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Article

An environmentally-friendly base organocatalyzed one-pot strategy for the regioselective synthesis of novel 3,6-diaryl-4-methylpyridazines

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ABSTRACT

This report describes a new three-component strategy for the regioselective synthesis of a series of tri-substituted pyridazines via a 1,4-diazabicyclo[2.2.2]octane (DABCO)-catalyzed condensation of propiophenones, arylglyoxalmonohydrates and hydrazine hydrate in water. This method provides a green and convenient one-pot route toward a diverse set of 3,6-diaryl-4-methylpyridazines bearing various aryl substituents. This procedure is highly regioselective, operationally simple, uses water as a safe, environmentally friendly solvent, and DABCO as a green base-organocatalyst, and affords good to excellent yields of products.

1. Introduction

Nitrogen-containing heterocycle pyridazine is a key intermediate in the synthesis of several fused heterocycles used in drug discovery [1]. Recently, pyridazines have been considered by GlaxoSmithKline to be one of the "most developable" heteroaromatic rings for drug design [2]. Pyridazine analogues have proven to be useful ligands for different targets, and have been proposed as "privileged structures" for drug discovery [3]. Several compounds with pyridazine rings demonstrate biological activity (Fig. 1, **1**–**4**), and there are many examples of naturally occurring pyridazines [4–7]. Pyridazines have also been recognized as selective GABA-A receptor antagonists, such as minaprine **1** [8]. Volonterio et al. [9] developed a synthesis of pyridazine-based scaffolds such as **2** to target protein/protein interaction as α-helix mimetics, and 3-amino-6-aryl-pyridazines are also considered to be an interesting pharmacophore in drug discovery. Some pyridazines show biological activity in a range of disease areas including obesity [10], neurodegenerative diseases [11], and inflammatory pain, e.g. the selective CB2 agonist **3** [12]. Several pyridazine-containing compounds have also been identified as kinase inhibitors, and compound **4** has been identified as a potent p38 MAPK inhibitor [13].

Multicomponent reactions (MCRs) are capable of achieving high levels of diversity in a concise transformation, as they involve more than two building blocks to be combined in practical, time-saving, one-pot operations. These reactions are perfectly suited to automated synthesis, and have attracted considerable interest owing to their exceptional synthetic efficiency, inherent simple experimental procedures, and their one-pot nature [14–17]. Typically, the purification of products resulting from MCRs is also facile, as all the organic reagents involved are consumed and incorporated into the target compound [18,19]. MCRs leading to interesting heterocyclic scaffolds are particularly useful for the construction of diverse chemical libraries of drug-like molecules.

The Paal–Knorr synthesis is one of the most common ap-

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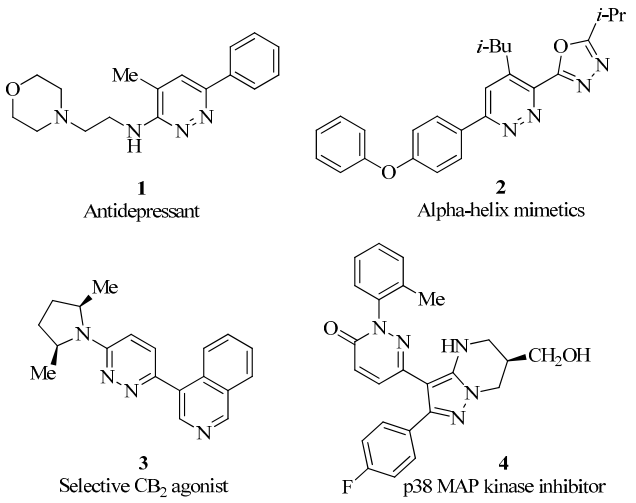


Fig. 1. Selected biologically active substituted pyridazines.

proaches for the construction various five- or six-membered heterocycles. In the Paal–Knorr synthesis of pyridazines, 1,4-dicarbonyl compounds are converted to pyridazines via a dehydrative cyclization in the presence of hydrazine, and subsequent oxidation [20–25].

As part of our ongoing program to develop efficient and robust MC methods for the preparation of heterocyclic compounds [25–30], we sought to develop a convenient preparation of 3,6-diaryl substituted 4-methylpyridazines **5–38** via a regioselective one-pot condensation reaction of substituted propiophenones **39a–d** with arylglyoxalmonohydrates **40a–j** and hydrazine in the presence of catalytic amounts of 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,5-diazabicyclo[4.3.0]non-7-ene (DBN) as shown in Scheme 1. To the best of our knowledge, there are no reports in the literature for the formation of pyridazine derivatives *via* base-organocatalyzed condensation of propiophenones with arylglyoxalmonohydrates in the presence of hydrazine hydrate.

2. Experimental

2.1. General procedures for the regioselective DABCO-catalyzed one-pot synthesis of 3,6-diaryl-4-methylpyridazine derivatives

To a mixture of arylglyoxalmonohydrate (1 mmol), propiophenone (1 mmol) and DABCO (50 mol%) in water (10 mL) were added hydrazine hydrate (4 mmol). The suspension was stirred at 25 °C until precipitation ceased (2–4 h). After completion of the reaction, the mixture was filtered and purified by recrystallization from ethanol.

2.2. Analytical data for the products

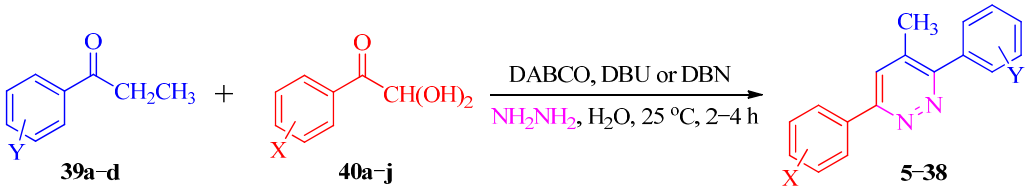
3-(3-Bromophenyl)-6-phenyl-4-methylpyridazine (**5**): white crystals; 86%; mp 115 °C. IR (KBr): ν_{max} = 3063, 2971, 2929, 1577, 1392, 1261, 1042, 886 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.39 (t, 1H, J = 7.8), 7.47–7.67 (m, 5H), 7.74 (s, 1H), 7.84 (s, 1H), 8.14 (d, 2H, J = 6.3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 122.5, 124.4, 124.7, 126.4, 127.8, 128.8, 129.8, 131.0, 132.8, 133.3, 136.1, 139.0, 157.8, 159.1. Anal. found, C, 62.83; H, 4.06; N, 8.68. $C_{17}H_{13}BrN_2$ requires C, 62.79; H, 4.03; N, 8.61.

