

# The multicomponent reaction of dimethoxycarbene, dimethyl butynedioate and electrophilic styrenes: an unprecedented synthesis of highly substituted cyclopentenone acetals

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Dedicated with best wishes to Professor Bert Fraser-Reid on the occasion of his 71st birthday

**Abstract**—The zwitterionic species generated by the addition of dimethoxycarbene to dimethyl butynedioate is trapped by arylidenemalononitrile to yield cyclopentenone derivatives.  
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From a historical perspective, multicomponent reactions (MCRs) entered the arena of organic chemistry with the advent of the venerable Strecker reaction.<sup>1</sup> In spite of the success of this reaction as well as that of a number of others that followed, MCRs did not have a major influence in organic synthesis for a long time. This situation, however, changed during the last few decades largely due to the efforts of Ugi, who demonstrated the exceptional versatility of isocyanides in MCRs and also provided a logical framework for MCRs.<sup>2,3</sup> Recently we have been interested in designing new MCRs using the simple strategy of generating zwitterions by the reaction of nucleophilic species with dimethyl butynedioate **2** and engaging them in cycloaddition to a variety of dipolarophiles, leading to heterocycles.<sup>4</sup> Among the systems we have studied, the cycloaddition of aldehydes and ketones to the zwitterion generated from dimethoxycarbene and dimethyl butynedioate constituting a facile synthesis of dihydrofuran derivatives was of special interest.<sup>5</sup> In view of the favourable outcome of the reaction, it was reasonable to assume that an electrophilic styrene would participate in this reaction, and in the event lead to a cyclopentannulation. The recent success of the MCR involving isocyanides, dimethyl butynedioate and electrophilic styrenes leading to cyclopentadiene

derivatives bode well for the scheme contemplated.<sup>6</sup> The preliminary results of our studies validating the above assumptions are presented here.

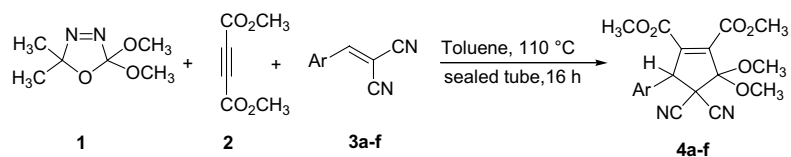
Our studies were initiated by exposing benzyldienemalonitrile to the zwitterionic species resulting from dimethyl butynedioate and dimethoxycarbene, the latter being generated in situ by the thermolysis of **1** in refluxing toluene following the Warkentin protocol.<sup>7</sup> A facile reaction leading to the cyclopentenone derivative **4a** occurred.

The structure of the product was established by spectroscopic methods. The IR spectrum of **4a** showed strong carbonyl absorption peaks at 1744 and 1721  $\text{cm}^{-1}$ . The nitrile absorption peak was visible at 2256  $\text{cm}^{-1}$ . In the  $^1\text{H}$  NMR spectrum, signals due to the methoxy protons were discernible as sharp singlets at  $\delta$  3.54 and 3.59. The benzylic proton showed its resonance peak as a singlet at  $\delta$  4.23. The  $^{13}\text{C}$  NMR spectrum was also in good agreement with the assigned structure. The peaks at  $\delta$  166.5 and 162.3 were typical of the two ester carbonyls. The peaks at  $\delta$  50.9 and 110.6 were assigned to the methine and the acetal carbons, respectively. The nitrile carbon was found to resonate at  $\delta$  107.9. All the other signals were in good agreement with the assigned structure.

The reaction appears to be general as illustrated by its application to a number of substituted benzyldienemalonitriles.<sup>18</sup> The results are summarized in Scheme 1.

**Keywords:** Multicomponent reactions; Dimethoxycarbene; Zwitterions; Cyclopentenones.

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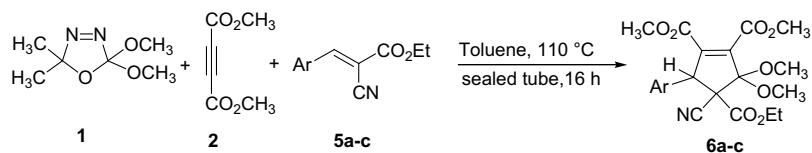


Entry	Ar	Product	Yield (%)
<b>3a</b>	phenyl	<b>4a</b>	59
<b>3b</b>	<i>m</i> -Cl-phenyl	<b>4b</b>	48
<b>3c</b>	<i>p</i> -F-phenyl	<b>4c</b>	57
<b>3d</b>	<i>p</i> -CH <sub>3</sub> -phenyl	<b>4d</b>	54
<b>3e</b>	<i>p</i> -CF <sub>3</sub> -phenyl	<b>4e</b>	48
<b>3f</b>	cinnamyl	<b>4f</b>	47

Scheme 1.

