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Pyridine Improves Aluminum Triiodide Induced Selective Cleavage of Alkyl *o*-Hydroxyphenyl Ethers: A Practical and Efficient Procedure for the Preparation of Hydroxychavicol by Demethylation of Eugenol

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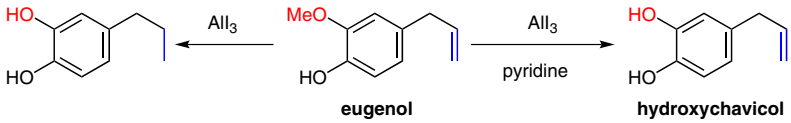

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Abstract Demethylation of eugenol with aluminum triiodide is complicated by an unexpected hydrogenation side reaction. The hydrogenation proceeds through a cascade deprotonation, hydroiodination, and hydrogen–halogen exchange process, and can be prevented by suppressing the hydroiodination in advance. A practical demethylation procedure is thus developed that delivers hydryoxychavicol in essentially quantitative yield by using pyridine as an additive. The method is selective towards cleaving alkyl *o*-hydroxyphenyl ethers and is compatible with a variety of functional groups.

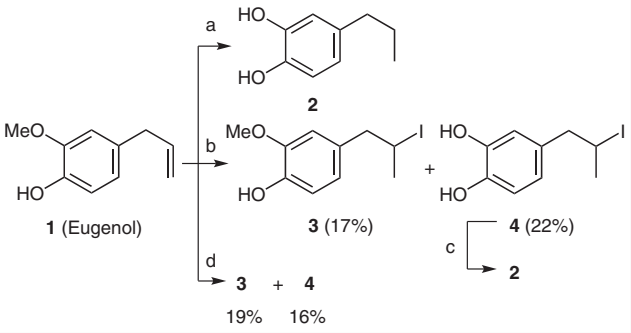
Key words eugenol, demethylation, hydroxychavicol, hydroiodination, hydrogen–halogen exchange, alkyl *o*-hydroxyphenyl ether, aluminum triidodide–pyridine

Hydroxychavicol is a phenolic antioxidant isolated from betel leaf.[1] The phytochemical shows potent pharmaceutical activities such as antimutagen,[2] antimicrobial,[3] and inhibitions of prostate cancer[4] and platelet aggregation.[5] It is also a useful building block for syntheses of pharmaceutical targets.[6] Demethylation of eugenol provides a short synthetic route to hydroxychavicol. While many methods exist in literature for cleaving ethers, deprotection of this type of methyl *o*-hydroxyphenyl ether proves difficult. Conventional Lewis acids such as BCl_3,[6c] BBr_3,[6a] $AlCl_3$–Me_2S,[7] $AlCl_3$–pyridine,[8] AlI_3,[9] LiCl–DMF,[10–11] $SiCl_4$–NaI,[12] and Ph_2PLi[13] were inefficient and afforded the product in merely moderate to low yields due to the existence of the *o*-phenolic hydroxyl and the acid-labile allyl group. The ether-cleaving effect of AlI_3 can be improved by using TBAI as an additive,[14] as witnessed by numerous late-stage exhaustive demethylation transformations.[15] Surprisingly, an unexpected hydrogenation of the allyl chain occurred concurrently with demethylation when treating eugenol with AlI_3–TBAI and afforded 4-propylcatechol in 81% yield.[16] A noteworthy progress was achieved by stabilized IBX affording hydroxychavicol in 77% yield.[17] Thus, a convenient and practical method is still lacking for the one-step demethylation of eugenol.

A survey of literature showed that olefins can be conveniently saturated through aluminum trihalide catalyzed ionic hydrogenation using alkanes as hydride donors.[18] This reaction had been applied successfully to hindered and deactivated substrates such as unsaturated fatty acids,[19] α,β-unsaturated ketones,[20,21] and α,β-unsaturated amides.[22] The inconsistent results for the demethylation of eugenol using AlI_3[9] and AlI_3–TBAI[16] as well as the remarkable high efficiency by the later reagent[16] prompted us to question if the hydrogenation side reaction could be suppressed.

We surmised that the *o*-hydroxyl group was possibly involved in the unexpected hydrogenation during AlI_3–TBAI induced demethylation,[16] and set out to intercept early intermediates. When a mixture of eugenol and AlI_3 (2 equiv) was stirred overnight in refluxing hexane in the absence of TBAI, **2** was isolated in 62% yield. The result is consistent with that reported by Deffieux and co-workers.[16] To our delight, two intermediates were isolated and were characterized as **3** and **4** when the amount of AlI_3 was reduced by half (Scheme 1).[23] Intermediate **3** is obviously the hydroiodination product of eugenol; accordingly, demethylation of **3** leads to intermediate **4**.

