One Pot Synthesis of β-Phosphonomalonates at Room Temperature Using Tetrabutylammonium Bromide as an Efficient Catalyst

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Abstract
A one pot solvent free procedure has been developed for the synthesis of β-phosphonomalonates by reacting of various aromatic aldehydes, malononitrile and triethyl phosphate through tandem Knoevenagel-phospha-Michael reaction at room temperature catalyzed by tetrabutylammonium bromide (5 mol%) as an efficient and eco-friendly catalyst with excellent yield (82-93%), easy work-up and short reaction time. The synthesized derivative of β-phosphonomalonates characterized and confirmed by FT-IR, $^1$HNMR, $^{13}$CNMR and HRMS data. This methodology is new, simple and efficient for the synthesis of β-phosphonomalonates with mild reaction condition, ease of handling, inexpensive way and good efficacy.

Keywords: Solvent-free, Aldehydes, Knoevenagel-phospha-Michael reaction mechanism, β-phosphonomalonates, Tetrabutylammonium bromide.

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Introduction
Organophosphorous compounds including β-phosphonomalonates have wide range of applicability in the field of agriculture as plant growth regulators [1], antibiotics [2], metabolic probes [3], peptide mimetics [4], enzyme inhibitor [5] and in treatment of bone disorder [6]. Various methods are reported for the synthesis of β-phosphonomalonates by using acids [7-8], base [9], microwave [10], radical initiators [11], transition metal (Palladium) [12], 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) [13], nano sized zinc oxide [14], Al(OTf)$_3$ [15], phosphomolybdic acid [16], 3-aminopropylated silica gel [17], nano n-propylsulphonated γ-Fe$_2$O$_3$ [18], diethyl amine [19], ethylenediamine diacetate [20], molecular iodine [21], silica bonded 2-hydroxy ethylammonium acetate [22], iron doped single walled carbon nanotubes [23], heterogeneous catalyst (clay supported heteropolyacid) [24] and polystyrene supported DABCO [25].

Reported methods for the synthesis of β-phosphonomalonates suffer long reaction time, drastic reaction conditions, low yield and use of expensive and toxic reagents. So, designing of efficient and green methodology for the synthesis of β-phosphonomalonates essentially required. The use of ionic liquid as catalyst got more attention recently because of a wide range of properties such as the ability to act as both catalyst and solvent [26]. In present work, we report a one-pot synthesis of β-phosphono malonates using tetrabutylammonium bromide (TBAB) as a highly efficient catalyst (Scheme 1) which offered several advantages including mild reaction conditions, short reaction time, easy workup and high yield. To the best of our knowledge, we are first to apply tetrabutylammonium bromide (TBAB) as an efficient catalyst for the synthesis of β-phosphono malonates.

Scheme 1 Synthesis of β-phosphono malonates

Experimental Details
All the reagents and chemicals were purchased from Hi-Media Biosciences and were used without further purification. Melting Points were determined by MFRS Laboratory equipment. IR spectra were recorded on PerkinElmer FT-IR spectrophotometer. $^1$HNMR and $^{13}$CNMR spectra were recorded on 400 MHz JEOL JNM ECS400 instrument using CDCl$_3$. HRMS values were measured by a Waters Micromass Q-Tof Micro spectrometer.
General procedure for the synthesis of β phosphono malonates derivatives
Substituted benzaldehyde (5m mole), malononitrile (5m mole) and triethyl phosphite (5m mole) were mixed with 5 mol% of TBAB in a round bottom flask and stirred at room temperature (Scheme1). After some time the reaction mixture was solidified indicating the completion of the reaction, which was further confirmed by TLC using hexane and ethyl acetate (80:20) solvent system and visualized using iodine vapors and UV detection. The obtained solid crude product was washed with water and recrystallized from ethanol to get pure product.

Result and Discussion
The reaction conditions were optimized by the representative reaction taking derivative of benzaldehyde, malononitrile and triethyl phosphite as starting material and tetrabutylammonium bromide as catalyst (Scheme1) under solvent free condition (Table 1). The reaction carried out without catalyst took longer time (5.5 hr) and afforded low yield (55%). The reaction without a catalyst under reflux condition took 1.5 hr to complete affording 67% yield. The reaction carried out using tetrabutylammonium bromide (20 mol%) as catalyst completed within 10 min affording 92% yield.

