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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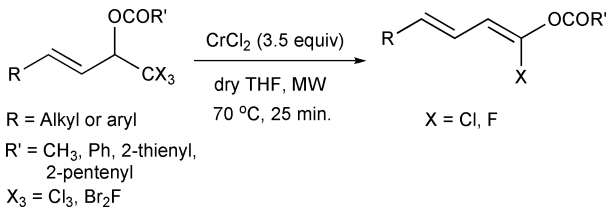
Functionalized (*Z*,*E*)-1-halo-1,3-dienol esters are synthesized in a highly stereoselective manner *via* $CrCl_2$-mediated rearrangement of allylic trihalomethylcarbinol esters induced by microwave irradiation.

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*)-1-chloro-1,3-dienes and *Z*-chloroalkenes exist,[3] (*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-1,3-dienol 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 procedures[6] 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 $CrCl_2$ 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 **2**[7] 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 $CrCl_2$, 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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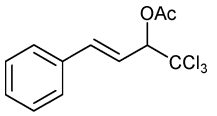
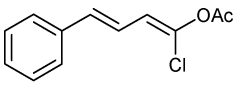
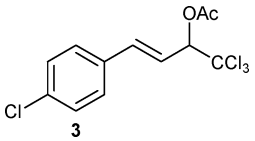
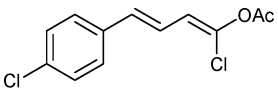
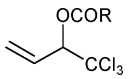
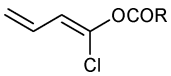
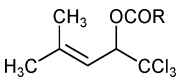
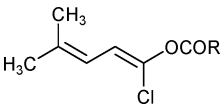
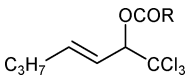
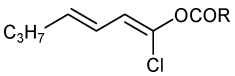
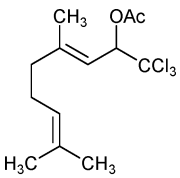
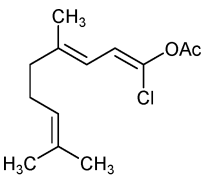
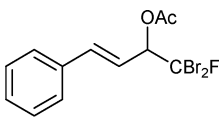
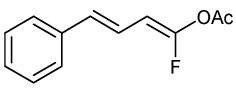
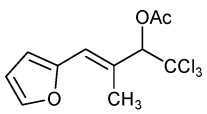
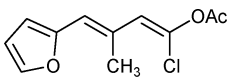
† Electronic supplementary information (ESI) available: Experimental procedures, spectral, and crystallographic data. CCDC reference numbers 715259 and 715260. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b903244b

‡ 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	 **1**	 **2**	92 (84)[b]
2	 **3**	 **4**	74 (30)[b]
			
3	**5** = R = CH_3	**6** = R = CH_3	90[c]
4	**7** = R = Ph	**8** = R = Ph	68
5	**9** = R = 2-thienyl	**10** = R = 2-thienyl	81
6	**11** = R = 2-pentenyl	**12** = R = 2-pentenyl	85
			
7	**13** = R = CH_3	**14** = R= CH_3	90[c]
8	**15** = R = Ph	**16** = R = Ph	77
			
9	**17** = R = CH_3	**18** = R = CH_3	90
10	**19** = R = *p*-OCH_3-C_6H_4	**20** = R = *p*-OCH_3-C_6H_4	83
11	 **21**	 **22**	64
12	 **23**	 **24**	74
13	 **25**	 **26**	68

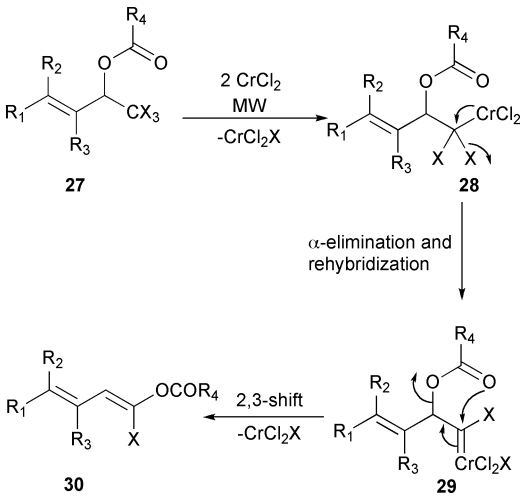
[a] Isolated yields by microwave irradiation reaction; [b] Yields in parentheses are from conventional heating for 10–12 h.[2a] [c] Yields are calculated based on the crude ^{1}H NMR spectra.

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 ^{1}H 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 ^{19}F-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 $CrCl_2X$ 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 stereoselectively, (*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.

Acknowledgements

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7 The (*Z*,*E*)-stereochemistry of **2** was unambiguously assigned by NOE experiments.
8 See supporting information for the X-ray crystal structure and additional data for **4**.
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10 For both substrates **5** and **13**, 85 to 90% of conversion was achieved, and rearranged products **6** and **14** were formed as single isomers based on the analysis of the crude ^{1}H-NMR spectra.
11 X-Ray crystal structure of **26** is provided in supporting information.
12 (*a*) The organochromium species undergo a rehybridization by placing a positive charge in a *p* orbital to produce a tight ion pair: M. Duraisamy and H. M. Walborsky, *J. Am. Chem. Soc.*, 1984, **106**, 5035–5037; (*b*) J. Rachon, V. Goedken and H. M. Walborsky, *J. Am. Chem. Soc.*, 1986, **108**, 7435–7436.
13 The *Z* stereochemistry of the products may be rationalized if one takes into account the possible conformations of the postulated Fisher carbene **29**. See reference 2a for a detailed explanation for the stereochemical model for the migration.
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