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Tandem Oxidation/Halogenation of Aryl Allylic Alcohols under Moffatt−Swern Conditions

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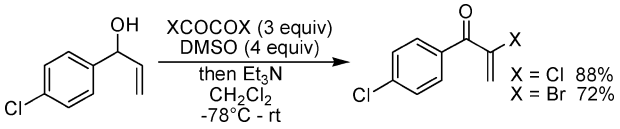
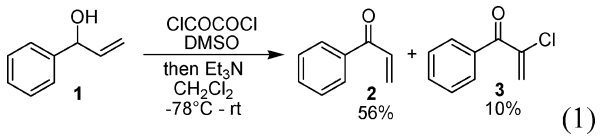


Aryl allylic alcohols are converted to halogenated unsaturated ketones or allylic halides using excess Moffatt−Swern reagent. Electron-poor aromatic rings favor formation of the halogenated ketone, while electron-donating substituents in the *ortho* or *para* positions favor formation of the allylic halide. The oxidation/halogenation reaction performs well with both oxalyl chloride and oxalyl bromide, providing access to the corresponding chlorides or bromides, respectively.

Tandem reactions play an increasingly important role in synthetic organic chemistry. With highly complex structures available using stepwise synthetic methods, attention has become focused on ways to increase efficiency, decrease costs, and minimize environmental impact. With their ability to perform multiple transformations in a single operation, tandem reactions improve efficiency by using less solvent and decreasing the number of necessary purification steps. In turn this leads to decreased costs with regard to chromatography absorbents, manpower, and waste disposal. Demand for more efficient and lower cost chemical processes has resulted in the increased development of tandem reactions for chemical synthesis in recent years.[1,2]

Investigations in our laboratory have revealed an unusual tandem oxidation/halogenation reaction that occurs under Moffatt−Swern oxidation conditions. An unrelated project in our group required the use of phenyl vinyl ketone (**2**). This compound is not commercially available because of its propensity to polymerize. Oxidation of commercially available α-vinylbenzyl alcohol (**1**) was performed using Moffatt−Swern conditions[3] to provide ketone **2** for our purposes. While ketone **2** was obtained as the major product, a modest amount of the corresponding α-chloro ketone **3** was also detected.

The Moffatt−Swern oxidation usually proceeds in high yield with no side reactions; however, some substrates have been shown to be problematic.[4] Activated alcohols sometimes undergo substitution by chloride ion to provide the corresponding alkyl chloride instead of the ketone.[5−8] This mode of reactivity can also be accessed by performing the reaction at higher temperatures. Chlorination of indoles[9] and aromatic rings[10] has also been reported in the presence of dimethylchlorosulfonium chloride, the active reagent in the Moffatt−Swern oxidation. Further, the use of excess reagent may result in the formation of α-chloro ketones in some systems.[11] Such halogenation has not previously been observed with any unsaturated ketones.



(1)

The direct, one-pot conversion of allylic alcohol **1** to α-chloro enone **3** results in a rapid increase of molecular complexity in a single flask under mild reaction conditions. Adventitiously this route allows for the formation of the α-halo ketone in a single step from a stable starting material, unlike direct halogenation of highly polymerizable ketone **2**[12] or methylenation of the hydrolytically sensitive α-halo ketone.[13] The halogenated enone product possesses multiple functional groups that may be elaborated in a variety of ways (1,2-addition, 1,4-addition, transition-metal-mediated coupling, etc.). Access to similar α-halogenated enones allows for exploration of their use in a number of synthetic projects involving natural products and diversity-oriented synthesis.[14] A study was therefore undertaken to define reaction conditions that favor the formation of α-chloro α,*β*-unsaturated ketone **3**.

Treatment of allylic alcohol **1** under Moffatt−Swern conditions using 1 equiv of oxalyl chloride and 2 equiv of DMSO provided ketone **2** in 56% yield along with a 10% yield of halogenated ketone **3** (Table 1, entry 1). Increasing the amount of oxalyl chloride and DMSO used in the reaction increased the amount of halogenated ketone isolated from the reaction (entries 2−4). No ketone oxidation products were detected in the absence of DMSO (entry 5); instead, a complex mixture was obtained. Typically the reactions were allowed to warm to room temperature after addition of the triethylamine (the final

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(14) For an example of heterocycle formation using halo ketones such as **3** see: Henry, N.; Sanchez, I.; Sabatie, A.; Beneteau, V.; Guillaumet, G.; Pujol, M. D. *Tetrahedron* **2006**, *62*, 2405.

