

# Very Efficient and Rapid Catalyst-free One-pot Three Component Synthesis of 2,5-Dihydro-5-imino-2-methylfuran-3,4-dicarboxylate Derivatives Under Ultrasound Irradiation

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We report a fast, efficient, and facile route for the synthesis of 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylate derivatives from the isocyanide, dialkyl acetylenedicarboxylate and acetic anhydride under ultrasound-assisted conditions. Utilization of easy reaction conditions, very high to excellent yields, and short reaction times makes this manipulation potentially very useful.

**Key Words :** Ultrasound irradiation, Isocyanide, Multicomponent reaction, 2,5-Dihydro-5-imino-2-methylfuran-3,4-dicarboxylate

## Introduction

In the last two decades, multicomponent reactions (MCR) have demonstrated themselves to be very powerful in the synthesis of natural products, as well as in combinatorial chemistry.<sup>1</sup> The combination of three or more different series of reagents allows the straightforward construction of large libraries while accepting a broad variety of chemical functionality.<sup>2-4</sup> By far, most applications of MCRs described are in the area of drug discovery where it is often crucial to access rapidly and efficiently a large diversity of structures.<sup>5</sup> Indeed, the ease of performance, the time-saving aspect, the versatility, the diversity of obtained scaffolds, and the very large chemical space explored have urged medicinal chemists to use MCRs.

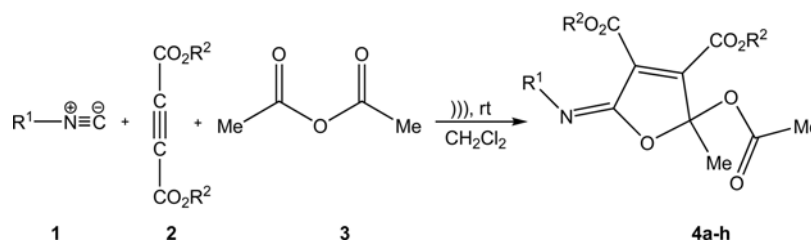
Furans and their derivatives, obtained from both synthetic and natural sources, have attracted much interest due to their wide ranging pharmaceutical applications.<sup>6-8</sup> Many naturally occurring furans show interesting biological activities, such as cytotoxic and antitumor properties<sup>9</sup> as well as antispasmodic<sup>10</sup> antimicrobial<sup>11,12</sup> and several other potentially useful activities.<sup>13</sup> Furthermore, 2,5-disubstituted furan-3,4-dicarboxylates are very important starting materials in the synthesis of natural products containing tetrahydrofuran rings.<sup>14</sup>

Ultrasound has increasingly been used in organic synthesis. A large number of ultrasonic reactions can be carried

out in higher yield, shorter reaction time or milder conditions.<sup>15-18</sup> As we know that the temperature of hot spots caused by the collapse of acoustic caves is generally as high as more than several hundred degrees, this energy can be transferred to the organic molecules and absorbed by them to dramatically raise their intrinsic energy. Due to the thermal effect of ultrasound wave, therefore, much larger amount of molecules can meet the demand for the active energy in a given reaction, leading to the apparent improvement of the reaction efficiency with increased rates and reduced reaction time. It is also observed that reactions under ultrasound irradiation are commonly easier to work-up than those in conventional stirring methods. To our best knowledge, there is no report in literature on preparation of 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylate derivatives using ultrasound irradiation. Herein, in a continuation of our interest in sonochemistry, we report the results of the synthesis of 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylate derivatives from corresponding isocyanides **1**, dialkyl acetylenedicarboxylates **2** and acetic anhydride (**3**) in CH<sub>2</sub>Cl<sub>2</sub> under ultrasound irradiation.

## Experimental

The chemical used in this work were purchased from Merck (Germany) and Fluka (Switzerland) without further purification. TLC was used to follow the reactions. IR spectra



**Scheme 1.** Three-component synthesis of 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylate derivatives **4** under ultrasound irradiation (see Table 1).

were performed as liquid films on a Jasco 6300 FTIR spectrometer.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{CDCl}_3$ ) were recorded on a BRUKER DRX-250 AVANCE spectrometer at 250 and 62.5 MHz, respectively. Sonication was performed in a Bandelin SONOPULS ultrasonic homogenizers (made in Germany) with 20 kHz processing frequency, a nominal power 250 W, uniform sonic waves and constant sound radiation. Preparative thin layer chromatography was prepared from Merck silica gel ( $\text{F}_{254}$ ) powder.

