N-Methylmorpholine and Urotropine as Useful Base Catalysts in Baylis–Hillman Reaction

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Abstract: N-Methylmorpholine and urotropine, inexpensive mild bases, have effectively been utilized as catalysts in Baylis–Hillman reaction to result in good to excellent yields (57–99%) of the products.

Key words: Baylis–Hillman reaction, N-methylmorpholine, urotropine, dioxane-water, base catalyst and activated alkenes

The Baylis–Hillman reaction is an emerging carbon–carbon bond forming reaction between a carbonyl compound and an activated alkene under the influence of a suitable catalyst, typically a tertiary amine or phosphine. This reaction has seen upsurge in its synthetic utility in the recent times. The catalysts often used are very substrate specific and the results are also very sensitive to precise reaction conditions. However, DABCO was found to be ineffective to many substrates. For instance, in the coupling of cyclohexenone with formaldehyde DABCO is not a reagent of choice. Though DMAP, DBU and tetramethyl guanidine (TMG) are known in literature as catalysts for Baylis–Hillman reaction, the development of new catalyst is still an attractive preposition due to the above cited reasons.

N-Methylmorpholine (NMM) is a commercially available solvent for resins, waxes, dyes and casein. It is also used as a base in mixed anhydride peptide synthesis to minimize racemization, as a deprotecting agent for Fmoc and in heterocyclization of thiosemicarbazides. Since NMM has lower pKa value of 7.5 than other bases (DABCO, 3-HQ, Me3N) and partial racemization of chiral aldehyde by DABCO is known in the literature, its use is recommended when unstable carbonyl compounds, chiral electrophiles and chiral Michael acceptors are employed as substrates in Baylis–Hillman reaction to minimize either decomposition or racemization.

Interestingly, urotropine is used as a reagent in ring closure reaction, synthesis of triaza-, tetraaza-heterocyclic derivatives and α-methylation of aryl alkyl ketones. Though, urotropine was reported as a base catalyst for Baylis–Hillman reaction, its scope and generality were not tested for various aldehydes and activated olefins. In continuation of our recent work on Baylis–Hillman reaction, herein we demonstrate the use of N-methylmorpholine (NMM) and urotropine as an inexpensive new tertiary amine catalysts in Baylis–Hillman reaction (Equation 1).

N-methylmorpholine (NMM), and urotropine are readily available tertiary amines and currently chosen as catalysts for our study as they are either hitherto unexplored or least studied in Baylis–Hillman reaction. Consequently, standardization of reaction conditions was performed using 4-nitrobenzaldehyde (1) and ethyl acrylate (6) in different solvents using stoichiometric amounts of NMM and urotropine at room temperature (Table 1). An optimum yield of adduct 10a (73%, NMM; 95%, urotropine) was obtained when the reaction was run for 24 hours in a 1:1 mixture of 1,4-dioxane–water. However, when the catalyst loading was decreased to 50 mol% or 25 mol% there was significant reduction of the yields. This amply demonstrates the necessity of stoichiometric amounts of NMM and urotropine at room temperature (Table 1). An optimum yield of adduct 10a (73%, NMM; 95%, urotropine) was obtained when the reaction was run for 24 hours in a 1:1 mixture of 1,4-dioxane–water. However, when the catalyst loading was decreased to 50 mol% or 25 mol% there was significant reduction of the yields. This amply demonstrates the necessity of stoichiometric amounts of NMM and urotropine for catalyzing Baylis–Hillman reaction. Consequently, standardization of reaction conditions was performed using 4-nitrobenzaldehyde (1) and ethyl acrylate (6) in different solvents using stoichiometric amounts of NMM and urotropine at room temperature (Table 1).

To broaden the scope of the Baylis–Hillman reaction catalyzed by NMM and urotropine, this study was then extended to other activated alkenes like methyl vinyl ketone, acrylonitrile and cyclohexenone under the conditions of Table 1.

