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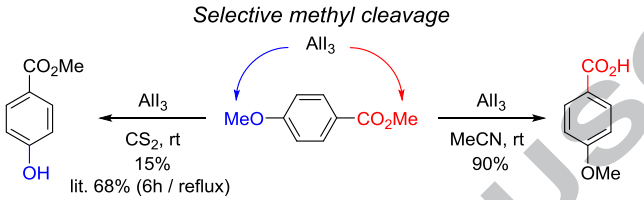

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ABSTRACT

The aluminum triiodide mediated chemoselective ester/ether C-O cleavage of methyl anisates was investigated. *o*-Anisate undergoes ether cleavage at low temperatures in carbon disulfide, cyclohexane and acetonitrile. Further cleavage of the ester group occurs at elevated temperatures to afford salicylic acid. The cleavage of *p*-anisate is solvent-dependent. In cyclohexane, the ester and ether groups were cleaved non-selectively to give equimolar amounts of *p*-anisic acid and methyl *p*-hydroxybenzoate. The ester group was preferentially cleaved in acetonitrile, compared to ether group cleavage in carbon disulfide. The ester cleavage reaction was improved using pyridine as an acid scavenger additive. Reasons for the contrasting reactivity of anisates toward AlI_3 were explored, and the methods were applied to cleavage of the *tert*-butyl ester of acemetacin which gave different products under these conditions.

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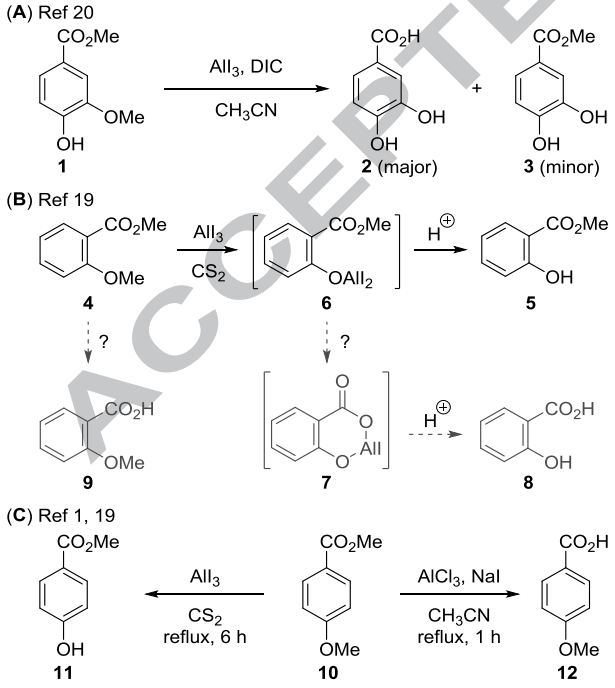
1. Introduction

Non-hydrolytic cleavage of esters is an important approach to unmask carboxylic acids, and can be effected by a number of Lewis acids such as aluminum chloride-sodium iodide,[1] aluminum halide-sulfide,[2] aluminum halide-thiol,[3] aluminum triiodide,[4] chloroaluminate ionic liquid,[5] boron tribromide,[6] ferric chloride,[7] iodotrimethylsilane,[8,9] lithium chloride,[10] and magnesium iodide[11,12] under mild conditions.[13] Since most of these Lewis acids are well known ether cleaving agents,[14-18] the selective cleavage of ester and ether C-O bonds is highly desirable.[1,2,19] We recently noted that the cleavage of methyl vanillate (**1**) by AlI_3 using 1,3-diisopropylcarbodiimide (DIC) as an acid scavenger afforded protocatechuic acid (**2**) along with small amounts of methyl protocatechuate (**3**), indicating that cleavage of the ester C-O bond is comparable to that of the catechol monomethyl ether with a neighboring hydroxyl group (Fig. 1A).[20] Thus, it was reasoned that the order of cleavage should be: catechol monomethyl ether > ester > typical aryl methyl ether. This postulate is, however, inconsistent with a previous finding that the cleavage of methyl *o*-anisate (**4**) by AlI_3 in carbon disulfide afforded methyl 2-hydroxybenzoate (**5**) in 76% yield (Fig. 1B).[19] Benzoate **5** is presumably formed *via* the acidification of aluminum phenolate **6**. Surprisingly, phenolate **6** did not undergo anchimerically assisted ester cleavage to spontaneously form a six-membered cyclic intermediate **7**, which would afford salicylic acid (**8**) upon acidification. It was also unknown if *o*-anisic acid (**9**) would be generated under these conditions. Similarly, cleavage of methyl *p*-anisate (**10**) gave methyl *p*-hydroxybenoate (**11**) in 68% yield,[19] contrasting with the aluminum trichloride-sodium iodide system mediated deprotection of **10** in acetonitrile at reflux that gave *p*-anisic acid (**12**) in 94% yield[1] (Fig. 1C). Herein, chemoselective cleavage of the ether and ester C-O bonds of methyl *o*-, *p*- and *m*-anisate by AlI_3 are reported.

