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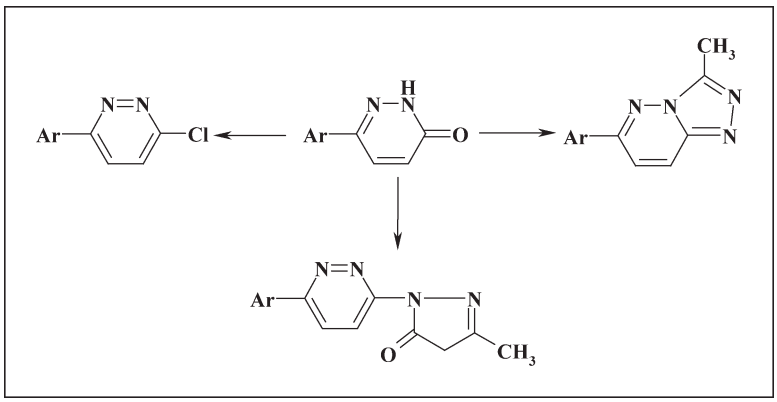

Synthesis of new heterocyclic compounds containing the pyridazinone moiety, which have a valuable biological activities, has been achieved through the nucleophilic addition of benzylamine to 4-(*p*-substituted phenyl)-4-oxo-2-butenoic acid **1a,b**, followed by cyclocondensation of the adducts **2a,b** to the corresponding pyridazin-3-one derivatives **3a,b**. The behavior of the latter compounds toward different nucleophilic and electrophilic reagents was investigated. The structures of the newly synthesized compounds were elucidated by elemental analysis and spectroscopic data.

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INTRODUCTION

A large number of pyridazinone derivatives were reported to exhibit insecticidal [1–5], herbicidal [2,6], antiallergenic [7], antihypertensive [8], analgesic [9], anti-inflammatory [10], and bacteriocidal activities [11]. This prompted us to synthesize a new series of heterocyclic pyridazinone derivatives through the reaction of 4-(*p*-bromophenyl) or 4-(*p*-methylphenyl)-4-oxo-2-butenoic acid **1a,b** [12] with benzylamine in dry benzene and yielded the addition products **2a,b**. The latters were reacted with hydrazine hydrate in ethanol to give the unexpected pyridazin-3-one derivatives **3a,b,** respectively, rather than the expected 4,5-dihydropyridazin-3(2*H*)-one derivatives **4a,b**. The products **3** were used for synthesis of some important heterocyclic compounds through their conversion to the corresponding 3-chloropyridazine derivatives **7a,b**, which act as a key factor in synthesis of different heterocyclic pyridazine derivatives.

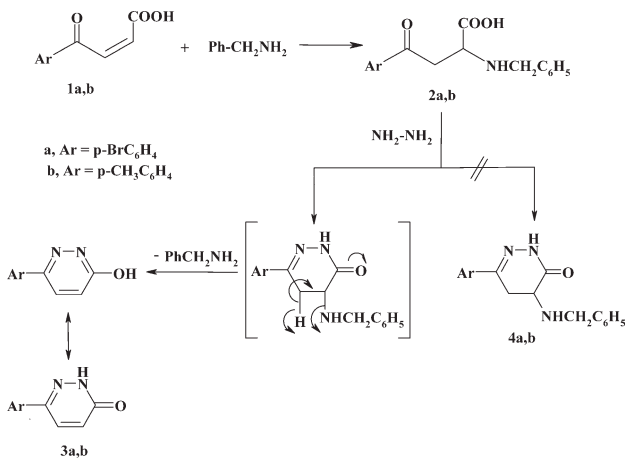
RESULTS AND DISCUSSION

The reaction of 4-(*p*-bromo- and *p*-methylphenyl)-4-oxo-2-butenoic acid **1a,b** and benzylamine in dry benzene gave 4-(*p*-bromo- and tolyl)-4-oxo-2-(benzylamino)butanoic acid **2a,b**. Condensation of the acid derivatives **2a,b** with hydrazine hydrate in boiling ethanol afforded the unexpected 6-(*p*-substituted phenyl)pyridazin-3(2*H*)-one **3a,b** with the fission of the benzylamino group in position 4 and aromatization of the pyridazine ring [13,14] (Scheme 1).

