



## Mild, versatile, and chemoselective indium(III) triflate-catalyzed deprotection of acetonides under microwave heating conditions

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### ABSTRACT

A series of acetonides (both terminal and internal isopropylidene acetals) have been deprotected under catalytic, neutral conditions to give their corresponding 1,2-diols. The reactions utilize indium(III) triflate in the presence of water and an organic solvent with mild microwave heating. Terminal acetonides are chemoselectively removed in the presence of internal acetonides; acid labile functional groups remain intact under these conditions, thereby greatly enhancing the scope of the reaction substrates that can be utilized with this approach.

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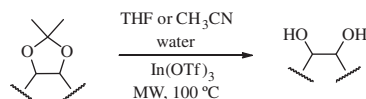
The incorporation of protection/deprotection strategies in synthetic organic chemistry is often crucial for the synthesis of complex molecules.<sup>1</sup> It is well established that both the terminal and internal acetonide groups are some of the most utilized moieties to protect 1,2- and 1,3-diols in the areas of carbohydrate,<sup>2</sup> nucleoside,<sup>3</sup> and natural product<sup>4</sup> chemistry which typically involve diols originating from sugar moieties. Numerous conditions exist for the deprotection of acetonides using Lewis acids such as  $\text{FeCl}_3\text{-H}_2\text{O/SiO}_2$ ,<sup>5a</sup>  $\text{CuCl}_2\cdot 2\text{H}_2\text{O}$ ,<sup>5b</sup>  $\text{Zn}(\text{NO}_3)_2\cdot 6\text{H}_2\text{O}$ ,<sup>5c</sup>  $\text{BiCl}_3$ ,<sup>5d</sup>  $\text{InCl}_3$ ,<sup>5e</sup>  $\text{Er}(\text{OTf})_3$ ,<sup>5f</sup> and  $\text{Yb}(\text{OTf})_3\cdot \text{H}_2\text{O}$ .<sup>5g</sup> Additionally protic conditions using aq HCl,<sup>6a</sup> aq HBr,<sup>6b</sup> TFA,<sup>6c</sup> Nafion-H,<sup>6d</sup> Dowex 50W-X8,<sup>6e</sup> acetic acid,<sup>6f</sup>  $p\text{TsOH}$ <sup>6g</sup> have also been reported. While most of the above-mentioned procedures are effective at removing terminal acetonides, more strongly acidic procedures are necessary to deprotect internal acetonides. These harsher reaction conditions and/or substantially longer reaction times are unsuitable for molecules possessing other acid labile protecting groups. The development of reaction conditions which allow for the chemoselective deprotection of various protecting groups is of paramount importance. As such, it was our objective to develop a mild and versatile chemoselective reaction protocol for the selective deprotection of both terminal and internal acetonides in the presence of acid labile protecting groups as well as the selective deprotection of terminal acetonides in the presence of internal acetonides.

We have recently reported the effective use of indium(III) triflate as a Lewis acid catalyst for both the protection and deprotection of acetals.<sup>7</sup> It was our finding that many widely used acid-sensitive functional groups such as *N*-Boc, *O*-TBDMS, *O*-THP,

*O*-benzyl, and tosylate remain intact during the protection/deprotection protocols developed. Additionally, the reaction rates for these conversions were greatly enhanced by the application of mild microwave heating. Considering the similarity between acetals deprotection with acetonides and our interest in indium(III) triflate-catalyzed reactions, we sought to expand the application of this method. To the best of our knowledge, there is only a single report<sup>8</sup> of the use of indium(III) triflate as a catalyst for the deprotection of acetonides. In this case, the examples are limited only to carbohydrate structures, some of the yields are moderate, chemoselective removal of terminal over internal acetonides is not demonstrated,<sup>9</sup> catalyst loading is fairly high, and reaction times are typically longer than our method.

We herein report our results for the indium(III) triflate-catalyzed chemoselective deprotection of internal and terminal acetonides in either acetonitrile/water or THF/water mixtures (Scheme 1).