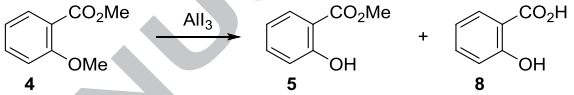
Figure 1. Selected ester/ether C-O cleavage reactions by AlI_3



2. Results and Discussion

Results for the demethylation of *o*-anisate **4** in cyclohexane and acetonitrile are summarized in Table 1. When the reaction was carried out in cyclohexane (80 °C) overnight, demethylation of **4** afforded acid **8** in 86% isolated yield (Entry 1). We reasoned that the reaction temperature might be a factor for the disagreement between this result and the reported isolation of benzoate **5** in 76% yield when **4** was treated with AlI_3 in carbon disulfide at reflux for 1 hour. Thus, when the reaction temperature was lowered to near the boiling point of carbon disulfide (45 °C), benzoate **5** was isolated in 67% yield along with acid **8** (Entry 2). The synthesis of **5** was further improved by lowering the temperature to room temperature (Entry 3). Next, acetonitrile was used; after stirring for 1 hour at room temperature, benzoate **5** and acid **8** were isolated in 68% and 16% yields, respectively (Entry 4). We have previously shown that ethyl acetate serves as a sacrificial ester that binds to AlI_3 to modulate its reactivity,[21] thus ethyl acetate was also added to the reaction mixture as a co-solvent in order to prevent ester cleavage. The reaction in acetonitrile and ethyl acetate (1:1) at 80 °C for 18 hours afforded acid **8** in 59% yield (Entry 5). The ester cleavage product, *o*-anisic acid (**9**), was not observed. These results suggest that the ether C-O bond of *o*-anisate **4** is more susceptible to AlI_3 attack than the ester moiety.

Table 1. Demethylation of methyl *o*-anisate (5 mmol) by AlI_3 (1.1 eq.) in various solvents (40 mL)[a]



4 5 8

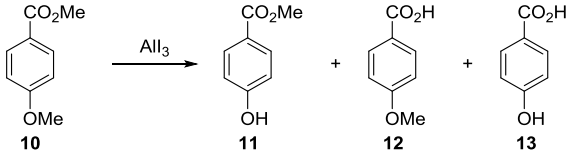
Entry	Solvent	*T* (°C)	time (h)	**5** (%)	**8** (%)
1	cyclohexane	80	18	/	86
2	cyclohexane	45	1	67	9
3	cyclohexane	rt	18	80	7
4	CH_3CN	rt	1	68	16
5[b]	CH_3CN	80	18	/	59

[a] Isolated yield.

[b] Ethyl acetate was added as a co-solvent (ethyl acetate/acetonitrile 1:1) to suppress ester cleavage.[21]

