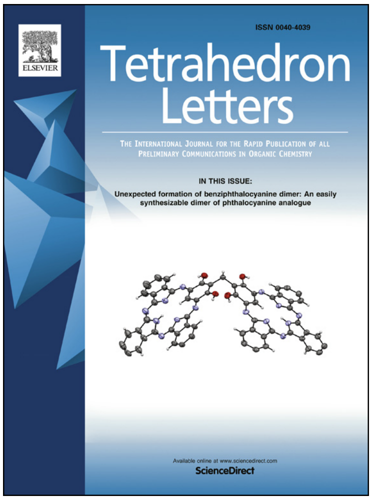

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Graphical Abstract

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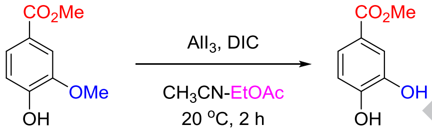

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Ethyl Acetate as a Co-solvent and Sacrificial Ester in the Aluminum Triiodide Promoted Chemoselective Demethylation of Methyl Vanillate

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ABSTRACT

A synthetic approach towards methyl protocatechuate *via* chemoselective ether cleavage of methyl vanillate without affecting the carboxylate group is disclosed utilizing a ternary reagent system consisting of aluminum triiodide, 1,3-diisopropylcarbodiimide and ethyl acetate. Ethyl acetate serves as a co-solvent and sacrificial ester. Methyl isovanillate, ethyl vanillate and methyl feruate were analogously demethylated to give methyl protocatechuate, ethyl protocatechuate and methyl caffeate, respectively, in fair to excellent yields.

Methyl protocatechuate is a natural antioxidant[1,2] with potent free radical scavenging[3,4] and neuroprotective[5] activities. It has also been used as a building block in the synthesis of dendrimers for anticancer drug delivery.[6] General approaches towards this phytochemical include the methyl esterification of protocatechuic acid,[7] exhaustive demethylation of methyl 3,4-dimethoxybenzoate using pyridinium hydrobromide perbromide,[8] and demethylenation of methyl 3,4-methylenedioxybenzoate using aluminium bromide-ethanethiol.[9] The direct demethylation of methyl vanillate was difficult, partly because of the *o*-hydroxy group, but has been elegantly realized by Bernini and co-workers using IBX/sodium hyposulfite (Fig. 1a).[10] However, this procedure is not entirely satisfactory since it is ineffective towards electron-deficient substrates such as vanillic acid due to the electron-withdrawing character of the carboxylic group.[10] We have recently developed a method suitable for cleaving alkyl aryl ethers using an aluminum triiodide-acid scavenger (ATAS) system.[11, 12] While ATAS worked efficiently with a range of substrates containing acid-labile functional groups, a mixture of methyl protocatechuate and protocatechuic acid were produced when methyl vanillate was demethylated by aluminum triiodide using 1,3-diisopropylcarbodiimide (DIC) as the acid scavenger.[12] The non-hydrolytic ester cleavage side-reaction could not be satisfactorily eliminated by lowering the reaction temperature or shortening the reaction time, and as a result, methyl protocatechuate was only obtained in 31% isolated yield (Fig. 1b).[12] Thus, it is desirable to develop a method that can chemoselectively cleave ether bonds without affecting the ester groups. Herein, we disclose that the transformation could be significantly improved by adding ethyl acetate as a co-solvent and sacrificial ester (Fig. 1c).

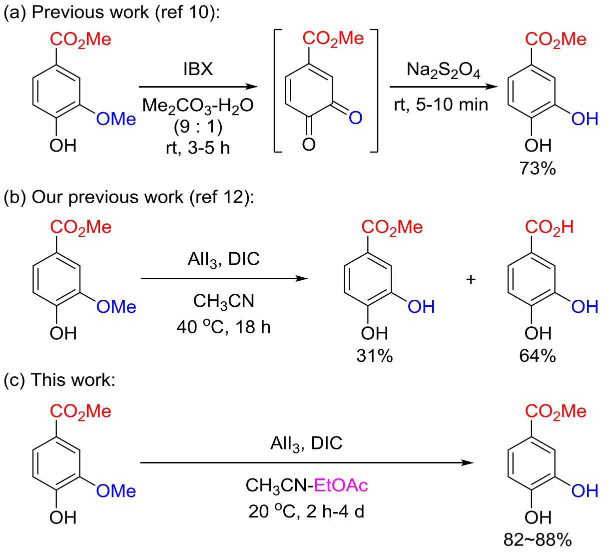

Figure 1. Selected methods for the demethylation of methyl vanillate

Initially, we reasoned that the neighboring *o*-hydroxyl group participation facilitated intramolecular demethylation reaction[12] should be much faster than aluminum triiodide mediated intermolecular ester cleavage, and thus assumed that the consumption of aluminum triiodide by an additive ester would be beneficial to the chemoselective demethylation of methyl vanillate (**1**) through competing ester cleavage. To support the

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assumption, methyl benzoate was selected as an additive. Unexpectedly, the conversion was rather slow in the presence of excess methyl benzoate (5 eq.), and methyl protocatechuate (**2**) was isolated in 78% yield after stirring for 18 h in hot acetonitrile (Fig. 2).

