Highly Controlled Ring-Opening of Siloxydifluorocyclopropanes: A Versatile Route to Cyclic Fluoroketones

Yoshiya Kageshima
Chiharu Suzuki
Kojun Oshiro
Hideki Amii*

Division of Molecular Science, Graduate School of Science and Technology, Gunma University, Kiryu, Gunma 376-8515, Japan
amii@gunma-u.ac.jp

Received: 22.10.2014
Accepted after revision: 31.10.2014
Published online: 20.11.2014

Abstract
A convenient access to cyclic fluoroketones that involves base-promoted ring-opening of siloxydifluorocyclopropanes is presented. Selective formation of \( \text{gem-difluorinated cycloalkanones} \) and monofluorinated enones has been achieved.

Key words fluorine, silicon, cyclopropane, ring-opening, ketone

Organofluorine compounds are of considerable interest in various industrial fields, and the introduction of fluorine atoms often endows organic molecules with attractive properties. Fluorine is an important element by virtue of the unique properties associated with the atom and its bond to carbon, its high electronegativity and its relatively small size. Given these attractive properties, fluoroorganic compounds find diverse applications in medicinal, agricultural, and material sciences. In particular, difluoromethylene compounds have received a great deal of attention because of their biological activities. A difluoromethylene carbon atom mimics the steric and electronic features of an ether oxygen atom or a carbonyl carbon atom. For the synthesis of difluoromethylene compounds, gem-difluorocyclopropanes are promising precursors; such compounds are readily prepared by a wide range of convenient synthetic routes. The transformations involving selective ring-opening of gem-difluorocyclopropanes provides a variety of useful fluoroorganic compounds. Meanwhile, siloxycyclopropanes are useful precursors of metal homoenolates in organic synthesis. Siloxydrofluorocyclopropanes are considered to be one of the most useful building blocks from which to obtain various difluoromethylene compounds. However, because of the lack of stability of fluorosiloxycyclopropanes, progress in the chemistry of fluorinated homoenolates has been much slower than that of nonfluorinated homoenolates. Herein, we report the ring opening of siloxydifluorocyclopropanes to afford gem-difluorinated cycloalkanones and monofluorinated enones selectively (Scheme 1).

Organofluorine compounds are of considerable interest in various industrial fields, and the introduction of fluorine atoms often endows organic molecules with attractive properties. Fluorine is an important element by virtue of the unique properties associated with the atom and its bond to carbon, its high electronegativity and its relatively small size. Given these attractive properties, fluoroorganic compounds find diverse applications in medicinal, agricultural, and material sciences. In particular, difluoromethylene compounds have received a great deal of attention because of their biological activities. A difluoromethylene carbon atom mimics the steric and electronic features of an ether oxygen atom or a carbonyl carbon atom. For the synthesis of difluoromethylene compounds, gem-difluorocyclopropanes are promising precursors; such compounds are readily prepared by a wide range of convenient synthetic routes. The transformations involving selective ring-opening of gem-difluorocyclopropanes provides a variety of useful fluoroorganic compounds. Meanwhile, siloxycyclopropanes are useful precursors of metal homoenolates in organic synthesis. Siloxydrofluorocyclopropanes are considered to be one of the most useful building blocks from which to obtain various difluoromethylene compounds. However, because of the lack of stability of fluorosiloxycyclopropanes, progress in the chemistry of fluorinated homoenolates has been much slower than that of nonfluorinated homoenolates. Herein, we report the ring opening of siloxydifluorocyclopropanes to afford gem-difluorinated cycloalkanones and monofluorinated enones selectively (Scheme 1).

Our initial studies focused on exhaustive formation of gem-difluorinated cycloalkanones. Previously, we demonstrated that sodium bromodifluoroacetate (BrCF₂CO₂Na) acts as a powerful difluorocarbene source to give difluorinated cyclopropanes and cyclopropenes. The use of BrCF₂CO₂Na was found to be effective for the selective formation of siloxydifluorocyclopropanes (Scheme 2).

In related pioneering work, in 1979, Kobayashi and Taguchi reported base-promoted ring-opening reactions of acetoxycyclopropane (Scheme 3). Under their reaction conditions, a mixture of difluoroketone and monofluorinated enones was obtained. However, because of the lack of stability of fluorosiloxycyclopropanes, progress in the chemistry of fluorinated homoenolates has been much slower than that of nonfluorinated homoenolates. Herein, we report the ring opening of siloxydifluorocyclopropanes to afford gem-difluorinated cycloalkanones and monofluorinated enones selectively (Scheme 1).

