Tetrahedron 67 (2011) 2870–2877

Contents lists available at ScienceDirect

Tetrahedron

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

Synthesis of *C*3-nitroalkylated-4-hydroxycoumarin and hydroxyiminodihydrofuroquinolinone derivatives via the Michael addition of cyclic 1,3-dicarbonyl compounds to β-nitrostyrenes

Deepak Kumar Barange, Veerababurao Kavala, Chun-Wei Kuo, Po-Min Lei, Ching-Fa Yao *

Department of Chemistry, National Taiwan Normal University, 88, Sec. 4, Tingchow Road, Taipei 116, Taiwan, ROC

ARTICLE INFO

Article history:
Received 4 November 2010
Received in revised form 28 January 2011
Accepted 22 February 2011
Available online 26 February 2011

ABSTRACT

Herein, we describe a practical and efficient method for the *C*3-alkylation of 4-hydroxycoumarin by sonication under 'on water' conditions and mild temperatures using various substituted β-nitrostyrenes. In addition, we report on the development of a convenient process for the regioselective synthesis of angular hydroxyiminodihydrofuroquinolinone catalyzed by base. 4-Hydroxycoumarin and 4-hydroxy-1-methylquinolin-2(1*H*)-one reacted smoothly with various nitroolefins to furnish *C*3-nitroalkylated hydroxycoumarin derivatives (by sonication and 'on water' conditions) and hydroxyiminodihydrofuroquinolinone derivatives (ambient condition) as a mixture of *Z* (minor) and *E* (major) isomers, respectively. The mild reaction conditions employed, ease of isolation of the products and excellent yields constitute important features of the methodology.

1. Introduction

Ultrasound irradiation is commonly used in both industry and academia owing to the green value of harmless acoustic waves. Sonochemistry[1,2] has several advantages in terms of waste reduction, energy savings and can avoid the use of high reaction temperatures. Organic reactions in aqueous media or 'on water'[3,4] have attracted considerable recent interest, primarily because of environmental and safety issues. The use of water as a solvent in sonochemistry is good combination from the point of view of green chemistry. Therefore, to develop a green protocol using 'on water' conditions in conjunction with sonication condition would be highly desirable.

Coumarin[5] and furoquinoline[6] scaffolds are commonly found in diverse natural products, biologically active compounds and pharmaceuticals. Among the various coumarin derivatives, 3-substituted-4-hydroxycoumarin has significant biological properties, which include anti-HIV, anticancer, antibiotic, antiviral and anticoagulants properties.[7] Warfarin[7f] **1** and coumatetralyl **2** are used for pesticides, specifically as a rodenticide and an anticoagulant.

Warfarin **1** and *C*3-nitroalkylated 4-hydroxycoumarin **5** have some resemblance in terms of functional group arrangement. On examining the structure of Warfarin and *C*3-nitroalkylated 4-hydroxycoumarin **5**, it is clear that both possess the similar basic core unit of 4-hydroxycoumarin (Fig. 2). The only distinction between these two structures is that the functionalities at *C*3 are different. Warfarin is an anticoagulant, which may be due to the presence of coumarin and a ketone group, whereas *C*3-nitroalkylated coumarin also contains a coumarin unit with an aliphatic nitro group at the *C*3 position, which could be transformed into a biologically active compound.

On the other hand, furoquinoline derivatives are an important class of compounds, because they belong to the known family of furoquinoline alkaloids, which possess a wide array of biological properties.[8] Among the linear and angular furoquinolinones, angular furoquinolinones[8a,9] (Fig. 1, structure **3** and **4**) are of interest, in terms of their synthetic and biological utilities.

The Michael addition with nitroalkenes is an important C–C bond forming reaction, which provides easy access to synthetically important nitroalkanes. During the last decade, our group developed several methodologies for the Michael addition of nitroalkenes[10] to various Michael acceptors. We recently reported that the reaction of nitroalkenes with cyclic 1,3-diketones **6** produced stereoisomeric hydroxyiminodihydrobenzofurans **7** in the presence of silica gel in methanol[11a] under microwave irradiation at 60 °C and the use of 2-hydroxynaphthoquinone **8** resulted in the generation of the Michael adduct **9** under 'on water' conditions (Scheme 1).[11b] These results encouraged us to examine the reaction of nitroalkenes with other 1,3-diketones, such as 4-hydroxycoumarin and 4-hydroxy-1-methylquinolin-2(1*H*)-one. There are several methods available for the synthesis of *C*3-alkylated/substituted 4-hydroxycoumarin.[12,13] However, to our knowledge, there is no direct method

* Corresponding author. Tel.: +886 2 29309092; fax: +886 2 29324249; e-mail address: cheyaocf@ntnu.edu.tw (C.-F. Yao).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.02.062

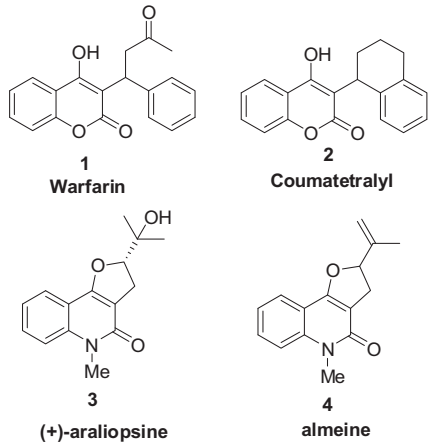


Fig. 1. Biologically active coumarin and angular furoquinolinone derivatives.

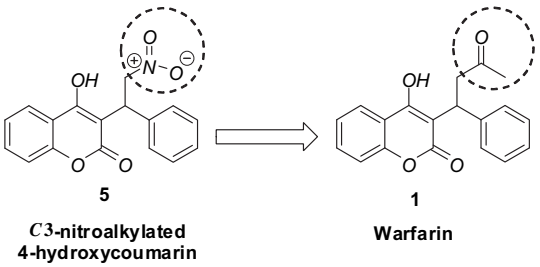
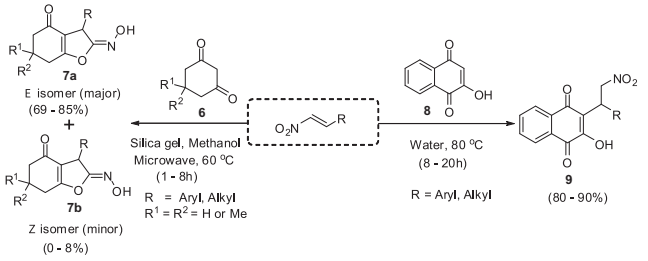


Fig. 2. Comparison between warfarin **1** and *C*3-nitroalkylated 4-hydroxycoumarin **5**.

available for the *C*3-alkylation of 4-hydroxycoumarin with nitroalkenes. Similarly, the synthesis of linear and angular furoquinolinone derivatives can be achieved via a number of methods.[8a,9,14] Saito et al. reported on the base catalyzed synthesis of benzofurans, but they were not able to isolate the cyclic oxime intermediate.[15] A general method for the synthesis of angular hydroxyiminodihydrofuroquinolinone has not been reported to date. Hence, in a continuation of efforts to develop green, efficient and catalyst-free methodologies[16] using nitroalkenes, we wish to report herein on a study of the reactions of nitroalkenes with 4-hydroxycoumarin and 4-hydroxy-1-methylquinolin-2(1*H*)-one under different conditions.



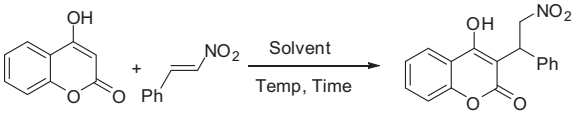
Scheme 1. Our previous synthetic approaches using nitroalkenes with cyclic 1,3-dicarbonyl compounds.

2. Results and discussion

In order to initially assess the reactivity of 1,3-dicarbonyl compounds, we examined the reaction of 4-hydroxycoumarin **10** (1 equiv) and nitrostyrene **11a** (1.2 equiv) at 30 °C using Et_3N as a basic catalyst in methanol (Table 1, entry 1). Unfortunately, no products were obtained. In the next experiment, we used 'on water' conditions at 30 °C, which was also resulted in no product (entry 2).

When the reaction temperature was increased to 80 °C, we were delighted to obtain the Michael adduct **12a** in 40% yield (entry 3).

Table 1
Optimization of reaction condition for *C*3-alkylation of 4-hydroxycoumarin



Entry	Solvent	Temp (°C)	Time (h)	Yield[a,b] (%)
1[c]	Methanol	30	12	n.d.
2	Water	30	12	n.d.
3	Water	80	12	40
4[d]	Water	30	4	95

n.d.=not detected.
[a] All the reactions were carried out using **10** (1.0 equiv) and **11a** (1.2 equiv) on 1.0 mmol scale.
[b] Yields were determined from crude ^1H NMR spectrum using toluene as an internal standard.
[c] Et_3N used as a base (5 mol %).
[d] Sonication condition.

However, the best yield was obtained, when the reaction was performed under 'on water' conditions using sonication and these conditions were chosen for further study (entry 4). The structure of **12a** was confirmed by ^1H, ^{13}C NMR and its Mass spectrum, and was further supported by X-ray crystallographic analysis (Fig. 3).

