-1} 3303 (NH), 2205 (C≡N), 1686, 1654 (2C=O), 1598 (C=N); ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H, CH_3), 7.16 (m, 1H, ArH), 7.29 (d, 1H, CH=CH, J = 15.6 Hz), 7.34–7.45 (m, 7H, ArH), 7.62–7.79 (m, 7H, ArH), 10.99 (br.s, D_2O exchangeable, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 21, 77.5, 109.3, 115.2, 120.6, 121, 124.8, 127.9, 128.1, 128.7, 129, 129.6, 130.4, 134.3, 135.5, 137.2, 141.2, 142.3, 154.6, 155.9, 180.6; MS m/z (%) 464 (M^+, 67.1), 387 (58.7), 186 (65.3), 103 (100), 77 (90.4), 51 (34.4); For $C_{27}H_{20}N_4O_2S$ Calcd: C, 69.81; H, 4.34; N, 12.06; S, 6.90. Found: C, 69.65; H, 4.55; N, 11.84; S, 6.94%.

3. Results and discussion

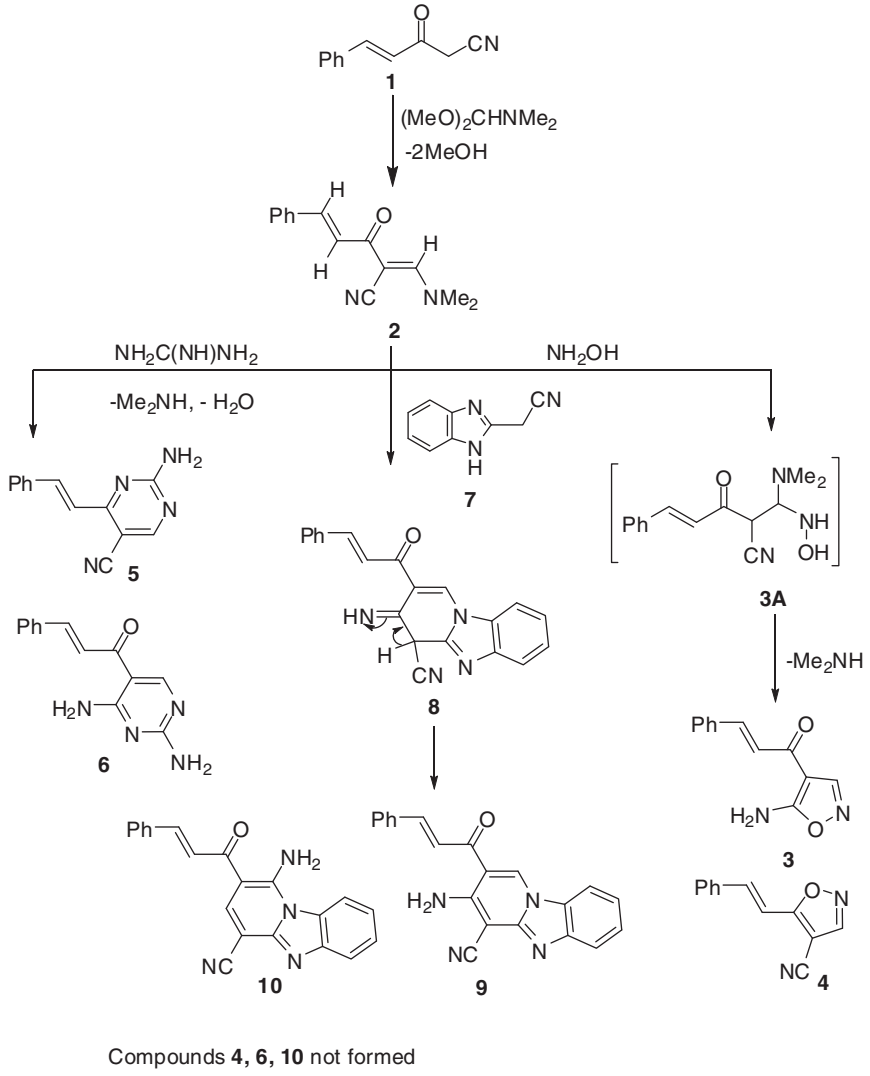
Treatment of (*E*)-3-oxo-5-phenyl-4-pentenenitrile (**1**) (Augustin et al., 1977) with dimethylformamide-dimethylacetal (DMF-DMA), in dry xylene, at reflux temperature, afforded a yellow product identified as (*E*)-2-(*N,N*-dimethylaminomethylene)-3-oxo-5-phenyl-4-pentenenitrile (**2**) (Scheme 1). The ^{1}H NMR spectrum of latter product showed a singlet signal at δ 3.44 corresponding to $N(CH_3)_2$ protons, two doublets at δ 7.40 and 7.69 with the same J value (15.6 Hz) for –C*H*=C*H*– protons and a singlet at δ 7.99 for C=C*H*–N, in addition to the aromatic-*H* mutiplets. The J value of the ethylenic protons (15.6 Hz) indicates that the structure of product **2** has the *E*-configuration. In addition, the proton signal at δ 7.99 assigns the *E*-configuration (Dawood, 2005), whereas for *Z*-isomers it appears around δ 6.9 (Bennett et al., 1972).

