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Michael Addition of 2,2-Difluoroketene Silyl Acetal. Preparation of 4,4-Difluoroglutamic Acid and 5,5-Difluorolysine

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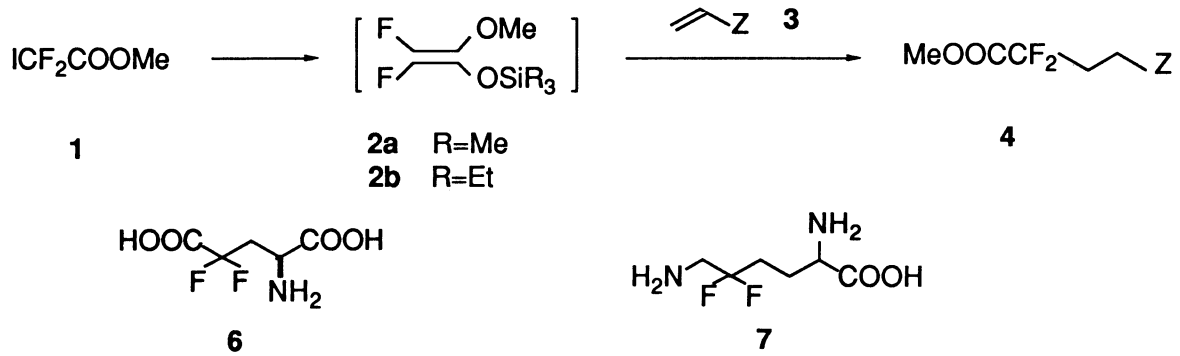
2,2-Difluoroketene silyl acetal , generated *in situ* by treating methyl difluoroiodoacetate with Zn followed by chlorosilane, readily reacted with α,β-unsaturated carbonyl compounds or acetals to give the 1,4-addition products, preferentially. The difluoro analogs of glutamic acid and lysine were prepared through the present reaction.

Introduction of fluorine into organic molecules brings about alteration of the physical and chemical properties of the parent molecules, which often results in enhanced biological activities or alteration of the physiological responses owing to the characteristic features of fluorine atom.[1] In recent years, bioactive compounds that contain the difluoromethylene group have been attracting increased interests[2] and several new methods for the preparation of functionalized difluoromethylene compounds have been developed.[3] Among these, the Reformatsky reaction of halodifluoroacetate has been widely utilized to introduce this group into organic molecules.[4] An efficient generation of 2,2-difluoroketene silyl acetals **2** from the iodide **1** and their synthetic utility involving the preparation of fluorinated sugars and amino acids was shown in the aldol reactions with aldehydes[5] and imines.[6] Alkylation of difluoroacetate by the reaction of the copper reagent with organic halides[7] and atom-transfer reaction of difluoroiodoacetate[8] are alternative methods in this field. In this report, we report the Michael addition of 2,2-difluoroketene silyl acetal **2** with α,β-unsaturated carbonyl compounds and acetals giving the 1,4-addition products preferentially, and as an application of the present reaction, preparations of 4,4-difluoroglutamic acid **6**[9] and 5,5-difluorolysine **7**[10] are also reported.

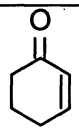
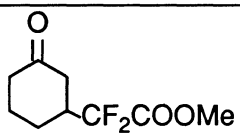
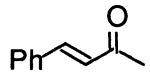
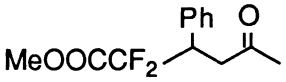
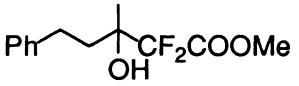
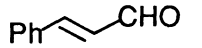
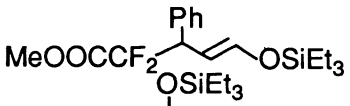
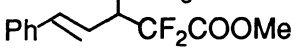
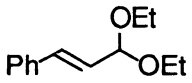
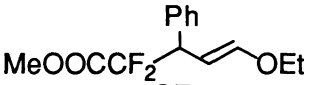
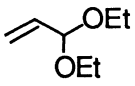
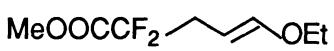
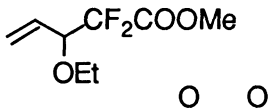
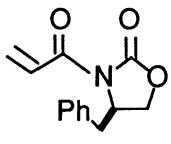
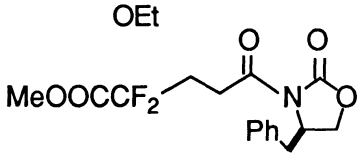
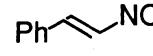
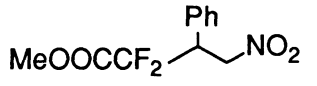