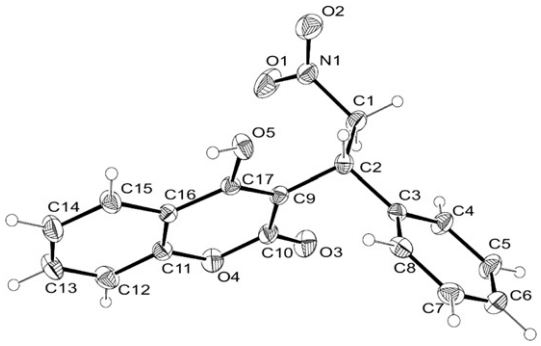
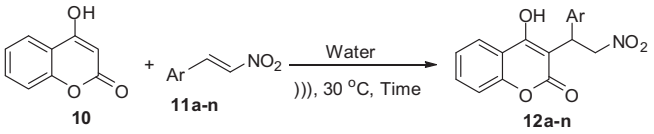


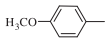
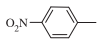
Fig. 3. X-ray crystal structure of **12a** (ORTEP diagram).[18]

To explore the scope and limitations of this methodology, we examined the reaction of 4-hydroxycoumarin **10** with various nitroalkenes **11a**–**n** under the optimized reaction conditions and the results are summarized in Table 2.

As indicated, the Michael addition of β-nitrostyrenes with 4-hydroxycoumarins was efficient in all the cases affording the corresponding *C*3-nitroalkylated-4-hydroxycoumarin derivatives **12a**–**n** in excellent yields (83–94%). Substituents, such as methyl (entry 2), methoxy (entries 3–5), chloro, fluoro, trifluoromethyl and nitro groups (entries 6–11) on the benzene ring of nitroalkenes were well tolerated under the present reaction conditions. The *C*-alkylation of 4-hydroxycoumarin was directed by electronic factors associated with the β-nitrostyrenes. The reaction time varied according to the nature of the substituent on the β-nitrostyrene. For example, the conjugate addition of 4-hydroxycoumarin to a β-nitrostyrene containing electron-donating groups (OCH_3 and CH_3) required a longer period of time for completion of the reaction (entries 2–5). While electron-withdrawing groups (Cl, F, CF_3, NO_2) required relatively short reaction time (entries 6–11). 4-Substituted nitroalkenes afforded good yields and required less time compared to 2-substituted nitroalkenes. Furthermore acid sensitive substituents, such as furan and thiophene groups survived under the present reaction conditions, affording excellent yields (entries 12 and 13). Interestingly, these reaction conditions were equally efficient for the sterically hindered (*E*)-2-(2-nitrovinyl) naphthalene

Table 2
Synthesis of 3-substituted 4-hydroxycoumarin derivatives

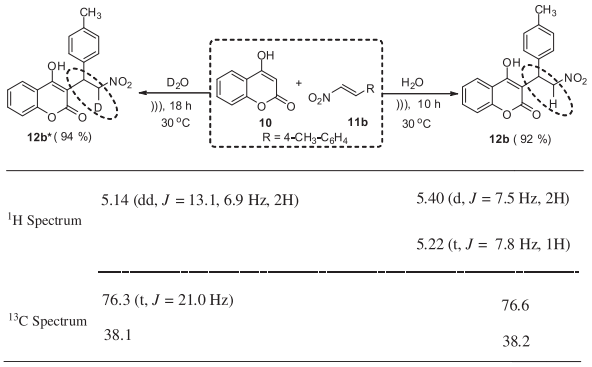


Entry	Ar	Product	Time (h)	Yield[a,b] (%)
1		**12a**	6	90
2		**12b**	10	92
3		**12c**	14	83
4		**12d**	12	87
5		**12e**	11	94
6		**12f**	10	84
7		**12g**	9	85
8		**12h**	8	94
9		**12i**	8	91
10		**12j**	9	94
11		**12k**	10	96
12		**12l**	14	85
13		**12m**	14	88
14		**12n**	16	85

[a] All reactions were carried out using **10** (1.0 equiv) and **11** (1.2 equiv) on a 2.0 mmol scale under sonication 'on water' conditions.
[b] Isolated yields.

derivative, affording the corresponding Michael adduct in good yield (entry 14). All of the products obtained were characterized by ^{1}H NMR, ^{13}C NMR, Mass and IR spectroscopic techniques.

We assumed that the Michael addition of nitrostyrenes with 4-hydroxycoumarin would proceed via the same mechanistic pathway as was described for the reaction of 2-hydroxynaphthoquinone with nitroalkenes.[11b] In order to confirm the mechanism we examined the Michael addition of 4-hydroxycoumarin **10** with the β-nitrostyrene **11b** in D_2O under sonication using the optimized conditions. This reaction afforded a 94% yield of **12b*** as a deuterated product. A comparison of the ^{1}H and ^{13}C NMR spectra of the deuterated and non deuterated compounds, one doublet of doublet in ^{1}H NMR spectrum at 5.14 (in δ ppm) appear, which is due to the presence of a deuterium atom at the 2-position. Whereas, in the case of the non deuterated compound one doublet and one triplet appeared at 5.40 and 5.22 (in δ ppm), respectively. In the ^{13}C spectrum of the deuterated compound one triplet was observed at 76.3 (in δ ppm) while, in the case of the non deuterated compound, only one singlet was observed. A comparison of ^{1}H NMR and ^{13}C NMR spectra of deuterated product **12b*** and normal product **12b** can be seen in Scheme 2, which indicates that the origin of the proton is from water.



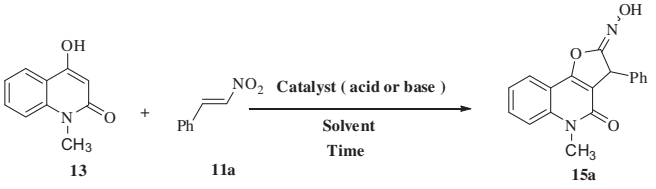
Scheme 2. Reaction of 4-hydroxycoumarin and (*E*)-1-methyl-4-(2-nitrovinyl) benzene in D_2O/H_2O under sonication at 30 °C.

The D_2O experiment supports the conclusion that this reaction follows the mechanism consistent with that proposed in our previously reported study.[11b]

Encouraged by the present results, we replaced the 4-hydroxycoumarin unit with an *N*-methyl-4-hydroxyquinolinone moiety, in order to evaluate the reactivity of other 1,3-dicarbonyl compounds. We initially carried out the reaction of 4-hydroxy-1-methylquinolin-2(1*H*)-one **13** with (*E*)-(2-nitrovinyl)benzene **11a** under sonication 'on water' conditions. As expected, we were unable to isolate the Michael adduct from this reaction. The Michael adduct underwent cyclization under sonication 'on water' conditions to afford the *Z*:*E* isomer of hydroxyiminodihydrofuroquinolinone in a ratio of 1:1 with 40% of yield (Table 3, entry 1).

We further proceeded to optimize the reaction to attain suitable conditions using the reaction of (*E*)-(2-nitrovinyl) benzene **11a** and 4-hydroxy-*N*-methylquinolinone **13** as a model.

Table 3
Optimization of reaction conditions for the synthesis of hydroxyiminodihydroquinolinone derivatives



Entry	Solvents	Acid/Base	Temp (°C)	Time (h)	Yields[a,e] (%)	Selectivity[c] (*Z*:*E*)
1[b]	Water	—	30	12	30	1: 1
2	Water	—	80	12	10	1: 1
3[d]	MeOH	Et_3N	30	1	80	1: 9
4[d]	MeOH	K_2CO_3	30	2	78	1: 9
5[f]	**MeOH**	**DIPEA**	**30**	**1**	**92**	**1: 40**
6[d]	MeOH	DABCO	30	1	80	1: 4
7[d]	MeOH	Silica gel	30	2	5	1: 1
8[d]	MeOH	TFA	30	12	n.d.	n.d.
9[d]	MeOH	PTSA	30	12	n.d.	n.d.
10[d]	MeOH	NH_2SO_3H	30	12	n.d.	n.d.

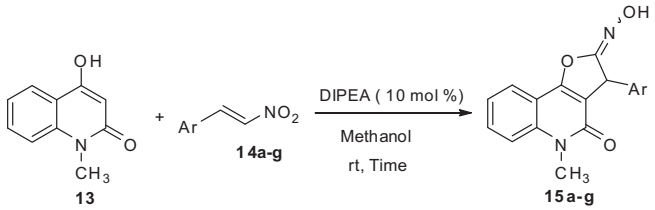
n.d.=not detected.
[a] All the reaction were carried out by using **13** (1.0 equiv) and **11a** (1.2 equiv) on 1.0 mmol scale.
[b] Sonication condition.
[c] Calculated based on crude ^{1}H NMR.
[d] 20 mol % of acid or base used.
[e] Based on crude ^{1}H NMR yield using toluene as an internal standard.
[f] 10 mol % of DIPEA used.

