Ultrasonics Sonochemistry 21 (2014) 472–477

Contents lists available at ScienceDirect

Ultrasonics Sonochemistry

journal homepage: www.elsevier.com/locate/ultson

Short Communication

Eco-efficient ultrasonic responsive synthesis of pyrimidines/pyridines

Ramakanth Pagadala, Suresh Maddila, Sreekantha B. Jonnalagadda *

School of Chemistry & Physics, University of KwaZulu-Natal, Westville Campus, Chiltern Hills, Durban 4000, South Africa

ARTICLE INFO

Article history:
Received 22 April 2013
Received in revised form 1 August 2013
Accepted 31 August 2013
Available online 8 September 2013

Keywords:
Ultrasound
Multicomponent reaction (MCR)
NaOH
Pyrimidine/pyridine derivatives

ABSTRACT

Using ultrasound irradiation, two simple one-pot multicomponent methods are described for syntheses of highly functionalized pyrimidine/pyridine derivatives in excellent yields in the presence of NaOH at room temperature. While one route involved aromatic aldehyde, thiourea and acetoacetanilide, the other employed aromatic aldehyde, malononitrile and benzyl mercaptane or EtOH. These approaches afford several advantages over former and contemporary reaction methodologies in terms of operational simplicity, simple work-up procedure, higher yield, short reaction time and environment friendly protocols.

1. Introduction

Water as a solvent offers many practical and economic advantages including low cost, safe handling and environmental compatibility and several organic reactions in aqueous media have been reported [1]. Water as solvent provides a proactive path for the sustainable progress of future science and technologies [2]. Ultrasonically accelerated organic synthesis has received significant attention in recent years [3]. The strategy of ultrasound as an energy source offers major advantages to promote organic reactions in the form of design and development. Benefits further include shorter reaction times and higher yields over conventional methods [4]. When an acoustic pressure wave propagates through a reaction mixture, it facilitates the breakdown of μm sized bubbles in the solution. Sonication of multi-component reaction systems accelerates the reaction by confirming a better contact and increasing the reaction rate [5]. Multicomponent reactions (MCRs) involving domino processes, which combine three or more reactants in a single chemical step can be efficiently accomplished by employing ultrasonic irradiation [6,7]. Assembling of N-heterocycles is one of the most important areas in synthetic organic chemistry. Among them, the synthesis of highly substituted heterocycles (pyrimidine/pyridine) by MCRs has become an attractive approach in modern synthetic chemistry [8]. Considering the enormous scope of functionalized pyrimidines [9] and pyridines [10], the design and development of new methodologies for the syntheses of pyrimidines/pyridines have attracted enormous attention from both synthetic and medicinal chemists [11]. Several methodologies have been reported for the synthesis of pyrimidine/pyridine derivatives [12], however, many of those methods suffer from various limitations. Because of the numerous merits of using ultra sonication and as ultrasound can provide high energy and pressure within seconds due to cavitation [13], the development of new methods for the synthesis of highly functionalized heterocyclic derivatives using this technique has became a prime area of interest. In addition, green chemistry has become the driving force for organic chemists to provide environmentally benign routes for the preparation of organic compounds. Thus, the development of new routes, which lead to these privileged heterocycles in higher yields in shorter reaction time and milder conditions in great demand; and such process using inexpensive eco-sustainable greener solvents, is a challenge. As part of our continuing pursuit in developing new domino reactions for synthesis of heterocyclic compounds [14], in this communication we report a simple, cost-effective, green and expeditious method for synthesis of pyrimidine/pyridine derivatives in higher yields, employing ultrasound as energy source.

2. Materials and methods

2.1. Apparatus and analysis

All chemicals used were reagent grade and were used as received without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C at 400 and 100 MHz (Bruker Avance) instrument, respectively, using TMS as internal standard. Chemical shifts are given in parts per million (ppm). The FT-IR spectroscopy of samples was carried out on a Perkin Elmer. Precisely 100 FT-IR spectrometer in the 400–4000 cm^{-1} region. LCMS mass spectra

* Corresponding author. Tel.: +27 31 260 7325/3090; fax: +27 31 260 3091.
E-mail address: jonnalagaddas@ukzn.ac.za (S.B. Jonnalagadda).

1350-4177/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ultsonch.2013.08.024

were recorded on a MASPEC low resolution mass spectrometer operating at 70 eV. The ultrasonic assisted reactions are carried out in a "Spectralab model UMC 20 Ultrsonic cleaner" with a frequency of 40 kHz and a nominal power 250 W. Melting points are uncorrected and were recorded on a hot stage melting point apparatus Ernst Leitz Wetzlar, Germany. Reactions were monitored and the purity of products was checked out on thin layer chromatography (TLC) on aluminum-backed plates coated with Merck Kieselgel 60 F254 silica gel, visualizing the spots under ultraviolet light and iodine chamber.

2.2. General procedure for the synthesis of pyrimidine derivatives under silent conditions (**4a–f**)

To a solution of freshly distilled benzaldehyde (1.0 mmol), thiourea (1.5 mmol) and acetoacetanilide (1.0 mmol) in water (5 mL) 15 mL of aqueous NaOH (1 equiv.) was added as a catalyst. The reaction mixture was stirred at room temperature (22 °C ± 5) for 6 h. After the starting material was consumed (reaction progress was monitored by TLC), a saturated aqueous NaCl (15 mL) solution was poured into the reaction mixture. The reaction mixture was stirred for 30 min and allowed the solid to settle. Solid deposit was collected by the filtration and was washed with water and dried to give crude product, which was further purified by column chromatography on silica gel (100–200 mesh) eluted with Hexane and ethyl acetate (Hexane/ethyl acetate = 3/2, V/V) to offer pure product.

