

## Organic &amp; Supramolecular Chemistry

## One-Pot Cleavage of Aryl Alkyl Ethers by Aluminum and Iodine in Acetonitrile

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Cleavage of aryl alkyl ethers was conducted in a one-pot one-stage manner by mixing the ethers, aluminum and iodine in acetonitrile without the *in situ* preparation of aluminum triiodide in advance. For ethers bearing acid-labile functional groups such as allyl, alkenyl and carbonyl, an acid scavenger (calcium oxide, 1,3-diisopropylcarbodiimide or dimethyl sulfoxide) was used to prevent side-reactions. This one-pot protocol is efficient and convenient for the removal of methyl,

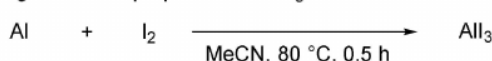
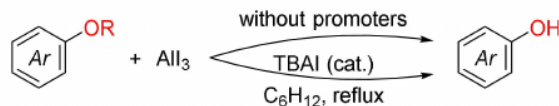
ethyl, isopropyl and *tert*-butyl groups from typical aryl alkyl ethers, catechol monomethyl and dimethyl ethers, and is compatible with a variety of functional groups including alkenyl, alkyl, allyl, amido, cyano, formyl, halogen, keto and nitro group. Methyl 2-anisate and eugenol acetate were exhaustively deprotected by the method that afforded salicylic acid and hydroxychavicol, respectively.

## Introduction

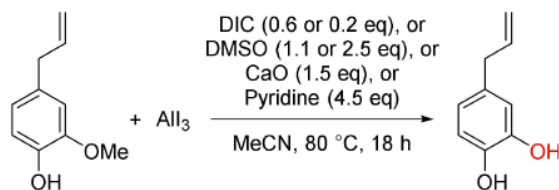
Aluminum triiodide is a powerful reagent<sup>[1]</sup> useful for iodination of alcohols,<sup>[2]</sup> dehydration of aldoximes,<sup>[3]</sup> deoxygenation of sulfoxides,<sup>[4]</sup> oxiranes<sup>[5]</sup> and *N*-heteroarene *N*-oxides,<sup>[6]</sup> and cleavage of ether<sup>[7]</sup> and ester<sup>[8]</sup> C–O bonds. This reagent is typically prepared *in situ* from aluminum and iodine prior to applications (Scheme 1A, stage 1). Ethers could be cleaved by adding substrates to the above prepared suspension of aluminum triiodide in refluxing acetonitrile, benzene or carbon disulfide (Scheme 1A, stage 2).<sup>[7]</sup> Its application in the cleavage of ethers could be facilitated by tetrabutylammonium iodide (TBAI).<sup>[9]</sup> For the cleavage of aryl alkyl ethers containing acid-labile functional groups, such as the demethylation of eugenol, it was reported that an unexpected side-reaction had occurred that afforded 4-propylcatechol as the sole product in very good yield.<sup>[10]</sup> We have demonstrated that the side-reaction was due to the *in situ* generation of hydrogen iodide *via* AlI<sub>3</sub> mediated deprotonation of the adjacent phenolic hydroxyl group, and could be prevented using proper Lewis bases such as 1,3-diisopropylcarbodiimide (DIC),<sup>[11]</sup> DMSO,<sup>[12]</sup> calcium oxide<sup>[13]</sup> and pyridine<sup>[14]</sup> as acid scavengers (Scheme 1B).

While the demethylation of eugenol proceeded smoothly using DMSO as the acid scavenger when performed on a 5 mmol scale, we have noted that the acid scavenging behavior of DMSO was markedly affected by the charging manner of eugenol when scaled up to above 35 mmol scale, an issue that

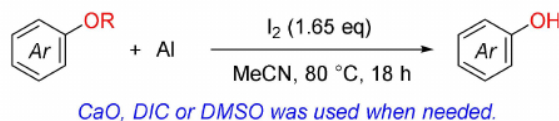
## A) Selected previous work (two-stage process)

Stage 1: *In situ* preparation of AlI<sub>3</sub>Stage 2: Cleavage of ethers using AlI<sub>3</sub>

