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DEFLUORINATIVE COUPLING REACTIONS OF *gem*-DIFLUOROOLEFINS WITH ORGANOLITHIUM REAGENTS. NOVEL, FACILE METHODS FOR CHAIN ELONGATIONS OF ALDEHYDES LEADING TO AMIDES, ACETYLENES, AND KETONES[1)]

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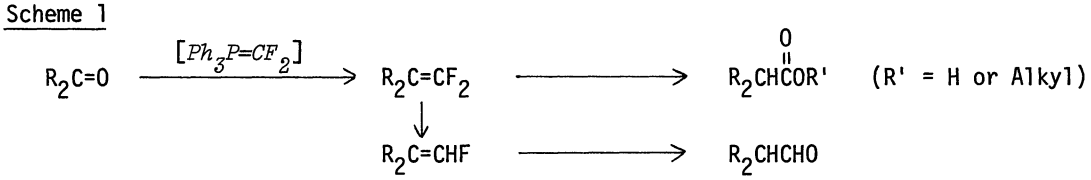
Three types of coupling reactions of *gem*-difluoroolefins derived easily from aldehydes with lithium reagents (R'Li and R'_2NLi) are described which constitute the facile procedures for conversions of aldehydes (RCHO) to amides ($RCH_2CONR'_2$), acetylenes (R-C≡C-R'), and ketones (RCH_2COR').

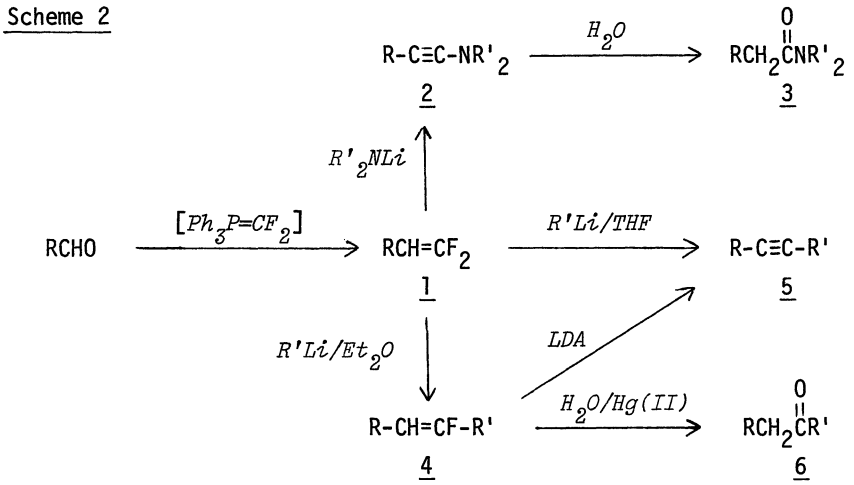
As part of the research program designed to find new applications of organofluorine compounds in *fluorine-free* organic synthesis, we have recently reported[2)] facile defluorinative elaborations of *gem*-difluoroolefins easily prepared *via* the difluoromethylenation[3)] of carbonyl compounds which allow the one-carbon homologations of carbonyl compounds leading to aldehydes, carboxylic acids, and esters (Scheme 1).

Scheme 1



In a continuation of these studies, we now wish to report defluorinative coupling reactions of *gem*-difluoroolefins (1) derived from aldehydes with organolithium reagents which are useful for the conversion of aldehydes to amides (3), acetylenes (5), and ketones (6), as depicted in Scheme 2.

Scheme 2



First of all, we should mention that the reaction of 1 with lithium amides allows the one-carbon homologation of aldehydes leading to the amides (3) since this type of reaction is known to afford the ynamines (2)[4] which are converted to 3 by spontaneous hydration[5] (see entries 1-3, Table 1). This synthetic sequence presents the first example of fluorine-mediated homologation of aldehydes leading to amides.[6,7]

Next, we examined carbon-carbon bond forming reactions of 1 with alkyllithium reagents in detail. We have now found that the reaction of 1 with 2.5 equiv of butyllithium in ether at -78°C afforded the alkylated monofluoroolefins (4) in good yields, whereas the use of THF instead of ether as the solvent gave rise to the acetylenes (5) along with small amounts of allenic compounds (entries 4-7, Table 1). Furthermore, we found that phenyllithium did not react with 1 in ether, but reacted in THF to give an approximately 1:1 mixture of the acetylenic and allenic products (entry 9). Although the observed remarkable solvent dependency on the reaction course has no straightforward explanation and still awaits detailed studies, both the selective C-C bond forming reactions are of synthetic value from the following viewpoints.

