

Short communication

Reaction of halothane with carbonyl compounds in the presence of lithium diisopropylamide

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Received 6 November 1997; received in revised form 19 December 1997; accepted 6 January 1998

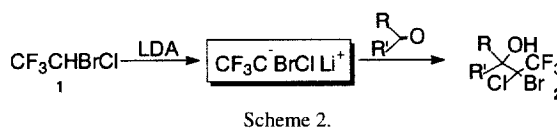
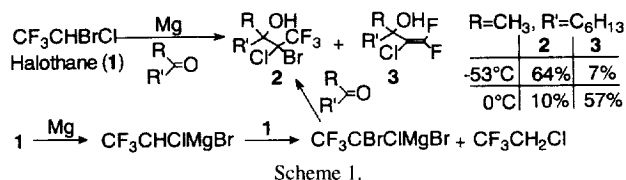
Abstract

Halothane, 2-bromo-2-chloro-1,1,1-trifluoroethane (**1**), reacts with carbonyl compounds in the presence of lithium diisopropylamide to give α -(1-bromo-1-chloro-2,2,2-trifluoroethyl) alcohols (**2**) in moderate to good yields. © 1998 Elsevier Science S.A. All rights reserved.

Keywords: Halothane; 2-Bromo-2-chloro-1,1,1-trifluoroethane; LDA; Aldehyde; Ketone; Nucleophilic addition

We have reported an abnormal Grignard reaction of halothane, 2-bromo-2-chloro-1,1,1-trifluoroethane (**1**) [1,2]. Thus, reaction of **1** with ketones in the presence of magnesium gave α -(1-bromo-1-chloro-2,2,2-trifluoroethyl) alcohols (**2**) in moderate yields at -53°C and α -(1-chloro-2,2-difluoroethyl) alcohols (**3**) at 0°C . Both products were transformed to various types of fluorine compounds [3,4] and **1** was found to be a useful building block for fluorine compounds. Unfortunately, this reaction with an aldehyde gave **3** in moderate yield, but not **2**. Mechanism of this abnormal reaction was speculated as shown in the bottom of Scheme 1.

In this speculation, **1** reacts with magnesium to give 1-chloro-2,2,2-trifluoroethylmagnesium bromide. This does not react with a carbonyl compound but react as a base with another mole of **1** to give 2-bromo-2-chloro-1,1,1-trifluoroethylmagnesium bromide, which reacts with a carbonyl compound to give **2**. Compound **3** must be formed by reduction of **2** with excess magnesium. As expected from the mechanism, a large excess of **1** is necessary: three equivalents of **1** for a carbonyl compound gave the best result. In the second step of this mechanism, the proton of **1** is abstracted with the Grignard reagent. If an appropriate base could abstract this proton and the carbanion, thus formed, could react with a



carbonyl compound, and compounds **2** would be formed much efficiently. Here, we would like to report our recent results based on the above expectation (Scheme 2).

In 1984, Hemer et al. [5] reported that the reaction of **1** with ethylmagnesium bromide resulted in the decomposition of the intermediate. This suggested that the carbanion from **1** is unstable, probably because it would suffer from α -elimination to form a carbene or β -elimination to form bromochlorodifluoroethene. We examined the reaction of **1** with carbonyl compounds in the presence of various bases, and found that lithium diisopropylamide (LDA) in DMF gave the best result, while butyllithium caused formation of a complex mixture and sodium hydride resulted in the recovery of the carbonyl compound.

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Table 1
Reaction of carbonyl compounds with halothane (**1**) in the presence of LDA

Run	Starting material	Yield %	S.M. %	Run	Starting material	Yield %	S.M. % ^a
1	Benzaldehyde	65	15	5	Acetophenone	76	11
2	Octyl aldehyde	47	11	6	Cyclohexanone	70	—
3	Cinnamaldehyde	67	12	7	Benzalacetone	67	14
4	2-Octanone	47	15	8	3-Methyl-2-cyclohexenone	44	— ^b

^aAll yields are isolation yields.

^b3-(1-Bromo-1-chloro-2,2,2-trifluoroethyl)-3-methylcyclohexanone (23%) was obtained.

The results of this reaction are shown in Table 1.^{1,2}

This reaction proceeded with both ketones and aldehydes and gave much better yields of **2** than the reaction of **1** in the presence of magnesium. Further, the latter reaction with alde-

¹ All the products were identified with authentic samples obtained by above references.

² A typical procedure is as follows. A solution of LDA (2.0 mmol), formed by mixing a solution of diisopropylamine (0.288 ml, 2.0 mmol) in THF (2 ml) with 1.6 M *n*-BuLi (2.0 mmol) in hexane, was added dropwise over 40 min at -78°C to a mixture of **1** (2.2 mmol, 0.232 ml) and benzaldehyde (1.0 mmol, 0.156 ml) in THF (3 ml). The reaction mixture was stirred at 0°C for 2 h, poured into 20% HCl and ice. The whole mixture was extracted with Et₂O. The Et₂O layer was washed with saturated NaCl, and dried over MgSO₄. After evaporation of the solvent, the residue was analyzed by GLC and found that it contained 2-bromo-2-chloro-1,1,1-trifluoro-3-phenyl-3-propanol and benzaldehyde in 78% and 16%, respectively. The residue was separated by a column chromatography (SiO₂, hexane: CH₂Cl₂, 3:2) to give 2-bromo-2-chloro-1,1,1-trifluoro-3-phenyl-3-propanol (195 mg, 65%) and benzaldehyde (16 mg, 15%). Use of one equivalent of **1** and LDA gave much smaller amount of **2**, while use of three equivalents of reagents did not improve the yield appreciably. Therefore, all the reactions shown above were carried out using two equivalents of **1** and LDA.

hydes gave only **3**, but not **2**. The reaction of 3-methyl-2-cyclohexenone gave a small amount of the 1,4-adduct, but other conjugated carbonyl compounds gave 1,2-adducts. This method needs much smaller amount of **1** and the reaction time is much shorter than the reaction in the presence of magnesium. As mentioned above, we have established conversion of **2** to other types of trifluoromethyl compounds. Therefore, this new reaction of **1** for **2** will increase the usefulness of halothane for synthesis of trifluoromethyl compounds.

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