Tetrahedron 71 (2015) 3290–3295

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The synthesis of cyclopropyl amines and cyclopropanols by the reaction of enamines and trimethylsilyl enol ethers with CH_2I_2 and Et_3Al

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ARTICLE INFO

Article history:
Received 20 November 2014
Received in revised form 13 March 2015
Accepted 30 March 2015
Available online 2 April 2015

Keywords:
Cyclopropyl amines
Cyclopropanols
Cyclopropanation
Aluminum carbenoids

ABSTRACT

The reaction of enamines with 2 equiv of Et_3Al and CH_2I_2 at room temperature in CH_2Cl_2 results in the formation of cyclopropyl amines in high yields (68–89%). Substituted 1-phenylcyclopropan-1-ols were also synthesized from trimethylsilyl enol ethers. The paper demonstrates the advantage of using aluminum carbenoids over traditional cyclopropanation reagents (diazomethane, Simmons–Smith and Furukawa reagents) for the preparation of cyclopropyl amines.

1. Introduction

Among the many approaches to the preparation of cyclopropane compounds, the most widely used are carbene-based methods such as cyclopropanation of unsaturated compounds with dihalocarbenes, diazoalkanes and zinc carbenoids[1] (the Simmons–Smith reagent ($Zn/Cu{-}CH_2I_2$),[2,3] Furukawa–Kawabata reagent ($Et_2Zn{-}{-}CH_2I_2$),[4,5] Wittig reagent ($ZnI_2{-}CH_2N_2$),[6] Sawada reagent ($EtZnI{-}{-}CH_2I_2$),[7] Denmark reagent ($Et_2Zn{-}CH_2Cl_2$),[8] Shi reagent ($Et_2Zn{-}CH_2I_2{-}CF_3CO_2H$),[9,10] Charette reagent ($Et_2Zn{-}CH_2I_2{-}2,4,6\text{-}Cl_3C_6H_2OH$)[11]). Due to limitations of these methods, new reagents based on carbenoids of other metals have also been developed. For example, the cyclopropanation of allyl alcohols and allenes proceeds successfully with samarium carbenoids. However, the high cost of samarium and the need for a 4–10 M equivalents of the metal[12–15] hinders the widespread use of samarium carbenoids. At the same time, the synthetic potential of aluminum carbenoids, which can be easily obtained from trialkylaluminums and CH_2I_2,[16] has not been well studied. Despite the fact that aluminum carbenoids were discovered almost simultaneously with zinc carbenoids, they have found very little application in organic chemistry. One of the reasons for this is a belated recognition of the role of solvent in the stabilization of aluminum carbenoids. Only in 1985 Maruoka and Yamamoto found that olefins give cyclopropanes in quantitative yield under the action of CH_2I_2 and trialkylaluminums in dichloromethane (DCM). At the beginning of our studies, there were only a few examples of successful use of aluminum carbenoids for the cyclopropanation of functionally substituted alkenes, such as geraniol, perillyl alcohol, benzyl ester of geraniol,[17] γ-silicon substituted allyl alcohol[18] and trimethyl((1-phenylvinyl)oxy)silane.[17] The conversion of the latter into phenyl substituted cyclopropanol is the only example of the cyclopropanation of enol ethers using aluminum carbenoid. At the same time, the importance of the problem of the synthesis of cyclopropanols and cyclopropylamines was clearly demonstrated by the growing popularity of Kulinkovich,[19,20] Kulinkovich-De Meyer[21–23] and Kulinkovich–Szymoniak[24–27] reactions. In this regard, it is clear that there is a need to study two aspects of the reaction of aluminum carbenoids with enol ethers and enamines: the limitations of the method and the possibility of developing an enantioselective version of the reaction. The present study investigates the first of these aspects.

2. Resultes and discussion

2.1. The synthesis of cyclopropanols from trimethylsilyl enol ethers under the action of CH_2I_2 and Et_3Al

While zinc carbenoids have been successfully used for cyclopropanation of a number of trimethylsilyl enol ethers,[10,28–33] only

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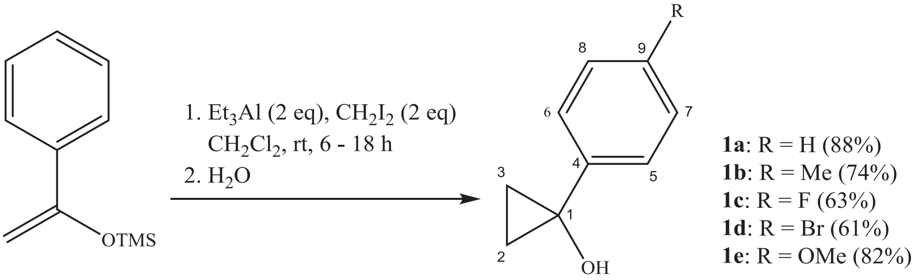
http://dx.doi.org/10.1016/j.tet.2015.03.113

one example of the preparation of substituted cyclopropanol using aluminum carbenoids has been reported.[17] From our previous studies, it is known that the reactivity of acetylenic compounds toward aluminum carbenoids strongly depends on the electronic factors.[34,35] However, it remains unclear how electron-accepting and electron-donating substituents in the aromatic ring system of aryl substituted trimethylsilyl enol ethers affect the reactivity of the substrate in the reaction with aluminum carbenoids.

