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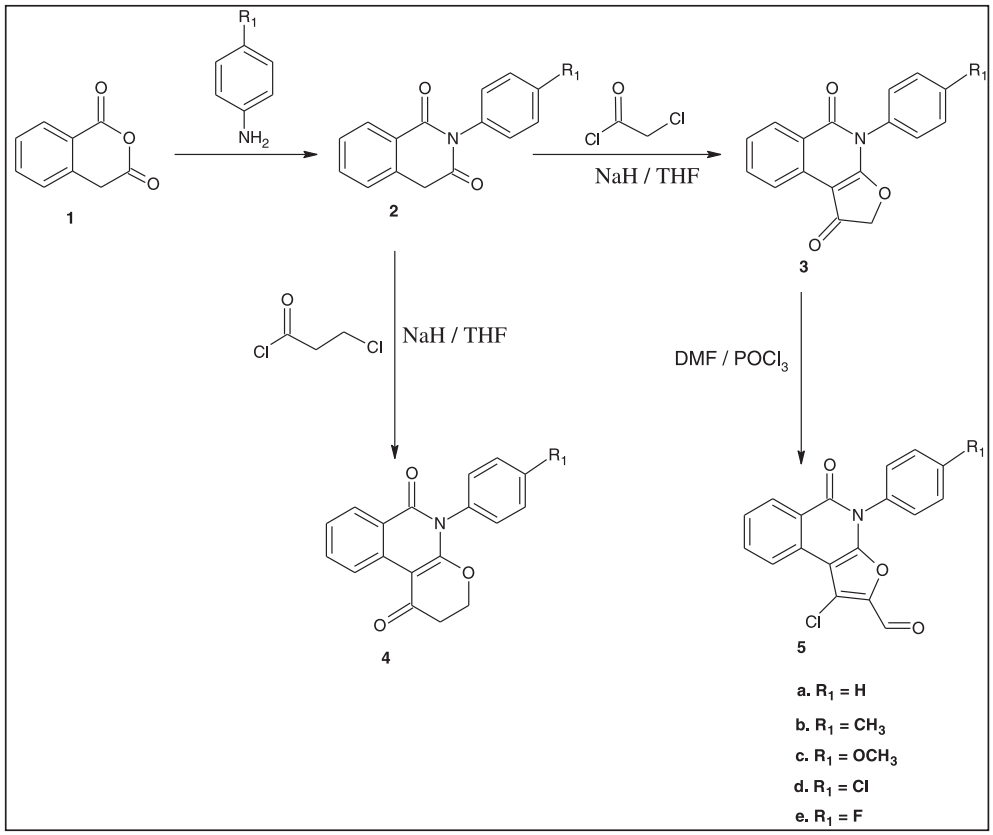
Received March 28, 2011
DOI 10.1002/jhet.1105
Published online 27 June 2013 in Wiley Online Library (wileyonlinelibrary.com).



Homophthalic anhydride **1** reacts with different aromatic amines to produce N-substituted homophthalimides **2** under microwave irradiation. A rapid microwave-assisted chemical synthesis of condensed 4-substituted furo [2,3-*c*]isoquinoline-1,5(2*H*,4*H*)-diones **3** and 5-substituted-2,3-dihydro-1*H*-pyrano[2,3-*c*]isoquinoline-1,6(5*H*)-diones **4** involving the condensation of a variety of alkanoyl chlorides with 2-arylisoquinoline-1,3-diones **2** in the presence of base and aprotic solvent is described for the first time. By contrast, the facile ring opening reaction of furo[2,3-*c*]isoquinoline-1,5(2*H*,4*H*)-dione **3** with Vilsmeier–Haack reagent under microwave irradiation yielded the α-β unsaturated carboxyaldehyde **5**. This novel and clean one-pot methodology, which is characterized by very short reaction time and easy workup procedure, can be exploited to generate some novel condensed isoquinoline derivatives.

J. Heterocyclic Chem., **50**, 828 (2013).

INTRODUCTION

Homophthalic anhydrides **1** are very important intermediates in organic synthesis because they have two active sites towards nucleophiles (C_1 and C_3 positions) and another active site towards electrophiles (C_4 position). They have been used for the construction of various types of compounds such as isoquinolinones [1], isocoumarins [2], phthalazines [3], and peri-hydroxy polycyclic aromatic compounds [4], leading to alkaloids, antibiotics, and pharmacologically important compounds. A great number of substituted isoquinoline-1,3(2*H*,4*H*)-dione derivatives have been published as

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HIV-1 reverse transcriptase (RT) polymerase, HIV-1 RT ribonuclease H (RNase H) inhibitors and were reported as a novel class of potent inhibitors that selectively inhibit CDK4 over CDK2 and CDK1 activities [5]. Furoisoquinolines [6] and condensed pyranoisoquinolines [7] have a long and distinguished history on their numerous biological and medicinal applications. The synthesis and biological evaluation [8] of potentially bioactive condensed isoquinolines, appropriately functionalized, especially at the C_3 position, have attracted considerable attention of medicinal chemists worldwide. Therefore, the synthesis of condensed isoquinolines has been a very important process, subject to improvement, from time to time. Prior art synthetic methodologies involve annulation of the isoquinoline ring that resulted in substituted carbocycles and heterocycles [9]. Of these, the most popularly used synthetic methodology is the "Principal Isoquinoline Synthesis", which involves mainly the cyclocondensation of homophthalic anhydride substrates with reagents such as aldehydes, ketones [10], and imines [11], giving rise to products of different heterocyclic families. Alternatively, use of alkanoyl chlorides for cyclocondensation with homophthalic anhydride substrate is less exploited and is reported under basic conditions [12]. The direct use of alkanoyl chlorides in these cyclocondensation is attractive as it offers more flexibility and generates a variety of 4- and 5-substituents in the resultant condensed isoquinolines. The direct use of the electrophilic properties of alkanoyl chlorides in such synthesis, although previously reported [13], has received only scant attention. Benzoylation of **1** can be accomplished by treatment with benzoyl chloride in the presence of base pyridine as a solvent [14]. Acetylation of **1** can be accomplished by treatment with acetyl chloride in the presence of pyridine as a base and solvent [15], but similar preparations of higher alkanoyl derivatives have not been reported.

Reactions that are adaptable for high speed throughout the synthesis have become an important component of the modern medicinal chemist's armory, as a great number of compounds can be produced through such rapid parallel synthetic programs [16]. Synthetic methods that enable the rapid production of an array of heterocycles, useful for the identification of new lead structures, are of critical importance from the point of new drug discovery. Moreover, isoquinolines have been extensively studied as building blocks for a wide range of important biologically active heterocyclic compounds such as furoisoquinolines and pyranoisoquinolines and show a significant pharmacological activity against a variety of molecular targets [17]. Therefore, these studies represent a simple introduction of a plethora of substituent into the structures of these substituted isoquinolines, which still constitutes a challenge for the scientific community.

In the present manuscript, we report on the synthesis of N-substituted homophthalimides by the reaction of homophthalic anhydride with different aromatic amines under microwave irradiation (MWI). The purpose of this investigation was to provide novel derivatives of 4-substituted furo[2,3-*c*]isoquinoline-1,5(2*H*,4*H*)-diones and 5-aryl-2,3-dihydro-1*H*-pyrano[2,3-*c*]isoquinoline-1,6(5*H*)-diones involving the condensation of variety of alkanoyl chlorides with 2-arylisoquinoline-1,3-diones in the presence of sodium hydride as a base with the use of tetrahydrofuran as a solvent by conventional method as well as MWI, and a comparison of both methods has been carried out. This obtained product furo[2,3-*c*]isoquinoline-1,5(2*H*,4*H*)-diones undergoes Vilsmeier–Haack formylation reactions under MWI affords the α-β unsaturated carboxyaldehyde.

