



# Sequential alkylation/transition metal catalysed annulation reactions of 1,3-dicarbonyl compounds with propargyl bromide

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## Abstract

$\beta$ -Diketones,  $\beta$ -ketoesters and  $\beta$ -ketonitriles in the presence of propargyl bromide, DBU and a catalytic amount of CuI in toluene give 2,3,5-trisubstituted furans through sequential alkylation/cyclisation/isomerisation reactions. © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* 1,3-dicarbonyls; propargylation; cyclisation.

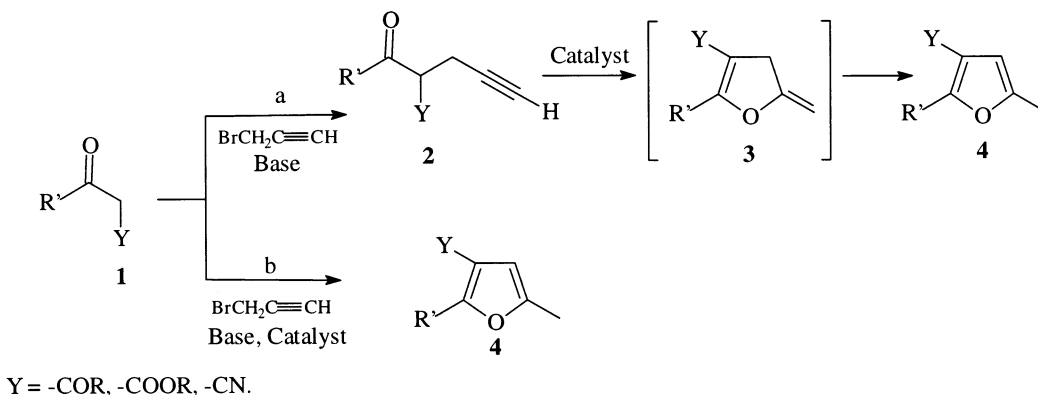
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The development of environmentally friendly procedures for the synthesis of organic compounds is becoming an area of growing importance.<sup>1</sup> Traditional stepwise formation of target molecules tends to be replaced by domino reactions.<sup>2</sup> Indeed, it would be much more efficient if one could form several bonds in one sequence without isolating the intermediates, changing the reaction conditions, or adding reagents. It is obvious that this type of reaction would allow the minimisation of waste since compared to stepwise reactions the amount of solvents, reagents and energy would be dramatically decreased.

In connection with our ongoing interest in developing new synthetic strategies for the construction of five-membered heterocyclic rings involving transition metal catalysed domino reactions,<sup>3</sup> we planned to prepare functionalised furans using a simpler, and more efficient one-pot procedure compared to the classical stepwise methodology (Scheme 1a). The derivatives **2**, easily obtained by means of the reaction of sodium salts of  $\beta$ -dicarbonyl compounds with propargyl halides<sup>4</sup> afford the furans **4** through ZnCO<sub>3</sub>-catalysed enolate cyclisation.<sup>5</sup> Examples of oxygen-carbon ring closures of enolisable pentynones and hexynones with acid, base and transition metal catalysis have also been described.<sup>6</sup>

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Scheme 1.

Based on the results of the monoalkylation of acetylacetone using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)<sup>7</sup> in a non-polar solvent, we report that  $\beta$ -diketones,  $\beta$ -ketoesters and  $\beta$ -ketonitriles in the presence of propargyl bromide, DBU and a catalytic amount of CuI in toluene give the expected furans through sequential monoalkylation/cyclisation/isomerisation<sup>8</sup> (Scheme 1b) (Table 2). To our knowledge this is the first synthesis of furans directly from 1,3-dicarbonyl compounds and propargyl bromide. Previously the synthesis of 2,3-disubstituted-5-methylene-4,5-dihydrofurans **3** by reacting alkyl 3-oxoalkanoates with sodium ethoxide in ethanol/DMF and treating the metallation product thus obtained with propargyl bromide in the presence of copper (I) bromide was reported. Then the derivatives **3** were isomerised to furans **4** in anhydrous ether in the presence of catalytic amounts of sulfuric acid.<sup>9</sup> In all the cases examined the domino reaction presents the advantage of elimination of the dialkylation reaction of **1**.

In the presence of ZnCl<sub>2</sub> and RuCl<sub>3</sub><sup>10</sup> as catalysts, yields of **4** are lower with respect to the CuI catalyst (compare entry 1 with entries 2, 3 of Table 1 and entries 4, 5, 6 of Table 2). We failed to synthesise **4a** in the presence of ZnCO<sub>3</sub> in refluxing ethanol (Table 1, entry 5). Disappointing results from a synthetic point of view are obtained in water or without any solvent (Table 1, entries 4 and 6; Table 2 entries 3 and 7).

Table 1  
Synthesis of **4a** from **1a**<sup>a</sup>

Entry	Solvent/catalyst	<b>4a</b> (% yield) <sup>b</sup>
1	PhCH <sub>3</sub> /CuI	91
2	PhCH <sub>3</sub> /ZnCl <sub>2</sub>	60
3	EtOH/ZnCl <sub>2</sub>	60
4	H <sub>2</sub> O, CH <sub>3</sub> CN/ZnCl <sub>2</sub>	18
5	EtOH/ZnCO <sub>3</sub>	–
6	–/CuI	31

<sup>a</sup> **1a**: propargyl bromide: DBU: catalyst = 1:1:2:0.1.

