**N-Methylimidazole as a Promising Catalyst for the Aza-Michael Addition Reaction of N-Heterocycles**

Bo Kai Liu, Qi Wu, Xue Qi Qian, De Shui Lv, Xian Fu Lin*

Department of Chemistry, Zhejiang University, Hangzhou 310027, P.R. of China

Fax +86(571)87952618; E-mail: llc123@zju.edu.cn

Received 25 April 2007; revised 25 May 2007

Abstract: N-Methylimidazole has been shown to be a promising catalyst for aza-Michael reactions. Various N-heterocycles were introduced to α,β-unsaturated carbonyl compounds employing N-methylimidazole (0.05 equiv) in a highly efficient, rapid and high yielding synthesis of N-heterocyclic derivatives.

Key words: N-methylimidazole, Michael additions, nucleophiles, heterocycles, α,β-unsaturated compounds

Currently, N-heterocycles are attracting increasing attention due to their bioactivity, in particular, N-heterocyclic derivatives containing β-amino carbonyl functionalities, which have potential therapeutic activity.1 Michael addition is a molecularly economic reaction and among the most practical and widely used methods for the synthesis of such β-amino-carbonyl compounds. Generally, the use of strong bases or acids for this reaction would lead to environmentally hazardous residues and undesirable byproducts. Over the past few years, a great number of alternative procedures had been reported which avoid such harsh conditions.2 Most aza-Michael reaction protocols employ transition-metal catalysts such as SmI₂, CeCl₃, InCl₃, Yb(OTf)₃, Bi(OTf)₃, Cu(OTf)₃, LiClO₄ or heterogeneous solid acids.3 Considering the substantial cost and high toxicity associated with these metal complex catalysts, chemists have been investigating novel alternatives. Recently, ionic liquids have been shown to play a similar role and catalyze the aza-Michael addition.4,5 The results in Table 1 demonstrate not only the action of N-methylimidazole as a catalyst, but also its efficient catalytic ability. The reaction was very sluggish in the absence of N-methylimidazole; only 3.5% yield was obtained after eight hours. A moderate yield was achieved using 0.01 equivalent of N-methylimidazole (Table 2, entry 1). Even prolonging the reaction to eight hours gave yields of less than 15%. A moderate yield was achieved using 0.05 equivalent of N-methylimidazole (Table 2, entry 3). When the amount of N-methylimidazole was increased to 0.05 equivalents, an excellent yield was achieved (Table 2, entry 4), showing that this was sufficient for efficient catalysis of the aza-Michael addition.

The results in Table 2 demonstrate not only the action of N-methylimidazole as catalyst, but also its efficient catalytic ability. The reaction was very sluggish in the absence of N-methylimidazole; only 3.5% yield was obtained after one hour (Table 2, entry 1). Even prolonging the reaction to eight hours gave yields of less than 15%. A moderate yield was achieved using 0.01 equivalent of N-methylimidazole (Table 2, entry 3). When the amount of N-methylimidazole was increased to 0.05 equivalents, an excellent yield was achieved (Table 2, entry 4), showing that this was sufficient for efficient catalysis of the aza-Michael addition (Table 2, entries 5–7). Having the optimal conditions in hand, a variety of structurally diverse five-membered N-heterocycles were react-

---

**Scheme 1**

The feasibility of our approach was first tested by mixing 4-nitroimidazole (1 mmol) and methyl acrylate (1.2 equiv) with N-methylimidazole (0.05 equiv) in dimethyl sulfoxide (DMSO; 1 mL) at 70 °C for 1 h. A single product was obtained after flash chromatography that was characterized by IR, ¹H NMR and ¹³C NMR. No byproducts were detected when the reaction was monitored by TLC and HPLC. We then screened several tertiary amines, all of which had the potential to promote this addition. The results are summarized in Table 1. N-Methylimidazole was found to be significantly more effective than pyridine and slightly more so than triethylamine, DBU and 4-(N,N-dimethylamino)pyridine (DMAP), indicating that N-methylimidazole was a novel and promising catalyst for aza-Michael addition.

