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Difluoromethylene compounds as precursors to ketones, carboxylic acids, esters, amides and carbonates

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Abstract

A review of difluoromethylene compounds as precursors to carbonyl compounds. Many ketones, carboxylic acids, esters, amides and carbonates, especially trifluoroalanine dipeptides, can be easily achieved due to the reactivity of difluoromethylene compounds or generated through the reactive difluoromethylene intermediates.

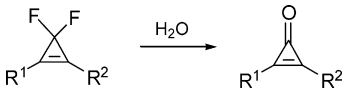
Keywords: Amide; Difluoromethylene; Difluorodiiodomethane; Carbonyl

1. Introduction

Difluoromethylene compounds are in great demand in medicinal chemistry and many synthetic methods have been developed for their preparation. [1–4]. In spite of the strength of the C–F bond, fluorine can be displaced readily from organic molecules in some cases. Thus, the difluoromethylene group often serves as a precursor for the introduction of the carbonyl moiety to form ketones, carboxylic acids, esters, amides or carbonates (Scheme 1). Reactions have been or will be designed by taking the advantage of fluorine as the functional group to realize the synthesis which may be elusive by other methods. On the other hand, harnessing the leaving propensity of fluorine can be helpful in designing a drug bearing the difluoromethylene group and avoiding the loss of fluorine during preparation procedures. The special reactive properties of the difluoromethylene group contribute significantly to the mechanism in the research for fluorinated drugs with potential for biomedical applications. Some of this chemistry is detailed below.

2. From stable difluoromethylene compounds

Although *gem*-difluorocyclopropenes are quantitatively converted to cyclopropenones in aqueous media, they are stable under anhydrous conditions [5] (Eq. (1)). *gem*-Difluorocyclopropane is much more stable and less likely to



(1)

hydrolyze than its cyclopropene analogue. This probably arises from the fact that the ring stain of the *gem*-difluorocyclopropene enhances the generation of a stable structure such as a cyclopropenone by hydrolysis when water is present.

When **5** was heated in perfluorobenzene, ketone **7** was obtained in 55% yield (Scheme 2). Fluorene trifluoride **8** was also isolated. Difluoromethylene product **8** was moisture sensitive and readily hydrolyzed to ketone **7** in aqueous solution and hydrolysis was the final step in the fluorine shift process as indicated in $H_2{}^{18}O$ labeled experiments [6]. In this case, no ring stain is expected in the five-member ring, but hydrolysis occurred. However, apparently no report of hydrolysis of the difluorodiphenylmethane chain analogue has appeared. It may be that the carbocation which results when a single fluorine remains associated with the ring structure is sufficiently stabilized as the intermediate permitting relatively easy replacement by the hydroxyl group.

Perfluoromethylenecyclopropane **9** is very susceptible to nucleophilic attack (Scheme 3). Amines and water added exothermally to **9** to gave amide **10** and acid **11** [7]. 2,2,3,3-Tetrafluoromethylenecyclopropane was synthesized from **9** and

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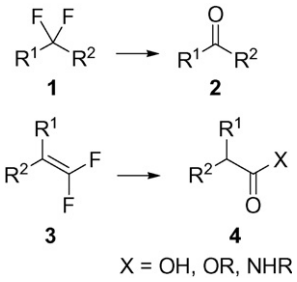
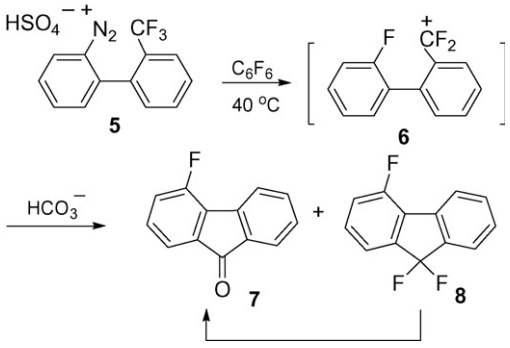
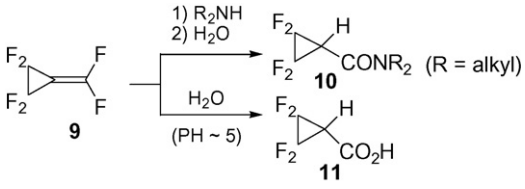


Scheme 1.



