Unusual rearrangement of dihalocyclopropanes

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Abstract. Dihalocyclopropanation of the double bond of some olefins, leading to dihalocyclopropanes, offered an opportunity to perform their rearrangement to dihalomethylvinyl with Hiyama type reagents, in presence of cationic system such as $\text{Cr}^{2+}/\text{Cr}^{3+}$. The chain elongation of alkenes via the gem-dihalocyclopropanes produced α, β -unsaturated aldehydes and acids.

1. Introduction

Dihalocyclopropanes are interesting starting materials to attempt some rearrangements. When attached to cyclic structures with an endocyclic-double-bond, the extension of the cycle takes place, usually with help of the phase transfer catalyst [1,2]. Conversely, the formation of allene is expected for some exocyclic double bond originated dihalocyclopropanes [3]. We recently have reported on Eliel's-reagents-induced reactions of dihalocyclopropane lactones, and demonstrated the formation of allenic derivatives (dihalo, monohalo and fully reduced) from exocyclic methylenes [4,5] with Hiyama reagents *in situ* formed ($\text{Cr}^{+2}/\text{Cr}^{+3}\text{H}^-$, DMF) [6].

This family of Lewis acid reagents, consisting of a pair of cations, is necessary to perform this rearrangement. During this reaction, the reduction of dihaloallene takes place because of both the formation *in situ* of Cr^{+2} cation and presence of the hydride ion.

We studied the behavior of the endocyclic double bond with the dihalocyclopropanes attached to a cyclic structure. When reacted with Hiyama reagent, new rearrangement products were observed with low yield. The structure, of these products displayed the dihalomethylvinyl moiety (Scheme 1).

This functional group is a potential precursor of α, β -unsaturated aldehydes or acids. Faced with what is a potentially new rearrangement, it was necessary to compare it to similar reactions involving either carbene addition, Lewis-acid-induced rearrangement, synthesis of α, β -unsaturated carbonyl compounds and, the Hiyama reaction. Closely related reactions included Reimer–Teimann, Doering–Laflamme, Ciamician–Dennstedt, retro-Griffin and Hiyama–Heatcock reactions, most of which are

Scheme 1. General rearrangement scheme.

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Scheme 2. Substrates used in this study.

Scheme 3. Rearrangement products of dihalocyclopropane.

performed on the aromatic compounds [7–11]. Finally, from a mechanistic standpoint, the obtention of dihalomethylvinyl from dihalocyclopropane should follow one electron mechanism rearrangement pathway suggested by Wang [12].

We examined over twenty dihalocyclopropanes of which only three cyclohexene (1) and dihydropyran (2) both of which are endocyclic, as well as limonene (4), which is not only endocyclic, but has a second exo double bond on a terminal methylene, react along the new dihalocyclopropane–dihalomethylvinyl direction with a reasonable yield (Scheme 2).

Subsequently, some other Lewis acids able to produce two neighboring oxidation states such as Ce^{+3} or Sm^{+2} as well as with Cr^{+3} alone (without hydride), were applied to 6, 7, 8 and 16 dichlorocyclopropane adduct rearrangement. The post-reaction mixtures were examined using NMR and GC-MS. The most interesting results were obtained for both Cr^{+2} experiments (Scheme 3).

2. Results and discussion

First, the dihalocyclopropane derivatives were prepared by phase transfer catalysis. The olefins 1, 2 and 3 gave dihalocyclopropanation in the range of 85–90% when tributyl-ammonium chloride (TEBA)

Fig. 1. (a) ¹H NMR spectrum of **6**. (b) ¹³C NMR spectrum of **6**.

catalyst was applied according to Makosza's procedure [1]. The proton NMR (200 MHz) showed characteristic of cyclopropane proton signals at 2.06 ppm for 7,7-dichloronorcarane (**6**) (Fig. 1a), 1.42 ppm and 3.22 ppm for 7,7-dichloro-oxonorcarane (**7**) (Fig. 2a) and 1.17 ppm for 1,1-dichlorospiro[2.5]octane (**8**) (Fig. 3a); the spectrum C-13 for corresponding cyclopropane moiety had signals at 20.2 ppm for **6** (Fig. 1b) and 24.5 and 59.0 for **7** (Fig. 2b), and 25.1 and 67.5 ppm for **8** (Fig. 3b). When **6** is subjected to Hiyama reagent formed *in situ* the corresponding aldehyde **10** (2-cyclohexenal), the acid **11** (1-cyclohexene carboxylic acid), the reduced starting material 1-methylcyclohexene (**14**) and the dichloro-substituted rearrangement product dichloromethylcyclohexene (**9**), were obtained with a respective yield of 8, 12, 6, 14% (total transformation of **6** yield 40%). In the case of the commercial Cr⁺² (Aldrich Chemicals, CrCl₂) neither aldehyde **10** nor monochlorosubstituted product **13** was observed, and the acid **11** and the totally reduced compound **14** were obtained with yield of only 4% and 6%, respectively (10% of total yield transformation).