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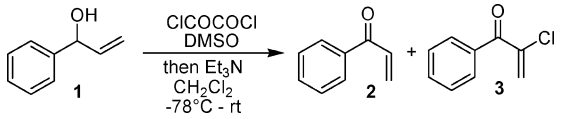
TABLE 1. Optimization of the Oxidation/Halogenation Reaction

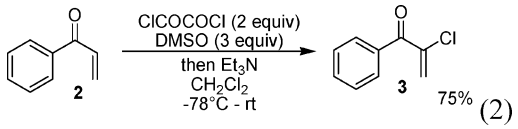


entry	ClCOCOCl amt (equiv)	DMSO amt (equiv)	yield of **2** (%)	yield of **3** (%)
1	1	2	56	10
2	2	2	34	55
3	2	3	10	78
4	3	4	6	81
5	2	0	0	0
6[a]	3	4	24	61
7[b]	1	2	78	7

[a] The Et_3N was precooled to −78 °C before addition, and the reaction was quenched at −78 °C with MeOH/H_2O after 1 h. [b] One equivalent of $BnEt_3NCl$ was added.

step of the reaction sequence; see the Experimental Section for details). To determine the effect of temperature on the oxidation/halogenation, precooled triethylamine was added and the reaction quenched at −78 °C with methanol. Though the reaction proceeds more slowly, both halogenation and oxidation occur at −78 °C (entry 6). Addition of an exogenous chloride source was also explored to see whether this would lead to more chlorinated product, but this had little effect on the reaction (entry 7).

The results in Table 1 suggest that phenyl vinyl ketone (**2**) is an intermediate on the reaction pathway to **3**. This hypothesis is supported by the observation that at no time was any halogenated allylic alcohol detected as a product from these reactions. Further support was provided by treatment of ketone **2** under Moffatt−Swern conditions, which provided halogenated ketone **3** in 75% yield (eq 2).



(2)

With clear evidence that vinyl ketone **2** is an intermediate, a mechanism for the reaction is shown in Figure 1. First, the alcohol is oxidized to the ketone. The excess dimethylsulfonium chloride then reacts with ketone **2**, forming a chloronium ion, which is opened by chloride ion to provide dichloride **5**. Base-induced elimination of the dichloride then provides ketone **3**.[15] This mechanism is consistent with previous studies on electrophilic chlorination of unsaturated ketones, which takes place in the presence of an acid scavenger such as triethylamine.[16] The second possibility of an addition/elimination mechanism initiated by conjugate addition of chloride ion has been ruled out for simple unsaturated ketones when pyridine and chlorine gas are

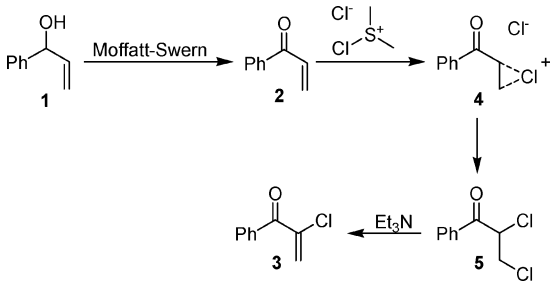


FIGURE 1. Proposed mechanism of the tandem oxidation/halogenation reaction.

used in the halogenation,[16] but cannot be completely excluded as the conditions used in this transformation are quite different.[17]

With conditions in hand that provide α-chloro ketone **3** selectively and in good yield, the generality of the tandem oxidation/halogenation reaction was examined with respect to substituents on the aromatic ring. Electron-withdrawing groups in the *meta* and *para* positions of the aromatic ring were well tolerated, providing good yields of the chlorinated ketones (Table 2, entries 2−6). Conversely, substrates with electron-withdrawing groups in the *ortho* position gave only trace amounts of product (entries 7 and 8), the balance of the material being made up of a complex mixture. No nonhalogenated ketone product could be detected in this mixture. Steric effects may slow the oxidation of the more hindered allylic alcohols in **25** and **28**, leading to the decreased yields of the product. While unfunctionalized and electron-poor substrates provide α-chloro α,*β*-unsaturated ketones, the presence of an electron-donating group on the aromatic ring can completely change the course of the reaction. For example, the presence of a methoxy substituent at the *meta* position results in the expected halogenated ketone **29**, while a methoxy group in the *ortho* or *para* position instead results in formation of the allylic chloride (entries 10 and 11).[18]

The formation of allylic chlorides **32** and **35** is difficult to explain from the corresponding ketone, as a reduction would have to take place under oxidative conditions. While dimethylchlorosulfonium chloride has been used to transform allylic alcohols to allylic chlorides,[19,20] typically only oxidation products are seen when triethylamine is added at low temperature.[7] Formation of the allylic chloride can be explained by interruption of the Moffatt−Swern oxidation by carbocation formation after activation of the alcohol (Figure 2). Addition of chloride ion to the cation provides the allylic chloride. The divergence of reactivity among allylic alcohols **32**, **35**, and **1** may be explained by carbocation formation only when a strong electron-donating group is present at the *ortho* or *para* position of the aromatic ring, which can stabilize the resulting carbocation.

