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Catalysis Communications 8 (2007) 211–214
CATALYSIS COMMUNICATIONS
www.elsevier.com/locate/catcom

On Water: A practical and efficient synthesis of quinoxaline derivatives catalyzed by $CuSO_4 \cdot 5H_2O$

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Received 24 April 2006; received in revised form 11 June 2006; accepted 12 June 2006
Available online 16 June 2006

Abstract

Cupric sulfate pentahydrate is an efficient catalyst for a one-pot synthesis of quinoxaline derivatives. The reaction can be performing in water as well as ethanol. The procedure presented is operationally simple, practical and green.

Keywords: 1,2-Diketones; 1,2-Diamines; Quinoxaline derivatives; $CuSO_4 \cdot 5H_2O$; Cupric sulfate pentahydrate

1. Introduction

The toxic and volatile nature of many organic solvents, particularly chlorinated hydrocarbons and benzene, which are widely used in organic synthetic procedures, has posed a serious threat to the environment. There has been considerable research recently into replacing the use of these volatile organic solvents with clean ones as reaction media [1]. Performing organic reactions in aqueous media has attracted much attention, because water would be considerably safe, non-toxic, environmentally friendly and cheap compared to organic solvents [2]. Moreover, when a water-soluble catalyst is used, the insoluble products can be separated by simple filtration and the catalyst system can be recycled. Therefore, development of a catalyst system that is not only stable toward water but also completely soluble in this solvent seems highly desirable.

Quinoxaline and its derivatives are an important class of benzoheterocycles [3] displaying a broad spectrum of biological activities [4] which have made them privileged structures in combinatorial drug discovery libraries [5]. They have also found applications as dyes [6] and building blocks in the synthesis of organic semiconductors [7], and they also serve as useful rigid subunits in macro cyclic receptors or molecular recognition [8] and chemically controllable switches [9].

A number of synthetic strategies have been developed for the preparation of substituted quinoxalines [3,10]. By far, the most common method relies on the condensation of an aryl 1,2-diamine with a 1,2-dicarbonyl compound in refluxing ethanol or acetic acid for 2–12 h giving 34–85% yields [11]. Numerous methods are available in the literature for the synthesis of quinoxaline derivatives including the Bi-catalyzed oxidative coupling of epoxides and ene-1,2-diamines [12], from α-hydroxy ketones via a tandem oxidation process using $Pd(OAc)_2$ or $RuCl_2$–$(PPh_3)_3$–TEMPO [13] and MnO_2 [14], heteroannulation of nitroketene *N*,*S*-arylaminoacetals with $POCl_3$ [15], a solid-phase synthesis on SynphaseTM Lanterns [16], cyclization of α-arylimino oximes of α-dicarbonyl compounds under reflux in acetic anhydride [17], condensation of *o*-phenylene diamines and 1,2-dicarbonyl compounds in MeOH/AcOH under microwave irradiation [18], and iodine catalyzed cyclocondensation of 1,2-dicarbonyl compounds and substituted *o*-phenylene diamines in DMSO [19] and CH_3CN [20]. Most of the existing methodologies suffer from disadvantages such as use of volatile organic solvents, unsatisfactory product yields, critical product isolation procedures, expensive and detrimental metal

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1566-7367/$ - see front matter
doi:10.1016/j.catcom.2006.06.013

precursors and harsh reaction conditions, which limit their use under the aspect of environmentally benign processes.

Recently we reported the use of $CuSO_4 \cdot 5H_2O$ for the synthesis of 1,1-diacetates under solvent-free condition [21]. This experience motivated us to use this catalyst for the synthesis of 2,3-disubstituted quinoxalines. As part of our ongoing interest in synthesis of heterocyclic compounds containing nitrogen [22], we disclose herein our results for the synthesis of quinoxalines using catalytic amounts of cupric sulfate pentahydrate in ethanol and water.

2. Experimental

Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ^1H NMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. All products were characterized by spectra and physical data.

2.1. Preparation of quinoxalines in water (method I): general procedure

A mixture of 1,2-diketone **1** (1 mmol), 1,2-diaminobenzene derivative **2** (1 mmol) and $CuSO_4 \cdot 5H_2O$ (10 mol%) in water (3 mL) was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the solid which separated was filtered and then recrystallized from ethanol to afford pure quinoxaline **3**.

2.2. Preparation of quinoxalines in ethanol (method II): general procedure

A mixture of 1,2-diketone **1** (1 mmol), 1,2-diaminobenzene derivative **2** (1 mmol) and $CuSO_4 \cdot 5H_2O$ (10 mol%) in EtOH (3 mL) was stirred at room temperature. Upon completion of the reaction, the reaction mixture was heated, the product dissolves in ethanol and the catalyst separated easily from the reaction mixture by simple filtration. The pure product **3** was crystallized from ethanol.

