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

Abdullah S. Al-Bogami [a], Tamer S. Saleh [a,b,*], Ehab M. Zayed [a,b]

[a] Chemistry Department, Faculty of Science, King Abdulaziz University, North Jeddah, P.O. Box 80203, Jeddah 21589, Saudi Arabia
[b] Green Chemistry Department, National Research Centre, Dokki, Cairo 12622, Egypt

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].

* Corresponding author. Current address: Chemistry Department, Faculty of Science, King Abdulaziz University-North Jeddah. Permanent address: Green Chemistry Department, National Research Centre, Dokki, Cairo 12622, Egypt. Tel.: +20 01001978724.
E-mail address: tamsaid@yahoo.com (T.S. Saleh).

1350-4177/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
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.

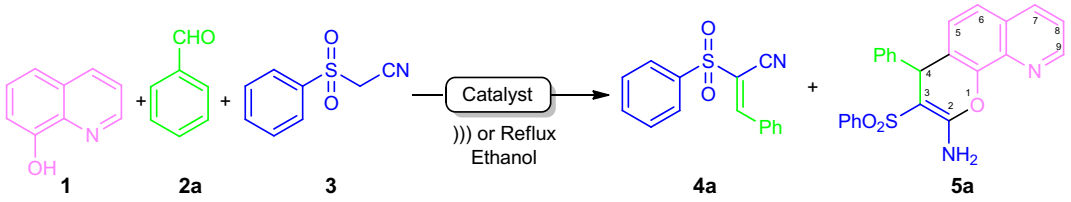
It is noteworthy to mention that we optimize first the reaction conditions for the formation of 4*H*-pyrano[3,2-h]quinoline derivative as in Table 2, to select the appropriate *p*-TsOH amounts necessary to perform these three-components one pot reaction under ultrasound irradiation, different amounts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

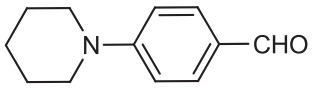


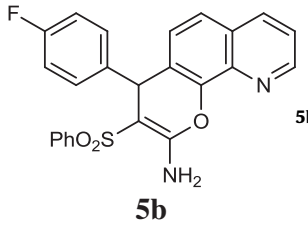
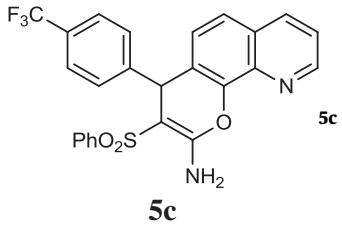
Fig. 1. Structure of 4-(piperidin-1-yl)benzaldehyde.

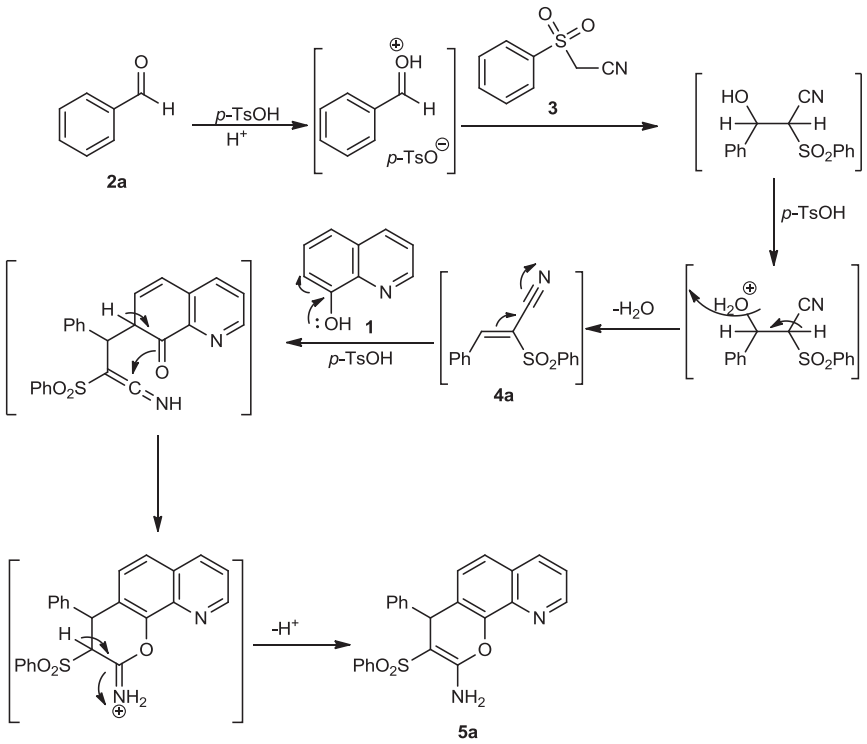
Table 2
Effect of *p*-TsOH on the % yield of compound **5a** under ultrasonic irradiations.

Entry	*p*-TsOH ratio	Solvent	Yield **5a** (%)	Time (min.)
1	0	EtOH	0	90
2	0.1	EtOH	86	45
3	0.2	EtOH	92	30
4	0.3	EtOH	95	30
5	0.4	EtOH	95	30

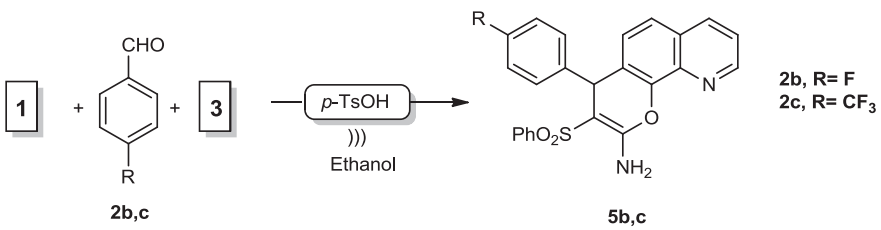
It is noteworthy to mention here that the Micheal addition step of **4a** which could not be fully consumed under adopted reaction condition (*p*-TsOH) in classical silent conditions even after 18 h, but consumed completely under ultrasonic irradiation to afford only one isolable product in excellent yield **5a** confirm the will established theory of effect of ultrasonic on organic reactions specially the previously mentioned about the ability of ultrasonic irradiation to produce the sufficient energy *via* the acoustic cavitation phenomenon.

