The Baylis-Hillman reaction: Rate acceleration in silica gel solid phase medium

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Remarkable rate acceleration in the Baylis-Hillman reaction of aromatic aldehydes with acrylates, particularly tert-butyl acrylate, in silica gel solid phase medium has been described.

The Baylis-Hillman reaction is an atom economyid versatile carbon-carbon bond forming reaction between the α-position of the activated alkenes and carbon electrophiles under the influence of catalytic amount of tertiary amine, particularly 1,4-azabicyclo[2.2.2]octane (DABCO), producing densely functionalized molecules which have been utilized in various important organic transformations.1-3 The most accepted mechanism of this reaction is described Scheme I, taking the reaction between alkyl acrylate and aldehyde as a model case. However, application of this reaction is somewhat crippled by slow reaction rate. Thus, the reaction requires several days to several weeks for completion, depending upon the reactivity of both activated alkene and electrophile.3 As it is desirable for any synthetic process, from both practical and economic point of view, to be accomplished faster and high yielding, various methods have been described to accelerate the Baylis-Hillman reaction. Thus, the application of high pressure,9-10 microwave irradiation11 have been reported to provide significant rate acceleration. Rafel d Leahy have reported that the reaction is faster at C.12 Kawamura and Kobayashi reported remarkable acceleration in the rate of Baylis-Hillman reaction catalyzed by DABCO, using lithium perchlorate as a -catalyst in ether at -25°C-0°C.13

Recently, Aggarwal and co-workers described that thium triflates accelerate the Baylis-Hillman upling of acrylates with aldehydes catalyzed by ABO.14,15 Later Aggarwal has also reported that 3U is far superior catalyst for the Baylis-Hillman action between activated alkenes and aldehydes giving the adducts at much faster rate than using ABO or 3-hydroxyquiniclidine.16

Literature survey reveals that rate increase also has been observed due to the presence of hydrogen bonding using methanol as solvent17 or using 3-hydroxyquiniclidine18 as a catalyst or terminal hydroxy acrylates as activated alkenes.19 Increased rates have also been reported when the reaction is carried out in water20 or fluorinated solvents21 due to hydrophobic and fluorophobie effects respectively.

During our investigations on applications of the Baylis-Hillman adducts in various stereoselective transformations, we required these adducts derived from tert-butyl acrylate. Literature survey reveals that the usual Baylis-Hillman reaction of benzaldehyde with tert-butyl acrylate under the catalytic influence of DABCO requires 28 days to provide the desired adduct tert-butyl 3-hydroxy-3-phenyl-2-methylpropanoate in 65% yield (93% yield based on converted aldehyde).22 Literature survey also reveals that the presence of very small amounts of acetic acid (3 mol%) provide better results, thus Baylis-Hillman reaction of benzaldehyde and 4-bromobenzaldehyde with tert-butyl acrylate under the catalytic influence
of DABCO (15 mol%) in the presence of acetic acid (3 mol%) requires 21 days to provide the desired adducts, tert-butyl 3-hydroxy-3-phenyl-2-methyleneepanoate and tert-butyl 3-hydroxy-3-(4-bromophenyl)-2-methyleneepanoate in 77% and 81% yields respectively (Scheme II). These are very inconveniently slow reactions and hence there is a necessity of finding simple methods for carrying out these reactions at faster rates.

Accordingly, we envisioned that appropriate solid phase medium reaction using silica gel or alumina (both neutral and acidic) might result in acceleration of the reaction rate. During our attempts in this direction we have carried out the reaction between benzaldehyde and tert-butyl acrylate in the presence of 15 mol% of DABCO under various conditions and the best results were obtained when the reaction was carried out in silica gel (>200 mesh) solid phase medium thus providing the required product, tert-butyl 3-hydroxy-3-phenyl-2-methyleneepanoate in 81% isolated yields in 36h time. Encouraged by the remarkable rate acceleration in this reaction we have subjected various aromatic aldehydes to the Baylis-Hillman reaction with tert-butyl acrylate in the silica gel solid phase medium to provide the desired adducts in good yields (eq 1, Table I).

