Microwave assisted phase transfer catalysis: an efficient solvent free method for the synthesis of cyclopropane derivatives

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Microwave assisted solvent free synthesis of cyclopropane derivatives 2a-e starting from active methylene compounds 1a-e and 1,2-dibromoethane under phase transfer conditions is described.

Note

Apart from domestic purpose, microwave ovens are routinely used to carry out organic reaction. The microwaves are non-ionizing radiations that transfer energy to ions in solution and other compounds having dipole moment. Hydrocarbons such as benzene, hexane, cyclohexane etc. and symmetrical molecules such as carbon tetrachloride absorb very little microwaves energy. But chloroform, DMF, ethylene glycol, chlorobenzene and other organic molecules with dipole moments absorb microwave and are heated up rapidly. The advantages of using microwave oven for organic reactions are: 1) small amount of solvent is needed, 2) the reaction can be carried out in shorter reaction time avoiding polymerization and 3) the yields are improved.

The coupling of microwave technology with solvent free phase transfer catalysis is the recent development in this area. This provides a clean, selective and efficient methodology to carry out organic reactions with substantial improvements in terms of reaction conditions, simplicity in operating procedures and yields.

As a part of the research programme on development of environment friendly methods for synthesis of organic compounds, we were interested in the synthesis of cyclopropanedicarboxylic acid derivatives starting from active methylene compounds such as diethyl malonate, ethyl acetooacetate, ethyl cyanoacetate etc., some of which are useful intermediates for anti-inflammatory and analgesic agents and leukotriene antagonists. Generally they are prepared by alkylation of active methylene compounds with dihaloethane using base and phase transfer catalyst in a suitable biphasic solvent system. This reaction usually requires longer reaction time and higher temperature. In most of the cases the ester group is hydrolyzed to acid under aqueous basic reaction conditions.

We wish to report microwave-assisted solvent free synthesis of cyclopropane derivatives from active methylene compounds and dibromoethane under PTC conditions. The cyclopropanation of diethyl malonate with dibromoethane was carried out in a domestic microwave oven using potassium carbonate and various phase transfer catalysts such as tricaprylmethylammonium chloride (Aliquat-336), triethylbenzylammonium chloride (TEBA) and tetrabutylammonium bromide (TBAB) etc. The combination of potassium carbonate and Aliquat-336 was found to be better for cyclopropanation of diethyl malonate.

A mixture of diethyl malonate (1 equivalent), K₂CO₃ (4 equivalent), dibromoethane (2 equivalent) and Aliquat-336 (catalytic) was mixed thoroughly and irradiated in a microwave oven for 10 minutes using 70% power in an open glass vessel. Ethyl acetate was added to the reaction mixture and the solid material was removed by filtration. The filtrate was concentrated under reduced pressure and residue was purified by column chromatography.

The structure of cyclopropanedicarboxylic acid diethyl ester 2a was established by IR and 1H NMR spectroscopy. The 1H NMR spectra of 2b and 2e showed singlets for cyclopropyl protons at δ 1.45 and 1.46 respectively. It is interesting to note that no product formation was observed in the absence of either phase transfer catalyst or potassium carbonate under microwave conditions. The same reaction when carried out without microwave irradiation, in refluxing toluene using K₂CO₃ and phase transfer catalyst, Aliquat-336, for 20 hr, only trace amount (GC-analysis) of diethyl cyclopropanedicarboxylate formation was observed. However, this reaction when carried out in refluxing ethanol, gave a complex mixture of products along with small amount (11%) of desired product 2a.

The generality of this reaction (Scheme I) was established by reacting the other active methylene compounds 1b-e with dibromoethane under similar
reaction conditions to get good yields (see Table 1) of
cyclopropyl compounds 2b-e.

However, malononitrile and ethyl ester of phenyl-
acetic acid did not give the cyclopropyl compounds
under these reaction conditions. The use of dichloro-
ethane instead of dibromoethane resulted in poor
yields of cyclopropyl compounds. Dimedone 3 when
reacted with dibromoethane under similar reaction
conditions, instead of desired cyclopropyl compound
gave a linear mono alkylated product 4 in good yields
(74%) along with small amount (5%) of dialkylated
product 5 (Scheme II).

In conclusion, we have demonstrated the applica-
tion of microwave irradiation for cyclopropopanation
of active methylene compounds with dibromoethane
under solvent free reaction conditions using phase
transfer catalysts.

