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ARTICLE

Oxidative Cleavage of Allyl Ethers by an Oxoammonium Salt

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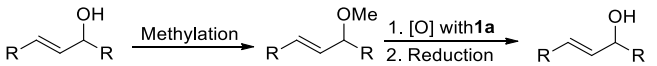
A method to oxidatively cleave allyl ethers to their corresponding aldehydes mediated by the oxoammonium salt 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (4-NHAc-TEMPO$^+$ BF_4^-, **1a**) is described. Using a biphasic solvent system and mild heating, cleavage proceeds readily, furnishing a variety of α,β-unsaturated aldehydes.

Introduction

Oxoammonium salts are recyclable, metal-free species that can allow for oxidation chemistry to be performed under extremely mild conditions.[1] Much of the literature involving oxoammonium salts centres around the conversion of alcohols to their corresponding carbonyl species.[1,2,3] A range of functional groups can be accessed using this strategy including aldehydes, ketones, and carboxylic acids.[2,3] However, their ability to facilitate non-traditional oxidation reactions (e.g. oxidative functionalisation) is of particular interest. As part of a broad program to expand the scope of oxoammonium salt-based transformations, we became interested in exploiting 4-NHAc-TEMPO$^+$ BF_4^- (Bobbitt's salt, **1a**) as a "hydride abstractor" in compounds or transient species bearing highly active C-H bonds. Specifically, we were interested in systems where we could capture the resulting oxidised species with a secondary reaction effecting a net oxidative functionalisation process. Such a strategy has been employed successfully by Garcia-Mancheño, Bailey, and by us (Fig. 1).[5-7] Bailey recently reported on the successful cleavage of benzyl ethers *via* treatment with **1a**.[6] Such a reaction is useful as a deprotection strategy for benzyl-protected alcohols.[6,8] We wondered whether allyl ethers, which bear a somewhat less reactive C-H bond, could also undergo oxidative cleavage. If successful, we envisioned that we could not only develop a route to α,β-unsaturated aldehydes but also effectively protect allyl alcohols by *simple methylation* and deprotect by oxidation and then reduction, thus furnishing a robust and unusual protecting group strategy (Scheme 1). We report our results here.



Scheme 1: Envisioned strategy for allyl ether protection and deprotection.

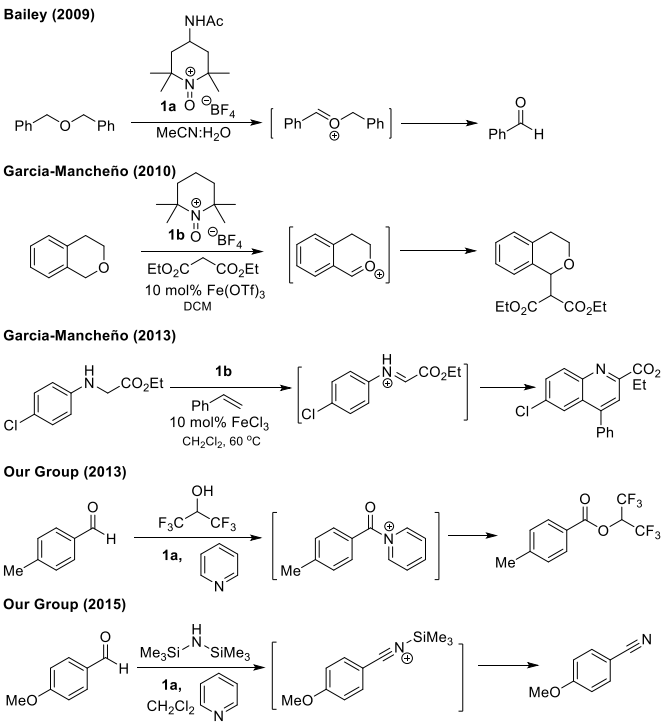
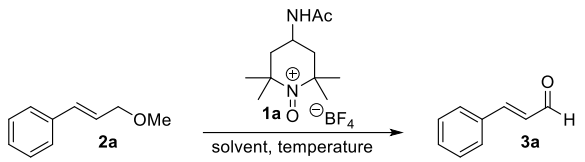