Thus, structure of compound **2b** is supported by its correct elemental analysis, and its mass spectrum which revealed the molecular ion peak at $m/z = 297$ (M^+ 2.5%) for the molecular formula $C_{18}H_{19}NO_3$. Also, the structure of compounds **3** were elucidated by their elemental analysis and spectroscopic data. Thus, the ^1H NMR (DMSO) of compound **3a** showed signals at $\delta =$ 7.25–8.14 ppm (6H, m, Ar—H and —CH=CH— of pyridazine ring) and 8.98 (broad s, 1H, NH). Its mass spectrum showed molecular ion peak at $m/z = 252$ ($M^+ +1$, 24.2%) corresponding to the molecular formula $C_{10}H_7N_2OBr$.

In contrast, condensation of **2a,b** with hydroxylamine hydrochloride in boiling pyridine yielded the corresponding 3-(*p*-substituted phenyl)-4,5-dihydro-5-(benzylamino)-1,2-oxazin-6-ones **5a,b** with no fission of the benzylamino group. In support for the products **5a,b**, the acid **2b** was easily dehydrated in boiling acetic

Scheme 1

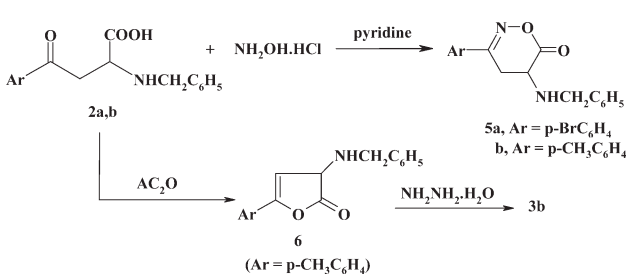


anhydride or heated at its melting point to yield 3-(benzylamino)-5-(4-methylphenyl)furan-2(3*H*)-one **6** (Scheme 2).

The structure of the oxazin-6-one derivative **5a** was confirmed by its correct elemental analysis and spectroscopic data. The IR of **5a** showed bands at 1683 cm^{-1} (C=O), 1588 cm^{-1} (C=N), and at 3287 cm^{-1} (NH). Its mass spectrum showed a molecular ion peaks at m/z = 359 (M^+, 7.7%) coincident with the molecular formula $C_{17}H_{15}N_2O_2Br$. The structure of the furanone derivative **6** was established by its correct elemental analysis, and its IR spectrum which showed a strong absorption at 1771 cm^{-1} characteristic for the C=O of the five membered lactone ring and a band at 3195 cm^{-1}due to NH. The mass spectrum revealed the molecular ion peak at m/z = 279 (M^+, 34.30%) for the molecular formula $C_{18}H_{17}NO_2$ and the base peak at m/z = 106 (100%). Also, the structure of **6** was further established by its hydrolysis with hot alkali to the corresponding acid **2b**. In addition, the reaction of compound **6** with hydrazine hydrate in boiling ethanol gave the pyridazinone **3b,** which was identified by m.p. and mixed m.p. determination.

The keto-enol tautomerism in the pyridazinone ring is elucidated by the formation of its chloroderivative by the reaction of pyridazinones **3a,b** with nucleophilic