The results in Table 2 demonstrate not only the action of N-methylimidazole as catalyst, but also its efficient catalytic ability. The reaction was very sluggish in the absence of N-methylimidazole; only 3.5% yield was obtained after one hour (Table 2, entry 1). Even prolonging the reaction to eight hours gave yields of less than 15%. A moderate yield was achieved using 0.01 equivalent of N-methylimidazole (Table 2, entry 3). When the amount of N-methylimidazole was increased to 0.05 equivalents, an excellent yield was achieved (Table 2, entry 4), showing that this was sufficient for efficient catalysis of the aza-Michael addition (Table 2, entries 5–7). Having the optimal conditions in hand, a variety of structurally diverse five-membered N-heterocycles were react-
ed with acrylates and methyl vinyl ketone. In all cases, the imidazole and its derivatives underwent aza-Michael addition successfully and the products 3a–p were obtained in good to excellent yields (Table 3). As seen from the Table 3, 4-nitroimidazole gave superior results, compared with imidazole (entry 10), in the reaction with methyl acrylate (entry 2). A competitive experiment using a 1:1 mixture of 4-nitroimidazole and imidazole, as the Michael donor, with methyl vinyl ketone was designed. The 4-nitroimidazole adduct was obtained in 54% yield, with the imidazole derived product forming in 35%, showing that the presence of an electron-withdrawing group enhanced the nucleophilicity and reactivity of the N-heterocycles (Scheme 2). Triazole was found to be more reactive than imidazole, 2-methylimidazole and 4-methylimidazole, both in the aza-Michael addition to methyl vinyl ketone (Table 3, entries 9, 11, 13 and 15) and to methyl acrylate (Table 3, entries 10, 12, 14 and 16). Examination of the results obtained with a range of acrylates revealed that the chain length of the ester played a minimal role in governing the reactivity of the conjugate addition. As the carbon chain of the alcohol moiety was increased in length, a slight decrease in yield was observed (Table 3, entries 2–4). Reactions with either α-methyl or β-methyl substituted acrylates proceeded significantly more slowly. Highly prolonged reaction times were required to achieve satisfactory yields of products in the reactions of 4-nitroimidazole with both methyl methacrylate and methyl crotonate (Table 3, entries 5 and 6). Apart from the steric hindrance of the Michael accepter, that of the Michael donor also had a subtle influence on the reaction. Compared with 4-nitroimidazole, 2-methyl-4-nitroimidazole gave slightly lower yields upon reaction with both methyl vinyl ketone (Table 3, entries 1 and 7) and methyl acrylate (Table 3, entries 2 and 8), due to the substitution at the 2-position. A similar observation was also found with 2-methylimidazole and imidazole (Table 3, entries 9–12). Interestingly, lower yields were obtained from reactions between nucleophiles bearing a 4-nitro group and methyl vinyl ketone than with methyl acrylate; the opposite was found when substrates without a 4-nitro group were used.

![Scheme 2](attachment:image.png)

**Scheme 2**

Encouraged by this result, we then examined the generality of this new strategy under identical reaction conditions. The protocol also proved to be effective for more complicated N-heterocycles such as pyrimidines and purines and the expected products were formed in good to excellent yields. Mono-adducts were obtained almost exclusively, in excellent yields, with only traces of the bis-adducts being detected. In the case of the aza-Michael addition of 5-fluorouracil to methyl vinyl ketone, 11% bis-adduct was observed, thus demonstrating its higher reactivity compared to the other two pyrimidines due to the electron-withdrawing substituent (Table 4, entry 1). Under the same conditions, only 69% yield was obtained after one hour, when 6-benzylamino-purine was employed. Two hours were required for the reaction to go to completion due to the purines lower reactivity (Table 4, entry 4). Similar results were obtained from reactions between N-heterocycles and methyl acrylate (Table 4, entries 5–8).