Table 3
Synthesis of 4*H*-pyrano[3,2-h]quinoline derivatives **5b,c** under ultrasonic irradiation.

Compound	Time (min.)	Yield (%)
 **5b**	30	92
 **5c**	45	95



Scheme 2. Suggested mechanism for synthesis of **5a**.



Scheme 3. *p*-TsOH catalysed synthesis of 4*H*-pyrano[3,2-h]quinoline derivatives **5b,c** under ultrasonic irradiation.

The scope and generality of this protocol was tested by various derivatives of aldehydes **2b,c** as shown in the Scheme 3 under the optimized reaction conditions and corresponding 4*H*-pyrano[3,2-h]quinoline derivatives **5b,c** were obtained in excellent yields (Table 3). The reaction worked-up was very well with all products.

Again, ultrasonic irradiation showed beneficial effect on MCRs reaction in terms of reaction time and percentage yields (92–95%).

The observed increase in rates of reaction can be attributed to the fact that ultrasound plays a dual role in creating higher interfacial area as well as facilitating the process of interfacial transport. [40]

We extended our study to find out the reactivity of β-ketosulfone **6a–c** towards 8-hydroxy quinoline **(1)** and aldehyde derivatives **2a–c** in MCRs fashion using *p*-TsOH as catalyst under both ultrasonic irradiation and silent conditions.

The reaction of 8-hydroxy quinoline **(1)** with the aldehyde derivatives **2a–c** and 1-Aryl-2-(phenylsulfonyl)ethanone **6a–c** in ethanol as solvent under ultrasonic irradiation at 70 °C afforded one product in each case (as evidenced by TLC) (Scheme 4). IR spectra of the latter products revealed absorption bands of C=N function in the region 1590–1623 cm^{-1} and two absorption bands due to sulfone group. Their ^1H NMR spectra exhibited singlet signal in region of 5.35–5.49 due to H-4_{Pyran} in addition to aromatic multiplet and quinoline protons signals in region 6.99–8.92 The latter spectroscopic data of the reaction products and their satisfactory elemental analyses supported the structure 2,4-diaryl-3-(phenylsulfonyl)-4*H*-pyrano[3,2-h]quinoline **7a–i**.

The above reaction was also carried out under silent condition to study the effect of ultrasound; the results of which are given in Table 4.

It was observed that from the results cited in Table 4, the reaction of β-ketosulfone **6a–c** towards 8-hydroxy quinoline **(1)** and aldehyde derivatives **2a–c** in MCRs using *p*-TsOH as catalyst under silent conditions have different behavior than the 2-(phenylsulfonyl)-acetonitrile **(3)**, in which only the isolable product obtained is the desired product **7a–i** as in Scheme 4, also it was observed that the reaction time increased considerably and yield of the products decreased under silent condition. Therefore, ultrasound was found to have beneficial effect on the synthesis of 2,4-diaryl-3-(phenylsulfonyl)-4*H*-pyrano[3,2-h]quinoline derivatives in which decrease time of above reactions from 8 to 13 h in conventional (silent) procedure to less than 1 h, also, a noticeable improvement in yields of reactions under ultrasonic irradiations.

The results obtained in Table 4 led us to assumption the plausible mechanism for the formation of 2,4-diaryl-3-(phenylsulfonyl)-4*H*-pyrano[3,2-h]quinoline derivatives **7a–i** in the presence of *p*-TsOH (Scheme 5). Taking compound **7a** as example the reaction starts with intermolecular condensation between benzaldehyde **2a** and 1-phenyl-2-(phenylsulfonyl)ethanone **6a** to form α,β-unsaturated carbonyl intermediate **8** then *via* an initial Michael addition of the the quinolinyl *C*-7 to the activated double bond in **8** to yield the corresponding acyclic non-isolable intermediates **9** followed by cyclization to afford the final product **7a** (Scheme 5).

Also, this mechanism was supported *via* reaction of equimolar amount of 1,3-diphenyl-2-(phenylsulfonyl)prop-2-en-1-one (Knoevenagl product which obtained from reaction of benzaldehyde **2a** with 1-phenyl-2-(phenylsulfonyl)ethanone **6a** [37]) and 8-hydroxy quinoline **(1)** in ethanol in presence of *p*-TsOH under ultrasonic irradiation the corresponding pure 2,4-diphenyl-3-(phenylsulfonyl)-4H-pyrano[3,2-h]quinoline derivatives (**7a**) has been obtained in a 87% yield (Scheme 5).

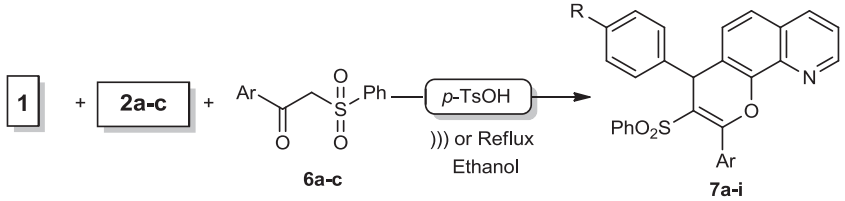
Also, the beneficial effect of ultrasonic irradiation on the synthesis of 2,4-diaryl-3-(phenylsulfonyl)-4*H*-pyrano[3,2-h]quinoline**s** in comparing the silent condition may be attributed to The ultrasonic cavitation induced shear forces and the jets produced near the surface of the vessel and the catalyst may activate the passive 8-hydroxy quinoline through sonolysis of the O–H bond. The reaction between the activated 8-hydroxy quinoline and the α,β-unsaturated carbonyl intermediate **8** may facilitate the formation of the corresponding intermediate **9** under sonic condition, and this intermediate **9** followed by cyclization to give desired product **7a–i** with the removal of a molecule of water as shown in Scheme 5.