Table 1 Effect of different condition for the synthesis of Diethyl 1-(phenyl)-2,2 dicyano ethyl phosphonate with TBAB catalyst

<table>
<thead>
<tr>
<th>Entry</th>
<th>Condition</th>
<th>Mol%</th>
<th>Time</th>
<th>Yield(^{a}) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Without Catalyst, Reflux</td>
<td>-</td>
<td>1.5hr</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>Without Catalyst, room temp</td>
<td>-</td>
<td>5.5 hr</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>TBAB, room temp</td>
<td>20</td>
<td>10 min</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>TBAB, room temp</td>
<td>10</td>
<td>10 min</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>TBAB, room temp</td>
<td>5</td>
<td>10 min</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>TBAB, room temp</td>
<td>2</td>
<td>30 min</td>
<td>81</td>
</tr>
</tbody>
</table>

\(^{a}\)Reaction Condition: Benzaldehyde (5mmol), malononitrile (5 mmol), triethyl phosphate (5 mmol), Tetrabutylammonium bromide, monitored by TLC

This clearly shows the importance of catalyst. The reaction was carried out at room temperature by taking a variable quantity of catalyst and it was found that 5 mol% of tetrabutylammonium bromide was the optimum quantity of catalyst. The same amount of catalyst was used for the synthesis of all the derivatives and all the reactions were carried out at room temperature under solventless condition. The reaction time and yield for different derivatives synthesized are depicted in Table 2. All the reaction completed within 2 to 30 minutes. The reaction time for the synthesized product having strong electron withdrawing group (4-NO\(_2\), 2,3 dichloro, 3- NO\(_2\)) on benzene ring was shorter (entries 4c, 4f and 4g).

Table 2 Tetrabutylammonium bromide (TBAB) catalyzed synthesis of β- phosphono malonates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Prod.</th>
<th>R</th>
<th>t/min</th>
<th>Yield(^{a})%</th>
<th>M.P./(^{\circ})C</th>
<th>Spectroscopic data [ref.]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found</td>
<td>Reported [ref.]</td>
</tr>
<tr>
<td>1</td>
<td>4a</td>
<td>3,4-(OCH(_3))(_2)-C(_6)H(_3)</td>
<td>20</td>
<td>93</td>
<td>98-99</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>4-Cl-C(_6)H(_4)</td>
<td>10</td>
<td>90</td>
<td>97-98</td>
<td>98 [20]</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>4-NO(_2)-C(_6)H(_4)</td>
<td>2</td>
<td>89</td>
<td>103-104</td>
<td>104-105 [23]</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>4-OH-C(_6)H(_4)</td>
<td>20</td>
<td>82</td>
<td>79-81</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>4e</td>
<td>C(_6)H(_5)</td>
<td>8</td>
<td>92</td>
<td>56-57</td>
<td>56-58 [20]</td>
</tr>
<tr>
<td>6</td>
<td>4f</td>
<td>2,3-(Cl(_2))-C(_6)H(_3)</td>
<td>5</td>
<td>93</td>
<td>70-72</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>4g</td>
<td>3-NO(_2)-C(_6)H(_4)</td>
<td>6</td>
<td>85</td>
<td>75-76</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^{a}\)Yield of isolated products

The plausible mechanism of reaction carried out by Knoevenagel condensation followed by phospho- micheal addition has been shown in Scheme 2. The carbonyl groups of aldehyde are activated by tetrabutylammonium bromide for nucleophilic attack. Comparison between the present protocol and also the reported protocols (Table 3) clearly indicates the prevalence of present protocol in terms of cost, simplicity, short reaction time and high yield over the reportable ones.
Scheme 2 Plausible mechanism for the formation of β-phosphonomalonates

