Organic LETTERS

Letter

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Difluorohomologation of Ketones

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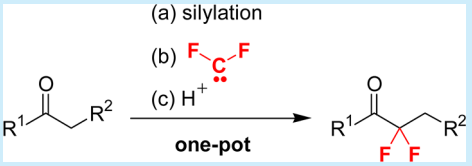
Supporting Information

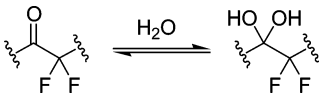
ABSTRACT: A method for the homologation of ketones with the CF_2 fragment is described. The reaction involves silylation, room-temperature difluorocyclopropanation of silyl enol ethers, and selective ring opening of cyclopropanes under acidic conditions. The whole three-step sequence is conveniently performed in a one-pot mode.



Organofluorine compounds have attracted significant attention in recent years, primarily because of their widespread applications in medicinal chemistry.[1] While many approved drugs contain either the trifluoromethyl group or the fluorine atom as a substituent, there are only a few examples of medicines bearing a difluoromethylene fragment.[1] At the same time, there is steadily growing interest toward CF_2-containing compounds that is not only associated with their utility in drug design[2] but also due to unique properties imparted by the CF_2 unit in various fields such as metal-free click cycloadditions,[3] conformation analysis,[4] and carbohydrate chemistry.[5]

α,α-Difluoroketones constitute a valuable class of compounds for drug discovery. Indeed, two fluorine atoms favor the formation of hydrates which can inhibit proteolytic enzymes by mimicking tetrahedral intermediates involved in peptide hydrolysis[6] (Scheme 1). Current methodologies for

Scheme 1. Hydrate Formation

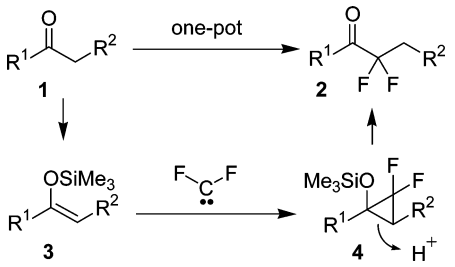


their synthesis rely either on modification of existing *α,α*-difluorocarbonyl functionality[7] or on direct difluorination of ketones which frequently require prior functionalization.[8]

Herein we report a practical protocol for the one-pot conversion of readily available carbonyl compounds **1** into their difluorinated homologues **2** (Scheme 2). Our concept is based on facile room-temperature difluorocyclopropanation of silyl enol ethers **3** and a discovery that cyclopropanes **4** may undergo selective ring opening.[9,10]

While conventional cyclopropanols are well studied,[11] their *gem*-difluorinated derivatives have remained virtually unexplored despite the fact that numerous methods for the addition of difluorocarbene to alkenes are known.[12] In particular, it has previously been described that silyl enol ethers **3** can be converted to difluorocyclopropanes **4** at elevated temperatures (using either $PhHgCF_3$/NaI at 80 °C[13] or $BrCF_2CO_2Na$ at 150 °C[14]). We decided to perform

Scheme 2. Concept for CF_2-Homologation



cyclopropanation of **3** under milder conditions using a system for difluorocarbene generation which was recently developed in our group.[15]

Silyl enol ether **3a** derived from acetophenone was selected as a model substrate, and it was treated with (bromodifluoromethyl)trimethylsilane (Me_3SiCF_2Br)[16,17] and hexamethylphosphoramide (HMPA) at room temperature within 2 h[15] (Table 1). Analysis of the reaction mixture by ^{19}F NMR indicated clean formation of cyclopropane **4a** as the sole product. However, when the reaction was worked up in a conventional manner using water/hexane extraction, the crude product contained **4a** along with ketones **2a** and **5** (Table 1, entry 1). Our attempts to isolate cyclopropane **4a** using nonaqueous workup followed by flash chromatography on silica gel were unsuccessful, again pointing to its instability.

