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# Imidazolium ylide mediated tandem Knoevenagel–Michael–O-cyclization sequence for the synthesis of multi-substituted 4,5-dihydrofurans

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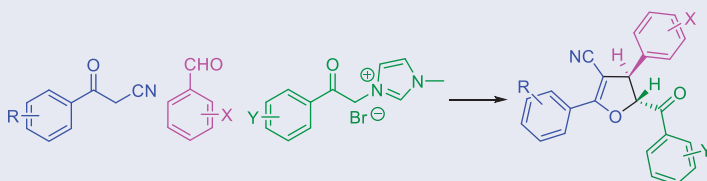
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## ABSTRACT

The stereoselective syntheses of novel *trans*-5-aryl-2,4-diaryl-4,5-dihydrofuran-3-carbonitriles have been achieved *via* a one-pot, three-component tandem protocol involving aryl acetonitriles, aromatic aldehydes, and imidazolium ylide in the presence of Et<sub>3</sub>N.

## GRAPHICAL ABSTRACT



## ARTICLE HISTORY

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## KEYWORDS


Aroylacetonitrile; 4,5-dihydrofuran; imidazolium ylide; Knoevenagel reaction; tandem reaction

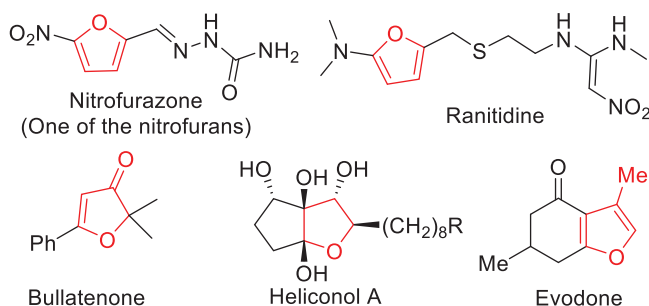
## Introduction

Furan derivatives are an important class of heterocycles ubiquitous in natural products and synthetic compounds.<sup>[1–3]</sup> Furans are constituents of a number of biologically active compounds<sup>[3]</sup> and are also valuable intermediates in organic syntheses.<sup>[4]</sup> For example, the nitrofurans are significant drugs used as antibiotics and antimicrobials (Fig. 1).<sup>[5]</sup> Ranitidine is used to treat peptic ulcer and gastroesophageal reflux diseases<sup>[6]</sup> whereas heliconol A, bullatenone, and evodone display antifungal and antibacterial activities.<sup>[7]</sup>

The biological significances of furan derivatives have attracted the interest of synthetic chemists *en route* to discover efficient methodologies for the synthesis of hybrid heterocycles comprising furan core.<sup>[8]</sup> After the first synthesis of furan by Limpricht in 1870, several methods have been reported.<sup>[9]</sup> Among the various methods available, the pyridinium ylide-assisted syntheses of furans have gained considerable attention.<sup>[10]</sup> It offers a facile and efficient access to diverse furan derivatives. Pyridinium ylides were first reported by Kröhnke<sup>[11]</sup> in 1935 and since then these ylides have been widely investigated as they react with various electrophiles to form a variety of hybrid heterocycles.<sup>[12]</sup>

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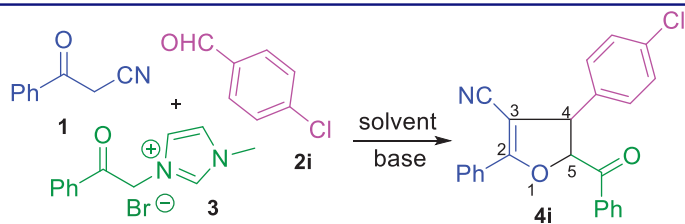
**Figure 1.** Selected drugs with furan nucleus.

Nevertheless, the use of pyridine has generated some limitations due to toxicity. On the other hand, the imidazolium salts are relatively low toxic and serve as the best alternate for pyridinium ylides.<sup>[13]</sup>

The imidazolium salts have been used as precursors of stable carbenes<sup>[14]</sup> and as ionic liquids for organic syntheses<sup>[15]</sup> apart from serving as efficient ligands for the preparation of various transition metal complexes possessing biological activities<sup>[16]</sup> and as efficient fluorescence materials.<sup>[17]</sup> Moreover, imidazolium salts have received less attention in synthetic organic chemistry. In this work, we envisaged to synthesize novel, highly substituted dihydrofuran derivatives through a one-pot three-component tandem strategy involving 1-methyl-3-(2-oxo-2-phenylethyl)-1*H*-imidazol-3-ium bromides, aroyl acetonitriles and aromatic aldehydes. This work also stems from our continuous effort in synthesizing hybrid heterocycles through tandem/domino reactions.<sup>[18]</sup> To the best of our knowledge, this is the first report for the synthesis of furans utilizing imidazolium salt.

