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Vanadium(V)-mediated rearrangement/halogenation cascade: Synthesis of α-haloenones from propargyl alcohols

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ABSTRACT

A method is described for the oxidative Meyer–Schuster-type rearrangement of propargylic alcohols to (*Z*)-α-chloro- and α-iodoenones using $VOCl_3$ as a multifunctional reagent. The vanadium reagent is found to serve as rearrangement promoter as well as an active chlorenium ion donor. Yields are improved when $VOCl_3$ is employed in conjunction with *N*-halosuccinimide reagents, giving some insights into the complex mechanism.

1. Introduction

The synthetic utility of α-haloenones has been widely recognized particularly as electrophilic partners in transition metal-mediated cross-coupling reactions.[1] The α-iodoenone substructure is most commonly used in this role, and is classically produced from the corresponding enone with an electrophilic I source in the presence of tertiary amines.[2] Protocols for preparing the corresponding α-chloroenones are considerably less common.[3] The α-haloenone moiety is also present in several bioactive molecules[4] and natural products.[5] A particularly notable example is a derivative of the natural product englerin A that exhibits increased inhibitory potency versus renal cancer cell growth and differs from the natural compound only by the presence of a Cl atom in place of a H on the cinnamate sidechain (Fig. 1).[4c] Together these features attest to the importance of halogenated compounds in chemical synthesis, natural products chemistry, and medicine.

Vanadium complexes exhibit diverse reactivity in multiple manifolds,[6] including those that facilitate C–halogen bond formation,[7] although the exact role of V in these specific cases is not well-established. The multiple stable oxidation states of V lead to a rich array of redox chemistry, and V(II), V(III), V(IV), and V(V) complexes are commercially available. The reactivity of these reagents is frequently facilitated by the electrophilicity of V itself in higher oxidation states and such V complexes are particularly valuable in cascade reactions involving oxidative steps.[8] Of particular interest are highly efficient allylic oxygen transposition reactions, such as the Meyer–Schuster rearrangement,[9] that are facilitated by V(V) complexes, although these do not typically involve oxidation events.[10] The relatively low cost of versatile precursors such as $VOCl_3$ ($39 for 100 g, Strem Chemicals) adds to the practicality of V-based synthetic methods.

Propargylic alcohols are attractive synthetic intermediates since they are readily available through addition of metallated alkynes to carbonyl compounds. The versatility of these systems is evident in Meyer–Schuster-type rearrangement reactions (Scheme 1),[9] wherein an internal redox isomerization transforms the alcohol into a conjugated carbonyl product.[11] From a synthetic perspective, the sequence of alkynylation of carbonyl compounds followed by rearrangement achieves a regiocontrolled C–C coupling that may be challenging through alternative means such as aldol condensation. In addition, the presumed intermediacy of a nucleophilic allenol or allenolate intermediate has piqued recent interest in developing this transformation for the synthesis of α-substituted enones.[11] Included in this set are some methods for the formation of α-bromo- and α-iodoenones.[12,13] However, means of synthesizing the chloroenone congeners through these strategies are absent from these reports. These methods are nonetheless an important

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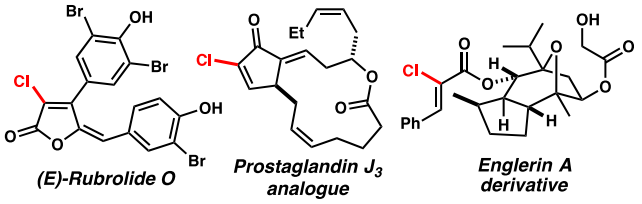
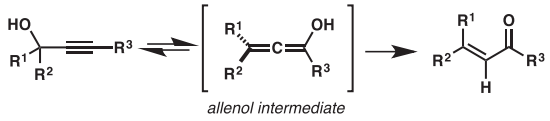


Fig. 1. Bioactive α-chloroenone compounds.

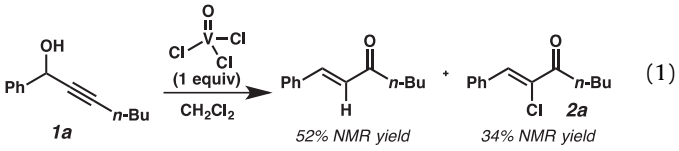


Scheme 1. The Meyer–Schuster rearrangement.

component of the growing family of transition metal-mediated redox isomerization/halogenation cascade reactions.[14] Although several of these Meyer–Schuster variants require the use of strong oxidants such as Cr(VI) salts or hypervalent iodine reagents or strong Brønsted acids such as HI,[12] recent progress has been made through transition metal catalysis or the use of alkoxyalkynes which avoid these harsh conditions.[13] Given our ongoing interests in novel halogenation protocols[15] and remote functionalization reactions,[16] we sought to investigate rearrangement cascades that might expand on the scope of this strategy and impact synthetic design while providing inroads toward the synthesis of useful α-chloroenones. Herein, we report the development of a protocol for synthesis of α-chloroenones from propargylic alcohols using an inexpensive V(V) complex that serves multiple roles including rearrangement promoter and halogen donor.