3-(3-Bromophenyl)-6-(4-bromophenyl)-4-methylpyridazine (**6**): yellow crystals; 72%; mp 157 °C. IR (KBr): ν_{max} = 3083, 3053, 2969, 1589, 1421, 1074, 1004, 850 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.39 (t, 1H, J = 8.1), 7.53–7.7 (m, 4H), 7.72 (s, 1H), 7.82 (s, 1H), 8.02 (d, 2H, J = 8.1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 122.5, 124.3, 124.7, 126.1, 127.5, 128.8, 129.5, 131.3, 133.1, 134.9, 136.3, 138.8, 157.7, 159.4. Anal. found, C, 50.57; H, 2.97; N, 7.00. $C_{17}H_{12}Br_2N_2$ requires C, 50.53; H, 2.99; N, 6.93.

3-(3-Bromophenyl)-6-(4-chlorophenyl)-4-methylpyridazine (**7**): yellow crystals; 88%; mp 176 °C. IR (KBr): ν_{max} = 3091, 3057, 3032, 1586, 1414, 1386, 1089, 893 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.39 (t, 1H, J = 7.8), 7.47–7.67 (m, 4H), 7.72 (s, 1H), 7.82 (s, 1H), 8.08 (d, 2H, J = 7.8). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 122.6, 124.4, 126.1, 127.3, 128.4, 128.8, 129.2, 130.0, 131.1, 133.3, 136.2, 138.9, 156.7, 159.4. Anal. found, C, 56.79; H, 3.32; N, 7.85. $C_{17}H_{12}BrClN_2$ requires C, 56.77; H, 3.36; N, 7.79.

3-(3-Bromophenyl)-6-(4-fluorophenyl)-4-methylpyridazine (**8**): white crystals; 82%; mp 141 °C. IR (KBr): ν_{max} = 3122, 3080, 3042, 2925, 1590, 1416, 1223, 1099, 843 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.17–7.3 (m, 2H), 7.40 (t, 1H, J = 7.8), 7.53–7.67 (m, 2H), 7.72 (s, 1H), 7.83 (s, 1H), 8.08–8.19 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 114.9, 115.2, 116.9, 117.2, 124.3, 126.1, 128.1, 128.8, 129.9, 131.2, 132.9, 136.2, 138.9, 156.8, 162.5. Anal. found, C, 54.54; H, 3.55; N, 8.20. $C_{17}H_{12}BrFN_2$ requires C, 59.49; H, 3.52; N, 8.16.

3-(3-Bromophenyl)-6-(4-methoxyphenyl)-4-methylpyridazine (**9**): white crystals; 78%; mp 119 °C. IR (KBr): ν_{max} = 3057, 3015, 2960, 2939, 2842, 1589, 1428, 1249, 1034, 842 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3H), 3.93 (s, 3H), 7.06 (d, 1H, J = 8.1), 7.34–7.5 (m, 2H), 7.53–7.69 (m, 3H), 7.54 (s, 1H),



X = 4-H, 4-Br, 4-Cl, 4-F, 4-OCH_3, 3-Br, 3-OCH_3, 3,4-$(OCH_3)_2$, 3,4-(OCH_2O), 4-OH-3-OCH_3
Y = 4-Br, 3-Br, 4-Cl, 4-CH_3

Scheme 1. Regioselective base-organocatalyzed one-pot synthesis of 3,6-diaryl-4-methylpyridazines.

7.79–7.89 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 56.2, 110.9, 113.0, 115.3, 118.4, 120.2, 124.8, 128.8, 131.0, 132.9, 136.1, 137.4, 139.0, 159.3. Anal. found, C, 60.87; H, 4.23; N, 7.99. $C_{18}H_{15}BrN_2O$ requires C, 60.86; H, 4.26; N, 7.89.

3,6-Bis(3-bromophenyl)-4-methylpyridazine (**10**): yellow crystals; 71%; mp 109 °C. IR (KBr): ν_{max} = 2960, 2931, 2859, 1584, 1566, 1379, 1426, 1065, 883 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48 (s, 3H), 7.36–7.48 (m, 2H), 7.53–7.7 (m, 3H), 7.74 (s, 1H), 7.84 (s, 1H), 8.09 (d, 1H, J = 7.8), 8.30 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 123.7, 126.5, 129.4, 129.7, 130.2, 130.9, 131.4, 132.0, 133.0, 133.7, 136.5, 137.9, 156.2, 159.9. Anal. found, C, 50.54; H, 2.31; N, 7.06. $C_{17}H_{12}Br_2N_2$ requires C, 50.53; H, 2.99; N, 6.93.

3-(3-Bromophenyl)-6-(3-methoxyphenyl)-4-methylpyridazine (**11**): white crystals; 70%; mp 104 °C. IR (KBr): ν_{max} = 3067, 3008, 2971, 2920, 2849, 1589, 1467, 1377, 1038, 855, 773 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.89 (s, 3H), 7.06 (d, 2H, J = 8.7), 7.38 (t, 1H, J = 8.1), 7.54–7.65 (m, 2H), 7.69 (s, 1H), 7.83 (s, 1H), 8.11 (d, 2H, J = 8.7). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 56.1, 113.3, 113.3, 115.4, 115.5, 123.8, 125.6, 127.5, 128.8, 130.8, 135.9, 139.2, 157.3, 158.6, 161.3. Anal. found, C, 60.83; H, 4.25; Br, N, 7.99. $C_{18}H_{15}BrN_2O$ requires C, 60.86; H, 4.26; N, 7.89.

3-(3-Bromophenyl)-6-(3,4-dimethoxyphenyl)-4-methylpyridazine (**12**): yellow crystals; 84%; mp 174 °C. IR (KBr): ν_{max} = 3066, 2998, 2939, 2842, 1587, 1422, 1021, 873, 768 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.96 (s, 3H), 4.01 (s, 3H), 6.98 (d, 1H, J = 7.5), 7.38 (t, 1H, J = 7.8), 7.70 (s, 1H), 7.83 (s, 1H), 7.94 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 55.1, 56.8, 109.0, 110.0, 110.3, 110.9, 111.9, 112.2, 120.4, 123.9, 128.8, 135.9, 139.1, 149.6, 150.8, 157.1, 158.7. Anal. found, C, 59.23; H, 4.45; N, 7.27. $C_{19}H_{17}BrN_2O_2$ requires C, 59.27; H, 4.46; N, 7.39.

