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Rapid lithiation of 1,1-difluoroalkenes

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Abstract

The dehydrofluorination reaction of trifluoroethoxy compounds to form 1,1-difluoroalkenes requires a two-fold excess of *n*-butyllithium. The initially formed alkene is rapidly lithiated by the reagent. Thus, when only one equivalent of base is used 50% of the difluoroalkene results along with 50% of starting material after quenching. © 1998 Elsevier Science S.A. All rights reserved.

Keywords: Dehydrofluorination reaction; Alkene

1. Introduction

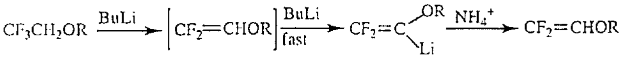
1,1-Difluoroalkenes are a worthy synthetic target. They are useful building blocks for the preparation of fluoroanalogues of natural products [1,2]. The terminal alkene is susceptible to both radical [3] and nucleophilic [4] attack. In some cases, electrophilic addition is also observed [5,6].

Terminal difluoroolefins have been prepared using Burton's difluoromethylene ylides [7], by S_N2' reactions on allylic trifluoromethyl compounds [8], by the loss of HBr from bromodifluoromethyl compounds [1], and by the addition of 2,2-difluorovinyllithium to electrophiles [2]. Stabilized difluorovinyl anions [9,10] have successfully been used to form 1,1-difluoroalkenes, but the simple loss of 1 mol of HF from trifluoroethyl compounds such as trifluoroacetoxy or trifluoroethyl sulfonates has not been observed. Exceptions include compounds with a group to acidify the proton on the carbon adjacent to the fluorine and where there is no possibility of further lithiation [11,12].

2. Results and discussion

A source of 1,1-difluoroalkenes for reaction with nitrones to ultimately give *β*-lactams compounds was sought. Elimination of HF from trifluoroethoxy appeared to be a reasonable reaction. However, problems with dehydrofluorination of trifluoroethoxy compounds were encountered.

We believed that problems arising during the dehydrofluorination of trifluoroethyl derivatives may be accounted for by the subsequent lithiation of the difluoroalkene that is formed. Lithiation of the 1,1-difluoroalkene is more rapid than its formation. Trapping of the vinyllithium species is competitive with its decomposition. In order to confirm that metallation is faster than elimination, we treated 2,2,2-trifluoroethoxy derivatives with an equimolar equivalent of *n*-butyllithium (It has been found that of *n*-butyllithium is as effective as LDA [13]). Indeed, upon quenching the reaction only one half of the trifluoroethyl derivative had been consumed. The scheme summarizes the observations. When 2 mol of *n*-butyllithium were used, conversion to the alkene was complete. (2,2,2-Trifluoroethoxy)benzene prepared by the method of Keegstra et al. [14] and 2,2,2-trifluoroethyl *p*-toluenesulfonate were chosen as substrates. The reaction, monitored by ^{19}F NMR [15], showed that an equimolar amount of base gave a 1:1 ratio of product to starting material while a two-fold excess of base gave only alkene, after quenching. Similar observations were made during the attempted dehydrofluorination of 2,2,2-trifluoroethyl diethyl carbamate [9]. Thus, synthesis of 1,1-difluoroalkenes from 2,2,2-trifluoroethoxy compounds requires a two-fold excess of base to first dehydrofluorinate and second lithiate the desired product. On work-up the desired alkene is liberated.



$$CF_3CH_2OR \xrightarrow{BuLi} \left[CF_2{=}CHOR \right] \xrightarrow[fast]{BuLi} CF_2{=}C\begin{smallmatrix} OR \\ Li \end{smallmatrix} \xrightarrow{NH_4^+} CF_2{=}CHOR$$

3. Experimental details

^{19}F NMR spectra were obtained at 282.33 MHz on a varian gemini 300 NMR spectrometer; chemical shifts were reported

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in ppm downfield from internal $CFCl_3$ (δ 0 ppm) as a reference.

3.1. Dehydrofluorination reactions

To a solution of CF_3CH_2OPh (0.39 g, 0.22 mmol) in 10 ml dry, distilled THF at −78°C was added *n*-butyllithium (3.2 ml, 0.69 M in hexanes, 0.22 mmol). After 40 min the solution was quenched with 2 ml sat. aq. NH_4Cl and a ^{19}F NMR spectrum was immediately obtained. It showed a 1:1 mixture of product and starting material. The reaction was performed with a two-fold excess of base, and after quenching, only a trace amount of starting material was present. The ^{19}F and ^{1}H NMR data were consistent with those that had previously been reported [15].

To a solution of 2,2,2-trifluoroethyl *p*-toluenesulfonate (Aldrich) (1.0 g, 3.9 mmol) in 25 ml dry, distilled THF at −78°C was added *n*-butyllithium (3.4 ml, 1.17 M in hexanes, 4.0 mmol). After 1.0 h the solution was quenched with 1.5 ml sat. aq. NH_4Cl and a ^{19}F NMR spectrum was immediately obtained. It showed a 1:1 mixture of product and starting material. Again when the reaction was performed with a two-fold excess of base, the starting material had been entirely consumed. ^{19}F NMR δ 90.7 (dd, $J_{HF}=14$ Hz, $J_{FF}=51$ Hz); 109.4 (d, $J_{FF}=51$ Hz). Attempted isolation of the vinyl tosylate led to decomposition products.

Acknowledgements

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