We have found that trimethylsilyl enol ethers that was prepared from substituted aryl methyl ketones react with CH_2I_2 and Et_3Al at room temperature in DCM to give the corresponding substituted cyclopropanols **1a**–**e** in high yields for 6–18 h (Scheme 1). Thus, the introduction of substituents in the aromatic ring did not change the character of the reaction. It is worth to note however that the introduction of electron withdrawing substituents (F, Br) reduced the yield of cyclopropanols due apparently to decrease of the nucleophilicity of the double bond.



Scheme 1. The preparation of cyclopropanols from trimethylsilyl enol ethers.

When replacing Et_3Al with i-Bu_3Al or Me_3Al, the yield of **1b** drops to 52% and 65%, respectively, due to incomplete conversion of the starting trimethylsilyl enol ether following a reaction time of 18 h. This result can be explained by a lower rate of formation of aluminum carbenoids in exchange reaction of CH_2I_2 with Me_3Al and i-Bu_3Al. It is known that Me_3Al tends to form stable dimers.[36] Lower activity of i-Bu_3Al compared to Et_3Al can be caused by steric factors that play a role in the reaction of Al–I exchange. As already mentioned, the solvent plays a crucial role in this reaction. Co-ordinating solvents (Et_2O, THF) prevent the reaction of Al–I exchange between Et_3Al and CH_2I_2, which is due to the formation of low reactive etherates $Et_3Al * OR_2$. The best results were obtained when the reaction was carried out in halogenated hydrocarbon solvents (DCM, dichloroethane, dibromoethane) that can be explained by increased stability of the in situ formed aluminum carbenoids[17] due to specific solvation. The use of dichloromethane is more preferable because dichloro- and dibromoethane are prone to rapid spontaneous decomposition in the presence of Et_3Al, especially when heated. Cyclopropane formation in hydrocarbon solvents (hexane, benzene) proceeded at a slower rate and with a lower yield. When using toluene as the solvent, the latter reacted with aluminum carbenoids to give alkylation side-products.

It is necessary to emphasize the importance of the sequence and the mode of addition of reagents in the procedure of trimethylsilyl enol ether cyclopropanation. In the early work,[37] Me_3Al was added slowly to the solution of CH_2I_2 and 3,4-pentadien-1-ol. However, slow addition of R_3Al to the solution of CH_2I_2 may lead to the formation of compounds of type $RAl(CH_2I)_2$ and $Al(CH_2I)_3$, which have a higher electrophilicity than R_3Al and are stronger Lewis acids that can promote side reactions. This is especially relevant for Et_3Al, which reacts with CH_2I_2 at a much faster rate compared to Me_3Al. On the other hand, we observed that premixing CH_2I_2 and Et_3Al with subsequent addition of trimethylsilyl enol ether leads to a lower yield of cyclopropanols due to the thermal instability of aluminum carbenoids. The best results were obtained when Et_3Al was added to a mixture of trimethylsilyl enol ether and CH_2I_2 in DCM at 0 °C.

Thus, aluminum carbenoids, along with zinc and samarium carbenoids, can be useful reagents for the synthesis of cyclopropanols. However, aluminum carbenoids become a reagent of choice when nucleophile-sensitive group is presented in the structure of trimethylsilyl enol ether.

2.2. The synthesis of cyclopropyl amines from enamines under the action of CH_2I_2 and Et_3Al

In contrast to trimethylsilyl enol ether, enamine cyclopropanation using zinc carbenoids proceeds in low yield due to side-reaction of *N*-alkylation of enamine by the electrophilic zinc reagents.[38] Thus, 1-(cyclohex-1-en-1-yl)pyrrolidine cyclopropanation product was obtained only in 8% yield using Simmons–Smith procedure (CH_2I_2–Cu/Zn),[39] 48% yield with Furukawa reagent (CH_2I_2–Et_2Zn)[40] and 22% yield by means of CH_2Br_2–Zn/CuAcCl.[41] The best result (61%) was achieved using $CuCl_2$-diazomethane method.[40] It should be noted that carbenoid cyclopropanation strategy to amino cyclopropanes using enamines has not been well explored. There are however a few approaches that need to be mentioned. This is the cyclopropanation of chiral enamides by Et_2Zn–$ClCH_2I$ reagent[42] and the preparation of cyclopropane amino acids from dehydroamino acids using aryl and unsaturated diazo compounds.[43]

In this regard, it was interesting to observe how aluminum carbenoids will react with enamines. We have found that the enamines, which were obtained from substituted arylmethylketones, aliphatic aldehydes and 2-phenylacetaldehyde, react with CH_2I_2 and Et_3Al at room temperature in DCM to give corresponding substituted cyclopropyl amines **2a**–**g** in high yields for 6 h (Scheme 2). The transformation proceeds stereospecifically, which follows from the NOESY spectra of enamines and cyclopropyl amines. High isomeric purity of obtained cyclopropylamines is due to the high stereoselectivity of the formation of enamines from aldehydes and amines and the high stereospecificity of subsequent cyclopropanation. Thermal decomposition of diaminoalkanes into enamines proceeds under thermodynamic control to form exclusively *E*-isomers.

The highest yield of cyclopropylamines was observed using Et_3Al as the organoaluminium compound and DCM as solvent. Since enamines can form quaternary ammonium salts under the action of alkyl iodides, the reaction procedure involves the addition of CH_2I_2 to the mixture of enamine and Et_3Al in DCM at 0 °C. Furthermore, when reaction was complete the reaction mixture was treated with a solution of EtMgBr to prevent the formation of ammonium salts.

Unlike the commonly used zinc carbenoids, the aluminum carbenoid used here reacts with enamines to give substituted cyclopropylamines in high yield. There are indications in the literature that the reason for the unsatisfactory behavior of zinc carbenoids in