3-(3-Bromophenyl)-6-(3,4-methylenedioxyphenyl)-4-methylpyridazine (**13**): yellow crystals, 80%; mp 153 °C. IR (KBr): ν_{max} = 3071, 2996, 2912, 2786, 1586, 1491, 1256, 1038, 874 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H), 6.06 (s, 2H), 6.96 (d, J = 8.1, 1H), 7.38 (t, J = 8.1, 1H), 7.68–7.53 (m, 4H), 7.72 (s, 1H), 7.82 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 101.5, 102.9, 106.4, 107.5, 107.8, 108.2, 109.5, 122.2, 124.1, 125.9, 128.8, 136.0, 139.1, 148.6, 149.3, 157.2, 158.8. Anal. found, C, 58.59; H, 3.49; N, 7.77. $C_{18}H_{13}BrN_2O_2$ requires C, 58.56; H, 3.55; N, 7.59.

3-(3-Bromophenyl)-6-(4-hydroxy-3-methoxyphenyl)-4-methylpyridazine (**14**): white crystals; 74%; mp 179 °C. IR (KBr): ν_{max} = 3328, 3083, 3057, 2969, 1589, 1421, 1398, 1389, 1074, 1005, 829, 697 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 4.03 (s, 3H), 5.93 (s, 1H), 7.39 (d, J = 8.4, 1H), 7.49 (t, J = 8.4, 1H), 7.63–7.58 (m, 2H), 7.71 (s, 1H), 7.85 (s, 1H), 8.00 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 57.0, 108.5, 110.5, 113.5, 119.0, 121.2, 123.8, 128.2, 130.9, 132.8, 135.8, 139.1, 146.3, 147.8, 158.9, 159.3. Anal. found, C, 58.23; H, 4.05; N, 7.76. $C_{18}H_{15}BrN_2O_2$ requires C, 58.24; H, 4.07; Br, N, 7.55.

3-(4-Bromophenyl)-6-phenyl-4-methylpyridazine (**15**): white crystals; 78%; mp 163 °C. IR (KBr): ν_{max} = 3055, 2930, 1587, 1445, 1389, 1075, 1004, 830 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 3H), 7.46–7.58 (m, 5H), 7.65 (d, 2H, J = 8.1), 7.74 (s, 1H), 8.13 (d, 2H, J = 6.3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 126.2, 126.5, 127.4, 127.9, 129.6, 130.8, 131.6, 132.3, 135.7, 136.2, 157.6, 159.5. Anal. found, C, 62.81; H, 4.05; N, 8.72. $C_{17}H_{13}BrN_2$ requires C, 62.79; H, 4.03; N, 8.61.

3,6-Bis(4-bromophenyl)-4-methylpyridazine (**16**): yellow crystals; 72%; mp 174 °C. IR (KBr): ν_{max} = 3085, 1590, 1483, 1401, 1072, 1002, 822 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3H), 7.55 (d, J = 8.4, 2H), 7.61–7.73 (m, 4H), 7.74 (s, 1H), 8.02 (d, 2H, J = 8.4). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 124.9, 127.7, 129.5, 129.7, 130.2, 130.9, 131.6, 132.0, 132.4, 133.0, 156.6, 159.6. Anal. found, C, 50.55; H, 2.96; N, 7.04. $C_{17}H_{12}Br_2N_2$ requires C, 50.53; H, 2.99; N, 6.93.

3-(4-Bromophenyl)-6-(4-chlorophenyl)-4-methylpyridazine (**17**): white crystals; 88%; mp 176 °C. IR (KBr): ν_{max} = 3095, 3030, 1593, 1483, 1400, 1073, 1006, 824 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.46–7.58 (m, 4H), 7.66 (d, 2H, J = 8.4), 7.71 (s, 1H), 8.08 (d, 2H, J = 8.4). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 124.6, 126.1, 128.1, 129.1, 129.8, 130.8, 131.6, 132.4, 135.6, 136.2, 156.5, 159.6. Anal. found, C, 56.80; H, 3.38; N, 7.89. $C_{17}H_{12}BrClN_2$ requires C, 56.77; H, 3.36; N, 7.79.

3-(4-Bromophenyl)-6-(4-fluorophenyl)-4-methylpyridazine (**18**): white crystals; 92%; mp 188 °C. IR (KBr): ν_{max} = 3080, 2975, 1593, 1505, 1379, 1228, 1071, 1001, 831 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.16–7.27 (m, 2H), 7.53 (d, 2H, J = 8.4), 7.64 (d, 2H, J = 8.1), 7.71 (s, 1H), 8.08–8.18 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 114.9, 115.2, 116.8, 117.1, 128.2, 129.9, 130.8, 132.4, 156.6, 159.4, 162.4, 165.7. Anal. found, C, 54.51; H, 3.53; N, 8.28. $C_{17}H_{12}BrFN_2$ requires C, 59.49; H, 3.52; N, 8.16.

3-(4-Bromophenyl)-6-(4-methoxyphenyl)-4-methylpyridazine (**19**): white crystals; 90%; mp 133 °C. IR (KBr): ν_{max} = 3000, 2970, 2930, 2835, 1589, 1492, 1399, 1256, 1034, 1000, 835 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.88 (s, 3H), 7.04 (d, 2H, J = 8.1), 7.53 (d, 2H, J = 7.8), 7.62 (d, 2H, J = 7.8), 7.67 (s, 1H), 8.09 (d, 2H, J = 8.1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 56.0, 113.3, 113.8, 114.7, 115.5, 127.6, 129.3, 130.7, 132.0, 132.3, 157.0, 158.9, 161.3. Anal. found, C, 60.89; H, 4.22; N, 8.03. $C_{18}H_{15}BrN_2O$ requires C, 60.86; H, 4.26; N, 7.89.

3-(4-Bromophenyl)-6-(3-bromophenyl)-4-methylpyridazine (**20**): white crystals; 71%; mp 132 °C. IR (KBr): ν_{max} = 3055, 3010, 1590, 1566, 1375, 1047, 1000, 886 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.40 (t, 1H, J = 8.1), 7.54 (d, 2H, J = 8.4), 7.59–7.71 (m, 3H), 7.72 (s, 1H), 8.07 (d, 1H, J = 7.8), 8.29 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 123.7, 126.5, 129.4, 129.7, 130.2, 130.9, 131.4, 132.0, 133.0, 133.7, 136.5, 137.9, 156.2, 159.9. Anal. found, C, 50.57; H, 2.30; N, 7.10. $C_{17}H_{12}Br_2N_2$ requires C, 50.53; H, 2.99; N, 6.93.