Organofluorine compounds are of considerable interest in various industrial fields, and the introduction of fluorine atoms often endows organic molecules with attractive properties. Fluorine is an important element by virtue of the unique properties associated with the atom and its bond to carbon, its high electronegativity and its relatively small size. Given these attractive properties, fluoroorganic compounds find diverse applications in medicinal, agricultural, and material sciences. In particular, difluoromethylene compounds have received a great deal of attention because of their biological activities. A difluoromethylene carbon atom mimics the steric and electronic features of an ether oxygen atom or a carbonyl carbon atom. For the synthesis of difluoromethylene compounds, gem-difluorocyclopropanes are promising precursors; such compounds are readily prepared by a wide range of convenient synthetic routes. The transformations involving selective ring-opening of gem-difluorocyclopropanes provides a variety of useful fluoroorganic compounds. Meanwhile, siloxycyclopropanes are useful precursors of metal homoenolates in organic synthesis. Siloxydrofluorocyclopropanes are considered to be one of the most useful building blocks from which to obtain various difluoromethylene compounds. However, because of the lack of stability of fluorosiloxycyclopropanes, progress in the chemistry of fluorinated homoenolates has been much slower than that of nonfluorinated homoenolates. Herein, we report the ring opening of siloxydifluorocyclopropanes to afford gem-difluorinated cycloalkanones and monofluorinated enones selectively (Scheme 1).

Our initial studies focused on exhaustive formation of gem-difluorinated cycloalkanones. Previously, we demonstrated that sodium bromodifluoroacetate (BrCF₂CO₂Na) acts as a powerful difluorocarbene source to give difluorinated cyclopropanes and cyclopropenes. The use of BrCF₂CO₂Na was found to be effective for the selective formation of siloxydifluorocyclopropanes (Scheme 2).

In related pioneering work, in 1979, Kobayashi and Taguchi reported base-promoted ring-opening reactions of acetoxycyclopropane (Scheme 3). Under their reaction conditions, a mixture of difluoroketone and monofluorinated enones was obtained. However, because of the lack of stability of fluorosiloxycyclopropanes, progress in the chemistry of fluorinated homoenolates has been much slower than that of nonfluorinated homoenolates. Herein, we report the ring opening of siloxydifluorocyclopropanes to afford gem-difluorinated cycloalkanones and monofluorinated enones selectively (Scheme 1).
enone 7, and its methanol adduct 8 were obtained due to the use of the strong bases such as LiOH and NaOH for deacetylation.

Taking advantage of the readily removable trimethylsilyl (TMS) protecting group, we have developed highly controlled ring-opening reactions of siloxydifluorocyclopropanes 2, which provide versatile synthetic routes to cyclic fluoroketones. To a stirred solution of siloxydifluorocyclopropane 2a in methanol was added sodium carbonate. After the reaction mixture was stirred at room temperature for 30 min, ring opening of 2a proceeded smoothly to provide difluorinated cycloheptanone 3a in 71% yield (Table 1, entry 1). Gratifyingly, no contamination by dehydrofluorinated product was observed (<1%) under the present conditions.

Other examples of the formation of gem-difluorinated cycloalkanones 3 are given in Table 1. By the use of alkaline metal carbonates (Na$_2$CO$_3$ or K$_2$CO$_3$), siloxydifluorocyclopropanes 2 underwent ring opening to give medium-sized difluorocycloalkanones 3 in moderate to good yields.

In contrast, through the use of fluoride such as tetrabutylammonium fluoride (TBAF) as a base, ring-opening dehydrofluorination of 2 took place predominantly. After a survey of suitable reaction conditions, treatment of 2 with TBAF in THF at –78 °C led to the formation of monofluorinated enones 4 (Scheme 4).

In summary, we have demonstrated a convenient and highly controlled route to gem-difluorinated cycloalkanones and monofluorinated enones. In the net transformations, one-carbon ring-enlargement and insertion of fluorinated methylene groups into the α-C–C bond in cycloalkanones 9 was achieved (Scheme 5). Further utilization of siloxydifluorocyclopropanes 2 as homoenolates is underway to explore other useful applications.
Acknowledgment

Financial support of the Ministry of Education, Culture, Sports, Science and Technology of Japan and the Japan Science and Technology Agency (JST) (ACT-C: Creation of Advanced Catalytic Transformation for the Sustainable Manufacturing at Low Energy; Low Environmental Load) is acknowledged. This work was partly supported by the ‘Element Innovation’ Project by the Ministry of Education, Culture, Sports, Science and Technology in Japan. We would like to thank Prof. Hiroshi Sano (Gunma University) for his useful suggestions. The authors thank Ms. Aya Takahashi (Gunma University) for her technical assistance. We are grateful to Central Glass Co., Ltd. for the gift of bromodifluoroacetic acid.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379599.