We first set out to optimize the deprotection of terminal acetonides. Time, temperature, heating conditions, and solvent were all investigated and are summarized in Table 1 for the conversion of (*S*)-4-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolane (**1**) to (*R*)-3-(benzyloxy)propane-1,2-diol (**2**). Unsurprisingly, the reaction of **1** in acetonitrile/water (9:1 v/v) without the addition of indium(III) triflate resulted in no consumption of the acetonide even at elevated temperatures (Table 1, entries 1 and 2).



Scheme 1.

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**Table 1**

Effect of time, temperature (both thermal and microwave irradiation), solvent, and catalyst loading on the deprotection of (*S*)-4-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolane (**1**) to (*R*)-3-(benzyloxy)propane-1,2-diol (**2**)



Entry	Time, temp (°C)	mol % In(OTf) <sub>3</sub>	Solvent conditions	Yield <sup>a</sup>
1	10 h, rt	0	CH <sub>3</sub> CN/H <sub>2</sub> O (9:1 v/v)	nr
2	20 min, MW <sup>b</sup> 120 °C	0	CH <sub>3</sub> CN/H <sub>2</sub> O (9:1 v/v)	nr
3	10 h, rt	1	CH <sub>3</sub> CN/H <sub>2</sub> O (9:1 v/v)	95%
4	5 min, MW <sup>b</sup> 100 °C	1	CH <sub>3</sub> CN/H <sub>2</sub> O (9:1 v/v)	93%
5	5 min, MW <sup>b</sup> 100 °C	1	THF/H <sub>2</sub> O (9:1 v/v)	94%
6	5 min, MW <sup>b</sup> 100 °C	0.3	CH <sub>3</sub> CN/H <sub>2</sub> O (9:1 v/v)	96% <sup>c</sup>
7	5 min, MW <sup>b</sup> 100 °C	0.3	CH <sub>3</sub> CN/H <sub>2</sub> O (2 mol equiv H <sub>2</sub> O)	93%

Typical reaction conditions: substrate (1.0 mmol), acetonitrile/water (5 mL, 9:1 v/v) unless otherwise noted.

<sup>a</sup> Isolated yields reported.

<sup>b</sup> Reaction heated using microwave irradiation.

<sup>c</sup> Substrate (5.0 mmol), acetonitrile/water (15 mL, 10% v/v water) and In(OTf)<sub>3</sub> (0.3 mol %).

Addition of only 1 mol % indium(III) triflate to the reaction mixture resulted in complete deprotection of **1** after 10 h at room temperature to give a 95% isolated yield of **2** (Table 1, entry 3). As expected, the combined effect of both indium(III) triflate catalysis and the application of microwave irradiation heating<sup>10</sup> at 100 °C for 5 min resulted in a dramatically reduced reaction time while maintaining excellent yield (93%, Table 1, entry 4). To further exemplify the utility of indium(III) triflate as a catalyst for these reactions, the catalyst loading was reduced to 0.3 mol % with no loss of yield or increase in reaction time (Table 1 entries 6 and 7). The use of neat water as the reaction solvent has recently been reported for this type of transformation.<sup>5f</sup> While water is a suitable solvent for some substrates, many typical organic molecules exhibit only very low solubility in water which limits the scope of substrates amenable for these procedures. We have found that either acetonitrile or THF in a 9:1 (v/v) mixture with water gives comparable isolated yields of 93–94% after only 5 min at 100 °C. (Table 1 entries 3–6). Significantly, reduction of catalyst loading to only 0.3 mol % and water as little as 2 mol equiv showed no impact on isolated yield or reaction time (Table 1, entry 7).