## B) Our previous work



## C) This work (one-stage, all materials were added in one-pot)



Scheme 1. Selected methods for the cleavage of ethers

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was resolved by adding eugenol dropwise to prevent the allyl side-chain from hydroiodination.<sup>[12]</sup> Thus, we reasoned that if DMSO and eugenol were present during the formation of the ether cleaving agent, such as in the one-pot preparation of ethyl iodide from aluminum, iodine and ethanol,<sup>[15]</sup> the acid scavenging performance of DMSO would be improved. We disclose herein that the ether cleaving operation could be conducted in a one-pot one-stage manner by mixing ethers, aluminum and iodine in acetonitrile that obviates the tedious

preparation of the Lewis acid (Scheme 1C). For substrates containing acid-labile groups such as allyl, acetophenyl or alkenyl group, an acid scavenger is necessitated for the chemoselective cleavages.

## Results and Discussion

Eugenol (**1**) was selected as the model substrate for the optimization of demethylation conditions. The results are summarized in Table 1. When conducted at 80 °C for 18 h,

**Table 1.** Optimization of conditions for the demethylation of eugenol<sup>[a]</sup>



Entry	T/°C	t/h	Yield/%
1	80	18	78
2	45	18	85
3	35	18	85
4	25	18	89
5 <sup>[b]</sup>	80	18	/
6 <sup>[c]</sup>	80	18	/
7 <sup>[d]</sup>	80	18	84
8 <sup>[e]</sup>	25	18	77
9 <sup>[e]</sup>	80	18	75

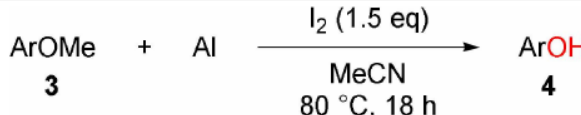
[a] Isolated yield, conditions: aluminum (~350 mg, excess), eugenol (5 mmol), DMSO (0.977 g, 12.5 mmol, 2.5 eq), and iodine (2.093 g, 8.25 mmol, 1.65 eq) were stirred in acetonitrile (40 mL) for 18 h at 80 °C. [b] Pyridine (4.5 eq) was used to take the place of DMSO as the acid scavenger. [c] The solvent was changed from acetonitrile to cyclohexane. [d] DMSO was replaced by DIC (0.6 eq). [e] Gram-scale (6 g, 40 mmol) synthesis.

hydroxychavicol (**2**) was obtained in 78% yield (entry 1). The yield was improved to 89% by lowering the temperature to 25 °C (entry 2–4). It was observed with surprise that no conversion had occurred when the acid scavenger was changed from DMSO to pyridine<sup>[14]</sup> (entry 5), or when conducted in cyclohexane using DMSO as the acid scavenger (entry 6). The former incidence was attributed to the formation of a charge transfer complex between pyridine<sup>[16]</sup> and iodine, which hampered the *in situ* formation of aluminum triiodide. As to the use of cyclohexane as the solvent, it is surmised that competing ether-iodine complex<sup>[17]</sup> formation might have occurred that suppressed the formation of aluminum oxide iodide. It was, however, more efficient to use 1,3-diisopropylcarbodiimide (DIC)<sup>[11]</sup> as the acid scavenger to prevent hydroiodination side-reaction (entry 7). Two gram-scale (40 mmol) syntheses were performed at 25 and 80 °C that afforded **2** in 77% and 75% yields, respectively (entry 8–9).

With the optimum ether cleaving conditions in hand, we then investigated the substrate scope and limitations. Since DMSO and DIC were used to scavenging HI for the protection

of acid-labile functional groups from side-reactions, these additives were used only when needed. It should also be noted that heating is necessitated for the cleavage of typical aryl alkyl ethers by either aluminum oxide iodide or aluminum triiodide in the absence of neighboring group participation effect.<sup>[18]</sup> Thus, the reactions were conducted in acetonitrile at 80 °C. The results are listed in Table 2. A variety of anisoles (**3a–3c**, **3e**