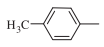
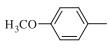
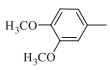
When the reaction was performed in water at 80 °C, only 10% of the product was obtained in 12 h (Table 3, Entry 2) with a 1:1 selectivity of *Z*:*E* isomers. When we next changed the solvent from water to methanol and the reaction was performed at 30 °C using

Et_3N/K_2CO_3, a substantial improvement in the yield and selectivity (1:9) of *Z*:*E* isomers (entries 3 and 4) was observed. The product yield was drastically increased to 92%, when DIPEA (*N*,*N*-diisopropylethylamine, Hunig's Base) was used, with excellent selectivity (1:40) of *Z*:*E* isomers (entry 5). No significant improvement was observed when DABCO was used. Using silica gel only 5% of product was obtained with poor selectivity of *Z*:*E* isomers (1:1). Other acid catalyst, such as TFA, PTSA and NH_2SO_3H were ineffective for this conversion.

After having established the optimized reaction conditions for the formation of hydroxyiminodihydrofuroquinolinones, we explored the generality and scope of this cyclization process. Thus, 4-hydroxy-*N*-methylquinolinone **13** was reacted with a variety of nitroalkenes **14** under the optimized conditions and the results are summarized in Table 4. As can be seen from Table 4 excellent yields (82–92%) of the desired hydroxyiminodihydrofuroquinolinone **15** were obtained.

Table 4
Synthesis of angular hydroxyiminodihydrofuroquinolinone derivatives



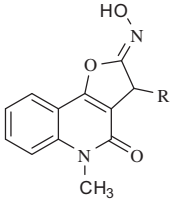
Entry	Ar	Product	Time (h)	Yield[a,b] (%)	*Z*:*E* Selectivity[d] (%)
1		**15a**	1	89	1 : 40
2		**15b**	1	88	1 : 40
3		**15c**	2	83	1 : 40
4		**15d**	2	87	1 : 40
5[c]		**15e**	0.5	82	1 : 9
6[c]		**15f**	2	84	1 : 9
7[c]		**15g**	3	85	1 : 9

[a] All reactions were carried out by using **13** (1.0 equiv) and **14** (1.2 equiv) on 1.0 mmol scale.
[b] Isolated yields.
[c] Two isomers were inseparable.
[d] *Z*/*E* selectivity was estimated by crude ^{1}H NMR determination.

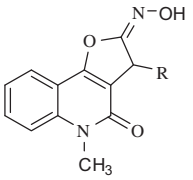
As indicted in Table 4, all of the nitroalkenes tested reacted smoothly with 4-hydroxy-*N*-methylquinolinone under the present reaction conditions, affording the corresponding product in excellent yields. Electronic effects play a significant role in reactions of aromatic nitroalkenes. The reaction time depends on the nature of the substituents on the benzene ring of β-nitrostyrenes. For example, the reaction involving electron rich nitrostyrene derivatives (4-CH_3, 4-OCH_3, 3,4-OCH_3) required a longer period of time for completion of the reaction and afforded *Z* and *E* isomers in a ratio of (1:40). While the reaction of nitrostyrenes bearing electron-withdrawing groups (2,6-Cl) proceeded smoothly within a short reaction time to generate the corresponding hydroxyiminodihydrofuroquinolinone derivatives in good yields, with *Z*:*E* ratio of 1:9. Sterically hindered nitroalkenes, such as (*E*)-2-(2-nitrovinyl) naphthalene required more time for completion of the reaction (entry 7) to afford the corresponding oxime products. It is noteworthy that we obtained an inseparable mixture of *E*:*Z* isomers. The *Z* isomer could not be isolated in pure form, from mixture of *E* and *Z* isomers (entries 5–7) since the solubility of the mixtures was very poor. However, it should be noted, that the mixture underwent a slow isomerization of *E* isomer to *Z* isomer upon heating.

The product assignment was carried out based on a ^{1}H NMR spectrum of the crude mixture of *Z* and *E* isomers. The *C*3-methine proton signal in ^{1}H NMR permits the *E* and *Z* isomers to be identified. The *C*3 proton ^{1}H NMR signal for (*Z*) isomers appeared in an upfield region compared to the (*E*) isomer, which appeared more downfield. Similarly, chemical shifts for the C=N–OH (oxime) proton also provide a route to distinguish between the *Z* and *E* isomers. The C=N–OH (oxime) proton in the ^{1}H NMR for the (*Z*) isomer was downfield compared to the analogous proton for the (*E*) isomer, which appeared at an unfield region in δ ppm. This is in good agreement with literature reports.[17] The ^{1}H NMR chemical shifts for the C=N–OH (oxime) and *C*3-methine (CH) proton for the *Z* and *E* isomers are shown in Table 5.

Table 5
^{1}H NMR chemical shifts (in δ ppm) for the C=N–O*H* (oxime) and methine (*CH*) proton signals for *Z* and *E* isomers



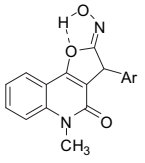
(*Z*) isomer (minor)



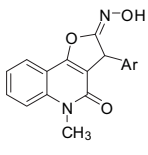
(*E*) isomer (major)

Entry	R	C=N–O*H*, (*Z* isomer)	Methine(*CH*), (*Z* isomer)	C=N–O*H*, (*E* isomer)	Methine(*CH*), (*E* isomer)
1	C_6H_5	—	—	10.32	5.40
2	4-CH_3–C_6H_4	—	—	10.28	5.34
3	4-OCH_3–C_6H_4	—	—	10.27	5.34
4	3,4-OCH_3–C_6H_3	—	—	10.31	5.35
5	2,6-Cl–C_6H_3	10.59	6.14	10.31	6.19
6	2-OCH_3–C_6H_4	10.36	5.40	10.01	5.48
7	2-Naphthyl	10.62	5.50	10.32	5.58

The proton signal for the *Z* isomeric oxime (C=N–O*H*) appeared in a more downfield region compared to the *E* isomeric oxime proton, due to intramolecular hydrogen bonding between the OH of the oxime group and the oxygen of the furan ring of *Z*-hydroxyiminodihydrofuroquinolinone. This also distinguishes the *Z* isomer from its counterpart *E* isomer and was in agreement with observations reported in the literature (Fig. 4).[17b,c]



***Z* isomer**
Intramolecular hydrogen bonding



***E* isomer**
No hydrogen bonding

Fig. 4. Hydrogen bonding in the *Z* isomer of hydroxyiminodihydrofuroquinolinone.

The structure of the *E* isomer of hydroxyiminodihydrofuroquinolinone was unambiguously confirmed by single crystal X-ray analysis of **15a** shown in Fig. 5.[18]

A plausible mechanism for the formation of the product is shown in Scheme 3. Initially, 4-hydroxy-*N*-methylquinolinone **13**

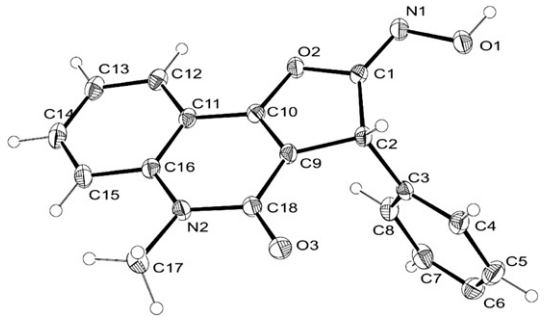
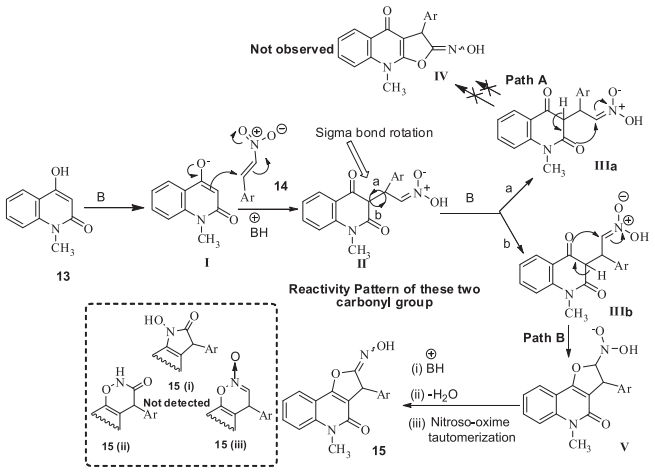


Fig. 5. X-ray crystal structure of **15a** (ORTEP diagram).



Scheme 3. Regioselective formation of Angular hydroxyiminodihydrofuroquinolinone derivatives.[19]

undergoes *C*-alkylation with β-nitrostyrenes to give intermediate **II**, which would enolize to form intermediates **IIIa** and **IIIb** under basic conditions. This intermediate then proceeds further based on the reactivity pattern of the carbonyl group. There are two possibilities for intramolecular cyclization. These intermediates can cyclize when the C=NO_2H is placed at the right position by free rotation of the sigma bond, and hence controls the regioselectivity of the reaction. Pathway **A** could afford the linear hydroxyiminodihydrofuroquinolinone **IV**, which was not observed under the present conditions. While pathway **B** proceeds through an intramolecular cyclization to afford intermediate **V**, which is then protonated, undergoes dehydration, followed by nitroso-oxime tautomerization to furnish the angular hydroxyiminodihydrofuroquinolinone derivatives. The possibility of forming other products, such as **15**(**i**), **15**(**ii**) and **15**(**iii**) was not observed under the present protocol.