We next turned to question if **4** could be hydrodeiodided to afford **2** under current conditions. Hydrogenation of alkyl halides by alkanes *via* hydrogen–halogen exchange



Scheme 1 *Reagents and conditions*: (a) AlI_3 (2.0 equiv), hexane, 80 °C, 18 h, 62%; (b) AlI_3 (1.0 equiv), hexane, 80 °C, 18 h; (c) AlI_3 (2.0 equiv), hexane, 80 °C, 18 h, 100%; (d) AlI_3 (1.1 equiv), CS_2, r.t., 18 h.

has long been known.[24] The reaction proceeds through intermolecular transfer of hydrides from alkanes to carbocation ions generated *in situ* by aluminum trihalide induced disassociation of alkyl halides. For example, several alkyl halides were hydro-dehalogenated by $AlCl_3$ under Friedel–Crafts alkylation conditions.[25,26] As expected, the propyl iodide **4** was successfully hydrodeiodinated by AlI_3 in refluxing hexane and afforded **2** in quantitative yield.

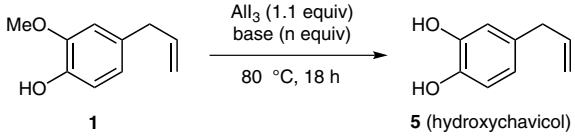
The isolation of **4** suggests that the hydro-deiodination proceeds slower than the intramolecular demethylation.[27] When carried out in a hydrogen-free solvent such as CS_2, **3** and **4** were still isolated (Scheme 1), suggesting that the hydroiodination shall be prevented in advance to harness the undesired hydrogenation of the allyl chain of eugenol (**1**).

We postulated that a HI scavenger might meet the need and leave the allyl group intact. Reported HI scavengers include limonene,[28] zeolites,[29] and phloroglucinol.[30,31] Both 3 Å and 4 Å molecular sieves were found to be ineffective for the transformation. The successful application of $AlCl_3$–pyridine[8] in demethylation of methyl *o*-hydroxyphenyl ethers inspired us to neutralize HI with an organic base for the ease of operation.[32] Fortunately, hydroxychavicol (**5**) was obtained upon the addition of pyridine and eugenol to a stirred suspension of AlI_3 in refluxing hexane.

Actions of various bases and solvents were investigated, as summarized in Table 1. When the solvent was changed from hexane to MeCN, the yield increased remarkably (entries 1 and 2), and reached 99% when 4.5 equivalents of pyridine were used (entry 2). The yield was markedly affected by the amount of pyridine (entries 2–5). Replacement of pyridine with $PhNMe_2$ resulted in complete consumption of eugenol although **5** was not observed (entry 6).

Application of sterically bulky DIPEA afforded the product in merely 15% yield (Table 1, entry 7), whereas no conversion was observed when triethylamine was used (Table 1, entry 8). Use of 2,6-lutidine gave a similar result (Table 1, entry 9) as pyridine. The effect of DMAP was between that of pyridine and $PhNMe_2$, and afforded **5** in a moderate yield (Table 1, entry 10). Thus the best demethylation conditions

Table 1 Screening of Demethylation Conditions



Entry	Base	n	Solvent	Yield (%)[a]
1	pyridine	4.5	hexane	67
2	pyridine	4.5	MeCN	99
3	pyridine	1.5	MeCN	75
4	pyridine	3	MeCN	78
5	pyridine	5	MeCN	93
6	$PhNMe_2$	4.5	MeCN	0[b]
7	DIPEA	4.5	MeCN	15[c]
8	Et_3N	4.5	MeCN	0[c]
9	2,6-lutidine	4.5	MeCN	92
10	DMAP	4.5	MeCN	48

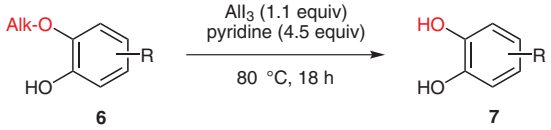
[a] Isolated yield.
[b] Eugenol disappeared.
[c] Low conversion.

consist of stirring eugenol with AlI_3 (1.1 equiv) and pyridine (4.5 equiv) in refluxing MeCN for 18 hours. The conditions are similar to that for $AlCl_3$–pyridine.[8,33]

One marked difference between $AlCl_3$ and AlI_3 exists in the fact that the former reagent can be used in combination with a variety of tertiary amines including $PhNMe_2$ and Et_3N in the demethylation of vanillin; the later reagent, however, turned to be completely ineffective when $PhNMe_2$ and Et_3N were used for the demethylation of eugenol (Table 1, entries 6 and 8). It is noteworthy that DIPEA turned to be slightly active towards eugenol (Table 1, entry 7). The discrepancy between DIPEA and Et_3N indicates that the catalyst of the demethylation is a complex formed by AlI_3 and the base used.