**Ultrasound-promoted Synthesis of (5Z)-Dimethyl 2-Acetoxy-5-(cyclohexylimino)-2,5-dihydro-2-methylfuran-3,4-dicarboxylate (4a).** A 50 mL flask was charged with acetic anhydride (0.11 g, 1.0 mmol) and dimethyl acetylenedicarboxylate (0.14 g, 1.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (15 mL). A solution of cyclohexyl isocyanide (0.11 g, 1 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was added to the flask at room temperature. The reaction mixture was sonicated under 15 kHz at room temperature for the period of time (The reaction was monitored by TLC in iodine tank). The solvent was removed under reduced pressure, and the viscous residue was purified by PLC [silica gel ( $\text{F}_{254}$ ) powder; petroleum ether/ethyl acetate 4:1].

The characterization data of the compounds are given below.

**(5Z)-Dimethyl 2-Acetoxy-5-(cyclohexylimino)-2,5-dihydro-2-methylfuran-3,4-dicarboxylate (4a):** Yellow oil (yield 64%). IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2936, 2854, 1752, 1737, 1695. MS,  $m/z$  (%): 333 ( $\text{M}^+ - 20$ , 2), 293 (2), 182 (20), 98 (30), 59 (30), 43 (100).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  1.18-1.63 (10H, m,  $5\text{CH}_2$  of cyclohexyl), 1.74 (3H, s,  $\text{CH}_3$ ), 1.94 (3H, s,  $\text{CH}_3$ ), 3.53 (1H, m, CH-N), 3.72 (3H, s, O- $\text{CH}_3$ ), 3.78 (3H, s, O- $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (62.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  21.43 ( $\text{CH}_3$ ), 25.47 ( $\text{CH}_3$ ), 25.12, 26.47, 24.54, 32.13, 34.38 (C-cyclohexyl), 50.45, 53.18 (2O- $\text{CH}_3$ ), 55.15 (CH-NH), 105.21 (O-C-O), 135.49, 140.00 (C-olefin), 153.26 (C-imine), 159.76, 162.74, 169.11 (3C=O).

**(5Z)-Diethyl 2-Acetoxy-5-(cyclohexylimino)-2,5-dihydro-2-methylfuran-3,4-dicarboxylate (4b):** Yellow oil (yield 52%). IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2938, 2860, 1741, 1684, 1609. MS,  $m/z$  (%): 381 ( $\text{M}^+$ , 1), 321 (5), 293 (5), 242 (10), 167 (10), 98 (35), 43 (100).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  1.19-1.64 (16H, m,  $5\text{CH}_2$  of cyclohexyl,  $2\text{OCH}_2\text{CH}_3$ ), 1.78 (3H, s,  $\text{CH}_3$ ), 2.02 (3H, s,  $\text{CH}_3$ ), 3.51 (1H, bs, CH-N), 4.08-4.29 (4H, m,  $2\text{OCH}_2\text{CH}_3$ ).  $^{13}\text{C}$  NMR (62.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  12.74, 14.14 ( $2\text{OCH}_2\text{CH}_3$ ), 22.06, 23.31 (2 $\text{CH}_3$ ), 24.38, 24.56, 25.14, 33.45, 33.21 (C-cyclohexyl), 56.61 (CH-N), 61.78, 62.12 ( $2\text{OCH}_2\text{CH}_3$ ), 107.02 (O-C-O), 137.44, 139.74 (C-olefin), 151.22 (C-imine), 161.12, 162.41, 168.35 (3C=O).

**(5Z)-Dimethyl 5-(tert-Butylimino)-2-acetoxy-2,5-dihydro-2-methylfuran-3,4-dicarboxylate (4c):** Yellow oil (62%). IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2957, 1756, 1734, 1690, 1623. MS,  $m/z$  (%): 328 ( $\text{M}^+ + 1$ , 5), 312 (3), 286 (2), 212 (20), 181 (30), 100 (15), 59 (98), 43 (100).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  1.23 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.85 (3H, s,  $\text{CH}_3$ ), 2.07 (3H, s,  $\text{CH}_3$ ), 3.77 (3H, s, O- $\text{CH}_3$ ), 3.90 (3H, s, O- $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (62.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  21.47, 24.52 (2 $\text{CH}_3$ ), 30.59 ( $\text{C}(\text{CH}_3)_3$ ), 51.95, 52.55 (2O- $\text{CH}_3$ ), 56.41 ( $\text{C}(\text{CH}_3)_3$ ), 108.74 (O-C-O),

138.54, 139.22 (C-olefin), 150.21 (C-imine), 159.12, 161.32, 168.52 (3C=O).

