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Scalable procedure for the fragmentation of hydroperoxides mediated by copper and iron tetrafluoroborate salts†

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Abstract

An improved protocol for the formal elimination of propene from organic substrates is reported. This process entails the ozonolytic conversion of an alkene to a methoxy hydroperoxide which undergoes fragmentation mediated by copper and iron. The use of soluble $\text{Cu}(\text{BF}_4)_2$ and $\text{Fe}(\text{BF}_4)_2$ results in reproducible results up to a 100 gram scale.

Introduction

The scalable synthesis of simple building block molecules can be a bottleneck in the drug discovery process. The development of scalable procedures to supply adequate quantities of desired intermediates is one avenue to overcome this problem.

As part of a program directed towards the synthesis of neurologically active terpenoid compounds, we required considerable quantities of 6-methylcyclohexenone (**2a**). An analysis of the known preparations of this compound suggested the most convenient method used dihydrocarvone (**1a**) as a starting material.¹ Schreiber and co-workers described that dihydrocarvone can be subjected to ozonolysis in methanol to yield an intermediate methoxy hydroperoxide species (**3**) (Scheme 1).² Earlier synthetic and mechanistic work by Iwaki and co-workers³ suggested that peroxide O–O bonds are cleaved in the presence of $\text{Fe}(\text{II})$ to generate a highly reactive alkoxy radical that undergoes β -fragmentation to form the corresponding alkyl radical.⁴ In the presence of $\text{Cu}(\text{II})$, an alkylcopper species is thought to be formed and undergoes a β -hydrogen elimination to generate an alkene.³ Hence, without the isolation of highly reactive intermediate **3**, sequential treatment of this methoxy hydroperoxide species with $\text{Cu}(\text{OAc})_2$ and FeSO_4 produced 6-methylcyclohexenone (**2a**) via the above described fragmentation reaction.^{2,4} Indeed, we found this process to sufficiently produce gram quantities of 6-methylcyclohexenone,⁵ albeit with variable efficiency. However, further increases in scale resulted in depreciations of yield.

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Results and discussion

Optimization of reaction conditions

To develop a more reliable procedure to produce the requisite quantities of the volatile **2a** (100 gram batches), we examined the effect of alternative copper and iron sources for the conversion of **1b** to the non-volatile **2b** (Table 1). When using the standard heterogeneous conditions, **2b** was obtained from **1b** in 77% yield. We hypothesized that the variable yield was attributed to the heterogeneity of the reaction mixture. Thus, replacement of Cu(OAc)₂ with a soluble and inexpensive salt, Cu(BF₄)₂ (45% aqueous),⁶ resulted in a comparable yield (75%) of the desired product (entry 2). A second modification was made to exchange FeSO₄ with the soluble Fe(BF₄)₂ (45% aqueous), which resulted in 71% yield (entry 3). Although these results demonstrated a slight depreciation in efficiency, these conditions produced a fully homogeneous reaction solution that was expected to provide more reproducible results while using inexpensive copper⁶ and iron⁷ sources. Control experiments in line with earlier work illustrated that both Cu(II) and Fe(II) were necessary for an efficient transformation (entries 4 and 5). A brief survey of readily available Cu(II) salts (Cu(OAc)₂, Cu(TFA)₂, CuSO₄, Cu(acac)₂, Cu(2-ethylhexanoate)₂, *etc.*), indicated that variation of this parameter had little effect on yield. In contrast, use of alternative Fe(II) salts led to greater variations in yield (*e.g.* Fe(acac)₂ and Fe(C₂O₄) were less efficient).

Examination of substrate scope

After establishing optimized conditions for this formal propene elimination, we investigated the scope of these newly developed homogeneous reaction conditions (Table 2). Using the soluble Cu(BF₄)₂ and Fe(BF₄)₂ salts, (+)-6-methylcyclohexenone (**2a**) was prepared from (+)-dihydrocarvone (**1a**) in 41% yield, along with 17% of the separable β,γ -unsaturated ketone (not shown). These conditions provided **2a** with an optical purity that was similar to that of the earlier reported conditions.⁸ However, if material of high optical purity is not required, we found that methanesulphonic acid treatment of the crude organic extracts quantitatively isomerized the alkene to the enone to provide a higher yield of the desired product (55%).