Experimental Section

All 1H NMR spectra were recorded in CDCl3 on a
Bruker AC 200 and Bruker MSL 300 spectrometers
and chemical shifts were reported in ppm downfield
from tetramethylsilane. Infrared spectra were re-
corded on a Perkin-Elmer Infracord spectrophotome-
ter Model 599-B using sodium chloride optics. Melt-
ing points were determined on a Thermonik Campbell
melting point apparatus and were uncorrected. A do-
meric microwave oven (800 Watt, BPL-make) is
used for carrying out reactions. Silica gel (SD’s 60-
120 mesh) was used for column chromatography.

General procedure for the preparation of cyclo-
propyl derivatives 2a-e from active methylene
compound 1a-e. A mixture of active methylene com-
 pound (4 mmole), dibromoethane (8 mmole), potas-
sium carbonate (16 mmole) and phase transfer cata-
lyst Aliquat-336 (0.2 g) was mixed together thor-
oughly and introduced in a microwave oven in an
open glass container. The microwave irradiation was
carried out for 10 min with 70% power. The reaction
mixture was cooled and ethyl acetate (30 mL) was
added. The solid material was removed by filtration
and the filtrate was washed with water and brine

Table 1—Synthesis of 2a-e and 4 by the reaction of active methylene compound 1a-e, 3 and dibromoethane under microwave irradiation.

<table>
<thead>
<tr>
<th>Entry No.</th>
<th>Product</th>
<th>R¹</th>
<th>R²</th>
<th>Yield</th>
<th>m.p.</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>CO₂Et</td>
<td>CO₂Et</td>
<td>88</td>
<td>Oil</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>COCH₃</td>
<td>CO₂Et</td>
<td>85</td>
<td>Oil</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>CN</td>
<td>CO₂Et</td>
<td>86</td>
<td>Oil</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>4-MePhSO₂</td>
<td>CO₂Et</td>
<td>83</td>
<td>75-77</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>COCH₃</td>
<td>COCH₃</td>
<td>65</td>
<td>Oil</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>--</td>
<td>--</td>
<td>74</td>
<td>Oil</td>
</tr>
</tbody>
</table>

* Isolated yield.
Cyclopropane-1,1-dicarboxylic acid diethyl ester 2a: Oil; 88%; IR (neat): 2983, 1731, 1371, 1321, 1209, 1135, 1031 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.25 (t, \(J = 7.5\) Hz, 3H); 4.2 (q, \(J = 7.5\) Hz, 2H); MS m/z, 141 (M-H).

Cyclopropane-1-acetyl-1-carboxylic acid ethyl ester 2b: Oil; 85%; IR (neat): 2983, 1728, 1699, 1627, 1371, 1359, 1311, 1188, 1141, 1027, 750 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.2 (t, \(J = 7\) Hz, 3H); 1.45 (s, 4H); 2.45 (s, 3H); 4.2 (q, \(J = 7\) Hz, 2H); MS m/z, 111 (M-H).

Cyclopropane-1-cyano-1-carboxylic acid ethyl ester 2c: Oil; 86%; IR (neat): 2985, 2939, 2248, 1731, 1371, 1311, 1278, 1161, 1024, 972, 923, 858 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.25 (t, \(J = 7\) Hz, 3H); 1.6 (m, 4H); 4.2 (q, \(J = 7\) Hz, 2H); MS m/z, 139 (M-H).

Cyclopropane-1-(4'-methylphenylsulphonyl)-1-carboxylic acid ethyl ester 2d: m.p. 75-77\(^\circ\)C; 86%; IR (neat): 1731, 1596, 1446, 1319 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.15 (t, \(J = 6.8\) Hz, 3H); 1.56-1.81 (m, 2H); 2.03-2.12 (m, 2H); 2.43 (s, 3H); 4.06 (q, \(J = 6.8\) Hz, 2H); 7.28 (d, \(J = 9.3\) Hz, 2H); 7.87 (d, \(J = 9.3\) Hz, 2H); MS m/z, 223 (M-H).

1,1-Diacetyl cyclopropane 2e: Oil; 65%; IR (neat): 1689, 1589, 1367 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.46 (s, 4H); 2.20 (s, 6H); MS m/z, 126 (M-H).

2-(2'-Bromoethyl)-5,5-dimethylcyclohexane-1,3-dione 4: Oil; 74%; IR (neat): 1654, 1608, 1469, 1398, 1361 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.05 (s, 6H); 2.21 (s, 2H); 2.32 (s, 2H); 3.56 (t, \(J = 5.9\) Hz, 2H); 4.13 (t, \(J = 5.9\) Hz, 2H); 5.28 (s, 1H); MS m/z, 246 (M-H).

References