In the presence of Cr⁺³ (Aldrich Chemicals, CrCl₃) none of the rearrangement products were observed (Table 1).

For dihalocyclopropane fixed on the dihydropyran (**2**) the *in situ* produced Cr⁺² reagent only lead to the formation of 2-(dichloromethyl)-3,4-dihydro-2H-pyran (**22**),¹ 3,4-dihydro-2H-pyran-2-

¹The position of the radical could be reversed.

Fig. 2. (a) ^1H NMR spectrum of 7. (b) ^{13}C NMR spectrum of 7.Table 1
Efficiencies of dihalocyclopropanes rearrangement of 6*

Condition	Total transformation (%)	Products			
		Totally reduced <u>14</u>	Aldehyde <u>10</u>	Acid <u>11</u>	Dichloromethylvinyl <u>9</u>
Cr^{+2} <i>in situ</i>	40	15	20	30	35
Cr^{+2} commercial	10	60	–	40	–

*Efficiency is reported on the basis of dihalocyclopropane derivative consumed.

carbaldehyde (23) and 2-(chloromethyl)-3,4-dihydro-2*H*-pyran (24), the dichloromethylvinyle 22, the aldehyde 23, and monochloro-substituted 24 products, with respective yield of 5%, 4% and 1% (the total yield is 10%). The commercial Cr^{+2} , however, produced only the dichloromethylvinyle 22 compound with a yield of 3% (Table 2). In neither reaction were seven-membered Makosza products obtained. The acid 25 was not observed in both series of experiments.

When the model exocyclic olefin methylenecyclohexane (3) was transformed into its dihalocyclopropane (8), and this derivative was tested with Hiyama reagent via similar reaction 9% of rearranged

Fig. 3. (a) H-1 NMR spectrum of 8. (b) C-13 NMR spectrum of 8.Table 2
Efficiencies of dihalocyclopropanes rearrangement of 7*

Condition	Total transformation (%)	Products		
		Dichloromethylvinyle <u>22</u>	Aldehyde <u>23</u>	Monochloro <u>24</u>
Cr ⁺² <i>in situ</i>	10	50	40	10
Cr ⁺² commercial	3	100	—	—

*Efficiency is reported on the basis of dihalocyclopropane derivative consumed.

allenic product (dichloroethenylidene)cyclohexane (15) was obtained (35% of total yield).

This confirms, that the formation of allene from the spiro dihalocyclopropane takes place, and the rearrangement does not stop on the dihalomethylvinyle step.

The dihalocyclopropanation of limonene (4) gives three different derivatives, separated by column chromatography (Al₂O₃, basic), resulting from the addition of cyclopropane moieties to, either one of the two (endocyclic or terminal methylene) or to both double bonds. The NMR spectrum of the tetrachloro derivative of limonene 7,7-dichloro-4-(2,2-dichloro-1-methylcyclopropyl)-1-

Fig. 4. GC-MS of double adduct 16. $M^+ = 300$, $M^+-(CH_2-CCl_2) = 204$, $M^+-(CH_2-CCl_2), Cl = 169$ (100%), $M^+-Cl-CCl_2-CH_3-C_2H_2 = 141$.

methylbicyclo[4.1.0]heptane (16), obtained with total yield of 41% from 4, displayed 1.95 and 2.18 ppm signals corresponding to H2 and to the methylene at H8, the characteristic protonated cyclopropane carbon in C-13 NMR resonated at 25.2, C2 and 20.4, C8 ppm and the GC-MS spectrum confirm the structure (Fig. 4).

Molecular modelling of 16 of the two isomeric structures showed lower energy for *cis* isomer 16 (17 kcal/mol, Fig. 7). From the GC-MS this ratio (*cis/trans*) was evaluated 95 : 5, the 16cis had a shorter retention time.