3-(4-Bromophenyl)-6-(3,4-dimethoxyphenyl)-4-methylpyridazine (**21**): yellow crystals; 91%; mp 174 °C. IR (KBr): ν_{max} = 2935, 2830, 1604, 1587, 1401, 1091, 1023, 838 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.95 (s, 3H), 4.01 (s, 3H), 7.99 (d, 1H, J = 8.4), 7.45–7.6 (m, 3H), 7.64 (d, 2H, J = 8.4), 7.71 (s, 1H), 7.94 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 56.7, 57.3, 109.0, 109.9, 110.4, 110.8, 111.8, 112.2, 130.1, 131.6, 132.0, 136.3, 149.5, 150.9, 156.9, 159.0. Anal. found, C, 59.30; H, 4.48; N, 7.42. $C_{19}H_{17}BrN_2O_2$ requires C, 59.27; H, 4.46; N, 7.39.

3-(4-Bromophenyl)-6-(3,4-methylenedioxyphenyl)-4-methylpyridazine (**22**): yellow crystals; 79%; mp 166 °C. IR (KBr): ν_{max} = 3075, 2900, 1592, 1504, 1451, 1250, 1107, 1001, 818 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 6.05 (s, 2H), 6.94 (d, 1H, J = 8.1), 7.52 (d, 2H, J = 8.1), 7.56–7.69 (m, 4H), 7.70 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 101.5, 106.5, 107.9, 108.1, 109.4, 122.1, 126.0, 129.7, 130.8, 131.6, 132.3, 136.2, 148.5, 157.0, 159.1. Anal. found, C, 58.56; H, 3.53; N, 7.69. $C_{18}H_{13}BrN_2O_2$ requires C, 58.56; H, 3.55; N, 7.59.

3-(4-Chlorophenyl)-6-phenyl-4-methylpyridazine (**23**): white crystals; 28%; mp 163 °C. IR (KBr): ν_{max} = 3087, 3070, 3041, 2927, 1597, 1587, 1490, 1451, 1092, 1006, 789 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.53–7.47 (m, 5H), 7.62 (d, 2H, J = 8.4), 7.73 (s, 1H), 8.13 (d, 2H, J = 6.3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 124.6, 126.0, 127.5, 128.8, 129.7, 129.8, 130.1, 131.6, 135.0, 136.0, 157.6, 159.4. Anal. found, C, 72.77; H, 4.69; N, 10.17. $C_{17}H_{13}ClN_2$ requires C, 72.73; H, 4.67; N, 9.98.

3-(4-Chlorophenyl)-6-(4-bromophenyl)-4-methylpyridazine (**24**): white crystals; 67%; mp 174 °C. IR (KBr): ν_{max} = 3090, 3055, 3035, 2960, 2925, 1592, 1486, 1404, 1091, 1004, 824 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.50 (d, 2H, J = 8.4), 7.57–7.69 (m, 4H), 7.72 (s, 1H), 8.02 (d, 2H, J = 8.4). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 124.6, 126.0, 127.6, 128.1, 129.8, 129.3, 131.5, 132.9, 135.2, 136.2, 156.5, 159.7. Anal. found, C, 56.81; H, 3.35; N, 7.95. $C_{17}H_{12}BrClN_2$ requires C, 56.77; H, 3.36; N, 7.79.

3,6-Bis(4-chlorophenyl)-4-methylpyridazine (**25**): white crystals; 66%; mp 181 °C. IR (KBr): ν_{max} = 3090, 3060, 3030, 1587, 1487, 1376, 1090, 1008, 827 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.47–7.56 (m, 4H), 7.62 (d, 2H, J = 8.1), 7.72 (s, 1H), 8.09 (d, 2H, J = 8.4). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 124.6, 126.0, 127.4, 127.5, 128.1, 129.1, 129.8, 130.4, 131.3, 136.2, 156.5, 159.6. Anal. found, C, 64.80; H, 3.81; N, 9.03. $C_{17}H_{12}Cl_2N_2$ requires C, 64.78; H, 3.84; N, 8.89.

3-(4-Chlorophenyl)-6-(4-fluorophenyl)-4-methylpyridazine (**26**): white crystals; 81%; mp 182 °C. IR (KBr): ν_{max} = 3090, 3080, 2970, 2925, 2855, 1596, 1487, 1389, 1089, 1003, 842 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.16–7.29 (m, 2H), 7.50 (d, 2H, J = 8.4), 7.62 (d, 2H, J = 8.4), 7.70 (s, 1H), 8.08–8.18 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 115.2, 115.8, 116.8, 117.1, 124.5, 129.7, 131.3, 136.1, 156.6, 159.4, 162.4, 165.7. Anal. found, C, 68.39; H, 4.07; N, 9.40. $C_{17}H_{12}ClFN_2$ requires C, 68.35; H, 4.05; N, 9.38.

3-(4-Chlorophenyl)-6-(4-methoxyphenyl)-4-methylpyridazine (**27**): white crystals; 78%; mp 150 °C. IR (KBr): ν_{max} = 3070, 3050, 3000, 2970, 2840, 1608, 1585, 1487, 1392, 1091, 1017, 824 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.92 (s, 3H), 7.05 (d, 2H, J = 8.4), 7.49 (d, 2H, J = 8.4), 7.62 (d, 2H, J = 8.4), 7.68 (s, 1H), 8.11 (d, 2H, J = 8.1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 56.0, 113.2, 113.8, 114.1, 115.5, 127.5, 129.2, 129.9, 131.3, 135.5, 135.9, 157.1, 158.9. Anal. found, C, 69.59; H, 4.88; N, 9.13. $C_{18}H_{15}ClN_2O$ requires C, 69.57; H, 4.86; N, 9.01.

3-(4-Chlorophenyl)-6-(3-bromophenyl)-4-methylpyridazine (**28**): yellow crystals; 71%; mp 132 °C. IR (KBr): ν_{max} = 3091, 3056, 3011, 2971, 2932, 1567, 1487, 1376, 1091, 1001, 843 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.40 (t, 1H, J = 7.8), 7.50 (d, 2H, J = 8.4), 7.57–7.67 (m, 3H), 7.72 (s, 1H), 8.07 (d, 1H, J = 7.8), 8.29 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 124.9, 126.3, 127.6, 129.2, 129.5, 130.8, 131.3, 131.8, 133.6, 135.2, 136.3, 138.1, 156.2, 159.8. Anal. found, C, 56.80; H, 3.38; N, 7.90. $C_{17}H_{12}BrClN_2$ requires C, 56.77; H, 3.36; N, 7.79.