The reactivity of the enaminone **2** toward some nitrogen nucleophiles was investigated. Thus, when compound **2** was treated with hydroxylamine in refluxing EtOH, it afforded a single product identified as (*E*)-5-amino-4-cinnamoylisoxazole (**3**) (Scheme 1). The IR spectrum of compound **3** was free of absorption band corresponding to a nitrile function and showed bands at 3250 and 3142 cm^{-1} corresponding to an amino group, in addition to a strong absorption band at 1640 cm^{-1} corresponding to a conjugated carbonyl group. Its mass spectrum revealed a molecular ion peak at m/z 214 (M^+). These data exclude the other possible structure **4** for the reaction product. Compound **3** is assumed to be formed through the addition of the hydroxylamine-*NH* to the activated double bond in compound **2** followed by intramolecular cyclization *via* nucleophilic attack of OH on CN group with the elimination of dimethylamine.

Compound **2** reacted also with guanidine in refluxing EtOH and afforded (*E*)-2-amino-4-styrylpyrimidine-5-carbonitrile (**5**). The IR spectrum of the reaction product showed amino and nitrile absorption bands at 3333, 3179 and 2214 cm^{-1}, respectively, and was free of carbonyl absorption bands which excludes the other possible structure **6**.

Reaction of compound **2** with 1*H*-benzimidazole-2-acetonitrile (**7**) under the same experimental conditions furnished a single product identified as 3-amino-2-cinnamoylpyrido-[1,2-*a*]benzimidazole-4-carbonitrile (**9**) as shown in Scheme 1. The other possible regioisomeric structure **10** was excluded based on the ^{1}H NMR spectrum of the reaction product which revealed a signal at 8.41 ppm due to =C*H*-N of the pyridine ring supporting structure **9**. Compound **9** seemed to be formed *via* the formation of the intermediate **8** in a mechanism similar to analogous examples reported previously (Dawood et al., 1999).

The behavior of (*E*)-2-(*N,N*-dimethylaminomethylene)-3-oxo-5-phenyl-4-pentenenitrile (**2**) toward some heterocyclic amines as potential precursors for fused heterocyclic systems was also investigated. Thus, when compound **2** was treated with 5-amino-3-phenyl-1*H*-pyrazole (**11**) in refluxing EtOH, in the presence of a catalytic amount of piperidine, it furnished 2-phenyl-5-styrylpyrazolo[1,5-*a*]pyrimidine-6-carbonitrile (**13**)