Finally, the improvement induced by ultrasound can be attributed to the well established theory of ultrasonic irradiation in which it differs from traditional energy sources (such as heat) in duration, pressure, and energy per molecule. Because of the immense temperatures and pressures and the extraordinary heating rate generated by cavitation bubble collapse, ultrasound provides an unusual mechanism [23,41,42] so reaction time decreases clearly and high yield obtained.

In addition, according to sonochemical reactions classification of Luche [43–45] and the recent fruitful highlights about forcing and controlling chemical reactions with ultrasound [23], we have both types false and true sonochemistry, in which some of the above mentioned reactions are considered true sonochemistry type which occur due to the effects derived directly from the "hot-spots" of cavitational collapse energy, which cause in our case what is called "sonochemical switching" means the products obtained under conventional conditions are different from those obtained under the influence of ultrasound [23,45] and the other mentioned reactions considered false sonochemistry type in which cavitation effect provides the mechanical energy for all subsequent chemical reactions, including bond scission induced by viscous frictional forces and same products produced under both silent and ultrasonic conditions, and the other mentioned reactions.

3. Conclusion

A novel and efficient green protocol three-components condensation reaction of 8-hydroxy quinoline, aldehydes and sulfone derivative has been developed for the synthesis of *4H*-pyrano [3,2-h]quinoline derivatives contains sulfone moiety under ultrasonic irradiation *via* utilization of *p*-TsOH as a catalyst. The simple one-pot nature of the reaction makes it an interesting alternative to other multi-step approaches. In general, improvements in rates and yield of reactions are observed when reactions were carried



Scheme 4. *p*-TsOH catalysed synthesis of 4*H*-pyrano[3,2-h]quinoline derivatives **7a-i** under ultrasonic irradiation.

Table 4
Synthesis of 2,4-diaryl-3-(phenylsulfonyl)-4*H*-pyrano[3,2-h]quinoline **7a–i**.

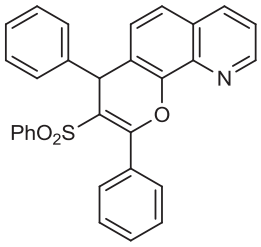
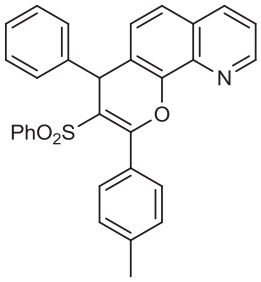
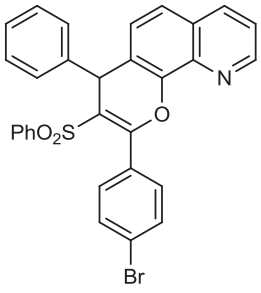
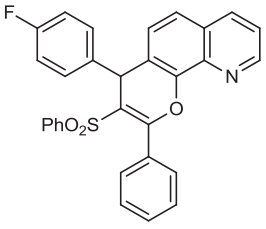
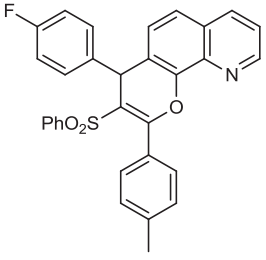
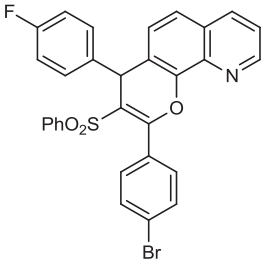
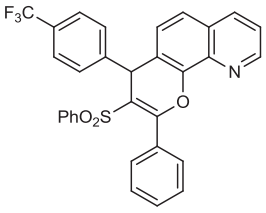
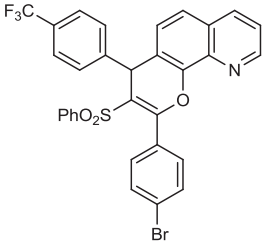
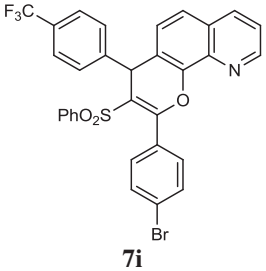
Entry	Product	Ultrasonic Irradiation		Silent condition	
		Time (min.)	Yield (%)	Time (h)	Yield (%)
1	 **7a**	45	91	8	69
2	 **7b**	45	93	8	70
3	 **7c**	45	93	8	69
4	 **7d**	45	90	10	62
5	 **7e**	45	90	10	65

Table 4 (*continued*)

Entry	Product	Ultrasonic Irradiation		Silent condition	
		Time (min.)	Yield (%)	Time (h)	Yield (%)
6	 **7f**	45	91	10	62
7	 **7g**	45	90	10	62
8	 **7h**	45	88	13	58
9	 **7i**	45	85	12	58

out under sonication compared with classical condition, due to the mechanical shocks resulting from the cavitational collapse which could provide what we have seen of chemical consequences. Moreover, the present work evidences an example to that sometimes ultrasound irradiations enable some reactions to occur which could not be carried out under silent condition.

