



## Gallium(III)-catalyzed tandem cycloisomerization/Friedel–Crafts alkylation: a facile synthesis of 2,5-disubstituted furans

B.V. Subba Reddy<sup>\*</sup>, B. Bramha Reddy, K.V. Raghavendra Rao, J.S. Yadav<sup>†</sup>

Natural Product Chemistry, Indian Institute of Chemical Technology, CSIR, Hyderabad 500 007, India

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### ABSTRACT

A tandem cycloisomerization/Friedel–Crafts alkylation of indoles has been achieved in a one-pot process to produce 2,5-disubstituted furans using gallium-catalyzed sequential nucleophilic addition onto metal-activated 1-alkynyl-2,3-epoxy acetates. The reaction proceeds efficiently under mild conditions with complete regioselectivity to afford the substituted furan derivatives in good yields with high diversity.

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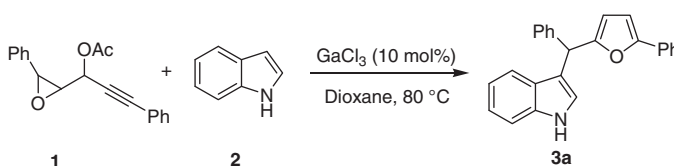
The furan subunits are often found in many natural products and biologically active molecules.<sup>1</sup> They are extensively used as synthetic intermediates for carbocycles and heterocycles in organic synthesis.<sup>2</sup> Therefore, several efforts have been devoted for the synthesis of furan scaffolds.<sup>3,4</sup> Recently, metal-mediated cyclizations of an allene or an alkyne with an oxygen functionality have appeared in the literature.<sup>5</sup> Among various approaches to substituted furans,<sup>3,4</sup> the cycloisomerization of alkynyl oxiranes catalyzed by transition metals is particularly versatile and attractive.<sup>6–8</sup> In general, furan synthesis from alkynyl oxiranes mostly involves the use of transition metal catalysts such as Hg(II), Mo, Ru, SmI<sub>2</sub>/Pd, Ag(I)/TsOH, Au(III), and Pt(II).<sup>6–8</sup> However, many of these methods involve the use of expensive catalysts and hazardous reagents in stoichiometric amounts. In case of Mo and Ru, the formation of furan is limited to terminal alkynes.

Recently there has been a growing interest in gallium mediated transformations due to its ability to activate alkynes under mild conditions.<sup>9</sup> In particular, gallium(III) chloride is considered to be an effective Lewis acid to activate alkynes/alkenes under extremely mild conditions.<sup>10</sup> However, there have been no reports on the use of gallium(III) chloride for the synthesis of 2,5-disubstituted furan derivatives.

In this Letter, we report a novel protocol for the one-pot synthesis of 3,5-disubstituted furan derivatives by means of a nucleophile induced cycloisomerization and Friedel–Crafts alkylation of

1-alkynyl-2,3-epoxy acetates. Accordingly, we first attempted the Friedel–Crafts alkylation of indole with 1-alkynyl-2,3-epoxy acetate using a catalytic amount of InCl<sub>3</sub>. Though the reaction proceeds in 1,4-dioxane at 80 °C, the desired 2,5-substituted furan derivative **3a** was obtained in 60% yield. In order to improve the conversion, we attempted the above reaction with various Lewis acids such as BiCl<sub>3</sub>, FeCl<sub>3</sub>, and GaCl<sub>3</sub>. Interestingly, the yield of **3a** was dramatically increased to 85% when GaCl<sub>3</sub> was used as a catalyst (Scheme 1).

Inspired by a high catalytic performance of GaCl<sub>3</sub>,<sup>11</sup> we carried out further reactions with GaCl<sub>3</sub>. Interestingly, a wide range of indoles participated well under the influence of gallium(III) chloride (Table 1, entries b–l). We next attempted the ability of other nucleophiles such as allyltrimethylsilane and acetyl acetone to initiate the cycloisomerization. Like an indole, allyltrimethylsilane also promoted the cycloisomerization of alkynyl-2,3-epoxy acetate to afford the allyl substituted furan derivative **4** in good yield (Scheme 2).