Scheme 2.

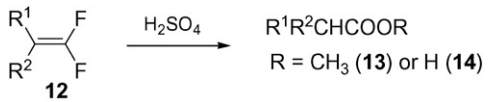


Scheme 3.

its thermal isomerization was studied [8]. In this case, the relief of the ring strain becomes the driving force again as was the case with the *gem*-difluorocyclopropene.

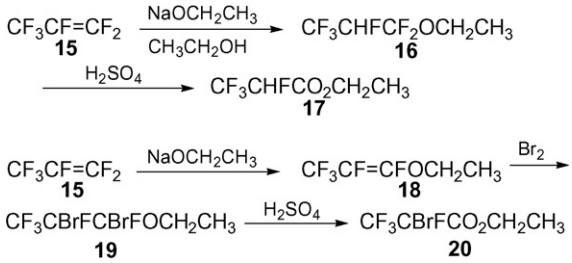
The *gem*-difluoroolefins were converted to carboxylic acids or esters by using concentrated sulfuric acid or mercury acetate in trifluoroacetic acid [9] (Scheme 4).

Carbocation intermediates were generated and attacked by water under acidic conditions. These reactions normally don't happen under basic reaction conditions indicating the stability of the *gem*-difluoroolefin towards alkali. If R^1 and R^2 are not activating moieties, hydroxide ion does not react at the difluoromethylene site.



12	R^1	R^2
a	H	Ph
b	H	$(CH_3)_2CHC_6H_4$
c	Me	Ph
d	Me	$(CH_3)_2CHCH_2C_6H_4$
e	H	*n*-C_6H_{13}
f	H	*n*-$C_{10}H_{21}$

Scheme 4.



Scheme 5.

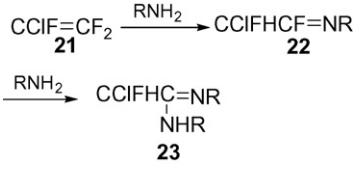
However, if the substituents are electron-withdrawing groups which enhance the elctrophilicity of CF_2, the addition by sodium ethoxide at difluoromethylene occurred readily. Thus, the preparations of ethyl 2,3,3,3-tetrafluoropropionate ($CF_3CHFCO_2C_2H_5$, **17**) and ethyl 2-bromo-2,3,3,3-tetrafluoropropionate ($CF_3CBrFCO_2C_2H_5$, **20**) were reported starting from hexafluoropropene ($CF_3CF{=}CF_2$, **15**) [10] (Scheme 5). Compound **16** was converted to the ester **17** in acidic solution. Compound **20** was prepared through **18** and **19**.

Amines are more nucleophilic than water and can be used to produce amides when they react with *gem*-difluoroolefins. Chlorotrifluoroethylene (**21**) when reacted with primary amines gave several α-chloro-α-fluoroacetamidines **23** [11] (Scheme 6). Imidoyl fluoride **22** was proposed as an intermediate.

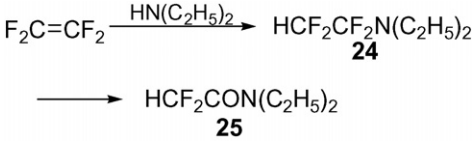
Tetrafluoroethene (TFE) reacted in a similar manner to form difluoroamidines [12]. Although their formation was indicated, imidoyl fluorides were not isolated. *N*-substituted α,α-difluoroacetamides were obtained by reactions of primary amines with TFE in the presence of borax [13]. It was proposed that the fluoroamides were produced by hydrolysis of intermediate amidines with borax serving as the source of water [12].