Preparation of the corresponding bromides was also explored, as bromides are often of greater utility in metal-catalyzed cross-

(15) Exposure of ketone **2** to the reaction conditions without addition of triethylamine produced 3-chloro-1-phenyl-1-propanone in high yield. This is consistent with literature reports on the reaction of ketone **2** with HCl; see: Heasley, V. L.; Shellhamer, D. F.; Carter, T. L.; Gipe, D. E.; Gipe, R. K.; Green, R. C.; Nordeen, J.; Rempel, T. D.; Spaite, D. W. *Tetrahedron Lett.* **1981**, *22*, 2467. Triethylamine functions as a HCl scavenger as well as a base for elimination of the dichloride.

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(17) The intermediacy of an α-chloro-*β*-dimethylsulfonium carbonyl compound was also considered, but given its slow rate of formation in nonpolar solvents such as methylene chloride, this hypothesis was discarded. See ref 12 for a discussion on the rate of formation of similar intermediates.

(18) Reaction of 1-(4-tolyl)-2-propen-1-ol with oxalyl chloride, DMSO, and Et_3N also gave the corresponding allylic chloride product (1-[(1*E*)-3-chloro-1-propenyl]-4-methylbenzene) in 75% yield.

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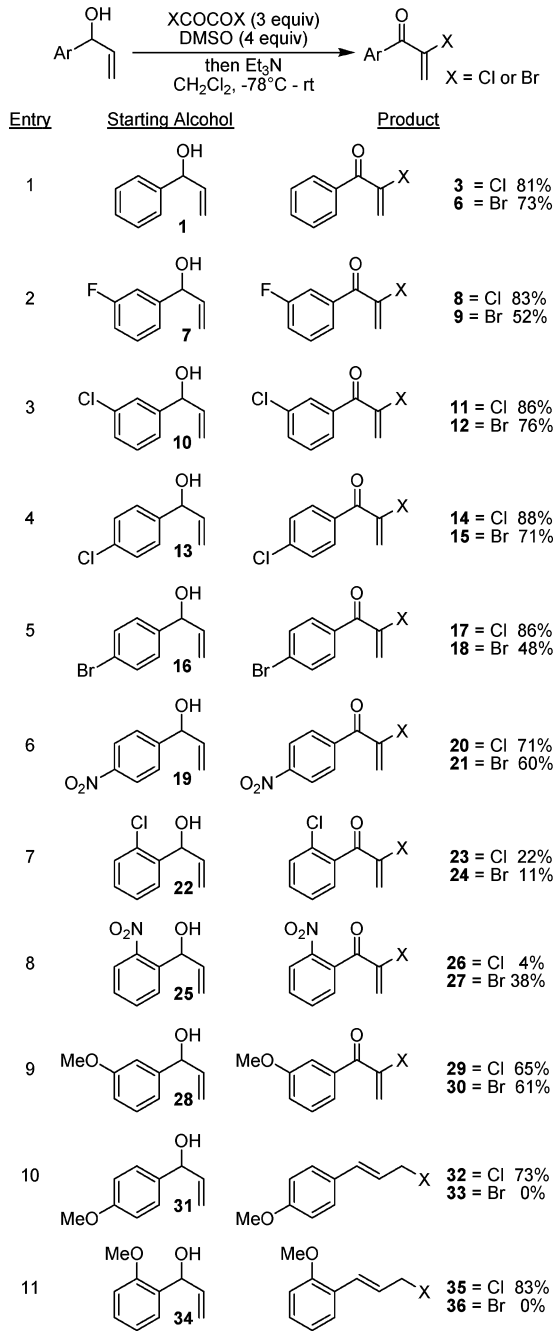
TABLE 2. Formation of α-Halo Unsaturated Ketones from Allylic Alcohols



coupling reactions. Use of oxalyl bromide instead of oxalyl chloride provided the corresponding α-bromo α,β-unsaturated ketones in good yields. Attempting to form the corresponding allylic bromide from allylic alcohols **31** and **34** using the more reactive oxalyl bromide was unsuccessful. The presence of a nucleophilic aromatic ring and a highly electrophilic allylic bromide led to the formation of numerous polymeric products instead.