A possible mechanism through which N-methylimidazole promotes the Michael addition of N-heterocycles to α,β-unsaturated carbonyl compounds could proceed via abstraction of the N–H proton of the N-heterocycle by N3 of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Screening Catalysts for the Michael Addition of 4-Nitroimidazole to Methyl Acrylate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry</td>
<td>Catalyst</td>
</tr>
<tr>
<td>1</td>
<td>N-methylimidazole</td>
</tr>
<tr>
<td>2</td>
<td>pyridine</td>
</tr>
<tr>
<td>3</td>
<td>Et$_3$N</td>
</tr>
<tr>
<td>4</td>
<td>DBU</td>
</tr>
<tr>
<td>5</td>
<td>DMAP</td>
</tr>
</tbody>
</table>

*Reaction conditions: 4-nitroimidazole (1 mmol), methyl acrylate (1.2 mmol) in DMSO (1 mL) containing catalyst (0.05 equiv) at 70 °C for 1 h.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Screening the Amount of N-Methylimidazole in the Michael Addition of 4-Nitroimidazole to Methyl Acrylate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry</td>
<td>N-Methylimidazole (equiv)</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0.01</td>
</tr>
<tr>
<td>4</td>
<td>0.05</td>
</tr>
<tr>
<td>5</td>
<td>0.10</td>
</tr>
<tr>
<td>6</td>
<td>0.20</td>
</tr>
<tr>
<td>7</td>
<td>0.50</td>
</tr>
</tbody>
</table>

*Reaction conditions: 4-nitroimidazole (1 mmol), methyl acrylate (1.2 mmol) in DMSO (1 mL) containing N-methylimidazole at 70 °C for 1 h.

*Isolated yield.

*Reacted for 8 h.
### Table 3  Michael Addition of Imidazole and its Derivatives to Acrylates and Methyl Vinyl Ketone

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Acceptor</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Imidazole" /></td>
<td><img src="image" alt="Acrylate" /></td>
<td>1</td>
<td>3a</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Imidazole" /></td>
<td><img src="image" alt="Acrylate" /></td>
<td>1</td>
<td>3b</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Imidazole" /></td>
<td><img src="image" alt="Acrylate" /></td>
<td>1</td>
<td>3c</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Imidazole" /></td>
<td><img src="image" alt="Acrylate" /></td>
<td>1</td>
<td>3d</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Imidazole" /></td>
<td><img src="image" alt="Acrylate" /></td>
<td>12</td>
<td>3e</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Imidazole" /></td>
<td><img src="image" alt="Acrylate" /></td>
<td>12</td>
<td>3f</td>
<td>99</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Imidazole" /></td>
<td><img src="image" alt="Acrylate" /></td>
<td>1</td>
<td>3g</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Imidazole" /></td>
<td><img src="image" alt="Acrylate" /></td>
<td>1</td>
<td>3h</td>
<td>95</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Imidazole" /></td>
<td><img src="image" alt="Acrylate" /></td>
<td>1</td>
<td>3i</td>
<td>92</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="Imidazole" /></td>
<td><img src="image" alt="Acrylate" /></td>
<td>1</td>
<td>3j</td>
<td>79</td>
</tr>
<tr>
<td>11</td>
<td><img src="image" alt="Imidazole" /></td>
<td><img src="image" alt="Acrylate" /></td>
<td>1</td>
<td>3k</td>
<td>90</td>
</tr>
<tr>
<td>12</td>
<td><img src="image" alt="Imidazole" /></td>
<td><img src="image" alt="Acrylate" /></td>
<td>1</td>
<td>3l</td>
<td>76</td>
</tr>
<tr>
<td>13</td>
<td><img src="image" alt="Imidazole" /></td>
<td><img src="image" alt="Acrylate" /></td>
<td>1</td>
<td>3m</td>
<td>92</td>
</tr>
<tr>
<td>14</td>
<td><img src="image" alt="Imidazole" /></td>
<td><img src="image" alt="Acrylate" /></td>
<td>1</td>
<td>3n</td>
<td>70</td>
</tr>
<tr>
<td>15</td>
<td><img src="image" alt="Imidazole" /></td>
<td><img src="image" alt="Acrylate" /></td>
<td>1</td>
<td>3o</td>
<td>99</td>
</tr>
<tr>
<td>16</td>
<td><img src="image" alt="Imidazole" /></td>
<td><img src="image" alt="Acrylate" /></td>
<td>1</td>
<td>3p</td>
<td>90</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: N-heterocycle (1 mmol), α,β-unsaturated carbonyl compound (1.2 mmol) in DMSO (1 mL) containing N-methylimidazole (0.05 equiv) at 70 °C.