The two other dihalocyclopropane derivatives 17 and 18, obtained in 3 : 1 ratio, respectively (total yield of 47%), displayed cyclopropane only on the endocyclic double bond and only on the methylene double bond of the other. The NMR characteristic features witnessing their differences are in particular proton and carbon signals of two double bond systems with two olefinic methylene protons and one cyclopropane methylene in the spectrum of 18 and one proton on the endocyclic double bond (H2 at 5.39 ppm) and methylene cyclopropane proton at 1.95 ppm for H8 and the GC-MS spectrum confirm the structures (Fig. 5a, b and c). The tetrachloro limonene derivative 16 produced under the Hiyama Cr^{+2} *in situ* reagent, yielded 5% of allene-aldehyde mixture products, while the mixture dichloro derivatives 17 and 18 (3 : 1) gave a small yield of allene-aldehyde mixture at ca 1%. These compounds were identified by proton and carbon-13 NMR, and confirmed by mass spectrometry.

The allene-aldehyde 19 was observed in both rearrangements of 16 with Cr^{+2} produced *in situ* and with commercial Cr^{+2} , but the dihalocyclopropane unsaturated aldehyde 20 was observed only with Cr^{+2} produced *in situ* (Scheme 4).

Of the two possible orientations of the dichlorocyclopropane moiety of 17 toward the α -isopropenyl group of the natural 4, the most stable is that whose isoprenyl is oriented *trans* (dichlorocyclopropane 17 trans). Molecular modelling of the two isomeric structures showed lower energy for *trans* isomer 17 (9.3 kcal/mol, Figs 8 and 9).

(a)

(b)

(c)

Fig. 5. (a) GC-MS of the mixture 17 and 18. For 17, $M^+ = 218$, $M^+ - \text{Cl} = 183$, $M^+ - \text{CH}_3 - \text{CCl}_2 = 121$, $(M^+ - \text{CH}_2 - \text{C} - \text{CCl}_2) - 2\text{H} = 107$ (100%). (b) GC-MS of 18, $M^+ = 218$, $M^+ - \text{Cl} = 183$, $M^+ - \text{CH}_2 - \text{CCl}_2 = 122$, $M^+ - \text{CH}_2 - \text{CCl}_2 - \text{H}_2 = 93$ (100%). (c) GC-MS of isomer of 18, $M^+ = 218$, $M^+ - \text{CH}_2 - \text{CCl}_2 = 122$, $M^+ - \text{CH}_2 - \text{CCl}_2 - \text{H}_2 = 93$ (100%).

Scheme 4. Limonene 4-dichlorocyclopropane adducts **16–18** and rearrangement products **19** and **20**.

Fig. 6. GC-MS of cubebene adduct **21**. $M^+ = 286$, $M^+ + 2 = 288$ (2Cl), $M^+ - iPr = 243, 245$ (2Cl) (100%), $M^+ - Cl = 251, 253$ (2Cl), $M^+ - (Cl-C_6H_{12}) = 167, 169$ (1Cl).

The rearrangement on mixture of **17** and **18**, was also being tested, according to Hiyama Cr^{+2} *in situ* formation condition. The compound **17** rearranges to aldehyde, and the isomer **18** produces monochloro allenic product in 3% of total yield. Commercial Cr^{+2} does not lead to any considerable rearrangement results.

Finally, we tested the dihalocyclopropanation of cubebene (**5**) and observed the formation of the dichlorocyclopropane derivative (**21**) in the α -position (Scheme 5). The NMR spectrum shows that the proton of double bond in **5** at 5.00 ppm, is shifted to 2.31 ppm which confirms the formation of a second cyclopropane ring. The GC-MS spectra showed a molecular ion at $m/z = 286$ corresponding to dihalocyclopropane cubebene (**21**), with the characteristic isotopic two chlorine pattern (Fig. 6). Three C-13

Fig. 7. Molecular modelling of **16 cis** and **trans**.

Fig. 8. Molecular modelling of **17 trans**.

Fig. 9. Molecular modelling of **18**.

signals provide at 46.6 at 37.4 and 67.5 respectively, are additional confirmation of the structure, assigned to C1, C2 and C16. Despite the successful transformation of cubebene (**5**) into the dihalocyclopropane derivative **21** (with 87% of total yield from proton NMR spectrum), the tentative rearrangement of this highly crowded molecule failed (Fig. 10).