3-(4-Chlorophenyl)-6-(3-methoxyphenyl)-4-methylpyridazine (**29**): white crystals, 77%, mp 150 °C. IR (KBr): ν_{max} = 3007, 2936, 2835, 1595, 1581, 1493, 1390, 1255, 1174, 1035, 843, 795 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.92 (s, 3H), 7.06 (d, J = 8.4 Hz, 1H), 7.44 (t, J = 8.4 Hz, 1H), 7.51 (d, J = 8.7 Hz, 2H), 7.64–7.61 (m, 3H), 7.74 (s, 1H), 7.81 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 54.6, 110.9, 120.2, 124.7, 127.5, 128.9, 129.5, 129.8, 131.0, 131.6, 135.4, 136.0, 137.5, 157.3, 159.5. Anal. found, C, 69.60; H, 4.84; N, 9.21. $C_{18}H_{15}ClN_2O$ requires C, 69.57; H, 4.86; N, 9.01.

3-(4-Chlorophenyl)-6-(3,4-dimethoxyphenyl)-4-methylpyridazine (**30**): white crystals; 78%; mp 182 °C. IR (KBr): ν_{max} = 3086, 3061, 3001, 2966, 2942, 2902, 2842, 2882, 1587, 1464, 1240, 1091, 1023, 838 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.95 (s, 3H), 4.00 (s, 3H), 6.98 (d, 1H, J = 8.4), 7.47 (d, 2H, J = 7.8), 7.51–7.64 (m, 3H), 7.69 (s, 1H), 7.93 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 55.3, 56.6, 108.8, 109.1, 109.8, 110.7, 111.3, 111.7, 125.6, 127.7, 128.6, 131.3, 135.5, 135.9, 156.9, 158.9. Anal. found, C, 66.99; H, 5.04; N, 8.31. $C_{17}H_{17}ClN_2O_2$ requires C, 66.96; H, 5.03; N, 8.22.

3-(4-Chlorophenyl)-6-(3,4-methylenedioxyphenyl)-4-methylpyridazine (**31**): yellow crystals, 80%, mp 166 °C. IR (KBr): ν_{max} = 3081, 3046, 3006, 2966, 2897, 2787, 1592, 1505, 1452, 1108, 1001, 819 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 6.05 (s, 2H), 6.94 (d, J = 8.1, 1H), 7.48 (d, J = 8.1, 2H), 7.66–7.54 (m, 4H), 7.71 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 101.5, 106.6, 107.4, 108.8, 109.3, 125.7, 127.5, 129.7, 130.3, 131.3, 135.5, 135.9, 148.5, 157.0, 159.0. Anal. found, C, 66.59; H, 4.04; N, 8.81. $C_{18}H_{13}ClN_2O_2$ requires C, 66.57; H, 4.03; N, 8.63.

3-(4-Chlorophenyl)-6-(4-hydroxy-3-methoxyphenyl)-4-methylpyridazine (**32**): white crystals; 78%; mp 150 °C. IR (KBr): ν_{max} = 3529, 3078, 3049, 2939, 1596, 1510, 1489, 1270, 1029, 824, 789 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 4.01 (s, 3H), 6.01 (s, 1H), 7.05 (d, 1H, J = 8.1), 7.51–7.47 (m, 3H), 7.62 (d, 2H, J = 8.1), 7.70 (s, 1H), 7.99 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.2, 56.9, 108.5, 110.4, 113.5, 115.6, 118.9, 120.8, 121.1, 123.9, 125.7, 127.4, 129.4, 129.7, 131.5, 135.9. Anal. found, C, 66.17; H, 4.61; N, 8.76. $C_{18}H_{15}ClN_2O_2$ requires C, 66.16; H, 4.63; N, 8.57.

3-(4-Methylphenyl)-6-phenyl-4-methylpyridazine (**33**): white crystals; 70%; mp 133 °C. IR (KBr): ν_{max} = 3055, 2930, 1586, 1490, 1392, 1092, 10018, 839 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 2.46 (s, 3H), 7.33 (d, 2H, J = 7.8), 7.45–7.60 (m, 5H), 7.74 (s, 1H), 8.13 (d, 2H, J = 6.3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 20.1, 125.0, 126.2, 126.6, 127.9, 128.1, 129.6, 130.0, 130.5, 136.5, 138.9, 157.2, 160.4. Anal. found, C, 83.07; H, 6.20; N, 10.91. $C_{18}H_{16}N_2$ requires C, 83.04; H, 6.19; N, 10.76.

3-(4-Methylphenyl)-6-(4-bromophenyl)-4-methylpyridazine (**34**): white crystals; 94%; mp 166 °C. IR (KBr): ν_{max} = 3090, 2922, 2850, 1588, 1486, 1407, 1073, 1003, 821 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 2.48 (s, 3H), 7.33 (d, 2H, J = 7.5), 7.57 (d, 2H, J = 7.5), 7.66 (d, 2H, J = 8.1), 7.75 (s, 1H), 8.03 (d, 2H, J = 8.1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 21.3, 124.8, 127.7, 128.2, 128.5, 129.5, 129.9, 130.1, 130.4, 131.4, 133.0, 156.2, 160.5. Anal. found, C, 63.78; H, 4.45; N, 8.30. $C_{18}H_{15}BrN_2$ requires C, 63.73; H, 4.46; N, 8.26.

3-(4-Methylphenyl)-6-(4-chlorophenyl)-4-methylpyridazine (**35**): yellow crystals; 68%; mp 184 °C. IR (KBr): ν_{max} = 3090, 3035, 1918, 1586, 1438, 1406, 1090, 1008, 824 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 2.47 (s, 3H), 7.33 (d, 2H, J = 7.8), 7.45–7.6 (m, 4H), 7.73 (s, 1H), 8.08 (d, 2H, J = 8.7). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 21.3, 125.0, 126.6, 127.4, 128.2, 129.2, 129.8, 130.0, 130.3, 136.9, 139.2, 156.1, 160.5. Anal. found, C, 73.39; H, 5.18; N, 9.66. $C_{18}H_{15}ClN_2$ requires C, 73.34; H, 5.13; N, 9.50.

