



# CATALYZED [2+2]-CYCLOADDITION REACTIONS OF HEXAFLUOROISOPROPYL 4-CHLORO-2-OXOBUT-3-YNATE WITH SIMPLE ALKENES

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## Abstract

It is shown for the first time that the [2+2]-cycloaddition reactions of hexafluoroisopropyl 4-chloro-2-oxobut-3-ynoate with simple alkenes, proceeding sluggishly in an excess of alkenes or in usual solvents, are strongly improved by hexafluoroisopropanol (**HFIP**). The yields of the target products also increase compared to the conventional methods. A general protocol for performing such transformations has been developed.

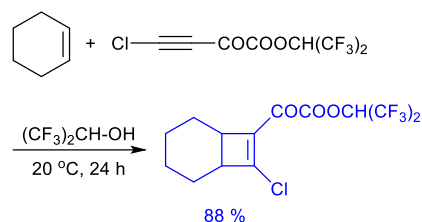
**Key words:** cycloaddition reactions, catalysis, hexafluoroisopropanol, simple alkenes, hexafluoroisopropyl 4-chloro-2-oxobut-3-ynoate.

## Introduction

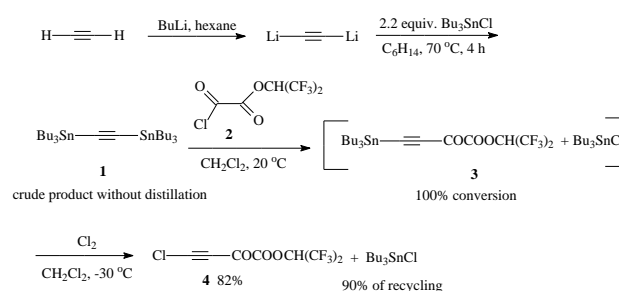
The chemistry of alkynes is one of the most interesting and rapidly growing fields of organic synthesis [1, 2]. Among other acetylenes, halogenated alkynes are of particular importance owing to their wide range of transformations and therefore high synthetic value [3]. They are frequently used in a variety of electrophilic alkynylation [4], Diels–Alder cycloaddition [5] and cross-coupling reactions [6]. Snider *et al.* [7] described the [2+2]-cycloaddition reactions of methyl chloropropiolate with alkenes catalyzed by  $\text{EtAlCl}_2$ . Earlier we have explored the synthesis and some cycloaddition reactions of haloalkynes, activated by extremely strong trifluoroacetyl and ethyloxalyl electron-withdrawing groups [8, 9]. The resulting cycloadducts contain a  $\beta$ -haloenone core and represent versatile reagents for heterocyclizations [10]. In our previous study [11], we synthesized hexafluoroisopropyl 4-chloro-2-oxobut-3-ynoate **4**, which is an extremely high electrophilic alkyne and undergoes unusual [2+2]-cycloaddition reactions with simple alkenes to give the corresponding  $\beta$ -haloenones with cyclobutene cores. However, the rates of cycloadditions and the yields of products were moderate in some cases. In this work, we significantly improved and simplified the synthesis of compound **4**, which can now be accomplished without the use of toxic and expensive  $\text{Me}_3\text{SnCl}$ , and showed the dramatic acceleration of cycloaddition reactions of **4** in **HFIP**.

## Results and discussion

Initially, we attempted the synthesis of compound **4** according to the published method using  $\text{Bu}_3\text{SnCl}$  instead of  $\text{Me}_3\text{SnCl}$ , since the former is less toxic and much cheaper compared to the latter [11]. It was stated that the suspension of lithium acetylide  $\text{Li}-\text{C}\equiv\text{C}-\text{Li}$  in hexane, prepared from  $\text{BuLi}$  and acetylene, reacts with 2.1 equiv. of  $\text{Bu}_3\text{SnCl}$  to give alkyne **1** in