2. Results and discussion

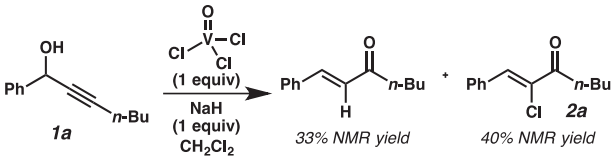
Our initial discovery occurred when we observed an unexpected product when attempting a rearrangement/aldol cascade reaction mediated by $VOCl_3$ instead of a more typical vanadyl ester reagent.[10] Under these conditions the aldol product was not observed and spectral data indicated that a significant proportion of the product mixture had incorporated a Cl atom (Eq. (1)). Another unanticipated finding was that the Cl was



(1)

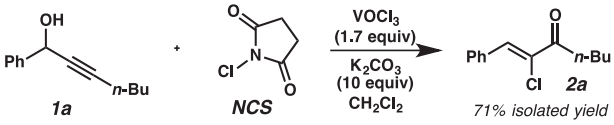
introduced at the α-carbon of the enone moiety, suggesting that $VOCl_3$ had behaved as a source of *electrophilic* Cl. In addition, only the *Z*-chloroenone was observed suggesting a significant stereocontrol effect.[17] Halogenation protocols using V(V) complexes as oxidants with halide salts have been reported, but frequently these involve halide anions or the formation of an electrophilic halenium donor through oxidation of halide anions.[7] In one instance a similar α-chloroenone side product was observed in very small quantities by Carrillo-Hermosilla and García-Álvarez and co-workers,[10i] but to our knowledge neither the direct reactivity of $VOCl_3$ as a halenium donor nor the optimization of the chlorination pathway in V-mediated Meyer–Schuster rearrangement has been reported. Control experiments indicated that $VOCl_3$ is not capable of chlorinating enone systems under our reaction conditions (*vide infra*), suggesting that an intermediate along the reaction pathway, perhaps the putative allenolate nucleophile, is responsible for the observed reactivity.

Seeking to improve the selectivity for the halogenative transformation, we considered the addition of a stoichiometric base to mitigate the formation of HCl which might serve as a competing electrophile for a putative allenolate intermediate. Pretreatment of the alcohol with NaH (1 equiv) did indeed reduce the quantity of protonated product, but the yield of the halogenated material increased only modestly (Eq. (2)). To



(2)

address this issue, we examined addition of an exogenous halogen source which could compete with a presumed intermolecular protonation event, serve to activate the putative V-based Cl^+ source, or potentially regenerate a V(V) complex if the metal were reduced. Indeed, addition of *N*-chlorosuccinimide (NCS) significantly improved yield under similar conditions (Eq. (3)). Notably the transformation with NCS as an additive does not

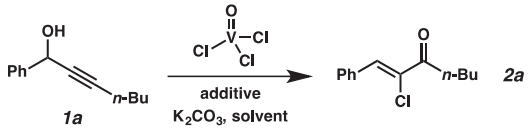


(3)

proceed in the absence of $VOCl_3$. With these results in hand, we embarked upon a detailed optimization of reaction parameters to develop a synthetically useful protocol.

We first investigated the quantity of $VOCl_3$ in the presence of NCS (Table 1, entries 2–5).[18] Presumably a greater concentration of $VOCl_3$ would force material through the postulated V-based

Table 1
Optimization of reaction conditions.[a]



Entry	Equiv $VOCl_3$	Additive (equiv)	Solvent	% yield of **2a**
1[b]	1.0	none	CH_2Cl_2	34
2	0.6	NCS (2.0)	CH_2Cl_2	34
3	1.7	NCS (2.0)	CH_2Cl_2	71
4	2.5	NCS (2.0)	CH_2Cl_2	74
5	3.1	NCS (2.0)	CH_2Cl_2	75
6	3.1	NCS (2.0)	DCE	65
7	3.1	NCS (2.0)	PhMe	44
8	3.1	NCS (2.0)	MeCN	22
9	3.1	NCS (2.0)	THF	38
10	3.1	NCS (2.0)	1,4-dioxane	14
11	3.1	NCS (0.5)	CH_2Cl_2	57
12	3.1	NCS (0.75)	CH_2Cl_2	63
13	3.1	NCS (1.0)	CH_2Cl_2	59
14	3.1	NCS (1.5)	CH_2Cl_2	65
15	3.1	NCS (3.0)	CH_2Cl_2	58
16	3.1	NCS (4.0)	CH_2Cl_2	50
17	3.1	Chloramine T (2.0)	CH_2Cl_2	23
18	3.1	DCDMH (2.0)	CH_2Cl_2	50
19	3.1	DCDMH (1.0)	CH_2Cl_2	58
20	3.1	SO_2Cl_2 (2.0)	CH_2Cl_2	38

[a] NMR yield from reaction of 0.3 mmol of substrate **1a**, $VOCl_3$, additive, and 10 equiv of K_2CO_3, in CH_2Cl_2 (0.1 M in **1a**) at 22 °C for 8 h.
[b] Reaction with no K_2CO_3 added.