The use of alkyl allylic alcohols under the oxidation/halogenation conditions provided only the α,β-unsaturated ketone with no incorporation of the halogen (Scheme 1). The presence of an aryl group vicinal to the ketone appears to be

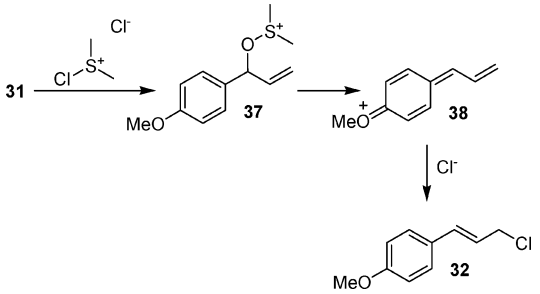
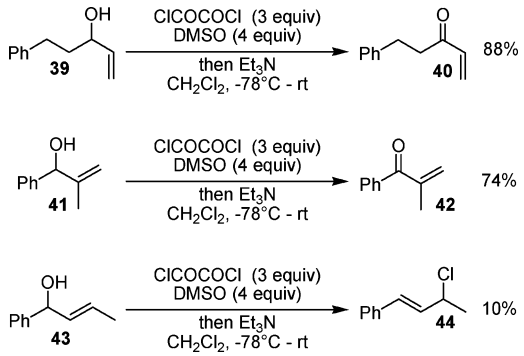


FIGURE 2. Mechanism of allylic chloride formation.

SCHEME 1



required for the tandem reaction, with the aromatic ring increasing the reactivity of the alkene toward halogenation. Introduction of a substituent on the alkene also impedes the course of the oxidation/halogenation reaction. Substitution at the α position of the alkene effectively stops the halogenation reaction due to sterics, producing ketone **42** with no trace of the dichloride. Substituents at the β position favor substitution by chloride ion as they help stabilize carbocation intermediates. For example, reaction of allylic alcohol **43** provided a mixture of products which did not include the halogenated or unhalogenated ketone. A small amount of allylic chloride **44** was isolated from this mixture.

In summary, we report a tandem oxidation/halogenation sequence for aryl allylic alcohols using excess Moffatt−Swern reagent. The reaction provides α-halo α,β-unsaturated ketones in a single step from their corresponding aryl allylic alcohols. Electron-withdrawing groups are tolerated at the *ortho* and *para* positions of the aromatic ring, and electron-donating substituents are tolerated at the *meta* positions. Both α-chloro enones and α-bromo enones can be accessed by using the appropriate activating agent for DMSO, providing highly functionalized substrates for use in further synthetic manipulations. Care should be taken in planning the oxidation of highly activated allylic alcohols under Moffatt−Swern conditions, as the formation of several side products can result.

Experimental Section

2-Chloro-1-phenyl-2-propen-1-one (3). A flame-dried flask was charged with dry CH_2Cl_2 (8 mL) and cooled to −78 °C with a dry ice/acetone bath. Oxalyl chloride (364 μL, 4.17 mmol) was then added followed by DMSO (0.394 μL, 5.55 mmol). The reaction was kept at −78 °C for 15 min, after which time α-vinylbenzyl alcohol (**1**) (186 mg, 1.39 mmol, dissolved in 3 mL of dry CH_2Cl_2) was added. The reaction was kept at −78 °C for 1 h, after which time triethylamine (1.16 mL, 8.33 mmol) was added and the reaction allowed to warm to room temperature over 30 min.

The reaction mixture was then poured over ice-cold 1 M HCl and extracted with hexanes. The combined extracts were dried (Na_2SO_4) and concentrated. Purification of the residue by silica gel chromatography (10% ethyl acetate/hexanes) gave **3**[21] (190 mg, 81% yield) as a yellow oil accompanied by phenyl vinyl ketone (**2**)[22] (12 mg, 6% yield).