2.3. Recycling of the catalyst

At the end of the reaction in ethanol, the catalyst was filtered, washed with diethyl ether, dried at 80 °C for 1 h, and re-used in another reaction. The recycled catalyst was used for five reactions without observation of appreciable loss in its catalytic activities. In the case of water as solvent, after evaporation of water, the catalyst was obtained and could be reused in another reaction.

2.4. Physical and spectra data of the products

(1) *2,3-Diphenylquinoxaline*: m.p. 126–127°C; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.2 (dd, $J = 3.43$, 6.30 Hz, 2H), 7.79 (dd, $J = 3.43$, 6.30 Hz, 2H), 7.5 (m, 4H), 7.39 (m, 6H); IR (KBr) ν_{max} (cm^{-1}): 3055, 1541, 1345, 768, 729.

(2) *2,3-Bis(4-methoxy-phenyl) quinoxaline*: m.p. 151–152 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.15 (dd, $J = 3.44$, 6.32 Hz, 2H), 7.7 (dd, $J = 3.39$, 6.36 Hz, 2H), 7.55 (d, $J = 8.75$ Hz, 4H), 6.89 (d, $J = 8.73$ Hz, 4H), 3.81 (s, 6H); IR (KBr) ν_{max} (cm^{-1}): 3003, 2931, 1604, 1510, 1345, 1057, 876.

(3) *6-Nitro-2,3-diphenylquinoxaline*: m.p. 193–194 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 9.2 (d, $J = 2.38$ Hz, 1H), 8.53 (dd, $J = 2.50$, 9.10 Hz, 1H,), 8.39 (d, $J = 9.17$ Hz, 1H), 7.6 (m, 4H), 7.42 (m, 6H); IR (KBr) ν_{max} (cm^{-1}): 3057, 2935, 1621, 1341, 1135, 699.

(4) *2,3-Bis(4-methoxy-phenyl)-6-nitroquinoxaline*: m.p. 192–194 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 9.1 (d, $J = 2.44$ Hz, 1H), 8.49 (dd, $J = 2.46$, 9.14 Hz, 1H), 8.24 (d, $J = 9.15$ Hz, 1H), 7.56 (m, 4H), 6.98 (d, $J = 7.9$ Hz, 4H), 3.9 (s, 6H); IR (KBr) ν_{max} (cm^{-1}): 2924, 1337, 1169, 1021, 835.

(5) *6-Methyl-2,3-diphenylquinoxaline*: m.p. 116–117 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.1 (d, $J = 8.55$ Hz, 1H), 7.96 (s, 1H), 7.63 (dd, $J = 1.72$, 8.56 Hz, 1H), 7.5 (m, 4H), 7.35 (m, 6H), 2.6 (s, 3H); IR (KBr) ν_{max} (cm^{-1}): 3063, 1660, 1592, 1210, 874, 719, 640.

(6) *2,3-Bis(4-methoxy-phenyl)-6-methylquinoxaline*: m.p. 125–127 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.05 (d, $J = 8.52$ Hz, 1H), 7.92 (s, 1H), 7.58 (dd, $J = 1.55$, 8.50 Hz, 1H), 7.48 (d, $J = 7.64$ Hz, 4H), 6.9 (d, $J = 8.75$ Hz, 4H), 3.9 (s, 6H), 2.6 (s, 3H); IR (KBr) ν_{max} (cm^{-1}): 2925, 2580, 1657, 1597, 1264, 1159, 833, 696.

3. Results and discussion

In a model condensation reaction, benzil **1a** and 1,2-diaminobenzene **2a** in EtOH were stirred at room temperature using a catalytic amount of $CuSO_4 \cdot 5H_2O$ (Scheme 1). After 8 min the reaction was completed. It is noteworthy to mention that $CuSO_4 \cdot 5H_2O$ is insoluble in ethanol. Then the reaction mixture was heated, the product dissolves in ethanol and the catalyst separated easily from the reaction mixture. Without any further recrystallization, the pure product **3a** was obtained (97% yield).

The applicability of the present methodology is further extended by performing the reaction in an aqueous media, to our surprise, the reaction was performed well in water and the reaction rates as well as the yields of products are satisfactory. $CuSO_4 \cdot 5H_2O$ is highly soluble in water and can be easily remove from the reaction mixture by simple filtration (Table 1). Using water as solvent, affected the rate of reaction and the reaction time, in comparison with ethanol, require only little longer time to complete. However, this process is green, environmental friendly, clean,