3. Conclusion

In summary, we report on the development of a simple and efficient method for the C-alkylation of 4-hydroxycoumarin derivatives under sonication 'on water' conditions using various substituted (phenyl and heteroaryl) β-nitrostyrenes. Angular hydroxyiminodihydrofuroquinolinone derivatives were also synthesized in a regioselective manner under mild conditions at room temperature. Operational simplicity, inexpensive reagents and good product yields are the key advantages of the present protocol. Further work is in progress to extend the scope of this methodology for the synthesis of more complex structures and studies of the biological activity of these compounds are underway.

4. Experimental

4.1. General

All reactions were performed in oven (130 °C) dried glassware under an inert atmosphere of argon unless otherwise specified. Solvents for extraction and chromatography were distilled before use. All chemicals used in this study were of commercial grade and were distilled prior to use. Analytical thin layer chromatography was performed with E. Merck silica gel 60 F_{254} aluminum plates. All purifications were carried out by flash chromatography using 230–400 mesh silica gel. ^{1}H and ^{13}C NMR were recorded with a Bruker Advance EX 400 FT NMR instrument. Chemical shifts are reported in parts per million (δ) using TMS as the internal standard and coupling constants are expressed in hertz. Mass spectra were obtained on a JOEL SX-102A spectrometer at an ionization potential of 70 eV and data are reported as mass/charge (m/z) with the percent relative abundance. High-resolution mass spectra (HRMS) were acquired with a FINNIGAN MAT-95XL spectrometer. The reactions were carried out in a thermostated (30±1 °C) ultrasonic cleaning bath (Branson Ultrasonics, Ultrasonic bath Model 3010R-DTH) at 50 kHz frequency. The ultrasonic cleaning bath had an output of 100 W and a power supply of 335 W.

4.2. General procedure for the C-alkylation of 4-hydroxycoumarin

A mixture of 4-hydroxycoumarin (**10**) (1 mmol) and β-nitrostyrene (**11**) (1.2 mmol) was suspended in 5 mL of water in a 20 mL vial. The vial was placed into the ultrasonic bath (Branson Ultrasonics, Ultrasonic bath Model 3010R-DTH, 50 kHz frequency) at 30 °C for the specific time mentioned in Table 2. The progress of the reaction was monitored by TLC. After completion of the reaction, the resulting solid product was filtered and washed with water (2×10 mL) and *n*-hexane (5×10 mL). Then solid was dried under vacuum to obtain the product (**12a**–**n**) in almost pure form in exellent yields (83–94%).

4.3. General procedure for the synthesis of hydroxyiminodihydrofuroquinolinone derivatives

A mixture of 4-hydroxy-*N*-methylquinolin-2(1*H*)one (**13**) (1 mmol) and β-nitrostyrene (**14**) (1.2 mmol) dissolved in 3 mL of methanol. To this solution, 10 mol% of DIPEA was added and the reaction mixture was stirred at room temperature for the time indicated in the Table 4. The progress of the reaction was monitored by TLC. After completion of the reaction, water was added, the resulting solid product was filtered and washed with water (2×10 mL) and *n*-hexane (5×10 mL). Then solid was dried under a vacuum to give the product (**15a**–**g**) as a mixture of *Z* and *E* isomers of angular hydroxyiminodihydrofuroquinolinone in exellent yields (82–92%).

4.4. Spectral data

*4.4.1. 4-Hydroxy-3-(2-nitro-1-phenylethyl)-2H-chromen-2-one (**12a**).* White solid; mp: 158–160 °C. FT-IR (KBr) ν/cm^{-1} 3440, 1701, 1607, 1550, 1378. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (d, J=8.0 Hz, 1H), 7.63 (t, J=7.8 Hz, 1H), 7.41–7.36 (m, 4H), 7.31 (t, J=7.3 Hz, 2H), 7.23 (d, J=7.0 Hz, 1H), 5.46 (dd, J=14.2, 8.2 Hz, 1H), 5.43 (dd, J=8.2, 6.8 Hz, 1H), 5.28 (dd, J=14.2, 6.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.0, 161.9, 152.2, 138.9, 132.4, 128.4, 127.5, 127.0, 124.0, 123.6, 116.3, 115.8, 104.1, 76.5, 38.5. MS (ESI) (m/z) (relative intensity) 334

[(M+Na)$^+$(70)], 312 [(M+H)$^+$(58)], 295 (48), 276 (20), 265 (40), 251 (100), 216 (42). HRMS (ESI): calcd for $C_{17}H_{13}NO_5$ [M+H]$^+$ 312.0872, found 312.0874 and calcd for $C_{18}H_{15}NO_5Na$ [M+Na]$^+$ 334.0691, found 334.0692.

*4.4.2. 4-Hydroxy-3-(2-nitro-1-p-tolylethyl)-2H-chromen-2-one (**12b**).* White solid; mp: 154–156 °C. FT-IR (KBr) ν/cm^{-1} 3438, 1684, 1620, 1520, 1350, 1120. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, J=8.2 Hz, 1H), 7.62 (t, J=7.8 Hz, 1H), 7.39–7.36 (m, 2H), 7.27 (d, J=7.9 Hz, 2H), 7.10 (d, J=7.8 Hz, 2H), 5.40 (d, J=7.5 Hz, 2H), 5.22 (t, J=7.8 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.8, 152.1, 131.1, 135.8, 132.4, 129.0, 127.4, 124.0, 123.5, 116.3, 115.8, 104.3, 76.6, 38.2, 20.5. MS (ESI) (m/z) (relative intensity) 348 [(M+Na)$^+$(30)], 326 [(M+H)$^+$(55)], 265 (100), 216 (65). HRMS (ESI): calcd for $C_{18}H_{15}NO_5$ [M+H]$^+$ 326.1028, found 326.1030 and calcd for $C_{18}H_{15}NO_5Na$ (M+Na)$^+$ 348.0848, found 348.0842.

*4.4.3. 4-Hydroxy-3-(1-(2-methoxyphenyl)-2-nitroethyl)-2H-chromen-2-one (**12c**).* White solid; mp: 176–177 °C. FT-IR (KBr) ν/cm^{-1} 3436, 1650, 1644, 1390, 1215. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, J=7.7 Hz, 1H), 7.63 (t, J=7.6 Hz, 1H), 7.38 (d, J=7.2 Hz, 1H), 7.24 (dd, J=6.8, 8.1 Hz, 2H), 6.98 (d, J=8.0 Hz, 1H), 6.87 (t, J=7.2 Hz, 1H), 6.87 (t, J=7.2 Hz, 1H), 5.48 (dd, J=13.1, 6.7 Hz, 1H), 5.36 (dd, J=12.8, 9.1 Hz, 1H), 5.16 (dd, J=9.1, 6.7 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 161.9, 156.8, 152.2, 132.3, 128.8, 128.2, 127.7, 123.9, 123.5, 120.1, 116.3, 115.9, 111.0, 102.8, 75.7, 55.5, 33.7. MS (ESI): (m/z) (relative intensity) 364 [(M+Na)$^+$(96)], 342 [(M+H)$^+$ (100)]. HRMS (ESI): calcd for $C_{18}H_{15}NO_6$ [M+H]$^+$ 342.0978, found 342.0983 and calcd for $C_{18}H_{15}NO_6Na$ [M+Na]$^+$ calcd 364.0797, found 364.0791.

*4.4.4. 4-Hydroxy-3-(1-(3-methoxyphenyl)-2-nitroethyl)-2H-chromen-2-one (**12d**).* White solid; mp: 170–171 °C. FT-IR (KBr) ν/cm^{-1} 3431, 1695, 1645, 1551, 1420, 1250. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, J=8.0 Hz, 1H), 7.62 (d, J=7.8 Hz, 1H), 7.37 (d, J=7.8 Hz, 2H), 7.21 (d, J=7.9 Hz, 1H), 7.97–7.95 (m, 2H), 6.82 (d, J=7.9 Hz, 1H), 5.42 (d, J=7.6 Hz, 2H), 5.25 (t, J=7.7 Hz, 1H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.0, 161.8, 159.2, 152.2, 140.3, 132.4, 129.5, 124.0, 123.6, 110.8, 116.3, 115.8, 113.8, 112.0, 104.0, 76.5, 54.9, 38.5. MS (ESI): (m/z) (relative intensity) 364 [(M+Na)$^+$(98)], 342 [(M+H)$^+$ (100)], 324 (70), 295 (75). HRMS (ESI): calcd for $C_{18}H_{15}NO_6$ [M+H]$^+$ 342.0978, found 342.0983 and calcd for $C_{18}H_{15}NO_6Na$ [M+Na]$^+$ calcd 364.0797, found 364.0795.