First, the reaction of 1 with alkyllithium in THF provides a novel, alternative approach to the conversion of aldehydes to unsymmetrical acetylenes (5). This fluorine-mediated sequence is in direct contrast to the previous bromine-[8] and chlorine-mediated sequence[9] depicted in Scheme 3, since the net effect of the former sequence allows *gem*-difluoroolefins to serve as an equivalent of acetylenic cation ($R\text{-}C{\equiv}C^{+}$) with "reactivity umpolung",[10] whereas in the latter ones both *gem*-dibromo- and chloroolefins serve as an equivalent of acetylenic anion ($R\text{-}C{\equiv}C^{-}$) of normal reactivity.

Scheme 3

$$RCHO \longrightarrow RCH{=}CX_2 \xrightarrow{BuLi} [R\text{-}C{\equiv}C\text{-}Li] \xrightarrow{R'X} R\text{-}C{\equiv}C\text{-}R'$$

X = Br, Cl

Furthermore, we found that the reaction of monofluoroolefin (4) described above with lithium diisopropylamide (LDA) also gave rise to the acetylene (5); this two-step procedure, albeit more tedious, exhibited a higher selectivity as compared with the direct reaction of 1 with alkyllithiums (entry 10 *vs.* entry 5).

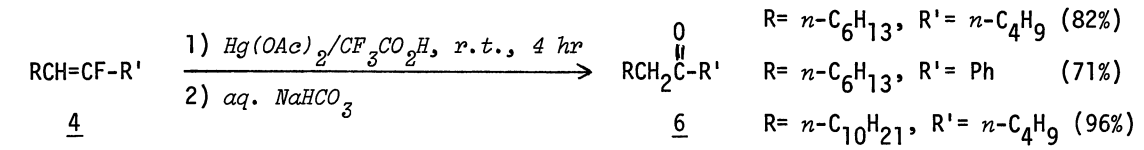
Secondly, the reaction of 1 with alkyllithiums in ether constitutes a new synthetic sequence for the chain elongation of aldehydes leading to the ketones (6) (see Scheme 1).[6] We found that the resulting monofluoroolefins (4) were easily converted to the ketones (6) in good yields[11] (Scheme 4) by the mercury-assisted procedure[2] previously reported by our laboratory for the hydrolysis of monofluoromethylene compounds to aldehydes.

Table 1. Reactions of Fluoroolefins (1 and 4) with Lithium Reagents[a]

Entry	Fluoroolefin[b]	Lithium Reagents [Solvent]		Product[c]	Isolated Yield (^{1}H NMR Yield)
1	n-$C_6H_{13}CH=CF_2$	LDA	[Et_2O]	n-C_6H_{13}-C≡C-N[$CH(CH_3)_2$]$_2$	70%[d]
2		$(CH_3CH_2)_2NLi$	[Et_2O]	n-C_6H_{13}-C≡C-N(CH_2CH_3)$_2$	45%[e]
3	$C_6H_5CH=CF_2$	$(CH_3CH_2)_2NLi$	[Et_2O]	C_6H_5-C≡C-N(CH_2CH_3)$_2$	73%[e]
4	n-$C_6H_{13}CH=CF_2$	n-C_4H_9Li	[Et_2O]	n-$C_6H_{13}CH=CF$-C_4H_9-n	76%[f]
5		n-C_4H_9Li	[THF]	n-C_6H_{13}-C≡C-C_4H_9-n	(66%)[g]
6	n-$C_{10}H_{21}CH=CF_2$	n-C_4H_9Li	[Et_2O]	n-$C_{10}H_{21}CH=CF$-C_4H_9-n	83%[h]
7		n-C_4H_9Li	[THF]	n-$C_{10}H_{21}$-C≡C-C_4H_9-n	(90%)[i]
8	n-$C_6H_{13}CH=CF_2$	C_6H_5Li	[Et_2O]	[j]	
9		C_6H_5Li	[THF]	n-C_6H_{13}-CH=CF-C_6H_5 (45%)[k] n-C_6H_{13}-C≡C-C_6H_5 (45%)	
10	n-$C_6H_{13}CH=CF$-C_4H_9-n[l]	LDA[m]	[THF]	n-C_6H_{13}-C≡C-C_4H_9-n	(89%)[n]