**Table 2.** Substrate scope and limitations<sup>[a]</sup>



<p><b>4a</b>, R = allyl: 62%<sup>[b]</sup></p> <p><b>4b</b>, R = propenyl: 40%<sup>[b]</sup></p> <p><b>4c</b>, R = OH: 87%</p> <p><b>4d</b>, R = CONH<sub>2</sub>: 5%</p> <p><b>4e</b>, R = CN: 85%</p> <p><b>4f</b>, R = Br: 44%</p> <p><b>4g</b>, R = I: 85%</p>	<p><b>4h</b>, R = CN: 52%</p> <p><b>4i</b>, R = OH: 60%</p>
<p><b>4j</b>, R = OH: 97%</p> <p><b>4k</b>, R = CN: 36%</p> <p><b>4l</b>, R = Cl: 26%</p> <p><b>4m</b>, R = CHO: 34%</p>	<p><b>4n</b>, R = <math>n\text{-C}_8\text{H}_{17}</math>: 89%<sup>[c]</sup></p> <p><b>4o</b>, R = CHO: 75%</p> <p><b>4p</b>, R = Ac: 84%<sup>[d]</sup></p> <p><b>4q</b>, R = NO<sub>2</sub>: 32%</p> <p><b>4r</b>, R = Me: 96%</p>
<p><b>4s</b>: 80%</p> <p><b>4t</b>: 79%</p>	
<p><b>4u</b>: 61%<sup>[f]</sup></p> <p><b>4v</b>: 36%<sup>[g]</sup></p> <p><b>4w</b>: 53%<sup>[h]</sup></p>	

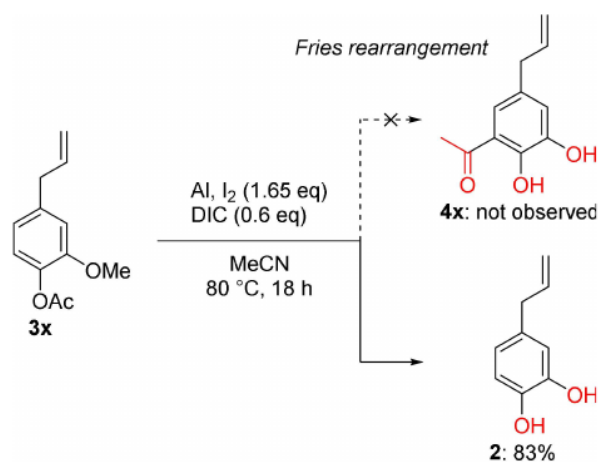
[a] Isolated yield, conditions: aluminum (about 350 mg, excess), substrate (5 mmol), and iodine (about 2.093 g, 8.25 mmol, 1.65 eq) were stirred in acetonitrile (40 mL) for 18 h at 80 °C. [b] DIC (0.2 eq) was used as an acid scavenger. [c] On 3 mmol scale using CaO (2.5 eq) as an acid scavenger. [d] CaO (1.5) was used. [e] 4-Methoxyphenol (**4c'**) was isolated as a minor product (38%). [f] 5-Methoxysalicylaldehyde (**4u'**) was isolated as a minor product (4%). [g] 4-Hydroxysalicylaldehyde (**4v'**) was isolated as a minor product (19%). [h] 1,2,4-Trihydroxybenzene (**4w'**) was isolated as a minor product (22%).

**3m**) were demethylated efficiently to give the corresponding phenols (**4a–4c**, **4e–4m**) in moderate to very good yields. The isolated yields for 2-chlorophenol (**4l**) and salicylaldehyde (**4m**) were low due to volatility issues under vacuum. Other catechol monomethyl ethers (**3n–3r**) were also cleaved efficiently by this one-pot one-stage method. Exhaustive demethylation was achieved for the deprotection of catechol dimethyl ether (**3j'**) and 1,4-dimethoxybenzene (**3c'**) that afforded catechol (**4j**) and quinol (**4c**) in 93% and 57% yields, respectively. The higher ether cleaving efficiencies for catechol monomethyl ether (**3j**) and catechol dimethyl ether (**3j'**) compared to that of 1,4-dimethoxybenzene (**3c'**) might be attributed to assistance of the neighboring group participation effect.<sup>[11b]</sup> It is noteworthy that essentially quantitative yields were obtained for the demethylation of guaiacol (**3j**) and 1,2-dimethoxybenzene (**3j**),

and the yield for the later was comparable to that by aluminum triiodide.<sup>[7]</sup> Two naphthyl methyl ethers (**3s** and **3t**) were also demethylated to afford naphthols **4s-4t** in good yields.