*4.4.5. 4-Hydroxy-3-(1-(4-methoxyphenyl)-2-nitroethyl)-2H-chromen-2-one (**12e**).* White solid; mp: 155–156 °C. FT-IR (KBr) ν/cm^{-1} 3432, 1644, 1545, 1320, 1150. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (d, J=7.8 Hz, 1H), 7.64 (t, J=7.5 Hz, 1H), 7.38–7.31 (m, 4H), 6.86 (d, J=8.1 Hz, 2H), 5.41–5.38 (m, 2H), 5.21 (d, J=7.44 Hz, 1H), 3.70 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.8, 161.7, 158.8, 156.3, 152.1, 132.4, 130.7, 128.7, 124.0, 123.6, 116.3, 115.8, 113.8, 104.4, 76.8, 55.0, 37.9. MS (ESI): (m/z) (relative intensity) 364 [(M+Na)$^+$(45)], 342 [(M+H)$^+$(40)], 295 (42), 281 (100). HRMS (ESI): calcd for $C_{18}H_{15}NO_6$ [M+H]$^+$ 342.0978, found 342.0979 and calcd for $C_{18}H_{15}NO_6Na$ [M+Na]$^+$ calcd 364.0797, found 364.0791.

*4.4.6. 4-Hydroxy-3-(2-nitro-1-(2-(trifluoromethyl)phenyl)ethyl)-2H-chromen-2-one (**12f**).* White solid; mp: 195–196 °C. FT-IR (KBr) ν/cm^{-1} 3424, 1675, 1625, 1550, 1490, 1250. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, J=6.4 Hz, 1H), 7.88 (d, J=7.2 Hz, 1H), 7.72 (d, J=7.0 Hz, 1H), 7.64–7.60 (m, 2H), 7.49–7.42 (m, 1H), 7.38–7.32 (m, 2H), 5.57–5.54 (m, 2H), 5.10–5.04 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.2, 161.7, 137.0, 132.6, 132.5 (q, J_{CF}=32 Hz), 130.6, 127.9, 127.4, 126.3 (q, J_{CF}=272 Hz), 125.8, 124.0 (q, J_{CF}=6.0 Hz), 123.5, 116.4, 115.6, 103.0, 75.9, 35.8. MS (ESI): (m/z) (relative intensity) 402 [(M+Na)$^+$(90)], 380 [(M+H)$^+$(65)], 362 (42), 342 (100), 299 (55). HRMS (ESI): calcd for $C_{18}H_{12}NO_5F_3$ [M+H]$^+$ 379.0668, found 379.0779 and calcd for $C_{18}H_{12}NO_5F_3Na$ (M+Na)$^+$ 402.0565, found 402.0576.

*4.4.7. 3-(1-(2-Fluorophenyl)-2-nitroethyl)-4-hydroxy-2H-chromen-2-one (**12g**).* White solid; mp: 180–181 °C. FT-IR (KBr) ν/cm^{-1} 3423, 1700, 1645, 1345, 1275. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.0 (d, J=7.8 Hz, 1H), 7.64 (t, J=7.3 Hz, 1H), 7.53 (t, J=7.6 Hz, 1H), 7.39–7.37 (m, 2H), 7.32–7.27 (m, 1H), 7.17–7.12 (m, 2H), 5.51 (t, J=7.2 Hz, 1H), 5.43–5.36 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) 162.3(d, J_{CF}=280 Hz), 161.3, 158.8, 152.3, 132.6, 129.4, 129 (d, J_{CF}=12 Hz), 125.4, 125.3, 124.3 (d, J_{CF}=4 Hz), 123.6, 116.4, 115.4 (d, J_{CF}=24 Hz), 102.6, 75.5, 32.4. MS (ESI): (m/z) (relative intensity) 352 [(M+Na)$^+$(70)], 330 [(M+H)$^+$(55)], 312 (78), 283 (40), 269 (70), 249 (30), 216 (100). HRMS (ESI): calcd for $C_{17}H_{12}NO_5F$ [M+H]$^+$ 330.0778, found 330.0779 and calcd for $C_{17}H_{12}NO_5FNa$ (M+Na)$^+$ 352.0597, found 352.0600.

*4.4.8. 3-(1-(4-Fluorophenyl)-2-nitroethyl)-4-hydroxy-2H-chromene-2-one (**12h**).* White solid; mp: 179–180 °C. FT-IR (KBr) ν/cm^{-1} 3436, 1648, 1551, 1508, 1376, 1276. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, J=8.0 Hz, 1H), 7.63 (t, J=7.8 Hz, 1H), 7.46–7.42, (m, 2H), 7.38–7.35 (m, 2H), 7.14 (t, J=8.0 Hz, 2H), 5.41 (d, J=7.9 Hz, 2H), 5.26 (d, J=7.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.4 (d, J_{CF}=244 Hz), 160.0, 152.2, 135.0, 132.5, 129.5 (d, J_{CF}=13 Hz), 124.0, 123.6 (d, J_{CF}=4 Hz), 116.3, 115.8, 115.2 (d, J_{CF}=24 Hz), 104.0, 76.5, 37.9. MS (ESI): (m/z) (relative intensity) 352 [(M+Na)$^+$(80)], 330 [(M+H)$^+$(40)], 269 (100), 216 (70). HRMS (ESI): calcd for $C_{17}H_{12}NO_5F$ [M+H]$^+$ 330.0778, found 330.0781 and calcd for $C_{17}H_{12}NO_5FNa$ (M+Na)$^+$ 352.0597, found 352.0600.

*4.4.9. 3-(1-(4-Chlorophenyl)-2-nitroethyl)-4-hydroxy-2H-chromen-2-one (**12i**).* White solid; mp: 181–182 °C. FT-IR (KBr) ν/cm^{-1} 3422, 1715, 1650, 1609, 1520, 1345. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, J=7.5 Hz, 1H), 7.64 (t, J=7.3 Hz, 1H), 7.43–7.36 (m, 6H), 5.44–5.40 (m, 2H), 5.26 (t, J=7.7 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.8, 152.1, 136.1, 135.8, 132.4, 129.0, 127.4, 124.0, 123.5, 116.3, 115.8, 104.3, 76.6, 38.2. MS (ESI) (m/z) (relative intensity) 368 [(M+Na)$^+$(62)], 346 [(M+H)$^+$(78)], 348 [(M+2) 44], 285 (100), 216 (80). HRMS (ESI): calcd for $C_{17}H_{12}NO_5Cl$ [M+H]$^+$ 346.0482, found 346.0484 and calcd for $C_{17}H_{12}NO_5ClNa$ (M+Na)$^+$ 368.0302, found 368.0306.

*4.4.10. 4-Hydroxy-3-(2-nitro-1-(4-nitrophenyl)ethyl)-2H-chromen-2-one (**12j**).* White solid; mp: 180–182 °C. FT-IR (KBr) ν/cm^{-1} 3443, 1714, 1664, 1552, 1346. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, J=8.0 Hz, 2H), 8.05 (d, J=7.5 Hz, 1H), 7.68–7.62 (m, 3H), 7.35 (d, J=6.8 Hz, 2H), 5.57–5.55 (m, 1H), 5.43–5.41 (m 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.6, 161.7, 152.3, 146.7, 146.4, 132.6, 128.8, 124.1, 123.7, 123.5, 116.5, 115.7, 103.0, 75.7, 38.2. MS (ESI) (m/z) (relative intensity) 379 [(M+Na)$^+$(35)], 357 [(M+H)$^+$(95)], 339 (52), 310 (75), 296 (40). HRMS (ESI): calcd for $C_{17}H_{12}N_2O_5$ [M+H]$^+$ 356.0645, found 356.0721 and calcd for $C_{17}H_{12}N_2O_5Na$ [M+Na]$^+$ 379.0542, found 379.0533.

*4.4.11. 4-Hydroxy-3-(2-nitro-1-(2-nitrophenyl)ethyl)-2H-chromen-2-one (**12k**).* White solid; mp: 194–195 °C. FT-IR (KBr) ν/cm^{-1} 3412, 1663, 1619, 1550, 1350. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, J=7.7 Hz, 1H), 7.87 (dd, J=7.0, 8.0 Hz, 2H), 7.69–7.61 (m, 2H), 7.51 (t, J=7.3 Hz, 1H), 7.36 (d, J=7.8 Hz, 2H), 5.61 (dd, J=14.0, 8.1 Hz, 1H), 5.53 (dd, J=8.1, 6.5 Hz, 1H), 5.32 (dd, J=14.8, 6.5 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.0, 161.9, 152.3, 149.4, 133.0, 132.7, 132.5, 130.0, 128.6, 124.1, 123.6, 116.7, 115.4, 102.9, 75.6, 34.3. MS (ESI): (m/z) (relative intensity) 379 [(M+Na)$^+$(93)], 357 [(M+H)$^+$(95)], 332 (48), 310 (42), 292 (21), 275 (36), 275 (36), 264 (50), 248 (15), 229 (16). HRMS (ESI): calcd for $C_{17}H_{12}N_2O_5$ [M+H]$^+$ 356.0645, found

356.0723 and calcd for $C_{17}H_{12}N_2O_5Na$ $[M+Na]^+$ 379.0542, found 379.0524.

