

## Indium trichloride catalyzed efficient one-pot synthesis of highly substituted furans

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**Abstract**—A one-pot synthesis of the substituted furans **3** could be achieved in good yields by reacting but-2-ene-1,4-diones **1** with acetoacetates **2** in the presence of a catalytic amount of InCl<sub>3</sub> (20 mol %) using *i*-PrOH as solvent at 80–90 °C for 4–8 h. InCl<sub>3</sub> was observed to give the optimum results among the various Lewis acids examined.

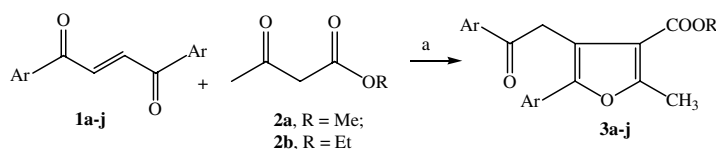
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Among the various skeletal features present in natural products, furans are not only key subunits but are also important chemicals of commerce in the form of furfural, tetrahydrofuran and their derivatives. They are found in a large number of natural products such as kalolides,<sup>1</sup> combranolides,<sup>2</sup> pheromones<sup>3</sup> and polyether antibiotics.<sup>4</sup> These heterocycles have found applications in many pharmaceuticals, fragrances and dyes.<sup>5</sup> Furan subunits have also been used as building blocks for a large number of heterocyclic compounds and as synthons in natural product synthesis.<sup>6</sup> As a consequence, the synthesis<sup>7</sup> of furan derivatives still attracts the attention of organic chemists. The most common strategy involved in the synthesis of furans is the cyclization<sup>8</sup> of 1,4-dicarbonyl compounds. Of the various other methods, syntheses<sup>9</sup> involving transition metal salts have recently been described for the preparation of substituted furan derivatives. Oh et al.<sup>10</sup> have synthesized highly substituted furans via Pt-catalyzed hydroxyl

or alkoxy assisted cyclization of 2-(1-alkynyl)-2-alkene-1-ones. It is well known that InCl<sub>3</sub> is capable of promoting Diels–Alder,<sup>11</sup> aldol,<sup>12</sup> and Friedel–Crafts<sup>13</sup> reactions amongst others,<sup>14</sup> which has prompted us to investigate InCl<sub>3</sub> as a catalyst in the one-pot synthesis of highly functionalized tetrasubstituted furan derivatives **3a–j** by reaction of but-2-ene-1,4-diones **1a–j** and acetoacetate esters **2a** or **2b** (Scheme 1).

Also, indium salts have remarkable tolerance towards coordinating functional groups.<sup>15</sup> In this reaction, but-2-ene-1,4-diones act as Michael acceptors and acetoacetates as the nucleophiles resulting in Michael adduct **A** which under the influence of InCl<sub>3</sub> forms a hemiketal which undergoes spontaneous dehydration to afford furans **3a–j** (Scheme 2).

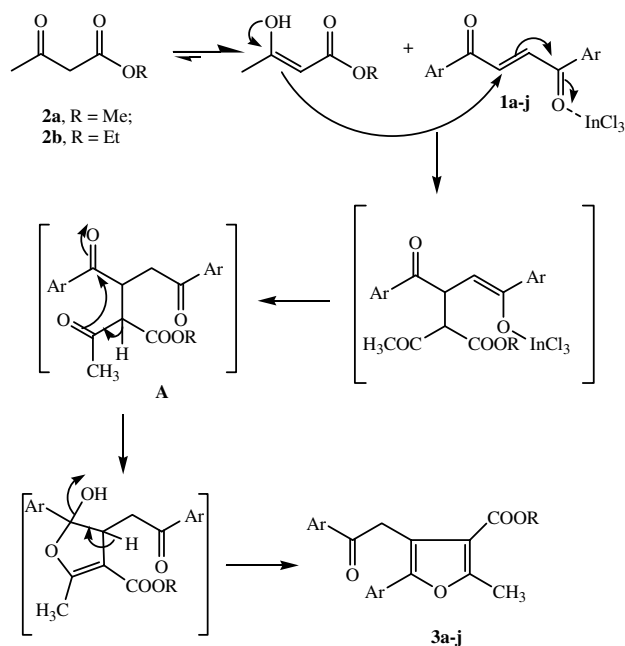
The reaction is exemplified by refluxing but-2-ene-1,4-dione **1c**, acetoacetate **2a** and InCl<sub>3</sub> (20 mol %) in



**Scheme 1.** Reagents and conditions: (a) InCl<sub>3</sub> (20 mol %) *i*-PrOH reflux at 80–90 °C.

**Keywords:** Indium trichloride; Furans; Cyclization; Dehydration.

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**Scheme 2.** Proposed mechanism for the  $\text{InCl}_3$  catalyzed formation of furans **3a–j**.

*i*-PrOH for 5.5 h, which resulted in the formation of furan **3c** in 82% yield. It should be mentioned that the treatment of substrate **1c** with acetylacetone led to the formation of a complex mixture of products. This efficient and relatively simple method was applied to prepare a number of substituted furan derivatives **3a–j** in very good yields (Table 1).