2,5-Dimethoxybenzaldehyde (**3u**) was demethylated to give 5-hydroxysalicylaldehyde (**4u**) as the major product (61%) along with trace amount of 5-methoxysalicylaldehyde (**4u'**). We have noted that when **3u** was treated by  $\text{AlCl}_3$ -NaI under the same conditions, the major product was 5-methoxysalicylaldehyde (**4u'**).<sup>[11b]</sup> These results indicated that the aluminum-iodine reagent system is a more powerful ether cleaving agent than  $\text{AlCl}_3$ -NaI. Contradictorily, the major product turned to be 4-methoxysalicylaldehyde (**4v**) when 2,4-dimethoxybenzaldehyde (**3v**) was demethylated under the same conditions. Similarly, demethylation of 1,2,4-trimethoxybenzene (**3w**) by aluminum and iodine in one-pot afforded 4-methoxycatechol (**4w**) as the major product (53%) along with minor trihydroxybenzene **4w'** (22%). The structure of **4w** was confirmed by HMBC and NOESY spectra (see supporting information).

Cleavage of ester C–O bond was also investigated using the optimum conditions. Eugenol acetate (**3x**) was treated with aluminum and iodine in hot acetonitrile for 18 hours, and a mixture of complicated products was obtained. When DIC (0.6 eq) was used as an acid scavenger, hydroxychavicol (**2**) was isolated as the sole product in 83% yield. A similar result was achieved using DMSO (2.5 eq) as the acid scavenger, which afforded **2** in 85% yield when conducted in the one-pot manner. It was reported that Fries rearrangement occurred when phenyl benzoate was cleaved by  $\text{AlI}_3$  in refluxing acetonitrile that afforded a mixture of 2- and 4-benzophenol.<sup>[8]</sup> Surprisingly, the Fries rearrangement product, 2',3'-dihydroxy-5'-allylacetophenone (**4x**), was not observed, as shown in Scheme 2.



Scheme 2. Unexpected cleavage of eugenol acetate

Similarly, when methyl 2-anisate (**3x'**) was exposed to the demethylation conditions, both the ether and ester C–O bonds were cleaved that afforded salicylic acid (**4x'**) in 90% yield (Table 3). It should be noted that the deprotection efficiency is

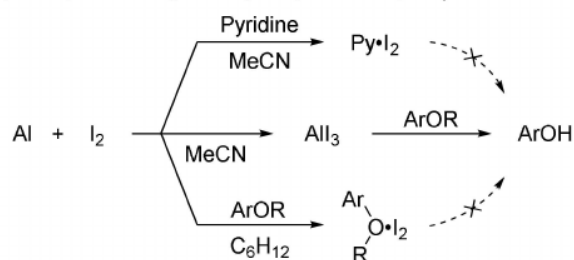
Table 3. Cleavage of other C–O bonds <sup>[a]</sup>		
ArOR <b>3</b>	Al + I <sub>2</sub>	ArOH <b>4</b>
MeCN 80 °C, 18 h		
Substrate <b>3</b>	Product <b>4</b>	Yield/%
		90
		89
		84
		66
		5
		86

[a] Isolated yield. Conditions: aluminum (about 350 mg, excess), substrate (5 mmol), and iodine (about 2.093 g, 8.25 mmol, 1.65 eq) were stirred for 18 h in MeCN at 80 °C.