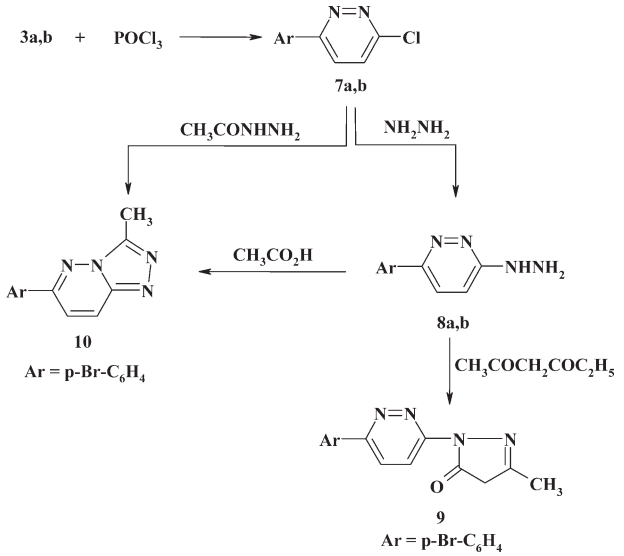
Scheme 2



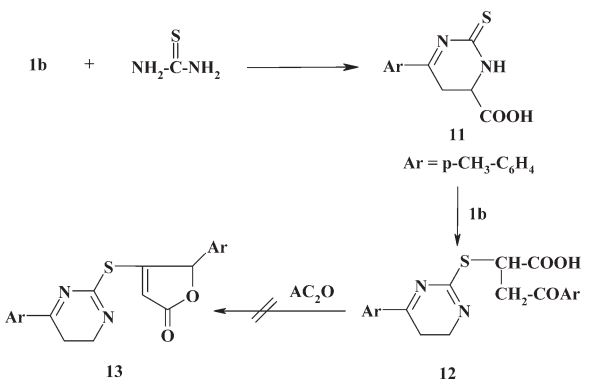
reagents like phosphorus oxychloride to give 3-chloropyridazines **7a,b** [15] which act as a key intermediate for the formation of different fused heterocyclic compounds which may have biological activities [16]. Thus, derivatives **7a,b** were submitted to react with hydrazine hydrate in boiling butanol to afford the corresponding hydrazine derivatives **8a,b** in good yield. On treatment of compound **8a** with ethylacetoacetate in boiling ethanol, 2-[6-(4-bromophenyl)pyridazin-3-yl]-5-methyl-2,4-dihydro-3H-pyrazol-3-one **9** was afforded. On the other hand, when compound **8a** was refluxed with acetic acid, the corresponding 6-(4-bromophenyl)-3-methyl[1,2,4]-triazolo[4,3-*b*]pyridazine **10** [17] was produced. The latter compound could be also obtained via the condensation of the chloropyridazine derivative **7a** with acetylhydrazine in boiling butanol (Scheme 3).

The structure of the compound **9** was confirmed by its elemental analysis and spectroscopic data. Thus, the IR of the compound showed absorption bands at 1643 cm^{-1} (C=O) and at 1582 cm^{-1} (C=N). The ^{1}H NMR (DMSO) exhibited signals at δ = 2.04 ppm (s, 3H, CH_3); 2.23 (s, 2H, CH_2), 7.41–8.42 (m, 6H, Ar'H). The mass spectrum revealed the molecular ion peak at m/z = 332 (M^+ +1, 100%) corresponding to the molecular formula $C_{14}H_{11}N_4OBr$. The structure of compound **10** was also elucidated by elemental analysis and spectroscopic data (IR, ^{1}H NMR, and Ms). Thus, the ^{1}H NMR of **10** showed signals at δ = 1.98 ppm (s, 3H, CH_3) and at 7.00–8.23 (m, 6H, C_6H_4, HC=CH). On the other hand, butenoic acid derivative **1b** was found to react with thiourea in boiling ethanol to give 6-(4-methylphenyl)-2-thioxo-2,3,4,5-tetrahydro-pyrimidine-4-carboxylic acid **11**. As a point of interest, the addition of the carboxylic acid **11** to another molecule of **1b** in dry benzene

Scheme 3



Scheme 4



containing a catalytic amount of pipredine has been achieved to afford the corresponding oxobutanoic acid derivative **12** but with cleavage of the carboxylic group of the pyridazine ring. An attempt to cyclize compound **12** through the dehydration with boiling acetic anhydride to afford the corresponding furanone derivative **13** has been failed (Scheme 4).