Scheme 1. Indole-induced formation of furan **3a**.

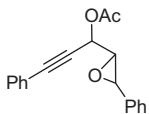

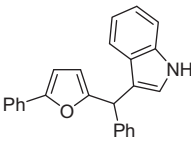
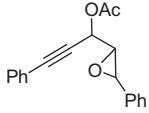
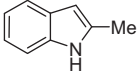
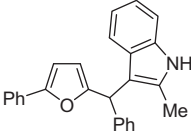
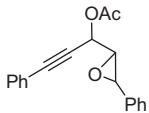
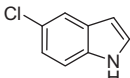
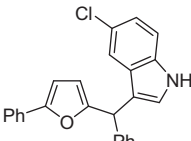
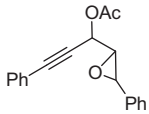
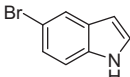
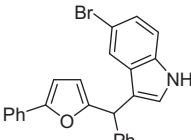
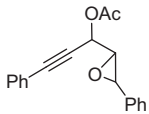

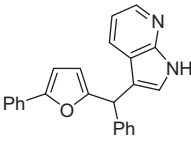
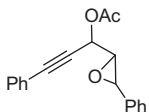
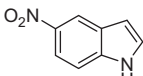
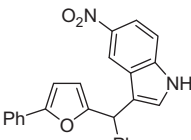
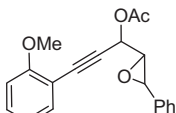

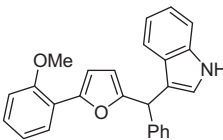
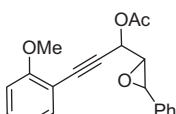
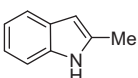
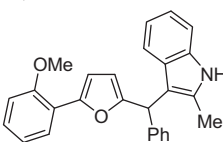
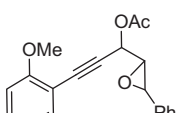
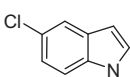
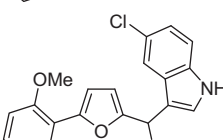
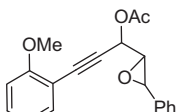
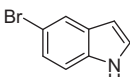
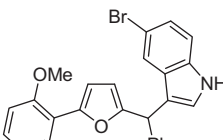
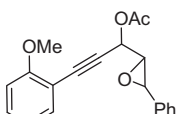
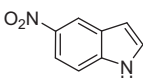
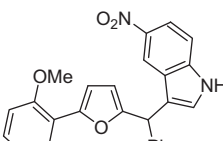
<sup>\*</sup> Corresponding author. Fax: +91 40 7160512.

E-mail address: [basireddy@iict.res.in](mailto:basireddy@iict.res.in) (B.V.S. Reddy).

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**Table 1**

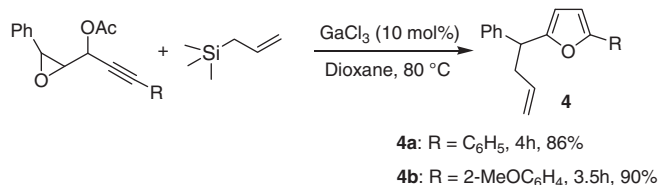
Cascade alkylation of indole and furan formation

Entry	Epoxy propargyl acetate ( <b>1</b> )	Indole ( <b>2</b> )	Product ( <b>3</b> ) <sup>a</sup>	Time (h)	Yield <sup>b</sup> (%)
<b>a</b>				4.5	85
<b>b</b>				5.0	82
<b>c</b>				6.0	80
<b>d</b>				6.0	80
<b>e</b>				6.0	85
<b>f</b>				6.0	78
<b>g</b>				4.0	86
<b>h</b>				5.0	78
<b>i</b>				5.5	80
<b>j</b>				5.5	80
<b>k</b>				6.0	80

