Highly stereoselective synthesis of (Z, E)-1-halo-1,3-dienol esters *via* rearrangement of Fischer chromium chloro-carbenes using microwave irradiation[†][‡]

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Functionalized (Z,E)-1-halo-1,3-dienol esters are synthesized in a highly stereoselective manner *via* CrCl₂-mediated rearrangement of allylic trihalomethylcarbinol esters induced by microwave irradiation.

The development of stereoselective molecular rearrangements is an emerging area in organic synthesis for the preparation of halogenated olefins.^{1,2} While numerous examples for the preparation of (Z)-1-haloenol esters, (Z)-2-haloenol ethers,² (Z,Z)-1chloro-1,3-dienes and Z-chloroalkenes exist, (Z,Z)- and (Z,E)-1-halo-1,3-dienol esters are uncommon and remain highly elusive intermediates, despite their obvious synthetic utility. Indeed, quite recently, halo-1,3-butadienyl esters have been successfully used in combination with alkylsulfonyl cyanides for the preparation of halogenopyridines.⁴ This report represents the sole example reported so far in the literature, but provides a tantalizing glimpse into the vast potential class of synthetic intermediates. Additionally, it has been found that (Z)-1-haloenol esters are potential prodrugs for Alzheimer disease.⁵ Considering the synthetic and biological relevance of 1-haloenols, a general strategic approach for the stereoselective preparation of 1-halo-1,3dienol esters is highly desirable. Inspired by our recent discovery that chromium (II) chloride in THF induces trihalomethylcarbinol esters and ethers to undergo efficient, stereoselective intramolecular rearrangement, to (Z)- α -haloenol esters and (Z)β-haloenol ethers, respectively, we became interested in the possibility of applying this reaction to allylic trihalomethylcarbinol substrates.2a

Herein, we describe the optimization of this reaction and its application in the first general method for the stereoselective preparation of (Z,E)-1-halo-1,3-dienol esters from allylic 1,1,1-trihalomethylcarbinol esters using microwave irradiation (Scheme 1). Relying upon our prior experience, various substituted allylic trihalomethylcarbinol esters were synthesized using



Scheme 1 Preparation of (Z, E)-1-halo-1,3-dienol esters.

standard procedures⁶ and treated with chromous chloride. Facing the challenge of achieving high stereoselectivity, we first examined the reactivity of compound 1 using reported conditions, *i.e.*, with 3 equiv of CrCl₂ in THF under reflux for 3.5 h.^{2a} Initial results were rather encouraging since the expected (Z,E)-1-chloro-1,3-dienol acetate 27 was isolated in 84% yield, along with 16% of starting material (Table 1, entry 1). However, we observed that exposure of the *p*-chloroarene **3** to the same experimental conditions failed to give the desired product 4 in an acceptable yield (30%), due to the low conversion of the starting material 3 (Table 1, entry 2). Prolonged reaction times proved to be unsatisfactory since the degradation of the rearranged product 4 and the formation of side products took place predominantly. Gratifyingly, it was eventually found, through an assay of diverse reaction conditions, that treatment of 3 with 3.5 equiv of CrCl₂ under microwave irradiation, enabled clean and rapid (25 min) formation of **4** as the sole (Z,E) isomer, in 74% of isolated yield (Table 1, entry 2). NOE experiments, corroborated by a single-crystal X-ray diffraction analysis, assessed unambiguously the (Z,E)-stereochemistry of the 1-chloro-1,3-dienol acetate 4.8

The benefit of the microwave irradiation proved to be a generally advantageous alternative to the initial thermal reaction,^{2a} and the yield of **2** could be improved up to 92% of the major (*Z*,*E*) product (Table 1, entry 1), along with 5% of the minor (*E*,*E*) isomer. While enhancing drastically the kinetic of the rearrangement,⁹ these new conditions did not affect the high stereoselectivity of the reaction, and more importantly, the stability and the viability of the reactive intermediate.

Table 1 summarizes the evaluation of the reaction scope under the optimized conditions. Importantly, all reactions proceeded to completion within short reaction times (25 min), regardless of the olefin substitution of the starting allylic trihalomethylcarbinol esters, or the nature of the migratory acyl group. A survey of electronically and sterically varied aryl, heteroaryl and olefinic substituents on the allylic trihalomethylcarbinol esters showed, similarly to 1 and 3, a high degree of stereospecificity in the

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[‡] Dedicated to the memory of Dr. Charles Mioskowski § Passed away on 2nd June 2007

 Table 1
 Synthesis of Z-1-halo-1,3-dienol esters

Entry	Trihalocarbinol ester	α -Halo-1,3-dienol ester	Yield (%) ^a
1	OAc CCl ₃	CI 2	92 (84) [*]
2		Cl 4	74 (30) [*]
3 4 5 6	$5 = R = CH_3$ 7 = R = Ph 9 = R = 2-thienyl 11 = R = 2-pentenyl $CH_3 OCOR$ $H_3C CCI_3$	$6 = R = CH_3$ $8 = R = Ph$ $10 = R = 2\text{-thienyl}$ $12 = R = 2\text{-pentenyl}$ H_3C Cl	90° 68 81 85
7 8	$13 = R = CH_3$ 15 = R = Ph OCOR C_3H_7 CCI ₃	$14 = R = CH_3$ 16 = R = Ph C_3H_7 CI	90° 77
9 10 11	$17 = R = CH_3$ $19 = R = p \cdot OCH_3 \cdot C_6H_4$ $CH_3 OAC$ $H_3C CH_3$ 21	$18 = R = CH_3$ $20 = R = p \cdot OCH_3 \cdot C_6H_4$ CH_3 H_3C CH_3	90 83 64
12	OAc CBr ₂ F	P OAc F OAc F	74
13	OAc CCI ₃ 25	CH ₃ CI	68

