Difluorohomologation of Ketones

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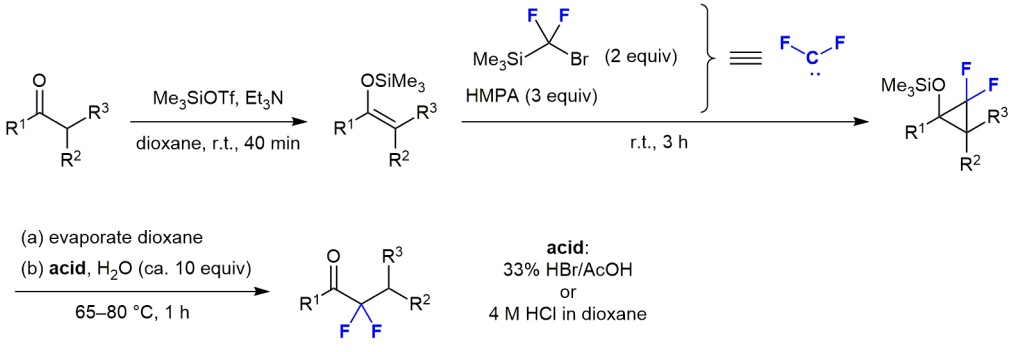
Despite significant developments in the synthesis of organofluorine compounds, efficient methods for accessing *gem*-difluorinated products are still limited. Indeed, the existing approaches involve either harsh deoxofluorination reagents or multiple functional group manipulations. α,α-Difluorinated ketones are attractive substrates for medicinal chemistry and drug discovery applications, since they efficiently form adducts (hemiketals), with water and other nucleophiles, that may resemble tetrahedral intermediates involved in the hydrolysis of peptides. Recently, a general protocol for the conversion of readily available ketones into their difluorohomologues (Scheme 1) was described by Alexander Dilman, Mikhail Kosobokov, Vitalij Levin and Marina Struchkova from Zelinsky Institute of Organic Chemistry (Moscow, Russian Federation). Professor Dilman said: "The method involves a sequence of three steps, which are performed in a single reaction flask! It starts with the generation of silyl enol ether by using trimethylsilyltriflate and triethylamine – a clean, virtually quantitative, and rapid process. Second, to the resulting mixture were successively added (bromodifluoromethyl) trimethylsilane (Me_3SiCF_2Br) and hexamethylphosphoramide (HMPA). In this step, Lewis basic HMPA attacks at silicon of Me_3SiCF_2Br and generates difluorocarbene, which readily (at room temperature!) reacts with the electron-rich enol–ether double bond to furnish difluorocyclopropanes." While difluorocyclopropanes are typically stable and isolable, these cyclopropanes, bearing a silyloxy group, turned out to be quite unpleasant to handle, revealed Professor Dilman. Indeed, while some of them (those derived from cyclic ketones) can be purified by chromatography and can even be distilled under vacuum, others (those derived from acetophenones) do not survive simple aqueous work-up. The latter observation suggested an opportunity for cyclopropane ring opening. But, in fact, a great amount of work was invested to optimize this particular stage.

"We were puzzled by the observation that under anhydrous conditions, protonation of silyloxycyclopropanes did not occur even under the action of strong acids such as trifluoroacetic or methanesulfonic acid," said Professor Dilman. This led to the idea that water is needed to hydrolyze the silyl ether into a free hydroxyl group. Finally, after a series of optimization experiments, it was established that the reaction proceeded most effectively when a small amount of water was added. "It is likely that a cyclopropanol, not silyloxycyclopropane, is the real species that undergoes ring opening," said Professor Dilman. "The hydroxyl group can engage in hydrogen bonding, thereby polarizing a C–C bond in the cyclopropane. Another feature of this step is that a solution of hydrogen bromide in acetic acid was the optimal acidic species to effect cyclopropanol protonation by heating to 80 °C," explained Professor Dilman. "Preliminary evaporation of dioxane was necessary, since otherwise dioxane itself reacts with hydrogen bromide, affording by-products which complicate product purification."

The majority of ketones worked well with this protocol, affording difluorohomologated ketones in good yields. However, for some substrates, heating with HBr/AcOH proved to be quite harsh (e.g., decomposition of ferrocene, or partial de-



Scheme 1 Difluorohomologation process

methylation of methoxy groups). In these cases, a less drastic treatment was used – hydrogen chloride in dioxane with heating at 65 °C (Figure 1).