Table 3 Comparison between various reported method and the present method for the synthesis of β-phosphonomalonates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Mol%</th>
<th>Time</th>
<th>Condition</th>
<th>Solvent</th>
<th>Yield(%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD)</td>
<td>20</td>
<td>30 min</td>
<td>RT</td>
<td>Toluene</td>
<td>96</td>
<td>[13]</td>
</tr>
<tr>
<td>2</td>
<td>Al(OTf)₃</td>
<td>10</td>
<td>45 min</td>
<td>Reflux</td>
<td>n-Hexane</td>
<td>93</td>
<td>[15]</td>
</tr>
<tr>
<td>3</td>
<td>Phosphomolybdic acid</td>
<td>2</td>
<td>30 min</td>
<td>80°C</td>
<td>-</td>
<td>88</td>
<td>[16]</td>
</tr>
<tr>
<td>4</td>
<td>Diethyl amine</td>
<td>10</td>
<td>15 min</td>
<td>RT</td>
<td>-</td>
<td>95</td>
<td>[19]</td>
</tr>
<tr>
<td>5</td>
<td>Ethylenediamine diacetate (EDDA)</td>
<td>20</td>
<td>12 hr</td>
<td>RT</td>
<td>Ethanol</td>
<td>86</td>
<td>[20]</td>
</tr>
<tr>
<td>6</td>
<td>Molecular iodine</td>
<td>10</td>
<td>2 hr</td>
<td>50°C</td>
<td>-</td>
<td>90</td>
<td>[21]</td>
</tr>
<tr>
<td>7</td>
<td>Iron doped single walled carbon nanotubes</td>
<td>10</td>
<td>1 hr</td>
<td>50°C</td>
<td>-</td>
<td>97</td>
<td>[23]</td>
</tr>
<tr>
<td>8</td>
<td>Clay supported heteropolyacid</td>
<td>5 mg</td>
<td>25 min</td>
<td>Ultrasonication</td>
<td>-</td>
<td>97</td>
<td>[24]</td>
</tr>
<tr>
<td>9</td>
<td>Tetra butyl ammonium bromide (TBAB)</td>
<td>5</td>
<td>2-15 min</td>
<td>RT</td>
<td>-</td>
<td>90-95</td>
<td>this work</td>
</tr>
</tbody>
</table>

Spectral analysis

Compound 4a: Yellow crystals; yield: 90%; m.p.: 98-99°C; IR (KBr) (cm⁻¹): 2222(CN str.), 1271(P=O str.); ^1HNMR (CDCl₃, 400MHz): 1.09 (t, 3H, J=7.32Hz), 1.46 (m, 3H, J=7.32Hz), 3.38(m,4H), 3.79 (dd, 1H), 3.93(s,3H), 3.97(s,3H), 7.63(d,1H), 7.38-7.4 (m,2H) ppm; ^13CNMR (CDCl₃, 400MHz): 13.76(CH₃), 19.83(CH₃), 24.22(CH), 56.06(CH₃), 56.26(CH₃), 56.40(CH), 78.86(CH₂), 111.15(CH), 114.49(CH), 123.32, 128.29, 149.57, 154.9, 159.24 ppm.

Compound 4b: Yellow crystals; yield: 90%; m.p.: 97-98°C; IR (KBr) (cm⁻¹): 2225(CN str.), 1280(P=O str.); ^1HNMR (CDCl₃, 400MHz): 1.03(t, 3H, J=7.32Hz), 1.45 (m, 3H, J=7.32Hz), 3.72(dd,1H), 4.11(dd,1H), 7.52 (d, 2H), 7.82(d, 2H) ppm; ^13CNMR (CDCl₃, 400MHz): 13.82(CH₃), 19.90(CH₃), 24.29(CH), 59.22(CH), 83.41(CH₂), 112.47(CN), 113.57(CN), 128.94, 129.37, 130.98, 141.28, 158.46 ppm.

Compound 4c: Yellow crystals; yield: 89%; m.p.: 103-104°C; IR (KBr) (cm⁻¹): 2220(CN str.), 1280(P=O str.); ^1HNMR (CDCl₃, 400MHz): 1.33(t,3H, J=7.32Hz), 1.43(t,3H, J=7.32Hz), 3.72(dd,1H), 4.11(dd,1H), 7.52 (d, 2H), 7.82(d, 2H) ppm; ^13CNMR (CDCl₃, 400MHz): 13.82(CH₃), 19.90(CH₃), 24.29(CH), 59.22(CH), 83.41(CH₂), 112.47(CN), 113.57(CN), 128.94, 129.37, 130.98, 141.28, 158.46 ppm.