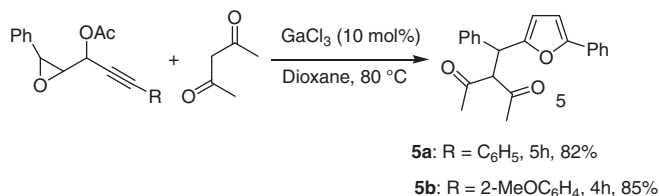
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Table 1 (continued)

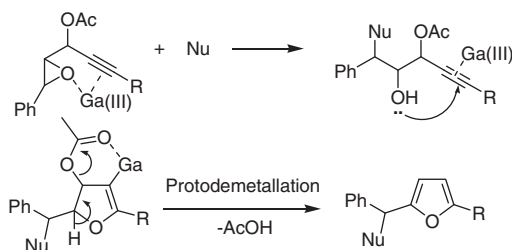
Entry	Epoxy propargyl acetate (1)	Indole (2)	Product (3) <sup>a</sup>	Time (h)	Yield <sup>b</sup> (%)
I				6.2	72

<sup>a</sup> All products were characterized by NMR, IR, and mass spectroscopy.<sup>b</sup> Yield refers to pure products after chromatography.

Scheme 2. Allyltrimethylsilane-induced formation of furan 4.



Scheme 3. Acetyl acetone-induced formation of furan 5.

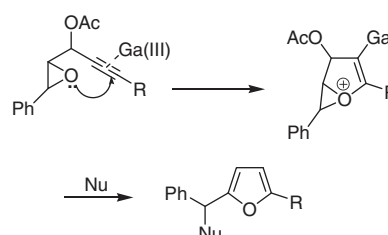


Scheme 4. A plausible reaction pathway.

Similarly, acetyl acetone also induced the cycloisomerization of alkynyl-2,3-epoxy acetate to furnish the corresponding 2,5-disubstituted furan derivative **5** in good yield (Scheme 3).

Other 1-alkynyl-2,3-epoxy acetates also underwent a smooth cycloisomerization with indoles to give the corresponding 3-indolyl furan derivatives in good yields (Table 1, entries b–i). The products are fully characterized by NMR, IR, and mass spectroscopy. Both electron-rich and electron-deficient indoles are found to be equally effective for this conversion (Table 1).

The catalytic efficiency of various metal halides such as InCl<sub>3</sub>, ZnCl<sub>2</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O, and metal triflates like In(OTf)<sub>3</sub>, Bi(OTf)<sub>3</sub>, Sc(OTf)<sub>3</sub>, Yb(OTf)<sub>3</sub> was screened for this conversion. Surprisingly, none of these catalysts gave the desired product in satisfactory yields. Furthermore, Brønsted acids such as montmorillonite K10, heteropoly acid, and ion-exchange resins failed to produce the desired product. In the absence of an external nucleophile, mixtures of hydroxyl- and chloro-substituted products were obtained. The effect of various solvents was examined for this reaction. Though,



Scheme 5. Alternative reaction pathway.

the reaction was successful in acetonitrile and 1,2-dichloroethane under reflux conditions, the desired product was obtained in low yields. Of these solvents, dioxane gave the best results. The scope of this method is illustrated with respect to various nucleophiles and alkynyl-2,3-epoxy acetates and the results are presented in Table 1.<sup>12</sup>

In absence of the catalyst, no reaction was observed even after long reaction time (12 h) under reflux conditions. Mechanistically, the reaction proceeds via the activation of both alkyne and epoxide by gallium(III). This is followed by the addition of nucleophile on epoxide and then isomerization of propargylic acetate results in the formation of 2,5-disubstituted furan as shown in Scheme 4.

Alternatively, gallium(III) activates the alkyne to initiate the formation of cyclic oxonium ion which is likely attacked by a nucleophile as shown in Scheme 5. Mechanistic studies showed that a cascade pathway rather than a direct intramolecular nucleophilic addition of the oxirane oxygen atom to the intermediate acetylene–metal  $\pi$ -complex occurs. Further studies addressing these issues are currently underway in our laboratory.

