A One-Step Synthesis of Cyclic α-Diazoacetones

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Base-catalyzed transfer of the diazo function from tosyl azide to methylene groups flanked by two electron-withdrawing substituents, e.g., malonic esters, β-diketones, benzyl ketones, is a well established and valuable synthetic procedure. Proton removal from the substrate appears to be the limiting factor, however, and less acidic substrates, such as simple ketones, cannot be converted directly to α-diazoacetones by this process; prior C-acylation has hitherto been necessary. When faced with the problem of preparing α-diazoacetone it was found that C-formylation or α-oxidation of the very hindered α-methylene group in the parent ketone was not possible.

Investigation of direct diazo-transfer processes was therefore undertaken, and we now communicate the successful outcome of that study.

The direct transfer of a diazo group to benzyl methyl ketone and a variety of esters and β-dicarbonyl compounds, from tosyl azide under phase-transfer conditions had been recorded, but we found the direct application of this procedure to ketones to be generally unproductive. When 2,4,6-trisopropylphenylsulfonyl azide was substituted for tosyl azide, however, the phase-transfer method gave good results with a variety of cyclic ketones. Tetrabutylammonium bromide and 18-crown-6 ether catalysts were used in combination; less satisfactory results were obtained from their individual usage.

Other arylsulfonyl azides were tested (mesityl, tosyl, 4-chlorophenyl, 4-nitrophenyl, and 2,4-dinitrophenyl) and found to be unsatisfactory.

The method may not offer significant advantages over established procedures for simple ketones [the yield of the simple ketone 2, however, is superior to that obtained (43%) from C-nitrosation and chloramine treatment], but provides the only satisfactory route to hindered derivatives, e.g., 4 and 6. The conversion may usually be effected also in the presence of base- and acid-labile functions, as demonstrated for substrates 1, 2, and 6.

2-Diazo-5-methoxy-1-tetralone (4); Typical Procedure:
To a solution of 5-methoxy-1-tetralone (100 mg, 0.57 mmol), tetrabutylammonium bromide (50 mg, 0.16 mmol), 18-crown-6 ether (5 mg), and 2,4,6-trisopropylphenylsulfonfyl azide (200 mg, 0.65 mmol) in benzene (10 ml) is added 66% aqueous potassium hydroxide (10 ml). The mixture is stirred vigorously at 35 °C for 30 min. Further azide (150 mg, 0.49 mmol) added, and stirring continued for 1.5 h, when T.L.C. analysis indicates that the reaction is complete. Ether (50 ml) is added and the organic layer separated. The aqueous layer is diluted with water (20 ml), extracted with ether (50 ml), then the combined ether layers are washed with water (5 ml) and saturated sodium chloride solution (5 ml) and dried with magnesium sulfate. Removal of solvent and preparative layer chromatography (Merck KGF, prepared 2 mm plates) gives a
### Table. Preparation and Physical Data of Cyclic α-Diazoketones

