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Article

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

Mehdi Rimaz *, Farkhondeh Aali

Department of Chemistry, Payame Noor University, PO Box 19395-3697, Tehran, Iran

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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-

* Corresponding author. Tel: +98-443-5625711; Fax: +98-443-5666999; E-mail: rimaz.mehdi@gmail.com
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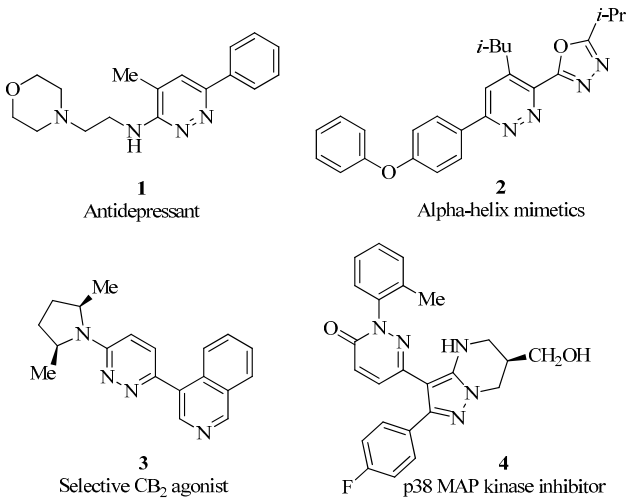


Fig. 1. Selected biologically active substituted pyridazines.

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

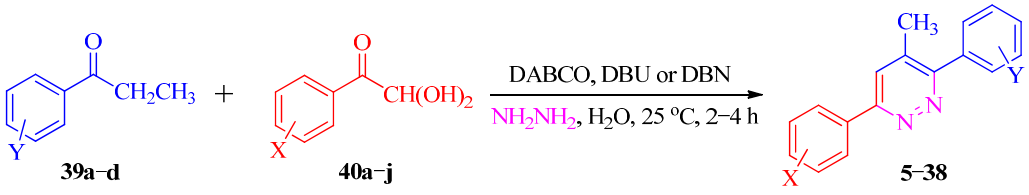
3-(3-Bromophenyl)-6-phenyl-4-methylpyridazine (**5**): white crystals; 86%; mp 115 °C. IR (KBr): ν_{max} = 3063, 2971, 2929, 1577, 1392, 1261, 1042, 886 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.39 (t, 1H, J = 7.8), 7.47–7.67 (m, 5H), 7.74 (s, 1H), 7.84 (s, 1H), 8.14 (d, 2H, J = 6.3). ^{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.