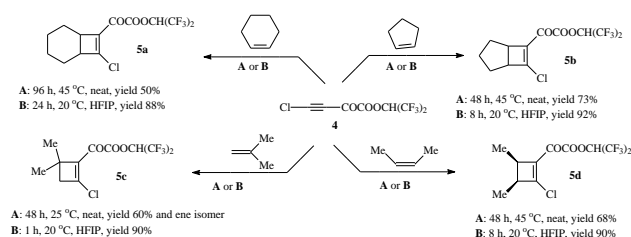
almost quantitative yield. Since **1** has very high boiling point, it was used in a crude form in the subsequent acylation with available chloride **2** to give alkyne **3** and  $\text{Bu}_3\text{SnCl}$  with the quantitative conversion. Because of the low thermal stability, compound **3** without distillation was further treated with chlorine at  $-30\text{ }^\circ\text{C}$  to give target compound **4** in high yield and the second equivalent of  $\text{Bu}_3\text{SnCl}$  (Scheme 1). Therefore, the synthesis of **4** was carried out as one-pot process and also allowed for the recovery of  $\text{Bu}_3\text{SnCl}$ , which can further be used in the same synthesis.



**Scheme 1.** Improved one-pot synthesis of alkyne **4**.

At the next step, we studied the [2+2]-cycloaddition reactions of **4** with simple alkenes in different solvents and the possibility to catalyze these transformations by the Lewis acids. Unfortunately, all our attempts to use  $\text{AlCl}_3$ ,  $\text{ZnCl}_2$ ,  $\text{SnCl}_4$ , and  $\text{BF}_3$  as the catalysts were unsuccessful and gave the inseparable mixtures of a range of products. Importantly, the Bronsted acids, such as acetic and trifluoroacetic acids, do not catalyze the process. Performing the reactions in polar solvents, such as acetonitrile, nitromethane, or sulfolane, also did not provided a significant acceleration of cycloadditions and even decreased the yields in comparison with the reactions with the excess alkene. Eventually it was stated that the addition of even 0.25 equiv. of **HFIP** as a solvent results in a noticeable acceleration of the

process, the best results being achieved in the presence of 1.5–2 equiv. of **HFIP** and 2 equiv. of an alkene. Using the examples of cyclohexene, cyclopentene, *cis*-butene-2, and isobutene, we observed considerable acceleration of the cycloaddition process (Scheme 2). For example, the reaction of **4** with cyclohexene in a 3-fold excess of cyclohexene (Path **A**) proceeded at 45 °C for 96 h to give about 50% of cycloadduct **5a**, whereas the same reaction in the presence of 2 equiv. of **HFIP** (Path **B**) was completed within 24 h at 20 °C to afford **5a** in 88% yield. Even more interesting results were obtained in the reactions of **4** with isobutene. Under the conditions of Path **A**, they afforded 60% of cycloadduct **5c** and 20% of an isomeric ene product, whereas under the conditions of Path **B**, compound **5c** was formed as a sole product in a higher yield and over a shorter reaction time. The reactions of **4** with cyclopentene and *cis*-butene-2 were also effectively catalyzed by **HFIP** to give the corresponding cycloadducts **5b,c** in high yields.



**Scheme 2.** Cycloaddition reactions of alkyne **4** in the presence of **HFIP**.

Currently, we are unable to specify the exact mechanism of the [2+2]-cycloaddition reactions accelerated by **HFIP**. However, one may suppose, that the molecule of **HFIP**, featuring strong donor properties and high polarity, coordinates with a 1,2-dicarbonyl core of **4**, thus reducing the electron density of the C≡C bond and enhancing its electrophilicity.

## Conclusions

In summary, we have significantly improved the method for obtaining hexafluoroisopropyl 4-chloro-2-oxobut-3-ynoate **4** that proved to be one of the strongest acetylenic enophile reported to date. The new protocol is performed as a one-pot procedure and allows one to avoid the use of expensive and toxic Me<sub>3</sub>SnCl. We also discovered a powerful catalytic effect imparted by **HFIP** to the [2+2]-cycloaddition reactions between 4-chloro-2-oxobut-3-ynoate and simple alkenes. The yields of the isolated cyclobutenes were very high.

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## Electronic supplementary information

Electronic supplementary information (ESI) available online: the experimental details, physical and spectral characteristics of the compounds obtained, NMR spectra of complex **2**, and the proposed reaction mechanism. For ESI, see DOI: 10.32931/ioXXXXx.

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