In this paper, we present a full account of the aforementioned chemistry that includes complete experimental details and a detailed characterization of all products.

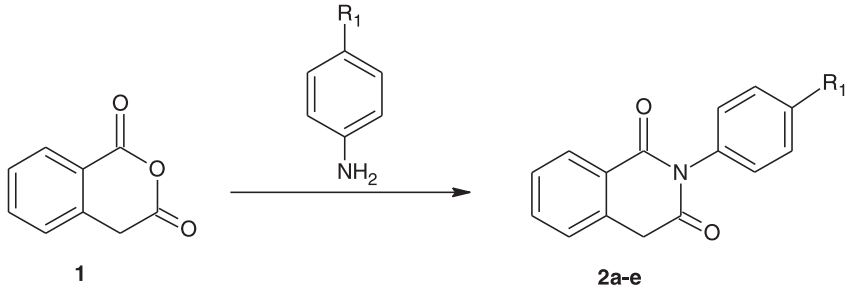
RESULTS AND DISCUSSION

The isoquinolines were synthesized by a direct one-pot process under thermal and microwave conditions. In the thermal conditions, a mixture of homophthalic anhydride and substituted aromatic amines was fused at 150–170 °C for 2–4 h yielded (65–78%) tetrahydroisoquinoline-1,3-diones [18] **2a–e** (Scheme 1) in a one-pot process. In the microwave conditions, the synthetic procedure involved homophthalic anhydride with substituted aromatic amines in 1,2-dichlorobenzene solution exposed under MWI at 150 °C at (initial power 200 W) for 20–25 min in a self-tuning single-mode CEM Discover™ synthesizer (CEM Corporation, Matthews, NC). This procedure is highly comparable with others reported in the literature [18], having the advantages such as higher yields and shortened reaction times. The comparison data of 2-substituted isoquinoline-1,3-diones **2a–e** synthesized under microwave as well as conventional conditions are presented in Table 1.

We envisaged the construction of furan ring on 3,4 bond of the isoquinoline-1,3(2*H*,4*H*)-diones **2** by utilizing the reactivity of active methylene group at C-4 position, which is highly reactive because it is located between two electron withdrawing groups; on one side, there is a carbonyl and on other side the benzene ring. This makes the protons of the methylene group highly acidic; because of this, it readily loses the proton in the presence of a suitable base as a result of which carbanion is generated and the adjacent enolizable carbonyl group is obtained, which is further stabilized by resonance.

Compound **2** is efficiently acylated by reaction with an alkanoyl chloride when conducted in pyridine. It appears that pyridine undergoes a reaction with the acid chloride to generate an intermediate *N*-acylpyridinium cation that is more reactive than the starting acid chloride. As a part of this work, we have found that prolonged heating of reaction mixture **2** with an alkanoyl chloride in the presence of

Scheme 1



1 **2a-e**

2a. $R_1 = H$

2b. $R_1 = CH_3$

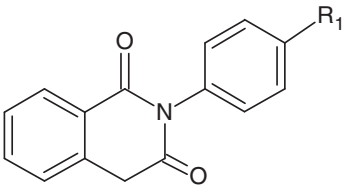
2c. $R_1 = OCH_3$

2d. $R_1 = Cl$

2e. $R_1 = F$

Table 1

Physical data and comparison between conventional and microwave synthesis of 2-substituted isoquinoline-1,3-diones (**2a–e**).



2a-e

	Conventional method[a]			Microwave-assisted method[b]		
R_1	Yield (%)	mp (°C)	Time (h)	Yield (%)	mp (°C)	Time (min)
–H	66	184–185 **2a**	2–3	78	184–185	20
$–CH_3$	76	154–156 **2b**	2–3	80	154–156	15
$–OCH_3$	70	179–180 **2c**	2–4	80	178–180	25
–Cl	68	171–172 **2d**	2–3	75	173–174	20
–F	75	198–200 **2e**	2–4	80	198–200	18

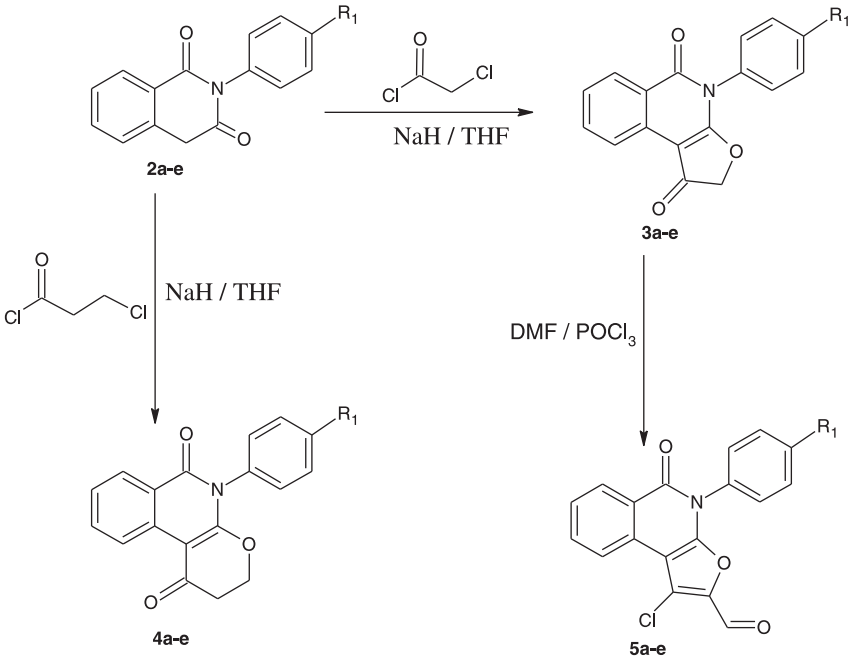
2a Reported mp 184–185 °C [18]. **2b** Reported mp 154–156 °C [18]. **2c** Reported mp 179–180 °C [18]. **2d** Reported mp 171–172 °C [18]. **2e** Reported mp 198–200 °C [18].
[a]Heated at 150–170 °C for 2–4 h.
[b]Irradiation at 200 W for 15–25 min.

triethylamine or excess of pyridine is refluxed and produced only traces of the desired alkanoyl derivative. Unfortunately, this method is not suitable for the preparation of nucleophile-sensitive compounds such as **3a–e** (Scheme 2).

We started the experiments by using different alkanoyl chlorides such as chloroacetyl chloride and 3-chloropropionyl chloride. The conventional methods for the synthesis of the target condensed 4-substituted furo[2,3-*c*] isoquinoline-1,5(2*H*,4*H*)-diones **3a–e** are through the cyclization of appropriate 2-substituted isoquinoline-1,3 (2*H*,4*H*)-diones **2a–e** with these alkanoyl chlorides under basic condition in dry polar aprotic solvent tetrahydrofuran at 0–5 °C for 5–6 h and heated on a water bath for 1–2 h, obtained with an overall yield of 65–80%. Similarly, reaction of sodium derivative 2-substituted isoquinoline-1,3 (2*H*,4*H*)-diones **2a–e** with 3-chloropropionyl chloride gave the corresponding 5-aryl-2,3-dihydro-1*H*-pyrano[2,3-*c*] isoquinoline-1,6(5*H*)-diones **4a–e**. This particular reaction mixture is stirred continuously at 0–5 °C for 7–8 h and then heated on a water bath for 2–3 h, obtained with an overall yield of 68–80%.