Scheme 1.

As described in a previous paper,[5] the ketene silyl acetals **2** are generated *in situ* by treating the iodide **1** with Zn in CH_3CN followed by the addition of chlorosilane. Results of the reactions of **2** with α,β-unsaturated carbonyl compounds or acetals are summarized in Table 1. Reaction of **2a** with cyclohexenone proceeded

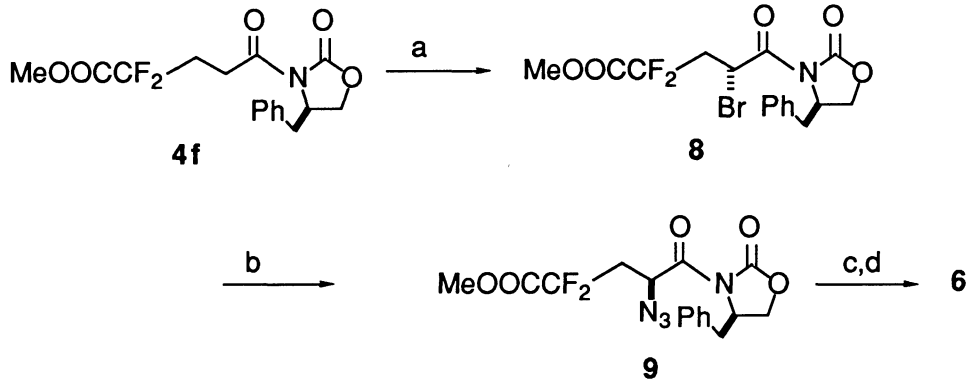
readily to give the 1,4-addition product **4a** in 95% yield after extractive work-up followed by chromatographic purification on silica gel (entry 1). Similar reaction of **2b** with cinnamaldehyde resulted in the formation of 1,4- and 1,2-addition products (ratio **4c/5c**=2.5) which were isolated as the triethylsilylated forms (entry 3),[11] while the Reformatsky reagent provided the 1,2-addition product **5c**, exclusively.[5] Low regioselectivities were observed in the cases of diethylacetal derivatives (entries 4, 5). Reaction of **2** with acryloyloxazolidinone or nitrostyrene proceeded rather slowly to give the addition products in moderate yields (entries 6, 7), while **2** did not react with α,β-unsaturated esters (PhCH=CHCOOMe e.g.) or vinyl phenylsulfone under the similar reaction conditions. Although it is difficult to discuss the reactivity of **2** due to the thermal instability of **2** to be isolated in pure form,[5] zinc halide in the reaction medium may facilitate the reaction of **2** and affect the regioselectivity.

Table 1. Reaction of 2,2-Difluoroketene Silyl Acetal **2** with Unsaturated Compound **3**

Entry	2	3	Temp/°C	Time	Product(s)		Yield/%
1	**2a**		0	30 min		**4a**	95[a]
2	**2a**		0	30 min		**4b**	64[a]
						**5b**	19[a]
3	**2b**		-15	30 min		**4c**[c]	50[b,d]
						**5c**	19[b,d]
4	**2b**		0	30 min		**4d**[e]	17[b]
						**5d**	56[b]
5	**2a**		0	30 min		**4e**[f]	35[b]
						**5e**	23[b]
6	**2b**		rt	15 h		**4f**	40[a]
7	**2a**		rt	15 h		**4g**	67[a]

a) Isolated yield after being treated with 3% HCl. b) Isolated yield after being treated with 2.5% $NaHCO_3$ solution. c) Only E-isomer. d) The ratio of **4c** and **5c** was determined by ^{19}F-NMR. e) E/Z=30/1. f) E/Z=30/1.

