Generation of Diphenyldiazomethane by Oxidation of Benzophenone Hydrazide with Magtrieve™

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Diphenyldiazomethane, a red crystalline solid, is a useful reagent for the protection of carboxylic acids by conversion to their diphenylmethyl (dpm, benzhydryl) esters.1 Dpm protecting group has been widely used due to its easy deprotection by mild acidic condition2a or hydrogenolysis,2b especially in the field of β-lactams and peptides.2c Diphenyldiazomethane has been prepared by the oxidation of benzophenone hydrazide with mercuric oxide,4a peracetic acid,4b iodosobenzene diacetate4c or OXONE®.4d However, some methods suffer from a disadvantage such as toxic nature of reagent,4a strong oxidative conditions4b or incompatibility with certain functional groups.4b,d For example, OXONE® may not be employed for the in situ protection of carboxylic acid containing sulfide group due to the possibility of the concomitant oxidation of sulfide group.5

Recently, MagtrieveTM, a magnetically retrievable oxidant (CrO2) has been shown to oxidize alcohols in high yields.6 We have already shown that this reagent can serve as an oxidant for the aromatization of 1,4-dihydropyridines in high yields.7 We now report that MagtrieveTM can also serve as an efficient reagent for the oxidation of benzophenone hydrazide to diphenyldiazomethane, enabling the one-pot protection of carboxylic acids including N-protected amino acids, as shown in Table 1.

Treatment of benzophenone hydrazide with MagtrieveTM in dichloromethane gave a purple color characteristic of diphenyldiazomethane, immediately. The oxidation was completed within 15 min at room temperature, based on TLC analysis (Rf of hydrazide = 0.33, Rf of product = 0.60 in EtOAc : hexanes (1 : 5)). Then, a solution of acid was added to the purple solution and the progress of the reaction was monitored with TLC. The reaction time was in a range of 0.1 h ~ 5 h, depending on the substrate. After the reaction was finished, MagtrieveTM was retrieved with magnet6 and the solution was concentrated to give a crude product, which was purified by column chromatography. The yield was good, except for the entry 6, where the dpm ester was decomposed during the column chromatography.

As a typical procedure, a solution of benzophenone hydrazide (206 mg, 1.05 mmol) in dichloromethane (15 mL) was treated with MagtrieveTM (1.51 g) and the mixture was stirred at room temperature. After 15 min, the oxidation was found to be completed. A solution of benzoic acid (122 mg, 1.00 mmol) in dichloromethane (2 mL) was added to the resulting purple solution and the whole mixture was stirred for 1.5 h. After the reaction was finished, MagtrieveTM was retrieved with magnet6 and the solution was concentrated to give a crude product, which was purified by column chromatography. The yield was good, except for the entry 6, where the dpm ester was decomposed during the column chromatography.

Table 1: Preparation of Diphenylmethyl Esters from Acids

<table>
<thead>
<tr>
<th>Entries</th>
<th>Acids</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>Lit. mp (°C) or EI-MS (m/e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C6H5CO2H</td>
<td>1.5</td>
<td>80</td>
<td>87-88</td>
<td>87.5-888</td>
</tr>
<tr>
<td>2</td>
<td>C6H5CH2CO2H</td>
<td>2</td>
<td>83</td>
<td>oil</td>
<td>91 (25), 118 (5), 167 (100), 165 (44), 184 (6)</td>
</tr>
<tr>
<td>3</td>
<td>C6H5CH(OH)CO2H</td>
<td>0.1</td>
<td>71</td>
<td>88.5-89</td>
<td>107 (38), 152 (8), 167 (100), 317 (M+, 0.1)</td>
</tr>
<tr>
<td>4</td>
<td>C6H5CH=CHCO2H</td>
<td>2</td>
<td>72</td>
<td>73</td>
<td>72.5d</td>
</tr>
<tr>
<td>5</td>
<td>C6H5(CH2)5CO2H</td>
<td>3</td>
<td>70</td>
<td>oil</td>
<td>152 (19), 167 (100), 184 (41), 296 (M+, 10)</td>
</tr>
<tr>
<td>6</td>
<td>BOC-L-leucine</td>
<td>0.25</td>
<td>54*</td>
<td>93-94</td>
<td>57 (70), 86 (74), 130 (66), 167 (100), 186 (19)</td>
</tr>
<tr>
<td>7</td>
<td>CbzNHCH2CO2H</td>
<td>5</td>
<td>71</td>
<td>oil</td>
<td>91 (69), 167 (100), 242 (43), 286 (12)</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>0.1</td>
<td>70</td>
<td>129-129.5</td>
<td>91 (41), 167 (47), 183 (100)</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>0.1</td>
<td>67</td>
<td>oil</td>
<td>91 (33), 155 (49), 167 (100)</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>4</td>
<td>79</td>
<td>144-145</td>
<td>140-143f, 91 (21), 167 (100), 382 (8), 556 (M+, 0.5)</td>
</tr>
</tbody>
</table>

*All reactions were conducted at room temperature in dichloromethane, except for the entries 7 and 10 where EtOAc was employed, using 1 mmol of acid, 1.05 mmol of benzophenone hydrazide and 1.51 g of MagtrieveTM. Yield refers to the pure isolated product. Relative intensity is given in the parenthesis. Beilstein E III 9, 2695. The product was decomposed during column chromatography, resulting in a lower yield. Kametani, T.; Sekine, H.; Honda, T. Heterocycles, 1983, 20, 1577.
retrieved and the solution was concentrated to give a crude product (275 mg), which was purified by column chromatography (hexanes : EtOAc = 5 : 1) to give diphenylmethyl benzoate in 80% yield, mp 87-88 °C (Lit.\textsuperscript{8} mp 87.5-88 °C).

In summary, Magtrieve\textsuperscript{TM} can serve as a new oxidant for the generation of diphenyldiazomethane from benzophenone hydrazone, offering a mild and nontoxic reaction condition as well as an easy workup. Since Magtrieve\textsuperscript{TM} does not oxidize sulfide group, the present method can be applied to the protection of sulfur-containing acids (entries 9 and 10).

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References