Ultrasonics Sonochemistry 20 (2013) 1194–1202

Contents lists available at SciVerse ScienceDirect

Ultrasonics Sonochemistry

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

Divergent reaction pathways for one-pot, three-component synthesis of novel *4H*-pyrano[3,2-h]quinolines under ultrasound irradiation

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ARTICLE INFO

Article history:
Received 7 December 2012
Received in revised form 19 February 2013
Accepted 16 March 2013
Available online 28 March 2013

Keywords:
Ultrasound irradiation
p-Toluenesulfonic acid
Pyranoquinoline derivatives
β-Ketosulfone
Multicomponent reaction (MCR)

ABSTRACT

The present paper deal with the multi-component condensation of 8-hydroxy quinoline, aromatic aldehydes, and sulfone derivatives catalyzed by *p*-toluenesulfonic acid for the synthesis of a series of *4H*-pyrano[3,2-h]quinoline derivatives in ethanol under ultrasonic irradiations. We provide a series of quinoline derivatives containing sulfone moiety interesting for biological screening tests. The reactions were carried out under both conventional and ultrasonic irradiation conditions. In general, improvement in rates and yields were observed when reactions were carried out under sonication compared with classical silent conditions. Also, also, sonochemical reaction give different reaction pathway other than silent reaction. These remarkable effects appeared in sonicated reactions can be reasonably interpreted in terms of acoustic cavitation phenomenon. Structures of the products were established on analytical and spectral data.

1. Introduction

Quinolines have amazing intrinsic pharmacological and biological activities such as antimalaria, antiflammatory, antiasthmatic, antibacterial and antihypersensitive activities [1]. In addition, quinolines are valuable synthons used for the preparation of nanostructures and polymers that combine enhanced electronic, optoelectronic or non-linear optical properties with excellent mechanical properties [2]. In spite of their importance from pharmacological, industrial and synthetic points of view, relatively few methods for their synthesis of its derivatives have been reported. Although compounds possessing this ring system have wide applications as drugs and pharmaceuticals [3,4]. In addition to, strategically positioned sulfone group in heterocyclic compounds plays an important roles in medicine. Recently, heteroaryl substituents have been attached to the sulfone, for example, pyrrolyl aryl sulfone (PASs) have been reported by Silvestri et al. [5] and Artico et al. [6–8] as a new class of human immunodeficiency virus type 1 (HIV-1) RT inhibitors acting at the non-nucleoside binding site of this enzyme. Therefore, a considerable efforts have been directed towards the preparation and synthetic manipulation of novel heterocyclic compounds contain sulfone moiety [9–12]. Although a variety of methods are used to prepare the heterocyclic compounds contain sulfone moiety, the synthetic access to polysubstituted-polyfunctionalized derivatives remains a serious challenge [13]. Multistep sequences are widespread in the literature, but even in these cases the preparation of some substitution patterns and functional group combinations is particularly difficult.

Multi-component reactions (MCRs) play an important role in combinatorial chemistry because of its ability to synthesize small drug-like molecules with several degrees of structural diversity. MCRs are defined as three or more different starting materials that react to form a product, where most, if not all of the atoms are incorporated in the final product. This reaction tool allows compounds to be synthesized in a few steps and usually in a one-pot operation [14]. Another typical benefit from these reactions is simplified purification, because all of the reagents are incorporated into the final product. In other words the recent introduction of MCRs into field of synthesis has brought interesting features typical of the ideal reaction, such as atom- and step economy, convergence, and exploratory power, together with new avenues in connectivity, leading to the straightforward synthesis of previously unobtainable scaffolds [15].

In the last few years the application of ultrasound in synthetic organic chemistry became more and more interesting "Sonochemistry" is a new trend in organic chemistry, offering a versatile and facile pathway for a large variety of syntheses. Thus, a large number of organic reactions can be carried out under ultrasonic irradiation in high yields, short reaction times and mild conditions [16–23].

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http://dx.doi.org/10.1016/j.ultsonch.2013.03.003

Motivated by the afore-mentioned findings, and in a continuation of our interest, in synthesis of a wide range of heterocyclic systems, for biological screening programme in our laboratory [24–32], and as a part of our growing interest in sonochemistry [33–37]. We describe here an environmentally benign protocol for facile sonochemical synthesis of novel 4*H*-pyrano[3,2-h]quinoline derivatives contains sulfone moiety through MCRs using *p*-toluene sulfonic acid as a catalyst. The structure of the products was established on different analytical and spectroscopic data.

2. Result and discussion

A wide variety of catalysts were scanned in an attempt to prepare 4*H*-pyrano[3,2-h]quinoline derivatives contains sulfone moiety in a multicomponent one-pot fashion, in which the 8-hydroxy quinoline **(1)**, benzaldehyde **(2a)** were allowed to react with 2-(phenylsulfonyl)- acetonitrile **(3)**, in ethanol under ultrasonic irradiation at 70 °C as a model reaction. (Scheme 1, Table 1).

Some catalysts, namely, piperidine, basic alumina, acidic alumina, and *p*-toluene sulphonic acid (*p*-TsOH) were selected. This group of catalysts except piperidine has the advantage low impact in the environment.

To find the specific effect of ultrasound on this reaction, the above mentioned reaction was carried out under the same conditions in the absence of ultrasound irradiation (Table 1).