In order to investigate the reactivity of Lewis acid in this reaction,  $\text{InCl}_3$  was replaced with other Lewis acids such as  $\text{AlCl}_3$ ,  $\text{FeCl}_3$ ,  $\text{ZnCl}_2$  and the acidic clay, Montmorillonite K10 and the reaction to prepare furan **3c** performed under the same conditions. It can be seen from Table 2 that  $\text{InCl}_3$  was the best catalyst.

The role of the solvent was also investigated. Among the various solvents used, *i*-PrOH afforded the maximum yield of the furan derivative **3c** (Table 3). It is well known that reactions of this type are more efficient in polar solvents as corroborated by this study (Table 3). It was also observed that the inclusion of water had very little or no part in this reaction.

**Table 1.**  $\text{InCl}_3$  catalyzed synthesis of furans **3a–j**

Entry	Ar	R	Furan	Time (h)	Isolated yield (%)
1	$\text{C}_6\text{H}_5$	Me	<b>3a</b>	4	87
2	$\text{C}_6\text{H}_5$	Et	<b>3b</b>	5	90
3	4-Me- $\text{C}_6\text{H}_4$	Me	<b>3c</b>	5.5	82
4	4-Me- $\text{C}_6\text{H}_4$	Et	<b>3d</b>	4.5	80
5	4-Br- $\text{C}_6\text{H}_4$	Me	<b>3e</b>	4	89
6	4-Br- $\text{C}_6\text{H}_4$	Et	<b>3f</b>	6	84
7	4-Cl- $\text{C}_6\text{H}_4$	Me	<b>3g</b>	5.5	78
8	4-Cl- $\text{C}_6\text{H}_4$	Et	<b>3h</b>	7	82
9	3-Cl,4-Me- $\text{C}_6\text{H}_3$	Me	<b>3i</b>	6	86
10	3-Cl,4-Me- $\text{C}_6\text{H}_3$	Et	<b>3j</b>	8	81

**Table 2.** Synthesis of furan **3c** using different Lewis acids

Lewis acid	Time <sup>a</sup> (h)	Isolated yield of <b>3c</b> (%)
$\text{InCl}_3$	5.5	82
$\text{FeCl}_3$	16	63
$\text{ZnCl}_2$	9	56
$\text{AlCl}_3$	20	43
Montmorillonite K10	30	24

<sup>a</sup> Extension of the reaction did not improve the product yields.

**Table 3.** Role of solvent in the synthesis of furan **3c**

Solvent	Time <sup>a</sup> (h)	Isolated yield of <b>3c</b> (%)
<i>i</i> -PrOH	5.5	82
<i>i</i> -PrOH- $\text{H}_2\text{O}$ (7:3)	10	70
THF	18	52
MeOH	9	56
$\text{CH}_3\text{CN}$	24	39

<sup>a</sup> Extension of the reaction did not improve the yields of the product.

All the compounds have been characterized from their spectroscopic data.

In summary, the present method developed by us leads to an efficient one-pot synthesis of fully substituted furans<sup>16</sup> and involves the  $\text{InCl}_3$  catalyzed Michael addition of acetoacetate esters to but-2-ene-1,4-diones followed by hemiketal formation and subsequent dehydration.

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### Supplementary data

Spectroscopic data of compounds **3a**, **3b** and **3d–j** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.019.

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16. *Typical procedure for the synthesis of tetrasubstituted furans:* To a solution of but-2-ene-1,4-dione **1c** (264 mg, 1 mmol) and methyl acetoacetate **2a** (128 mg, 1.1 mmol) in dry *i*-PrOH (7 ml) was added anhydrous InCl<sub>3</sub> (45 mg, 20 mol %). The reaction mixture was then stirred under reflux at 80–90 °C for 5.5 h. After complete disappearance of the starting material [monitored by TLC using petroleum ether–chloroform (6:4)], the solvent was removed from the reaction mixture on a rotary evaporator. The residue was then diluted with water (10 ml) and extracted with CHCl<sub>3</sub> (3 × 25 ml). The organic layer was separated, washed with brine and then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent resulted in a solid which was chromatographed over silica gel using petroleum ether and an increasing proportion of ethyl acetate as eluent. Petroleum ether–ethyl acetate (96:4) eluent gave a solid which was recrystallized from chloroform–petroleum ether (2:8) to give **3c** as a white solid (297 mg, 82%); mp 82–84 °C; FT-IR (KBr):  $\nu$  1708, 1609, 1447, 1249, 1101 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  2.34 (s, 3H), 2.43 (s, 3H), 2.63 (s, 3H), 3.62 (s, 3H), 4.43 (s, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.96 (d, *J* = 8.1 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  14.86, 21.67, 22.06, 35.78, 51.38, 114.36, 114.86, 127.02 (2 × C), 127.85, 128.72 (2 × C), 129.71 (2 × C), 129.74 (2 × C), 134.99, 138.33, 144.18, 150.79, 159.27, 165.08, 197.32; ESI-MS *m/z*: 385 [M+Na]<sup>+</sup>. Anal. Calcd for C<sub>23</sub>H<sub>22</sub>O<sub>4</sub>: C, 76.22; H, 6.12. Found: C, 76.15; H, 6.21.