<sup>b</sup> Isolated yield.
the N-methylimidazole (Scheme 3). Such an abstraction would enhance the nucleophilicity of the N-heterocycle for addition to electron-deficient alkenes.

It is worth noting that current understanding of the role of ionic liquids in reactions is still in its infancy, although high polarity is recognized as being the driving force.\textsuperscript{15} Since imidazole-type ionic liquids are synthesized from N-methylimidazole, this preliminary investigation of N-methylimidazole as a catalyst thus provides valuable clues for further understanding the role of ionic liquids in promoting certain reactions.

In conclusion, we have developed a novel strategy for the Michael addition reaction of N-heterocycles to \(\alpha,\beta\)-unsaturated carbonyl compounds under the catalytic action of N-methylimidazole. This new methodology constitutes a straightforward, highly efficient, cheap and green synthesis of \(\beta\)-amino carbonyl compounds. Further applications of N-methylimidazole for various organic syntheses and the relationship between N-methylimidazole and ionic liquids are under investigation.

\(1\)H and \(13\)C NMR spectra were recorded on a Bruker AVANCE DMX-500 spectrometer at 500 MHz and 125 MHz in CDCl\textsubscript{3} or DMSO-\textsubscript{d}\textsubscript{6}, respectively. Chemical shifts are reported in ppm (\(\delta\)).

### Table 4  Michael Addition of Pyrimidine and Purine Derivatives to Methyl Vinyl Ketone and Methyl Acrylate\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Acceptor</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>[O]</td>
<td>1</td>
<td>3q</td>
<td>73\textsuperscript{c}</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>[O]</td>
<td>1</td>
<td>3r</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>[O]</td>
<td>1</td>
<td>3s</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>NHBn</td>
<td>[O]</td>
<td>2</td>
<td>3t</td>
<td>69\textsuperscript{d}</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>[O]</td>
<td>1</td>
<td>3u</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>[O]</td>
<td>1</td>
<td>3v</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>[O]</td>
<td>1</td>
<td>3w</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td>NHBn</td>
<td>[O]</td>
<td>2</td>
<td>3x</td>
<td>84</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: N-heterocycle (1 mmol), \(\alpha,\beta\)-unsaturated carbonyl compound (1.2 mmol) in DMSO (1 mL) containing N-methylimidazole (0.05 equiv) at 70 °C.
\textsuperscript{b} Isolated yield.
\textsuperscript{c} Bis-adduct (3y; 11%) was also formed.
\textsuperscript{d} Reacted for 1 h.
Butyl 3-(4-Nitroimidazol-1-yl)propionate (3d)\textsuperscript{16a}

Colorless solid; mp 48 °C.