Reactions of secondary amines with TFE are very exothermic. Although the products could be isolated by distillation at reduced pressure, they were not stable to heat and were hydrolyzed very easily to form the corresponding α,α-difluoroacetamides. For example, tetrafluoroethyldiethylamine, **24**, from TFE and diethylamine, was quantitatively hydrolyzed to *N*,*N*-diethyl-α,α-difluoroacetamide **25** [12] (Scheme 7).

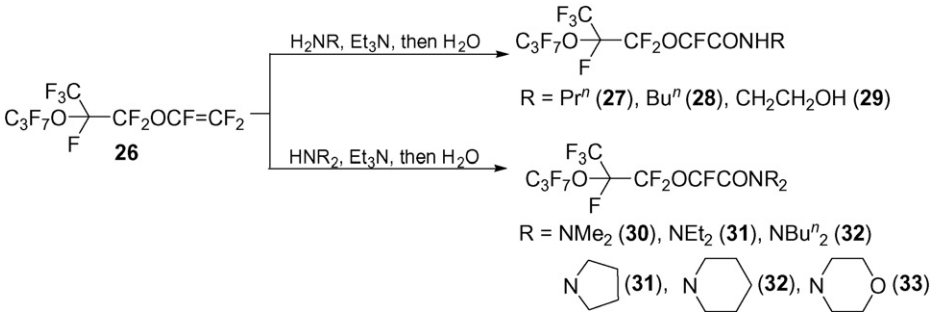
Similarly, 1,1,2-trifluoro-2-(2′-heptafluoropropoxyhexafluoropropoxy)ethylene **26**, a *β*,*β*-difluoroenol ether, reacted with a variety of primary and secondary amines to afford the



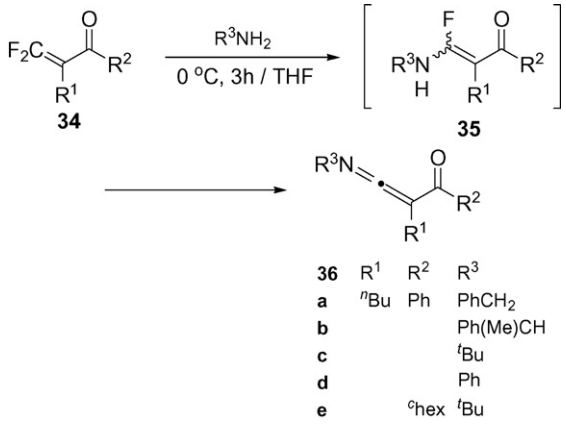
Scheme 6.



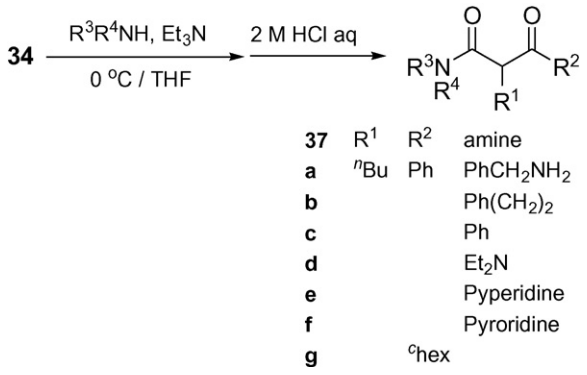
Scheme 7.



Scheme 8.



Scheme 9.

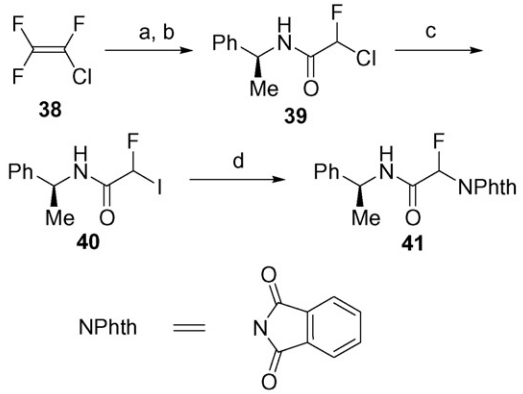


Scheme 10.

corresponding amides (**27**–**33**) [14] (Scheme 8). Acid fluorides were assumed as the intermediates for the formation of primary amides **27**–**29**.