It is clear from results cited in Table 1 that, under silent method even after 12 h, no reaction occurs in absence of a catalyst. In addition, only Knoevenagal product **4a** was obtained after 2 h under ultrasound irradiation in moderate yield in absence of a catalyst (entry 1). in case of using piperidine, basic alumina and acidic alumina as a catalyst only the Knoevenagel product **4a** was obtained with a trace amount of expected 4*H*-pyrano[3,2-h]quinoline derivative **5a**, under silent condition but under ultrasonic irradiation the Knoevenagel product **4a** was obtained as minor product and the major product is the expected 4*H*-pyrano[3,2-h]quinoline derivative **5a** (Table 1, entries 3 and 4), and the desired product **5a** obtained only as one isolable product with best yield (95%) using *p*-toluene sulphonic acid and good yield (85%) using piperidine under ultrasonic irradiations, Obviously, the Knoevenagel product obtained **4a** is reluctant to undergo Michael addition reaction with 8-hydroxy quinoline **(1)** under silent condition may be need more and more time. Therefore, it was found that the ultrasound irradiations enable this reaction to occur which could not be carried out under silent condition. This may be attributed to the fact that ultrasonic irradiation give the reactants sufficient energy to exceed energy barrier of the reaction and so 4*H*-pyrano[3,2-h]quinoline derivative **5a** formed. This sufficient energy can be reasonably interpreted in terms of the physical phenomenon called acoustic cavitation, that is, formation, growth, and collapse of micrometer-sized bubbles when a pressure wave of enough intensity propagates through a liquid. Acoustic cavitation is also accompanied by mechanical effects [23]. Also, the intensity of cavitations increase depending on type of solvent and frequency used in which we use in the above mentioned reaction ethanol and Cavities are more readily formed when using a solvent with a high vapor pressure low viscosity, and low surface tension [38,18].

Table 1
Optimization of the conditions for the three component reaction.

Entry	Catalyst	Ultrasonic irradiation			Silent condition		
		Time (min.)	Yield (%)		Time (h)	Yield (%)	
			(**4a**)	(**5a**)		(**4a**)	(**5a**)
1	None	120	68	0	12	0	0
2	Piperidine	45	0	85	6	91	Trace
3	Basic alumina	45	8	82	8	88	Trace
4	Acidic alumina	45	14	80	8	85	Trace
5	*p*-TsOH	30	0	95	5	39	56

It is important to mention here that, although using of piperidine as catalyst for the above mentioned reaction give good yield under ultrasonic irradiation but it has some limitation in which not applicable for all aldehyde derivatives (such as 4-flurobenzaldehyde) it give rapidly a product identified as 4-(piperidin-1-yl) benzaldehyde as in Fig. 1 [39]. In addition to its hazardous effect on environment.

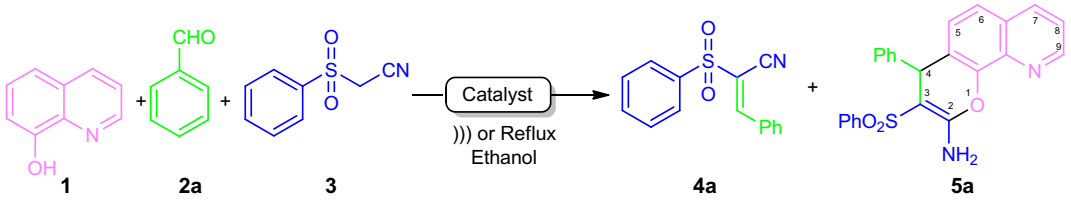
It is noteworthy to mention that we optimize first the reaction conditions for the formation of 4*H*-pyrano[3,2-h]quinoline derivative as in Table 2, to select the appropriate *p*-TsOH amounts necessary to perform these three-components one pot reaction under ultrasound irradiation, different amounts of *p*-TsOH (mol/mol) ratios were tested.

Table 2 represents the effect of *p*-TsOH on the % yield of compound 5a From the results cited in Table 2, it is clear that 0.3 mol equiv of *p*-TsOH furnishes the respective product in a quantitative yield (Table 2, entry 3).

The isolated product **5a** gave satisfactory elemental analyses and spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, MS) consistent with their assigned structure. Their IR spectra of the product showed C=N absorption band at 1621 cm^{-1} and presence of two bands due to sulfone group 1135, 1363 cm^{-1} in addition to two bands due to amino group at 3313, 3422 cm^{-1}. The mass spectra of the isolated product **5a** showed, a peak corresponding to the molecular ion at 414, its ^{1}H NMR spectrum revealed a D_2O exchangeable singlet signal at δ 4.39 due to NH_2 protons, singlet signal at δ 5.10 due to H-4$_{pyran}$ proton in addition to aromatic multiplet and H-8$_{quinoline}$ proton at δ 7.06–7.71, and two doublet signals at 8.30, 8.91 due to H-7$_{quinoline}$ proton and H-9$_{quinoline}$ proton respectively.

To our knowledge, there are no established mechanisms for the formation of 4*H*-pyrano[3,2-h]quinoline utilizing *p*-TsOH; a reasonable possibility for The formation of 4*H*-pyrano[3,2-h]quinoline derivative from MCRs [the reaction of 8-hydroxy quinoline, aldehyde derivatives and 2-(phenylsulfonyl)-acetonitrile **(3)**] is shown in Scheme 2.

The reaction presumably proceeds first as the Knoevenagel reaction occurs in the presence of *p*-TsOH catalyst *via* an initial formation of Knoevenagel product **4a** by the condensation of protonated aldehydes **2a** and sulfone derivatives **3**. Then, Micheal addition of intermediate **4a** with 8-hydroxy quinoline **(1)** followed by cyclization and rearrangement provides desired product **5a**.



Scheme 1. Optimization of the conditions for the three component reaction.