Compounds **4, 6, 10** not formed

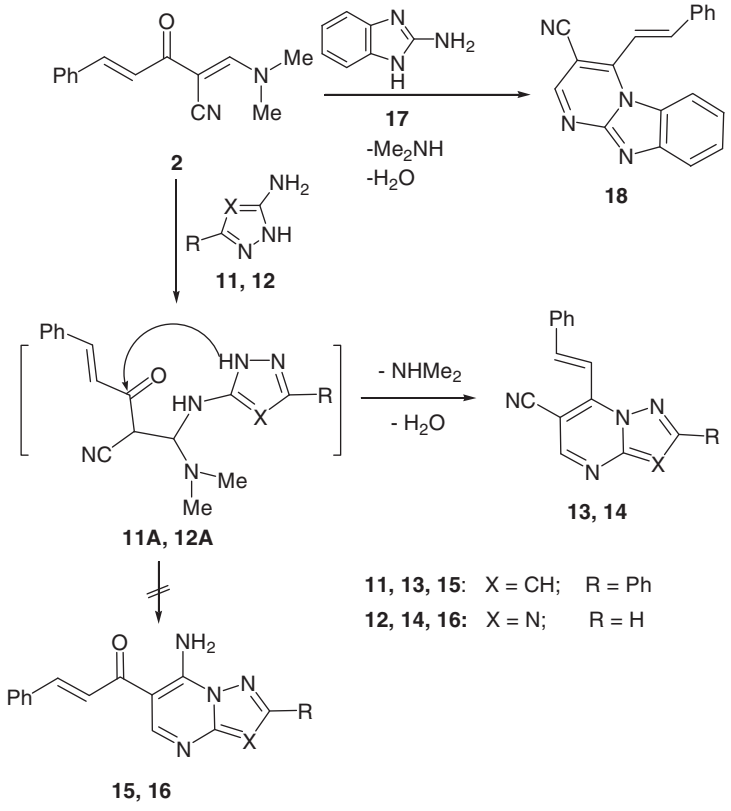
Scheme 1 Reactions of the enaminone **2** with nitrogen nucleophiles.

as outlined in Scheme 2. The IR spectrum of the latter product showed an absorption band at 2213 cm^{-1} corresponding to nitrile function and revealed the lack of a band corresponding to carbonyl function. Its mass spectrum revealed a peak corresponding to its molecular ion at *m*/*z* 322. The formation of compound **13** can be explained on the basis of an initial *Michael* type addition of the NH_2 of the aminopyrazole **11** to the enamine-double bond in compound **2** to afford the non-isolable intermediate **11A** followed by an intramolecular cyclization *via* elimination of dimethylamine and water molecule to give the styrylpyrazolo[1,5-*a*]pyrimidine derivative **13** analogous to previous reports (Cebasek et al., 2004; Jakse et al., 2004; Stanovnik and Svete, 2004) (Scheme 2). The other possible structure **15** was easily excluded on the basis of the spectral data of the isolated product. For example, the IR spectrum of the reaction product was found to be free of amino and carbonyl absorption bands.

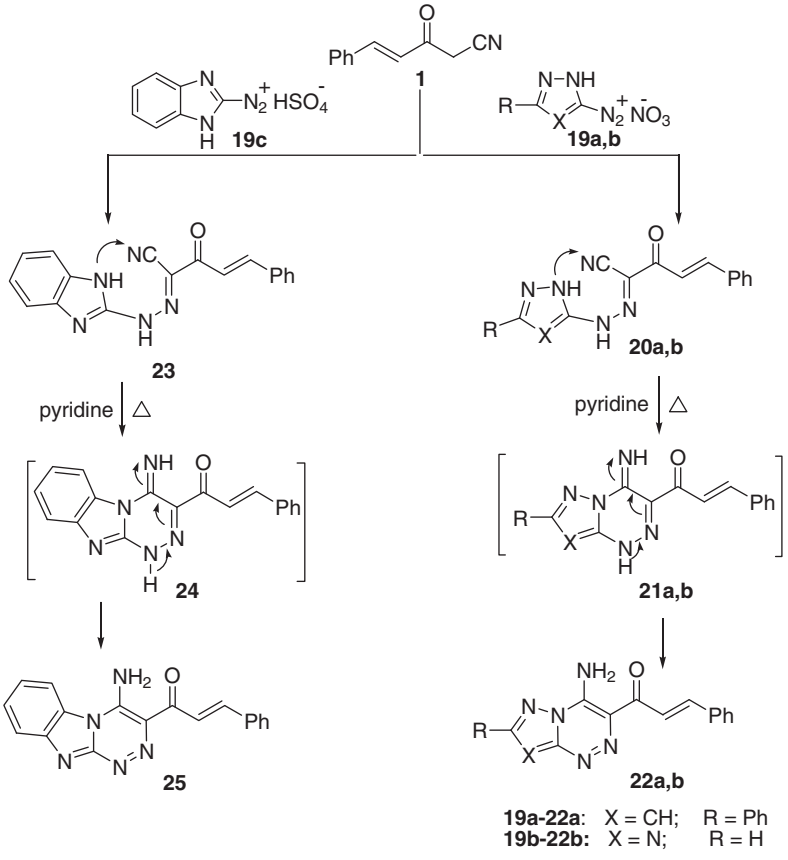
In a similar manner, compound **2** reacts with 3-amino-1,2,4-triazole (**12**) and with 2-aminobenzimidazole (**17**) under similar reaction conditions to afford 5-styryl-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carbonitrile (**14**) and the styrylpyrimido[1,2-*a*]benzimidazole derivative **18**, respectively (Scheme 2). The structures of the isolated products were confirmed on the basis of their elemental analyses and spectral data (*cf.* experimental part).