Interestingly, these same reactions under MWI at 150 W were accomplished by the use of tetrahydrofuran as a

Scheme 2



solvent and 60% sodium hydride as a base in very short periods. The physical data for the 4-substituted furo[2,3-*c*] isoquinoline-1,5(2*H*,4*H*)-diones **3a–e** and 5-substituted pyrano[2,3-*c*]isoquinolines-1,6(5*H*)-diones **4a–e** synthesized under MWI is presented in Table 2. The reaction time varied depending upon the type of alkanoyl chlorides used. The reactions with chloroacetyl chloride were completed in 30–40 min to obtain the condensed 4-substituted furo[2,3-*c*]isoquinoline-1,5(2*H*,4*H*)-diones **3a–e** with isolated yields ranging from 72% to 90%. Similarly, reactions with 3-chloropropionyl chloride were completed in 35–45 min and afforded the condensed 5-substituted-2,3-dihydro-1*H*-pyrano[2,3-*c*]isoquinoline-1,6(5*H*)-diones **4a–e** in 75–90% yields (Scheme 2). Thus, in all the aforementioned cases, there is considerable reduction in the reaction times, when conventional heating is replaced by microwave-assisted heating, that is, from 8–14 h to 30–45 min, respectively. Considerable improvement in yields was also observed.

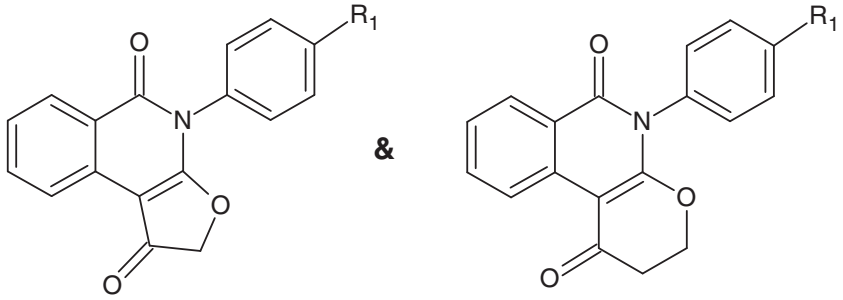
Thus, the ^{1}H NMR spectra of **3a–e** taken in anhydrous $CDCl_3$ do not show the –OH resonance form. It showed a singlet of two protons at δ 4.70 attributed to –O–CH_2–CO– of the furanone moiety. The structure is such in furo [2,3-*c*]isoquinoline-1,5(2*H*,4*H*)-dione agreement by ^{13}C NMR predicted value for the all-carbonyl tautomer is δ 76.30 for all compounds **3a–e**. It gave a positive DNP test, and chlorine was found to be absent. This compound contained furo[2,3-*c*]isoquinoline-1,5(2*H*,4*H*)-dione **3a**, and its mass spectrum (ESI mode) showed molecular ion peak at 278 M^+.

^{1}H NMR spectra of **4a–e** taken in anhydrous $CDCl_3$ (−OH) resonance was not observed. It shows the presence of two triplet of two protons δ 2.82 and δ 4.58 attributed to O–CH_2–CH_2–CO– of the pyranone moiety. It gave a positive DNP test, and chlorine was found to be absent. This compound contained pyrano[2,3-*c*]isoquinoline-1,6(5*H*)-dione **4a**, and its mass spectrum (ESI mode) showed molecular ion peak at 292 M^+.

In contrast to the facile nucleophile-mediated furan ring opening reaction of **3**, the ring system of **3** is stable under electrophilic conditions. The methylene group in the furan ring of compound **3** is sufficiently active. We therefore decided to introduce Vilsmeier–Haack formylation at the active methylene group. Vilsmeier–Haack reagent was prepared by dropwise addition of phosphorus oxychloride to an ice-cold solution of dimethylformamide. The reaction mixture was warmed on water bath at 80 °C for 3–4 h and then poured into ice-cold water, which resulted in the

Table 2

Physical data of other 4-substituted isoquinoline-1,5-diones (**3a–e**) and 5-substituted isoquinoline-1,6-diones (**4a–e**).



3a-e **4a-e**

		Conventional method[a]			Microwave-assisted method[b]		
	R_1	Yield (%)	mp (°C)	Time (h)	Yield (%)	mp (°C)	Time (min)
3a	–H	66	225–226	8–10	72	225–226	25
3b	$-CH_3$	76	274–276	9–10	89	274–276	35
3c	$-OCH_3$	80	258–259	8–10	90	258–259	25
3d	–Cl	70	248–249	8–9	82	248–249	40
3e	–F	68	195–196	8–10	75	195–196	30
4a	–H	75	212–213	12–14	85	212–213	35
4b	$-CH_3$	80	230–231	14–15	88	230–231	40
4c	$-OCH_3$	68	199–200	13–14	75	199–200	30
4d	–Cl	80	214–215	12–14	85	214–215	40
4e	–F	70	194–195	12–13	82	194–195	30

[a]Stirred for 5–6 h at 0–5 °C and then refluxed for 1–2 h (**3a–e**); stirred for 7–8 h at 0–5 °C and refluxed for 2–3 h (**4a–e**).
[b]Irradiation at 150 W for 30–40 min (**3a–e**); irradiation at 150 W for 35–45 min (**4a–e**).

formation of the desired compound 1-chloro-5-oxo-4-substituted-4,5-dihydrofuro[2,3-*c*]isoquinoline-2-carbaldehyde **5a–e** with overall yield (66–80%). Classically, this reaction was completed in 3–4 h, so we thought that the same reaction can be carried out under MWI to reduce the reaction time. Dimethylformamide was added dropwise to the ice-cold solution of $POCl_3$ at 0 °C with constant stirring. To this, **3** was added, and the reaction mixture was exposed to MWI at 80 °C (initial power 120 W) for 10–15 min in a self-tuning single-mode CEM Discover synthesizer, which resulted in the formation of the desired compound with overall yield (70–90%) **5a–e**. The comparison between conventional and microwave methodologies has been shown in Table 3. Although there was an increase in yield compared with that in the classical method, there was remarkable reduction in reaction time.

CONCLUSION

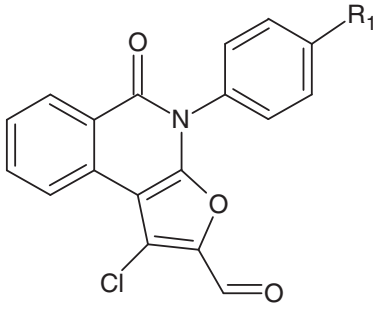
An experimental procedure to obtain N-substituted homophthalimides under MWI from homophthalic anhydride that reacts with different aromatic amines and 1,2-dichlorobenzene as a solvent is described in Table 1. A novel one-pot microwave-assisted synthesis of the condensed 4-substituted furoisoquinoline-1,5-diones **3a–e** and 5-substituted pyranoisoquinoline 1,6-diones **4a–e** from 2-substituted isoquinoline-1,3-diones **2a–e** in the presence of sodium hydride as a base and variety of alkanoyl chlorides in tetrahydrofuran as a solvent was performed by MWI in a controlled temperature with simultaneous cooling system in open vessel with the use of the CEM Discover synthesizer. This novel synthesis involving chlorides as building blocks, under MWI for these condensed 4-substituted furoisoquinoline-1,5-diones and 5-substituted pyranoisoquinoline-1,6-diones, requires only 20–45 min as compared with the conventional heating protocols that require 6–14 h, thereby showing a significant acceleration in reaction rates (Table 2). Varying the reaction condition of furo[2,3-*c*]isoquinoline-1,5(2*H*,4*H*)-diones **3a–e** with Vilsmeier–Haack reagent exposed under MWI 10–15 min yielded the α-β unsaturated carboxyaldehyde **5a–e** (Table 3). Coupled with simple workup procedures and superior yields, the methodology is eminently suitable for the generation of diverse libraries.

EXPERIMENTAL

Microwave reactions were conducted with the use of a CEM Discover Synthesis unit (CEM Corp. Matthews, NC). The machine consists of a continuous focused microwave power delivery system with operator selectable power output from 0 to 300 W reactions were performed in open vessel and glass vessels (capacity 10 mL) sealed with a septum. The pressure is controlled

Table 3

A comparison between conventional and microwave synthesis of 1-chloro-5-oxo-4-substituted-4,5-dihydrofuro[2,3-*c*]isoquinoline-2-carbaldehyde (**5a–e**).