Fragmentation of difluorocyclopropanol derivatives to fluoroenones of type **5** has been observed in the literature.[10,18] At the same time, facile formation of ketone **2a** by protonation of the cyclopropane C−C bond was unexpected, and this prompted us to perform a screening of conditions to effect this process selectively. Thus, stirring of a dichloromethane solution of **4a** with aqueous acid or base in a biphasic system again gave mixtures (entries 2 and 3). Surprisingly, addition of methanesulfonic or trifluoroacetic acids did not affect cyclopropane **4a** (entries 4 and 5). Addition of solutions of HCl in dioxane or HBr in acetic acid

Received: January 12, 2015

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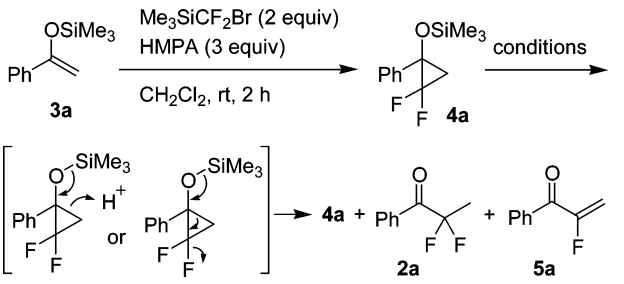
DOI: 10.1021/acs.orglett.5b00097
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Reaction of Enol Ether 3a



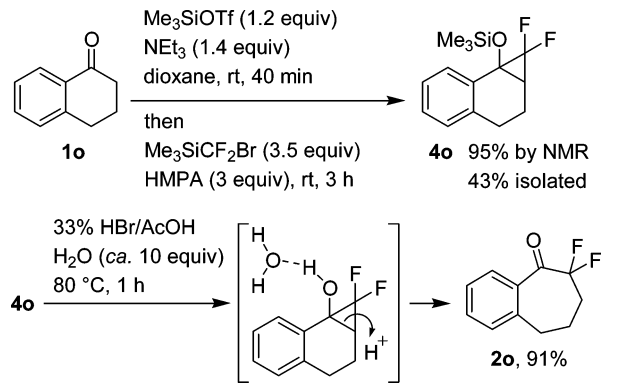
no.	conditions	4a:2a:5a[a]
1	workup with water/hexane	50:25:25[b]
2	stirring with sat. aq Na_2CO_3, rt, 1 h	50:0:50
3	stirring with conc aq HCl, rt, 1 h	9:69:26
4	MsOH (5 equiv), rt, 1 h	100:−:−
5	TFA (5 equiv), rt, 1 h	100:−:−
6	4 M HCl (in dioxane) [8 equiv], rt, 18 h	22:78:−
7	33% HBr in AcOH [11 equiv], rt, 1 h	6:94:−
8[c]	4 M HCl in dioxane [8 equiv], 65 °C, 1 h	−:100:−

[a]Ratio was determined by ^{19}F NMR for reaction mixtures. [b]Determined by ^{19}F NMR of crude product. [c]Transformation of **3a** to **4a** was performed in dioxane.

to a dichloromethane solution of **4a** provided homogeneous systems. This effected the desired transformation of **4a** to **2a**, though incomplete conversions were frequently observed (entries 6 and 7). It should be pointed out that formation of fluoroenone **5a** was completely suppressed under these strongly acidic conditions. Finally, use of dioxane as a solvent for the difluorocarbene generation step and treatment of the cyclopropane with 4 M HCl/dioxane at 65 °C during 1 h provided difluoroketone **2a** as the sole product (entry 8).

Then we decided to perform CF_2-insertion into a cyclic substrate. Since transformation of ketones into silyl enol ethers using a silyltriflate/triethylamine combination is an efficient process,[19] we tried to perform difluorocyclopropanation in the same flask, simply by adding Me_3SiCF_2Br and HMPA to a solution of formed silyl enol ether. This concept was verified starting from α-tetralone **1o**, which led to clean formation of cyclopropane **4o** (Scheme 3). Unexpectedly, product **4o** turned out to be quite stable and reluctant to undergo fragmentation on workup. However, this compound undergoes partial decomposition on silica gel, and after chromatography it was isolated in 43% yield as a stable liquid.[20] The enhanced stability of **4o** proved to be a problem, and its reaction with 4 M HCl in dioxane was slow even on heating! Switching to a more acidic system, HBr in acetic acid, provided noticeable acceleration in the conversion of **4o**, but the reaction rate was not reproducible. Based on the latter phenomenon, we conjectured that the reaction is limited by desilylation of silyl ether, with the cyclopropanol being the true intermediate undergoing the ring opening.[21] A hydroxyl group can engage in hydrogen bonding with a molecule of solvent or adventitious water thereby fostering cyclopropane fragmentation. Rewardingly, the addition of about 10 equiv of water (100 μL per 0.5 mmol of substrate) and heating with HBr/AcOH within 1 h gave difluoroketone **2o** in excellent yield (Scheme 3). Finally, the whole sequence involving silylation, cyclopropanation, and ring opening was performed in a one-pot manner. In this case, evaporation of dioxane was necessary before the addition of HBr/AcOH, and this procedure afforded ketone **2o** in 92% yield based on tetralone.[22]