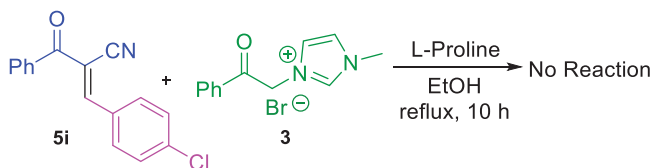
## Results and discussion

Initially, in order to determine the optimum conditions for this one pot transformation, the reaction of benzoyl acetonitrile **1**, 4-chlorobenzaldehyde **2i** and imidazolium salt **3**, presumably affording 5-benzoyl-4-(4-chlorophenyl)-2-phenyl-4,5-dihydro-furan-3-carbonitrile **4i** was investigated. Organic bases such as *L*-proline, piperidine, pyrrolidine, DABCO, DBU, and Et<sub>3</sub>N (1 equiv. in each case) were screened in refluxing ethanol (Table 1). From the observations, Et<sub>3</sub>N was found to be the ideal base, wherein the reaction completed in 3 h resulting quantitative yield of the product **4i** (97%). Furthermore, after completion of the reaction, the product **4i** precipitated in the reaction vessel and was isolated just by filtration (Table 1, entry 6). Other bases employed in the reaction resulted in comparatively lesser yield of **4i** and the product needed to be isolated after column chromatography. In the presence of *L*-proline (Table 1, entry 1), the reaction failed to afford the product **4i** but a light yellow precipitate was formed after 4 h, which was found to be the Knoevenagel intermediate **5i** (Scheme 1). However, the reaction of **5i** with **3** in the presence of *L*-proline failed to afford the product **4i** (Scheme 1). The reaction afforded lesser yield of **4i** when carried out in solvents like acetonitrile, methanol, and tetrahydrofuran (Table 1, entries 7–9). Hence, ethanol was the ideal solvent for this reaction.

**Table 1.** Optimization of reaction conditions.

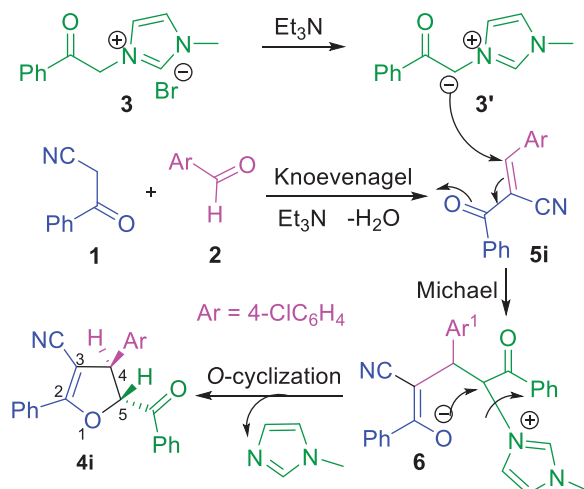
Entry	Base	Solvent	Time (h)	Yield (%) <sup>a</sup>
1	L-Proline	EtOH	8	– <sup>b</sup>
2	Piperidine	EtOH	9	23
3	Pyrrrolidine	EtOH	8	27
4	DBU	EtOH	10	45
5	DABCO	EtOH	10	36
6	Et <sub>3</sub> N	EtOH	3	97
7	Et <sub>3</sub> N	CH <sub>3</sub> CN	4	85
8	Et <sub>3</sub> N	MeOH	6	70
9	Et <sub>3</sub> N	THF	9	40

<sup>a</sup>Isolated yield; <sup>b</sup>Expected product not formed.

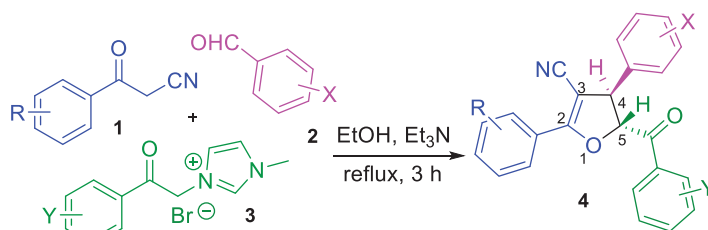
**Scheme 1.** Reaction of intermediate **5i** and **3**.