5a-e

		Conventional method[a]			Microwave-assisted method[b]		
	R_1	Yield (%)	mp (°C)	Time (h)	Yield (%)	mp (°C)	Time (min)
5a	–H	66	250–252	3–4	70	250–252	10
5b	$-CH_3$	76	245–247	2–3	89	245–247	15
5c	$-OCH_3$	80	268–270	2–4	90	268–270	12
5d	–Cl	70	255–257	2–3	82	255–257	15
5e	–F	68	260–262	2–4	75	260–262	12

[a]Heated at 80 °C for 3–4 h.
[b]Irradiation at 120 W for 10–15 min.

by a load cell connected to the vessel via a 14-gauge needle, which penetrates just below the septum surface. The temperature of the contents of the vessel was monitored with the use of a calibrated IR temperature control mounted under the reaction vessel. All experiments were performed with the use of a stirring option whereby the contents of the vessel are stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. Tetrahydrofuran was distilled from benzophenone ketyl immediately before use. All reactions were conducted under a nitrogen atmosphere. The melting points were determined in open capillary on Veego (VMP-D) electronic apparatus and are uncorrected. The IR spectra of synthesized compounds were recorded on Perkin Elmer BX2 FT-IR Spectrophotometer in KBr and reported in cm^{-1}. ^1H NMR spectra were measured on a Varian Mercury YH-400 FT NMR spectrometer in $CDCl_3$, DMSO-d_6 with chemical shifts (δ) given in ppm relative to TMS as internal standard. Thin-layer chromatography was performed on precoated silica plates (Merck Silica gel F 254) with the use of hexane–ethyl acetate (4.5 mL : 0.5 mL) and chloroform–methanol (4.5 mL : 0.5 mL) as the solvent systems, and the spots were visualized by exposure to iodine vapors or under UV light.

General procedure: Reaction of homophthalic anhydride 1 with aromatic amines

Conventional method (A). A mixture of homophthalic anhydride **1** (0.01 mol) and substituted aromatic amines (0.01 mol) was fused in an oil bath for 2–4 h at 150–170 °C. A clear thick solution was obtained, which on cooling at room temperature gave the gray hard solid. This solid was then refluxed with acetic acid (20 mL) in the same flask for 20 min. The resulted solution on cooling gave crystallized solid. The product was recrystallized from acetic acid and yielded the appropriate condensed 2-substituted isoquinoline-1,3(2*H*,4*H*)-diones **2a–e**.

Microwave method (B). A mixture of the appropriate aromatic amine substrates (0.001 mol), homophthalic anhydride **1** (0.001 mol), and 5 mL 1,2 dichlorobenzene was exposed to MWI at 150 °C (initial power 200 W) for 20–25 min in a self-tuning single-mode CEM Discover synthesizer. The progress of reaction was monitored by (using TLC) after 5-min intervals. The resulting reaction mixture was allowed to cool at room temperature and poured into ice water. The resulting precipitated solid was collected by filtration, washed with chilled water, and dried. The crude product on recrystallization from methanol yielded the condensed 2-substituted isoquinoline-1,3(2*H*,4*H*)-diones **2a–e**.

2-Phenylisoquinoline-1,3(2H,4H)-dione (2a). mp 184–185 °C; IR (KBr, *v*, cm^{-1}): –CO 1683, 1729; ^1H NMR ($CDCl_3$): δ (ppm) 4.23 (s, 2H, $-CH_2$), 7.21 (d, 2H, Ar–H), 7.35 (d, 1H, Ar–H), 7.43–7.49 (m, 4H, Ar–H), 7.61 (t, 1H, Ar–H), 8.22 (d, 1H, Ar–H); MS (APCI, *m/z*): 238.21 $[M+H]^+$. *Anal*. Calcd for $C_{15}H_{12}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.92; H, 4.68; N, 5.91.

2-p-Tolylisoquinoline-1,3(2H,4H)-dione (2b). This compound was obtained according to the aforementioned general procedure; mp 154–156 °C; IR (KBr, *v*, cm^{-1}): –CO 1671, 1713; ^1H NMR ($CDCl_3$): δ (ppm) 2.42 (s, 3H, $-CH_3$), 4.22 (s, 2H, $-CH_2$), 7.09 (d, 2H, Ar–H), 7.30 (m, 3H, Ar–H), 7.46 (t, 1H, Ar–H), 7.62 (t,1H, Ar–H), 8.23 (d, 1H, Ar–H); MS (APCI, *m/z*): 252.10 $[M+H]^+$. *Anal*. Calcd for $C_{16}H_{14}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.46; H, 5.20; N, 5.59.

2-(4-Methoxyphenyl)isoquinoline-1,3(2H,4H)-dione (2c). This compound was obtained according to the aforementioned general procedure; mp 179–180 °C; IR (KBr, *v*, cm^{-1}): –CO 1659, 1740; ^1H NMR ($CDCl_3$): δ (ppm) 3.85 (s, 3H, $–OCH_3$), 4.22 (s, 2H, $–CH_2$), 7.02 (d, 2H, Ar–H), 7.12 (d, 2H, Ar–H), 7.34 (d, 1H, Ar–H), 7.48 (t, 1H, Ar–H), 7.64 (t, 1H, Ar–H), 8.24 (d, 1H, Ar–H); MS (APCI, *m/z*): 268.23 $[M+H]^+$. *Anal*. Calcd for $C_{16}H_{14}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.94; H, 4.92; N, 5.21.

2-(4-Chlorophenyl)isoquinoline-1,3(2H,4H)-dione (2d). This compound was obtained according to the aforementioned general procedure; mp 173–175 °C; IR (KBr, *v*, cm^{-1}): –CO 1635, 1750; ^1H NMR ($CDCl_3$): δ (ppm) 4.23 (s, 2H, $–CH_2$), 7.15 (d, 2H, Ar–H), 7.32 (d, 1H, Ar–H), 7.46 (m, 3H, Ar–H), 7.64 (t, 1H, Ar–H), 8.24 (d, 1H, Ar–H); MS (APCI, *m/z*): 272.20 $[M+H]^+$. *Anal*. Calcd for $C_{15}H_{11}ClNO_2$: C, 66.31; H, 3.71; N, 5.16. Found: C, 66.32; H, 3.74; N, 5.17.

2-(4-Fluorophenyl)isoquinoline-1,3(2H,4H)-dione (2e). This compound was obtained according to the aforementioned general procedure; mp 198–200 °C; IR (KBr, *v*, cm^{-1}): –CO 1675, 1730; ^1H NMR ($CDCl_3$): δ (ppm) 4.23 (s, 2H, $–CH_2$), 7.18–7.20 (m, 4H, Ar–H), 7.36 (d, 1H, Ar–H), 7.49 (t, 1H, Ar–H), 7.66 (t, 1H, Ar–H), 8.24 (d, 1H, Ar–H); MS (APCI, *m/z*): 256.19 $[M+H]^+$. *Anal*. Calcd for $C_{15}H_{11}FNO_2$: C, 70.58; H, 3.95; N, 5.49. Found: C, 70.60; H, 3.97; N, 5.51.

