

Formation of polysubstituted chlorocyclopropanes from electrophilic olefins and activated trichloromethyl compounds

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Abstract—Chlorocyclopropanes and bicyclic chlorocyclopropanes are prepared in non basic conditions by electroreductive or Mg-promoted Barbier activation of PhCCl₃ or Cl₃CCO₂Me in the presence of acyclic or cyclic α,β -unsaturated carbonyl compounds.

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1. Introduction

Cyclopropane containing molecules usually display interesting specific structural and physico-chemical properties. The presence of substituents on the C3 ring enables further transformations such as functional group interconversions or couplings with other molecules. Thus, 1-chlorocyclopropanecarboxylic acids are precursors of various aminocyclopropanecarboxylic acids^{1a,b} known for their biological activity² whereas 2-chlorocyclopropanecarboxylic acids are precursors of agrochemicals,³ and have also been used recently in the synthesis of Callipeltoside A, a novel antitumor agent, with the aim of elucidating its structure and notably the C-20 and C-21 configurations.⁴

The formation of polysubstituted chlorocyclopropanes from the coupling of acyclic α,β -unsaturated esters or cyclic α,β -unsaturated ketones with α,α -dichlorocarbanions, or equivalent nucleophilic organometallic species stabilized by an electron withdrawing group such as CO₂R or Ph, has already been reported in the literature. These nucleophilic intermediates are generated either by basic treatments (i.e., sodium hydride,⁵ LDA,⁶ electrogenerated bases,⁷ two-phase-solid-liquid system⁸ or LiHMDS-DBU⁹) of alkyl dichloroacetates and α,α -dichlorotoluene, or by an oxidative addition of a carbon–chlorine bond of the

corresponding trichloromethyl compounds (Cl₃C–Y: Y = CO₂R, Ph) onto a soluble Cu(0)–isonitrile complex.¹⁰ These preparations of chlorocyclopropanes involve either a conjugate nucleophilic addition followed by subsequent ring closure (MIRC reaction^{11a,b}) or carbenoid intermediates. Cyclocondensation to olefins is also mentioned with the ambiphilic chloroaryl carbenes photolytically generated from 3-chloro-3-aryldiazirines.¹² Moreover it must be noted that substituted 1-chlorocyclopropanecarboxaldehydes, precursors of methyl 1-chlorocyclopropanecarboxylates are synthesized via a semi-benzilic Favorski rearrangement of substituted 2,2-dichlorocyclobutanols obtained by reduction of the corresponding cyclobutanones.¹³

We have already investigated the synthesis of methyl 2,2-diphenylcyclopropanecarboxylates and of 2-acyl-1,1-diphenylcyclopropanes.^{14a–c} We have notably reported two methods: one is an indirect electroreductive coupling between dichlorodiphenylmethane and cyclic or acyclic α,β -unsaturated carbonyl compounds (referred to below as process A),^{14a,b} whereas the other one is a Mg-mediated Barbier type reaction in DMF (referred to below as process B).^{14c} This last route uses the same couples of reagents as those involved in process A, but it does not apply to α,β -unsaturated methyl ketones.

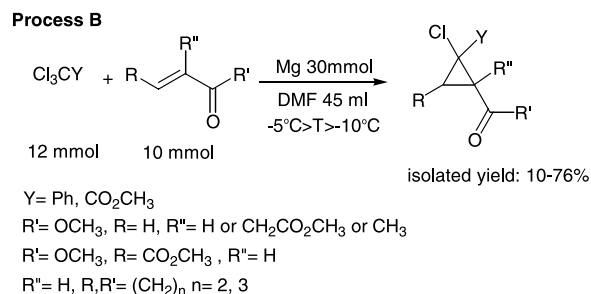
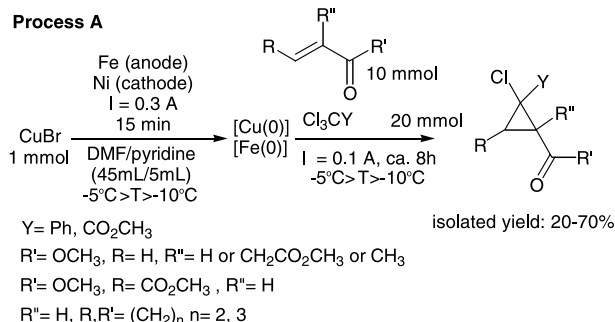
2. Results and discussion

In this paper, we report the preparation of polysubstituted chlorocyclopropanes from α,β -unsaturated acyclic esters or