The behavior of 3-oxo-5-phenyl-4-pentenenitrile (**1**) toward some heterocyclic diazonium salts was also investigated. Thus, when compound **1** was treated with 3-phenylpyrazol-5-diazonium chloride (**19a**), it afforded the corresponding pyrazolylhydrazone derivative **20a** (Scheme 3). The IR spectrum of the isolated hydrazone showed two NH bands at 3382 and 3206 cm^{-1}, in addition to nitrile and carbonyl absorption bands at 2205 and 1666 cm^{-1}, respectively. The hydrazone **20a** underwent an intramolecular cyclization upon boiling in pyridine *via* addition of NH to CN to afford the corresponding 4-aminopyrazolo[5,1-*c*][1,2,4]triazine derivative **22a**. The IR spectrum of the latter product was free of band corresponding to nitrile function and revealed absorption bands at 3420, 3185 and 1668 cm^{-1} due to amino function and a conjugated carbonyl group, respectively. Its mass spectrum showed a peak corresponding to the molecular ion at *m*/*z* 341.

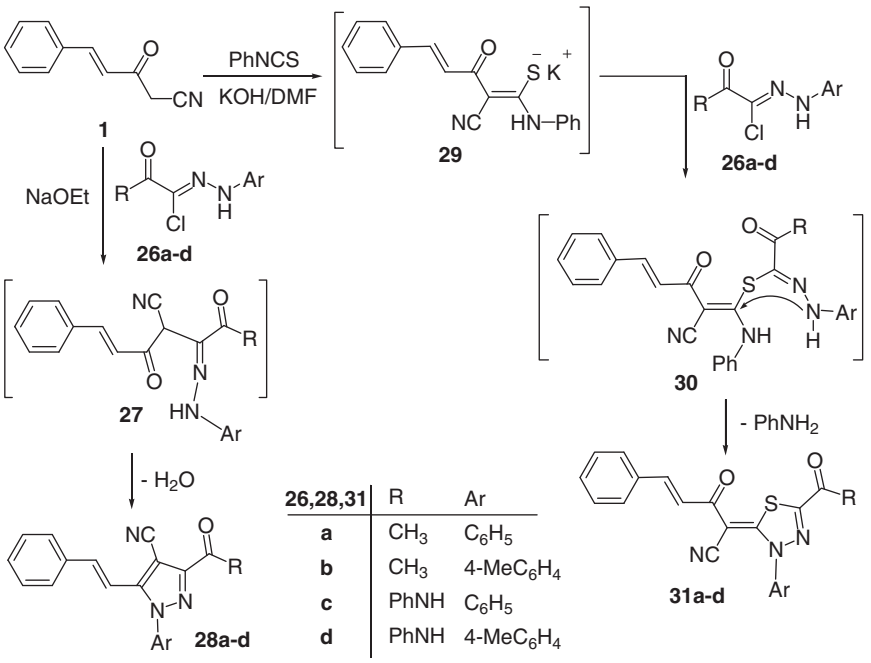
Similarly, compound **1** coupled smoothly also with the diazonium salt of 5-amino-l,2,4-triazole (**19b**) and afforded the corresponding hydrazone derivative **20b**. The latter product



Scheme 2 Reactions of the enaminone **2** with heterocyclic amines.