[a]Unless otherwise noted, the reaction was carried out as follows. A solution of butyllithium in hexane (1.5 *M*, 8 ml) was added to a solution of *gem*-difluoroolefin (5 mmol) in the given solvent (10 ml) at -78°C over a period of 20 min. The mixture was warmed to room temperature and stirred for 2 hr. The resultant mixture was poured into water and usual work-up of the ethereal extract gave the product. [b]Unless otherwise indicated, optimal preparations of these fluoroolefins have been reported in ref 3. [c]All products exhibited data (IR, ^{19}F-and ^{1}H-NMR, and/or MS) in accord with the assigned structures or with the reported literature values. [d]Bp 65-67°C/2 mmHg. [e]Cited from ref 4. [f]Bp 114-116°C/26 mmHg; *E*/*Z*=1.6 : 1 (by ^{19}F NMR assay); ^{19}F NMR(Et_2O, ext. CF_3CO_2H) δ+25.4 (m, $J_{F-H(olefinic)}$=19.0 Hz) and δ+30.4 (m, $J_{F-H(olefinic)}$=32.0 Hz). [g]Contaminated with 28% allenic product(s). [h]Bp 124-125°C/7 mmHg. [i]Contaminated with 9% allenic product(s). [j]The starting material was recovered completely. [k]Bp 98°C/2 mmHg: *E*/*Z*=1 : 3 (by ^{19}F NMR assay): ^{19}F NMR δ+23.0 ($J_{F-H(olefinic)}$=20.0 Hz) and δ+41.5($J_{F-H(olefinic)}$=32.0 Hz). [l]Obtained *via* the reaction in entry 4. [m]Exactly 1.0 equiv of the lithium reagent was used. [n]Contaminated with 9% of allenic product(s).

Scheme 4



Although these fluorine-mediated synthetic sequences for the conversion of aldehydes to acetylenes and ketones are limited by the availability of organolithium reagents, they appear more advantageous over the previous methods in the points of the easy accessibility of *gem*-difluoroolefins[3] and simplicity of the procedures. Thus, the present methods should find unique application in certain synthetic transformations.

In summary, the present work, coupled with our preceding one,[3] demonstrates that combinations of facile difluoromethylenation of aldehydes (RCHO) with appropriate defluorinative elaborations permit ready access to a broad variety of homologated functionalities such as RCH_2CHO, RCH_2COR', RCH_2COOR', $RCH_2CONR'_2$, and R-C≡C-R'. Thus, these works serve to illustrate the potential applicability of organofluorine compounds in *fluorine-free* organic synthesis.

References and Notes

1) Part VIII on "Applications of Organofluorine Reagents in Organic Synthesis." Part VII: ref. 3. This work was supported in part by a Grant-in-Aid for Scientific Research (to T. N. and N. I.) from the Ministry of Education.

2) S. Hayashi, T. Nakai, N. Ishikawa, *Chem. Lett.*, 1980, 651.

3) S. Hayashi, T. Nakai, N. Ishikawa, D. J. Burton, D. G. Naae, and H. S. Kesling, *Chem. Lett.*, 1979, 983.

4) D. R. Strobach, *J. Org. Chem.*, 36, 1438 (1971).

5) For a recent review on the ynamine chemistry, see J. Ficini, *Tetrahedron*, 34, 3 (1978).

6) For a recent review on one-carbon homologations of carbonyl compounds, see S. F. Martin, *Synthesis*, 1979, 673.

7) For more recent examples, see A. E. Kluge and I. S. Cloudsdale, *J. Org. Chem.*, 44, 4847 (1979); M. Mikolajczyk, S. Grzejszczak, A. Chefczynska, and A. Zatorski, *ibid*, 44, 2967 (1979).

8) E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 1972, 3769.

9) J. Villieras, P. Perriot, and J. F. Normant, *Synthesis*, 1975, 458.

10) For the terminology, see D. Seebach, *Angew. Chem. Int. Ed. Engl.* 8, 639 (1969).

11) These ketones exhibited the physical (mp or bp) and spectral (IR and NMR) data in accord with the assigned structures or with the reported literature values.

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