^{*a*} Isolated yields by microwave irradiation reaction; ^{*b*} Yields in parentheses are from conventional heating for 10–12 h.^{2a} ^{*c*} Yields are calculated based on the crude ¹H NMR spectra.

rearrangement step, and in most cases, excellent yields were obtained (Table 1). Interestingly, even low molecular weight substrates such as 5 and 13 were specifically converted to the corresponding (Z)-1-chlorodienol acetates 6 and 14, however, isolation of the compounds was tedious due to their high volatility (entries 3, 7).¹⁰ These practical problems were easily overcome by substitution of the acetyl group by a heavier

migratory benzoyl (Bz) substituent. Accordingly, analogues 7 and 15 afforded, without any complications, the expected (Z)-1-chloro-1,3-dienol benzoates 8 and 16 in good isolated yields (entries 4, 8). For both cases, 8 to 12% of the minor (*E*)-1-chloro-1,3-dienol benzoate isomers were also identified in a complex inseparable mixture. It is worthwhile mentioning that the rearrangement conditions also tolerate thienoyl and pentenoyl

moieties as migratory groups; substrates **9** and **11** were smoothly, and exclusively converted to (*Z*)-**10** and (*Z*)-**12**, respectively, in excellent isolated yields (entries 5, 6). Disubstituted (*E*)-allylic trichloromethylcarbinol esters **17** and **19** also behaved well and provided the corresponding (*Z*,*E*)-1-chloro-1,3-dienol acetate **18** and benzoate **20** almost exclusively (entries 9, 10). For these reagents (**17** and **19**) the formations of the minor (*E*,*E*)-1-chloro-1,3-dienol esters isomers were observed in low quantities, based upon the analysis of the ¹H NMR spectrum of the crude reaction mixture (<5%).

It was also found that the rearrangement of the citral derivative **21**, provided 64% of the desired (*Z*,*E*)-1-chloro-1,3-dienol acetate **22**, accompanied with 12% of the (*E*,*E*)-isomer (Entry 11). Extension of our methodology to the formation of (*Z*,*E*)-1-fluoro-1,3-dienol acetate **24** was successfully achieved when 1-fluorodibromomethylcarbinol **23** was subjected to the same optimized conditions (Entry 12). The stereochemistry of the resulting (*Z*,*E*)-1-fluoro-1,3-dienol acetate **24** (single isomer) was assigned and confirmed by ¹⁹F-NMR spectroscopy. Finally, the substrate survey showed also that *E*-furan trichloromethyl carbinol **25** reacted with chromium(II) chloride in similar fashion. The expected (*Z*,*E*)-1-chloro-1,3-dienol acetate **26** was isolated in pure form with 68% of yield, along with 24% of a 60:40 mixture of minor (*E*,*E*)-1-chloro-1,3-dienol acetate, and an unidentified product (Entry 13).¹¹

It is important to point out that for all substrates evaluated the stereochemistry of the starting allylic trihalomethylcarbinol esters (1,3 and 17–25) did not suffer from any competitive isomerization, in our experimental conditions. Mechanistically, all the results described in this communication can be accommodated by the rational considerations depicted in Scheme 2.



Scheme 2 Plausible mechanism for the formation of 30.

As reported earlier,^{2a} it is believed that the reaction of **27** proceeds through the initial formation of the dihalocarbenoid intermediate **28**, that undergoes a rapid α -elimination of CrCl₂X through metal-assisted ionization,¹² to afford the postulated homoallylic Fischer chloro carbene **29**. An intramolecular suprafacial nucleophilic rearrangement involving the nonbonded (*n*) electrons of the carbonyl group takes place, converting this highly reactive species into the observed (*Z*,*E*)-1-chloro-1,3-dienol

ester **30**.¹³ Interestingly, the reactions of Fischer chromium(III) carbene complexes (FCCs) under microwave irradiation are unknown. Moreover, only one report can be found in the literature involving Fischer chromium(0) alkoxy carbene complexes. Indeed, recently, Barluenga *et al.* have successfully used Fischer alkoxy carbene complexes, generated with microwave irradiation, for the diastereoselective cyclopropanation of electron-deficient alkenes.¹⁴

To the best of our knowledge, the reactions reported herein, are the first examples of highly stereoselective intramolecular rearrangement of homoallylic Fischer chloro carbenes, *in situ* generated under microwaves irradiation, and affording stere-oselectively, (Z,E)-1-halo-1,3-dienol esters of valuable synthetic interest.

Conclusion

In conclusion, we have developed a novel, simple and versatile method for the stereoselective preparation of (Z,E)-1-halo-1,3-dienol esters which are useful intermediates in organic synthesis. Further studies on the use of Fischer chromium(III) carbene complexes (FCCs) as intermediates in chemistry, are under progress in our laboratories.

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