A Practical Indium Tribromide Catalysed Addition of Indoles to Nitroalkenes in Aqueous Media

Marco Bandini,* Paolo Melchiorre, Alfonso Melloni, Achille Umani-Ronchi*

Dipartimento di Chimica ‘G. Cianiian’, Università di Bologna, Via Selmi 2, 40126 Bologna, Italy
Fax +39(51)2099456; E-mail: bandini@ciam.unibo.it, umani@ciam.unibo.it

Received 27 March 2002; revised 9 April 2002

Abstract: The 1,4-conjugate addition of indoles to nitroalkenes was efficiently carried out in aqueous media using a catalytic amount of indium tribromide (5 mol%). The reusability of the indium tribromide was tested by performing consecutive cycles with the same catalyst.

Key words: alkaloids, catalysis, indium, indoles, Michael additions

In recent years, catalytic Michael-type additions of nucleophiles to nitroalkenes have emerged as a powerful method for the formation of new carbon–carbon bonds in organic synthesis.1 In particular, the use of electron-rich hetero-aromatic compounds such as indoles, acting as nucleophiles, allows the synthesis of 2-indolyl-1-nitroalkanes 1, highly versatile intermediates for the preparation of several classes of biological active compounds such as melatonin analogs 2,2 1,2,3,4-tetrahydro-β-carbolines (THBCs) 3 and ‘triptans’ 4 (Scheme).

Since pioneering papers published by Noland et al. on the addition of indolylmagnesium iodide to nitro-olefins,5 many efforts have been devoted to the development of Friedel–Crafts type addition of indoles to nitroalkenes.6 However, the tendency of electron-rich hetero-aromatic rings to polymerize under acid-catalysed conditions makes these processes still challenging.

During our ongoing studies on the conjugate addition of indoles to α,β-unsaturated ketones catalysed by indium tribromide,7 we found that InBr3 (1 mol%) smoothly promoted the addition of 2-methylindole (5a) to trans-β-nitrostyrene (6a) in CH2Cl2 affording the desired 2-phenyl-2-[3-(2-methylindolyl)]nitroethane (7aa) in 93% isolated yield after 16 h.8 However, due to the well known tolerance of indium salts towards aqueous conditions and considering the higher reactivity of nitroalkenes in comparison to other Michael acceptors, we tested the effectiveness of the catalytic protocol in aqueous media.

Thus, we started an investigation of Michael additions between nitro-olefin 6a and variously substituted indoles catalysed by InBr3 in H2O–THF (9:1) as the solvent leading to a library of β-nitroindoles 7 (Table 1).

It is noteworthy that while in the absence of InBr3 the reaction afforded the desired product only in 28% yield after 48 h (Table 1, entry 1), the use of 5 mol% of anhyd InBr3 furnished a complete conversion (Table 1, entry 2) after 2 h.9 The protocol was significantly effective for the addition of several substituted electron-rich indoles such as N-methyl-2-methylindolene (5e) and 5-methoxyindole (5e) that furnished the products in excellent yields: 92 and 88%, respectively (Table 1, entries 4 and 6). Under the reported conditions, even indolyl rings bearing electron-withdrawing groups such as the 5-bromoindole (5d) are
A Practical Indium Tribromide Catalysed Addition of Indoles to Nitroalkenes in Aqueous Media

Table 1  InBr₃ Catalysed Addition of Indoles to trans-β-Nitrostyrene (6a)^

<table>
<thead>
<tr>
<th>Entry</th>
<th>Indole</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>24</td>
<td>7aa</td>
<td>28(^\circ)</td>
</tr>
<tr>
<td>2</td>
<td>5a</td>
<td>2</td>
<td>7aa</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>5b</td>
<td>16</td>
<td>7ba</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>5e</td>
<td>2</td>
<td>7ca</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>5d</td>
<td>3</td>
<td>7da</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>5e</td>
<td>2</td>
<td>7ea</td>
<td>88</td>
</tr>
<tr>
<td>7</td>
<td>5f</td>
<td>16</td>
<td>7fa</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>5g</td>
<td>16</td>
<td>7ga</td>
<td>75</td>
</tr>
</tbody>
</table>

^All the reactions were carried out with 5 mol% of catalyst at r.t. unless otherwise indicated.