The structures of the compounds **11** and **12** were confirmed by their elemental analysis and spectroscopic data. Thus, the IR of the compound **11** showed bands at 3242 cm^{-1} (NH), 1678 (C=O), and at 1491 (C=S). Its mass spectrum revealed the molecular ion peak at m/z = 248 (M^+, 29.5%) related to the molecular formula $C_{12}H_{12}N_2O_2S$. The structure of **12** was also proved by its correct elemental analysis and spectroscopic data. The IR of the compound showed the absence of the band related to the NH group and exhibited bands at 1682 cm^{-1} (C=O), and 1642 (C=O), and at 1355 (C—S—C). The mass spectrum of the compound revealed the molecular ion peak at m/z = 394 (M^+, 4.0%) corresponding to the molecular formula $C_{22}H_{22}N_2O_3S$.

EXPERIMENTAL

The Infrared spectra were recorded on a BRUKER IFS-25 FT-IR spectrophotometer using KBr at the region 400–4000 cm^{-1}, ^1H and ^{13}C on a BRUKER AVANCE/200 ULTRA-SHLIELD™ transform instrument using TMS as internal standard, Mass spectra were obtained with an Shimad 24 GCMS-QP 1000EX., Elemental analyses were determined on FISONS instruments DP200 series 2 and Euro EA3000 series Euro Vector. Elemental analyses for (CHNS) of all compounds are in accordance with the theoretical values within (0.4%) error. All melting points were uncorrected. Compounds **1a,b** were synthesized according to the literature procedure [18,19]. Compounds **3a,b**, **7a,b,** and **8a,b** could be obtained through other procedures [20,21].

Synthesis of 2-(benzylamino)-4-(4-bromo- (methyl)-phenyl)-4-oxobutanoic acid 2a,b. A mixture of compounds **1a,b** (0.01 mol) was refluxed with an equimolar amount of benzylamine for 3 h in 50 mL dry benzene. The reaction mixture was cooled and left at room temperature over night to precipitate the products as pale yellow needles. The solid products were collected and recrystallized from ethanol.

2a. Pale yellow (76%), m.p. 177°C, ν_{max}/cm^{-1} (KBr) 3292 (NH), 1677 and 1651 (C=O); m/z 362 (Calcd. for $C_{17}H_{16}NO_3Br$: C, 56.35; H, 4.42; N, 3.87% Found: C, 56.02; H, 4.41; N, 3.62%).

2b. Pale yellow (67%), m.p. 187°C, ν_{max}/cm^{-1} (KBr) 3289 (NH), 1671 and 1655 (C=O); ^1H NMR (DMSO) δ = 1.98 ppm (s, 3H, CH_3), 2.26 (s, 2H, C—CH_2), 2.45 (s, 2H, N—CH_2) 3.42 (s, 1H, CH), 7.22–8.14 (m, 9H, ArH), 9.10 (s, 1H, NH), and 12.21 (s, 1H, COOH); m/z 297 (Calcd. for $C_{18}H_{19}NO_3$: C, 72.72; H, 6.39; N, 4.71% Found: C, 72.50; H, 6.41; N, 4.62%).

Synthesis of 6-(4-bromo-(methyl)phenyl)pyridazin-3(2*H*)-one 3a,b. Equivalent amounts of **2a,b** (0.01 mol) and hydrazine hydrate were refluxed in 50 mL ethanol for 10 h. The reaction mixture was concentrated and left to precipitate the products, which were filtered off to give yellow crystals of **3a,b**.

3a. Yellow (87%), m.p. 195°C, ν_{max}/cm^{-1} (KBr) 3311 (NH) and 1648 (C=O); ^1H NMR (DMSO) δ = 7.25–8.14 ppm (6H, m, Ar—H and —CH=CH— of pyridazine ring) and 8.98 (broad s, 1H, NH); m/z 252 (Calcd. for $C_{10}H_7N_2OBr$: C, 47.80; H, 2.78; N, 11.15% Found: C, 47.55; H, 2.41; N, 11.00%).

3b. Yellow (88%), m.p. 227°C, ν_{max}/cm^{-1} (KBr) 3294 (NH), 1648 (C=O); m/z 186 (Calcd. for $C_{11}H_{10}N_2O$: C, 70.96; H, 5.37; N, 15.05% Found: C, 70.48; H, 5.66; N, 15.22%).