*4.4.12. 4-Hydroxy-3-(2-nitro-1-(thiophen-2-yl)ethyl)-2H-chromen-2-one (**12l**).* Gray solid; mp: 173–174 °C. FT-IR (KBr) ν/cm^{-1} 3443, 1705, 1645, 1518, 1380, 1240. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, J=7.9 Hz, 1H), 7.65 (t, J=6.8 Hz, 1H), 7.39–7.38 (m, 3H), 7.08 (s, 1H), 6.95 (s, 1H), 5.53 (t, J=7.5 Hz, 1H), 5.40 (d, J=8.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.1, 161.5, 152.2, 141.1, 132.6, 126.7, 125.5, 125.0, 124.1, 123.7, 116.4, 115.7, 103.5, 77.2, 34.5. MS (ESI): (m/z) (relative intensity) 318 [$(M+H)^+$(60)], 271 (20), 257 (98), 216 (15). HRMS (ESI): calcd for $C_{15}H_{11}NO_5S$ $[M+H]^+$ 317.0358, found 317.0438 and calcd for $C_{15}H_{11}NO_6Na$ $[M+Na]^+$ 340.0256, found 340.0259.

*4.4.13. 3-(1-(Furan-2-yl)-2-nitroethyl)-4-hydroxy-2H-chromen-2-one (**12m**).* Light green colour; mp: 174–176 °C. FT-IR (KBr) ν/cm^{-1} 3443, 1650, 1600, 1510, 1355, 1215. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, J=6.8 Hz, 1H), 7.65 (s, 1H), 7.54 (s, 1H), 7.39 (d, J=6.8 Hz, 2H), 6.39–6.37 (m, 1H), 6.26–6.23 (m, 1H), 5.37–5.35 (m, 2H), 5.31–5.28 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.5, 161.4, 152.3, 151.4, 141.9, 132.6, 124.1, 123.7, 116.4, 115.8, 110.6, 106.3, 101.3, 75.2, 33.3. MS (ESI): (m/z) (relative intensity) 301 (M^+, 100), 437 (38), 324 [$(M+Na)^+$(98)], 302 [$(M+H)^+$(58)], 277 (24), 255 (95), 241 (62). HRMS (ESI): calcd for $C_{15}H_{11}NO_6$ $[M+H]^+$ 302.0665, found 302.0674 and calcd for $C_{15}H_{11}NO_6Na$ $[M+Na]^+$ 324.0484, found 324.0479.

*4.4.14. 4-Hydroxy-3-(1-(naphthalen-2-yl)-2-nitroethyl)-2H-chromen-2-one (**12n**).* Pale yellow solid; mp: 164–165 °C. FT-IR (KBr) ν/cm^{-1} 3435, 1645, 1520, 1312, 1250. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (d, J=8.2 Hz, 1H), 7.96–7.84 (m 4H), 7.64 (t, J=8.2 Hz, 1H), 7.56 (d, J=8.2 Hz, 1H), 7.49–7.44 (m, 2H), 7.39–7.38 (m, 2H), 5.61–5.53 (m, 2H) 5.50–5.45 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 161.8, 152.2, 136.4, 132.8, 132.5, 132.0, 128.0, 127.7, 127.3, 126.2, 126.0, 125.8, 124.0, 123.6, 116.3, 115.8, 104.0, 76.4, 38.6. MS (ESI): (m/z) (relative intensity) 384 [$(M+Na)^+$(45)], 362 [$(M+H)^+$(75)], 315 (42), 301 (100), 283 (48), 266 (27), 223 (58). HRMS (ESI): calcd for $C_{21}H_{15}NO_5$ $[M+H]^+$ 362.1028, found 362.1016 and calcd for $C_{21}H_{15}NO_5Na$ $[M+Na]^+$ 384.0848, found 384.0848.

*4.4.15. Deuterated compound of (**12b***).* Yellow solid; mp: 120–122 °C. FT-IR (KBr) ν/cm^{-1} 3429, 2920, 1671, 1209, 552. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, J=7.8 Hz, 1H), 7.55 (t, J=7.8 Hz, 1H), 7.33–7.30 (m, 4H), 7.17 (d, J=7.6 Hz, 2H), 5.14 (dd, J=13.1, 6.9 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.7, 161.7, 152.1, 136.2, 135.8, 132.4, 129.0, 127.4, 124.0, 123.5, 116.3, 115.7, 104.3, 76.3 (t, J=21.0 Hz), 38.1, 20.5. MS (ESI) (m/z) (relative intensity) 265 (8), 325 (14), 326(M^+, 20). HRMS (ESI): calcd for $C_{18}H_{14}DNO_5$ $(M+H)^+$ 326.1013 found 326.1004 and for $C_{18}H_{14}DNNaO_5$ $(M+Na)^+$ 349.0911 found 349.0916.

*4.4.16. (E)-2-(Hydroxyimino)-5-methyl-3-phenyl-2,3-dihydrofuro [3,2-c]quinolin-4(5H)-one (**15a**).* White solid; mp: 140–142 °C. FT-IR (KBr) ν/cm^{-1} 3431, 1685, 1602, 1551, 1335, 1135. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, C=N–OH, (*E*) isomer, 1H), 7.88 (d, J=6.4 Hz, 1H), 7.75 (t, J=7.2 Hz, 1H), 7.63 (d, J=8.0 Hz, 1H), 7.40 (t, J=7.2 Hz, 1H), 7.28–7.21 (m, 5H), 5.40 (s, 1H), 3.55 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.0, 158.3, 157.9, 140.2, 136.0, 132.1, 128.2, 128.0, 126.9, 122.4, 122.2, 115.5, 111.7, 110.1, 46.1, 28.8. MS (EI): (m/z) (relative intensity) 306 (M^+, 100), 289 (35), 248 (22). HRMS (EI): calcd for $C_{18}H_{14}N_2O_4$ $(M)^+$ 306.1004, found 306.1006.

*4.4.17. (E)-2-(Hydroxyimino)-5-methyl-3-p-tolyl-2,3-dihydrofuro [3,2-c]quinolin-4(5H)-one (**15b**).* White solid; mp: 165–167 °C. FT-IR (KBr) ν/cm^{-1} 3438, 1687, 1630, 1556, 1335, 1125. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, C=N–OH, (*E*) isomer, 1H), 7.87 (d, J=6.8 Hz, 1H), 7.77–7.75 (m, 1H), 7.63 (d, J=8.6 Hz, 1H), 7.39 (t, J=7.4 Hz, 1H), 7.17 (d, J=8.6 Hz, 2H), 6.83 (d, J=8.6 Hz, 2H), 5.34 (s, 1H), 3.71 (s, 3H), 3.55 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1, 158.2, 157.7, 140.4, 136.1, 133.0, 132.0, 128.7, 127.9, 122.4, 122.2, 115.5, 111.8, 110.1, 45.7, 28.7, 20.5. MS (EI): (m/z) (relative intensity) 320 (M^+, 100), 303 (45), 287 (22), 274 (18). HRMS (EI): calcd for $C_{19}H_{16}N_2O_3$ $(M)^+$ 320.1161, found 320.1164.

*4.4.18. (E)-2-(Hydroxyimino)-3-(4-methoxyphenyl)-5-methyl-2,3-dihydrofuro[3,2-c]quinolin-4(5H)-one (**15c**).* White solid; mp: 130–132 °C. FT-IR (KBr) ν/cm^{-1} 3442, 1690, 1553, 1325, 1135. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, C=N–OH, (*E*) isomer, 1H), 7.87 (d, J=7.7 Hz, 1H), 7.88 (t, J=7.8 Hz, 1H), 7.62 (d, J=8.6 Hz, 1H), 7.39 (t, J=7.5 Hz, 1H), 7.15–7.06 (m, 4H), 5.34 (s, 1H), 3.54 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.2, 158.2, 158.1, 157.8, 140.3, 132.0, 129.1, 127.9, 122.4, 122.2, 115.4, 113.6, 111.8, 110.1, 55.0, 45.3, 28.7, 30. MS (EI): (m/z) (relative intensity) 336 (M^+, 100), 319 (45), 287 (38). HRMS (EI): calcd for $C_{19}H_{16}N_2O_4$ $(M)^+$ 336.1110, found 336.1107.

*4.4.19. (E)-3-(3,4-Dimethoxyphenyl)-2-(hydroxyimino)-5-methyl-2,3-dihydrofuro[3,2-c]quinolin-4(5H)-one (**15d**).* White solid; mp: 166–168 °C. FT-IR (KBr) ν/cm^{-1} 3435, 1650, 1570, 1390, 1215. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (s, C=N–OH, (*E*) isomer, 1H), 7.87 (d, J=7.8 Hz, 1H), 7.74 (t, J=7.8 Hz, 1H), 7.63 (d, J=8.6 Hz, 1H), 7.39 (t, J=7.5 Hz, 1H), 6.95 (s, 1H), 6.83 (d, J=8.3 Hz, 1H), 6.70 (d, J=8.2 Hz, 1H), 5.35 (s, 1H), 3.70 (s, 6H), 3.59 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1, 158.1, 157.8, 148.3, 147.9, 140.3, 132.0, 128.3, 122.2, 119.7, 115.5, 112.6, 111.8, 111.7, 110.1, 55.5, 45.6, 28.8. MS (EI): (m/z) (relative intensity) 366 (M^+, 8), 350 (100), 335 (25). HRMS (EI): calcd for $C_{20}H_{18}N_2O_5$ $(M)^+$ 366.1216, found 366.1227.