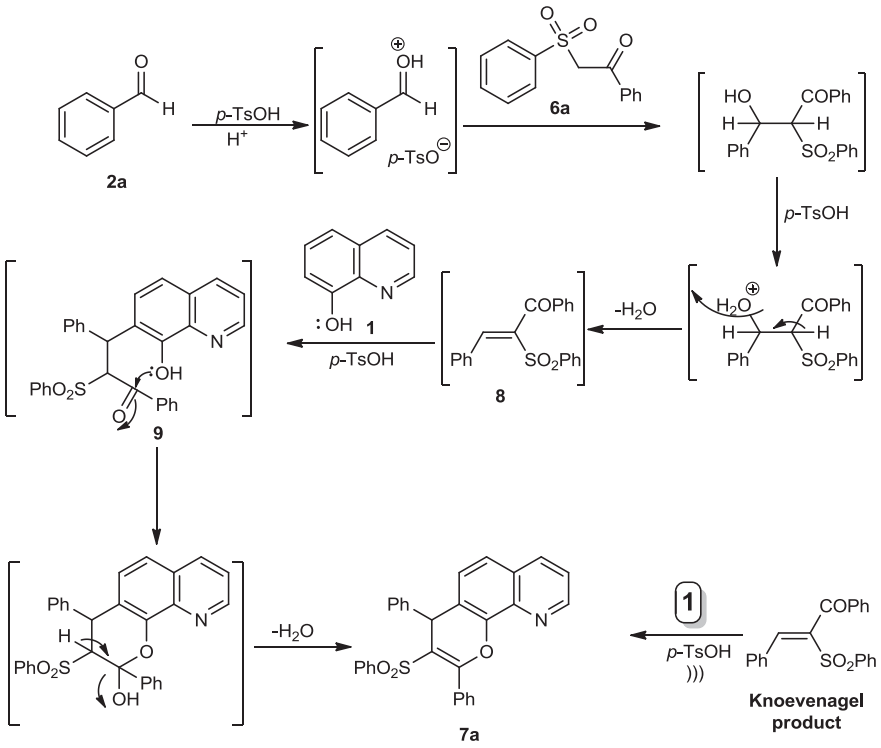
4. Experimental

4.1. General

All organic solvents were purchased from commercial sources and used as received or dried using standard procedures, unless otherwise stated. All chemicals were purchased from Merck, Aldrich or Acros and used without further purification, thin-layer chromatography (TLC) was performed on precoated Merck 60 GF254 silica gel plates with a fluorescent indicator, and detection by means of UV light at 254 and 360 nm. All melting points were measured on a Stuart melting point apparatus and are uncorrected. IR spectra were recorded in IR spectra were recorded in The Smart iTR which is an ultra-high-performance, versatile Attenuated Total Reflectance (ATR) sampling accessory on The Nicolet iS10 FT-IR spectrometer. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in dimethyl sulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on the Thermo Scientific ITQ 1100™ mass spectrometer. Elemental analyses were carried out on Euro*V*ector instrument C, H, N, S analyzer EA3000 Series.

Sonication was performed by Techno-gaz sonicator (with a frequency of 37 kHz and ultrasonic peak max 320 W).

2-(phenylsulfonyl)acetonitrile **(3)** [46] and 1-aryl-2-(phenylsulfonyl) ethanone **6a–c** [47] were prepared according to the reported literature.



Scheme 5. Suggested Mechanism for synthesis of **7a**.

4.2. Typical procedure for synthesis of 4-aryl-3-(phenylsulfonyl)-4H-pyrano[3,2-h]quinolin-2-amine 5a-c

4.2.1. Sonicated reactions

In an Erlenmeyer flask, a mixture of 8-hydroxy quinoline (1 mmol) (**1**), aldehyde (1 mmol) (**2a–c**) and 2-(phenylsulfonyl)acetonitrile (1 mmol) **(3)** in ethanol (20 ml) in the presence of 0.3 (mol/mol) ratio *p*-TsOH as catalyst subjected to ultrasonic irradiations for appropriate time (*cf.* Tables 1 and 3). All The reactions were kept at 70–80 °C (the temperature inside reaction vessel was 70–75 °C and the reaction flask was put in the mid of sonicator bath to achieve effective cavitations). The sonochemical reactions were continued until the starting materials were no longer detectable by TLC. The precipitate formed was collected by filtration then washed with water (2 × 20 ml), dried and purified by recrystallization from chloroform.

The above reaction was studied also by using various catalysts (i) in presence of 4 drops (0.5 ml) of piperidine, this process was performed on the same scale described above and only one product obtained identified as **5a** in 85% yield (*cf.* Table 1) the product was purified as described above. (ii) In presence of 0.5 g of basic alumina or acidic alumina, also, these processes were performed on the same scale described above and the progress of the reaction was monitored by TLC, the same two products were formed in each case (*cf.* Table 1) in different percent yield, After completion of the reaction, the reaction mixture was filtered and the filtrate was concentrated in *vacuo* and the residual solid was taken in ethanol and boiled to separate the first fraction [identified as compound **4a** (soluble in ethanol)] and the second fraction recrystallised from chloroform to afford compound identified as **5a** as pure product). (iii) The reaction was also performed on the same scale described above without any catalyst to afford only one isolable product identified as **4a** in 68% yield recrystalized from ethanol.

4.2.2. Silent reactions

These processes were performed on the same scale described above for sonicated reaction. Here the reactant and catalyst were put in ethanol under reflux for suitable time (*cf.* Table 1) until the starting materials were no longer detectable by TLC. The products were obtained and purified as described above in sonicated reaction.

Physical and spectral data of the compounds **4a** and **5a–c** are listed below:

*4.2.2.1. 3-Phenyl-2-(phenylsulfonyl)acrylonitrile (**4a**) [48].* IR (KBr): 2194 (C≡N), 1129, 1347 (SO_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.11–7.72 (m, 10H, ArH's), 8.16 (s, 1H, =CH); 13C NMR (75.46 MHz, $CDCl_3$) δ: 110.25, 118.43, 125.87, 126.81, 126.82, 127.00, 127.01, 127.58, 128.55, 128.56, 130.11, 132.79, 138.65, 148.72. MS (*m*/*z*): 269 (M^+). (Found: C, 67.16; H, 4.02; N, 5.10; S, 11.83. $C_{15}H_{11}NO_2S$ requires C, 66.89; H, 4.12; N, 5.20; S, 11.90.)