Having optimized a convenient protocol for the conjugate addition of indoles to 6a, we became interested in exploring this process with several nitroalkenes (6a-d). The results are collected in Table 2.

The Michael additions proceeded cleanly and, in particular, commercially available trans-2-(2-nitrovinyl)thiophene (6c) and 2-(2-nitrovinyl)furan (6d) afforded a clear reaction mixture and the products were isolated in excellent yields (up to 99%). However, when 1-nitro-1-cyclohexene (6b) was reacted with 5a, the desired 7ab was obtained only in moderate yield and diastereoselectivity (44%; 66:34, entry 1, Table 2). This result proves the higher reactivity of β-aryl-α-nitroalkenes with respect to simple α,β-unsaturated nitro derivatives in our catalytic protocol.

A typical request for the design of environmentally friendly catalytic processes is the recovery and reusability of the catalyst. Thus, we tested this possibility simply by carrying out consecutive Michael addition reactions between 5a and 6a (InBr₃, 10 mol%) with the same catalyst loading (Table 3). The experiment was easily performed by a careful separation of the organic compounds (extraction with CH₂Cl₂) from the aqueous phase after each run. The reusability of the catalyst was remarkable, in fact after five runs the compound 7aa was isolated in almost quantitative yields.

At the end of the reactions, the pH of the aqueous phase was measured to be about 3.5, probably due to a partial acidic hydrolysis of the indium salt in water. However, the possibility that the Bronsted acid formed in situ could be the real promoter of the Michael reaction was denied by a comparative experiment carried out between 6a and 5a in an acidic solution (pH 3, by HBr 10⁻³ M). Under these conditions, the reaction, monitored by TLC, was significantly slower (10 h for a complete conversion) and a tentative experiment of reusability failed.

In summary, with the present study we described a general and mild InBr₃ catalysed protocol for the conjugate addition of indoles to nitroalkenes. The reactions are easily performed and remarkably tolerant of substituents at different positions of the indolyl rings. The simple process performed in aqueous media provides the access to highly functionalised compounds in excellent yields and allows
the reusability of the catalyst for several times without loss of effectiveness.

\(^1\)H NMR spectra were recorded by means of Varian Gemini-200 (200 MHz) or Varian INOVA-300 (300 MHz) spectrometers. Chemical shifts are given in \(\delta\) with respect to TMS and coupling constants \(J\) are measured in Hz. Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet) and coupling constant in Hz. \(^1\)C NMR spectra were recorded on a Varian Gemini-200 (50 MHz) or Varian INOVA-300 (75 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuterochloroform: \(\delta = 77.0\)). Column flash chromatographies were run over 270–400 mesh silica gel. Commercially available anhyd InBr\(_3\), indoles and nitroalkenes were purchased from the Aldrich and Co. and used as received. Elemental analyses were carried out by using a EACE 1110 CHNOS analyser. \(^1\)H and \(^13\)C NMR spectra were recorded in CDCl\(_3\) using tetramethylsilane as the internal standard (deuterochloroform: \(\delta = 0.00\)). The melting points were uncorrected. The spectrophotometer. IR spectra of neat compounds are expressed by wave number (cm\(^{-1}\)). The melting points were uncorrected. The spectra of neat compounds are expressed by wave number (cm\(^{-1}\)). The melting points were uncorrected. The compound 7ba has been previously described.\(^8\)

**Catalytic Michael addition; Typical Procedure**

To a round-bottomed flask were added solvent (H\(_2\)O–THF, 2\(\times\)1; 2 mL), anhyd InBr\(_3\) (5 mg, 0.015 mmol) and nitroalkene (0.3 mmol). After 10 min stirring, the resulting pale-yellow solution, indole (0.45 mmol) was added. The reaction was stirred at r.t. until complete consumption of the nitro compound (checked by TLC) and then extracted with Et\(_2\)O (3 \(\times\) 5 mL). The organic phases were collected, dried (Na\(_2\)SO\(_4\)) and concentrated under reduced pressure.

**Yield:** 93%; pale pink solid; mp 98–101 °C; flash chromatography (cyclohexane–Et\(_2\)O, 85:15), \(R_f = 0.30\).

**IR (Nujol):** 3393, 3031, 2923, 2853, 1551, 1460, 1378 cm\(^{-1}\). (cyclohexane–Et\(_2\)O, 85:15), \(R_f = 0.30\).

**Yield:** 92%; pale yellow solid; mp 116–120 °C; flash chromatography (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.25\).