Synthesis of 5-(benzylamino)-3-(4-bromo-(methyl)-phenyl)-4,5-dihydro-6*H*-1,2-oxazin-6-one 5a,b. A mixture of **2a,b** (0.01 mol) and hydroxylamine hydrochloride (0.01 mol) in 20 mL pyridine was refluxed for 6 h. The reaction mixture was cooled and poured onto ice/HCl mixture. The obtained solid was collected by filtration and recrystallized from suitable solvent.

5a. Pale brown (68%), m.p. 140°C, from benzene, ν_{max}/cm^{-1} (KBr) 3287 (NH), 1683 (C=O), 1588 (C=N); m/z 359 (Calcd. for $C_{17}H_{15}N_2O_2Br$: C, 56.82; H, 4.18; N, 7.79% Found: C, 56.99; H, 4.42; N, 8.02.00%).

5b. White (64%), m.p. 250°C, from EtOH, ν_{max}/cm^{-1} (KBr) 3289 (NH), 1684 (C=O), 1588 (C=N); ^1H NMR (DMSO) δ = 1.99 ppm (s, 3H, CH_3), 2.32 (s, 2H, C—CH_2), 2.58 (s, 2H, N—CH_2), 3.11 (s, 1H, CH), 7.00–8.24 (m, 9H, ArH), 9.14 (s, 1H, NH); m/z 294 (Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.46; H, 6.12; N, 9.52% Found: C, 73.26; H, 6.41; N, 9.50%).

Synthesis of 3-(benzylamino)-5-(4-methylphenyl)furan-2(3*H*)-one 6. Compound 2b (0.01 mol) was refluxed in 50 mL acetic anhydride for 8 h. The solution was concentrated over water bath and kept to separate the solid product which was collected and recrystallized from acetic acid.

6. White (64%), m.p. 155°C, ν_{max}/cm^{-1} (KBr) 3195 (NH), 1771 (C=O), ^1H NMR (DMSO) δ = 1.84 ppm (s, 3H, CH_3), 2.11 (s, 2H, CH_2), 2.89–3.15 (s, 2H, 2CH), 6.98–8.01 (m, 9H, ArH), 8.99 (s, 1H, NH); m/z 279 (Calcd. for $C_{18}H_{17}NO_2$: C, 77.42; H, 6.09; N, 5.01% Found: C, 77.11; H, 6.21; N, 4.89%).

Synthesis of 3-(4-bromo- (methyl)phenyl)-6-chloropyridazine 7a,b. A mixture of the pyridazinones **3a,b** (0.01 mol) and $POCl_3$ (10 mL) was heated in water bath for 4 h. After cooling, the reaction mixture was poured onto a mixture of ice/

water. The precipitate was collected by filtration, and the solid product was recrystallized from methanol.

7a. Brown (77%), m.p. 199°C, ν_{max}/cm^{-1} (KBr) 1612 (C=N), (Calcd. for $C_{10}H_6N_2ClBr$: C, 44.56; H, 2.24; N, 10.39% Found: C, 44.24; H, 2.22; N, 10.41.00%).

7b. Gray (65%), m.p. 165C, ν_{max}/cm^{-1} (KBr) 1612 (C=N), *m/z* 204 (Calcd. for $C_{11}H_9N_2Cl$: C, 64.56; H, 4.43; N, 13.69% Found: C, 64.68; H, 4.18; N, 13.22%).

Synthesis of 3-(4-bromo- (methyl)phenyl)-6-hydrazinopyridazine 8a,b. A mixture of compounds **7a,b** (0.01 mol) and hydrazine hydrate (0.015 mol) was refluxed for 6 h in *n*-butanol (50 mL), and the solid obtained was collected and recrystallized from suitable solvent.

8a. Pale brown (75%), m.p. 184°C, from MeOH, ν_{max}/cm^{-1} (KBr) 3319–3199 (NH, NH_2), *m/z* 265 (Calcd. for $C_{10}H_9N_4Br$: C, 45.30; H, 3.42; N, 21.13% Found: C, 45.00; H, 3.69; N, 20.98%).

8b. Yellow (71%), m.p. 155°C, from EtOH, ν_{max}/cm^{-1} (KBr) 3314–3195 (NH, NH_2), *m/z* 200 (Calcd. for $C_{11}H_{12}N_4$: C, 65.98; H, 6.04; N, 27.98% Found: C, 66.02; H, 6.11; N, 27.68%).