With the optimised conditions in hand,[34] we next turned to screen its scope and limitations, as listed in Table 2. Dehydrodieugenol (**6a**) was demethylated in a similar mode to give **7a** in 96% yield (entry 1). Vanillin (**6b**) and isovanillin (**6c**) were converted into protocatecualdehyde (**7b**) in 94% yields (entries 2 and 3). Cleavage of ethylvanillin (**6d**) and 2-isopropoxyphenol (**6e**) proceeded in moderate yields (entries 4 and 5). It is interesting to note that $AlCl_3$–pyridine is suitable for demethylation only; bulkier alkyl groups such as an ethyl group will result in markedly reduced yields.[33] The method is compatible with substrates **6e–j** containing cyano (entry 6), nitro (entry 7), formyl (entries 2–4, 7, 10), carboxylic (entry 8), acetyl (entry 9), and halogen (entry 10) groups, and delivered the corresponding catechols **7c–h** in moderate to high yields.

Table 2 Scope and Limitations of AlI_3–Pyridine for Cleaving Alkyl *o*-Hydroxyphenyl Ethers[34]



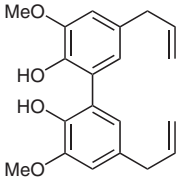
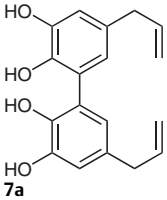
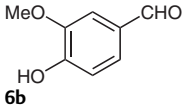
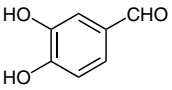
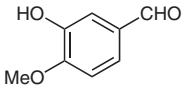
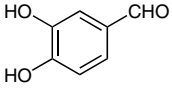
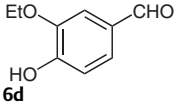
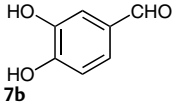
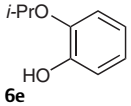
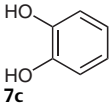
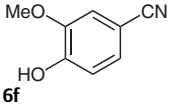
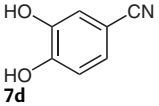
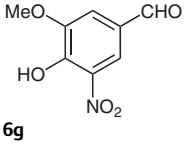
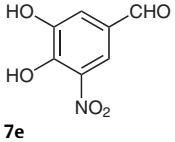
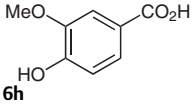
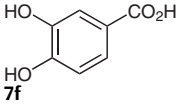
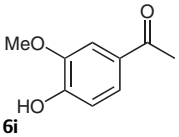
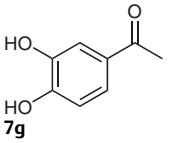
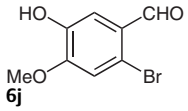
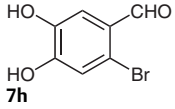
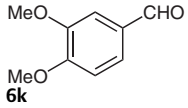
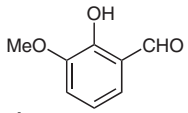
Entry	Substrate	Product	Yield (%)[a,b]
1	 **6a**	 **7a**	96
2	 **6b**	 **7b**	94
3	 **6c**	 **7b**	94
4	 **6d**	 **7b**	59
5	 **6e**	 **7c**	64
6	 **6f**	 **7d**	88
7	 **6g**	 **7e**	71
8	 **6h**	 **7f**	65
9	 **6i**	 **7g**	75