The structure of dihyrofuran **4i** was elucidated with the help of ESI-mass, FT-IR, <sup>1</sup>H, <sup>13</sup>C and 2D NMR spectroscopy. The ESI-mass of **4i** had a characteristic molecular ion peak at 385.89 (M<sup>+</sup>). The IR spectrum of **4i** showed strong absorptions at 1691 and 2197 cm<sup>-1</sup> due to the carbonyl and nitrile groups, respectively. In the <sup>1</sup>H NMR spectrum of **4i**, the two doublets at 4.78 and 5.85 ppm (*J* = 5.7 Hz) were assigned to H-4 and H-5, respectively. The distinct assignment of these chemical shifts arises from the fact that H-4 showed HMBC with the nitrile carbon whereas H-5 did not. Further, H-4 showed (i) C,H-COSY correlation with carbon signal at 51.8 ppm due to C-4 and (ii) HMBC with carbon signals at 84.8, 89.3, 129.2, 137.8, 166.5, and 192.2 ppm, which were assigned to C-3, C-5, C-2'', C-1'', C-2 and C=O, respectively. Further, H-5 showed C,H-COSY correlation with carbon signal at 89.3 ppm due to C-5 and HMBC with carbon signals at 51.8, 84.8, 137.8, and 166.5 ppm, which can be assigned to C-4, C-3, C-1'' and C-2, respectively. The <sup>1</sup>H and <sup>13</sup>C chemical shifts and selected HMBC of **4i** are given in the [supplementary data](#) (Fig. S39).

A plausible mechanism for the formation of **4i** is given in [Scheme 2](#). Initially, the imidazolium salt **3** in the presence of base forms imidazolium ylide **3'** *in situ*. The simultaneous Knoevenagel condensation of benzoyl acetonitrile **1** and 4-chlorobenzaldehyde **2i** affords the intermediate **5i**. Subsequently, the ylide **3'** upon Michael addition with the  $\alpha,\beta$ -unsaturated ketone **5i** affords the intermediate **6**, which undergoes an intramolecular O-cyclization to afford the final product **4i** with the removal of *N*-methylimidazole.