Compound 4d: Brown crystals; yield: 72%; m.p. 79-81°C; IR (KBr) (cm⁻¹): 3347(OH str.), 2223(CN str.), 1256(P=O, str.); ^1HNMR (CDCl₃, 400MHz): 0.97 (t,3H, J=7.32Hz), 1.26 (t,3H, J=7.32Hz), 4.29(m,4H), 5.08(OH,s), 7.02 (d,2H), 7.7(d,1H), 7.8(d, 1H) ppm; ^13CNMR (CDCl₃, 400MHz):
13.74(CH₃), 19.83(CH₃), 24.10(CH), 59.11(CH), 64.21(CH₂), 64.26(CH₃), 113.96(CN), 115.06(CN), 117.30, 122.94, 128.98, 131.12, 134.05, 159.37 ppm.

Compound 4e: Cream crystals; yield: 92%; m.p. 56-57°C; IR (KBr) (cm⁻¹): 2231(CN str.), 1316(P=O, str.).

¹HNMR (CDCl₃, 400MHz): 1.25 (t, 3H, J=7.32Hz), 1.34 (t, 3H, J=7.32Hz), 3.23 (dd, 2H), 3.71(m,2H), 4.11(m,2H), 7.54 (t,1H), 7.6(t,2H), 7.9(d, 2H) ppm; ¹³CNMR (CDCl₃, 400MHz): 13.72(CH₃), 19.83(CH₃), 24.10(CH), 59.11(CH), 82.89(CH₂), 112.65(CN), 113.82(CN), 129.73, 130.83, 131.01, 134.05, 159.37 ppm.

Conclusion

In summary, we have developed highly efficient, an eco-friendly method for the synthesis of β-phosphonomalonate derivatives via Knoevenagel condensation followed by a Phosphomicheal addition in solventless condition, in the presence of tetrabutylammonium bromide as a catalyst with less reaction time and high yield.

Supporting Materials

Figure 1 FTIR spectrum of 4a
Figure 2 $^1$HNMR (400Mz) spectrum of 4a in CDCl$_3$

Figure 3 $^{13}$CNMR (400Mz) spectrum of 4a in CDCl$_3$
Figure 4 FTIR spectrum of 4b

Figure 5 Expended $^1$HNMR (400Mz) spectrum of 4b in CDCl$_3$
Figure 6 Expended $^1$HNMR (400Mz) spectrum of 4b in CDCl$_3$

Figure 7 $^{13}$CNMR (400Mz) spectrum of 4b in CDCl$_3$
Figure 8 FTIR spectrum of 4c

Figure 9 $^1$HNMR (400Mz) spectrum of 4c in CDCl$_3$
Figure 10 $^{13}$CNMR (400Mz) spectrum of 4c in CDCl$_3$

Figure 11 FTIR spectrum of 4d
Figure 12 $^1$HNMR (400Mz) spectrum of 4d in CDCl$_3$

Figure 13 $^{13}$CNMR (400Mz) spectrum of 4d in CDCl$_3$
**Figure 14** FTIR spectrum of 4e.

**Figure 15** $^1$HNMR (400Mz) spectrum of 4e in CDCl$_3$.
Figure 16 $^{13}$C NMR (400Mz) spectrum of 4e in CDCl$_3$

Figure 17 FTIR spectrum of 4f
Figure 18 $^1$HNMR (400Mz) spectrum of 4f in CDCl$_3$

Figure 19 $^{13}$CNMR (400Mz) spectrum of 4f in CDCl$_3$
Figure 20 FTIR spectrum of 4g

Figure 21 $^1$HNMR (400Mz) spectrum of 4g in CDCl$_3$
Figure 22 13CNMR (400Mz) spectrum of 4g in CDCl₃

Figure 23 HRMS of 4f
Acknowledgements

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References


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