*4.2.2.2. 2-Amino-4-phenyl-3-(phenylsulfonyl)-4H-pyrano[3,2-h]quinoline (**5a**).* Mp = 251 °C; IR (KBr): 3422, 3313 (NH_2), 1135, 1363 (SO_2), 1621 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 4.39 (s, 2H, NH_2, D_2O-exchangeable), 5.10 (s, 1H, pyran-H), 7.06–7.71 (m, 13H, ArH's and H-8), 8.30 (d, *J* = 7.8 Hz, 1H, H-7), 8.91 (dd, *J* = 5.4 and 2.4 Hz, 1H, H-9); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 24.54, 81.01, 114.28, 115.12, 115.98, 121.13, 125.63, 126.54, 126.55, 127.45, 127.46, 128.00, 128.01, 129.12, 131.19, 133.42, 135.48, 140.00, 141.01, 146.85, 150.00, 153.12. MS (*m*/*z*): 414 (M^+). (Found: C, 69.84; H, 4.26; N, 6.60; S, 7.64. $C_{24}H_{18}N_2O_3S$ requires C, 69.55; H, 4.38; N, 6.67; S, 7.74.)

*4.2.2.3. 2-Amino-4-(4-flurophenyl)-3-(phenylsulfonyl)-4H-pyrano[3,2-h] quinoline (**5b**).* Mp = 265 °C; IR (KBr): 3409, 3366 (NH_2), 1143, 1283 (SO_2), 1611 (CN) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 4.22 (s, 2H, NH_2, D_2O-exchangeable), 5.06 (s, 1H, Pyran-H), 7.14–7.82 (m, 12H, ArH's and H-8), 8.28 (d, *J* = 7.8 Hz, 1H, H-7), 8.89 (dd, *J* = 5.7 and 2.4 Hz, 1H, H-9); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 23.99, 83.81, 111.47, 111.48, 116.91, 118.07, 120.00, 122.47, 124.51, 124.52, 126.25, 126.26, 128.98, 128.99, 129.46, 129.47, 130.12, 131.19, 135.48, 140.78, 145.45, 151.80, 154.12,

158.17. MS (*m*/*z*): 432 (M^+). (Found: C, 66.97; H, 3.84; N, 6.37; S, 7.32. $C_{24}H_{17}FN_2O_3S$ requires C, 66.65; H, 3.96; N, 6.48; S, 7.41.)

*4.2.2.4. 2-Amino-3-(phenylsulfonyl)4-(4-(trifluoromethyl)phenyl)-4H-pyrano[3,2-h quinoline (**5c**).* Mp = 281–282 °C; IR (KBr): 3392, 3320 (NH_2), 1128, 1318 (SO_2), 1612 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 4.19 (s, 2H, NH_2, D_2O-exchangeable), 5.26 (s, 1H, Pyran-H), 6.83–8.22 (m, 13H, ArH's, H-8and H-7), 8.79 (dd, J = 5.4 and 2.4 Hz 1H, H-9); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 23.05, 80.25, 115.22, 115.91, 118.31, 120.10, 121.62, 121.63, 125.63, 127.34, 127.35, 127.45, 127.97, 127.98, 128.01, 129.87, 131.17, 133.09, 136.14, 139.45, 142.88, 148.85, 151.04, 155.49. MS (*m*/*z*): 482 (M^+). (Found: C, 62.46; H, 3.48; N, 5.80; S, 658. $C_{25}H_{17}F_3N_2O_3S$ requires C, 62.23; H, 3.55; N, 5.81; S, 6.65.)

4.3. Typical procedure for synthesis of 2,4-diaryl-3-(phenylsulfonyl)-4H-pyrano[3,2-h]quinoline derivatives 7a-i

4.3.1. Sonicated reactions

In an Erlenmeyer flask, a mixture of 8-hydroxy quinoline (1 mmol) **(1)**, aldehyde (1 mmol) **2a–c** 1-aryl-2-(phenylsulfonyl)ethanone (1 mmol) **6a–c**, and *p*-TsOH 0.3 (mol/mol) ratio as catalyst were taken in ethanol (20 ml) and subjected to ultrasonic irradiatios for appropriate time (*cf.* Table 4). All the reactions were kept at 70–80 °C (the temperature inside reaction vessel was 70–75 °C and the reaction flask was put in the mid of sonicator bath to achieve effective cavitations). After completion of the reaction as indicated by TLC (EtOAc/n-hexane, 1:2), the reaction mixture was allowed to cool. The solvent was removed by evaporation and the residue was washed with H_2O (2 × 20 ml). The solid products were purified by recrystallization from chloroform.

4.3.2. Silent reactions

These processes were performed on the same scale described above for sonicated reactions. Here the reactant and catalyst were put in ethanol under reflux for suitable time (*cf.* Table 4) until the starting materials were no longer detectable by TLC. The products were obtained and purified as described above in sonicated reaction.

The synthesized compounds with their physical data are listed below.