General procedure: Reaction of 2-arylisoquinoline-1,3(2*H*,4*H*)-diones 2a–e with chloroacetyl chloride

Conventional method (A). A solution of 2-arylisoquinoline-1,3(2*H*,4*H*)-diones **2a–e** (0.01 mol) in tetrahydrofuran (25 mL) is mixed with a suspension of 60% sodium hydride (0.02 mol) in tetrahydrofuran (20 mL), and the mixture was stirred under nitrogen atmosphere for 1 h. After being cooled at 0 °C, chloroacetyl chloride (0.02 mol) was added dropwise for a period of 20 min with continuous stirring for 5–6 h at 0 °C. The reaction was then heated on a water bath for 1–2 h. The completion of the reaction mixture was checked by TLC. Further, dry methanol (10 mL) was added to quench the excess of sodium hydride. The reaction mixture was then concentrated under reduced pressure and filtered, and the product was washed with water. The crude product on recrystallization from methanol yielded the appropriate condensed 4-substituted furo[2,3-*c*]isoquinoline-1,5(2*H*,4*H*)-diones **3a–e**.

Microwave method (B). To a solution of 2-arylisoquinoline-1,3(2*H*,4*H*)-diones **2a–e** (0.01 mol) in tetrahydrofuran (25 mL), a suspension of 60% sodium hydride (0.02 mol) in tetrahydrofuran (20 mL) was charged in a round-bottom glass flask containing a magnetic stirring bar and fitted with a reflux condenser, which was attached to a water aspirator. The flask was placed in a CEM Discover Focused Microwave Synthesis System, which is designed to house a round-bottom flask (50 mL). Reaction mixture was stirred under nitrogen atmosphere, and chloroacetyl chloride (0.02 mol) diluted in tetrahydrofuran (20 mL) was added dropwise at 0 °C. The reaction mixture was exposed to MWI at 45 °C (initial power 150 W) for 30–40 min in a self-tuning single-mode CEM Discover synthesizer. After cooling, dry methanol (10 mL) was added to quench the excess of sodium hydride. The reaction mixture was then concentrated under reduced pressure and filtered, and the product was washed with water. Recrystallization from methanol yielded the appropriate condensed 4-substituted furo[2,3-*c*]isoquinoline-1,5(2*H*,4*H*)-diones **3a–e**.

***4-Phenylfuro[2,3-c]*isoquinoline-1,5(2*H*,4*H*)-dione (3a).** mp 225–226 °C; IR (KBr, *v*, cm^{-1}): –CO 1619, 1675; ^1H NMR ($CDCl_3$): δ (ppm) 4.75 (s, 2H, $–CH_2$), 7.38 (d, 2H, Ar–H), 7.47 (t, 1H, Ar–H), 7.56–7.60 (m, 3H, Ar–H), 7.74 (d, 1H, Ar–H), 8.31 (d, 1H, Ar–H), 8.41 (d, 1H, Ar–H); ^{13}C NMR ($CDCl_3$): δ (ppm) 76.45, 94.29, 121.40, 122.68, 126.23, 128.10, 129.0, 129.54, 129.71, 131.06, 132.50, 134.54, 162.46, 172.96, 190.98; MS (ESI, *m/z*): 278.39 $[M+H]^+$. *Anal*. Calcd for $C_{17}H_{11}NO_3$: C, 73.64; H, 4.00; N, 5.05. Found: C, 73.60; H, 3.98; N, 5.01.

***4-(4-Methylphenyl)furo[2,3-c]*isoquinoline-1,5(2*H*,4*H*)-dione (3b).** This compound was obtained according to the aforementioned general procedure; mp 258–259 °C; IR (KBr, *v*, cm^1): –CO 1625, 1667; ^1H NMR ($CDCl_3$): δ (ppm) 2.48 (s, 3H, $–CH_3$), 4.76 (s, 2H, $–CH_2$), 7.26 (d, 2H, Ar–H), 7.39–7.47 (m, 3H, Ar–H), 7.75 (t, 1H, Ar–H), 8.32 (d, 1H, Ar–H), 8.42 (d, 1H, Ar–H); ^{13}C NMR ($CDCl_3$): δ (ppm) 21.52, 94.55, 121.72, 122.99, 126.40, 128.04, 129.30, 130.08, 130.50, 131.34, 134.78, 140.23, 162.91, 173.38, 191.24; MS (ESI, *m/z*): 292.35 $[M+H]^+$. *Anal*. Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.26; H, 4.48; N, 4.84.

***4-(4-Methoxyphenyl)furo[2,3-c]*isoquinoline-1,5(2*H*,4*H*)-dione (3c).** This compound was obtained according to the aforementioned general procedure; mp 274–275 °C; IR (KBr, *v*, cm^{-1}): –CO 1623, 1656; ^1H NMR ($CDCl_3$): δ (ppm) 3.86 (s, 3H, $–OCH_3$), 4.87 (s, 2H, $–CH_2$), 7.10 (d, 2H, Ar–H), 7.41–7.48 (m, 3H, Ar–H), 7.81 (t, 1H, Ar–H), 8.18 (d, 1H, Ar–H), 8.33 (d, 1H, Ar–H); ^{13}C NMR ($CDCl_3$): δ (ppm) 55.87, 94.58, 115.10, 121.73, 123.02, 125.17, 126.50, 129.33, 129.41, 129.51, 131.38, 134.80, 160.60, 163.07, 173.57, 191.27; MS (ESI, *m/z*): 308.31 $[M+H]^+$. *Anal*. Calcd for $C_{18}H_{13}NO_4$: C, 70.34; H, 4.26; N, 4.56. Found: C, 70.30; H, 4.30; N, 4.58.

***4-(4-Chlorophenyl)furo[2,3-c]*isoquinoline-1,5(2*H*,4*H*)-dione (3d).** This compound was obtained according to the aforementioned general procedure; mp 248–249 °C; IR (KBr, *v*, cm^{-1}): –CO 1627, 1675; ^1H NMR ($CDCl_3$): δ (ppm) 4.75 (s, 2H, $–CH_2$), 7.33 (m, 2H, Ar–H), 7.46 (t, 1H, Ar–H), 7.55–7.57 (m, 2H, Ar–H), 7.77 (m, 1H, Ar–H), 8.30 (d, 1H, Ar–H), 8.41 (d, 1H, Ar–H); ^{13}C NMR ($CDCl_3$): δ (ppm) 76.77, 94.72, 121.59, 123.09, 126.69, 129.35, 129.79, 130.10, 131.17, 131.31, 135.02, 136.11, 162.62, 172.96, 191.13; MS (ESI, *m/z*): 312.31 $[M+H]^+$. *Anal*. Calcd for $C_{17}H_{10}ClNO_3$: C, 65.50; H, 3.23; N, 11.37. Found: C, 65.55; H, 3.26; N, 11.40.

***4-(4-Fluorophenyl)furo[2,3-c]*isoquinoline-1,5(2*H*,4*H*)-dione (3e).** This compound was obtained according to the aforementioned general procedure; mp 195–196 °C; IR (KBr, *v*, cm^{-1}): –CO 1623, 1669; ^1H NMR ($CDCl_3$): δ (ppm) 4.74 (s, 2H, $–CH_2$), 7.24 (m, 2H, Ar–H), 7.29–7.46 (m, 3H, Ar–H), 7.74 (d, 1H, Ar–H), 8.27 (d, 1H, Ar–H), 8.40 (d, 1H, Ar–H); ^{13}C NMR ($CDCl_3$): δ (ppm) 76.39, 94.26, 116.44, 121.14, 122.53, 126.18, 128.18, 128.86, 129.94, 130.03, 130.91, 134.52, 162.36, 164.05, 172.95, 190.85; MS (ESI, *m/z*): 296.25 $[M+H]^+$. *Anal*. Calcd for $C_{17}H_{10}FNO_3$: C, 69.15; H, 3.41; N, 4.74. Found: C, 69.12; H, 3.45; N, 4.70.