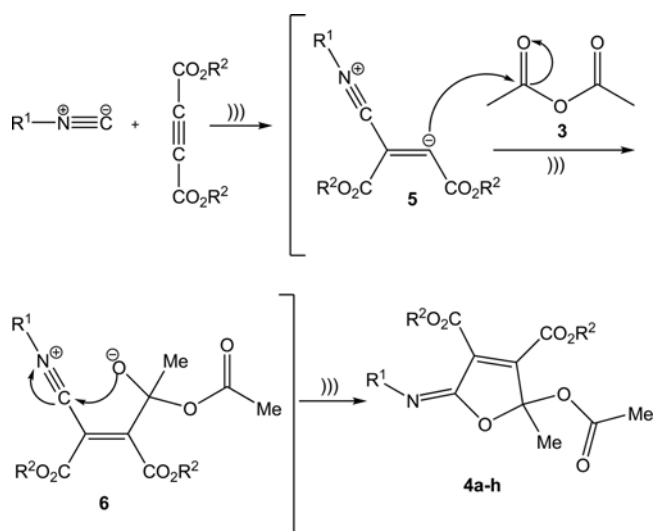
**(5Z)-Diethyl 5-(tert-butylimino)-2-acetoxy-2,5-dihydro-2-methylfuran-3,4-dicarboxylate (4d):** Yellow oil (42%). IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2963, 2878, 1721, 1736, 1665, 1617. MS,  $m/z$  (%): 427 ( $\text{M}^+$ , 2), 356 ( $\text{M}^+ + 1$ , 60), 314 (30), 240 (25), 195 (10), 167 (30), 100 (25), 58 (95), 43 (100).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  1.19 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.23-1.39 (6H, m,  $2\text{OCH}_2\text{CH}_3$ ), 1.80 (3H, s,  $\text{CH}_3$ ), 2.01 (3H, s,  $\text{CH}_3$ ), 4.14-4.38 (4H, m,  $2\text{OCH}_2$ ).  $^{13}\text{C}$  NMR (62.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  13.80, 14.09 ( $2\text{OCH}_2\text{CH}_3$ ), 21.51, 24.12 (2 $\text{CH}_3$ ), 31.40 ( $\text{C}(\text{CH}_3)_3$ ), 55.13 ( $\text{C}(\text{CH}_3)_3$ ), 60.98, 62.03 ( $2\text{OCH}_2\text{CH}_3$ ), 108.01 (O-C-O), 138.31, 138.89 (C-olefin), 150.31 (C-imine), 160.03, 161.87, 168.21 (3C=O).

**(5Z)-Di-tert-butyl 5-(tert-Butylimino)-2-acetoxy-2,5-dihydro-2-methylfuran-3,4-dicarboxylate (4e):** Yellow oil (45%). IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2952, 1752, 1729, 1688, 1621. MS,  $m/z$  (%): 411 ( $\text{M}^+ + 1$ , 2), 368 (5), 326 (5), 284 (50), 224 (100), 184 (75), 57 (90), 43 (50).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  (ppm) 1.19 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.48 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.46 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.52 (3H, s,  $\text{CH}_3$ ), 1.74 (3H, s,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (62.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  21.32, 23.85 (2 $\text{CH}_3$ ), 27.65, 28.03, 29.42 (3 $\text{C}(\text{CH}_3)_3$ ), 54.58 ( $\text{C}(\text{CH}_3)_3$ ), 83.21, 83.43 (2O- $\text{C}(\text{CH}_3)_3$ ), 107.21 (O-C-O), 138.41, 138.78, (C-olefin), 150.26 (C-imine), 160.11, 160.89, 168.12 (3C=O).

**(5E)-Dimethyl 5-(2,4,4-Trimethylpentan-2-ylimino)-2-acetoxy-2,5-dihydro-2-methylfuran-3,4-dicarboxylate (4f):** Yellow oil (43%). IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2941, 1752, 1739, 1685, 1621. MS,  $m/z$  (%): 384 ( $\text{M}^+ + 1$ , 5), 308 (10), 230 (10), 212 (15), 181 (25), 100 (15), 59 (95), 43 (100).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.96 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.24 (3H, s,  $\text{CH}_3$ ), 1.25 (3H, s,  $\text{CH}_3$ ), 1.80 (3H, s,  $\text{CH}_3$ ), 1.85-2.09 (5H, m,  $\text{CH}_2$  and  $\text{CH}_3$ ), 3.74 (3H, s, O- $\text{CH}_3$ ), 3.84 (3H, s, O- $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (62.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  21.48, 24.19, 29.33, 30.01 (4 $\text{CH}_3$ ), 31.52 ( $\text{C}(\text{CH}_3)_3$ ), 31.89 ( $\text{CH}_2$ ), 52.62, 52.85 (2O- $\text{CH}_3$ ), 55.28 ( $\text{C}(\text{CH}_3)_3$ ), 58.68 (N- $\text{C}(\text{CH}_3)_2$ ), 107.75 (O-C-O), 138.41, 139.56 (C-olefin), 148.90 (C-imine), 160.52, 162.41, 168.38 (3C=O).