Scheme 3 Reactions of the enaminone **2** with heterocyclic diazonium salts.



Scheme 4 Reactions of the enaminone **2** with hydrazonoyl chlorides and with phenyl isothiocyanate.

underwent an intramolecular cyclization when refluxed in pyridine to afford the corresponding 4-amino-3-cinnamoyl-1,2,4-triazolo[5,1-c][1,2,4]triazine (**22b**) as depicted in Scheme 3. The structures of the hydrazone **20b** and the pyrazol[5,1-*c*][1,2,4]triazine **22b** were established on the basis of their elemental analyses and spectral data. For example, the IR spectrum of compound **20b** showed bands at 3360, 3146, 2215 and 1669 cm^{-1} corresponding to 2 NH, a nitrile and a conjugated carbonyl group, respectively. The structure of the pyrazol[5,1-*c*][1,2,4]triazine **22b**, revealed the absence of band corresponding to nitrile function and showed two bands at 3415 and 3182 cm^{-1} characteristics for the NH_2 group, in addition to a conjugated carbonyl absorption band at 1665 cm^{-1}. The mass spectra of compounds **20b** and **22b** showed, in each case, a peak corresponding to the molecular ion.

Coupling of compound **1** with the diazonium salt of 2-aminobenzimidazole **19c** afforded 2-(benzimidazol-2-ylhydrazono)-5-phenyl-3-oxo-4-pentennitrile (**23**) which underwent intramolecular cyclization when boiled in pyridine to afford the corresponding 4-amino-3-cinnamoyl[1,2,4]triazino[4,3-a]benzimidazole (**25**). The structures of the products **23** and **25** were established on the basis of their elemental analyses and spectral data (*cf*. experimental).

Next, treatment of 3-oxo-5-phenyl-4-pentenenitrile (**1**) with the hydrazonoyl chloride **26a**, in the presence of sodium ethoxide, afforded the corresponding pyrazole derivative **28a** (Scheme 4). The IR spectrum of the isolated product revealed strong absorption bands at 2227 and 1680 cm^{-1} corresponding to nitrile and carbonyl functions, respectively. Its ^1H NMR spectrum exhibited two doublets at δ 6.76 and 7.82, with the same J value (16.6 Hz) typical to *E*-configuration, in addition to a singlet at δ 2.65 and a multiplet at δ 7.34–7.67 due to methyl and phenyl protons, respectively. In addition, its mass spectrum showed a peak corresponding to the molecular ion at m/z 313.m/z 313.

In a similar manner, compound **1** reacted with the hydrazonoyl chlorides **26b–d**, in the presence of sodium ethoxide, to afford the corresponding pyrazole derivatives **28b–d**. The IR spectra of the isolated products revealed, in each case, a strong absorption band in the region 2220–2235 cm^{-1} corresponding to a nitrile function and an absorption band near 1690 cm^{-1} corresponding to a carbonyl group. Their mass spectra showed, in each case, a peak corresponding to the molecular ion.

Treatment of compound **1** with phenyl isothiocyanate, in DMF, in the presence of potassium hydroxide, at room temperature afforded the corresponding non-isolable potassium salt **29** which reacted *in situ* with hydrazonoyl chloride **26a** to afford 2-(cinnamoyl)cyanomethylene-3-phenyl-5-acetyl-2,3-dihydro-1,3,4-thiadiazole (**31a**) *via* the non-isolable acyclic intermediate **30**.

Similarly, when the intermediate potassium salt **29** was treated with equimolar amounts of the appropriate hydrazonoyl chlorides **26b–d,** it afforded the corresponding 1,3,4-thiadiazole derivatives **31b–d** (Scheme 4). The elemental analyses and spectral data of the reaction products are in complete agreement with their assigned structures [*cf*. Experimental part].

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