Synthesis of 2-[6-(4-bromophenyl)pyridazin-3-yl]-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one 9. A mixture of equivalent amounts of compound **8a** (0.01 mol) and ethylacetoacetate in 50 mL ethanol was refluxed for 6 h. The reaction mixture was concentrated to separate the solid product, filtered off, and recrystallized from ethanol.

9. White (62%), m.p. 235°C, ν_{max}/cm^{-1} (KBr), 1643 (C=O), 1582 (C=N); ^{1}H NMR (DMSO) δ = 2.04 (s, 3H, CH_3), 2.23 (s, 2H, CH_2), 7.41–8.22 (m, 6H, ArH); *m/z* 331 (Calcd. for $C_{14}H_{11}N_4OBr$: C, 50.77; H, 3.35; N, 16.92% Found: C, 50.25; H, 3.45; N, 16.65%).

Synthesis of 6-(4-bromophenyl)-3-methyl[1,2,4]triazolo[4,3-b]pyridazine 10. ***Method A.*** A mixture of **8a** (0.01 mol) and acetic acid (30 mL) was refluxed for 8 h. The reaction mixture was left to cool, and the precipitated solid product was collected by filtration and recrystallized from ethanol.

Method B. A mixture of **8a** (0.01 mol) and acetohydrazide (0.01 mol) was refluxed for 5 h in absolute ethanol (20 mL). The reaction mixture was diluted by water, collected by filtration, and recrystallized from ethanol.

10. Brown (56%), m.p. 212°C, ^{1}H NMR (DMSO) δ = 1.98 ppm (s, 3H, CH_3), 7.00–8.23 (m, 6H, C_6H_4, HC=CH); *m/z* 289 (Calcd. for $C_{12}H_9N_4Br$: C, 49.85; H, 3.14; N, 19.38%. Found: C, 49.95; H, 3.33; N, 19.01%).

Synthesis of 6-(4-methylphenyl)-2-thioxo-2,3,4,5-tetrahydropyrimidine-4-carboxylic acid 11. Compound **1b** (0.01 mol) was refluxed with thiourea (0.01 mol) in 30 mL acetic acid for 3 h. The reaction mixture was cooled, left at room temperature over night, and filtered off to give pale yellow needles of the product that was recrystallized from ethanol.

11. Yellow (64%), m.p. 250°C, ν_{max}/cm^{-1} (KBr) 3242 (NH), 1678 (C=O), 1491 (C=S); ^{1}H NMR (DMSO) δ = 2.12 ppm (s, 3H, CH_3), 2.23 (s, 2H, CH_2), 3.34 (s, 1H, CH), 6.88–7.81 (m, 4H, ArH), 8.78 (s, 1H, NH), 12.41 (s, 1H, COOH); *m/z* 248 (Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28; S, 12.91%. Found: C, 58.24; H, 5.01; N, 11.28; S, 12.84%).

Synthesis of 4-(4-methylphenyl)-2-{[6-(4-methylphenyl)-4,5-dihydropyrimidin-2-yl]thio}-4-oxobutanoic acid 12. A mixture of **1b** (0.01 mol) and compound **11** (0.01 mol) was refluxed in dry benzene (30 mL) containing few drops of pipredine for 6 h. The solution was evaporated and the product was collected and recrystallized from ethanol.

12. Pale yellow (58%), m.p. 183°C, ν_{max}/cm^{-1} (KBr) 1682, 1642 (2C=O), 1355 (C—S—C); ^{1}H NMR (DMSO) δ = 2.11 ppm (s, 6H, $2CH_3$), 2.12–2.35 (broad s, 6H, $3CH_2$), 3.11 (d, 1H, CH), 6.94–8.23 (m, 8H, ArH), 12.44 (s, 1H, COOH); *m/z* 394 (Calcd. for $C_{22}H_{22}N_2O_3S$: C, 66.98; H, 5.62; N, 7.10; S, 8.13%. Found: C, 67.11; H, 5.33; N, 6.99; S, 8.00%).

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