Scheme 3. Reaction of Tetralone 1n

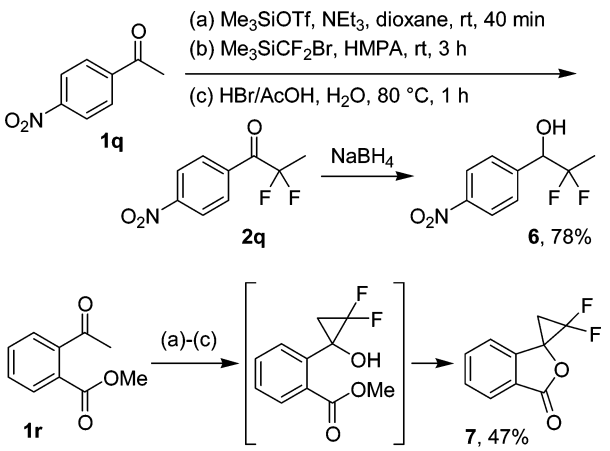


Under the optimized conditions, a variety of ketones were subjected to the one-pot CF_2-homologation (Table 2). Acyclic and cyclic ketones provided products **2** in good yields. Even isopropyl-substituted ketone **1n** reacted nicely despite the fact that intermediate cyclorpopane has to be attacked by the proton at the quaternary carbon (entry 14). In the reaction of α,β-unsaturated substrate **1j**, analysis of the final reaction mixture indicated partial addition of HBr to the C=C double bond, but typical basic workup (aq Na_2CO_3) caused elimination of HBr leading to product **2j** in excellent yield (entry 10). In reactions of ketones **1e−g**, the products were unstable to HBr/AcOH (partial demethylation for **2e**; deallylation for **2f**; decomposition for **2g**), but switching to a milder HCl/dioxane system afforded good yields of ketones **2e−g** (entries 5−7).

In the reaction of *p*-nitroacetophenone **1q**, expected difluoroketone **2q** was difficult to purify by chromatography, likely, because of the addition of water at the C=O group, which is typical for fluorinated carbonyl compounds. In this case, the crude product was reduced with sodium borohydride affording alcohol **6** in 78% yield based on ketone **1q** (Scheme 4).The reaction of acetophenone **1r** bearing an *ortho*-methoxycarbonyl group led to spirocyclic product **7**, which may form by lactonization of intermediate cyclopropanol.

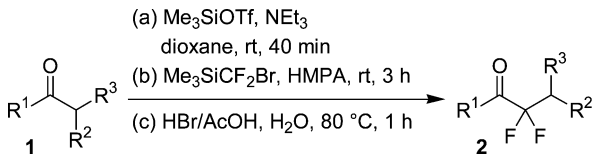
When a typical one-pot procedure was applied to 1,1-diphenylacetone (**1s**) and 1-adamantyl methyl ketone (**1t**),

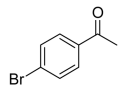
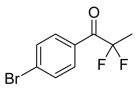
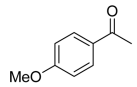
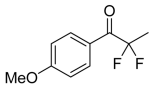
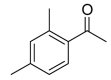
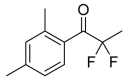
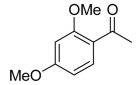
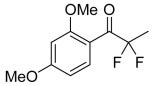
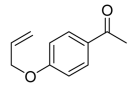
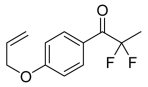
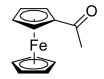
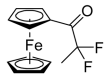
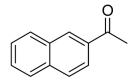
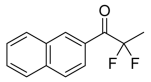
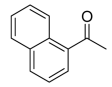
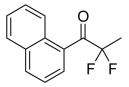
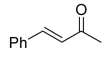
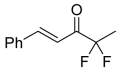
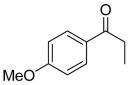
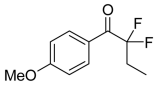
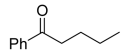
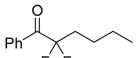
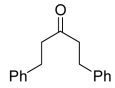
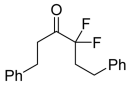
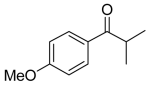
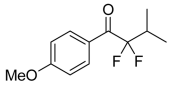
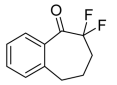
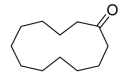
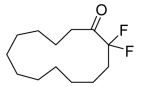
Scheme 4. Reactions of Substrates 1p,q