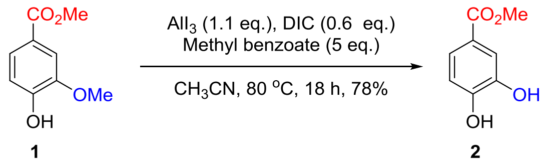
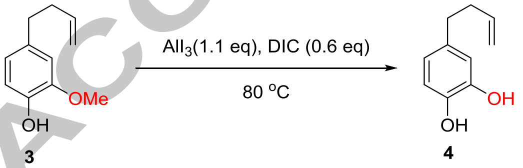


Figure 2. Demethylation of methyl vanillate using methyl benzoate as a sacrificial ester

The unnecessary complication in product isolation made the use of methyl benzoate less appealing. We reasoned that if the aluminum triiodide promoted ether cleavage was faster than ester cleavage, it would be feasible to run the demethylation transformation in an ester solvent. Common solvents for aluminum triiodide mediated reactions include carbon disulfide, hexanes, benzene and acetonitrile.[13] The use of ester solvents, however, should be handled with care because of the known ester cleavage reaction by aluminum triiodide.[13] A survey of the literature showed that ethyl acetate was once employed as the solvent in the aluminum trichloride-pyridine mediated demethylation of curcumin.[14] Coincidentally, we previously noted that the cleavage of methyl *o*-hydroxyphenyl ethers by ATAS is rather fast when facilitated by neighboring *o*-hydroxyl group participation.[11, 12] Thus, eugenol (**3**) was selected as the model compound for the evaluation of ethyl acetate as a solvent in the aluminum triiodide mediated demethylation (Table 1). Under optimized conditions for the demethylation of *o*-hydroxyphenyl methyl ethers using aluminum triiodide (1.1 eq.) and DIC (0.6 eq.) in hot acetonitrile,[12] hydroxychavicol (**4**) was isolated in 96% yield when quenched 3 min after the start of the reaction, with the recovery of 2% unreacted eugenol (Entry 1). The conversion was complete in 25 min (Entry 2). Next, acetonitrile was removed under reduced pressure after completion of the *in situ* preparation of aluminum triiodide,[12] and to the residue was added a solution of eugenol and DIC in ethyl acetate. Pleasingly, **4** was isolated in 76% yield after stirring overnight at reflux (Entry 3). The low isolated yield of **4** in ethyl acetate is consistent with the assumption that aluminum triiodide was partially consumed by competing ester cleavage.

Table 1. Demethylation of eugenol by aluminum triiodide



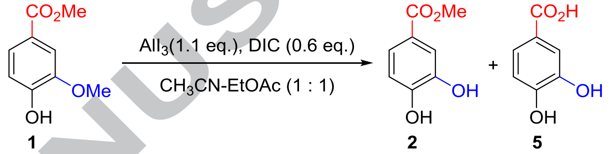
Entry	Solvent	Time	Isolated yield **4** (%)
1	CH_3CN	3 min	96[a]
2	CH_3CN	25 min	98
3	**EtOAc**	**18 h**	**76**[b]

[a] ~2% unreacted eugenol (**3**) was recovered.

[b] Conversion was incomplete.

Next, we reasoned that it might be feasible to demethylate methyl vanillate (**1**) in the presence of excess ethyl acetate. After the preparation of aluminum triiodide, acetonitrile was not removed for the convenience of operation. The selected conditions are as follows: to a suspension of aluminum triiodide (5.5 mmol, 1.1 eq.) in acetonitrile (20 mL) was added a solution of DIC (379 mg, 3.0 mmol, 0.6 eq.) and methyl vanillate (5 mmol) in ethyl acetate (20 mL). The results are summarized in Table 2. Partial ester cleavage was observed after stirring the reaction mixture for 5 h at 80 °C, affording methyl protocatechuate (**2**) as the major product in 72% yield along with protocatechuic acid (**5**) as a by-product in 14% yield (Entry 1). When conducted at 50 °C (Entry 2), the conversion was typically complete within 1 h as indicated by TLC analysis. However, it was still crucial to quench the reaction in time, since prolonged stirring gave **5** in 11% isolated yield when the reaction was quenched after 150 min (Entry 3). Upon quenching the reaction after stirring at room temperature for 2 h, **2** was isolated in 82% yield without the formation of **5** (Entry 4). The reaction was sluggish at a lower temperature (15 °C) and the conversion was incomplete after stirring for 18 h, as observed by TLC (Entry 5). Unexpectedly, no further conversion was observed during prolonged stirring, affording **2** in 68% isolated yield, possibly because the aluminum triiodide was deactivated by moisture. When the reaction was scaled up to 33 mmol, the transformation became sluggish, and took 4 d to reach completion (Entry 6). Finally, methyl acetate was also used, in which the reaction at 80 °C for 2 d proceeded without noticeable ester cleavage side-reaction (Entry 7).