Next, the cleavage of *p*-anisate **10** was examined (Table 2). Upon treating **10** with AlI_3 in carbon disulfide for 18 hours at room temperature, phenol **11** was isolated as the sole product (Entry 1), albeit in much lower yield (15%) compared to that reported for stirring at reflux in carbon disulfide for 1 hour (68%).[19] The *p*-anisic acid (**12**) and *p*-hydroxybenzoic acid (**13**) were not observed. When the reaction was conducted in cyclohexane, all three products were isolated after stirring overnight at room temperature (Entry 2). Surprisingly, acid **12** was isolated in excellent yield when performed in acetonitrile for 18 hours at room temperature (Entry 3). This transformation was further improved using pyridine as an additive which serves as both coordination ligand and acid scavenger[22] (Entries 4-5). An attempt to suppress ester cleavage using ethyl acetate[21] was not successful, and afforded acid **12** in 13% yield after stirring overnight at 80 °C (Entry 6). The phenol **11**, however, was not observed, suggesting that AlI_3 was deactivated significantly by ethyl acetate. Thus, the AlI_3-ethyl acetate complex,[21] like the AlI_3-pyridine complex,[22] is unreactive towards the normal aryl methyl ether C-O bond. Since AlI_3 is known as a reactive cleaving agent for both aryl methyl ethers and esters, cleavage of the two methyl groups in one operation was attempted. As expected, both the ester and ether C-O bonds were cleaved to afford **13** in excellent yield when exposed to excess AlI_3 in acetonitrile at 80 °C (Entry 7).

Table 2. Demethylation of methyl *p*-anisate (5 mmol) by AlI_3 (1.1 eq.) in various solvents (40 mL)[a]



Entry	Solvent	*T*(°C)	time(h)	**11** (%)	**12** (%)	**13** (%)
1	CS_2	rt	18	15[b] (68[c])	/	/
2	cyclohexane	rt	18	30	36	17
3	CH_3CN	rt	18	/	90	/
4[d]	CH_3CN	80	18	/	96	/
5[e]	CH_3CN	80	18	/	98	/
6[f]	CH_3CN	80	18	/	13	/
7[g]	CH_3CN	80	18	/	/	91

[a] Isolated yield.

[b] Unreacted **10** (67%) was recovered.

[c] Lit.[19] yield for stirring over 6 h in CS_2 at reflux.

[d] Pyridine (3 eq.) was added to modulate the reactivity of AlI_3 through coordination.[23]

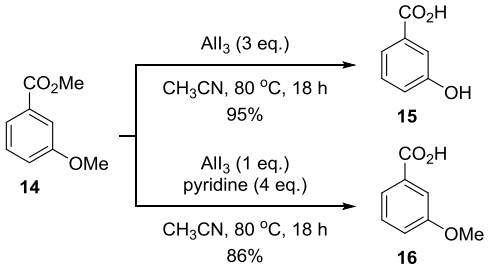
[e] Pyridine (4 eq.) was used.

[f] Ethyl acetate was used (see Table 1, Entry 4).

[g] Excess AlI_3 (3 eq.) was used.

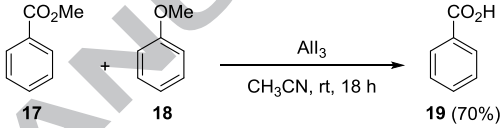
Cleavage of methyl *m*-anisate (**14**) by AlI_3 was also investigated (Fig. 2). Exposure of **14** to excess AlI_3 in acetonitrile (80 °C) afforded *m*-hydroxybenzoic acid (**15**) in 95% yield. When treated with AlI_3-pyridine, **14** was chemoselectively cleaved to give *m*-anisic acid (**16**) in excellent yield.