While 0.3 mol % indium(III) triflate and 2 mol equiv water gave excellent results, we felt that the conditions of CH<sub>3</sub>CN/H<sub>2</sub>O (9:1 v/v); 1 mol % In(OTf)<sub>3</sub> were more widely applicable and of greatest utility. Having identified these optimal reaction conditions, we next set out to explore the range of substrates that were accessible (Table 2). As expected, the deprotection of (*R*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (**3**) cleanly gave triol **4** in 99% isolated yield after microwave heating for 5 min at 100 °C. Even in the absence of heating, indium(III) triflate catalyzed this reaction that proceeded in excellent yield after 24 h at room temperature (Table 2, entry 1c). Notably, the mild conditions developed using microwave heating serves to dramatically reduce reaction times from hours to minutes, highlighting the benefit of these conditions over other methods. As expected, internal acetonides required more vigorous conditions to facilitate their deprotection. For example **5**, **15**, and **17** all required microwave heating at 120 °C to complete their deprotection (Table 1, entries 2, 7, and 8). Selective deprotection of terminal acetonides in the presence of internal acetonides was demonstrated by the deprotection of **19**; the terminal acetonide moiety was selectively deprotected after microwave heating for 5 min at 100 °C leaving the internal

acetonide intact. Further irradiation for 30 min at 120 °C led to complete deprotection of the terminal acetonide to give **21** in high yield (Table 2 entry 10).<sup>11</sup> Even 2,2-dimethyl-1,3-benzodioxole **22**, which typically requires very harsh conditions<sup>12</sup> to facilitate the acetonide deprotection, was cleanly converted to **23** within 30 min at 120 °C.

Of particular interest was the chemoselective acetonide deprotection in the presence of other acid-labile groups. Substrates possessing common protecting groups such as *N*-Boc (**7**), *O*-TBDMS (**9**), *O*-THP (**11**), tosylate (**13**), and *O*-benzyl (**1**) all underwent chemoselective deprotection of the acetonide group with no loss of the other acid-labile protecting groups.

The scale of the microwave-heated reaction is limited only by the constraints of the microwave reactor. Specifically, the conversion of **1** to **2** (Table 1, entry 6) and **19** to **20** (Table 2, entry 9b) was increased from 1 to 5 mmol scale to give comparable yields and purity results.

For a larger scale, the deprotection at room temperature or with thermal heating can be used without detriment to the yield. 2,2-Dimethyl-1,3-dioxolan-4-ylmethyl *p*-toluenesulfonate (**13**) was cleanly converted on 20 mmol scale to the corresponding diol (**14**) overnight at room temperature (Table 2, entry 6d). As stated earlier, it is again important to note that the reduction of indium(III) triflate catalyst from 1.0 to 0.3 mol % and the reduction in the amount of added water had no adverse effect on time of reaction completion, yield, or purity.

In summary, we report herein the first indium(III) triflate-catalyzed deprotection of internal and terminal acetonides under microwave irradiation heating to give the corresponding diols in excellent yield. Reactions are scalable and highly reproducible to afford excellent yields of the desired products, typically better than previously reported for a number of different 'tricky'<sup>5f</sup> substrates. Overall the reaction times range from 5 min for terminal acetonides to 30 min for the more difficult internal acetonides. Terminal acetonides can be selectively deprotected in the presence of internal acetonides by simply controlling the reaction temperature and time. A significant advance over previously reported procedures is the use of an organic co-solvent, such as THF or acetonitrile, with water to greatly enhance the solvating capability of the reaction solution which translates into a wider range of substrates that can be utilized under these conditions.

**Table 2**  
Indium(III) triflate-catalyzed deprotection of acetonides<sup>13,14</sup>

Entry	Substrate	Time	Conditions <sup>a</sup>	Product <sup>b</sup>	Yield <sup>c</sup> (%)
1a		5 min	100 °C		99
b		5 min	100 °C		99 <sup>d</sup>
c		24 h	rt		97
2a		30 min	120 °C		95
b					94 <sup>f</sup>
3		5 min	100 °C		99
4		5 min	100 °C		96 <sup>d</sup>
5		5 min	100 °C		96 <sup>d</sup>
6a		5 min	100 °C		98
b					94 <sup>d</sup>
c		8 h	rt		93 <sup>f</sup>
d					94 <sup>g</sup>
7		5 min	120 °C		98
8		30 min	120 °C		87
9a		5 min	100 °C		94
b					96 <sup>e</sup>
10	<b>19</b>	30 min	120 °C		91
11a		5 min			76
b		30 min	120 °C		91

<sup>a</sup> Typical reaction conditions: substrate (1.0 mmol), acetonitrile/water (5 mL, 9:1 v/v) and In(OTf)<sub>3</sub> (1.0 mol %) unless otherwise noted. All reactions conducted under microwave irradiation.