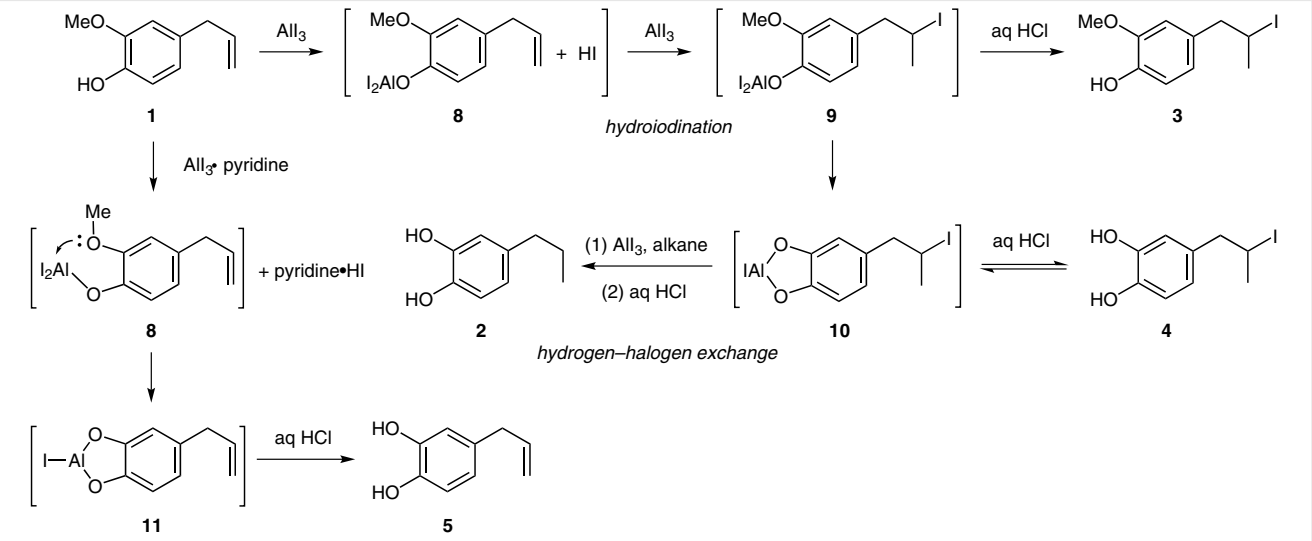
Table 2 (continued)

Entry	Substrate	Product	Yield (%)[a,b]
10	 **6j**	 **7h**	87
11	 **6k**	–	0[c]
12	 **6l**	–	0[c]

[a] Isolated yield.
[b] All products were characterized by NMR spectroscopy and were compared with literature data.
[c] No conversion.

The method has its limitations. It is ineffective towards veratraldehyde (**6k**), demonstrating that the *o*-hydroxyl group is crucial to the ether cleavage (Table 2, entry 11). It also suggests that AlI_3 lost its extraordinary oxophilicity[15] in the presence of pyridine.[35] Another limitation arises from competing coordination between methoxy oxygen and basic *ortho* functional groups. Thus no conversion was observed when treating *o*-vanillin (**6l**) with AlI_3–pyridine (Table 2, entry 12). Demethylation of the substrate by $AlCl_3$–pyridine was similarly unsuccessful because the formyl oxygen is more basic than methoxy oxygen.[33]

Based on these findings, a mechanism for the reaction between AlI_3 and eugenol is proposed, see Scheme 2. The *o*-hydroxyl group serves as an anchor for deprotonation and subsequent demethylation. Deprotonation of the hydroxyl group of eugenol by AlI_3 gives equal molar amount of phenolate **8** and HI. Subsequent hydroiodination gives the isopropyl iodide **9**. Demethylation of **9** leads to a five-membered cyclic intermediate **10**. Hydrolysis of **9** and **10** gives **3** and **4**, respectively. Hydrogen–halogen exchange between **10** and an alkane (the solvent) in the presence of AlI_3 followed by hydrolysis eventually furnishes **2**. Lange's mechanism for $AlCl_3$–pyridine-catalyzed cleavage of alkyl *o*-hydroxyphenyl ethers[33] was adopted to interpret the reaction between hydroxychavicol and AlI_3–pyridine. The base coordinates with AlI_3 to form a complex, which is active towards phenolic hydroxyl group. Eugenol is then deprotonated by the complex to give phenolate **8**, and the concurrent HI is scavenged by another molecule of base. Coordination of the *o*-methoxyl group to the Lewis acidic center gives a five-membered cyclic intermediate **11** after releasing methyl iodide either as a gas or a water soluble salt. Finally, hydrolysis of phenolate **11** furnishes hydroxychavicol (**5**). The role



Scheme 2 Proposed mechanism for AlI_3-induced demethylation and hydrogenation of eugenol

of pyridine–HI in the demethylation can be negated, since pyridine–HI-catalyzed intramolecular hydrogen-bonding-enhanced demethylation does not occur in MeCN.[36]

In summary, AlI_3-induced demethylation and hydrogenation of eugenol was studied. The hydrogenation proceeds through a cascade deprotonation, hydroiodination, and hydrogen–halogen exchange process. The side reaction could be suppressed by blocking the hydroiodination in advance. A practical ether cleavage procedure is developed for the demethylation of eugenol and affords hydroxychavicol in essentially quantitative yield. The method is compatible with a variety of functional groups. Further evaluation of this ether cleavage method as well as the scope of AlI_3–alkane-induced ionic hydrogenation of olefins and alkyl halides is in progress and will be disclosed in due course.