Figure 2. Cleavage of methyl *m*-benzoate by AlI_3-pyridine



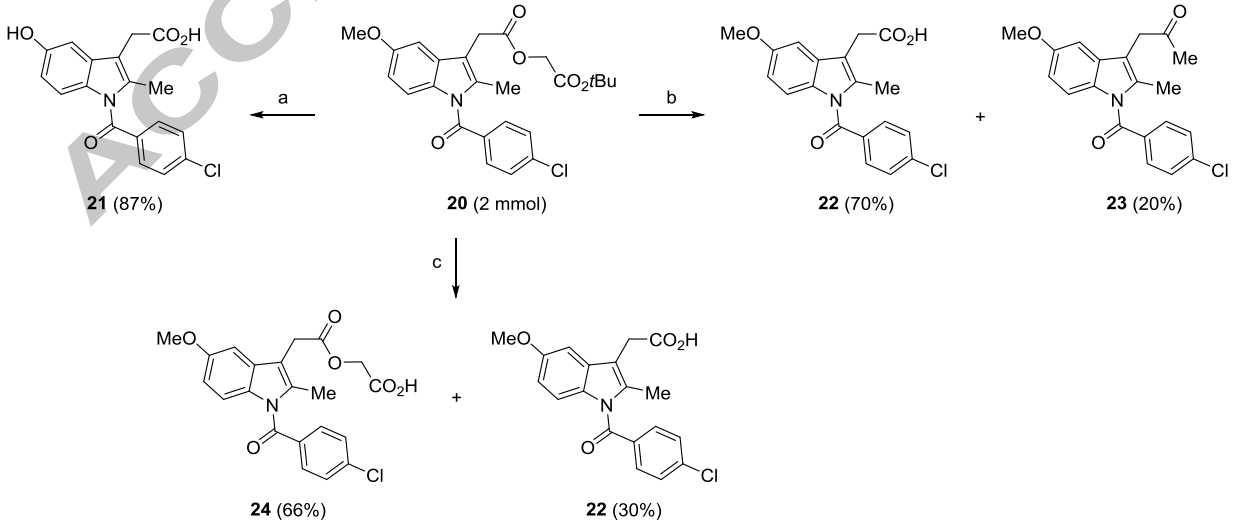
The ease of ester cleavage for *p*- and *m*-anisate in acetonitrile suggests that the ester C-O is more vulnerable to AlI_3 attack than the phenyl methyl ether C-O bond. To further strengthen the postulation, a competing experiment was designed. Thus, a 1:1 mixture of methyl benzoate (**17**) and anisole (**18**) was treated with AlI_3 in acetonitrile at room temperature, which afforded benzoic acid (**19**) solely in 70% isolated yield (Fig. 3). Interestingly, anisole **18** alone was unreactive towards the conditions, and the conversion took place only at elevated temperatures.[19]

Figure 3. Competing cleavage of methyl benzoate (5.5 mmol) and anisole (5.5 mmol) by AlI_3 (5.5 mmol)



The above-mentioned ether and ester cleavage conditions were extended to the chemoselective cleavage of the *t*-butyl ester of acemetacin (**20**),[24] as shown in Figure 4. When treated with AlI_3 (1.1 eq.) in acetonitrile (80 °C), both the methoxy and ester C-O bonds of ester **20** were cleaved to give *O*-desmethyl indometacin (**21**) in 87% isolated yield. Ester cleavage of ester **20** by AlI_3-pyridine afforded indometacin (**22**), a non-steroidal anti-inflammatory drug (NSAID),[25] as the major product in 70% yield. Unexpectedly, a ketone (**23**) was also isolated as the minor product in 20% yield. The side-reaction is surmised to proceed *via* decarboxylative coupling with acetonitrile to give an imine intermediate. Hydrolysis of the imine gives the by-product. Acemetacin (**24**), the glycolic acid ester of **22**,[26] was obtained in 66% yield when ester **20** was treated with equimolar AlI_3 in acetonitrile at room temperature.

Figure 4. Selective cleavage of the ester and ether C-O bonds of the *t*-butyl ester of acemetacin by AlI_3

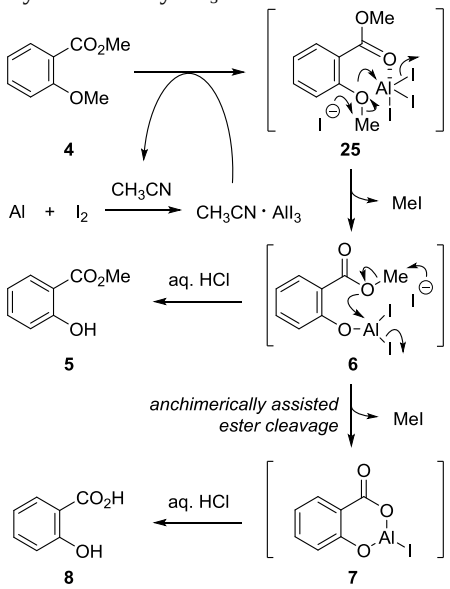


Reagents and conditions: a) AlI_3 (1.1 eq.), CH_3CN (20 mL), 80 °C, 18 h; b) AlI_3 (1.1 eq.), CH_3CN (20 mL), pyridine (4.5 eq.), 80 °C, 18 h; c) AlI_3 (1 eq.), CH_3CN (20 mL), 20 °C, 6 h.