*4.3.2.1. 2,4-Diphenyl-3-(phenylsulfonyl)-4H-pyrano[3,2-h]quinoline (**7a**).* Mp = 272 °C; IR (KBr): 1611 (C=N), 1158, 1325 (SO_2) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.02 (s, 1H, pyran-H), 6.87–8.12 (m, 18H, ArH's+H-8), 8.29 (d, J = 7.8 Hz, 1H, H-7), 8.42 (d, J = 4.2 Hz, 1H, H-9); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 24.54, 97.23, 116.35, 116.89, 118.00, 124.56, 125.12, 126.32, 126.33, 127.11, 127.12, 127.58, 127.59, 128.00, 128.56, 128.99, 129.01, 129.58, 131.47, 132.55, 134.25, 139.00, 147.11, 147.19, 152.06. MS (*m*/*z*): 475 (M^+). (Found: C, 76.02; H, 4.34; N, 2.89; S, 6.66. $C_{30}H_{21}NO_3S$ requires C, 75.77; H, 4.45; N, 2.95; S, 6.74.)

*4.3.2.2. 4-Phenyl-3-(phenylsulfonyl)-2-(4-methylphenyl)-4H-pyrano[3,2-h] quinoline (**7b**).* Mp = 284 °C; IR (KBr): 1606 (C=N), 1149, 1299 (SO_2) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.39 (s, 3H, CH_3), 5.19 (s, 1H, pyran-H), 6.92–7.95 (m, 17H, ArH's+H-8), 8.41 (d, J = 7.8 Hz, 1H, H-7), 8.89 (d, J = 4.5 Hz 1H, H-9); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 19.58, 24.98, 99.89, 115.23, 115.98, 116.25, 121.36, 124.58, 126.21, 126.22, 126.69, 127.00, 127.01, 127.58, 127.97, 128.45, 128.46, 128.98, 128.99, 130.14, 132.54, 133.47, 133.98, 140.11, 140.78, 147.58, 151.32. MS (*m*/*z*): 489 (M^+). (Found: C, 76.34; H, 4.64; N, 2.76; S, 6.46. $C_{31}H_{23}NO_3S$ requires C, 76.05; H, 4.74; N, 2.86; S, 6.55.)

*4.3.2.3. 2-(4-Bromophenyl)-4-phenyl-3-(phenylsulfonyl)-4H-pyrano[3,2-h]quinoline (**7c**).* Mp = >300 °C; IR (KBr): 1599 (C = N), 1159, 1318 (SO_2) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.22 (s, 1H, pyran-H), 6.98–7.88 (m, 17H, ArH's+H-8), 8.47 (d, J = 8.2 Hz, 1H, H-7), 8.79 (d, J = 4.2 Hz, 1H, H-9); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 25.66, 98.25, 116.16, 116.98, 117.55, 123.78, 125.12, 126.88, 126.89, 127.87, 127.88, 127.98, 128.09, 128.10, 130.11, 130.61, 132.55, 136.00, 138.11, 141.58, 149.11, 150.02, 151.85. MS (*m*/*z*): 554 (M^+). (Found: C, 65.29; H, 3.57; N, 2.40; S, 5.68. $C_{30}H_{20}BrNO_3S$ requires C, 64.99; H, 3.64; N, 2.53; S, 5.78.)

*4.3.2.4. 4-(4-Fluorophenyl)-2-phenyl-3-(phenylsulfonyl)-4H-pyrano[3,2-h]quinoline (**7d**).* Mp = 290 °C; IR (KBr): 1591 (C=N), 1152, 1233 (SO_2) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.59 (s, 1H, pyran-H), 7.09–7.84 (m, 17H, ArH's+H-8), 8.19 (d, J = 8.2 Hz, 1H, H-7), 8.65 (dd, J = 4.5 and 1.5 Hz, 1H, H-9); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 24.94, 100.02, 116.04, 116.05, 119.54, 119.87, 120.08, 124.58, 125.87, 125.88, 126.14, 126.15, 126.98, 127.11, 127.12, 128.00, 128.01, 128.99, 130.32, 133.89, 134.54, 136.00, 139.11, 145.05, 150.29, 152.33, 159.07. MS (*m*/*z*): 493 (M^+). (Found: C, 73.32; H, 3.96; N, 2.72; S, 6.42. $C_{30}H_{20}FNO_3S$ requires C, 73.01; H, 4.08; N, 2.84; S, 6.50.)

*4.3.2.5. 4-(4-Fluorophenyl)-3-(phenylsulfonyl)-2-(4-methylphenyl)-4H-pyrano[3,2-h]quinoline (**7e**).* Mp = >300 °C; IR (KBr): 1606 (C=N), 1195, 1366 (SO_2) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.45 (s, 3H, CH_3), 5.46 (s, 1H, pyran-H), 6.89–7.88 (m, 16H, ArH's+H-8), 8.52 (d, J = 8.2 Hz, 1H, H-7), 8.79 (dd, J = 4.5 and 1.8 Hz, 1H, H-9); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 21.26, 25.36, 99.63, 115.42, 115.43, 119.10, 119.54, 120.03, 125.36, 125.89, 125.98, 125.99, 126.80, 126.81, 127.00, 127.12, 127.13, 128.00, 128.01, 128.19, 128.20, 130.02, 131.89, 135.65, 138.11, 147.08, 149.14, 158.00. MS (*m*/*z*): 507 (M^+). (Found: C, 73.58; H, 4.32; N, 2.68; S, 6.23. $C_{31}H_{22}FNO_3S$ requires C, 73.36; H, 4.37; N, 2.76; S, 6.32.)

*4.3.2.6. 2-(4-Bromophenyl)-4-(4-fluorophenyl)-3-(phenylsulfonyl)-4H-pyrano[3,2-h]quinoline (**7f**).* Mp = 292 °C; IR (KBr): 1606 (C=N), 1199, 1328 (SO_2) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.09 (s, 1H, pyran-H), 6.95–7.83 (m, 16H, ArH's+H-8), 8.25 (d, 1H, J = 8.40 Hz, H-7), 8.71 (d, J = 4.2 Hz 1H, H-9); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 26.11, 98.94, 116.01, 116.02, 118.11, 118.59, 118.97, 125.47, 125.89, 125.90, 126.08, 126.97, 126.98, 127.00, 130.12, 130.13, 131.54, 132.33, 135.88, 135.96, 138.11, 148.32, 148.89, 150.01, 160.31. MS (*m*/*z*): 572 (M^+). (Found: C, 63.22; H, 3.21; N, 2.36; S, 5.55. $C_{30}H_{19}BrFNO_3S$ requires C, 62.94; H, 3.35; N, 2.45; S, 5.60.)