IR (KBr): 1727, 1521, 1488 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (DMSO-\textit{d}_{6}): \(\delta = 7.84\ (s, 1\ H), 7.51\ (s, 1\ H), 4.36\ (t, J = 6.1\ Hz, 2\ H), 4.12\ (t, J = 6.7\ Hz, 2\ H), 2.86\ (t, J = 6.1\ Hz, 2\ H), 1.60\ (m, 2\ H), 1.33\ (m, 2\ H), 0.94\ (t, J = 7.4\ Hz, 3\ H).\)

\textsuperscript{13}C NMR (DMSO-\textit{d}_{6}): \(\delta = 170.3, 148.9, 136.6, 119.6, 65.7, 43.8, 35.5, 30.7, 19.2, 13.8.\)

ESI-MS: \(m/z = 214\ [M + 1].\)

Methyl 2-Methyl-3-(4-nitroimidazol-1-yl)propionate (3e)\textsuperscript{16a}

Colorless solid; mp 64–65 °C.

IR (KBr): 1726, 1527, 1485 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}): \(\delta = 7.8\ (s, 1\ H), 7.46\ (s, 1\ H), 4.32–4.13\ (m, 2\ H), 3.71\ (s, 3\ H), 2.95\ (m, 1\ H), 1.28\ (d, J = 7.2\ Hz, 3\ H).\)

\textsuperscript{13}C NMR (CDCl\textsubscript{3}): \(\delta = 173.7, 148.4, 136.8, 119.9, 52.7, 50.4, 41.2, 21.5.\)

ESI-MS: \(m/z = 214.2\ [M + 1].\)

Methyl 3-(2-Methyl-4-nitroimidazol-1-yl)propionate (3h)\textsuperscript{16a}

ESI-MS: \(m/z = 242\ [M + 1].\)

4-(2-Methyl-4-nitroimidazol-1-yl)butan-2-one (3g)\textsuperscript{16b}

ESI-MS: \(m/z = 214.2\ [M + 1].\)

Methyl 3-(4-Nitroimidazol-1-yl)butanoate (3f)\textsuperscript{16a}

ESI-MS: \(m/z = 214\ [M + Na].\)

Methyl 3-(2-Methyl-4-nitroimidazol-1-yl)propionate (3h)\textsuperscript{16a}

Yellow liquid.

IR (KBr): 1706, 1680, 1653 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}): \(\delta = 8.24\ (s, 1\ H), 4.12\ (t, J = 6.7\ Hz, 2\ H), 3.07\ (t, J = 6.9\ Hz, 2\ H), 2.38\ (s, 3\ H), 2.10\ (s, 3\ H).\)

\textsuperscript{13}C NMR (CDCl\textsubscript{3}): \(\delta = 206.6\ 145.8, 122.6, 42.8, 41.7, 30.3, 15.2.\)

ESI-MS: \(m/z = 275\ [M + Na].\)

Methyl 3-(2-Methyl-4-nitroimidazol-1-yl)propionate (3h)\textsuperscript{16a}

Yellow liquid.

IR (neat): 1706, 1680, 1653 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}): \(\delta = 7.76\ (s, 1\ H), 4.25\ (t, J = 6.4\ Hz, 2\ H), 3.72\ (s, 3\ H), 2.82\ (t, J = 6.4\ Hz, 2\ H), 2.48\ (s, 3\ H).\)

\textsuperscript{13}C NMR (CDCl\textsubscript{3}): \(\delta = 173.2, 148.9, 147.8, 123.1, 54.7, 45.0, 36.9, 15.5.\)

ESI-MS: \(m/z = 214\ [M + 1].\)

Butyl 3-(4-Nitroimidazol-1-yl)propionate (3d)\textsuperscript{16a}

Colorless solid; mp 84 °C.

IR (KBr): 1734, 1543, 1489 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}): \(\delta = 8.24\ (s, 1\ H), 4.79\ (m, 1\ H), 3.68\ (s, 3\ H), 2.84\ (d, J = 6.9\ Hz, 2\ H), 1.64\ (d, J = 7.0\ Hz, 3\ H).\)

\textsuperscript{13}C NMR (CDCl\textsubscript{3}): \(\delta = 170.0, 148.7, 135.4, 117.5, 52.5, 51.8, 42.0, 21.5.\)

Methyl 2-Methyl-3-(4-nitroimidazol-1-yl)propionate (3e)\textsuperscript{16a}

Yellow solid; mp 87–89 °C.