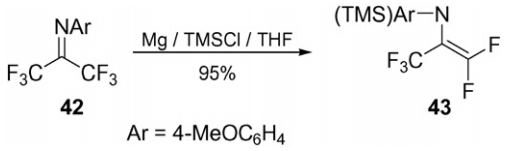
Another stable intermediate type, α-oxoketenimines (**36a**–**e**), was isolated without water quenching in 66–84% yields by the reaction of 2,2-difluorovinyl ketones and primary amines (Scheme 9). Amides **37** were obtained in 75–93% yields by treatment of **34** with primary or secondary amines at 0 °C in the presence of trimethylamine followed by hydrolysis (Scheme 10). The reaction provided a facile method for acetoacetylation of primary and secondary amines [15]. This is an example of the synthetic application of this methodology.

Another application of difluoroolefins to the synthesis of biologically interesting molecules was reported. A design to get protected fluoroglycine **41** from chlorotrifluroethene **38** is shown in Scheme 11. Chlorofluoroacetamide, **39**, which was

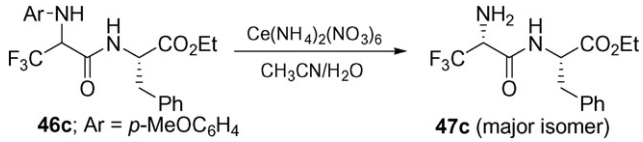


a, (s)-PhCH(Me)NH_2/ Et_2O/ sealed tube/ r.t./ 140 h; b, 10% H_2SO_4 (aq)/ reflux/ 2h (33% overall for a and b); c, NaI/ Me_2CO/ reflux/ 120 h (92%); d, KNPhth/ DMF/ r.t./ 5-6 h (50%)

Scheme 11.



Scheme 12.

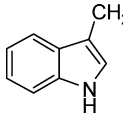
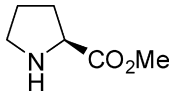


Scheme 14.

obtained from the reaction of **38** with (s)-1-phenylethylamine, was treated with sodium iodide in acetone followed by substitution with potassium phthalimide in DMF to give **41** [16]. Both diastereomers of **41** were isolated by recrystallization and/or flash chromatography.

Traditionally, condensation of two amino acids is used for amide bond formation; in that process, expensive dehydrating reagents are often used. Uneyama and co-workers [17] reported a novel route to trifluoroalanine dipeptides via non-condensation of amino acids by using 2-aminoperfluoropropene as a synthon. The method could be used to synthesize structurally unique and highly functionalized peptides. The key compound **43** was prepared in a 95% yield by the magnesium-promoted defluorinative *N*-silylation of imine **42** (Scheme 12). Enamine **43** readily reacted even with the less nucleophilic amino group of amino esters due to the strong electron-withdrawing effect of two substituted fluorine atoms and trifluoromethyl group. However, it was stable enough to be easily handled and is storable at −5 °C. Thus, **43** smoothly proceeded in reactions with a variety of amino esters in DMF at room temperature within 1.5 h (Scheme 13). After the subsequent acid-catalyzed hydrolysis of the intermediate, imidoyl fluoride, **45**, the desired trifluoroalanine dipeptides, **46**, were obtained as diastereomeric mixtures in 68–93% yields (Table 1). The *N*-protecting group, 4-methoxyphenyl, could be removed easily by using cerium ammonium nitrate to give deprotected dipeptides **47** (**47a**; R_1 = H, R_2 = Bn, 83%, **47c**; R_1 = $PhCH_2$, R_2 = Et, 80%). The diastereoisomers of dipeptides **47c** could be isolated in an enantiomerically pure form by column chromatography (Scheme 14). X-ray crystallographic analysis was used to determine the absolute stereochemistry of the hydrochloric acid salt of the major diastereomer **47c**. The preparation of the optical pure (*R*,*S*) and (*S*,*S*) trifluoroalaninephenylalanine dipeptides was reported for the first time.