Reaction of 2-arylisoquinoline-1,3(2*H*,4*H*)-diones with 3-chloropropionyl chloride

Conventional method (A). A solution of 2-arylisoquinoline-1,3(2*H*,4*H*)-diones (0.01 mol) in tetrahydrofuran (25 mL) was added to a suspension of sodium hydride (0.02 mol) in tetrahydrofuran (20 mL), and the mixture was stirred under nitrogen atmosphere for 1 h. After being cooled at 0 °C, 3-chloropropionyl chloride (0.02 mol) was added dropwise for a period of 20 min with continuous stirring for 7–8 h at 0 °C. The reaction was then heated on a water bath for 2–3 h. The completion of the reaction mixture was checked by TLC. Further, dry methanol (10 mL) was added to quench the excess of sodium hydride. The reaction mixture was then concentrated under reduced pressure and filtered, and the product was washed with water. The crude product on recrystallization from methanol yielded the condensed 5-(4-substituted)-2,3-dihydro-1*H*-pyrano[2,3-*c*] isoquinoline-1,6(5*H*)-diones **4a–e**.

Microwave method (B). To a solution of 2-arylisoquinoline-1,3(2*H*,4*H*)-diones (0.01 mol) in tetrahydrofuran (25 mL), a suspension of 60% sodium hydride (0.02 mol) in tetrahydrofuran (20 mL) was charged in a round-bottom glass flask containing a magnetic stirring bar and fitted with a reflux condenser, which was attached to a water aspirator. The flask was placed in a CEM Discover Focused Microwave Synthesis system, which is designed to house a round-bottom flask (50 mL). Reaction mixture was stirred under nitrogen atmosphere, in which 3-chloropropionyl chloride (0.02 mol) diluted in tetrahydrofuran (20 mL) was added dropwise at 0 °C. The reaction mixture was exposed to MWI at 45 °C (initial power 150 W) for 35–45 min in a self-tuning single-mode CEM Discover synthesizer. After cooling, dry methanol (10 mL) was added to quench the excess of sodium hydride. Further, the reaction mixture was concentrated under reduced pressure. The filtered product washed with water recrystallization from methanol yielded the condensed 5-(4-substituted)-2,3-dihydro-1*H*-pyrano[2,3-*c*]isoquinoline-1,6(5*H*)-diones **4a–e**.

***5-Phenyl-2,3-dihydro-1H*-pyrano[2,3-*c*]isoquinoline-1,6(5*H*)-dione (4a).** mp 212–213 °C; IR (KBr, *v*, cm^{-1}): –CO 1647, 1672; ^1H NMR ($CDCl_3$): δ (ppm) 2.81 (t, 2H, $–CH_2$), 4.56 (t, 2H, $–CH_2$), 7.27 (m, 2H, Ar–H), 7.43 (q, 1H, Ar–H), 7.51–7.56 (m, 3H, Ar–H), 7.75 (d, 1H, Ar–H), 8.32 (m, 1H, Ar–H), 9.25 (d, 1H, Ar–H); ^{13}C NMR ($CDCl_3$): δ (ppm) 37.2, 68.6, 95.8, 122.1, 125.5, 125.9, 128.1, 128.4, 129.1, 129.5, 134.2, 134.3, 135.0, 161.4, 162.4, 188.6; MS (APCI, *m/z*): 292.16 $[M+H]^+$. *Anal*. Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.25; H, 4.48; N, 4.85.

5-(4-Methylphenyl)-2,3-dihydro-1H-pyrano[2,3-c]isoquinoline-1,6(5H)-dione (4b). This compound was obtained according to the aforementioned general procedure; mp 199.0–199.2 °C; IR (KBr, *v*, cm^{-1}): –CO 1651, 1674; ^1H NMR ($CDCl_3$): δ (ppm) 2.46 (s, 3H, $–CH_3$), 2.80 (t, 2H, $–CH_2$), 4.57 (t, 2H, $–CH_2$), 7.15 (d, 2H, Ar–H), 7.34–7.42 (m, 3H, Ar–H), 7.70 (q, 1H, Ar–H), 8.32 (d, 1H, Ar–H), 9.23 (d, 1H, Ar–H); ^{13}C NMR ($CDCl_3$): δ (ppm) 21.4, 37.2, 68.6, 95.8, 122.0, 125.4, 125.8, 128.1, 130.2, 132.3, 134.2, 139.1, 161.5, 162.4, 188.7; MS (ESI, *m/z*): 306.40 $[M+H]^+$. *Anal*. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.71; H, 4.92; N, 4.56.

5-(4-Methoxyphenyl)-2,3-dihydro-1H-pyrano[2,3-c]isoquinoline-1,6(5H)-dione (4c). This compound was obtained according to the aforementioned general procedure; mp 230–231 °C; IR (KBr, *v*, cm^{-1}): –CO 1645, 1682; ^1H NMR ($CDCl_3$): δ (ppm) 2.80 (t, 2H, $–CH_2$), 3.85 (s, 3H, $–OCH_3$), 4.57 (t, 2H, $–CH_2$), 7.01 (t, 2H, Ar–H), 7.14 (q, 2H, Ar–H), 7.39 (m, 1H, Ar–H), 7.69 (m, 1H, Ar–H), 8.31 (d, 1H, Ar–H), 9.23 (d, 1H, Ar–H); ^{13}C NMR ($CDCl_3$): δ (ppm) 37.1, 55.5, 68.6, 95.8, 114.7, 122.0, 125.4, 125.8, 127.3, 128.1, 129.3, 134.1, 134.2, 159.8, 161.7, 162.5, 188.6; MS (ESI, *m/z*): 322.31 $[M+H]^+$. *Anal*. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 71.05; H, 4.68; N, 4.38.

5-(4-Chlorophenyl)-2,3-dihydro-1H-pyrano[2,3-c]isoquinoline-1,6(5H)-dione (4d). This compound was obtained according to the aforementioned general procedure; mp 214.0–215 °C; IR (KBr, *v*, cm^{-1}): –CO 1650, 1674; ^1H NMR ($CDCl_3$): δ (ppm) 2.77 (t, 2H, $–CH_2$), 4.63 (t, 2H, $–CH_2$), 7.41 (t, 3H, Ar–H), 7.59 (d, 2H, Ar–H), 7.77 (t, 1H, Ar–H), 8.20 (d, 1H, Ar–H), 9.20 (d, 1H, Ar–H); ^{13}C NMR ($CDCl_3$): δ (ppm) 37.33, 68.83, 96.11, 122.10, 125.72, 126.20, 128.29, 129.90, 129.98, 133.55, 134.23, 134.65, 135.27, 161.21, 162.33, 188.61; MS (ESI, *m/z*): 326.65 $[M+H]^+$. *Anal*. Calcd for $C_{18}H_{12}ClNO_3$: C, 66.37; H, 3.71; N, 4.30. Found: C, 66.38; H, 3.72; N, 4.28.

5-(4-Fluorophenyl)-2,3-dihydro-1H-pyrano[2,3-c]isoquinoline-1,6(5H)-dione (4e). This compound was obtained according to the aforementioned general procedure; mp 194.3–194.6 °C; IR (KBr, *v*, cm^{-1}): –CO 1661, 1685; ^1H NMR ($CDCl_3$): δ (ppm) 2.75 (t, 2H, $–CH_2$), 4.52 (t, 2H, $–CH_2$), 7.12–7.19 (m, 4H, Ar–H), 7.35 (t, 1H, Ar–H), 7.65 (t, 1H, Ar–H), 8.23 (m, 1H, Ar–H), 9.15 (d, 1H, Ar–H); ^{13}C NMR ($CDCl_3$) :δ (ppm) 36.8, 68.4, 95.6, 116.1, 116.3, 121.6, 125.2, 125.6, 127.7, 129.9, 130.0, 130.4, 133.8, 134.1 161.0, 162.0, 163.5, 188.2; MS (ESI, *m/z*): 310.18 $[M+H]^+$. *Anal*. Calcd for $C_{18}H_{12}FNO_3$: C, 69.90; H, 3.91; N, 4.53. Found: C, 69.92; H, 3.90; N, 4.50.