With a view to further understanding this reaction we have also carried out the reaction of benzaldehyde and p-tolualdehyde with methyl and ethyl acrylates in silica gel solid phase medium in the presence of 15 mol% DABCO (Table I). These results are indeed reasonably encouraging. With a view to have a direct comparison of these solid phase medium reaction results with that of the usual DABCO catalyzed reactions, we have also carried out parallel experiments with the catalytic amount of DABCO only (without silica gel) under similar conditions and a quick comparison has been presented in the Table I. We have also presented the literature results (yields and reaction times) for known molecules in the Table I.

In conclusion, we have demonstrated the application of silica gel as solid phase medium for performing the Baylis-Hillman reaction particularly between tert-butyl acrylate and aromatic aldehydes under the influence of catalytic amount of DABCO (15 mol%) at increased rates.
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All melting points were recorded on a Superfit (dia) capillary melting point apparatus and are corrected. IR spectra were recorded on JASCO-FT model 5300 or Perkin Elmer model 1310 spectrometer using samples as neat liquids or as KBr files. 1 H NMR (200 MHz) and 13 C NMR (50 MHz) spectra were recorded in CDCl3 on Bruker-AC-200 spectrometer using TMS as an internal standard. Spectral analyses were recorded on Perkin-Elmer 0C-CHN analyzer.

General Procedure for the Baylis-Hillman action in silica gel solid phase medium. Aldehyde (9 mmole), acrylate (15 mmole), and DABCO (1.5 mole, 0.168 g), silica gel (2-200 mesh, 2.95-75 g) were thoroughly and uniformly mixed and is mixture was left at room temperature. Reactions are monitored by TLC. After appropriate time (see table 1), ethyl acetate (10 mL) was added and stirred vigorously and filtered. The solid silica gel was washed with ethyl acetate (4×10 mL). The combined fraction was dried over anhyd. Na2SO4 and concentrated. The crude product was purified by column chromatography (silica gel, 10% ethyl acetate hexanes) followed by distillation or by crystallization (ethyl acetate;hexanes, 1:4) at 0°C to ovide the pure Baylis-Hillman alcohols (1-10). The compounds 1-3, 8, and 10 are known in the literature and their spectral data (IR, 1 H and/or 13 C NMR) data are reported. Spectral data of these molecules are in agreement with literature data.25

tert-Butyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate 4: Colorless crystals; yield: 66%; m.p. 41-43 °C; IR: 1639, 1714, 3414 cm⁻¹; 1 H NMR: δ 1.40 (s, 9H), 2.33 (s, 3H), 2.98 (b, 1H), 5.47 (s, 1H), 5.71 (s, 1H), 6.23 (s, 1H), 7.14 (d, 2H, J = 7.6 Hz), 7.24 (d, 2H, J = 7.6 Hz); 13 C NMR: δ 16.35, 17.75, 89.11, 27.35, 69.52, 81.50, 120.95, 126.14, 126.26, 127.72, 130.38, 135.70, 139.20, 143.37, 166.07. Anal. Caled for C16H22O3: C, 72.55; H, 8.12. Found: C, 72.65; H, 8.10 %.

tert-Butyl 3-hydroxy-2-methylene-3-(2-methylphenyl)propanoate 5: Colorless crystals; yield: 78%; m.p. 54-55 °C; IR: 1640, 1716, 3350 cm⁻¹; 1 H NMR: δ 1.43 (s, 9H), 2.33 (s, 3H), 2.90 (b, 1H), 5.50 (s, 1H), 5.74 (s, 1H), 6.23 (s, 1H), 7.13-7.27 (m, 3H), 7.35-7.43 (m, 1H); 13 C NMR: δ 19.11, 27.97, 69.52, 81.50, 125.05, 126.14, 126.26, 127.72, 130.38, 135.70, 139.20, 143.37, 166.07. Anal. Caled for C16H22O3: C, 72.55; H, 8.12. Found: C, 72.71; H, 8.16 %.