Table 1
Syntheses of trifluoroalanine dipeptides **46** by the reaction of **43** with amino esters **44**

44	R^1	R^2	% Yield	de[a]
44a	H	Bn	91	–
44b	CH_3	Me	86	14
44c	$PhCH_2$	Et	93	28
44d	$(CH_3)_2CHCH_2$	Me	85	48
44e	$HOCH_2$	Me	80	8
44f	$HOC_6H_4CH_2$	Me	68	18
44g	$CH_3SCH_2CH_2$	Me	88	21
44h		Me	79	19
44i		–	69	26

[a] Diastereomeric ratios were analyzed by HPLC.

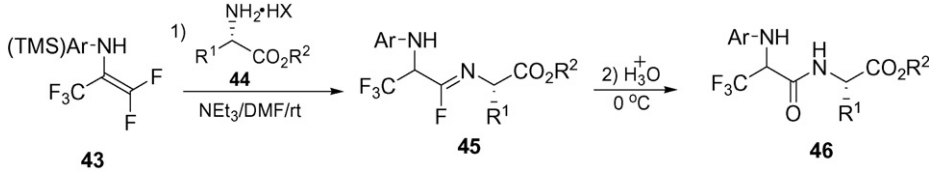
3. From intermediate difluoromethylene compounds

Bromodifluoromethyl-containing and iododifluoromethyl-containing compounds (for example, **48**, **49**, **57** and **63**, **65**, **69** given below) generated carboxylic acids or esters when they were treated with aqueous bases. The intermediates involved various *gem*-difluoroalkenes and are demonstrated in the following examples.

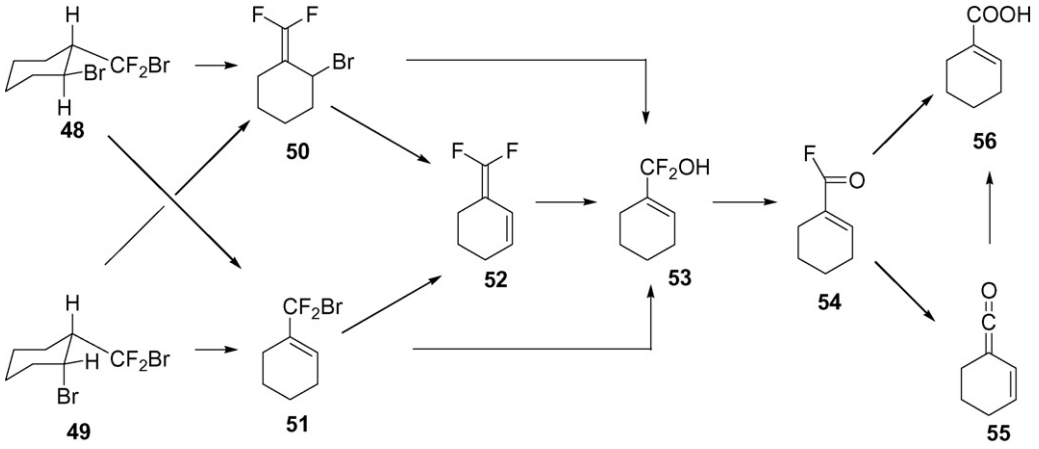
1-Cyclohexene-1-carboxylic acid, **56**, was the exclusive organic product when a mixture of dibromides, **48** and **49**, was heated in the presence of excess aqueous potassium hydroxide. Intermediate products **51**, **52** and **54** were distilled as they were formed. Compound **52** was subjected to basic conditions to form **56**. The author proposed that the acid was formed partly via the *gem*-difluorodiene, **52**, and possibly through nucleophilic substitution on **51** by hydroxide [18] (Scheme 15). By an S_N2' or addition-elimination process, **50** can further react to give **53**. The unstable α, α-difluoro alcohol **53** subsequently eliminates HF to give the acyl fluoride **54**.