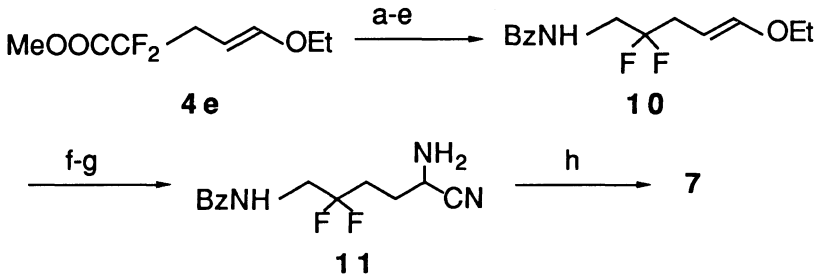
4,4-Difluoroglutamic acid **6** was prepared from **4f** according to the boron enolate methodology[12] as shown in Scheme 2. Thus, NBS-bromination of the Z-boron enolate formed by treating **4f** with dibutylboron triflate and iPr_2NEt provided the bromide **8** (2R/2S=8.6), which was converted to the azide **9** in 64% yield. Hydrolysis of the ester and imide groups of the major 2S-isomer of **9** and the subsequent hydrogenation provided (+)-4,4-difluoroglutamic acid **6** in 74% yield.[13]



a) Bu_2BOTf, iPr_2NEt/CH_2Cl_2 then NBS, b) NaN_3/DMF, c) $LiOH/THF\text{-}H_2O$,
d) H_2, Pd-C(5%)/EtOH

Scheme 2.

Conversion of **4e** into (±)-5,5-difluorolysine **7** is as follows. Ester group of **4e** was converted to N-benzoylamide **10** via displacement of the triflate with sodium azide followed by the reduction with triphenylphosphine and benzoylation. Acidic hydrolysis of the vinyl ether group to the aldehyde which, in turn, submitted to the Strecker synthesis giving the difluorolysine **7** [230°C dec., (lit.[10] 227-230°C dec.)].



a) $NaBH_4/MeOH$, b) Tf_2O, iPr_2NEt/CH_2Cl_2, c) NaN_3/DMF, d) $Ph_3P/THF\text{-}H_2O$,
e) BzCl, Py/CH_2Cl_2 (**10**, 55% from **4e**), f) 1N-HCl/THF,
g) KCN, NH_4Cl/NH_4OH-dioxane (**11**, 92% from **10**), h) 6N-HCl (**7**, 74%)

Scheme 3.

In conclusion, 2,2-difluoroketene silyl acetal **2**, formed *in situ* by treating the iodide **1** with zinc followed by chlorosilane showed a high reactivity towards α,β-unsaturated carbonyl compounds or acetals giving 1,4-

addition products, whose functionality is potentially useful for the preparation of difluoro compounds of biological interest.

References

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13) (+)-**6**: $[\alpha]_D$ +5.38 (c 1.04, H_2O); ^{1}H-NMR(D_2O)δ: 2.53(1H, ddt, J=8.4, 14, and 16 Hz, 3-H), 2.70(1H, ddt, J=3.4, 14, and 16 Hz, 3-H), 4.18(1H, dd, J=3.4 and 8.4 Hz, 2-H); ^{19}F-NMR(D_2O, benzotrifluoride as external standard) -38.9 ppm(t, J=16 Hz). We also prepared (-)-**6** from (S)-enantiomer of the acryloyloxazolidinone by the similar procedure for (+)-**6**. The (S)-MTPA-amides of dimethyl ester of both (+)-**6** and (-)-**6** were found to be diastereomerically pure based on their 400MHz-^{1}H-NMR spectra.

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