Further examination of the substrate scope demonstrated that the Robinson annulation adducts^{9,10} **1b** and **1c** were suitable substrates, providing the allylic alcohols **2b** and **2c** in 70% and 57% yield, respectively. While it was determined that (–)-isopulegol, **1d**, could be transformed to the allylic alcohol **2d**¹¹ under the previously reported conditions using Cu(OAc)₂ and FeSO₄ in 43% yield, use of the tetrafluoroborate salts reported herein resulted in significantly lower yields of the desired product. Although the yield is modest for the degradation of isopulegol, it is noteworthy that the product **2d** was previously prepared by a five-step sequence in 2% overall yield after a resolution,¹² or from (+)-pulegone in five steps with a 25% overall yield.¹³

β -Fragmentation of the quaternary substituted isopropylidene substrate **1e** proceeds to form **2e** in 58% yield. Since substrate **1e** was prepared from **2e** by an organocuprate conjugate addition of an isopropylidene nucleophile to an enone, this transformation represents a

method to temporarily mask enone functionality. Intermediate transformations could be conducted exploiting the differential reactivities of ketones and enones.

Enone **1f** was also tolerated under the reaction conditions to form dienone **2f** in a 61% yield.⁹ If air was excluded from the reaction, nootkatone (**1g**), a readily available diterpenoid natural product, yielded the kinetically favoured alkene product **2g** in 58% yield. While **2g** could be isolated by column chromatography with SiO₂, it was observed that the double bond isomerized into the thermodynamically favoured position to form a conjugated dienone (not shown) when the purified compound was allowed to stand in CDCl₃ at room temperature.

100 gram synthesis of 6-methylcyclohexenone

Following an examination of the substrate scope, we applied the use of Cu(BF₄)₂ and Fe(BF₄)₂ to the synthesis of 6-methylcyclohexenone (**2a**) on a 100 gram scale (Scheme 2). As a point of comparison, using the previously reported heterogeneous conditions gave the desired product **2a** in 37% yield. In contrast, employing the newly developed homogeneous reaction conditions yielded **2a** in 55% yield on the same scale. Furthermore, the aqueous work-up of the homogeneous reaction solution is more conveniently performed due to the increased solubility of the metal salts.

Conclusions

This report described an improved procedure for the *in situ* generation and fragmentation of methoxy hydroperoxides to form alkenes by employing soluble Cu(II) and Fe(II) tetrafluoroborate salts. These homogeneous conditions have been employed for the scalable synthesis of an important building block chemical, 6-methylcyclohexenone, and may be useful for other applications.

While this work has focused on the derivatization of readily abundant isopropylidene-containing compounds, other uses for this chemistry could be envisioned. The conjugate addition of an organocopper isopropylidene nucleophile to an enone, followed by ozonolysis and copper- and iron-mediated fragmentation to reform an enone, as in **2e** → **1e** → **2e**, formally represents a protection–deprotection sequence of the reactive enone functional group. This protection–deprotection sequence could be coupled productively with a variety of synthetic transformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Synthesis of (+)-6-methycyclohexenone from (+)-dihydrocarvone.²

Heterogeneous Conditions

Homogeneous Conditions

Scheme 2.
Scalable synthesis of 6-methylcyclohexenone.

Table 1

 β -Fragmentation optimization

Entry	Cu(II)	Fe(II)	% Yield ^a
1	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	$\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$	77
2	$\text{Cu}(\text{BF}_4)_2$ (aq.)	$\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$	75
3	$\text{Cu}(\text{BF}_4)_2$ (aq.)	$\text{Fe}(\text{BF}_4)_2$ (aq.)	71
4	None	$\text{Fe}(\text{BF}_4)_2$ (aq.)	7
5	$\text{Cu}(\text{BF}_4)_2$ (aq.)	None	0

^aYield determined by ^1H -NMR analysis after aqueous work-up using 1,3,5-trimethoxybenzene as an internal standard.

Table 2

 β -Fragmentation substrate scope

$ \begin{array}{c} \text{R} \quad \text{Me} \\ \diagdown \quad \diagup \\ \text{C} \quad \text{C} \\ \diagup \quad \diagdown \\ \text{R} \quad \text{Me} \end{array} \xrightarrow[\text{ii) 1.5 equiv Cu(BF}_4)_2, \text{ 1.2 equiv Fe(BF}_4)_2, -20\text{--}23\text{ }^\circ\text{C}]{\text{i) O}_3, \text{ MeOH, } -40\text{ }^\circ\text{C}} \begin{array}{c} \text{R} \quad \text{R} \\ \diagdown \quad \diagup \\ \text{C} \quad \text{C} \\ \diagup \quad \diagdown \\ \text{R} \quad \text{R} \end{array} $		
1	2	
Substrate	Product	% Yield ^a
41 ^b , 55 ^c
2b 70
1c R = Me	2c R = Me	2c 57
43 ^d
58 ^c
61
58

^a Isolated yield.^b 17% of the β,γ -enone was isolated.^c Treated with MsOH during aqueous work-up.^d 2.0 equiv. of Cu(OAc) $_2$ ·H $_2$ O & 1.2 equiv. of FeSO $_4$ ·7H $_2$ O was employed.