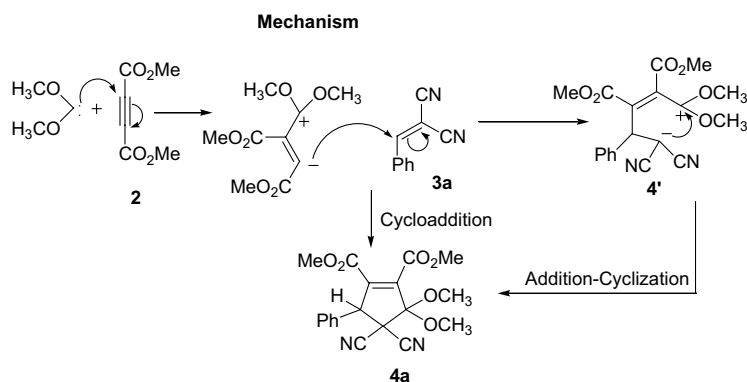
A similar reaction was found to occur when cyanocinnamates were used instead of the benzylidenemalononitrile, but the products were formed in low yields (Scheme 2).

A mechanistic rationalization for these reactions is given in Scheme 3. The initial event is the formation of the zwitterion from dimethoxycarbene and dimethyl butynedioate **2**. The zwitterion can add to the



Entry	Ar	Product	Yield (%)
<b>5a</b>	<i>p</i> -CF <sub>3</sub> -phenyl	<b>6a</b>	39
<b>5b</b>	<i>p</i> -F-phenyl	<b>6b</b>	25
<b>5c</b>	<i>p</i> -NO <sub>2</sub> -phenyl	<b>6c</b>	15

Scheme 2.



Scheme 3.



Entry	Ar	Product	Yield(%)
<b>4b</b>	<i>m</i> -Cl-phenyl	<b>8b</b>	45
<b>4c</b>	<i>p</i> -F-phenyl	<b>8c</b>	35
<b>4e</b>	<i>p</i> -CF <sub>3</sub> -phenyl	<b>8e</b>	60

Scheme 4.

electrophilic carbon–carbon double bond of **3a** resulting in the formation of **4'** which then undergoes cyclization to deliver the product **4a**. Although less likely, the alternative concerted 1,3-dipolar cycloaddition of the zwitterion to the styrene *la* Huisgen cannot be ruled out at the present time.

In an attempt to unmask the carbonyl group of the cycloadducts, we treated them with BBr<sub>3</sub>. Interestingly, in all the cases investigated, the hydrated cyclopentenones were obtained, albeit in modest yields. (Scheme 4).

In conclusion, we have encountered a facile multicomponent reaction which offers a convenient entry into the synthesis of highly substituted cyclopentenone derivatives. The reaction is especially noteworthy since this is the first MCR involving dimethoxycarbene and dimethyl butynedioate leading to the formation of a carbocycle.

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- Typical experimental procedure*: (a) A mixture of cinnamyl malononitrile **3f** (100 mg, 0.55 mmol), DMAD **2** (118 mg, 0.83 mmol) and oxadiazoline **1** (178 mg, 1.11 mmol) was refluxed in dry toluene in a sealed tube for 16 h. The solvent was removed under vacuum and the residue subjected to column chromatography on a silica gel column using 80:20 hexane–ethyl acetate solvent mixture to afford **4f** as a white solid (103 mg, 47%). IR (neat)  $\nu_{\max}$ : 2955, 2856, 2256, 1748, 1720, 1620, 1435, 1256, 1234, 1159, 1036 cm<sup>-1</sup>. <sup>1</sup>H NMR:  $\delta$  7.99 (d, 1H, *J* = 16.9 Hz), 7.60 (d, 2H, *J* = 7.4 Hz), 7.47–7.38 (m, 4H), 4.19 (s, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.68 (s, 3H), 3.52 (s, 3H). <sup>13</sup>C NMR:  $\delta$  166.8, 162.9, 140.2, 135.3, 130.2, 128.9, 128.1, 118.1, 111.4, 111.2, 108.1, 56.6, 52.7, 52.6, 52.3, 51.2. Analysis calculated for C<sub>21</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>: C, 63.63, H, 5.09, N, 7.07. Found: C, 63.78, H, 5.04, N, 7.14. (b) A mixture of **4e** (57 mg, 0.13 mmol) and excess BBr<sub>3</sub> (0.1 ml, 10.6 mmol) were treated at ice temperature in dichloromethane under inert atmosphere for about 3 h. Solvent and excess BBr<sub>3</sub> were removed and the residue was subjected to column chromatography to afford **8e** as a brown viscous liquid (34 mg, 66%). IR (neat)  $\nu_{\max}$ : 3314, 3206, 2259, 2212, 1748, 1720, 1645, 1599, 1532, 1444, 1326 cm<sup>-1</sup>. <sup>1</sup>H NMR:  $\delta$  7.76 (d, 2H, *J* = 8.0 Hz), 7.41 (d, 2H, *J* = 7.9 Hz), 6.90 (s, 2H), 4.15 (s, 1H), 3.69 (s, 6H). <sup>13</sup>C NMR:  $\delta$  171.1, 167.5, 165.7, 158.1, 157.1, 137.3, 132.5, 132.1, 128.0, 126.3, 126.2, 125.3, 121.7, 114.7, 105.0, 70.6, 60.4, 53.1, 50.5. LRMS FAB(+): (M+H) Calculated for C<sub>18</sub>H<sub>14</sub>F<sub>3</sub>N<sub>2</sub>O<sub>6</sub>: 411.0804. Found: 411.9962.