Table 1—Baylis-Hillman reaction between aromatic aldehydes and acrylates in silica gel solid phase medium: A comparison with usual DABCO catalyzed reactions

<table>
<thead>
<tr>
<th>CHO</th>
<th>COOR</th>
<th>Time in hrs/days</th>
<th>Product</th>
<th>Yields (%)</th>
<th>Literature results</th>
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<td></td>
<td></td>
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<tr>
<td>enyl</td>
<td>Me</td>
<td>12h</td>
<td>1-14</td>
<td>78</td>
<td>6d (94%)</td>
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<tr>
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<td>Me</td>
<td>48h</td>
<td>2-14</td>
<td>79</td>
<td>30d (95%)</td>
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<tr>
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<td>Bu'</td>
<td>36h</td>
<td>3-14</td>
<td>81</td>
<td>28d (91% )</td>
</tr>
<tr>
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<td>10d</td>
<td>4</td>
<td>66</td>
<td>-</td>
</tr>
<tr>
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<td>Bu'</td>
<td>12d</td>
<td>5</td>
<td>78</td>
<td>-</td>
</tr>
<tr>
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<td>Bu'</td>
<td>16d</td>
<td>6</td>
<td>62</td>
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<td>7</td>
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<tr>
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<td>Bu'</td>
<td>6d</td>
<td>8-14</td>
<td>65</td>
<td>21d (81% )</td>
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<tr>
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<td>Bu'</td>
<td>19d</td>
<td>9</td>
<td>63</td>
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<tr>
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<td>Et</td>
<td>14h</td>
<td>10-21</td>
<td>80</td>
<td>7d (83% )</td>
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</table>

All reactions were carried out on 10 mmole scale of aldehyde with acrylate (15 mmole), DABCO (1.5 mmole), and silica gel (2.50-75 g). b) All reactions were carried out on 10 mmole scale of aldehyde with acrylate (15 mmole) and DABCO (1.5 mmole). c) These eutectics (1-3, 10) were obtained as colorless liquids, and the molecules (4-9) were obtained as solids. d) Yields of the pure products (10) (based on aldehyde) after column chromatography (silica gel 10% ethyl acetate in hexanes) followed by crystallization (ethyl anexanes, 1:4) at 0°C or distillation.
(d, 1H, J = 5.6 Hz), 5.72 (s, 1H), 6.24 (s, 1H), 7.19 (d, 2H, J = 8.0 Hz), 7.28 (d, 2H, J = 8.0 Hz); 13C NMR: 23.97,
28.00, 33.85, 73.38, 81.51, 124.77, 126.39, 126.64,
139.22, 143.91, 148.41, 165.80. Anal. Calcd for
C17H24O3: C, 73.88; H, 8.75. Found: C, 74.09;
H, 8.73 %.

**tert-Butyl 3-hydroxy-2-methylene-3-(naphth-1-
yl)propanoate 9:** Colorless crystals; yield: 63 %; m.p.
95-98 °C; IR: 1639, 1714, 3412 cm⁻¹; 1H NMR:
1.42 (s, 9H), 1.91 (b, 1H), 5.51 (s, 1H), 6.27 (s, 1H),
6.34 (s, 1H), 7.44-8.09 (m, 7H); 13C NMR:
27.97, 69.38, 81.54, 123.84, 124.41, 125.34,
125.58, 125.71, 126.15, 128.49, 128.71, 131.02,
133.85, 137.01, 143.62, 166.10. Anal. Calcd for
C18H29O3: C, 76.03; H, 7.09. Found: C, 75.85; H, 7.12 %.

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**References**


24. These molecules were earlier prepared and well characterized. For molecules 1, 3 and 10 see ref. 22. For molecules 3 and 8, see ref. 23. For molecule 2, see ref. 25.