2.3. General procedure for the synthesis of pyrimidines catalyzed by NaOH in aqueous medium under ultrasound irradiation (**4a–f**)

A 100 mL conical flask was charged with freshly distilled benzaldehyde (1.0 mmol), thiourea (1.5 mmol) and acetoacetanilide (1.0 mmol) in water (5 mL); and 15 mL of aqueous NaOH (1 equiv.) was added to act as catalyst. The reaction flask was put in the ultrasonic bath, where the surface of reactants is slightly lower than the level of the water, and irradiated at room temperature (22 °C ± 5) for the period of time (The reaction was monitored by TLC) as indicated in Table 1. The reaction temperature of ultrasonic bath was controlled manually by addition or removal of small amounts water. After completion of the reaction, saturated aqueous NaCl (15 mL) solution was poured into the reaction mixture. The reaction mixture set on one side for the solid to settle. Solid deposit was collected by the filtration and was washed with water and dried to give crude product, which was further purified by column chromatography on silica gel (100–200 mesh) eluted with Hexane and ethyl acetate (Hexane/ethyl acetate = 3/2, V/V) to offer pure product.

2.3.1. Compound **4a**

Off-white solid: mp 215 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.45 (3H, s), 5.89 (1H, s), 7.20–7.36 (10H, m), 8.42 (1H, s), 8.79 (1H, s), 9.70 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.9, 54.2, 77.9, 119.4 (Ar, 2 carbons), 120.7, 123.8, 126.3 (Ar, 2 carbons), 128.5 (Ar, 2 carbons), 129.6 (Ar, 2 carbons), 130.9, 138.0, 138.9, 166.5, 175.7; IR (KBr, cm^{-1}): 3414, 3182, 3075, 1660, 1598; LCMS of [$C_{18}H_{17}N_3OS$ + Na] (*m/z*): 346 (100%).

2.3.2. Compound **4b**

Off-white solid: mp 230 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.44 (3H, s), 3.71 (3H, s), 5.88 (1H, s), 7.19–7.52 (9H, m), 8.40 (1H, s), 8.80 (1H, s), 9.69 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.8, 54.2, 55.3, 77.8, 119.4, 120.6 (Ar, 2 carbons), 123.9, 128.6 (Ar, 2 carbons), 129.7 (Ar, 2 carbons), 130.9 (Ar, 2 carbons), 131.2, 138.1, 138.9, 166.7, 175.8; IR (KBr, cm^{-1}): 3401, 3189, 3062, 1659, 1586; LCMS of [$C_{19}H_{19}N_3O_2S$ + H$^+$] (*m/z*): 354 (100%).

2.3.3. Compound **4c**

White solid: mp 228 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.45 (3H, s), 5.96 (1H, s), 7.21–7.52 (9H, m), 8.50 (1H, s), 8.83 (1H, s), 9.71 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.1, 54.2, 77.9, 119.5, 120.8 (Ar, 2 carbons), 123.7, 128.6 (Ar, 2 carbons), 129.8 (Ar, 2 carbons), 131.0 (Ar, 2 carbons), 138.0, 138.8, 166.6, 175.7; IR (KBr, cm^{-1}): 3408, 3194, 3067, 1661, 1597; LCMS of [$C_{18}H_{16}BrN_3OS$ + H$^+$] (*m/z*): 403 (100%).

2.3.4. Compound **4d**

White solid: mp 220 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.45 (3H, s), 5.95 (1H, s), 7.21–7.52 (9H, m), 8.47 (1H, s), 8.82 (1H, s), 9.70 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.1, 54.2, 77.8, 119.4, 120.8 (Ar, 2 carbons), 123.5, 128.7 (Ar, 2 carbons), 129.8 (Ar, 2 carbons), 131.0 (Ar, 2 carbons), 137.8, 138.8, 156.3, 166.5, 175.4; IR (KBr, cm^{-1}): 3401, 3190, 3058, 1664, 1594; LCMS of [$C_{18}H_{16}ClN_3OS$ + H$^+$] (*m/z*): 358 (100%).

2.3.5. Compound **4e**

Off-white solid: mp 310 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.43 (3H, s), 5.95 (1H, s), 7.20–7.52 (9H, m), 8.48 (1H, s), 8.83

Table 1
Optimization of reaction conditions of the multi-component reactions.

Entry	Product No.	Base	Amount (equiv.)	Solvent	Conventional		Sonication	
					Time (h)	Yield[a] (%)	Time (h)	Yield[a] (%)
1	**4a**	K_2CO_3	1.0	H_2O	12.0	b	4.0	b
2	**4a**	NaOH	0.5	H_2O	10.0	59.0	4.0	65
3	**4a**	NaOH	1.0	H_2O	6.0	75.0	2.0	90
4	**4a**	NaOH	1.0	CH_2Cl_2	10.0	b	c	c
5	**4a**	NaOH	1.0	DMF	10.0	b	4.0	b
6	**4a**	NaOH	1.0	EtOH	8.0	50.0	4.0	65
7	**7a**	NaOH	0.5	H_2O	8.0	b	4.0	b
8	**7a**	NaOH	1.0	H_2O	8.0	b	4.0	b
9	**7a**	NaOH	1.0	CH_2Cl_2	10.0	b	c	c
10	**7a**	NaOH	0.5	EtOH	8.0	50.0	4.0	70
11	**7a**	NaOH	1.0	EtOH	6.0	65.0	2.0	98
12	**9a**	NaOH	1.5	H_2O	8.0	b	4.0	b
13	**9a**	NaOH	1.0	CH_2Cl_2	10.0	b	c	c
14	**9a**	NaOH	1.0	EtOH	6.0	60.0	2.0	96

[a] Isolated yields.
[b] Products was not found.
[c] Reaction was not performed.