<table>
<thead>
<tr>
<th>Diazoketone&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Reaction Conditions</th>
<th>Yield&lt;sup&gt;d&lt;/sup&gt;</th>
<th>m.p.</th>
<th>High-Resolution M.S.&lt;sup&gt;e&lt;/sup&gt;</th>
<th>I.R. (Nujol)</th>
<th>'H-N.M.R. (CDCl&lt;sub&gt;3&lt;/sub&gt;, 100 MHz)</th>
<th>δ [ppm]</th>
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<tr>
<td></td>
<td></td>
<td>[%]</td>
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<tr>
<td>2</td>
<td>4 h, 25°C</td>
<td>63</td>
<td>97–101&lt;sup&gt;d&lt;/sup&gt;</td>
<td>248.1158 (M&lt;sup&gt;+&lt;/sup&gt;) (calc. for C&lt;sub&gt;13&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;; 248.1161)</td>
<td>2105; 1637</td>
<td>1.32 (s, 3H); 1.48–2.80 (6H); 3.40 (e, 2H); 3.96 (s, 4H); 5.46 (e, 1H)</td>
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<td>1.37 (s, 6H); 1.48 (s, 3H); 3.07 (s, 2H); 3.38; 3.50</td>
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<td>3</td>
<td>4 h, 35°C</td>
<td>73</td>
<td>136–139&lt;sup&gt;d&lt;/sup&gt;</td>
<td>268.1465 (M&lt;sup&gt;+&lt;/sup&gt; – N₂) (calc. for C&lt;sub&gt;13&lt;/sub&gt;H&lt;sub&gt;10&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;; 268.1463)</td>
<td>2080; 1600</td>
<td>5.92 (t, 1H, J = 4 Hz); 6.66 (d, 1H, J = 2 Hz); 6.78 (dd, 1H, J = 8, 2 Hz)</td>
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<td>7.23 (d, 1H, J = 8 Hz); 7.64 (d, 1H, J = 8 Hz);</td>
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<td>4</td>
<td>2 h, 35°C</td>
<td>54 (73)%</td>
<td>86–88</td>
<td>202.0739 (M&lt;sup&gt;+&lt;/sup&gt;) (calc. for C&lt;sub&gt;11&lt;/sub&gt;H&lt;sub&gt;10&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;; 202.0742)</td>
<td>2090&lt;sup&gt;c&lt;/sup&gt;; 1640&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2.98 (m, 4H, W = 9 Hz); 3.85 (s, 3H); 7.00 (d, 1H, J = 8 Hz); 7.28 (t, 1H, J = 8 Hz); 7.64 (d, 1H, J = 8 Hz)</td>
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<td>2.98 (s, 4H); 3.84 (s, 3H); 6.66 (d, 1H, J = 2 Hz); 6.83 (dd, 1H, J = 8, 2 Hz); 7.96</td>
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<td>5</td>
<td>3 h, 40°C</td>
<td>48</td>
<td>75–76</td>
<td>202.0743 (M&lt;sup&gt;+&lt;/sup&gt;) (calc. for C&lt;sub&gt;11&lt;/sub&gt;H&lt;sub&gt;10&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;; 202.0742)</td>
<td>2105; 1640</td>
<td>2.98 (s, 4H); 3.84 (s, 3H); 1.40 (s, 3H); 1.90–2.50 (m, 4H); 2.99 (s, 1H); 3.85 (s, 3H); 4.91 (dd, 1H, J = 9, 6 Hz); 7.08</td>
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<td>7.22 (d, 1H, J = 8 Hz); 7.38–7.62 (m, 4H); 8.06 (m, 2H)</td>
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<td>6</td>
<td>10 h, 35°C</td>
<td>84</td>
<td>184–186&lt;sup&gt;e&lt;/sup&gt;</td>
<td>390.1830 (M&lt;sup&gt;+&lt;/sup&gt; – N₂) (calc. for C&lt;sub&gt;13&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;; 390.1831)</td>
<td>2105; 1702, 1620</td>
<td>1.85 (s, 3H); 1.22 (s, 3H); 2.33 (t, 2H); 4.21 (dd, 1H, J = 9, 6 Hz); 7.08</td>
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<td>7.22 (d, 1H, J = 8 Hz); 7.38–7.62 (m, 4H); 8.06 (m, 2H)</td>
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<sup>a</sup> Substrates for diazoketone preparation were obtained in the following manner: 2, oxidation of the related alcohol<sup>b</sup>; 3, literature procedure<sup>c</sup>; 6, benzoylation followed by allylic oxidation (chromic anhydride/pyridine/dichloromethane) then hydrogenation (5% palladium on carbon/ethyl acetate, 4 atm, 20°C) of 3β-hydroxy-13-methoxy-7-oxo-4,10-trimethylpodocarpa-8,11,13-triene<sup>d</sup>.

<sup>b</sup> Yields are given for pure crystalline compounds. All diazoketones except 6 were rather unstable, resulting in loss of compound during purification.

<sup>c</sup> Satisfactory microanalyses could not be obtained due to decomposition of the unstable α-diazoketones. The purity of the products was established by all other criteria, however, the very characteristic spectral data (especially I.R.), in combination with the high-resolution mass measurements, provide adequate characterization.

<sup>d</sup> Yields estimated from ¹H-N.M.R. spectra.

<sup>e</sup> I.R. measured in chloroform.

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<sup>2</sup> M. Regitz, Synthes 1972, 351.