Nucleophilic 5-endo-trig Cyclization of 3,3-Difluoroallylic Ketone Enolates: Synthesis of 5-Fluorinated 2-Alkyldiene-2,3-dihydrofurans

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Abstract: 3,3-Difluoroallylic ketones readily undergo nucleophilic 5-endo-trig cyclization through their metal enolates to afford 5-fluorinated 2-alkylidene-2,3-dihydrofurans. O-Cyclization exclusively occurred via intramolecular substitution of the vinylic fluorines.

Key words: cyclization, fluorine, alkenes, furans, 5-endo-trig, ketone enolates, vinylic substitution

gem-Difluoroalkenes (1,1-difluoro-1-alkenes) have unique reactivities toward nucleophiles, which are based on their electron-deficient and highly polarized nature. They facilitate extraordinary substitution reactions, which hardly proceed in normal alkenes.1 Difluoroalkenes readily undergo vinylic nucleophilic substitution (SNV) via addition to electrophilic difluoromethylene carbons and subsequent fluoride elimination. We have already reported syntheses of ring-fluorinated heterocycles by conducting the SNV reaction of difluoroalkenes in an intramolecular fashion.2 As well as sp3 heteroatom and carbon nucleophiles,3 sp2 nucleophiles4 have also participated in the 6-endo-trig cyclization to afford six-membered heterocycles (Scheme 1, eq 1). Furthermore, the high reactivity of 1,1-difluoro-1-alkenes has even allowed normally ‘disfavored’ 5-endo-trig cyclization,5-9 which provides scaffolds for 2-fluoro-4,5-dihydroheteroles and 2-fluorobenzoheteroles (Scheme 1, eq 2).10 Addressing the next challenge to the ‘disfavored’ process, we herein demonstrate the 5-endo-trig cyclization with the metal enolates of 3,3-difluoroallylic ketones, which are sp2 atom-based ambident nucleophiles and rotationally restricted around the anionic centers (Scheme 1, eq 3). This process efficiently provides 2-alkylidene-2,3-dihydrofurans11 by (i) constructing the heterocyclic ring and (ii) introducing a fluorine substituent and an alkylidene group onto the prescribed ring carbon.

The starting 3,3-difluoroallylic ketones are readily accessible through the following chemoselective difluoromethylation protocol.1.3-Ketoaldehydes 1, the precursors of 3,3-difluoroallylic ketones 2, were synthesized by the acylation of either morpholine enamines 3 or metal N-tert-butyl enamides prepared by deprotonation of imines 4, followed by hydrolysis (Scheme 2).12 Finally, difluoroallylic ketones 2 were obtained in moderate to high yield (27–86%) via difluoromethylation of ketoaldehydes 1 by a triaminophosphonium difluoromethylide, generated in situ from dibromodifluoromethane and tris(dimethylamino)phosphine (Scheme 2).13 Success of the exclusively selective difluoromethylation of 1 was due to the much higher reactivity of formyl groups compared to ketone carbonyl groups.

First, we sought bases suitable for the enolate formation and the subsequent 5-endo-trig cyclization by using difluoroallylic ketone 2a as a model substrate (Table 1). Lithium diisopropylamide (LDA) afforded the O-cyclization product 5a as a single isomer, albeit in low yield, while the C-cyclization product 6a was not detected at all (Table 1, entry 1).14 Two-fold increase in the amount of LDA (2 equiv) turned out to be effective for the cyclization (Table 1, entry 2). Also, potassium hydride (1 equiv) exclusively gave 5a and drastically improved its yield up to 79% (Table 1, entry 3). As in the case of LDA, use of doubled amounts of potassium hydride (2 equiv) was highly effective, leading to a 91% yield of the desired dihydrofuran 5a (Table 1, entry 4). Thus, the nucleophilic 5-endo-trig cy-
clization successfully proceeded even with rotationally restricted sp² nucleophiles in 2a. This is likely due to the large polarization of the CF₂=C moiety.¹⁰a

The optimized conditions obtained above for 2a were successfully applied to the cyclizations of a variety of difluoroallylic ketones 2 (Table 2).¹⁵,¹⁶ Ketones 2b–g, which are dimethylated at the allylic position, gave corresponding fluorine-containing dihydrofurans 5b–g in good to excellent yield. Difluoroallylic benzylic ketones 2e and 2f gave 2-benzylidene dihydrofurans 5e and 5f, respectively. Reactions of difluoroallylic ketones 2h–j, which possess a cyclohexane ring at the allylic position, constructed a spirocyclic structure in 5h–j. The reactions of α,α',α'',α'''-tetra-substituted ketones 2g and 2j were sluggish under the same conditions. However, the longer reaction time or the

Table 1  Screening of Bases Suitable for 5-endo-trig Cyclization of 2a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv)</th>
<th>Time (h)</th>
<th>Yield of 5a (%)</th>
<th>Yield of 6a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA (1.0)</td>
<td>5</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>LDA (2.0)</td>
<td>4</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>KH (1.0)</td>
<td>2</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>KH (2.0)</td>
<td>2</td>
<td>91</td>
<td></td>
</tr>
</tbody>
</table>

* Not detected.