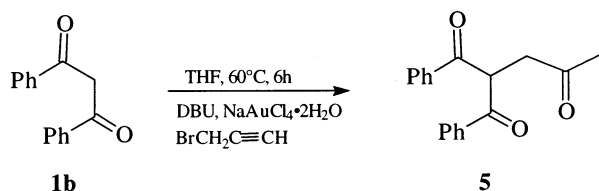
<sup>b</sup> Isolated yields.

Table 2  
Synthesis of 2,3,5-trisubstituted furans **4** from **1**

Entry	Substrate <b>1</b> R' =; Y =	Solvent/Catalyst	Product	Yield (%) <sup>a</sup>
1	<b>1a</b> Ph; COOEt	PhCH <sub>3</sub> /CuI	<b>4a</b>	91
2	<b>1b</b> Ph; COPh	PhCH <sub>3</sub> /CuI	<b>4b</b>	55
3	<b>1b</b>	EtOH, H <sub>2</sub> O/CuI	<b>4b</b>	15
4	<b>1c</b> Ph; CN	PhCH <sub>3</sub> /CuI	<b>4c</b>	55
5	<b>1c</b>	PhCH <sub>3</sub> /RuCl <sub>3</sub>	<b>4c</b>	40
6	<b>1c</b>	EtOH/ZnCl <sub>2</sub>	<b>4c</b>	40
7	<b>1c</b>	EtOH, H <sub>2</sub> O/ZnCl <sub>2</sub>	<b>4c</b>	20
8	<b>1d</b> CH <sub>3</sub> ; COCH <sub>3</sub>	PhCH <sub>3</sub> /CuI	<b>4d</b>	65
9	<b>1e</b> CH <sub>3</sub> ; COOCH <sub>3</sub>	PhCH <sub>3</sub> /CuI	<b>4e</b>	70
10	<b>1f</b> Ph; COCH <sub>3</sub>	PhCH <sub>3</sub> /CuI	<b>4f</b> + <b>4f'</b>	60

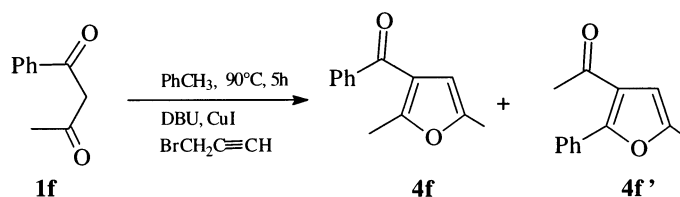
<sup>a</sup> Isolated yields.

The reaction of **1b** with propargyl bromide/DBU in THF–H<sub>2</sub>O in the presence of a catalytic amount of NaAuCl<sub>4</sub>·2H<sub>2</sub>O (**1b**:NaAuCl<sub>4</sub>·2H<sub>2</sub>O = 1:0.02) gave the tricarbonyl derivative **5** (40% yield) (Scheme 2). It is very likely that **5** may derive from **2b** generated in situ, which undergoes a regioselective hydration<sup>11</sup> by Au(III) catalysis.



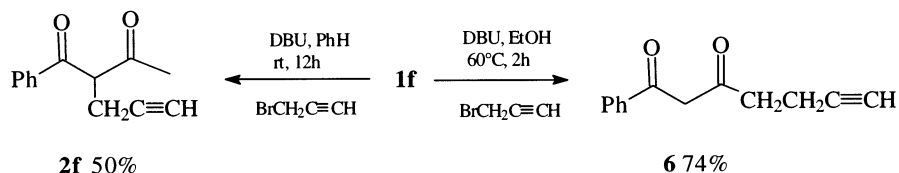
Scheme 2.

When the 1-phenyl-1,3-butanedione **1f**, which can give two isomeric enolate anions, was treated with propargyl bromide/DBU/CuI in toluene the *exo-dig* annulation reaction of the less stable enolate anion occurs preferentially to give **4f** (Scheme 3) (Table 2, entry 10) as the main reaction product (**4f**:**4f'** = 2).



Scheme 3.

Very surprisingly, **6** is obtained through regioselective  $\gamma$ -propargylation<sup>12</sup> of **1f** (Scheme 4) (41% yield) using the EtOH/DBU/ZnCl<sub>2</sub> system. Better results are obtained without the catalyst (74% yield). The product of  $\alpha$ -propargylation **2f** is readily available in benzene/DBU at rt.



Scheme 4.

In conclusion,  $\beta$ -diketones,  $\beta$ -ketoesters and  $\beta$ -ketonitriles in the presence of propargyl bromide, DBU and a catalytic amount of CuI in refluxing toluene can give directly 2,3,5-trisubstituted furans. A sequential propargylation/Au(III) catalysed hydration of **1b** to give a tricarbonyl derivative may occur. DBU/EtOH promoted  $\gamma$ -propargylation of 1,3-dicarbonyl-compounds is under further investigation because it is promising to overcome some of the drawbacks of the functionalisation of the terminal carbon atom of 1,3-dicarbonyl compounds.

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8. Typical experimental procedure: to a solution of **1c** (0.2 g, 1.38 mmol) in toluene were added propargyl bromide (0.164 g, 1.38 mmol), DBU (0.42 g, 2.76 mmol) and CuI (0.026 g, 0.138 mmol). The resulting mixture was heated at 90°C under N<sub>2</sub> for 3 h. The mixture, cooled to room temperature, was chromatographed on silica gel eluting with a 97/3 *n*-hexane/EtOAc mixture to give **4c** (0.140 g, 55% yield): mp 69–71°C; IR (KBr) 2195 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.93 (m, 2H), 7.41 (m, 3H), 6.22 (s, 1H), 2.34 (s, 3H); <sup>13</sup>C NMR  $\delta$  158.2, 152.3, 129.5, 129.2, 128.8, 128.2, 124.8, 108.8, 91.7, 13.2.
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