3-(4-Methylphenyl)-6-(4-fluorophenyl)-4-methylpyridazine (**36**): white crystals; 69%; mp 175 °C. IR (KBr): ν_{max} = 3075, 2920, 1590, 1506, 1378, 1222, 1099, 818 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 2.47 (s, 3H), 7.17–7.29 (m, 2H), 7.33 (d, 2H, J = 7.8), 7.56 (d, 2H, J = 7.8), 7.70 (s, 1H), 8.09–8.18 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 21.3, 115.2, 116.1, 116.7, 117.0, 126.1, 128.1, 128.3, 129.9, 156.3, 160.4, 162.4, 165.7. Anal. found, C, 77.70; H, 5.46; N, 10.20. $C_{18}H_{15}FN_2$ requires C, 77.68; H, 5.43; N, 10.07.

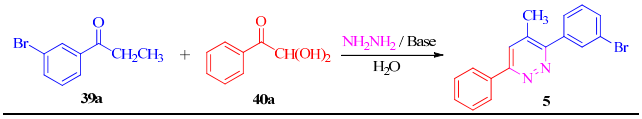
3-(4-Methylphenyl)-6-(4-methoxyphenyl)-4-methylpyridazine (**37**): yellow crystals; 75%; mp 134 °C. IR (KBr): ν_{max} = 3005, 2925, 2835, 1609, 1583, 1395, 1256, 1023, 845 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.44 (s, 3H), 3.88 (s, 3H), 7.04 (d, 2H, J = 8.1), 7.31 (d, 2H, J = 7.8), 7.56 (d, 2H, J = 7.8), 7.69 (s, 1H), 8.11 (d, 2H, J = 8.7). ^{13}C NMR (7.5 MHz, $CDCl_3$) δ 20.1, 21.3, 56.0, 113.3, 113.7, 115.0, 115.5, 126.0, 127.6, 128.1, 130.0, 138.9, 156.7, 159.8, 161.2. Anal. found, C, 78.57; H, 6.24; N, 9.77. $C_{19}H_{18}N_2O$ requires C, 78.59; H, 6.25; N, 9.65.

3-(4-Methylphenyl)-6-(3,4-dimethoxyphenyl)-4-methylpyridazine (**38**): white crystals; 61%; mp 170 °C. IR (KBr): ν_{max} = 3005, 2940, 2840, 1605, 1588, 1422, 1259, 1025, 821 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 2.46 (s, 3H), 3.94 (s, 3H), 4.01 (s, 3H), 6.98 (d, 1H, J = 8.4), 7.31 (d, 2H, J = 7.5), 7.48–7.64 (m, 3H), 7.74 (s, 1H), 7.96 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 21.3, 55.2, 56.7, 109.2, 109.9, 110.4, 110.9, 11.8, 112.2, 126.4, 128.5, 129.9, 139.0, 149.5, 151.0, 156.4, 159.9. Anal. found, C, 75.00; H, 6.32; N, 8.84. $C_{20}H_{20}N_2O_2$ requires C, 74.98; H, 6.29; N, 8.74.

3. Results and discussion

During our research program on the synthesis of aryl-substituted pyridazine derivatives [25], we used the reaction of 3-bromopropiophenone (**39a**) with phenylglyoxalmonohydrate (**40a**) and hydrazine hydrate in water as a model reaction. This one-pot system afforded hydrazone compounds as by-products at room temperature, 50 °C and at reflux (Table 1, entries 1–3). This could be a reflection of the low acidity of the α-hydrogens on propiophenone, and so we investigated the use of organic bases such as DABCO, DBU and DBN to catalyze this reaction. With an initial concentration of 10 mol% of either DABCO, DBU or DBN at 25 °C for 6 h, the desired pyridazine derivative was afforded in 25%, 15% and 10% yield, respectively (Table 1, entries 4–6). The influence of solvent was also investigated, and the results are summarized in Table 1. No product was isolated when the reaction was carried out in pure EtOH (entries 7–9), and a much longer time was needed when the reaction was carried out in a 1:1 ratio of EtOH:H_2O (entries 10–12). Attempts to improve the reaction conditions by running the reaction in H_2O, EtOH and H_2O:EtOH (1:1) in the presence of 10 mol% of the organic bases at 50 °C failed. Monitoring the reaction progress via TLC showed that an increase in the reaction temperature led to an increase in by-product formation, and no pyridazine products were formed. The above results indicated that H_2O accelerated the reaction, and it was found to the best solvent for this reaction at room temperature (25 °C). Encouraged by these results, we continued to focus on optimizing the amounts of the basic organocatalysts for the reaction. Tuning the catalyst concentration revealed that increasing the amounts of DBU and DBN from 20 to 40 mol% led to a small increase in the yield (Table 1, entries 13–18). Using 50 mol% of both DBU and DBN caused a decrease in yield (Table 1, entries 19 and 20). Surprisingly, in the case of DABCO, an increase in concentration caused a significant increase in the yield of the pyridazine product (Table 1, entries 21–23), and adding 50 mol% of DABCO to the reaction mixture led to the best result (Table 1, entry 24). Further increases in the molar ratio of DABCO did not improve the reaction yield and, in contrast, it caused a significant decrease in the efficiency of the reaction (Table 1, entry 25).