Table 1 Baylis–Hillman Reaction of 4-NO₂-PhCHO with Ethyl Acrylate Catalyzed by NMM and Urotropine in Different Solvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>NMM, yield (%)</th>
<th>Urotropine, yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DMF</td>
<td>39</td>
<td>56</td>
</tr>
<tr>
<td>DMSO</td>
<td>48</td>
<td>69</td>
</tr>
<tr>
<td>Sulpholane</td>
<td>0</td>
<td>80</td>
</tr>
<tr>
<td>Dioxane–water</td>
<td>73</td>
<td>95</td>
</tr>
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</table>
same set of reaction conditions. However, the Baylis–Hillman reaction of 1 with methyl vinyl ketone (7) resulted in unidentified product (16%) in addition to the expected adduct 10b (51%). The product yield was enhanced to 68% when DMSO was used as a solvent. Indeed, the Baylis–Hillman reaction of aldehydes 1, 2, and 3 with methyl vinyl ketone (7) catalyzed by NMM and urotropine under the changed solvent conditions (DMSO) afforded only the normal adducts 10b, 11b, and 12b in 62–85% yields. The Baylis–Hillman reactions of other activated alkenes, namely acrylonitrile (8) and cyclohexenone (9) were performed in dioxane–water (1:1) at ambient temperature for 24–36 h to afford the desired products 10c, 11c, 12c, 10d, 11d, 12d and 14d in the yields as mentioned in Table 2.

### Table 2  Baylis–Hillman Reaction of Aldehydes with Activated Alkenes Using NMM and Urotropine as Catalysts\(^a\)–\(^c\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Alkene</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Urotropine</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>6</td>
<td>Dioxane–H(_2)O</td>
<td>24</td>
<td>10a, 73</td>
<td>24</td>
<td>10a, 95</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>6</td>
<td>Dioxane–H(_2)O</td>
<td>36</td>
<td>11a, 62</td>
<td>34</td>
<td>11a, 92</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>6</td>
<td>Dioxane–H(_2)O</td>
<td>24</td>
<td>12a, 69</td>
<td>24</td>
<td>12a, 76</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>7</td>
<td>DMSO</td>
<td>24</td>
<td>10b, 68</td>
<td>20</td>
<td>10b, 85</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>7</td>
<td>DMSO</td>
<td>36</td>
<td>11b, 62</td>
<td>28</td>
<td>11b, 73</td>
<td></td>
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<tr>
<td>6</td>
<td>3</td>
<td>7</td>
<td>DMSO</td>
<td>24</td>
<td>12b, 72</td>
<td>16</td>
<td>12b, 84</td>
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<tr>
<td>7</td>
<td>1</td>
<td>8</td>
<td>Dioxane–H(_2)O</td>
<td>24</td>
<td>10c, 98</td>
<td>20</td>
<td>10c, 99</td>
<td></td>
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<tr>
<td>8</td>
<td>2</td>
<td>8</td>
<td>Dioxane–H(_2)O</td>
<td>36</td>
<td>11c, 96</td>
<td>24</td>
<td>11c, 99</td>
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<tr>
<td>9</td>
<td>3</td>
<td>8</td>
<td>Dioxane–H(_2)O</td>
<td>24</td>
<td>12c, 88</td>
<td>18</td>
<td>12c, 91</td>
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<tr>
<td>10</td>
<td>4</td>
<td>8</td>
<td>Dioxane–H(_2)O</td>
<td>48</td>
<td>13c, 64</td>
<td>35</td>
<td>13c, 71</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>9</td>
<td>Dioxane–H(_2)O</td>
<td>24</td>
<td>10d, 71</td>
<td>20</td>
<td>10d, 83</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>9</td>
<td>Dioxane–H(_2)O</td>
<td>36</td>
<td>11d, 63</td>
<td>24</td>
<td>11d, 68</td>
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<tr>
<td>13</td>
<td>5</td>
<td>9</td>
<td>Dioxane–H(_2)O</td>
<td>36</td>
<td>14d, 60</td>
<td>32</td>
<td>14d, 62</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) All reactions were carried out in aldehyde (1 mmol) with activated alkenes (3 mmol), NMM (1 mmol)/urotropine (1 mmol) at ambient temperature for 16–48 h.

\(^b\) All the products were characterized by \(^1\)H NMR and other spectral data.

\(^c\) Yields of isolated products.

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### Scheme 1

Interestingly, less reactive benzaldehyde $4$ also on reaction with acrylonitrile ($8$) afforded the adduct $13c$ under the same reaction conditions. Another important observation that needs special mention is that formaldehyde ($5$) underwent Baylis–Hillman reaction with cyclohexenone ($9$) to afford $14d$ (60%) under this new base catalyzed reaction conditions.

In conclusion, we have successfully introduced inexpensive and commercially available $N$-methylmorpholine (NMM) and urotropine as new base catalysts for the Baylis–Hillman reaction at ambient temperature in aqueous dioxane (1:1) for 16–48 hours to afford the corresponding adducts in good to excellent yields. Of the two bases studied, urotropine was found to result in better yields of adducts.