IR (KBr): 1706, 1680, 1653 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}): \(\delta = 8.24\ (s, 1\ H), 4.12\ (t, J = 6.7\ Hz, 2\ H), 3.07\ (t, J = 6.9\ Hz, 2\ H), 2.38\ (s, 3\ H), 2.10\ (s, 3\ H).\)

\textsuperscript{13}C NMR (CDCl\textsubscript{3}): \(\delta = 206.6\ 145.8, 122.6, 42.8, 41.7, 30.3, 15.2.\)

ESI-MS: \(m/z = 275\ [M + Na].\)

Methyl 3-(2-Methyl-4-nitroimidazol-1-yl)propionate (3h)\textsuperscript{16a}

Colorless oil.

IR (neat): 1729, 1508 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}): \(\delta = 7.46\ (s, 1\ H), 6.99\ (s, 1\ H), 6.92\ (s, 1\ H), 4.22\ (t, J = 6.4\ Hz, 2\ H), 2.92\ (t, J = 6.4\ Hz, 2\ H), 2.14\ (s, 3\ H).\)

\textsuperscript{13}C NMR (CDCl\textsubscript{3}): \(\delta = 170.8, 148.9, 148.7, 123.1, 54.7, 45.0, 36.9, 15.5.\)

ESI-MS: \(m/z = 139\ [M + 1].\)

Methyl 3-(2-Methyl-4-nitroimidazol-1-yl)propionate (3h)\textsuperscript{16a}

Yellow oil.
IR (neat): 1732, 1509 cm⁻¹.

³¹P NMR (CDCl₃): δ = 6.83 (s, 1 H), 6.84 (s, 1 H), 4.16 (t, J = 6.8 Hz, 2 H), 3.69 (s, 3 H), 2.16 (s, 3 H), 2.15 (s, 3 H).

¹³C NMR (CDCl₃): δ = 170.6, 144.1, 126.4, 118.6, 51.6, 41.0, 34.0, 12.4.

ESI-MS: m/z = 183 [M + 1].

4-(2-Methylimidazol-1-yl)butan-2-one (3k)¹⁶c
Colorless oil.
IR (KBr): 1716, 1507, 1375 cm⁻¹.

1H NMR (CDCl₃): δ = 7.44 (s, 0.4 H), 7.38 (s, 0.6 H), 6.75 (s, 0.4 H), 6.62 (s, 0.6 H), 4.17 (m, 2 H), 3.69 (s, 3 H), 2.75 (m, 2 H), 2.21 (d, J = 2.1 Hz, 3 H).

¹³C NMR (CDCl₃): δ = 171.2, 171.0, 138.6, 136.9, 136.4, 126.9, 126.8, 115.5, 44.5, 43.9, 41.0, 38.7, 30.8, 13.6, 9.1.

ESI-MS: m/z = 183 [M + 1].

Methyl 3-(2-Methylimidazol-1-yl)propionate (3l)¹⁶a
Colorless oil.
IR (neat): 1732, 1508 cm⁻¹.

¹H NMR (CDCl₃): δ = 6.90 (s, 1 H), 6.84 (s, 1 H), 4.16 (t, J = 6.8 Hz, 2 H), 3.69 (s, 3 H), 2.74 (t, J = 6.8 Hz, 2 H), 2.41 (s, 3 H).

¹³C NMR (CDCl₃): δ = 170.6, 144.1, 126.8, 118.6, 51.6, 41.0, 34.8, 12.4.

ESI-MS: m/z = 155 [M + 1].

Methyl 3-(2-Methylimidazol-1-yl)propionate (3m)¹⁶a (Mixture with 5-Methylimidazolyl Product)
Yellow oil.
IR (neat): 1715, 1500 cm⁻¹.