DOI: 10.1021/acs.orglett.5b00097
Org. Lett. XXXX, XXX, XXX−XXX

Table 2. CF_2-Homologation of Ketones

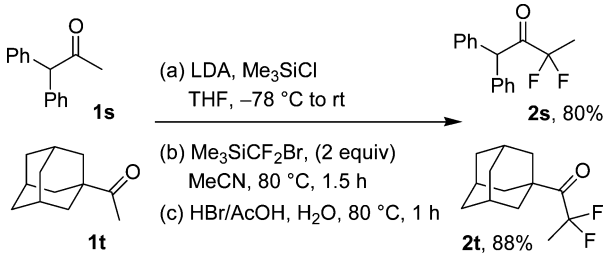


no.	substrate		product		yield of **2**, %[a]
1		**1a**		**2a**	71[b] (95[c])
2		**1b**		**2b**	89
3		**1c**		**2c**	95
4		**1d**		**2d**	82
5[d]		**1e**		**2e**	90
6[d]		**1f**		**2f**	95
7[d]		**1g**		**2g**	73
8		**1h**		**2h**	96
9		**1i**		**2i**	67
10		**1j**		**2j**	86
11		**1k**		**2k**	80
12		**1l**		**2l**	65
13		**1m**		**2m**	67
14		**1n**		**2n**	74
15		**1o**		**2o**	92
16		**1p**		**2p**	70

[a]Isolated yield. [b]The decrease in isolated yield is due to volatility of the product. [c]Determined by ^{19}F NMR with internal standard. [d]Ring opening was performed using 4 M HCl in dioxane, 65 °C, 1 h.

moderate yields of homologation products were obtained (22% for **2s**, 43% for **2t**), which may be associated with steric hindrance slowing down either silylation or cyclopropanation steps. For these substrates, a different one-pot protocol was developed (Scheme 5). Ketones were silylated with LDA/

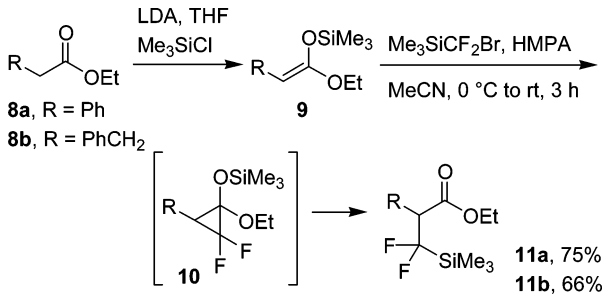
Scheme 5. Reactions of Substrates 1r,s



Me_3SiCl in THF under conventional conditions,[23] followed by solvent exchange to acetonitrile and addition of Me_3SiCF_2Br and heating at 80 °C.[24] Subsequent treatment of intermediate cyclopropanes with HBr/AcOH furnished products **2s,t** in high yields.

It was also interesting to perform homologation of esters. Thus, esters **8a,b** were first treated with LDA and Me_3SiCl in THF to generate silyl ketene acetals **9** (Scheme 6). The latter

Scheme 6. Reactions of Esters



substances were not isolated but, after solvent exchange to acetonitrile, were treated with Me_3SiCF_2Br/HMPA. As a result, products **11a,b** were isolated in reasonable yields, formally corresponding to the alkylation of starting esters **8a,b**.[25] Presumably, initially formed cyclopropanes **10** are unstable at room temperature, owing to the strong donating effect of two oxygen atoms, and undergo rearrangement into products **11**.

In summary, a convenient protocol for the CF_2-homologation of ketones is described. The key feature of the method is the selective protonation of difluorocyclopropane at the nonfluorinated fragment. At the same time, the opportunity to effect difluorocyclopropantion of silyl enol ethers under very mild conditions allows the three-step sequence to be performed in a one-pot fashion.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization data, copies of NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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DOI: 10.1021/acs.orglett.5b00097
Org. Lett. XXXX, XXX, XXX−XXX

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Ministry of Science (Project MD-3256.2015.3), Russian Foundation for Basic Research (Project 15-33-20133), and the Russian Academy of Sciences.

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(21) In support of this proposition is the fact that acetophenone-derived cyclopropane **4a** did not react with anhydrous MsOH and TFA in dichloromethane solution (see Table 1).

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DOI: 10.1021/acs.orglett.5b00097
Org. Lett. XXXX, XXX, XXX−XXX