**IR (Nujol):** 3398, 2923, 2853, 1539, 1459, 1376 cm\(^{-1}\). (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.30\).

**Yield:** 98%; pale yellow viscous oil; flash chromatography (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.30\).

**IR (Nujol):** 3429, 2930, 1549, 1459, 1376 cm\(^{-1}\). (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.30\).

**Yield:** 98%; pale yellow viscous oil; flash chromatography (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.30\).

**IR (Nujol):** 3404, 2923, 2852, 1547, 1458, 1376 cm\(^{-1}\). (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.30\).

**Yield:** 75%; yellow solid; mp 111–114 ºC; flash chromatography (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.30\).

**IR (Nujol):** 3393, 3028, 2914, 1549, 1474, 1376, 1333, 741, 701 cm\(^{-1}\). (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.30\).

**IR (Nujol):** 3404, 2923, 2852, 1547, 1458, 1376 cm\(^{-1}\). (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.30\).

**Yield:** 44%; pale yellow solid; dr 66:34; flash chromatography (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.30\).

**IR (Nujol):** 3393, 2923, 2853, 1539, 1459, 1376 cm\(^{-1}\). (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.30\).

**Yield:** 1.45–1.58 (m, 2 H), 1.63–1.80 (m, 1 H), 1.88–2.10 (m, 4 H), 2.42 (s, 3 H), 2.84–2.94 (m, 1 H), 3.33 (dt, \(J = 4.2, 13.5\) Hz, 1 H), 7.04–7.13 (m, 2 H), 7.25 (d, \(J = 7.2\) Hz, 1 H), 7.50 (d, \(J = 8.7\) Hz, 1 H), 7.77 (br, 1 H); (minor diastereoisomer) 2.36 (s, 3 H), 3.34–3.43 (m, 1 H), 5.09 (dt, \(J = 4.2, 11.1\) Hz, 1 H), 7.58 (d, \(J = 8.4\) Hz, 1 H).

**Yield:** 88%; pale yellow viscous oil; flash chromatography (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.30\).

**IR (Nujol):** 3351, 2942, 2850, 1558, 1481, 1370, 1213 cm\(^{-1}\).

**Yield:** 98%; pale yellow viscous oil; flash chromatography (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.30\).

**IR (Nujol):** 3564, 55.85, 77.77, 100.41, 107.26, 110.39, 111.05, 112.20, 112.60, 123.25, 126.01, 131.27, 142.11, 152.04, 154.08.

**Anal. Caled for (C\(_9\)H\(_8\)N\(_2\))O\(_2\); C, 68.91; H, 5.44; N, 9.45. Found: C, 68.85; H, 5.40; N, 9.44.**

**Yield:** 98%; pale yellow viscous oil; flash chromatography (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.30\).

**IR (Nujol):** 3404, 2923, 2852, 1547, 1458, 1376 cm\(^{-1}\). (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.30\).

**Yield:** 75%; yellow solid; mp 111–114 ºC; flash chromatography (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.30\).

**IR (Nujol):** 3393, 2923, 2853, 1547, 1463, 1376, 743 cm\(^{-1}\). (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.30\).

**Yield:** 92%; orange solid; mp 135–139 ºC; flash chromatography (cyclohexane–Et\(_2\)O, 85:15), \(R_f = 0.27\).

**IR (Nujol):** 3312, 2925, 2853, 1547, 1463, 1376, 743 cm\(^{-1}\). (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.30\).

**Yield:** 98%; pale yellow viscous oil; flash chromatography (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.30\).

**IR (Nujol):** 3393, 2923, 2853, 1539, 1459, 1376 cm\(^{-1}\). (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.30\).

**Yield:** 92%; orange solid; mp 135–139 ºC; flash chromatography (cyclohexane–Et\(_2\)O, 85:15), \(R_f = 0.27\).

**IR (Nujol):** 3312, 2925, 2853, 1547, 1463, 1376, 743 cm\(^{-1}\). (cyclohexane–Et\(_2\)O, 9:1), \(R_f = 0.30\).
120.99, 123.39, 126.47, 131.93, 134.71; (minor diastereoisomer) 11.74, 24.61, 25.67, 32.50, 89.16, 119.16, 120.79, 127.92, 129.06. Anal. Calcd for (C_{15}H_{14}N_{2}O_{3}): C, 66.66; H, 5.22; N, 10.36. Found: C, 66.72; H, 6.97; N, 10.84.