*4.4.20. 3-(2,6-Dichlorophenyl)-2-(hydroxyimino)-5-methyl-2,3-dihydrofuro[3,2-c]quinolin-4(5H)-one (**15e**).* White solid; FT-IR (KBr) ν/cm^{-1} 3434, 1674, 1520, 1332. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, C=N–OH, (*Z*) isomer, 1H), 10.31 (s, C=N–OH, (*E*) isomer, 1H), 7.89–7.87 (m, (*E*) isomer and (*Z*) isomer, 2H), 7.78–7.74 (m, (*E*) isomer and (*Z*) isomer, 2H), 7.64–7.62 (m, (*E*) isomer and (*Z*) isomer, 2H), 7.55–7.52 (m, (*E*) isomer, 1H), 7.41–7.36 (m, (*E*) isomer and (*Z*) isomer, 2H), 7.31–7.30 (m, (*E*) isomer, 2H), 6.19 (s, (*E*) isomer, 1H), 6.14 (s, (*E*) isomer, 1H), 3.56 (s, (*Z*) isomer, 3H), 3.54 (s, (*E*) isomer, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 158.4, 156.4, 157.7, 137.6, 137.2, 132.1, 130.0, 129.2, 129.1, 128.4, 128.2, 128.1, 127.9, 127.8, 126.6, 124.4, 122.7, 119.0, 116.8, 115.8, 92.1, 85.0, 30.4, 30.1, 29.5, 29.2. MS (EI) (m/z) (relative intensity) 376.0 (M+2, 65), 374 (M^+, 100), 323 (22), 296 (40), 248 (70). HRMS (EI): calcd for $C_{18}H_{12}N_2O_3Cl_2$ $(M)^+$ 374.0219, found 374.0231.

*4.4.21. 2-(Hydroxyimino)-3-(2-methoxyphenyl)-5-methyl-2,3-dihydrofuro[3,2-c]quinolin-4(5H)-one (**15f**).* White solid; FT-IR (KBr) ν/cm^{-1} 3443, 1678, 1544, 1335, 113. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, C=N–OH, (*Z*) isomer, 1H), 10.01 (s, C=N–OH, (*E*) isomer, 1H,), 7.89–7.87 (m, (*E*) isomer and (*Z*) isomer, 2H), 7.75–7.71 (m, (*E*) isomer and (*Z*) isomer, 2H), 7.40–7.37 (m, (*E*) isomer and (*Z*) isomer, 2H), 7.25–7.17 (m, (*E*) isomer and (*Z*) isomer, 4H), 6.99–6.86 (m, (*E*) isomer and (*Z*) isomer, 4H), 5.48 (s, (*E*) isomer, 1H), 5.40 (s, (*Z*) isomer, 1H), 3.66 (s, (*Z*) isomer, 3H), 3.62 (s, (*E*) isomer, 3H), 3.55 (s, (*Z*) isomer, 3H), 3.52 (s, (*E*) isomer, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.3, 158.5, 158.0, 157.8, 157.0, 156.9, 140.2, 135.0, 134.9, 131.8, 131.6, 128.6, 128.3, 127.6, 125.0, 124.6, 122.2, 122.1, 120.4, 120.1, 115.4, 115.4, 111.8, 111.4, 110.2, 55.9, 55.8, 55.6, 28.8, 28.7, 28.6. MS (EI): (m/z) (relative intensity) 336 (M^+, 22), 320 (100), 288 (35), 262 (28). HRMS (EI): calcd for $C_{19}H_{16}N_2O_4$ $(M+H)^+$ 336.1105, found 336.1104.

*4.4.22. 2-(Hydroxyimino)-5-methyl-3-(naphthalen-2-yl)-2,3-dihydrofuro[3,2-c]quinolin-4(5H)-one (**15g**).* White solid; FT-IR (KBr) ν/cm^{-1} 3422, 1670, 1638, 1548, 1419, 1320. ^{1}H NMR (400 MHz, DMSO-

d_6) δ 10.62 (s, C=N–OH, (*Z*) isomer, 1H), 10.32 (s, C=N–OH, (*E*) isomer, 1H), 7.94–7.91 (m, (*E*) isomer, 1H), 7.88–7.83 (m, (*E*) isomer and (*Z*) isomer, 2H), 7.81–7.78 (m, (*E*) isomer and (*Z*) isomer, 2H), 7.77–7.73 (m, (*E*) isomer and (*Z*) isomer, 2H), 7.64 (d, *J*=8.6 Hz, (*E*) isomer 4H), 7.53–7.56 (m, (*E*) isomer and (*Z*) isomer, 2H), 7.44–7.34 (m, (*E*) isomer, 2H), 5.58 (s, (*E*) isomer, 1H), 5.40 (s, (*Z*) isomer, 1H), 3.58 (s, (*Z*) isomer, 3H), 3.53 (s, (*E*) isomer, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.3, 158.6, 158.0, 157.8, 140.6, 133.8, 133.0, 132.3 (2C), 127.9, 127.7, 127.5, 126.7, 126.5, 126.3, 126.0, 122.7, 122.5, 115.7, 111.9, 110.3, 48.7, 46.4, 28.9. MS (EI): (*m*/*z*) (relative intensity) 356 (M^+, 5), 340 (100), 327 (55), 312 (45), 250 (17). HRMS (EI): calcd for $C_{22}H_{16}N_2O_3$ $(M)^+$ 356.1155, found 356.1170.

Acknowledgements

We wish to express our sincere gratitude to the National Science Council of the Republic of China and National Taiwan Normal University (99T3030-2 and 99-D) for providing financial support for this work. DKB is grateful to MOFA for a Taiwan Scholarship.

Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.02.062.