In summary, we have developed a novel strategy for the synthesis of 2,5-disubstituted furan derivatives by means of gallium-catalyzed addition of nucleophile onto metal activated alkynyl-2,3-epoxy acetate. This method involves the cycloisomerization of alkynyl-2,3-epoxy acetates followed by the Friedel–Crafts alkylation of indoles.

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12. **General procedure:** A mixture of 1-alkynyl-2,3-epoxy acetate (1.0 mmol), indole (1.5 mmol), and GaCl<sub>3</sub> (10 mol %) in dioxane (5 mL) was heated at 80 °C for the appropriate time. After completion of the reaction as indicated by TLC, the solvent was removed and the resulting residue was diluted with water and extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford pure 2,5-disubstituted furan. The spectral data of the products was identical with the data reported in the literature.<sup>6–8</sup> Spectral data for selected products: **3j**: **5-Bromo-3-((5-(2-methoxyphenyl)furan-2-yl)(phenyl)methyl)-1H-indole**: Pale yellow colour liquid, IR (neat):  $\nu_{\max}$  3425, 2922, 2853, 1599, 1457, 1245, 756 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.95 (s, 1H), 7.59–7.49 (m, 3H), 7.31–7.06 (m, 7H), 6.89–6.73 (m, 3H), 6.48 (d, 1H, *J* = 3.0 Hz), 6.05 (br s, 1H), 5.90 (d, 1H, *J* = 3.0 Hz), 3.76 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  156.6, 151.3, 149.8, 139.5, 133.4, 131.0, 129.6, 129.1, 128.5, 127.8, 126.8, 124.9, 124.8, 124.3, 123.4, 122.1, 120.4, 117.1, 114.1, 112.6, 112.4, 110.6, 109.3, 105.5, 55.5, 34.8; EIMS: *m/z*: 427 [M<sup>+</sup>], 429 [M<sup>2+</sup>]. **4a**: **2-Phenyl-5-(1-phenylbut-3-enyl)furan**: Brown liquid, IR (neat):  $\nu_{\max}$  3027, 2923, 2853, 1490, 1444, 1262, 1151, 967, 755 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.60–7.52 (m, 2H), 7.34–7.12 (m, 8H), 6.50 (d, 1H, *J* = 2.9 Hz), 6.06 (d, 1H, *J* = 2.9 Hz), 5.77–5.67 (m, 1H), 5.07–4.94 (m, 2H), 4.07–4.01 (m, 1H), 2.94–2.86 (m, 1H), 2.73–2.65 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  156.9, 152.6, 142.0, 136.0, 131.0, 130.8, 128.7, 128.5, 128.4, 127.9, 126.8, 126.6, 123.4, 116.6, 107.9, 105.5, 45.5, 39.2; EIMS (M+H): *m/z*: 275. **5a**: **3-(Phenyl(5-phenylfuran-2-yl)methyl)pentane-2,4-dione**: Colorless liquid, IR (neat):  $\nu_{\max}$  3028, 2921, 2851, 1739, 1598, 1490, 1439, 1354, 1280, 1249, 1149, 755 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.55–7.50 (m, 2H), 7.35–7.18 (m, 8H), 6.47 (d, 1H, *J* = 3.2 Hz), 6.03 (d, 1H, *J* = 3.2 Hz), 4.89 (d, 1H, *J* = 11.8 Hz), 4.56 (d, 1H, *J* = 11.8 Hz), 2.19 (s, 3H), 1.93 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  202.2, 201.9, 153.7, 153.3, 138.5, 130.8, 130.4, 128.8, 128.6, 128.2, 127.5, 127.3, 123.4, 109.0, 105.7, 73.3, 45.1, 30.1, 29.1; EIMS (M+Na): *m/z*: 355.