7ac Yield: 95%; yellow solid; mp 95–98 °C; flash chromatography (cyclohexane–Et_{2}O, 9:1), R_{f} 0.31.

IR (Nujol): 3101, 3046, 2922, 2854, 1545, 1471, 1377, 712 cm^{-1}.

1^1H NMR (200 MHz, CDCl_{3}): δ = 2.41 (s, 3 H), 5.12–5.25 (m, 2 H), 6.95–6.97 (m, 2 H), 7.06–7.29 (m, 4 H), 7.40 (d, J = 7.0 Hz, 1 H), 7.98 (br, 1 H).

13C NMR (50 MHz, CDCl_{3}): δ = 135.48, 142.06, 152.35.

Anal. Calcd for (C_{16}H_{16}N_{2}O_{3}): C, 67.59; H, 5.67; N, 9.84. Found: C, 67.55; H, 5.63; N, 9.84.

1H NMR (200 MHz, CDCl_{3}): δ = 2.41 (s, 3 H), 4.96 (dd, J = 10.6, 3.6 Hz, 1 H), 5.16–5.25 (m, 2 H), 6.09–6.11 (m, 1 H), 6.31 (dd, J = 2.0, 3.4 Hz, 1 H), 7.06–7.15 (m, 2 H), 7.27–7.29 (m, 1 H), 7.38–7.42 (m, 2 H), 7.95 (br, 1 H).

13C NMR (50 MHz, CDCl_{3}): δ = 132.99, 135.35, 143.31.

Anal. Calcd for (C_{15}H_{14}N_{2}O_{2}S): C, 62.92; H, 4.93; N, 9.78. Found: C, 62.85; H, 4.89; N, 9.77.

7ad Yield: 99%; yellow viscous oil; flash chromatography (cyclohexane–Et_{2}O, 9:1), R_{f} 0.31.

Yield: 65%; yellow solid; mp 115–118 °C; flash chromatography (cyclohexane–Et_{2}O, 85:15), R_{f} 0.30.

1H NMR (200 MHz, CDCl_{3}): δ = 2.42 (s, 3 H), 3.67 (s, 3 H), 4.90–4.91 (m, 1 H), 5.16–5.27 (m, 2 H), 6.09 (dd, J = 3.4 Hz, 1 H), 6.29 (dd, J = 1.8, 3.2 Hz), 7.08 (dt, J = 1.2, 6.6 Hz, 1 H), 7.16 (dt, J = 1.2, 6.6 Hz, 1 H), 7.26–7.30 (m, 1 H), 7.37–7.41 (m, 2 H), 7.59 (dd, J = 1.8, 3.2 Hz).

13C NMR (50 MHz, CDCl_{3}): δ = 10.29, 29.52, 35.50, 77.00, 105.45, 106.98, 108.92, 110.26, 118.36, 119.15, 120.79, 125.49, 134.70, 136.70, 141.70, 152.28.

Anal. Calcd for (C_{15}H_{14}N_{2}O_{3}): C, 67.59; H, 5.67; N, 9.85. Found: C, 67.55; H, 5.63; N, 9.78.

Acknowledgements

We would like to thank M.U.R.S.T. (Progetto Nazionale ‘Stereolezione in Sintesi Organica: Metodologie ed Applicazioni’) and Bologna University (funds for selected research topics) for the financial support of this research.

References


(8) Recently, Yadav et al. reported that InCl$_3$ (10 mol%) was also able to promote the conjugate addition of indole 5b to 6a in 78% yield using CH$_2$Cl$_2$ as the solvent. However, only one example of conjugate addition to nitroalkenes was described, see: Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. Synthesis 2001, 2165. Under our conditions, InCl$_3$ was found less effective in comparison to InBr$_3$ in the addition of 5a to 6a, 82% yield.
(9) Other common Lewis acids were found to be less effective in terms of chemical yields and reaction times (i.e. AlCl$_3$, 68% yield, 24 h).