Solvents were dried over standard drying agents and freshly distilled under vacuum. Organic solutions were dried over anhyd Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane, 1:9–1.5:8.5) to afford adducts $10a$–$d$, $11a$–$c$, $12a$–$c$, $13c$ and $14d$ in 60–99% yields. The compounds were characterized by IR, $^1$H NMR, and mass spectroscopy.

**General Experimental Procedure**

To the arylaldehyde (1 mmol) in 1,4-dioxane–water (1:1, 2 mL), NMM (1 mmol) or urotropine (1 mmol) and activated alkene (3 mmol) were added and the reaction mixture stirred for 24–48 h at r.t. Then the reaction mixture was diluted with water (20 mL), extracted with Et$_2$O ($3 	imes 15$ mL), washed with brine (30 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane, 1:9–1.5:8.5) to afford adducts $10a$–$d$, $11a$–$c$, $12a$–$c$, $13c$ and $14d$ in 60–99% yields. The compounds were characterized by IR, $^1$H NMR, and mass spectroscopy.

10a

Yellow oil.

IR (neat): 3472, 1689 cm$^{-1}$.

$^1$H NMR (200 MHz, CDCl$_3$, TMS): $\delta = 8.24$ (d, $J = 8.7$ Hz, 2 H, Ar-H), 7.63 (d, $J = 8.4$ Hz, 2 H, Ar-H), 6.39 (s, 1 H, olefinic), 6.20 (s, 1 H, olefinic), 6.02 (s, 1 H, allylic), 5.36 (br s, 1 H, OH).

$^{13}$C NMR (50 MHz, CDCl$_3$): $\delta = 72.07, 123.22, 126.07, 130.59, 147.09, 147.88$.

EIMS: $m/z = 204$ [M$^+$].

Anal. Calcd for C$_9$H$_{11}$NO$_3$: C, 59.73; H, 5.01. Found: C, 59.57; H, 5.06.

10b

Yellow oil.

IR (neat): 3440, 2228 cm$^{-1}$.

$^1$H NMR (200 MHz, CDCl$_3$, TMS): $\delta = 8.24$ (d, $J = 8.7$ Hz, 2 H, Ar-H), 7.63 (d, $J = 8.4$ Hz, 2 H, Ar-H), 6.39 (s, 1 H, olefinic), 6.20 (s, 1 H, olefinic), 6.02 (s, 1 H, allylic), 5.36 (br s, 1 H, OH).

$^{13}$C NMR (50 MHz, CDCl$_3$): $\delta = 72.07, 123.22, 126.07, 130.59, 147.09, 147.88$.

EIMS: $m/z = 204$ [M$^+$].

Anal. Calcd for C$_9$H$_{11}$NO$_3$: C, 59.73; H, 5.01. Found: C, 59.57; H, 5.06.

10c

Yellow oil.

IR (neat): 3441, 1694 cm$^{-1}$.

$^1$H NMR (200 MHz, CDCl$_3$, TMS): $\delta = 8.20$ (d, $J = 8.7$ Hz, 2 H, Ar-H), 7.54 (d, $J = 8.4$ Hz, 2 H, Ar-H), 6.78 (t, $J = 5.4$ Hz, 1 H, olefinic), 5.60 (s, 1 H, allylic), 3.41 (br s, 1 H, OH), 2.49–2.42 [m, 4 H, (CH$_2$)$_2$], 2.08–2.02 (m, 2 H, CH$_2$).

$^{13}$C NMR (50 MHz, CDCl$_3$): $\delta = 22.42, 25.76, 38.44, 72.19, 123.75, 127.24, 140.31, 147.34, 148.16, 149.25, 199.78$.

EIMS: $m/z = 246$ [M$^+$ – 1].


10d

Yellow oil.

IR (neat): 3472, 2219 cm$^{-1}$.

$^1$H NMR (200 MHz, CDCl$_3$, TMS): $\delta = 7.45–7.11$ (m, 5 H, Ar-H), 6.25 (s, 1 H, olefinic), 6.04 (s, 1 H, olefinic), 5.19 (s, 1 H, allylic), 2.54 (s, 1 H, OH).

$^{13}$C NMR (50 MHz, CDCl$_3$): $\delta = 131.87, 131.05, 129.25, 128.41, 123.74, 84.40, 63.02, 29.67$.

EIMS: $m/z = 183$ [M$^+$].

Anal. Calcd for C$_9$H$_{11}$NO: C, 78.67; H, 4.95. Found: C, 78.72; H, 4.90.

The compounds $11a$–$c$, $12a$, $12b$, $13a$, $13c$ and $14a$ are known in the literature and the data obtained for these compounds is comparable with the reported values.

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