The observation that **57** was converted to acid **62** suggests an SN_2' attack on **59** by hydroxide as an alternative pathway. The bridgehead diene **58** could not be the intermediate because ring strain of the C=C double bond at the bridgehead carbon would result in a highly energetic intermediate [19] (Scheme 16).

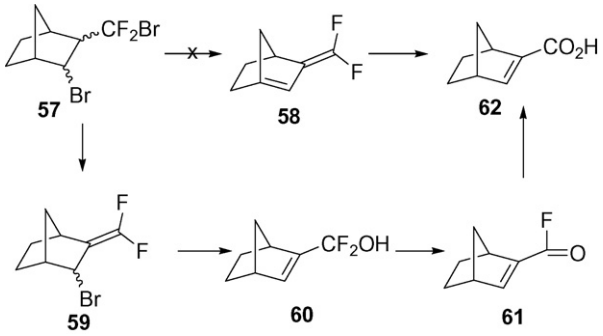
Concomitantly with work on the bromodifluoromethyl group, its analogue iododifluoromethyl group was investigated. The reaction of difluorodiiodomethane with alkynes in the presence of hydrogen peroxide or lead tetraacetate (LTA)



Scheme 13.

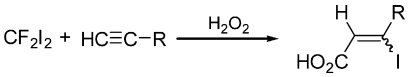


Scheme 15.



Scheme 16.

afforded the corresponding β-iodo-α,β-unsaturated carboxylic acids or esters (Eqs. (2) and (3)). Although the normal radical addition product, 1,1-difluoro-1,3-diiodo-2-alkene



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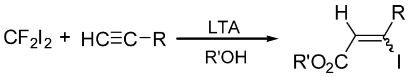


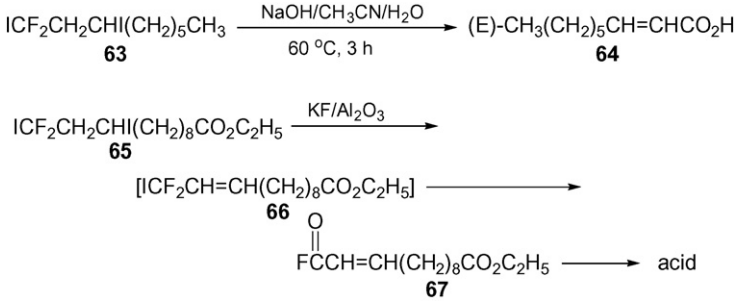
(3)

($ICF_2CH{=}CHIR$), was not found, it was believed to be the intermediate [20,21].

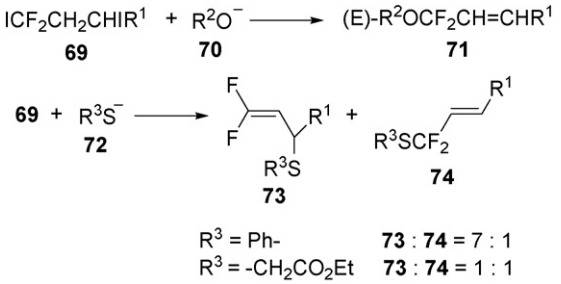
Similarly, α,β-unsaturated carboxylic acid **64** was obtained (Scheme 17) when **63** reacted with aqueous sodium hydroxide in acetonitrile at 60 °C for 3 h. Treatment of **65** with KF/Al_2O_3/DMF gave a small amount of α,β-unsaturated carboxylic acid fluoride **67** which was considered to be the precursor of the acid [22]. Compound **66** was detected by ^{19}F NMR but could not be isolated.