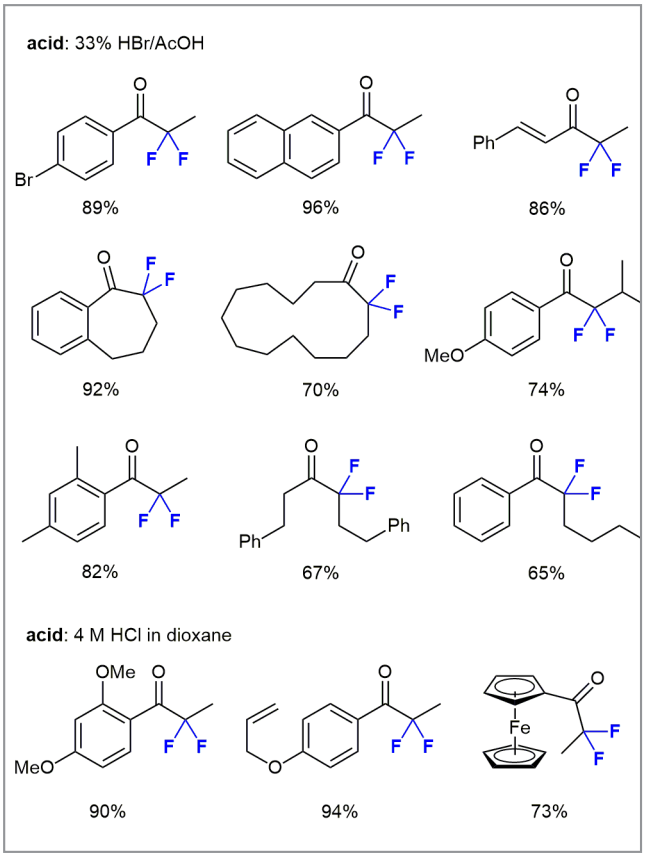


Figure 1 Substrate scope

With sterically hindered substrates (Figure 2), a different one-pot procedure was developed, involving generation of silyl enol ethers by means of conventional deprotonation of ketones with lithium diisopropylamide followed by quenching with Me_3SiCl. Subsequent difluorocarbene addition and cyclopropane ring opening were carried out under typical conditions.

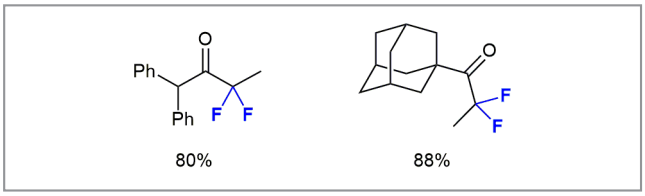


Figure 2 Difluorohomologation of hindered substrates

Professor Dilman concluded: "Taken together, these procedures allow for a straightforward transformation of a wide variety of ketones into their difluorohomologated counterparts. The key reagent, Me_3SiCF_2Br, is now available commercially from several companies, even on kilogram scale, or can be prepared according to literature procedures."

Professor David O'Hagan from the School of Chemistry, University of St. Andrews (UK), an organofluorine chemistry expert, commented: "This is a nice straightforward and general method for the synthesis of α,α-difluoro ketones. The authors demonstrate that the chemistry can be carried out on a wide range of ketones, and such products have proven useful, for example as rationally designed inhibitors for hydrolytic enzymes. There is no doubt that the CF_2 group is enjoying a high profile at present, largely due to the availability of a next generation of reagents that can generate difluorocarbene. This chemistry from Dilman's lab is another nice example demonstrating the utility and versatility of difluorocarbene in organic synthesis."

About the authors

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Mikhail Kosobokov was born in Orel (Russia) in 1988. After finishing his MSc degree in organic chemistry from Lomonosov State University (Moscow, Russia) in 2011, he joined Professor A. Dilman's group. Mikhail defended his PhD thesis in 2014, developing chemistry of the fluorinated silicon reagents. He is currently working as postdoctoral associate with Professor Norio Shibata (Nagoya, Japan).

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Prof. A. Dilman

Alexander Dilman was born in 1976 in Moscow (Russia). From 1991–1993 he studied at the Moscow Chemical Lyceum (a high school specialized on chemistry). In 1993, he entered the Higher Chemical College, and then, in 1999, continued education in the Graduate School of Zelinsky Institute of Organic Chemistry (with Professor S. L. Ioffe). After obtaining his PhD degree in 2001, he spent one year as a postdoctoral researcher in the group of Professor H. B. Kagan at the Université Paris Sud (France). In 2003, he returned to the Zelinsky Institute and started independent work. In 2008, he completed his habilitation studies (Dr. Sci. in Russia), and in 2011 became a head of laboratory. His interests include the chemistry of fluorine and silicon.