An Efficient Three-Component Reaction Involving Triazolylidene Carbene, DMAD, and Aldehydes for the Synthesis of Furanone Derivatives

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Abstract: An efficient synthesis of furanone derivatives via the multicomponent reaction involving triazolylidene carbene, dimethyl acetylenedicarboxylates, and aldehydes is described.

Key words: zwitterion, triazolylidene carbene, DMAD, furanone, multicomponent reactions

In recent years, nucleophilic heterocyclic carbenes (NHCs) have received much attention both from the theoretical and synthetic standpoints.1 Breslow’s original demonstration of the role of thiazolylidene in the thiamine catalyzed decarboxylation of pyruvates,2 Wanzlick’s attempts3 towards the synthesis of imidazolylidene carbene, and Arduengo’s isolation of a stable diaminocarbene4 paved the way for the entry of these reactive species into the realm of organic synthesis. Inter alia, these unique intermediates serve as excellent nucleophilic catalysts in various reactions, namely, benzoin condensation,2,5 transesterification,6 and Michael–Stetter reaction,1a,7 as ligands in metal-containing catalysts,8 and these are increasingly used for the generation of homoenolates from α,β-unsaturated aldehydes.9 In spite of the use of NHCs as catalysts and ligands for transition metals, their utility in multicomponent reactions remained unexplored. The first report of multicomponent reactions (MCRs) involving NHC originated from our laboratory,10 and this was followed by work from elsewhere.11

The generation and isolation of a triazolylidene carbene was first reported by Enders et al.12 Subsequently Leeper13 and Enders14 reported the syntheses of chiral triazolium salts as precursors for catalysts capable of inducing enantioselectivity in the benzoin reaction. Rovis and co-workers have demonstrated the utility of chiral triazolylidene in a highly enantioselective intramolecular Stetter reaction.15

In this context and in view of our general interest in multicomponent reactions triggered by nucleophilic carbenes and other species,16 we undertook an investigation of the reaction of triazolylidene carbene with dimethyl acetylenedicarboxylate (DMAD) and aldehydes and the results are presented in this paper. It may be noted that the propensity of this carbene to engage in MCR has not been studied previously.

In an initial experiment, a toluene solution of methoxytriazoline, DMAD, and 4-methylbenzaldehyde was heated under reflux for 12 hours. After the completion of the reaction as indicated by TLC, the solvent was distilled off in vacuo. The residue on chromatographic purification afforded the furanone derivative 4a in 56% yield (Scheme 1).

Scheme 1

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5 generated in situ from the methoxytriazoline derivative adds to DMAD (2) to form the zwitterion 6, which then attacks the carbonyl group of the aldehyde to form the intermediate 7. Conceivably, the latter adds to the appropriately positioned ester carbonyl in preference to the iminium ion to afford 8, which is subsequently deprotonated by methoxide to deliver the furanone derivative 9 (Scheme 2).

Interestingly, terephthalaldehyde (10) when treated with two equivalents of DMAD and triazolylidene carbene affords 11 in 46% yield (Scheme 3).

### Table 1 Furanones 4 Prepared

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>3-chlorophenyl</td>
<td>4b</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>3-nitrophenyl</td>
<td>4c</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>1-naphthyl</td>
<td>4d</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>4-nitrophenyl</td>
<td>4e</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>phenyl</td>
<td>4f</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>4-methoxyphenyl</td>
<td>4g</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>2-furyl</td>
<td>4h</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>4-fluorophenyl</td>
<td>4i</td>
<td>61</td>
</tr>
<tr>
<td>9</td>
<td>3,4-dichlorophenyl</td>
<td>4j</td>
<td>68</td>
</tr>
</tbody>
</table>

Scheme 2

Scheme 3

Figure 1 ORTEP diagram of compound 4a
for ded both mono- and bisadducts 11 and 12, respectively, in moderate yields.

In conclusion, we have devised a novel multicomponent reaction involving triazolylidene, DMAD and aldehyde that provides access to fully substituted furanone derivatives in good yields. It may be mentioned that the presence of furanone moiety in a wide range of biologically active molecules clearly establishes the synthetic utility of this reaction.

All reactions were carried out in oven-dried glassware under argon. Progress of the reaction was monitored by TLC (visualization was effected by exposure to UV light or I₂). While purification was effected by silica gel column chromatography. Petroleum ether (PE) was used at the fraction boiling in the range 80–80 °C. ¹H NMR spectra were recorded at r.t. in CDCl₃ at an operating frequency of 300 MHz (75 MHz for ¹³C NMR). IR spectra were recorded on Bomem MB Series FT-IR spectrophotometer. Melting points were determined using a Büchi melting point apparatus and are uncorrected.

### Furanone 4a; Typical procedure

A solution of methoxytriazoline 1 (204 mg, 0.60 mmol), DMAD (2: 73 mg, 0.52 mmol), and 4-methylbenzaldehyde (204 mg, 0.60 mmol) in toluene (5 mL) was heated to reflux for 12 h under N₂. After the completion of the reaction as indicated by TLC, the solvent was removed in vacuo. The residue was subjected to column chromatography on silica gel (100–200 mesh) using 60:40 PE–EtOAc as eluent. High-resolution mass spectra were recorded under EI/HRMS (at 5000 resolution) using JEOL JMS 600H mass spectrometer.

### Viscous yellow liquid.

1H NMR (300 MHz, CDCl₃): δ = 8.12 (d, J = 7.9 Hz, 2 H), 7.73 (d, J = 7.4 Hz, 2 H), 7.50–7.32 (m, 13 H), 6.78 (d, J = 6.7 Hz, 2 H), 3.33 (s, 3 H), 2.30 (s, 3 H).