Figure 1: Oxidative functionalisation reactions using oxoammonium salts

Results and Discussion

We began our study by preparing allyl ether **2a** (*via* deprotonation of the corresponding alcohol followed by methylation with MeI) and subjecting it to a variety of conditions (Table 1). We initially screened the conditions established by Bailey for the cleavage of benzyl ethers.[6] While we obtained good conversion to the desired aldehyde, we observed significant carboxylic acid formation (Table 1, Entry 1). To minimise the formation of this over-oxidised product, we conducted a solvent screen. Knowing that the presence of water would be critical to the cleavage reaction, we screened a variety of solvent mixtures. Ether solvents (Entries 3 & 4) gave less promising results while acetone (Entry 2) gave multiple products, which could result from Aldol or Michael-like pathways. Dichloromethane gave somewhat more promising results with no observed acid formation (Entry 5). Attempts to enhance conversion by altering the CH_2Cl_2 to H_2O ratio gave only modest improvement (Entries 6 & 7) with a ratio of 8:2 CH_2Cl_2:H_2O proving optimal. We next decided to heat the reaction to 45 °C and found that the conversion could be nearly doubled (Entry 8). However, extending the reaction time failed to improve conversion (Entry 9). We decided to increase the loading of **1a** because we believed that both heating in an aqueous medium, and the methanol generated as a by-product of the reaction would consume some of the oxidant.[9] Using 2.1 equiv of **1a** and extending the reaction time to 12 h, we obtained complete conversion to the desired aldehyde **3a** (Entry 10). Isolation of the resulting aldehyde proved simple, giving an excellent yield of **3a**.

Table 1 Optimisation of reaction conditions for the oxidative cleavage of allyl ethers[a]

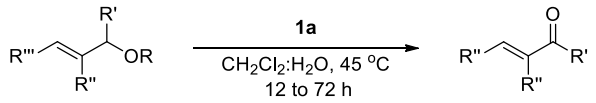


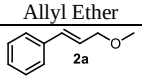
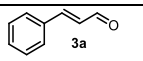
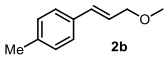
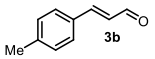
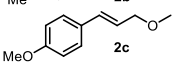
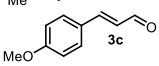
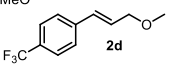
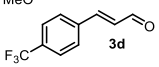
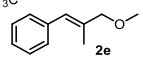
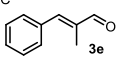
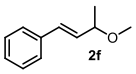
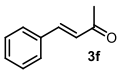
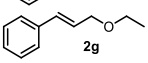
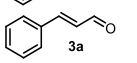
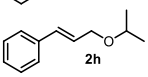
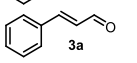
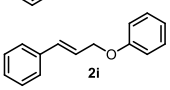
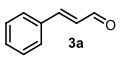
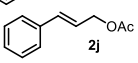
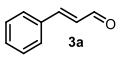
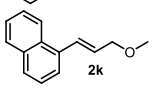
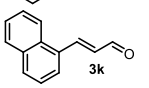
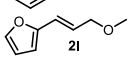
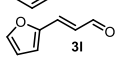
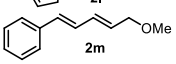
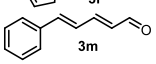
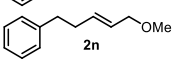
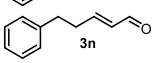
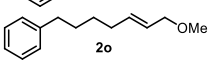
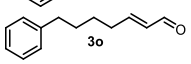
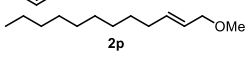
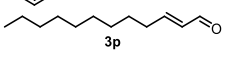
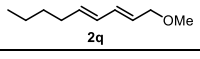
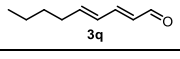
Entry	Solvent[b]	Temp. (°C)	**1a** (eq.)	Time (h)	**3a** (%)[c]
1	MeCN: H_2O (9:1)	rt	1.1	2	84
2	Acetone:H_2O (9:1)	rt	1.1	2	-
3	THF:H_2O (9:1)	rt	1.1	2	17
4	Et_2O:H_2O (9:1)	rt	1.1	2	Trace
5	CH_2Cl_2: H_2O (9:1)	rt	1.1	2	28
6	CH_2Cl_2: H_2O (9:1)	rt	1.1	2	35
7	CH_2Cl_2: H_2O (9:1)	rt	1.1	2	32
8	CH_2Cl_2: H_2O (9:1)	45	1.1	2	68
9	CH_2Cl_2: H_2O (9:1)	45	1.1	4	66
10	CH_2Cl_2: H_2O (9:1)	45	2.1	12	100 (93)

[a] Conditions unless otherwise noted: **2a** (0.5 mmol, 1 equiv), solvent (2.5 mL). [b] Solvent ratios are by volume. [c] Values in parentheses indicate isolated yields, all other values are percent conversions by ^{1}HNMR spectroscopy.