¹H NMR (CDCl₃): δ = 7.42 (s, 0.6 H), 7.35 (s, 0.6 H), 6.72 (s, 1 H), 6.60 (s, 0.9 H), 4.13 (m, 3 H), 2.88 (m, 3 H), 2.20 (m, 1.5 H), 2.18 (s, 3 H), 2.16 (s, 1.5 H), 2.15 (s, 3 H).

¹³C NMR (CDCl₃): δ = 170.6, 144.1, 126.8, 118.6, 51.6, 41.0, 38.7, 30.8, 13.6, 9.2.

ESI-MS: m/z = 153 [M + 1].

Methyl 3-(2-Methylimidazol-1-yl)propionate (3n)¹⁶a
Colorless oil.
IR (neat): 1732, 1508 cm⁻¹.

¹H NMR (CDCl₃): δ = 7.44 (s, 0.4 H), 7.38 (s, 0.6 H), 6.75 (s, 0.4 H), 6.62 (s, 0.6 H), 4.17 (m, 2 H), 3.69 (s, 3 H), 2.75 (m, 2 H), 2.21 (d, J = 2.1 Hz, 3 H).

¹³C NMR (CDCl₃): δ = 171.2, 171.0, 138.6, 136.9, 136.4, 126.9, 115.4, 52.1, 42.3, 40.0, 35.8, 35.3, 13.6, 9.1.

ESI-MS: m/z = 183 [M + 1].

Methyl 3-(2-Methylimidazol-1-yl)propionate (3o)¹⁶d
Colorless oil.
IR (KBr): 1716, 1507, 1375 cm⁻¹.

¹H NMR (CDCl₃): δ = 8.13 (s, 1 H), 7.90 (s, 1 H), 4.37 (t, J = 6.1 Hz, 2 H), 3.05 (t, J = 6.1 Hz, 2 H), 2.16 (s, 3 H).

¹³C NMR (CDCl₃): δ = 205.3, 152.3, 144.2, 43.9, 42.7, 30.5.

ESI-MS: m/z = 162 [M + Na].

Methyl 3-(1,2,4-Triazol-1-yl)propionate (3p)¹⁶a
Colorless oil.
IR (neat): 1735, 1507, 1440 cm⁻¹.
\( ^1 \text{H NMR (DMSO-\text{d}_6)}: \delta = 9.03 \text{ (s, 1 H), 7.40} \text{ (d, J = 7.9 Hz, 1 H), 5.68} \text{ (d, J = 7.9 Hz, 1 H), 4.00} \text{ (t, J = 5.9 Hz, 2 H), 3.71} \text{ (s, 3 H), 2.80} \text{ (t, J = 5.9 Hz, 2 H).} \)

\( ^{13} \text{C NMR (DMSO-\text{d}_6)}: \delta = 172.1, 164.0, 151.0, 146.0, 102.0, 52.4, 45.5, 33.0. \)

ESI-MS: \( m/z = 199 \) [M + 1].

1-(2-Methoxycarbonyl)ethyl)thymidine \((3w)^{16a} \)

Colorless solid; mp 120–121 °C.

IR (KBr): 1735, 1698, 1655 cm\(^{-1}\).

\( ^1 \text{H NMR (DMSO-\text{d}_6)}: \delta = 8.87 \text{ (s, 1 H), 7.20} \text{ (s, 1 H), 3.96} \text{ (t, J = 6.6 Hz, 2 H), 2.87} \text{ (t, J = 6.7 Hz, 2 H), 2.68} \text{ (t, J = 6.7 Hz, 2 H), 2.70} \text{ (t, J = 7.5 Hz, 2 H), 2.10} \text{ (d, J = 4.3 Hz, 6 H).} \)

\( ^{13} \text{C NMR (DMSO-\text{d}_6)}: \delta = 207.2, 157.0, 149.7, 140.1, 138.3, 130.1, 129.9, 44.9, 41.5, 40.8, 36.9, 30.3. \)

ESI-MS: \( m/z = 293 \) [M + Na].

Reference


(5) Loh, T. P.; Wei, L. L. Synlett 1998, 975.