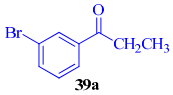
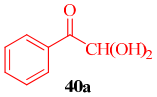
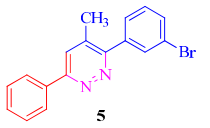
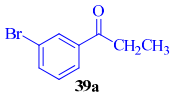
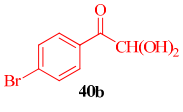
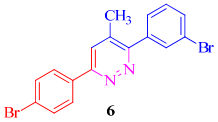
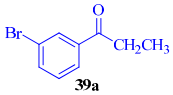
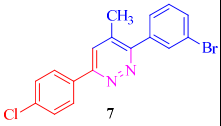
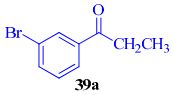
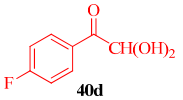
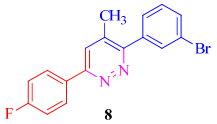
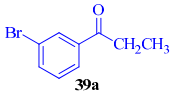
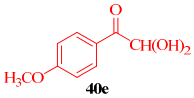
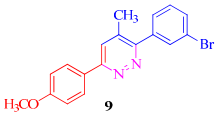
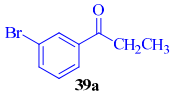
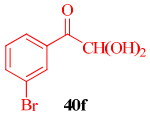
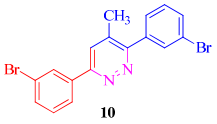
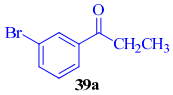
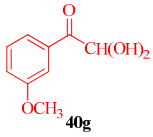
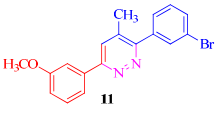
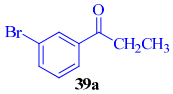
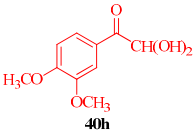
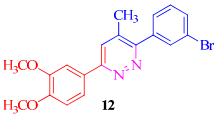
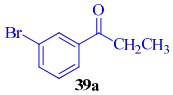
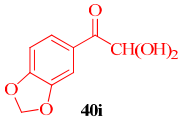
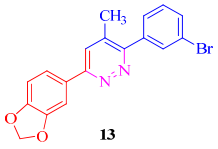
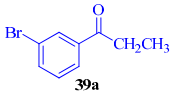
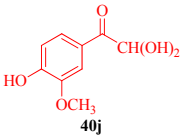
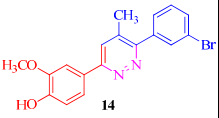
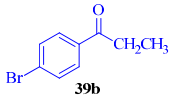
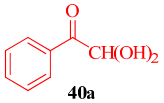
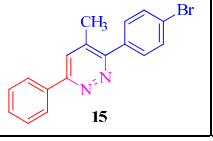
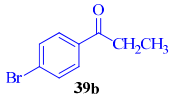
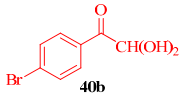
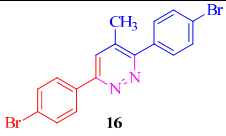
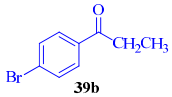
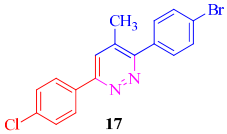
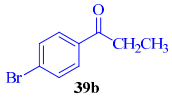
Table 1
Optimization of the reaction conditions.



Entry	Catalyst (mol%)	Solvent	Temp. (°C)	Time (h)	Yield of **5** (%)
1	—	H_2O	25	24	0
2	—	H_2O	50	24	0
3	—	H_2O	100	24	0
4	DABCO (10)	H_2O	25	6	15
5	DBU (10)	H_2O	25	6	10
6	DBN (10)	H_2O	50	6	trace
7	DABCO (10)	EtOH	25	24	0
8	DBU (10)	EtOH	25	24	0
9	DBN (10)	EtOH	25	24	0
10	DABCO (10)	EtOH:H_2O (1:1)	25	12	10
11	DBU (10)	EtOH:H_2O (1:1)	25	24	trace
12	DBN (10)	EtOH:H_2O (1:1)	25	24	0
13	DBU (20)	H_2O	25	24	30
14	DBN (20)	H_2O	25	24	37
15	DBU (30)	H_2O	25	24	45
16	DBN (30)	H_2O	25	24	22
17	DBU (40)	H_2O	25	24	27
18	DBN (40)	H_2O	25	24	33
19	DBU (50)	H_2O	25	24	35
20	DBN (50)	H_2O	25	24	21
21	DABCO (20)	H_2O	25	6	39
22	DABCO (30)	H_2O	25	4	48
23	DABCO (40)	H_2O	25	4	59
24	DABCO (50)	H_2O	25	3	86
25	DABCO (60)	H_2O	25	6	42

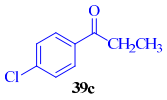
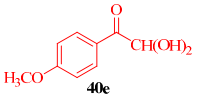
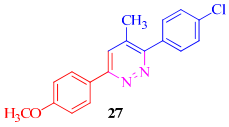
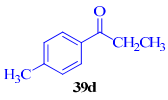
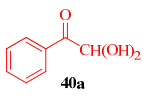
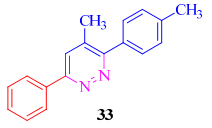
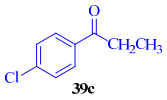
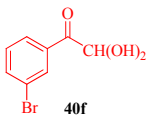
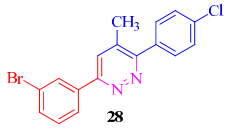
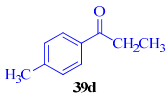
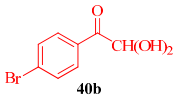
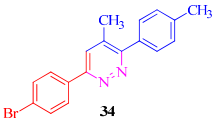
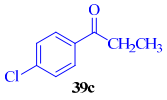
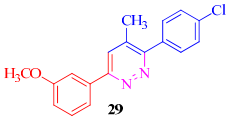
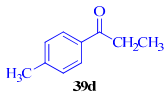
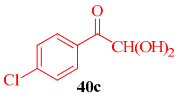
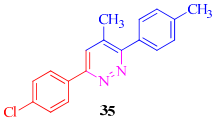
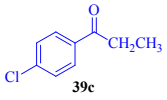
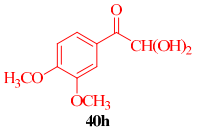
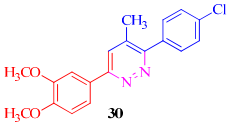
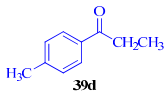
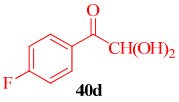
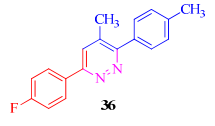
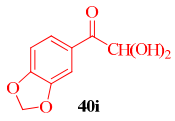
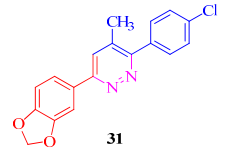
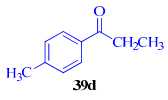
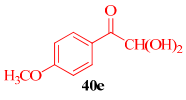
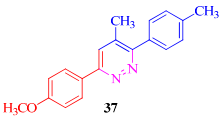
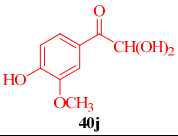
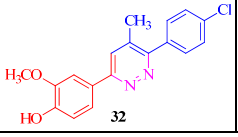
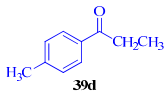
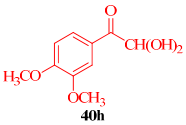
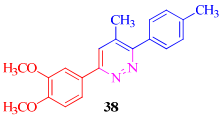
With the optimized reaction conditions in hand, we moved on to examine the substrate scope using a wide variety of propiophenones and arylglyoxal monohydrates (Table 2). Arylglyoxalmonohydrates bearing electron-withdrawing groups gave better yields, in shorter reaction times, than the arylglyoxalmonohydrates bearing electron-donating groups. It is worth-

Table 2
Substrate scope study using different propiophenones and arylglyoxalmonohydrates.