We next turned our attention to examining the substrate scope of this oxidative cleavage process. The results are shown in Table 2. Initially, we elected to screen various cinnamyl analogues because they would be sterically similar to **2a** (Entries1-4). Electronic changes to this extended π-system generally had little to no effect on reaction yield. The exception to this was **2c** (Entry 3) which gave only a moderate yield of **3c**. Variance in the electronic nature of these substrates did have a marked effect on reaction rate with **2d** requiring 72 h and additional loadings of **1a** to reach complete conversion. We next introduced steric hindrance at and nearby the reactive methylene group (Entries 5 & 6). This did not impede oxidation and we obtained near quantitative yields of the corresponding aldehydes. Steric hindrance did, however, retard the rate of the reaction similarly to **2d**. We next explored whether other alkyl groups could serve as suitable replacements for the methyl ether group (Entries 7-9). Both isopropyl and ethyl functionalities could be used successfully without compromising yield or reaction rate. A phenyl ether failed, likely due to electron density delocalisation into the aromatic system thereby raising the activation barrier for oxidation. This delocalisation concept was further evidenced by the failure of the ester **2j** to oxidise (Entry 10). Since preparation of both the ethyl and isopropyl ethers proved more difficult than our standard methylation approach, we elected to continue exploring methylated substrates exclusively.

Table 2 Scope of the methodology for oxidative cleavage of allyl ethers [a]



Entry	Allyl Ether	Product	Yield (%)[b]
1			93
2			79
3			54
4[c]			90
5[c]			99
6[d]			91
7			93
8			88
9			-
10			-
11			90
12			14
13			89
14[e]			72
15[f]			86
16[g]			73
17			83

[a] Conditions: allyl ether (10 mmol, 1 equiv), **1a** (21 mmol, 2.1 equiv), CH_2Cl_2 (40 mL), H_2O (10 mL). [b] Isolated yield. [c] 3.3 equiv of **1a** were used over the course of the reaction [d] 2.9 equiv of **1a** were used over the course of the reaction [e] 2.5 equiv of **1a** were used over the course of the reaction [f] 3.7 equiv of **1a** were used over the course of the reaction [g] 3.1 equiv of **1a** were used over the course of the reaction

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A representative polycyclic example (Entry 11) proved amenable to oxidative cleavage, but a heterocycle-containing system (Entry 12) gave markedly diminished yield, due to polymerisation. Extended conjugation did not pose a problem and gave excellent yield of the desired aldehyde (Entry 13).

The success of cleavage does not necessitate conjugation into an aromatic system. Distancing the aryl ring from the olefin had little effect on the success or the yield of the oxidative cleavage (Entries 14 & 15). Furthermore, reactivity was unaffected by complete removal of the ring (Entry 16). These systems (Entries 14-16) did require longer reaction times, likely due to the diminished stabilisation of the intermediate oxonium ion. A non-aryl substituted diene retained reactivity towards oxidative cleavage in both yield and reaction rate, thus supporting this assertion (Entry 17).

A plausible mechanism for the oxidative cleavage is given in Fig. 2. We suggest that the key step in the mechanism is the transfer of a hydride from the allyl ether to the electrophilic oxygen of the oxoammonium cation. Subsequent hydration of the resulting oxonium ion yields a hemiacetal. The equilibrium of this species favours the keto-form, leading to the formation of the desired aldehyde.[10] Such a mechanism is consistent with the mechanism proposed by Bailey for the oxidative cleavage of benzyl ethers.[6,11]