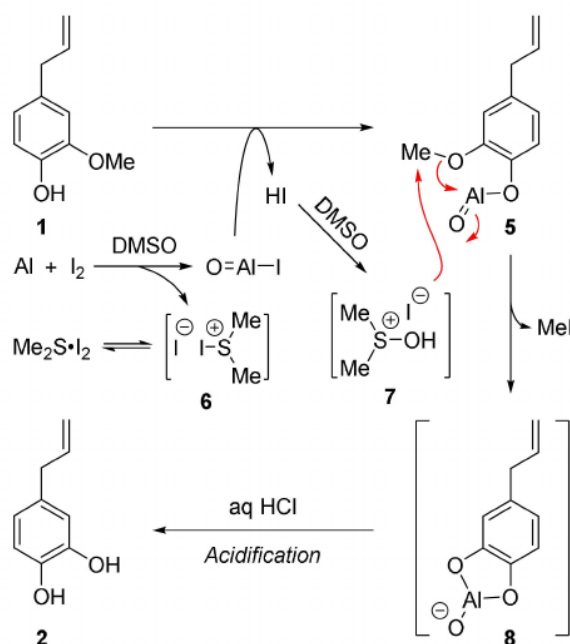
comparable to that using  $\text{AlI}_3$  via the two-stage process.<sup>[18]</sup> Sterically hindered ethyl and isopropyl groups were also readily removed when catechol monoalkyl ethers **3y** and **3y'** were treated with the optimum conditions, giving catechol (**4j**) in 89% and 84% yield, respectively. Interestingly, whereas the cleavage of 1,3-benzodioxole (**3z**) was efficient (66%) under current conditions, 1,4-benzodioxane (**3z'**) remained intact, and only trace amount of catechol (**4j**) was isolated (5%). The result is similar to that using aluminum iodide.<sup>[12]</sup> It is noteworthy that *tert*-butyl group was also readily cleaved off from 1-*tert*-butoxy-4-chlorobenzene (**3za**) under current conditions that afforded 4-chlorophenol (**4y**) in 86% yield.

Based on our previous study,<sup>[12]</sup> a proposed mechanism for the one-pot ether cleavage is shown in Scheme 3. For the cleavage of typical aryl methyl ethers in the absence of acid scavengers, or for the cleavage of ethers containing acid-labile groups using DIC as the acid scavenger, the *in situ* generated aluminum triiodide<sup>[7]</sup> serves as the ether cleaving agent (Scheme 3A). When pyridine is used as the acid scavenger, a 1:1 charge transfer complex ( $\text{py}\cdot\text{I}_2$ )<sup>[16]</sup> would be formed that prevents the formation of aluminum triiodide for ether cleavage. Similar situation takes place when performed in cyclohexane, where a charge transfer complex between ether oxygen and iodine would be formed.<sup>[17]</sup>

For the demethylation of eugenol (**1**) using DMSO as the acid scavenger, aluminum oxide iodide ( $\text{O}=\text{Al}\cdot\text{I}$ )<sup>[12]</sup> would be *in situ* generated from aluminum, iodine and DMSO, which after deprotonation of **1** affords aluminum phenolate **5** and HI (Scheme 3B). The reaction between DMSO and iodine affords

A) One-pot cleavage of aryl alkyl ethers by AlI<sub>3</sub>

## B) Ether cleavage using DMSO as the acid scavenger



Scheme 3. Proposed ether cleaving mechanisms

ion pair **6** as an iodide nucleophile. Ion pair **7** is similarly generated between DMSO and HI. Attack of the methoxy carbon of intermediate **5** by iodide **6** or **7** affords a five-membered cyclic intermediate **8**, which then furnishes hydroxychavicol (**2**) upon acidic work-up.

## Conclusions

In conclusion, a one-pot ether cleaving procedure is developed using aluminum and iodine in a one-stage manner that could be used for the efficient cleavage of typical aryl alkyl ethers, catechol monomethyl and dimethyl ethers. Various functional groups such as alkenyl, alkyl, allyl, amido, cyano, formyl, halogen, keto and nitro are well tolerated. For ethers containing acid-labile groups, acid scavengers such as CaO, DIC and DMSO could be used. The method is convenient for ether

cleavages compared to the conventional step-wise process. Ester C-O bond was also cleaved during the demethylation of methyl 2-anisate that afforded salicylic acid in an excellent yield. Fries rearrangement, a reaction path known for the cleavage of phenyl benzoate by aluminum triiodide, did not happen during the deprotection of eugenol acetate. Instead, hydroxychavicol was obtained as the sole product in ~80% yield when DMSO or DIC was used as the acid scavenger.

## Supporting Information Summary

<sup>1</sup>HNMR spectra of **2** and **4a-4y**, <sup>13</sup>CNMR spectra of **2**, **4a-4h**, **4k-4n**, **4s**, **4t**, **4u'-4w'**, **4y**, HMBC and NOESY spectra of **4w**.

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## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** acid scavenger · aluminum oxide iodide · eugenol · Fries rearrangement · neighboring group participation

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