Therefore, the above results apparently show that iododifluoromethyl alkenes ($ICF_2CH{=}CHR^1$, **68**) and 1,1-difluoro-1,3-diiodo-2-alkene ($ICF_2CH{=}CHIR$) were labile, and easily hydrolyzed whereas the bromo-analogues were stable [23,24]. Interestingly, when some nucleophiles were used as dehydroiodination agents and also as traps, derivatives were obtained with **68**. For example, the reaction of **69** with sodium phenoxide **70** in DMF at room temperature for 4 h gave E-difluoroallylphenyl ether **71** exclusively in high yield. Sodium thionates, **72**, in DMF were found to react quickly with **69** at room temperature to give two products **73** and **74** [22] (Scheme 18).

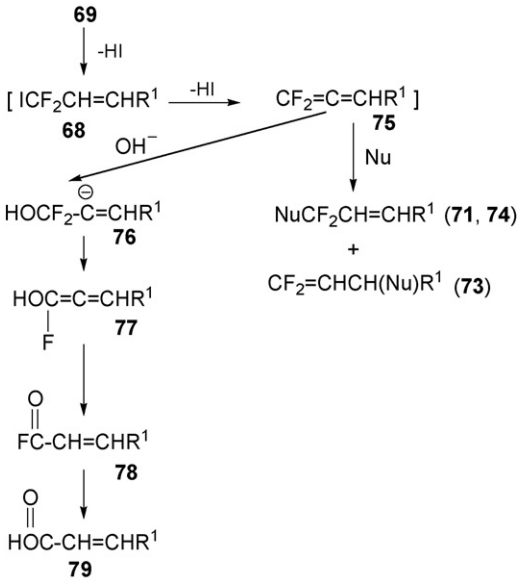
A mechanism through a difluoroallene intermediate ($CF_2{=}C{=}CHR^1$, **75**) resulting from repeated eliminations of HI from **69** was proposed. In **75**, methine carbon and terminal CF_2 were two electrophilic reaction sites. A weaker nucleophile mainly added to the methine group to give **73** and partly reacted at CF_2 group to afford **74**. The opposite results were obtained for stronger nucleophiles, the substitution occurring exclusively at the difluoromethylene site. When a simple base was used as mentioned above, the generation of the products (α,β-unsaturated carbonyl fluoride and carboxylic acid) could be also rationalized in terms of attacking of



Scheme 17.



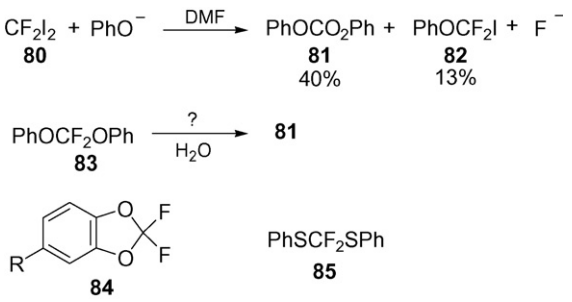
Scheme 18.



Scheme 19.

hydroxyl anion on the terminal CF_2 of allene. The formation of the allene **75** apparently depended on both the proton affinity of the base and the good leaving ability of allylic iodine (Scheme 19).

The difluoromethylene group could also be transferred to the carbonyl moiety in carbonate. The reaction of difluorodiiodomethane with sodium phenoxide gave diphenyl carbonate as the major product with a small amount of difluoroiodomethyl phenyl ether accompanying with fluoride [25]. The reason for carbonate formation was unclear. It is supposed that **81** arises from hydrolysis of $PhOCF_2OPh$, **83**, whereas its bis(thio)analogue, **85**, was stable (Scheme 20). The two neighboring



Scheme 20.

oxygen atoms activate the CF_2 carbon greatly enhancing the susceptibility of **83** to hydrolysis. The cyclic analogue 2,2-difluoro-1,3-benzodioxole (**84**) is stable and recent biomedical research based on a large number of its derivatives has been patented [26]. The difference in the CF_2 reactivity in a chain structure compared with a cyclic one remains ambiguous.

4. Conclusion

In summary, the reactivity of difluoromethylene compounds or their intermediates is demonstrated in their transformations to ketones, carboxylic acids, esters, amides and carbonates. Promising applications await exploration.

Acknowledgements

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