**(5Z)-Diethyl 5-(2,4,4-Trimethylpentan-2-ylimino)-2-acetoxy-2,5-dihydro-2-methylfuran-3,4-dicarboxylate (4g):** Yellow oil (55%). IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2981, 2910, 1750, 1719, 1688, 1603. MS,  $m/z$  (%): 354 ( $\text{M}^+ - 57$ , 2), 366 (100), 298 (10), 240 (10), 167 (20), 57 (100), 43 (90).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.83 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.17-1.26 (12H, m, 2 $\text{CH}_3$ ,  $2\text{OCH}_2\text{CH}_3$ ), 1.42-1.47 (2H, m,  $\text{CH}_2$ ), 1.71 (3H, s,  $\text{CH}_3$ ), 1.88 (3H, s,  $\text{CH}_3$ ), 4.10-4.27 (4H, m,  $2\text{OCH}_2$ ).  $^{13}\text{C}$  NMR (62.5 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  13.68, 13.99 ( $2\text{OCH}_2\text{CH}_3$ ), 21.36, 24.09 (2 $\text{CH}_3$ ), 30.01 ( $\text{C}(\text{CH}_3)_3$ ), 30.58 ( $\text{C}(\text{CH}_3)_2$ ), 31.80 ( $\text{CH}_2$ ), 55.24 ( $\text{C}(\text{CH}_3)_3$ ), 58.42 (N- $\text{C}(\text{CH}_3)_2$ ), 61.12, 61.78 ( $2\text{OCH}_2\text{CH}_3$ ), 107.31 (O-C-O), 137.91, 139.32 (C-olefin), 148.83 (C-imine), 160.06, 161.65, 168.10 (3C=O).

**(5Z)-Diethyl 5-(2,6-Dimethylphenylimino)-2-acetoxy-2,5-dihydro-2-methylfuran-3,4-dicarboxylate (4h):** Yellow oil (61%). IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2981, 2936, 1756, 1720, 1691, 1632. MS,  $m/z$  (%): 403 ( $\text{M}^+$ , 15), 318 (30), 241 (5), 167 (5), 120 (55), 57 (10), 43 (100).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  1.28-1.48 (6H, m,  $2\text{OCH}_2\text{CH}_3$ ), 1.82 (3H, s,  $\text{CH}_3$ ),



**Scheme 2.** Proposed mechanism for the formation of 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylate derivatives **4a-h** under ultrasound irradiation.

2.08 (3H, s, CH<sub>3</sub>), 2.15 (6H, s, 2CH<sub>3</sub>), 4.27-4.51 (4H, m, 2OCH<sub>2</sub>), 6.88-7.05 (3H, m, arom). <sup>13</sup>C NMR (62.5 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 13.84, 14.19 (2OCH<sub>2</sub>CH<sub>3</sub>), 18.02 (CH<sub>3</sub>), 21.33, 24.99 (2CH<sub>3</sub>), 62.16, 62.47 (2OCH<sub>2</sub>CH<sub>3</sub>), 107.28 (O-C-O), 123.84, 127.44, 127.43, 136.18, 141.98, 143.70 (C-olefin and C-arom), 152.09 (C-imine), 159.69, 161.23, 168.49 (3C=O).

## Results and Discussion

In this article, we report a facile synthesis of 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylate derivatives under ultrasound irradiation and catalyst-free conditions. Thus, isocyanides **1** and dialkyl acetylenedicarboxylates **2** in the presence of acetic anhydride **3** undergo a fast and convenient 1:1:1 addition reaction in CH<sub>2</sub>Cl<sub>2</sub> at room temperature, to produce the 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylate derivatives **4a-h** in 90-98% yields (Scheme 1). The reaction proceeds fast and cleanly under ultrasonic condi-

**Table 1.** Synthesis of (5*Z*)-dimethyl 2-acetoxy-5-(cyclohexylimino)-2,5-dihydro-2-methylfuran-3,4-dicarboxylate **4a** in different solvent systems under normal conditions

Entry	Solvent	Time (h)	Yield <sup>a</sup> (%)
1	Acetonitrile	12	44
2	CH <sub>2</sub> Cl <sub>2</sub> <sup>b</sup>	12 h/20 min	60/98 <sup>b</sup>
3	CHCl <sub>3</sub>	12	53
4	Ethanol	12	33
5	Methanol	12	34
6	Solvent free	12	21

<sup>a</sup>Isolated yield. <sup>b</sup>At room temperature/ultrasonic irradiation.

tions and no side reactions were observed.