References and Notes


(17) Sodium bromodifluoroacetate is available from Tokyo Chemical Industry Co., Ltd. Otherwise, this reagent is prepared by the reaction of bromodifluoroacetic acid (available from SynQuest Laboratories, Inc.) with NaOH; see ref. 16.

(18) Formation of Siloxydifluorocyclopropanes 2: General Procedure: To a solution of silyl enol ether 1a (851 mg, 5.0 mmol) in diglyme (20 mL), was added a diglyme solution (20 mL) of sodium bromodifluoroacetate (1.48 g, 7.5 mmol) at 150 °C. The reaction mixture was stirred for 10 min at 150 °C, then, after cooling to room temperature, the reaction was quenched by the addition of water. Organic materials were extracted three times with hexane and the combined organic layers were washed with brine and dried over Na2SO4. After removal of the solvent under reduced pressure, the residue was purified by silica gel.
column chromatography (hexane–EtOAc, 50:1) to give 2a\textsuperscript{15,16} (800 mg, 73%) as a colorless oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, TMS): \(\delta = 2.22–2.10\) (m, 1 H), 1.96–1.78 (m, 2 H), 1.64–1.40 (m, 2 H), 1.38–1.20 (m, 4 H), 0.17 (s, 9 H). \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}, C\textsubscript{6}F\textsubscript{6}): \(\delta = 25.9\) (dd, \(J_{F-F} = 161.7\), \(J_{H-F} = 23.3\) Hz, 1 F), 15.4 (d, \(J_{F-F} = 161.7\) Hz, 1 F). GC-MS: \(m/z\) (%) = 220 (4) \([M]+\), 205 (10), 81 (31), 73 (100).

(19) \textbf{Formation of gem-Difluorinated Cycloalkanones 3; General Procedure:} A mixture containing siloxydifluorocyclopropane 2a (594 mg, 2.7 mmol) and Na\textsubscript{2}CO\textsubscript{3} (286 mg, 2.7 mmol) in MeOH (30 mL) was stirred at room temperature under an atmosphere of argon for 30 min. Organic materials were extracted three times with Et\textsubscript{2}O, and the combined organic layers were washed with brine and dried over Na\textsubscript{2}SO\textsubscript{4}. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (hexane–EtOAc, 5:1) to give 3a (283 mg, 71%) as a colorless oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, TMS): \(\delta = 2.70–2.64\) (m, 2 H), 2.15–2.03 (m, 2 H), 1.88–1.80 (m, 2 H), 1.76–1.62 (m, 4 H). \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}, C\textsubscript{6}F\textsubscript{6}): \(\delta = \text{not reported}\) (s, 2 F). \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \(\delta = 201.3\) (t, \(J = 249.2\) Hz), 118.6 (t, \(J = 249.2\) Hz), 38.8, 33.7 (t, \(J = 23.7\) Hz), 27.5, 23.6, 22.8 (t, \(J = 5.7\) Hz). GC-MS: \(m/z\) (%) = 148 (3) \([M]+\), 119 (15), 84 (61), 55 (100). IR (NaCl): 1739 cm\textsuperscript{–1}. Anal. Calcd for C\textsubscript{7}H\textsubscript{10}F\textsubscript{2}O: C, 56.75; H, 6.80. Found: C, 56.41; H, 6.89.

(20) \textbf{Formation of Fluorinated Cyclic Enones 4; General Procedure:} To a solution of siloxydifluorocyclopropane 2a (66.0 mg, 0.3 mmol) in diglyme (3.0 mL) was added TBAF (1 M in THF, 0.3 mL, 0.3 mmol) at \(-78\) °C under an atmosphere of argon. The reaction mixture was then stirred for 150 min at room temperature. Organic materials were extracted three times with Et\textsubscript{2}O and the combined organic layers were washed with brine and dried over Na\textsubscript{2}SO\textsubscript{4}. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (hexane–EtOAc, 5:1) to give 4a\textsuperscript{21} (34.9 mg, 91%) as a colorless oil. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}, TMS): \(\delta = 6.25\) (dt, \(J_{H-F} = 21.6, 6.6\) Hz, 1 H), 2.70–2.64 (m, 2 H), 1.89–1.87 (m, 2 H), 1.74–1.62 (m, 4 H). \textsuperscript{19}F NMR (282 MHz, CDCl\textsubscript{3}, C\textsubscript{6}F\textsubscript{6}): \(\delta = 43.0\) (d, \(J_{H-F} = 21.6\) Hz, 1 F). GC-MS: \(m/z\) (%) = 128 (4) \([M]+\), 85 (64), 72 (100). IR (NaCl): 1698 cm\textsuperscript{–1}.


© Georg Thieme Verlag Stuttgart · New York — Synlett 2015, 26, 63–66