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Cyclization of α, α-Difluoromethyl Radicals: A New Route to the Preparation of Difluorocyclopentane Derivatives[1]

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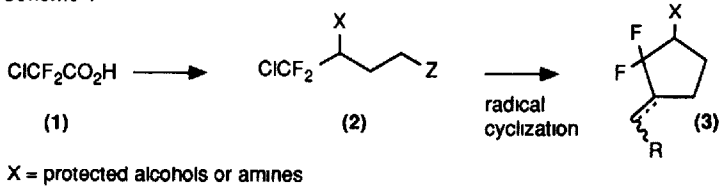
ABSTRACT *Intramolecular cyclization of difluoromethyl radicals with olefins, silylacetylenes and enol acetates afforded a variety of substituted difluorocyclopentanes*

Biologically active fluoro-organic compounds such as fluorinated prostaglandins[3], nucleosides[4] and sugars[5] have attracted much attention in recent years However, synthesis of these compounds has involved the fluorination of sensitive functionalities using highly reactive reagents such as $FClO_3$, SF_4, $(C_2H_5)_2NSF_3$ *etc* , often leading to poor yields of the desired products Therefore, new synthetic methodologies for the preparation of fluoroorganic compounds are highly desirable In connection with our interest in fluorinated carbacyclic nucleosides, we have developed an alternative approach to the preparation of functionalized difluorocyclopentane derivatives by free radical cyclization reactions of chlorodifluoromethyl olefins and alkynes (Scheme I) which are readily obtainable from chlorodifluoro acetic acid

Scheme 1



X = protected alcohols or amines

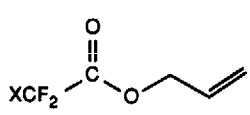
Z = -HC=CH$_2$, -C≡C-SiMe$_3$, -CH=CH-OAc

Radical cyclization reactions have been used increasingly in organic synthesis for the construction of 5- and 6- membered rings[6] However, to our knowledge, the cyclization of difluoromethyl radicals has not been previously explored We report here preliminary results from this investigation

Initial attempts at the radical cyclization of allyl ester (**4**) [(n-Bu)$_3$SnH/AIBN] led to a complex mixture of products Furthermore, application of Curran's atom transfer cyclization method[7] to ester (**5**) [(n-Bu)$_6$ Sn$_2$/AIBN] gave only recovered starting material These unsatisfactory results are ascribed to the unfavorable s-*cis* conformation associated with the ester functions[8] of (**4**) and (**5**) To circumvent this problem, our efforts were focussed on the cyclization of difluoromethyl radicals lacking the ester function

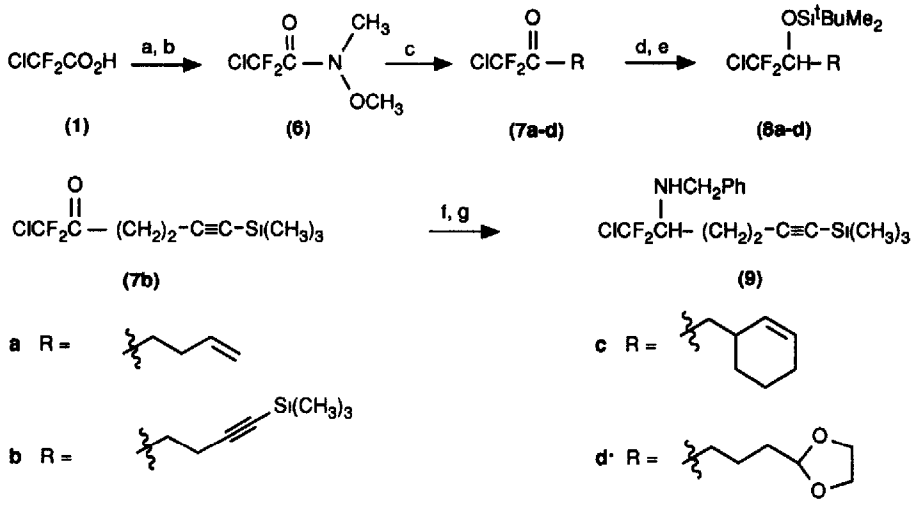
The requisite olefins and alkynes were prepared as outlined in Scheme 2[9] Following the literature procedures[10], ketone (**7a**) was obtained in low yield (~25%) by treatment of acid (**1**) with but-3-enyl magnesium bromide An improved method involving reaction of amide (**6**) with the appropriate Grignard reagents (**10b-d**) was

used to prepare ketones (7b)-(7d)[11]



