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One-pot synthesis of pyrimidines under solvent-free conditions

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ABSTRACT

N,N,N',N'-Tetrabromobenzene-1,3-disulfonamide was used as an efficient catalyst for the one-pot synthesis of pyrimidine derivatives in excellent yields from triethoxymethane, ammonium acetate, and various ketone derivatives at 100–110 °C under solvent-free conditions.

1. Introduction

The development of simple synthetic routes for complex organic molecules from readily available reagents is an important task in organic synthesis [1]. Multicomponent reactions (MCRs) are significant tools for the rapid and efficient synthesis of a wide variety of organic molecules [2]. These reactions have been investigated extensively in organic and diversely oriented synthesis; this is primarily due to their ability to generate complex molecular functionalities from simple starting materials via a one-pot reaction.

In recent years, solvent-free organic reactions [3–6] have captured great interest because of their many advantages such as high efficiency and selectivity, easy separation and purification, mild reaction conditions, reduction in waste, and benefit to the industry as well as to the environment. Solvent-free organic reactions based on grinding two macroscopic particles together mostly involve the formation of a liquid phase prior to the reaction, that is, the formation of an eutectic melt of uniform distribution, where the reacting components, being in proximity, are poised to react in a controlled way [7]. The possibility of performing multicomponent reactions under solvent-free conditions with a heterogeneous catalyst could enhance their efficiency from an economic as well as an ecological point of view [8].

Pyrimidine is an important heterocycle with a variety of biological activities. Azaheterocycles constitute a very important class of compounds. In particular, pyrimidine derivatives include a large number of natural products, pharmaceuticals, and functional materials (Fig. 1) [9–12]. Several examples of pharmaceutically important compounds include trimethoprim [13] and Gleevec

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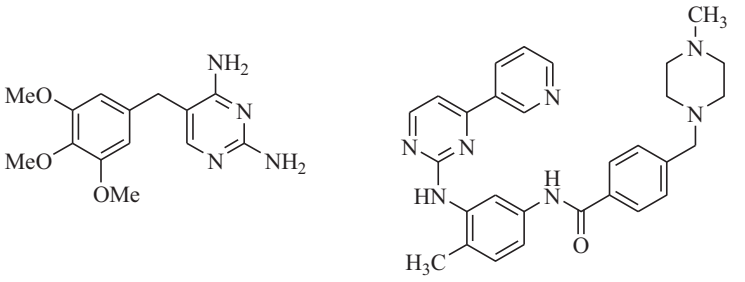

Trimethoprim **Imatinib mesylate**

Fig. 1. Examples of biologically active pyrimidines.

(imatinib mesylate) [14]. Natural and unnatural polymers also contain pyrimidine derivatives [15–17]. While development of important methodologies for the synthesis of pyrimidines enjoys a rich history, the discovery of new strategies for the convergent synthesis of pyrimidines remains a vibrant area of chemical research.

Many methods are available for the synthesis of the pyrimidine ring system. The most common method used involves the reaction of a 1, 3-dicarbonyl component with a reagent bearing an N–C–N fragment such as urea [18], amidine [19], or guanidine [20]. In recent years, $ZnCl_2$ [21], and TsOH [22] have been utilized for this synthesis. Thus, the synthesis of pyrimidine is an important and useful task in organic chemistry.

2. Experimental

All commercially available chemicals were obtained from Merck and Fluka companies, and used without further purification unless otherwise stated. Nuclear magnetic resonance ^1H and ^{13}C NMR spectra (Sharif University and Urmia University) were recorded on Bruker Avance 300 and 500 MHz FT NMR spectrometers. Infrared (IR) spectroscopy was conducted on a PerkinElmer GX FT–IR spectrometer. Mass spectra were recorded on a Shimadzu QP 1100 BX Mass Spectrometer. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer (University of Tarbiatmoallem, Tehran).

2.1. General procedure for synthesis of pyrimidine

A mixture of triethoxymethane (3 mmol), ammonium acetate (2 mmol), ketone (1 mmol), and TBBDA (0.1 g, 18 mol %) was heated at 100–110 °C for the appropriate time. After completion of the reaction (TLC acetone/*n*-hexane [2:10]), the mixture was cooled, and cold CH_2Cl_2 (15 mL) was added, then the catalyst was removed by filtration. The organic phase was washed with water (3 × 10 mL), dried and concentrated. The product was purified by TLC (TLC acetone/*n*-hexane [2:10]).