*4.3.2.7. 2-Phenyl-3-(phenylsulfonyl)-4-(4-(trifluoromethyl)phenyl)-4H-pyrano[3,2-h]quinoline (**7g**).* Mp = >300 °C; IR (KBr): 1621 (C=N), 1149, 1305 (SO_2) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.19 (s, 1H, pyran-H), 7.06–7.84 (m, 17H, ArH's+H-8), 8.43 (d, J = 7.8 Hz, 1H, H-7), 8.79 (dd, J = 4.5 and 1.8 Hz 1H, H-9); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 25.98, 99.58, 118.16, 118.89, 123.55, 124.56, 124.57, 126.32, 126.98, 126.99, 127.55, 127.56, 128.00, 128.59, 128.60, 129.11, 129.12, 129.88, 129.89, 131.54, 132.60, 133.05, 135.69, 140.11, 143.12, 148.10, 148.98, 152.09. MS (*m*/*z*): 543 (M^+). (Found: C, 68.76; H, 3.60; N, 2.49; S, 5.84. $C_{31}H_{20}F_3NO_3S$ requires C, 68.50; H, 3.71; N, 2.58; S, 5.90.)

4.3.2.8. 3-(Phenylsulfonyl)-2-(4-methylphenyl)-4-(4-(trifluoromethyl) phenyl)-4H-pyrano[3,2-h]quinoline (7 h). Mp = >300 °C; IR (KBr): 1616 (C=N), 1159, 1298 (SO_2) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.21 (s, 3H, CH_3), 5.22 (s, 1H, pyran-H), 7.13–7.91 (m, 16H, ArH's+H-8), 8.19 (d, J = 8.2 Hz, 1H, H-7), 8.59 (dd, J = 4.5 and 1.5 Hz, 1H, H-9); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 22.12, 25.65, 98.29, 118.54, 118.78, 118.99, 123.45, 124.11, 124.12, 125.00,

125.65, 125.66, 125.85, 126.01, 126.02, 127.02, 127.03, 127.41, 127.50, 127.51, 128.00, 128.01, 131.20, 131.92, 133.40, 135.66, 139.11, 140.01, 148.23, 148.85, 152.00. MS (*m*/*z*): 557 (M^+). (Found: C, 69.22; H, 3.84; N, 2.43; S, 5.68. $C_{32}H_{22}F_3NO_3S$ requires C, 68.93; H, 3.98; N, 2.51; S, 5.75.)

4.3.2.9. 2-(4-Bromophenyl)-3-(phenylsulfonyl)-4-(4-(trifluoromethyl) phenyl)-4H-pyrano[3,2-h]quinoline(7i). Mp = >300 °C; IR (KBr): 1614 (C=N), 1149, 1284 (SO_2) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.50 (s, 1H, pyran-H), 7.20–8.01 (m, 16H, ArH's+H-8), 8.25 (d, *J* = 7.8 Hz, 1H, H-7), 8.63 (dd, *J* = 4.2 and 1.5 Hz, 1H, H-9); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 25.95, 99.13, 119.15, 119.89, 120.11, 122.36, 123.15, 125.44, 126.45, 126.46, 127.11, 127.56, 127.57, 128.11, 128.12, 128.98, 129.14, 129.15, 130.00, 130.01, 131.64, 132.14, 136.21, 138.79, 141.08, 149.17, 149.82, 152.34. MS (*m*/*z*): 622 (M^+). (Found: C, 60.15; H, 2.96; N, 2.14; S, 5.05. $C_{31}H_{19}BrF_3NO_3S$ requires C, 59.82; H, 3.08; N, 2.25; S, 5.15.)

Acknowldgements

This work was funded by the Deanship of Scientific Research (DSR), King Abdulaziz University, Jeddah, under Grant No. (15-965-D1432). The authors, therefore, acknowledge with thanks DSR technical and financial support.