References and notes

1. (a) Meciarova, M.; Toma, S.; Magdolen, P. *Ultrason. Sonochem.* **2003**, *10*, 265–270; (b) *Practical Sonochemistry. Power Ultrasound: Uses and Applications*; Mason, T. J., Peters, D., Eds.; Horwood Publishing Ltd: London, UK, 2002; (c) Del Campo, F. J.; Maisonhaute, E.; Compton, R. G.; Marken, F.; Aldaz, A. *J. Electroanal. Chem.* **2001**, *506*, 170–177; (d) *Synthetic Organic Sonochemistry*; Luche, J.-L., Ed.; Plenum: New York, NY, 1998; (e) Mason, T. J. *Chem. Soc. Rev.* **1997**, *26*, 433–451; (f) Suslick, K. S.; Casadonte, D. J.; Green, M. L. H.; Thompson, M. E. *Ultrasonics* **1987**, *25*, 56–59.
2. (a) Jiang, N.; Ragauskas, A. J. *Tetrahedron Lett.* **2010**, *51*, 4479–4481; (b) Scondo, A.; Dumarcay-Charbonnier, F.; Barth, D.; Marsura, A. *Tetrahedron Lett.* **2009**, *50*, 5582–5584; (c) Luzzio, F. A.; Chen, J. *J. Org. Chem.* **2008**, *73*, 5621–5624; (d) Li, J.-T.; Zhai, X.-L.; Lin, Z.-P.; Zhang, X.-H. *Lett. Org. Chem.* **2008**, *5*, 579–582; (e) Cintas, P.; Cravotto, G. *Chem. Soc. Rev.* **2006**, *35*, 180–196 and references cited therein.
3. (a) Polshettiwar, V.; Varma, R. S. *Acc. Chem. Res.* **2008**, *41*, 629–639; (b) Lindström, U. M. *Organic Reactions in Water: Principles, Strategies and Applications*; Blackwell: New York, NY, 2007; 41; 629; (c) Pirrung, M. C. *Chem.—Eur. J.* **2006**, *12*, 1312–1317; (d) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095–3166; (e) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751–2772; (f) Shu, K.; Kei, M. *Acc. Chem. Res.* **2002**, *35*, 209–217; (g) Li, C. J.; Chang, T. H. *Organic Reactions in Aqueous Media*; Wiley: New York, NY, 1997; 7950; (h) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159–164.
4. (a) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275–3279; (b) Klijin, J. E.; Engberts, J. B. F. N. *Nature* **2005**, *435*, 746–747.
5. (a) Yamamoto, Y.; Kurazono, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1626–1628; (b) Xia, Y.; Yang, Z.-Y.; Xia, P.; Hackl, T.; Hamel, E.; Mauger, A.; Wu, J.-H.; Lee, K.-H. *J. Med. Chem.* **2001**, *44*, 3932–3936; (c) Naser-Hijazi, B.; Stolze, B.; Zanker, K. S. *Second Proceedings of the International Society of Coumarin Investigators*; Springer: Berlin, 1994; (d) Murray, R. D. H.; Mendez, J.; Brown, S. A. *The Natural Coumarins: Occurrence, Chemistry, and Biochemistry*; Wiley: New York, NY, 1982.
6. (a) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 650–668; (b) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 476–493.
7. For biological activities of coumarin: (a) Argotte-Ramos, R.; Ramırez-Avila, G.; Rodrıguez-Gutierrez, M. d. C.; Ovilla-Munoz, M.; Lanz-Mendoza, H.; Rodrıguez, M. H.; Gonzalez-Cortazar, M.; Alvarez, L. *J. Nat. Prod.* **2006**, *69*, 1442–1444; (b) Verotta, L.; Lovaglio, E.; Vidari, G.; Finzi, P. V.; Neri, M. G.; Raimondi, A.; Parapini, S.; Taramelli, D.; Riva, A.; Bombardelli, E. *Phytochemistry* **2004**, *65*, 2867–2879; (c) Garazd, M. M.; Garazd, Y. L.; Khilya, V. P. *Khim. Prir. Soedin.* **2003**, *39*, 47–82; (d) Guilet, D.; Helesbeux, J.-J.; Seraphin, D.; Sevenet, T.; Richomme, P.; Bruneton, J. *J. Nat. Prod.* **2001**, *64*, 563–568; (e) Patil, A. D.; Freyer, A. J.; Eggleston, D. S.; Haltiwanger, R. C.; Bean, M. F.; Taylor, P. B.; Caranfa, M. J.; Breen, A. L.; Bartus, H. R.; Johnson, R. K.; Hertzberg, R. P.; Westley, J. W. *J. Med. Chem.* **1993**, *36*, 4131–4138; (f) O'Reilly, R. A. *N. Engl. J. Med.* **1976**, *295*, 354–357.
8. (a) Butenschon, I.; Moller, K.; Hansel, W. *J. Med. Chem.* **2001**, *44*, 1249–1256; (b) Cahalan, M. D.; Chandy, K. G. *Curr. Opin. Biotechnol.* **1997**, *8*, 749–756; (c) Slaughter, R. S.; Garcia, M. L.; Kaczorowski, G. J. *Curr. Pharm. Des.* **1996**, *2*, 610–623.
9. For the syntheis of Angular furoquinolinone: (a) Venkataraman, S.; Barange, D. K.; Pal, M. *Tetrahedron Lett.* **2006**, *47*, 7317–7322; (b) Fayol, A.; Zhu, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3633–3635; (c) Bar, G.; Parsons, A. F.; Thomas, C. B. *Tetrahedron* **2001**, *57*, 4719–4728; (d) Pirrung, M. C.; Blume, F. *Org. Lett.* **1999**, *64*, 3642–3649.
10. (a) Tu, Z.; Raju, B. R.; Liou, T.-R.; Kavala, V.; Kuo, C.-W.; Jang, Y.; Shih, Y.-H.; Yao, C.-F. *Tetrahedron* **2009**, *65*, 2436–2442; (b) Gao, S.; Tu, Z.; Kuo, C.-W.; Liu, J.-T.; Chu, C.-M.; Yao, C.-F. *Org. Biomol. Chem.* **2006**, *4*, 2851–2857; (c) Lin, C.; Hsu, J.; Sastry, M. N. V.; Fang, H.; Tu, Z.; Liu, J.-T.; Yao, C.-F. *Tetrahedron* **2005**, *61*, 11751–11757; (d) Jang, Y.-J.; Yan, M.-C.; Lin, Y.-F.; Yao, C.-F. *J. Org. Chem.* **2004**, *69*, 3961–3963; (e) Yan, M.-C.; Tu, Z.; Lin, C.; Ko, S.; Hsu, J.; Yao, C.-F. *J. Org. Chem.* **2004**, *69*, 1565–1570; (f) Jang, Y.-J.; Lin, W.-W.; Shih, Y.-K.; Liu, J.-T.; Hwang, M.-H.; Yao, C.-F. *Tetrahedron* **2003**, *59*, 4979–4992; (g) Jang, Y.-J.; Shih, Y.-K.; Liu, J.-Y.; Kuo, W.-Y.; Yao, C.-F. *Chem.—Eur. J.* **2003**, *9*, 2123–2128; (h) Yan, M.-C.; Tu, Z.; Lin, C.; Yao, C.-F. *Tetrahedron Lett.* **2002**, *43*, 7991–7994; (i) Liu, J.-Y.; Liu., J.-T.; Yao, C.-F. *Tetrahedron Lett.* **2001**, *42*, 3613–3615; (j) Chu, C.-M.; Liu, J.-T.; Lin, W.-W.; Yao, C.-F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 47–52; (k) Yao, C.-F.; Chu, C.-M.; Liu, J.-T. *J. Org. Chem.* **1998**, *63*, 719–722.
11. (a) Barange, D. K.; Raju, B. R.; Kavala, V.; Kuo, C.-W.; Tu, Y.-C.; Yao, C.-F. *Tetrahedron* **2010**, *66*, 3754–3760; (b) Barange, D. K.; Kavala, V.; Kuo, C.-W.; Tseng, C.; Tu, Y.-C.; Yao, C.-F. *Tetrahedron Lett.* **2009**, *50*, 5116–5119.
12. For the recent publications on C3-alkylation of 4-hydroxycoumarin: (a) Moghaddam, F. M.; Mirjafary, Z.; Saeidian, H.; Taheri, S.; Soltanzadeh, B. *Tetrahedron* **2010**, *66*, 3673–3681; (b) Yang, H.-M.; Li, L.; Jiang, K.-Z.; Jiang, J.-X.; Lai, G.-Q.; Xu, K.-Z. *Tetrahedron* **2010**, *60*, 9708–9713; (c) Theerthagiri, P.; Lalitha, A. *Tetrahedron Lett.* **2010**, *51*, 5454–5458; (d) Grigg, R.; Whitney, S.; Sridharan, V.; Keep, A.; Derrick, A. *Tetrahedron* **2009**, *65*, 7468–7473; (e) Lin, X.; Dai, X.; Mao, Z.; Wang, Y. *Tetrahedron* **2009**, *65*, 9233–9237; (f) Khoshkholgh, M. J.; Lotfi, M.; Balalaie, S.; Rominger, F. *Tetrahedron* **2009**, *65*, 4228–4234; (g) Reddy, C. H.; Srikanth, B.; Rao, N. N.; Shin, D.-S. *Tetrahedron* **2009**, *64*, 11666–11672.
13. (a) Huang, W.; Wang, J.; Shen, Q.; Zhou, X. *Tetrahedron* **2007**, *64*, 11636–11643; (b) Xie, J.-W.; Yue, L.; Chen, W.; Du, W.; Zhu, J.; Deng, J.-G.; Chen, Y.-C. *Org. Lett.* **2007**, *9*, 413–415; (c) Zhang, L.; Meng, T.; Fan, R.; Wu, J. *J. Org. Chem.* **2007**, *72*, 7279–7286; (d) Chen, Y.-S.; Kuo, P.-U.; Shie, T.-L.; Yang, D.-Y. *Tetrahedron* **2006**, *62*, 9410–9416; (e) Dittmer, D. C.; Li, Q.; Avilov, D. V. *J. Org. Chem.* **2005**, *70*, 4682–4686; (f) Chen, D. U.; Kuo, P. Y.; Yang, D. Y. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2665–2668; (g) Grigg, R.; Nurnabi, M.; Rahul, M.; Sarkar, A. *Tetrahedron* **2004**, *59*, 3359–3373; (h) Halland, N.; Hansen, T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955–4957; (i) Cravotto, G.; Nano, G. M.; Palmisano, G.; Tagliapietra, S. *Synthesis* **2003**, *8*, 1286–1291.
14. For the syntheis of furoquinolinone: (a) Bhoga, U.; Mali, R. S.; Adapa, S. R. *Tetrahedron Lett.* **2004**, *45*, 9483–9485 and references cited therein; (b) Rajamanickam, P.; Shanmugam, P. *Indian J. Chem.* **1987**, *26B*, 910–913; (c) Kano, S.; Shibuya, S.; Ebata, T. *Heterocycles* **1981**, *15*, 1011–1015; (d) Narasimhan, N. S.; Mali, R. S. *Tetrahedron* **1974**, *30*, 4153–4157.
15. Ishikawa, T.; Miyahara, T.; Asakura, M.; Higuchi, S.; Miyauchi, Y.; Saito, S. *Org. Lett.* **2005**, *7*, 1211–1214.
16. (a) Habib, P. M.; Kavala, V.; Kuo, C.-W.; Yao, C.-F. *Tetrahedron Lett.* **2008**, *49*, 7005–7008; (b) Habib, P. M.; Kavala, V.; Raju, B. R.; Kuo, C.-W.; Huang, W. C.; Yao, C.-F. *Eur. J. Org. Chem.* **2009**, 4503–4514.
17. (a) Ansell, G. B.; Moore, D. W.; Neilsen, A. T. *J. Chem. Soc. B* **1971**, 2376–2382; (b) Nagy, P. I.; Kökösi, J.; Gergely, A.; Rácz, A. *J. Phys. Chem. A* **2003**, *107*, 7861–7868; (c) Dominianni, S. J.; Chaney, M. O.; Jones, N. D. *Tetrahedron Lett.* **1970**, *54*, 4735–4736.
18. CCDC number of the **12a** and **15a** are 793324 and 793322 respectively. These data can be obtained free of charge from Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/datarequest/cif.
19. We are thankful the reviewer for his valuable suggestion regarding the mechanism.