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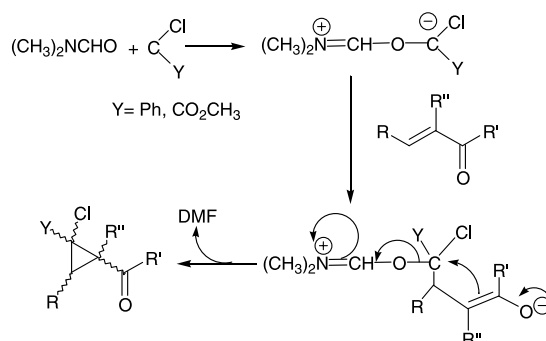
Scheme 1.

from cyclic α,β -unsaturated ketones and methyl trichloroacetate or α,α,α -trichlorotoluene (Scheme 1). It offers the opportunity to use and study both methods (processes A and B) and to compare their respective advantages and limitations, which proved to be rather complementary. The results are listed in Table 1.

These results first show that both methods generate nucleophilic intermediates, which add more or less efficiently to the olefin depending on its nature. More interestingly, these two methods are complementary. Thus, methacrylic acid esters show low reactivity in the electrochemical process (A) while yields obtained from the chemical method (B) are high (Table 1, entries 5 and 6). Such behaviour has already been observed with crotonic and methacrylic acids esters in other electrochemical reactions.¹⁶ On the contrary, yields are higher from the electrochemical method than from the chemical one when maleic or fumaric acid esters are involved (Table 1, entries 7–10). This may indicate the occurrence, in process B, of side reactions at the olefins due to their reducibility, whereas in the electrochemical process, the cathode potential is self-controlled according to the most easily reduced species, in this case the copper salts. All the other cases studied gave similar results from both methods.

The mechanisms involved in either process have not been fully elucidated so far. The occurrence of a non complexed carbene species can, however, be ruled out in both cases, due notably to the absence of stereocontrol in the ring formation (Table 1, entries 7, 9 and 8, 10). In addition, would the carbene be formed (chlorophenylcarbene and chloromethoxycarbonylcarbene) it would be rather electrophilic, as described in the literature,^{12a,b,17,18} and should therefore react with electron-rich olefins like tetramethylethylene, or cyclohexene, which has never been observed.

In the Mg-Barbier type process (B), a route via α,α -dichloromagnesium compounds, which are known to lose



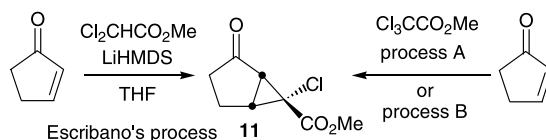
Scheme 2.

rapidly MgX_2 to form carbene intermediates,¹⁹ is not likely since no reaction was observed in the presence of nucleophilic olefins. So, we think that a first formed carbene species reacts with DMF to form a nucleophilic intermediate in a process similar to the formation of the DMF–SOCl₂ complex described by Newman²⁰ (Scheme 2). The role of DMF is even crucial in this process. Indeed, very surprisingly, no reaction occurred in diethylether or in THF instead of DMF as solvent. On the contrary, addition of an equal amount of DMF to an ether solution of PhCCl₃ and methyl acrylate induced the cyclopropanation to start.

With reference to the complementarity of both processes (A and B), it is clear that they do not involve the same type of nucleophilic species derived from the trichloromethyl compounds. In the electrochemical process (A), the reactive intermediate could be a copper–iron bi-metallic nucleophilic complex, which is not yet identified.

In the presence of acyclic α,β -unsaturated esters, chlorocyclopropanes are prepared, according to both methods, with a low to moderate diastereoselectivity (Table 1, entries 1–6) but, when cyclic enones are used as electrophilic olefins, the diastereoselectivity of the cyclopropanation becomes very high (Table 1, entries 11–14): only one of the two possible structures (*endo*-chlorine or *exo*-chlorine adduct) is obtained.

We have assigned to the compound **11** an *endo*-chlorine structure by comparison with the results obtained by Escribano et al.⁹ Actually, whatever the route used (process A or B, or Escribano's process⁹) (Scheme 3), the same bicyclic compound is formed, as determined by GC-analysis, and from the ¹H and ¹³C NMR spectra.



Scheme 3.

The *endo*-chlorine structure was established by Escribano⁹ from X-ray diffraction experiments. Our 1D ¹H NOE-Difference NMR experiments, using selective excitation with a shaped pulse (gradient version) on the methoxy group, are consistent with the assignment given by Escribano. Indeed, the NOE effect (Fig. 1) is mainly seen at the H-1 and H-5 bridge-head protons. However, our measurement of the ³J (¹H–¹³C) coupling constant between

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