References

[1] G. Jegou, S.A. Janekhe, Macromolecule 34 (2001) 7926.
[2] B. Jiang, Y.G. Si, J. Org. Chem. 67 (2002) 9449.
[3] W. Peters, W.H.G. Richards (Eds.), Antimalarial Drugs II, Springer Verlag, Berlin Heidelberg, New York, Tokyo, 1984.
[4] R.A. Corral, O.O. Orazi, Tetrahedron Lett. 7 (1967) 583.
[5] R. Silvestri, M. Artico, G. La Regina, G. De Martino, M. La Colla, R. Loddo, P. La Colla, Il Farmaco 59 (2004) 201.
[6] M. Artico, R. Silvestri, G. Stefancich, S. Massa, E. Pagnozzi, D. Musiu, F. Scintu, E. Pinna, E. Tinti, P. La Colla, Arch. Pharm. (Weinheim) 328 (1995) 223.
[7] M. Artico, R. Silvestri, S. Massa, A.G. Loi, S. Corrias, G. Piras, P. LaColla, J. Med. Chem. 39 (1996) 522.
[8] M. Artico, R. Silvestri, E. Pagnozzi, B. Bruno, E. Novellino, G. Greco, S. Massa, A. Ettorre, A.G. Loi, F. Scintu, P. La Colla, J. Med. Chem. 43 (2000) 1886.
[9] Tamer S. Saleh, N.M. Abd-El-Rahman, Ultrason. Sonochem. 16 (2009) 237.
[10] Mohamed.R. Shaaban, Tamer.S. Saleh, Abdelrahman.S. Mayhoub, Ahmed Mansour, Ahmad M. Farag, Bioorg. Med. Chem. 16 (2008) 6344.
[11] A.A. El-Kateb, N.M. Abd El-Rahman, T.S. Saleh, I.F. Zeid, M.F. Mady, Life Sci. J. 9 (2012) 711.
[12] Mohamed R. Shaaban, Tamer S. Saleh, Abdelrahman S. Mayhoub, Ahmad M. Farag, Eur. J. Med. Chem. 46 (2011) 3960.
[13] L.D. Larsen, D. Cai, Quinolines, Six-Membered Hetarenes with One Nitrogen or Phosphorus Atom, in: D. Black (Ed.), Science of Synthesis, Vol. 15, Georg Thieme Verlag, Stuttgart, Germany, 2005, pp. 551–660.
[14] A. Strecker, Ann. Chem. Pharm. 75 (1850) 27.
[15] J. Zhu, H. Bienaymé (Eds.), Multicomponent Reactions, Wiley- VCH, Weinheim, Germany, 2005.
[16] J.S. Wilkes, Green Chem. 4 (2002) 73.
[17] G. Cravotto, V.V. Fokin, D. Garella, A. Binello, L. Boffa, A. Barge, J. Comb. Chem. 12 (2010) 13.
[18] G. Cravotto, P. Cintas, Chem. Soc. Rev. 35 (2006) 180.
[19] L. Pizzuti, P.L.G. Martins, B.A. Ribeiro, F.H. Quina, E. Pinto, A.F.C. Flores, D. Venzke, C.M.P. Pereira, Ultrason. Sonochem. 17 (2010) 34.
[20] B.S. Singh, H.R. Lobo, D.V. Pinjari, K.J. Jarag, A.B. Pandit, G.S. Shankarling Ultrason, Sonochemistry 20 (2013) 633.
[21] K.J. Jarag, D.V. Pinjari, A.B. Pandit, G.S. Shankarling Ultrason, Sonochemistry 18 (2011) 617.
[22] T.J. Mason, Ultrasonics 30 (1992) 192.
[23] G. Cravotto, P. Cintas, Angew. Chem., Int. Ed. 46 (2007) 5476.
[24] M.R. Shaaban, T.S. Saleh, F.H. Osman, A.M. Farag, J. Heterocycl. Chem. 44 (2007) 177.
[25] M.R. Shaaban, T.S. Saleh, A.M. Farag, Heterocycles 78 (2009) 151.
[26] M.R. Shaaban, T.S. Saleh, A.M. Farag, Heterocycles 78 (2009) 699.
[27] H.A. Abdel-Aziz, T.S. Saleh, H.S.A. El-Zahabi, Arch. Pharm. 343 (2010) 24.
[28] M. Mokhtar, T.S. Saleh, S.N. Basahel, J. Mol. Catal. A: Chem. 353–354 (2012) 122.
[29] A.S. Albogami, Asian J. Chem. 23 (2011) 23.
[30] A.S. Albogami, A.M. Almajid, M.A. Al-Saad, A.M. Mosa, S.A. Almazroa, H.Z. Alkhathlan, Molecules 14 (2009) 2147.
[31] A.S. Albogami, Synth. Commun. 41 (2011) 2952.
[32] A.S. Albogami, U. Karama, A.A. Mousa, V. Khan, S.A. Al-mazroa, H.Z. Alkhathlan, Orient. J. Chem. 28 (2012) 619.
[33] N.M. Abd El-Rahman, T.S. Saleh, M.F. Mady, Ultrason. Sonochem. 16 (2009) 70.
[34] T.S. Saleh, N.M. Abd El-Rahman, A.A. Elkateb, N.O. Shaker, N.A. Mahmoud, S.A. Gabal, Ultrason. Sonochem. 19 (2012) 491.
[35] N. S. Ahmed, T. S. Saleh, E. H. El-Mossalamy, Current organic chemistry, in press..
[36] M. Mokhtar, T.S. Saleh, N.S. Ahmed, S.A. Al-Thabaiti, R.A. Al-Shareef, Ultrason. Sonochem. 18 (2010) 172.
[37] T.S. Saleh, T.M.A. Eldebss, H.M. Albishri, Ultrason. Sonochem. 19 (2012) 49.
[38] J. Lindley, T.J. Mason, Chem. Soc. Rev. 16 (1987) 275.
[39] M. Meciarova, S. Toma, P. Magdolen, Ultrason. Sonochem. 10 (2003) 265.
[40] P.R. Gogate, R.K. Tayal, A.B. Pandit, Curr. Sci. 91 (2006) 35.
[41] A. Loupy, J.L. Luche, Sonochemistry in biphasic system, in: J.-L. Luche (Ed.), Synthetic Organic Sonochemistry, Plenum Press, 1998, pp. 107–165.
[42] K.S. Suslick, Science 247 (1990) 1439.
[43] J.-L. Luche, Ultrason. Sonochem. 1 (1994) S111.
[44] N. Cabello, P. Cintas, J.-L. Luche, Ultrason. Sonochem. 10 (2003) 25.
[45] J. Berlan, T.J. Mason, Dosimetry for power ultrasound and sonochemistry, in: T.J. Mason (Ed.), Advances in Sonochemistry, vol. 4, JAI Press, 1996, pp. 54–55.
[46] M.R. Shabaan, Heterocycles 75 (2008) 3005.
[47] M. Takahashi, T. Mamiya, M. Wakao, J. Heterocycl. Chem. 23 (1986) 77.
[48] F. Fringuelli, G. Pani, O. Piennatti, F. Pizza, Tetrahedron 30 (1994) 11499.