Based on these findings, a proposed mechanism is depicted in Figure 5. The *in-situ* preparation of AlI_3 in acetonitrile gives the

Lewis acid as a complex ($CH_3CN{\cdot}AlI_3$).[27,28] Exchange of the solvent ligand by the methyl *o*-anisate (**4**) carbonyl oxygen leads to the formation of complex **25**. This complex then undergoes demethylation *via* a six-membered transition state to afford aluminum phenolate **6**. Cleavage of the ester group is also anchimerically assisted to give a six-membered cyclic intermediate (**7**). Acidification of **6** and **7** affords **5** and **8**, respectively. It should be noted that $AlCl_3$ will be deactivated in acetonitrile through similar coordination ($CH_3CN{\cdot}AlCl_3$)[27] which makes the Lewis acid unreactive for cleaving normal aryl methyl ethers.[1]

Figure 5. Proposed mechanism for the selective cleavage of methyl *o*-anisate by AlI_3



Regarding the ester preference for the reaction of *p*-anisate **10** in acetonitrile and ethyl acetate, the *p*-methoxy group remained intact due to the absence of a neighboring group participation effect, and thus methyl anisate was cleaved to afford acid **12** and eventually **13** when in the presence of excess AlI_3. Similarly, the ester group was cleaved preferentially in the competing cleavage experiment of methyl benzoate **17** and anisole **18** when treated with equimolar AlI_3. When performed in cyclohexane (Table 2, Entry 2), coordination of the ester/ether oxygen to the Lewis acidic center became non-selective, and the non-selective cleavage of the ester and ether C-O occurred, giving an equimolar mixture of phenol **11** and acid **12**. Further cleavage of **11** and **12** by AlI_3 afforded acid **13**. Since *p*-anisate **10** was non-selectively cleaved by AlI_3 in cyclohexane, the low polarity of carbon disulfide is unlikely to be a factor for the chemoselectivity in cleaving **10** (Table 2, Entry 1). Additionally, carbon disulfide has little tendency to coordinate to the Lewis acidic center.[11] Thus, the ether cleavage preference of AlI_3 in carbon disulfide remains unclear.

3. Conclusion

In summary, the mode for AlI_3 mediated ether and ester cleavage of methyl *o*-anisate is different from those of *m*-anisate and *p*-anisate. Cleavage of *o*-anisate is markedly affected by an anchimeric assistance effect and tends to afford *o*-hydroxybenzoate *via* ether cleavage. Further cleavage of the benzoate at elevated temperatures affords salicylic acid involving a second anchimeric assistance. Cleavage of *m*- or *p*-anisate, on the other hand, is more susceptible to solvents, and gave variant products in carbon disulfide, cyclohexane or acetonitrile under different conditions. The ester C-O bond is preferentially cleavage by AlI_3 in acetonitrile to afford *m*- or *p*-anisic acid. This non-hydrolytic ester cleavage transformation can be improved using pyridine as a coordination ligand to the Lewis acidic center. When in the presence of excess AlI_3, both ester and ether C-O bonds are cleaved to afford *m*- or *p*-hydroxybenzoic acid. These conditions were applied to the chemo-selective cleavage of the *t*-butyl ester of acemetacin, which gave acemetacin and indomethacin when conducted at room temperature, and *O*-desmethyl indometacin at 80 °C. The use of AlI_3-pyridine in acetonitrile (80 °C) afforded indometacin along with an unexpected ketone. Investigation of the ketone formation side-reaction is in progress and will be disclosed in due course.

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Supplementary Material

Supplementary data (experimental procedures, compound characterization data, ^1H and ^{13}C NMR spectra of **5**, **8**, **11**-**13**, **15**, **16**, **19**, **21**-**24**, HSQC and HMBC spectrum of **23**) associated with this article can be found, in the online version, at.

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Highlights

1. Selective cleavage of methyl anisates by AlI_3 is studied.

2. Cleavage of methyl *o*-anisate is anchimerically assisted.

3. Solvents affect the cleavage of methyl *m*- and *p*-anisate.

4. AlI_3-pyridine cleaves esters at mild conditions effectively.

5. Excess AlI_3 cleaves both esters and aryl methyl ethers.