<sup>b</sup> All products were characterized by mass and <sup>1</sup>H NMR spectroscopy.

<sup>c</sup> Isolated yields.

<sup>d</sup> Substrate (1.0 mmol), THF/water (5 mL, 9:1 v/v) and In(OTf)<sub>3</sub> (1.0 mol %).

<sup>e</sup> Substrate (5.0 mmol), acetonitrile/water (15 mL, 9:1 v/v) and In(OTf)<sub>3</sub> (0.3 mol %).

<sup>f</sup> 2.0 mol equiv water added to CH<sub>3</sub>CN as reaction solvent.

<sup>g</sup> Substrate (20 mmol), acetonitrile (50 mL), water (3.0 mol equiv), and In(OTf)<sub>3</sub> (0.3 mol %), rt, 8 h.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.116.

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  - Additionally we have demonstrated chemoselective terminal acetonide deprotection of **19** at room temperature for 8 h to cleanly give **20**. Subsequent microwave heating at 120 °C for 30 min then gave **21** in excellent yield. While this particular example demonstrates the chemoselective removal of a terminal versus internal acetonide using both room temperature and microwave heating conditions at 100 °C, depending on the nature of the substrates, future investigators may want to first use the room temperature conditions to selectively remove a terminal acetonide in the presence of an internal acetonide, albeit with increased reaction times.
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  - (**R**)-3-(benzyloxy)propane-1,2-diol (**2**): A Biotage microwave process tube with stir bar was charged with (S)-4-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolane (1, 222 mg, 1.0 mmol) in acetonitrile:water (5 mL, 9:1 v/v) and In(OTf)<sub>3</sub> (1.0 mol%). The resulting mixture was heated under microwave conditions at 100 °C for 5 min after which time the solvents were removed under vacuum. The crude product was taken up into dichloromethane (10 mL) and treated with PS-trisamine resin (30 mg) for 5 min to remove residual indium salts, filtered and concentrated to dryness under vacuum to give (R)-3-(benzyloxy)propane-1,2-diol (2, 0.170 g, 93%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.38–7.28 (5H, m), 4.53 (2H, s), 3.87–3.80 (1H, m), 3.69–3.47 (4H, m), 2.89 (2H, br s); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 137.7, 128.5, 127.9, 127.8, 73.6, 71.8, 70.8, 64.1; APCI MS m/z 183.1 [M + 1]<sup>+</sup>; HPLC 98.3% (220 nm, AUC).
  - (3S,4S)-3,4-dihydroxydihydrofuran-2(3H)-one (**6**): A Biotage microwave process tube with stir bar was charged with (3aS,6aS)-2,2-dimethyl-dihydrofuro[3,4-d][1,3]dioxol-4(3aH)-one (5, 158 mg, 1.0 mmol) in acetonitrile:water (5 mL, 9:1 v/v) and In(OTf)<sub>3</sub> (1.0 mol%). The resulting mixture was heated under microwave conditions at 120 °C for 30 min after which time the solvents were removed under vacuum. The crude product was taken up into dichloromethane (10 mL) and treated with PS-trisamine resin (30 mg) for 5 min to remove residual indium salts, filtered and concentrated to dryness under vacuum to give (3S,4S)-3,4-dihydroxy-dihydrofuran-2(3H)-one (6, 0.112g, 95%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 5.60 (2H, br s), 4.37 (1H, d, J = 4.7 Hz), 4.28 (1H, dd, J<sup>1</sup> = 9.85 Hz, J<sup>2</sup> = 3.05 Hz), 4.24–4.21 (1H, m), 4.04 (1H, d, J = 9.8 Hz); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 176.3, 71.7, 69.4, 68.3; APCI MS m/z 119.2 [M + 1]<sup>+</sup>; HPLC 98.2% (220 nm, AUC).