The optimized conditions obtained above for 2a were successfully applied to the cyclizations of a variety of difluoroallylic ketones 2 (Table 2).¹⁵,¹⁶ Ketones 2b–g, which are dimethylated at the allylic position, gave corresponding fluorine-containing dihydrofurans 5b–g in good to excellent yield. Difluoroallylic benzylic ketones 2e and 2f gave 2-benzylidene dihydrofurans 5e and 5f, respectively. Reactions of difluoroallylic ketones 2h–j, which possess a cyclohexane ring at the allylic position, constructed a spirocyclic structure in 5h–j. The reactions of α,α',α'',α'''-tetra-substituted ketones 2g and 2j were sluggish under the same conditions. However, the longer reaction time or the

Table 2  5-endo-trig Cyclization of 3,3-Difluoroallylic Ketones 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield of 5 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>5a</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>5b</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>5c</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>5d</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>5e</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>5f</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
<td>5g</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>5h</td>
<td>91</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>5i</td>
<td>94</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>5j</td>
<td>97</td>
</tr>
</tbody>
</table>

* Pyridine was used as the solvent instead of THF.
use of pyridine as the solvent instead of THF improved the yields of 5g or 5j, respectively. Intriguingly, dihydrofuranc derivatives Sa-f and Si were obtained as single isomers about the exo double bond, judging from 1H NMR and 13C NMR studies. The configurations of Sa-f and Si were assigned as Z-isomers by a NOESY experiment of 5b.17 This Z-selectivity in the formation of dihydrofurans Sa-f and Si is interpreted as follows: the Z-enolates seem to be generated predominantly by deprotonation of difluoroallyl ketones 2 because of steric repulsion between substituents at both of the α positions of the carbonyl groups in 2. The subsequent cyclization presumably proceeds through the Z-enolates with retention of stereochemistry.

Difluoroallyl ketones 2, as shown in Table 2, underwent 5-endotrig O-cyclization via their enolate forms. The reaction afforded the corresponding 2-alkylidene-5-fluoro-2,3-dihydrofurans 5 without the formation of C-cyclization products, 3-fluorocyclopent-3-en-1-ones 6. Although 5-endotrig cyclization is assigned as disfavored in Baldwin’s rules,5 the reactivity of 1,1-difluoro-1-alkenes allows the substrates to undergo such an extraordinary cyclization.

In summary, we have demonstrated that 3,3-difluoroallyl ketones are effective substrates for Baldwin’s rules. In this process, a fluorine substituent was functionalized; it is expected that these compounds would serve as parts of bioactive molecules and versatile intermediates.18

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) For recent reviews, see: (a) Uneyama, K. Organo Fluorine Chemistry, Chap. 2.3; Blackwell Publishing: Oxford, 2006.
(12) For selected examples of conventional synthetic methodologies for 2-alkylidene-3-dihydrofurans, see: (a) Tiecco, M.; Testaferrari, L.; Tingoli, M.; Marinì, F. J. Org. Chem. 1993, 58, 1349; and references cited therein.
(13) For the synthesis of 1,3-ketoaldehydes from enamines, see: KuhlmeY, S.-R.; Adolph, H.; Rieth, K.; Opitz, G. Liebigs Ann. Chem. 1979, 617.
(15) Baldwin noted that when endocyclic alkylation of ketone enolates constructs five-membered rings, O-cyclization would be preferable because of an in-plane approach to enolates. The chemoselectivity in our case could be partially explained by a similar reasoning, albeit with the sp2-CF2 electrophile instead of sp3-C electrophiles. See: Baldwin, J. E.; Kruse, L. J. J. Chem. Soc., Chem. Commun. 1977, 233.
were washed with brine and dried over MgSO₄. After removal of the solvent under reduced pressure, the residue was purified by TLC on silica gel (EtOAc–hexane, 1:5) to give 5b (122 mg, 97%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃): δ = 1.26 (d, J_{HF} = 1.1 Hz, 6 H), 3.45 (d, J = 7.5 Hz, 2 H), 4.20 (d, J_{HF} = 5.4 Hz, 1 H), 4.73 (td, J = 7.5 Hz, J_{HF} = 3.4 Hz, 1 H), 7.18–7.22 (m, 3 H), 7.27–7.30 (m, 2 H). ¹³C NMR (126 MHz, CDCl₃): δ = 30.1 (d, J_{CF} = 2 Hz), 30.9, 44.2 (d, J_{CF} = 2 Hz), 79.7 (d, J_{CF} = 8 Hz), 99.4, 125.9, 128.2, 128.4, 141.0, 157.5 (d, J_{CF} = 276 Hz), 160.6 (d, J_{CF} = 3 Hz).

¹⁹F NMR (470 MHz, CDCl₃): δ = 46.2 (s). IR (neat): 3028, 2970, 2931, 1801, 1726, 1703, 1454, 1247, 1129, 1126, 1088, 993, 748, 698 cm⁻¹. Anal. Calcd for C₁₄H₁₅FO: C, 77.04; H, 6.93. Found: C, 76.80; H, 7.16%.

(16) 3,3-Disubstituted 5-fluoro-2-alkylidene-2,3-dihydrofurans 5 are air- and heat-stable.

(17) In the NOESY experiment of dihydrofuran 5b, substantial correlation between the methyl protons and the vinylic proton H₄ was observed. No NOE correlation was detected between the methyl protons and the allylic protons H₅ (Figure 1).

Figure 1 NOE correlation between protons in dihydrofuran 5b

(18) For a review on bioactivities of fluorinated compounds, see: Müller, K.; Faeh, C.; Diederich, F. Science 2007, 317, 1881.