**Scheme 2.** Proposed mechanism for the formation **4i**.

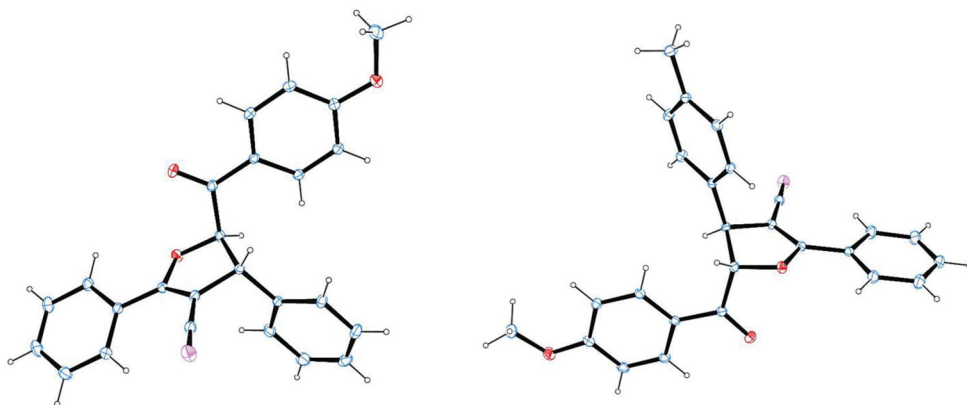


**Scheme 3.** Synthesis of tetra-substituted dihydrofurans **4**.

**Table 2.** Library of dihydrofurans **4a–s**.

Entry	Comp	R	X	Y	Yield <sup>a</sup> (%)
1	<b>4a</b>	H	H	H	96 (92) <sup>[19]</sup>
2	<b>4b</b>	H	H	4-MeO	92
3	<b>4c</b>	H	2-Cl	H	94
4	<b>4d</b>	H	2-Cl	4-MeO	91
5	<b>4e</b>	H	2-Me	4-F	94
6	<b>4f</b>	H	3-Br	H	94 (92) <sup>[19]</sup>
7	<b>4g</b>	H	3-Br	4-MeO	92
8	<b>4h</b>	H	4-Br	4-MeO	92
9	<b>4i</b>	H	4-Cl	H	97
10	<b>4j</b>	H	4-Cl	4-MeO	94
11	<b>4k</b>	H	4-F	4-MeO	94
12	<b>4l</b>	H	4-Me	4-MeO	93
13	<b>4m</b>	4-Cl	4-Me	H	90
14	<b>4n</b>	4-Cl	4-Me	4-MeO	91
15	<b>4o</b>	4-Me	4-MeO	4-Cl	93
16	<b>4p</b>	4-Me	4-MeO	4-F	93
17	<b>4q</b>	4-Cl	2-Me	H	95
18	<b>4r</b>	4-Cl	2-Me	4-Cl	93
19	<b>4s</b>	3-Cl	4-F	4-MeO	94

<sup>a</sup>Quantitative yields obtained, except for the loss during workup.



**Figure 2.** ORTEP diagrams of **4b** and **4l**.

With the optimal condition, *viz.* Et<sub>3</sub>N–EtOH base–solvent pair in hand and the structure of **4i** established, the synthesis of a library of dihydrofuran-3-carbonitriles **4** was performed by varying aryl acetonitriles **1**, aromatic aldehydes **2**, and imidazolium ylides **3** (Scheme 3). The imidazolium salts **3** were prepared following literature procedure.<sup>[10f]</sup> All the reactions occurred smoothly under the optimized condition with the available variations. A total of nineteen novel dihydrofuran derivatives **4a–s** were synthesized in quantitative yields (Table 2).

The structure of all the dihydrofurans **4a–s** was elucidated unambiguously with the help of NMR spectroscopy and in the cases of **4b** and **4l**, the structure was further confirmed from single-crystal X-ray studies.<sup>[20]</sup> The ORTEP diagram (Fig. 2) revealed that H-4 and H-5 are *trans*.

## Conclusions

This work reports the one-pot three-component tandem reactions for the expedient synthesis of 5-aryloxy-2,4-diphenyl-4,5-dihydrofuran-3-carbonitriles **4** in quantitative yields. This reaction proceeded *via* a tandem Knoevenagel condensation–Michael addition–O-cyclization process and resulted in the formation of three new bonds (two C–C and one C–O) in a single synthetic operation.

## Experimental section

### General procedure for the synthesis of dihydrofurans **4**

A mixture of aryl acetonitrile **1** (1.0 mmol), aromatic aldehyde **2** (1.0 mmol), and imidazolium salt **3** (1.0 mmol) was dissolved in EtOH (10 mL). Then Et<sub>3</sub>N (1.0 mmol) was added and the mixture refluxed on a water bath. The progress of the reaction was monitored by TLC. After 3 h the reaction mixture was cooled and the precipitated solid was filtered and washed with cold ethanol and dried under vacuum to obtain pure **4**.

**5-Benzoyl-4-(4-chlorophenyl)-2-phenyl-4,5-dihydrofuran-3-carbonitrile 4i** Yellow solid; Yield 97%; mp 185 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 4.78 (d, 1H, *J* = 5.7 Hz, Ar-CH), 5.85 (d, 1H, *J* = 5.7 Hz, Ar-CH), 7.30 (d, 2H, *J* = 8.4 Hz), 7.41 (d, 2H, *J*

= 8.4 Hz), 7.41–7.54 (m, 5H), 7.66 (t, 1H,  $J = 7.5$  Hz), 7.94 (d, 2H,  $J = 7.8$  Hz), 8.03 (d, 2H,  $J = 7.8$  Hz);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 51.8, 84.8, 89.3, 116.0, 127.0, 127.4, 128.8, 128.9, 129.0, 129.2, 129.6, 132.0, 133.5, 134.4, 134.5, 137.7, 166.5, 192.2; Anal. Calcd for  $\text{C}_{24}\text{H}_{16}\text{ClNO}_2$ : C, 74.71; H, 4.18; N, 3.63%. Found C, 74.60; H, 4.10; N, 3.74%.

Full experimental detail,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. This material can be found via the “Supplementary Content” section of this article’s webpage.

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- [20] Crystallographic data for compounds **4b** and **4l** in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers 1,023,393 and 1,023,391, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0) 1223 336033 or e-mail:[deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)).