13C NMR (CDCl₃): δ = 164.9, 163.6, 151.9, 146.2, 137.9, 133.5, 131.3, 130.1, 129.4, 128.9, 128.3, 127.9, 123.9, 109.7, 67.1, 50.9, 21.2.

HRMS (EI): m/z calc'd for C₃₃H₂₅N₃O₅: 552.1845; found: 552.1984.

### Viscous red liquid.

1H NMR (300 MHz, CDCl₃): δ = 7.71 (d, J = 6.9 Hz, 2 H), 7.59–7.33 (m, 14 H), 7.18–7.13 (m, 2 H), 3.36 (s, 3 H).

13C NMR (CDCl₃): δ = 163.3, 152.0, 143.6, 137.1, 133.6, 133.5, 131.8, 131.5, 130.3, 129.5, 129.2, 128.8, 128.7, 127.8, 125.7, 123.9, 123.4, 68.9, 51.1.

LRMS (FAB): m/z calc'd for C₃₃H₂₅N₃O₅: 552.1845; found: 552.1984.

### Viscous yellow liquid.

1H NMR (300 MHz, CDCl₃): δ = 8.09 (d, J = 9.2 Hz, 2 H), 7.86 (d, J = 9.2 Hz, 2 H), 7.73–7.70 (m, 2 H), 7.52–7.37 (m, 13 H), 3.42 (s, 3 H).

13C NMR (CDCl₃): δ = 166.3, 151.9, 146.2, 137.9, 133.5, 131.8, 130.1, 129.4, 129.2, 128.9, 128.3, 127.8, 124.9, 124.8, 124.7, 110.3, 68.7, 50.9.

HRMS (EI): m/z calc'd for C₃₃H₂₅N₃O₅: 558.15; found: 558.1507.

### Viscous red liquid.

1H NMR (300 MHz, CDCl₃): δ = 7.72 (d, J = 7.9 Hz, 2 H), 7.76 (d, J = 7.0 Hz, 2 H), 7.50–7.16 (m, 15 H), 3.32 (s, 3 H).

13C NMR (CDCl₃): δ = 165.2, 163.5, 151.9, 145.8, 137.2, 133.6, 131.4, 130.1, 129.4, 129.2, 127.9, 123.9, 110.3, 68.7, 50.9.

HRMS (EI): m/z calc'd for C₃₃H₂₅N₃O₅: 513.1689; found: 513.1633.

### Viscous red liquid.

1H NMR (300 MHz, CDCl₃): δ = 7.72 (d, J = 7.9 Hz, 2 H), 7.65 (d, J = 7.7 Hz, 2 H), 7.50–7.32 (m, 13 H), 6.78 (d, J = 7.5 Hz, 2 H), 3.78 (s, 3 H), 3.32 (s, 3 H).

13C NMR (CDCl₃): δ = 164.8, 163.5, 159.5, 151.8, 137.3, 133.7, 131.3, 130.0, 129.6, 129.4, 129.1, 128.9, 128.3, 127.8, 124.1, 123.3, 122.9, 112.9, 108.8, 55.0, 50.8.

HRMS (EI): m/z calc'd for C₃₃H₂₅N₃O₅: 543.1794; found: 543.1762.

### Viscous yellow liquid.

1H NMR (300 MHz, CDCl₃): δ = 7.71–7.68 (m, 3 H), 7.67–7.27 (m, 13 H), 6.83 (d, J = 3.5 Hz, 2 H), 6.36 (d, J = 2.6 Hz, 1 H), 3.39 (s, 3 H).

13C NMR (CDCl₃): δ = 167.5, 164.4, 142.2, 137.3, 133.6, 132.5, 131.4, 130.7, 129.5, 129.2, 128.8, 127.8, 124.1, 123.3, 111.4, 110.5, 67.9, 50.9, 38.8, 31.9, 30.4.

LRMS (FAB): m/z calc'd for C₃₃H₂₅N₃O₅: 503.15; found: 503.95.
IR (film): 2963, 1696, 1562, 1498, 1285, 1099, 992, 768 cm⁻¹.

Viscous red liquid.

1H NMR (300 MHz, CDCl₃): δ = 7.73–7.66 (m, 4 H), 7.52–7.37 (m, 13 H), 6.94 (t, J = 7.8 Hz, 2 H), 5.42 (s, 3 H).

13C NMR (CDCl₃): δ = 164.8, 163.4, 151.9, 145.0, 137.3, 133.7, 131.4, 130.2, 130.1, 129.9, 129.5, 129.2, 129.1, 128.9, 128.8, 127.8, 126.5, 124.0, 123.4, 114.8, 110.1, 68.5, 51.0.

LRMS (FAB): m/z calcld for C₃₅H₂₃N₃O₅: 581.0909; found: 581.0881.

11 Viscous red liquid.

IR (film): 3066, 2934, 1717, 1698, 1544, 1457, 1367, 1231, 1148, 764 cm⁻¹.

HRMS (EI): m/z calcld for C₅₈H₄₀N₆O₈: 948.29; found: 948.29.

12 Viscous red liquid.

IR (film): 3070, 2934, 1717, 1698, 1544, 1450, 1271, 1114, 1070, 992, 768 cm⁻¹.

HRMS (EI): m/z calcld for C₃₂H₂₂FN₃O₄: 531.16; found: 531.71.

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References


(2) Breslow, R. J. Am. Chem. Soc. 1958, 80, 3719.


(17) CCDC file 656836 contains the supplementary crystallographic data for compound 4a. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/products/csd/request.