Entry	Propiophenone	Arylglyoxal-monohydrate	Product
1	 39a	 40a	 5
2	 39a	 40b	 6
3	 39a	 40c	 7
4	 39a	 40d	 8
5	 39a	 40e	 9
6	 39a	 40f	 10
7	 39a	 40g	 11
8	 39a	 40h	 12
9	 39a	 40i	 13
10	 39a	 40j	 14
11	 39b	 40a	 15
12	 39b	 40b	 16
13	 39b	 40c	 17
14	 39b	40d	18
15	39b	40e	19
16	39b	40f	20
17	39b	40h	21
18	39b	40i	22
19	39c	40a	23
20	39c	40b	24
21	39c	40c	25
22	39c	40d	26

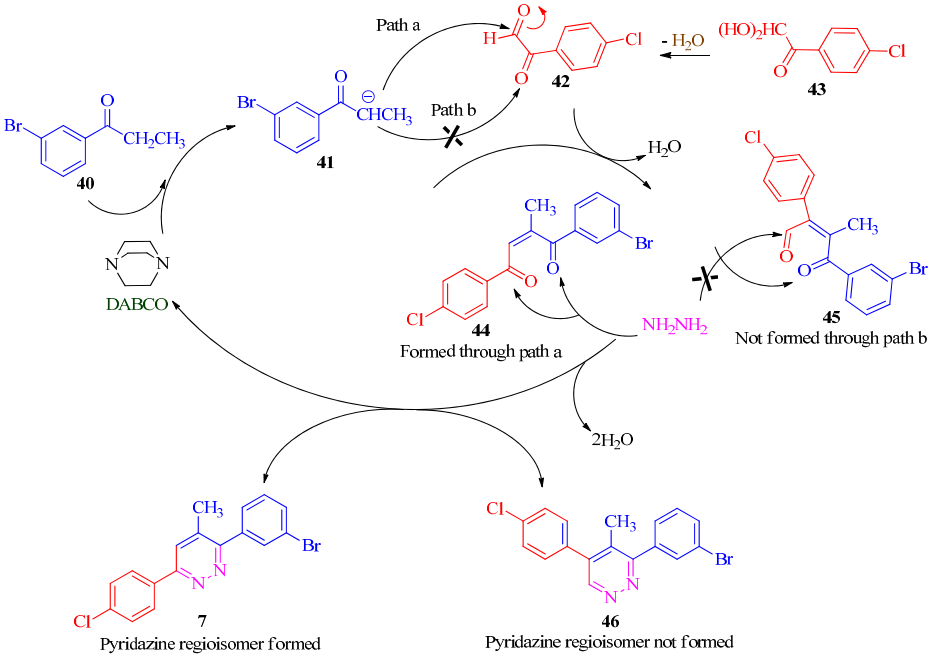
(To be continued)

Table 2 (continued)

Entry	Propiophenone	Arylglyoxal-monohydrate	Product	Entry	Propiophenone	Arylglyoxal-monohydrate	Product
23	 **39c**	 **40e**	 **27**	29	 **39d**	 **40a**	 **33**
24	 **39c**	 **40f**	 **28**	30	 **39d**	 **40b**	 **34**
25	 **39c**	 **40g**	 **29**	31	 **39d**	 **40c**	 **35**
26	 **39c**	 **40h**	 **30**	32	 **39d**	 **40d**	 **36**
27	 **39c**	 **40i**	 **31**	33	 **39d**	 **40e**	 **37**
28	 **39c**	 **40j**	 **32**	34	 **39d**	 **40h**	 **38**

while to note that all of the reactions proceeded selectively to generate the 3,6-diaryl-4-methylpyridazine as a single regioisomer.

Full characterization including IR, ^{1}H NMR, ^{13}C NMR and elemental analysis proved the identity of all the pyridazine products **5**–**38**. The diagnostic singlet around $\delta \approx 7.70$ in the ^{1}H NMR spectra was ascribed to the C_5–H of the pyridazine ring. All of the compounds **5**–**38** are believed to be the only regioisomers present, and no evidence for the formation of the other isomer was observed for all new pyridazine derivatives. As



Scheme 2. Proposed mechanism for the regioselective DABCO-catalyzed synthesis of 3,6-diaryl-4-methylpyridazine derivatives.

the formyl group is more electrophilic than the keto group in the arylglyoxal scaffold [25–30] (Scheme 2), the regioselectivity is due to carbanion **41** attacking the formyl group of arylglyoxal **42**, leading to the formation of Knoevenagel adduct **44** through path a. In the IR spectra, the characteristic absorption band at 1580 cm^{-1} can be assigned to the C=N bonds of the pyridazine ring. In the ^{13}C NMR, two signals located at the lowest fields, between $\delta \approx 156–159$, were assigned as the carbon atoms of the corresponding C=N groups. Efforts toward preparing a single crystal from these substituted pyridazines is ongoing.

4. Conclusions

We have developed an eco-friendly, regioselective and highly efficient three component base-organocatalyzed reaction involving various arylglyoxalmonohydrates, substituted propiophenones and hydrazine hydrate, to produce novel 3,6-diaryl-4-methylpyridazines bearing diverse aryl substituents. Mild reaction conditions, operational simplicity and facile workup are the main advantages of this synthetic strategy.

Acknowledgments

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Graphical Abstract

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An environmentally-friendly base organocatalyzed one-pot strategy for the regioselective synthesis of novel 3,6-diaryl-4-methylpyridazines

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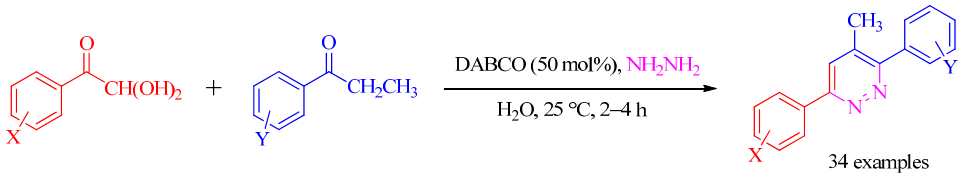
Payame Noor University, Iran



X = 4-H, 4-Br, 4-Cl, 4-F, 4-OCH_3, 3-Br, 3-OCH_3, 3,4-$(OCH_3)_2$, 3,4-(OCH_2O), 4-OH-3-OCH_3
Y = 4-Br, 3-Br, 4-Cl, 4-CH_3

This work describes the regioselective synthesis of novel 3,6-diaryl-4-methylpyridazines directly from a DABCO-catalyzed three-component condensation of propiophenones, arylglyoxalmonohydrates and hydrazine hydrate in water.

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