Table 2. Demethylation of methyl vanillate using aluminum triiodide[a]



Entry	Temp.	Time	Yield **2** (%)
1	80 °C	5 h	72[b]
2	50 °C	2 h	83
3	50 °C	2.5 h	81[c]
4	**20 °C**	**2 h**	**82**
5	15 °C	10 d	68[d]
6	20 °C	4 d	88[e]
7	80 °C	2 d	85[f]

[a] Isolated yield;

[b] Compound **5** was isolated in 14% yield;

[c] Compound **5** was isolated in 11% yield;

[d] No further conversion was observed after 1 d, and thus the reaction was halted after 10 d.

[e] Reaction was carried on a 33 mmol scale.

[f] Ethyl acetate was replaced by methyl acetate.

The method was then extended to methyl isovanillate (**6a**), ethyl vanillate (**6b**) and methyl ferulate (**6c**), affording the corresponding demethylated products in good to excellent yields (Fig. 3). The demethylation of **6c** was slower than **3** or **6a**, and took 4 h to reach completion.

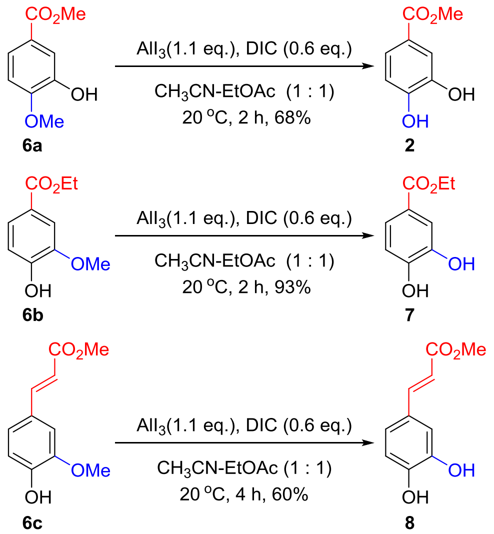


Figure 2. Demethylation of methyl isovanillate **6a**, ethyl vanillate **6b** and methyl ferulate **6c**

A plausible mechanism is depicted in Figure 4. The deprotonation of phenol **1** proceeds faster than ester cleavage, and the resultant aluminum phenolate (**9**) undergoes demethylation in the presence of neighboring *o*-hydroxyl group participation to give a five-membered cyclic intermediate (**10**), which affords methyl protocatechul (**2**) upon acidic work-up. The ester groups of the aluminum iodide intermediates (**9** and **10**) may also be affected by aluminum triiodide; this leads to intermediate **11** which after acidification affords protocatechuaic acid (**5**). In the presence of excess ethyl acetate, the reactive aluminum iodide species (aluminum triiodide, **9** and **10**) are sacrifically consumed by ethyl acetate, and in competition with intermediate **10**, give rise to the improved synthesis of **2**.

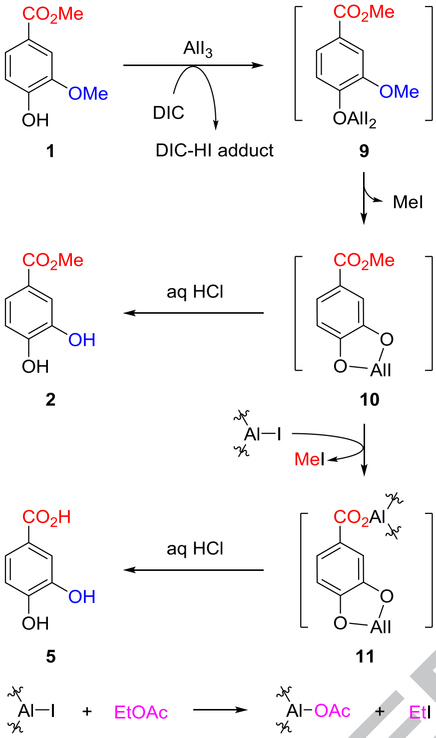


Figure 3. Proposed reaction mechanism

In summary, a convenient and chemoselective ether cleaving method using a ternary reagent system consisting of AlI_3, DIC and ethyl acetate was developed for the demethylation of methyl vanillate to provide methyl protocatechuate in good yield. DIC was used as the acid scavenger, and EtOAc the sacrificial ester as well as co-solvent. The method was successfully extended to ethyl vanillate and methyl ferulate. Further modification of the ATAS demethylation method is currently in progress and will be reported in due course.

Acknowledgments

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Supplementary Material

General procedure, and NMR spectra of **2**, **7** and **8**.

1. An efficient and chemoselective ether cleaving agent was developed.
2. The agent consists of AlI_3, an acid scavenger, and a sacrificial ester.
3. 1,3-Diisopropylcarbodiimide was used as a scavenger for *in situ* generated HI.
4. Ethyl acetate was used as the sacrificial ester as well as a co-solvent.
5. Four alkyl *o*-hydroxyphenyl ethers were cleaved to afford catechols in good yields.

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