Fig. 10. Molecular modelling of cubebene adduct 21. Scheme 5. Cubebene (5) dichlorocyclopropane adduct.

3. Conclusion

This preliminary report on the rearrangement of dihalocyclopropane derivatives of several compounds promoted by Hiyama $\text{Cr}^{+2}/\text{Cr}^{+3}$ system confirmed the formation of new dihalomethylvinyl intermediate product further hydrolyzed to the α, β -unsaturated aldehyde and acid. Although, the yield of this reaction is small and the total yield of transformation of starting material does not exceed 40%, this reaction is apparently new. In particular, the difference between this reaction and the Makosza extended dihalocarbocyclic compound is striking. The relative efficiency of the syntheses of α, β -unsaturated aldehyde with Cr^{+2} created *in situ* and α, β -unsaturated acid with commercial Cr^{+2} , could be related to the purity of the reagent and a higher ratio of $\text{Cr}^{+2}/\text{Cr}^{+3}$ generated by the *in situ* route.

The major dihalomethylvinyl product, 9 or 22 were observed with a maximum of 15% for both dihalocyclopropanes 6 and 7. The simultaneous presence of $\text{Cr}^{+2}/\text{Cr}^{+3}$ resulting from the reduction of $\text{Cr}^{+3}/\text{H}^-$ seems to be necessary to obtain this rearrangement.

The rearrangement of some dihalocyclopropane derivatives of natural product could be a simple way to introduce aldehyde or acid functions on to these molecules.

More work is in progress in order to specify the influence of the neighboring group of varying different electronic effects on the direction of this rearrangement, in particular, the effect of electron-withdrawing groups placed near the dihalocyclopropane substrate site.

4. Experimental

All products were bought from Aldrich Chemicals. The NMR spectra were recorded on Bruker 200 MHz, in CDCl_3 . Chemical shifts were reported in δ (ppm) with TMS as internal reference. The GC-MS spectra were recorded on the Nermag Riber 30-10 GC-MS system with BP1 capillary column (25 m, $\varnothing$ 0.3 μm) and Agilent 6890 series, column HP-5MS (5% phenyl-methylpolysiloxane) 30 cm, $\varnothing$ 0.25 μm .

4.1. General procedure of synthesis of dihalocyclopropane

In 500 ml round-bottomed flask, a NaOH 50% solution (15 g of hydroxide/15 ml of water) was prepared (ice bath), 25 ml of chloroform with 1 g of catalyst tributylammonium chloride (TEBA) were added to the NaOH solution, finally 10 ml of the substrate 1 (same volume for 2, 3 and 4) except 5 was added, and the mixture was stirred for 2 h, (24 h for 4 and 5) at room temperature. The reaction was controlled with TLC, then after the addition of water extracted with CH₂Cl₂ and the products were purified via the chromatography column on silica gel (basic alumina for 4).

4.2. General procedure of the rearrangement with Cr⁺² in situ

A solution of 0.5 g of chromium chloride (III) and 0.6 g of LiAlH₄ with 5 ml of THF were mixed in a 50 ml round-bottomed flask, and stirred for 30 minutes. The changing color from violet to green indicated the formation of Cr⁺². The solvent was replaced with 8 ml of DMF and 0.1 g of the dihalocyclopropane adduct were added at room temperature. The mixture was stirred for 24 h. After the hydrolytic workup (10 ml of water and 10 ml of hexane–ether (1 : 1) mixture) the sample analyzed via the GC-MS.

4.3. General procedure of the rearrangement with Cr⁺² (commercial)

A solution of 0.5 of chromium chloride (II) and 0.1 g of the dihalocyclopropane adduct with 8 ml of DMF were mixed, in a 50 ml round-bottomed flask, and stirred for 24 h at room temperature. After the usual workup (10 ml of water and 10 ml of hexane–ether (1 : 1) mixture) the sample was analyzed via the GC-MS.

Molecular modeling calculations were done with help of HyperchemTM 6.03 (©2000 Hypercube, Inc.). All spectral material (H-1, C-13, 1D, 2D NMR, GC-MS, EI and CI) for compounds of this paper are available on request from the corresponding author (C.K. Jankowski) at the e-mail address of the Université de Moncton.

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