On the basis of the well-established chemistry of isocyanides,<sup>19-24,26</sup> it is reasonable to assume that the 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylate derivatives **4** may result from initial addition of the isocyanide to the acetylenic ester and subsequent addition to the electron-poor carbonyl group of acetic anhydride **3** leading to a dipolar specie **6**. Cyclization of **6** leads then to the 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylate **4** (Scheme 2).

Before taking up the reaction using ultrasonic irradiation, it was tried out using different solvents such as methanol, ethanol, acetonitrile, dichloromethane and chloroform as well as solvent free system under normal reaction conditions (Table 1). However, it was noticed that the highest yield and shorter reaction duration was achievable with CH<sub>2</sub>Cl<sub>2</sub> while the others took longer duration to yield lesser product.

To delineate the role of ultrasound, this experiment was examined by the reaction of several isocyanides, acetylenic esters and acetic anhydride with ultrasonic irradiation at the room temperature in CH<sub>2</sub>Cl<sub>2</sub> (Table 2). When the reaction was carried out under ultrasonic irradiation it gave comparatively excellent yields of products and took shorter reaction time (Table 2).

The following is expected to be plausible reason for the higher yield and lesser reaction time during ultrasonic irradiation: Cavitation is a process of formation of bubbles having dynamic life during ultrasonic irradiation. These

**Table 2.** Comparison of the times and yields of the reactions with or without sonication for the synthesis of 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylate derivatives

Entry	R <sup>1</sup>	R <sup>2</sup>	Product	With sonication <sup>a</sup>		Without sonication <sup>b</sup>	
				Yield <sup>c</sup> (%)	Time (min)	Yield (%)	Time (h)
1	Cyclohexyl	Me	<b>4a</b>	98	20	60 <sup>26</sup>	12
2	Cyclohexyl	Et	<b>4b</b>	93	18	55 <sup>26</sup>	12
3	<i>tert</i> -Butyl	Me	<b>4c</b>	97	20	53 <sup>26</sup>	12
4	<i>tert</i> -Butyl	Et	<b>4d</b>	90	17	49 <sup>26</sup>	12
5	<i>tert</i> -Butyl	C(Me) <sub>3</sub>	<b>4e</b>	92	18	53 <sup>26</sup>	12
6	1,1,3,3-Tetramethylbutyl	Me	<b>4f</b>	91	20	47 <sup>26</sup>	12
7	1,1,3,3-Tetramethylbutyl	Et	<b>4g</b>	96	22	52 <sup>26</sup>	12
8	2,6-(Me) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Et	<b>4h</b>	97	19	58 <sup>26</sup>	12

<sup>a</sup>Reaction condition: Reaction of isocyanides and dialkyl acetylenedicarboxylates in the presence of acetic anhydride in CH<sub>2</sub>Cl<sub>2</sub> at room temperature under ultrasound irradiation. <sup>b</sup>Reaction condition: Reaction of isocyanides and dialkyl acetylenedicarboxylates in the presence of acetic anhydride in CH<sub>2</sub>Cl<sub>2</sub> at room temperature under high stirring condition.<sup>26</sup> <sup>c</sup>Yields of isolated products.

bubbles can be filled with gas or vapour and occur in organic solvents used in the ultrasonic irradiation. When these bubbles burst, it results in high temperature and high pressure which facilitate the intermolecular reaction. Apart from this, the shock wave produced by the bubble collapse can disrupt the solvent structure which can influence the reactivity by altering solvation of the reactive species present in the reaction mixture. Sonochemical rate enhancement is a known phenomenon in organic reactions.<sup>25</sup> It can be attributed that by the same mechanism, the yield of 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylate is higher in ultrasound than in normal chemical reaction.

### Conclusion

In this work, we have developed a mild, highly efficient and improved protocol for the preparation of a series of 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylates. Our sonochemical method offers several advantages over existing methods, including improved yields, cleaner reactions, simple work-up and very short reaction times, which makes it a useful and environmentally attractive strategy for the synthesis of furan derivatives, compounds with promising bio-activity.

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