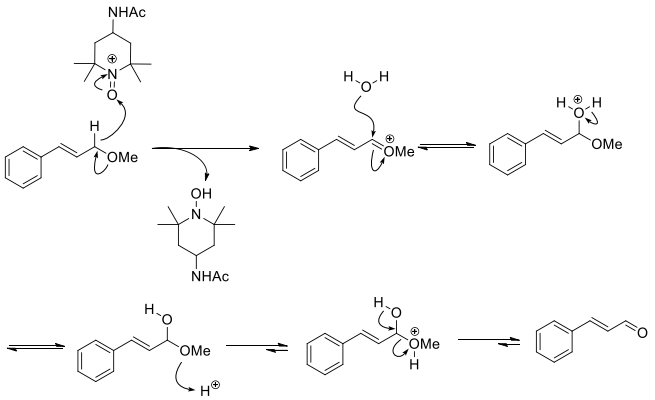
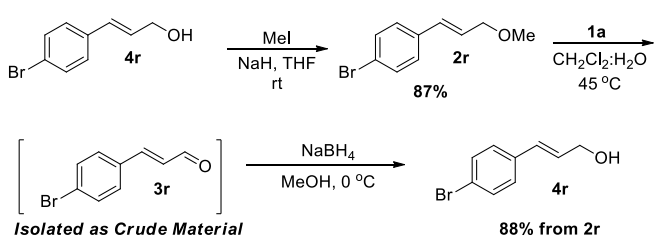


Figure 2: Plausible reaction mechanism.

Given this mechanism, we suggest that the biphasic reaction conditions are critical to efficacious and selective formation of the aldehyde.[12] Due to the limited solubility of **1a** in dichloromethane, only a small amount of the active oxidant is available at any given time. This deters indiscriminate oxidation (e.g. over-oxidation to the corresponding carboxylic acid). In addition, the organic layer serves to protect the resulting aldehyde from hydration as only a minimal amount of water would be present. Finally, the methanol produced during the course of cleavage would enter the aqueous phase, potentially driving the equilibrium forward.



Scheme 2: Protection and deprotection sequence of an allyl alcohol.

To conclude our study, we subjected a representative allyl alcohol to our posited protection/deprotection strategy to assess its viability from the standpoint of simplicity and yield. We were pleased to find that we could readily protect and deprotect **4r** in good yield over the three chemical steps. Indeed the intermediate aldehyde (in this case **3r**) need not be purified; the crude aldehyde can be carried directly into the reduction step. These high yielding steps therefore validate this approach as a plausible protecting group strategy.

Conclusions

In summary, we describe a mild, facile approach to the oxidative cleavage of allyl ethers to their corresponding aldehydes mediated by an oxoammonium cation. The reaction is compatible with a variety of allyl ethers, both those with extended conjugation and those without. The suggested mechanism hinges on a hydride transfer from the reactive methylene of the allyl ether. Hydrolysis of the intermediate oxonium ion yields the desired aldehyde.

Experimental section

Representative Procedure for Oxidative Cleavage: Synthesis of Cinnamaldehyde (3a)

To a 100 mL round bottom flask equipped with a stir bar was added **2a** (1.48 g, 0.010 mol, 1 equiv). CH_2Cl_2 (40 mL), and deionized water (10 mL). After stirring for five minutes, the oxoammonium salt **1a** (6.302 g, 0.021 mol, 2.1 equiv) was added to the flask and the flask was equipped with a reflux condenser. The flask was heated to 45 °C and allowed to stir overnight. The reaction mixture gradually became orange during this time. Reaction progress was monitored by ^{1}H NMR spectroscopy. After 12 h the reaction was judged to be complete. At this time the reaction mixture was cooled to room temperature and transferred to a separatory funnel. The mixture was diluted with deionized water (100 mL) and Et_2O (150 mL) the layers were separated. The aqueous layer was extracted with Et_2O (5 × 50 mL). The combined organic layers were washed with deionized water (2 × 100 mL) and brine (150 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed in vacuo by rotary evaporation to give the crude aldehyde. Further purification was accomplished by SiO_2 plug (95:5 Hex:EtOAc to 90:10 Hex:EtOAc), giving the pure aldehyde (1.23 g, 93%) as clear, pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 6.75 (dd, J=15.97, 7.71 Hz, 1 H) 7.43 - 7.50 (m, 3 H) 7.52 - 7.64 (m, 3 H) 9.74 (d, J=7.68 Hz, 1 H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 128.66 (CH) 128.76 (CH) 129.27 (CH) 131.43 (CH) 134.18 (C) 152.89 (CH) 193.80 (C) GC-MS (EI) 132 ([M]+, 58%) 131 (100%) 103 (62%) 77 (51%) 63 (12%) 51 (38%).

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Notes and references

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† Electronic supplementary information (ESI) available: Experimental details, characterization of substrate precursors/substrates/products, and copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra. See DOI: 10.1039/b000000x/

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