General procedure: Vilsmeier–Haack formylation of 4-substituted furo[2,3-*c*]isoquinoline-1,5(2*H*,4*H*)-diones 3a–e

Conventional method (A). Dimethylformamide (0.01 mol) was added dropwise to the ice-cold solution of $POCl_3$ (0.03 mol) at 0 °C with constant stirring. The complex thus formed was further stirred for 45 min, and 4-arylfuro[2,3-*c*] isoquinoline-1,5(2*H*,4*H*)-diones **3a–e** (0.01 mol) was added to this. Then, the reaction mixture was heated on a water bath at 80 °C for 4–5 h, cooled to room temperature, and poured in an ice-water mixture (50–75 mL). The reaction mixture was neutralized with saturated $NaHCO_3$ solution. The separated solid was collected by filtration, washed with water, dried, and recrystallized from appropriate solvent.

Microwave method (B). Dimethylformamide (0.01 mol) was charged in a round-bottom glass flask containing a magnetic stirring bar fitted with a reflux condenser, which was attached to a water aspirator, and $POCl_3$ (0.03 mol) was added dropwise to the ice-cold solution at 0 °C with constant stirring. The complex thus formed was further stirred for 45 min, and 4-arylfuro[2,3-*c*]isoquinoline-1,5 (2*H*,4*H*)-dione **3a–e** (0.01 mol) was added to this. The flask was placed in a CEM Discover Focused Microwave Synthesis System, exposed to MWI at 80 °C (initial power 150 W) for 10–15 min. After the reaction was completed, the flask was removed from the MW cavity, and the mixture was cooled to room temperature, poured in an ice-water mixture (50–75 mL), and neutralized with a saturated $NaHCO_3$ solution. The separated solid was collected by filtration, washed with water, dried, and recrystallized from appropriate solvent **5a–e**.

1-Chloro-4-(phenyl)-5-oxo-1,2,4,5-tetrahydrofuro[2,3-c] **isoquinoline-2-carbaldehyde (5a**). This compound was obtained according to the aforementioned general procedure; mp 250–252 °C; IR (KBr, *v*, cm^{-1}): –CHO 1657, –CO 1687; ^1H NMR ($CDCl_3$): δ (ppm) 7.42 (d, 2H, Ar–H), 7.55–7.63 (m, 4H, Ar–H), 7.84 (t, 1H, Ar–H), 8.47 (d, 2H, Ar–H), 9.71 (s, 1H, –CHO); ^{13}C NMR ($CDCl_3$): δ (ppm) 100.3, 122.2, 124.1, 127.6, 128.0, 129.9, 130.1, 130.2, 132.6, 134, 142.4, 151.3, 161.4, 173.7; MS (APCI, *m*/*z*): 324.19 $[M+H]^+$. *Anal*. Calcd for $C_{18}H_{10}ClNO_3$: C, 66.78; H, 3.11; N, 4.33. Found: C, 66.79; H, 3.12; N, 4.34.

1-Chloro-4-(4-methylphenyl)-5-oxo-1,2,4,5-tetrahydrofuro[2,3-c]isoquinoline-2-carbaldehyde (5b). This compound was obtained according to the aforementioned general procedure; mp 245–247 °C; IR (KBr, *v*, cm^{-1}): –CHO 1627, –CO 1657; ^1H NMR ($CDCl_3$): δ (ppm) 2.48 (s, 3H, $-CH_3$), 7.28 (d, 2H, Ar–H), 7.39 (d, 2H, Ar–H), 7.57 (t, 1H, Ar–H), 7.82 (t, 1H, Ar–H), 8.45 (m, 2H, Ar–H), 9.70 (s, 1H, –CHO); ^{13}C NMR ($CDCl_3$): δ (ppm) 21.4, 100.2, 124.1, 127.5, 127.7, 130.1, 130.2, 130.6, 133.9, 140.1, 142.4, 151.5, 161.3, 173.7; MS (APCI, *m*/*z*): 337.87 $[M+H]^+$. *Anal*. Calcd for $C_{19}H_{12}ClNO_3$: C, 67.56; H, 3.58; N, 4.15. Found: C, 67.57; H, 3.59; N, 4.16.

1-Chloro-4-(4-methoxylphenyl)-5-oxo-1,2,4,5-tetrahydrofuro [2,3-c]isoquinoline-2-carbaldehyde (5c). This compound was obtained according to the aforementioned general procedure; mp 268–270 °C; IR (KBr, *v*, cm^{-1}): –CHO 1614, –CO 1660; ^1H NMR ($CDCl_3$): δ (ppm) 3.8 (s, 3H, $-OCH_3$), 7.07 (d, 2H, Ar–H), 7.30 (d, 2H, Ar–H), 7.6 (t, 1H, Ar–H), 7.82 (t, 1H, Ar–H), 8.3 (d, 2H, Ar–H), 9.70 (s, 1H, –CHO); ^{13}C NMR ($CDCl_3$): δ (ppm) 55.80, 100.42, 115.41, 122.51, 124.56, 125.16, 127.75, 129.29, 130.27, 130.42, 134.15, 142.5, 151.80, 160.64, 161.17, 173.80; MS (APCI, *m*/*z*): 354.22 $[M+H]^+$. *Anal*. Calcd for $C_{19}H_{12}ClNO_4$: C, 64.51; H, 3.42; N, 3.96. Found: C, 64.53; H, 3.43; N, 3.94.

1-Chloro-4-(4-chlorophenyl)-5-oxo-4,5-dihydrofuro[2,3-c] isoquinoline-2-carbaldehyde (5d). This compound was obtained according to the aforementioned general procedure; mp 255–257 °C; IR (KBr, *v*, cm^{-1}): –CHO 1660, –CO 1691; ^1H NMR ($CDCl_3$): δ (ppm) 7.35 (d, 2H, Ar–H), 7.6 (m, 3H, Ar–H), 7.81 (t, 1H, Ar–H), 8.42 (d, 1H, Ar–H), 8.52 (d, 1H, Ar–H), 9.65 (s, 1H, –CHO); ^{13}C NMR ($CDCl_3$): δ (ppm) 100.59, 122.43, 124.22, 127.96, 129.62, 130.27, 130.44, 130.49, 131.20, 134.42, 136.20, 142.72, 151.08, 161.27, 173.87; MS (APCI, *m*/*z*): 358.19 $[M+H]^+$. *Anal*. Calcd for $C_{18}H_9Cl_2NO_3$: C, 60.36; H, 2.53; N, 3.91. Found: C, 60.37; H, 2.52; N, 3.92.

1-Chloro-4-(4-fluorophenyl)-5-oxo-4,5-dihydrofuro[2,3-c] **isoquinoline-2-carbaldehyde (5e**). This compound was obtained according to the aforementioned general procedure; mp 260–262 °C; IR (KBr, *v*, cm^{-1}): –CHO 1650, –CO 1680; ^1H NMR ($CDCl_3$): δ (ppm) 7.22 (m, 2H, Ar–H), 7.35 (m, 2H, Ar–H), 7.56 (t, 1H, Ar–H), 7.81 (s, 1H, Ar–H), 8.40 (m, 2H, Ar–H), 9.65 (s, 1H, –CHO); ^{13}C NMR ($CDCl_3$): δ (ppm) 100.3, 116.7, 117.0, 122.0, 123.8, 127.5, 128.2, 129.8, 129.9, 130.0, 134.0, 142.2, 150.9, 161.0, 161.6, 173.5; MS (APCI, *m*/*z*): 342.7 $[M+H]^+$. *Anal*. Calcd for $C_{18}H_9ClFNO_3$: C, 63.27; H, 2.65; N, 4.10. Found: C, 63.28; H, 2.67; N, 4.09.

Acknowledgments. We thank Dr Michael J. Collins for the very helpful discussion and the CEM Corporation for providing the Discover Microwave synthesizer.