2-Chloro-1-(4-chlorophenyl)prop-2-en-1-one (14). A flame-dried flask was charged with dry CH_2Cl_2 (8 mL) and cooled to −78 °C with a dry ice/acetone bath. Oxalyl chloride (292 μL, 3.35 mmol) was then added followed by DMSO (317 μL, 4.46 mmol). The reaction was kept at −78 °C for 15 min, after which time allylic alcohol **13** (188 mg, 1.11 mmol, dissolved in 3 mL of dry CH_2Cl_2) was added. The reaction was kept at −78 °C for 1 h, after which time triethylamine (0.93 mL, 6.68 mmol) was added and the reaction allowed to warm to room temperature over 30 min. The reaction mixture was then poured over ice-cold 1 M HCl and extracted with hexanes. The combined extracts were dried (Na_2SO_4) and concentrated. Purification of the residue by silica gel chromatography (10% ethyl acetate/hexanes) gave **14** (200 mg, 88% yield) as a thick yellow oil: TLC $R_f = 0.49$ (10% ethyl acetate/hexanes); IR (film from CH_2Cl_2) 3116, 1677, 1588, 1486, 1401 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, $J = 9.3$ Hz, 2H), 7.45 (d, $J = 9.0$, 2H), 6.28 (d, $J = 2.1$ Hz, 1H), 6.08 (d, $J = 2.1$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.7, 139.9, 138.3, 134.0, 131.1, 129.0, 126.4. Anal. Calcd for $C_9H_6Cl_2O$: C, 53.77; H, 3.01. Found: C, 53.50; H, 3.01.

2-Bromo-1-(4-chlorophenyl)prop-2-en-1-one (15). A flame-dried flask was charged with dry CH_2Cl_2 (8 mL) and cooled to −78 °C with a dry ice/acetone bath. Oxalyl bromide (297 μL, 3.15 mmol) was then added followed by DMSO (0.299 μL, 4.20 mmol). The reaction was kept at −78 °C for 15 min, after which time allylic alcohol **13** (177 mg, 1.05 mmol, dissolved in 3 mL of dry CH_2Cl_2) was added. The reaction was kept at −78 °C for 1 h, after which time triethylamine (0.88 mL, 6.30 mmol) was added and the reaction allowed to warm to room temperature over 30 min. The reaction mixture was then poured over ice-cold 1 M HCl and extracted with hexanes. The combined extracts were dried (Na_2SO_4) and concentrated. Purification of the residue by silica gel chromatography (10% ethyl acetate/hexanes) gave **15** (184 mg, 71% yield) as a thick yellow oil: TLC $R_f = 0.47$ (10% ethyl acetate/hexanes); IR (film from CH_2Cl_2) 3103, 1673, 1589, 1486, 1401, 1387 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, $J = 8.7$, 2H), 7.46 (d, $J = 8.4$ Hz, 2H), 6.52 (d, $J = 2.4$ Hz, 1H), 6.44 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.2, 140.0, 133.5, 131.4, 130.2, 129.1 (only six resonances are seen in ^{13}C NMR due to overlapping signals). Anal. Calcd for C_9H_6BrClO: C, 44.03; H, 2.46. Found: C, 44.12; H, 2.30.

(*E*)-1-(3-Chloroprop-1-enyl)-2-methoxybenzene (35). A flame-dried flask was charged with dry CH_2Cl_2 (8 mL) and cooled to −78 °C with a dry ice/acetone bath. Oxalyl chloride (287 μL, 3.30 mmol) was then added followed by DMSO (304 μL, 4.40 mmol). The reaction was kept at −78 °C for 15 min, after which time allylic alcohol **13** (180 mg, 1.10 mmol, dissolved in 3 mL of dry CH_2Cl_2) was added. The reaction was kept at −78 °C for 1 h, after which time triethylamine (0.92 mL, 6.60 mmol) was added and the reaction allowed to warm to room temperature over 30 min. The reaction mixture was then poured over ice-cold 1 M HCl and extracted with hexanes. The combined extracts were dried (Na_2SO_4) and concentrated. Purification of the residue by silica gel chromatography (10% ethyl acetate/hexanes) gave **35** (167 mg, 83% yield) as a yellow oil: TLC $R_f = 0.11$ (10% ethyl acetate/hexanes); IR (film from CH_2Cl_2) 3002, 2957, 2837, 1676 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (dd, $J = 7.8$, 1.8 Hz, 1H), 7.23 (m, 1H), 6.96 (d, $J = 16.5$ Hz, 1H), 6.88 (m, 2H), 6.33 (dt, $J = 15.9$, 7.5 Hz, 1H), 4.23 (dd, $J = 7.5$, 1.2 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 129.5, 129.3, 127.4, 125.7, 125.0, 120.8, 111.0, 55.6, 46.3. Anal. Calcd for $C_{10}H_{11}ClO$: C, 65.76; H, 6.07. Found: C, 65.84; H, 6.15.

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Supporting Information Available: Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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