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(23) **Characterization Data**
Compound **2**: white solid; 62%. R_f = 0.77 (PE–EtOAc = 3:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.77 (d, *J* = 8.0 Hz, 1 H), 6.70 (d, *J* = 2.0 Hz, 1 H), 6.61 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1 H), 5.20 (s, 1 H), 5.07 (s, 1 H), 2.47 (t, *J* = 7.6 Hz, 2 H), 1.58 (sext, *J* = 7.6 Hz, 2 H), 0.91 (t, *J* = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.23, 141.14, 136.09, 120.90, 115.55, 115.19, 37.33, 24.68, 13.78.
Compound **3**: Purification of **3** by column chromatography was unsuccessful. It is thermally unstable and decomposed during an attempted vacuum distillation at above 110 °C. Yellow oil (contains about 10% of unidentified impurity); 17%. R_f = 0.62 (PE–EtOAc = 3:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87–6.83 (m, 1 H), 6.70–6.66 (m, 2 H), 5.53 (s, 1 H), 5.17 (s, 1 H), 4.30 (sext, *J* = 6.8 Hz, 1 H), 3.89 (s, 3 H), 3.22 (dd, J_1 = 14.0 Hz, J_2 = 7.2 Hz,1 H), 2.98 (dd, J_1 = 14.0 Hz, J_2 = 7.6 Hz, 1 H), 1.88 (d, *J* = 7.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.42, 114.48, 131.72, 121.84, 114.37, 111.59, 56.02, 49.22, 29.39, 27.99. ESI-HRMS: *m/z* calcd for $C_{10}H_{13}O_2I$: 291.9960; found: 291.9955 [M^+].
Compound **4**: white solid; 22%. R_f = 0.35 (PE–EtOAc = 3:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.79 (d, *J* = 8.0 Hz, 1 H), 6.71 (d, *J* = 2.0 Hz, 1 H), 6.62 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1 H), 6.26 (s, 1 H), 5.17 (s, 1 H), 4.27 (sext, *J* = 7.2 Hz, 1 H), 3.17 (dd, J_1 = 14.0 Hz, J_2 = 7.2 Hz, 1 H), 2.93 (dd, J_1 = 14.0 Hz, J_2 = 7.2 Hz,1 H), 1.87 (d, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.3, 142.1, 133.0, 121.7, 116.1, 115.4, 48.7, 29.1, 28.0. MS (EI): *m/z* (%) = 278 (41) [M^+], 151 (100). HRMS (EI): *m/z* calcd for $C_9H_{11}O_2I$: 277.9804; found: 277.9801 [M^+].
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(34) **General Procedure**
To a solution of AlI_3 (36.6 mmol, 1.1 equiv) in MeCN (100 mL) was added dropwise a solution of pyridine (12.2 g, 154.2 mmol, 4.6 equiv) and eugenol (5.4 g, 33.0 mmol). The mixture was stirred at 80 °C for 18 h. After cooling to room temperature, the mixture was quenched with aq HCl (2 mol/L, 50 mL), and was extracted with EtOAc (4 × 50 mL). The combined organic phases were washed with brine and dried by $MgSO_4$. After evaporation of solvents by a rotary evaporator, the residue was purified through flash column chromatography to afford **5** as a white solid (4.9 g, 99%). R_f = 0.46 (PE–EtOAc = 3:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80 (d, *J* = 8.0 Hz, 1 H), 6.72 (d, *J* = 2.0 Hz, 1 H), 6.63 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1 H), 6.10 (br s, 2 H), 5.92 (ddt, J_1 = 17.2 Hz, J_2 = 10.4 Hz, J_2 = 6.8 Hz, 1 H), 5.05 (dq, J_1 = 16.8 Hz, J_2 = 1.6 Hz, 1 H), 5.03 (dq, J_1 = 10.0 Hz, J_2 = 1.6 Hz, 1 H), 3.26 (d, *J* = 6.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.35, 141.54, 137.65, 133.60, 121.33, 116.09, 115.80, 115.71, 39.50.
(35) Eugenol methyl ether can be exhaustively demethylated by AlI_3. Similarly, 5-allylresorcinol can be prepared by treating 5-allyl-1,3-dimethoxybenzene with AlI_3, see: Coolen, H. K.; Meeuwis, J. A.; Van Leeuwen, P. W.; Nolte, R. J. *J. Am. Chem. Soc.* **1995**, *117*, 11906.
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