2.2. Physical and spectroscopic data

2.2.1. Spectra data of 4-phenylpyrimidine

A pale yellow powder (66%); mp 57–60 °C (57.8–58.5 °C) [12]; R_f (17% acetone/*n*-hexane) 0.26; IR (KBr) (υ_{max}, cm^{-1}) 1603, 1577, 1541; δ_H (500 MHz, $CDCl_3$) 7.56–7.59 (3H, m), 7.80 (1H, dd, J = 5.34, 1.17 Hz), 8.14–8.16 (2H, m), 8.82 (1H, d, J = 5.35 Hz), 9.33 (1H, s); δ_C (75 MHz, DMSO); 118.2, 121.9, 126.1, 131.2, 133.7, 159.1, 159.4, 160.7 (Table 2, entry 1).

2.2.2. Spectra data of 4-(4-bromophenyl)pyrimidine

A pale yellow powder (66%); mp 71–73 °C [13]; R_f (17% acetone/*n*-hexane) 0.21; IR (KBr) (υ_{max}, cm^{-1}) 1590, 1574, 1538; δ_H (500 MHz, $CDCl_3$) 7.68 (2H, d, J = 8.54 Hz), 7.73 (1H, dd, J = 5.36, 1.07 Hz), 8.01 (2H, d, J = 8.54 Hz), 8.82 (1H, d, J = 5.36 Hz), 9.30 (1H, s); δ_C (125 MHz, $CDCl_3$); 117.1. 126.4, 129.4, 132.7, 135.7, 157.8, 159.4, 163.3 (Table 2, entry 2).

2.2.3. Spectra data of 4-(4-chlorophenyl)pyrimidine

A pale yellow powder (61%); mp72–74 °C (75.9–76.8 °C)[12]; R_f (17% acetone/*n*-hexane) 0.19; IR (KBr) (υ_{max}, cm^{-1}) 1594, 1578, 1539; δ_H (500 MHz, DMSO) 7.63 (2H, d, J = 8.57 Hz), 8.13 (1H, d, J = 5.29 Hz), 8.25 (2H, d, J = 8.55 Hz), 8.88 (1H, d, J = 5.36 Hz), 9.26 (1H, s); δ_C (125 MHz, DMSO); 118.1, 129.6, 130.0, 135.6, 136.9, 159.1, 159.6, 162.2 (Table 2, entry 3).

2.2.4. Spectra data of 4-(4-fluorophenyl)pyrimidine

A colorless crystal (54%); mp 75–76 °C; R_f (17% acetone/*n*-hexane) 0.21; IR (KBr) (υ_{max}, cm^{-1}) 1601, 1581, 1542; δ_H (500 MHz, $CDCl_3$) 7.25 (2H, t, J = 11.55 Hz), 7.75 (1H, dd, J = 5.36, 0.93 Hz), 8.15–8.19 (2H, m), 8.83 (1H, d, J = 5.38 Hz), 9.31 (1H, s); δ_C (125 MHz, $CDCl_3$); 116.5, 116.7, 117.0, 129.7, 129.8, 157.4, 159.0, 163.6, 166.3. (Found: C, 69.08; H, 4.04; N, 16.34. $C_{10}H_7N_2F$ requires C, 68.96; H, 4.05; N, 16.08%) (Table 2, entry 4).

2.2.5. Spectra data of 4-(4-nitrophenyl)pyrimidine

Yellow powder (55%); mp 100–102 °C; R_f (17% acetone/*n*-hexane) 0.22; IR (KBr) (υ_{max}, cm^{-1})1603, 1577, 1546, 1521, 1349; δ_H (500 MHz, $CDCl_3$) 7.85 (1H, dd, J = 5.26, 0.97 Hz), 8.33 (2H, d, J = 7.13 Hz), 8.42 (2H, d, J = 7.13 Hz), 8.94 (1H, d, J = 5.19 Hz), 9.40 (1H, s); δ_C (125 MHz, $CDCl_3$); 118.0, 124.6, 128.6, 142.6, 158.4, 159.7, 161.9 (Table 2, entry 5).

2.2.6. Spectra data of 4-p-tolylpyrimidine

A pale yellow powder (51%); mp 62–63 °C; R_f (17% acetone/*n*-hexane) 0.27; IR (KBr) (υ_{max}, cm^{-1}) 2920,