(4) X = Cl
(5) X = I

Scheme 2



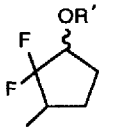
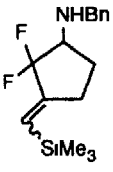
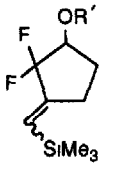
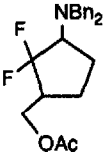
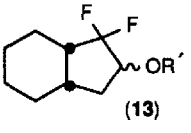
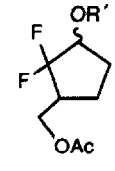
Reagents (a) NaOH then PCl_3 (b) $CH_3NH(OCH_3)$•HCl - Et_3N-CH_2Cl_2 (61%) (c) RMgBr (10b-d) THF (45-92%) (d) LAH Et_2O (82-93%) (e) NaH then $^tBu(CH_3)_2SiCl$ (70-81%) (f) $PhCH_2NH_2$ - 4Å molecular sieves - C_6H_6 (g) $NaBH_3CN$ - CH_3OH - HCl (52% for two steps)

Reduction of ketones (7a)-(7d) and subsequent protection of the resultant alcohols gave silyl ethers (8a)-(8d) Reductive amination of ketone (7b) with benzylamine and sodium cyanoborohydride afforded amine (9)

In contrast to the findings obtained with difluoromethyl esters (4) and (5), cyclization of the difluoromethyl radicals generated from olefins and alkynes (8a)-(8c) with tributyltin hydride (addition *via* a syringe pump) and AIBN proceeded smoothly to afford the difluorocyclopentane derivatives (11)-(13) in good yields (Table 1) It is noteworthy that alkyne (9), with a protected amine functionality, underwent cyclization without difficulty On the other hand, attempted cyclization of the precursor alkyne (7b) with a carbonyl function adjacent to the difluoromethyl radical led to a mixture of products

To test other potential radical acceptors in the cyclization reaction and to find a direct entry to hydroxymethyl substituted difluorocyclopentanes, we investigated the cyclization of enol acetates (17) and (19) These were

Table I Radical Cyclization of Chlorodifluoromethyl Alkenes and Alkynes[a,b]

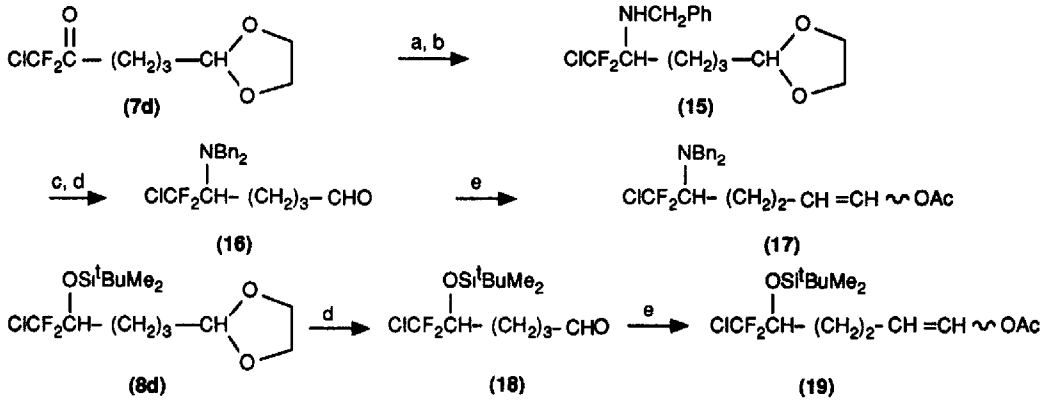
Substrates	Products	% Yield [c]	Substrates	Products	% Yield [c]
(8a)	 (11)	59[d]	(9)	 (14)	60
(8b)	 (12)	81	(17)	 (20)	28[f]
(8c)	 (13)	82[e]	(19)	 (21)	81[d]