REFERENCES AND NOTES

[1] (a) Haimova, M. A.; Mollov, N. M.; Ivanova, S. C.; Dimitrova, A. I.; Ognyanov, Tetrahedron 1977, 33, 331; (b) Cushman, M.; Gentry, J.; Dekow, F. W. J. Org Chem 1977, 42, 1111; (c) Haimova, M. A.; Ognyanov, V. I.; Mollov, N. M. Synthesis 1980, 845; (d) Cushman, M.; Choong, T. C.; Valko J. T.; Koleck, M. P. J Org Chem 1980, 45, 5067; (e) Coppola, G. M. J Heterocycl Chem 1981, 18, 767; (f) Cushman, M.; Abbaspour, A.; Gupta, Y. P. J Am Chem Soc 1983, 105, 2873; (g) Cushman, M.; Mohan P. J Med Chem 1984, 27, 544.

[2] (a) Muller, E. Justus Liebigs Ann Chem 1931, 491, 251; (b) Knabe, J.; Schaller, K. D. Arch Pharm (Weinheim Ger) 1967, 62, 300 [Chem. Abstr. 67, 2970y (1967)]; (c) Diekmann B. Dtsch Ges 1914, 47, 1428; (d) Nozawa, K.; Yamada, M.; Tsuda, Y.; Kawai K.; Nakajima, S. Chem Pharm Bull, 1981, 29, 2491, 3486.

[3] Deodhar K. D.; Deval, S. D. Synthesis 1983, 5, 421.

[4] (a) Tamura, Y.; Wada, A.; Sasho, M.; Kita, Y. Tetrahedron Lett 1981, 22, 4283; (b) *idem*, Chem Pharm Bull 1983, 31, 2691; (c) Tamura, Y.; Wada, A.; Sasho, M.; Fukunaga, K.; Maeda H.; Kita, Y. J. Org Chem 1982, 47, 4376; (d) Tamura, Y.; Sasho, M.; Nakagawa, K.;

Tsugoshi, T.; Kita, Y. ibid 1984, 49, 473; (e) Tamura, Y.; Sasho, M.; Akai, S.; Kita, Y. Tetrahedron 1984, 40, 4539; Kita, Y.; (f) Tamura, Y. Yuki Gosei Kagaku Kyokai Shi 1984, 42, 860.

[5] Billamboz, M.; Bailly, F.; Bameca, M. L.; De Luca L.; Mouscadet, F.; Calmels, C.; Line, M.; Cotelle P. J Med Chem 2008, 51, 7717.

[6] (a) Desouza, E. P.; Fernandes, P. S. Chem Inform 1992, 23, 49 DOI: 10.1002/chin.199249177; (b) Pinto, E.; Fernandes, P. S. Chem Inform 1994, 25, 40 DOI: 10.1002/chin.199440158.

[7] Nadkarni, D. R.; Usgoankar, R. N. Indian J Chem, Sec-B 1980, 19b, 253. Chem Abstr 1981, Vol. 94, 121368a.

[8] (a) Scott, J.; Williams, R. M. Chem Rev 2002, 102, 1669; (b) Lin, H.-R.; Safo, M. K.; Abraham, D. J. Bioorg Med Chem Lett 2007, 17, 2581; (c) Saito, N.; Koizumi, Y.; Tanaka, C.; Suwanborirux, K.; Amnuoypol, S.; Kubo, A. Heterocycles 2003, 61, 79; (d) Rothweiler, U.; Czarna, A.; Krajewski, M.; Ciombor, J.; Kalinski, C.; Khazak, V.; Ross G.; Skobeleva, N.; Weber, L.; Holak, T. A. Chem Med Chem 2008, 3, 1118.

[9] (a) Gitto, R.; Ferro, S.; Agnello, S.; De Luca, L.; De Sarro, G.; Russo, E.; Vullo, D.; Supuran, C. T.; Chimirri, A. Bioorg Med Chem 2009, 17, 3659; (b) Gitto, R.; Barreca, M. L.; Francica, E.; Caruso, R.; De Luca, L.; Russo, E.; De Sarro, G.; Chimirri, A. Arkivoc 2004, 5, 170; (c) Yang, J.; Hua, W.-Y.; Wang, F.-X.; Wang, Z.-Y.; Wang, X. Bioorg Med Chem 2004, 12, 6547; (d) Okuda, K.; Kotake, Y.; Ohta, S. Bioorg Med Chem Lett 2003, 13, 2853; (e) Yamada, N.; Kadowaki, S.; Takahashi, K.; Umeu, K. Biochem Pharmacol 1992, 44, 1211; (f) Houlihan, W. J.; Gogerty, J. H.; Parrino, V. A.; Ryan, E. J Med Chem 1983, 26, 765.

[10] (a) Bogdanov, M. G.; Palamareva M. S. Tetrahedron 2004, 60, 2525; (b) Poulain, N. Y. R.; Tartar, A.; Gesquiere, J.-C. Tetrahedron 1999, 55, 13735; (c) Haimova, M.; Stanoeva, E.; lvanova, S.; Palamareva, M.; Spassov, S. Bulg Acad Sci 1977, 10, 489; (d) Okunaka, R.; Honda, T.; Kondo, M.; Tamura, Y.; Kita Y. Chem Pharm Bull 1991, 39, 1298; (e) Girota, N.; Wendler, N. J Org Chem 1969, 34, 3192; (f) Nozawa, K.; Yamada, M.; Tsuda, Y.; Kawai, K.; Nakajima, S. Chem Pharm Bull 1981, 29, 3486; (g) Kaji, M.; Yamada, M.; Nozawa, K.; Kawai, K. Org Prep Proced Int 1986, 18, 253; (h) Dyke, S. E.; Sainsbury, M.; Moon, B. J Chem Soc 1971, 3935.

[11] (a) Vara, Y.; Bello, T.; Aldaba, E.; Arrieta, A.; Pizarro, J. L.; Arriortua, M. I.; Lopez, X.; Cossio, P.; Org Lett 2008, 10, 4759; (b) Yadav, J. S.; Subba, B. V.; Reddy, A.; Reddy, R.; Narsaiah, A. V. Synthesis 2007, 3191; (c) Tang, P. Y. Ng, Y.; Knosp, W. M.; Stadler, H. S.; Shaw, J. T. Angew Chem 2007, 119, 5448; Angew. Chem Int Ed 2007, 46, 5352; (d) Christov, P. P.; Palamareva, M. D.; Naturforsch, Z. J. Chem Sci 2007, 62, 1305; (e) Kandinska, M. I.; Palamareva, M. D. Molecules 2006, 11, 403; Christov, P. P.; Kozekov, I. D.; Palamareva, M. D. J. Heterocycl Chem 2006, 43, 1015.

[12] Trirodkar, R. B.; Usgoankar, R. N. Curr Sci 1968, 37, 164.

[13] Trirodkar, R. B.; Usgoankar, R. N. Curr Sci 1974, 43, 651.

[14] Modi, R. A.; Usgoankar, R. N. Curr Sci 1976, 45, 832.

[15] Yoon, T.; Lombaert, S.; Brodbeck, R. M.; Guliaanello, J.; Chandrasekhar, Hovath, R.; Kehne, J.; Hoffman, D.; Doller, D.; Hodgetts, K. Bioorg Med Chem Lett 2008, 18, 891.

[16] Teppei, K.; Tominari, C.; Hirata, A.; Sera, M.; Takahashi, Y.; Junko, N.; Satoshi, H. Chem Pharm Bull 2005, 53, 393.

[17] Okuda, K.; Yoshida, M.; Hirota, T.; Sasaki, K. Chem Pharm Bull 2010, 58, 363.

[18] Nakagawa, A.; Uno, S.; Makishima, M.; Miyachi, H.; Hashimoto, Y. Bioorg Med Chem 2008, 16, 7046.