(a) R′ = tert-butyldimethylsilyl Bn = benzyl (b) Cyclizations were carried out by slow addition of tributytin hydride (1 2 eq - 2 4 eq) to a solution (0 08 M) of substrate in refluxing benzene over a period of 10 h (c) Yields of products after purification by flash chromatography on silica gel (d) 1 1 cis/trans isomers were obtained (e) 1 1 α/β TBDMS ethers were obtained (f) Only one isomer was obtained See ref 12

prepared from acetals (**7d**) and (**8d**) as shown in Scheme 3 Conversion of aldehydes (**16**) and (**18**) to the enol acetates (**17**) and (**19**) followed the procedures reported by Secrist *et al* [13] When heated with n-Bu_3SnH/AIBN in benzene, enol acetates (**17**) and (**19**) cyclized as expected to afford 1,3-disubstituted difluorocyclopentanes (**20**) and (**21**),[14] respectively (Table 1) The low yield obtained for the cyclization of enol acetate (**17**) is presumably attributable to the steric hindrance imposed by the dibenzylamine on the adjacent radical center

In conclusion, we have developed a new method for the preparation of functionalized difluorocyclopentanes by the intramolecular cyclization of difluoromethyl radicals This methodology should provide an access to a variety of difluoro methylene - containing five membered ring compounds difficult to obtain by other methods

Scheme 3



Reagents (a) $PhCH_2NH_2$/4Å sieves (b) $NaBH_3CN/CH_3OH/HCl$ (c) $PhCH_2Br/K_2CO_3$ (d) p-TsOH/acetone (e) Ac_2O/DMAP/Et_3N

References and Notes

1 Contribution No 836 from the Institute of Organic Chemistry
2 Syntex Postdoctoral Fellow 1988-1990
3 Fried, J , Mitra, D K , Nagarajan, M , Mehrotra, M , *J Med Chem* **1980**, *23*, 234.
4 Marecek, J F , Prestwich, G D *Tetrahedron Lett* **1989** *30*, 5401
5 Borthwick, A D , Evans, D N , Kirk, B E , Biggadike, K , Exall, A M , Youds, P , Roberts, S.M , Knight, D.J., Coates, J A V. *J Med Chem* **1990**, *33*, 179
6 (a) Curran, D P. *Synthesis* **1988**, 417 and 489 (b) Giese, B Radicals in Organic Synthesis· Formation of Carbon - Carbon Bonds, Pergamon Press, Oxford, **1986**
7. Curran, D P , Chang, C -T J Org Chem **1989**, *54*, 3140
8 (a) Stork, G ; Mah, R Heterocycles **1989**, *28*, 723 (b) Hanessian, S , Di Fabio, R , Marcoux, J.-F. J. Org Chem **1990**, *55*, 3436 (c) Barth, F and O-Yang, C *Tetrahedron Lett* **1990**, *31*, 1121
9 All new compounds were characterized by ^1H NMR and mass spectra Satisfactory elemental analysis and/or high resolution mass spectra were obtained for all compounds
10 Sykes, A , Tatlow, J C , Thomas, C R *J Chem Soc* **1956**, 835.
11 Nahm, S and Weinreb, S.M *Tetrahedron Lett* **1981**, *22*, 3815
12 No conclusive information could be obtained from nOe (nmr) experiments regarding the stereochemistry of this compound We are in the process of attempting an x-ray structure determination on (**20**)
13. Cousineau, T J , Cook, S L., Secrist III, J.A. *Synthetic Communications* **1979**, *9*, 157.
14 Acetates (**20**) and (**21**) are potentially useful intermediates for the synthesis of 2′,3′-dideoxy-6′,6′-difluoro-carbacyclic nucleosides The synthesis of 6′-fluorocarbacyclic nucleosides has been recently reported. Coe, D M., Hilpert, H , Noble, S A , Peel, M R , Roberts, S.M. and Storer, R *J Chem Soc , Chem Commun* **1991**, 312

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