CHEMISTRY LETTERS, pp. 623-624, 1989.

Free-Radical Approach to C-C Bond Formation on a Trifluoromethyl-Substituted Carbon. Intramolecular Cyclization

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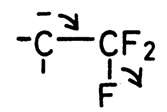
A trifluoromethyl-substituted carbon radical, generated by radical deoxygenation of α-trifluoromethyl alcohol, intramolecularly formed C-C bond to give a five- or six-membered cyclic compound.

Free-radical mediated reactions have a number of advantages over more familiar ionic reactions.1) For example, radicals containing a leaving group on the β-carbon atom can be used for C-C bond formation without undesirable competitive β-elimination reactions that are sometimes encountered in anionic counterparts. C-C bond formation on a trifluoromethyl (CF_3)-substituted carbon via ionic reaction is problematic; carbanion (1) induces β-elimination of a fluoride anion, and generation of carbocation (2) is very difficult owing to marked electron-withdrawing effect on its stability. Thus, an efficient method for C-C bond formation on a CF_3-substituted carbon is required in organofluorine chemistry. Approach to this problem through the intermediary carbon radical (3) should be effective. This paper reports a method for the generation of a CF_3-substituted carbon radical by deoxygenation of the α-trifluoromethyl alcohol (CF_3CHOH-), and its reaction leading to intramolecular C-C bond formation.2)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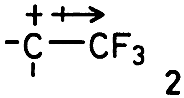
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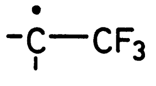
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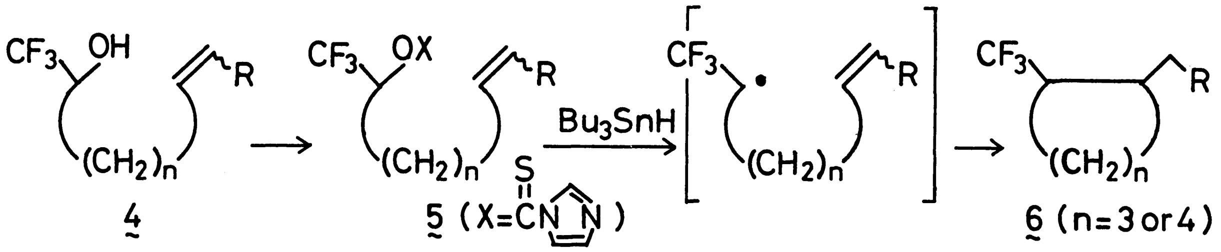
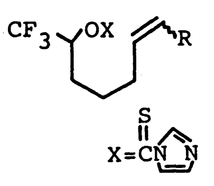
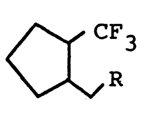
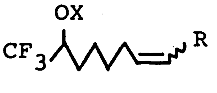
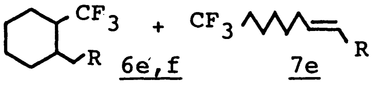
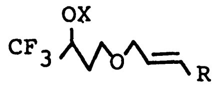
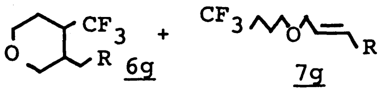


α-Trifluoromethyl alcohol derivatives (4) containing a suitably placed acceptor double bond were prepared as substrates. The radical deoxygenation of the α-trifluoromethyl alcohol moiety of 4 was successfully carried out using the O-thiocarbonylimidazolide derivatives (5).3) Alcohol derivatives (4) were treated with 1,1′-thiocarbonyldiimidazole in tetrahydrofuran at reflux temperature until the starting material was consumed to afford O-thiocarbonylimidazolides (5) in high yields (94% - 97%).

Radical reaction of 5 with tributyltin hydride (Bu$_3$SnH, 1.1 equiv.) and azobisisobutyronitrile (AIBN, catalytic amount) in benzene at reflux temperature gave the cyclized product. The results are shown in the Table 1. In the case of 5a, cyclization proceeded in 5-exo mode to give 1-decyl-2-trifluoromethylcyclopentane (6a) as a stereoisomeric mixture in 83% yield. Similarly, the radical cyclization of 5b, 5c, and 5d gave regioselectively CF$_3$-substituted cyclopentanes (6b, 6c, and 6d), respectively. In these radical reactions, the CF$_3$-substituted carbon radical effectively promoted C-C bond formation and no side reaction was detected. Six-membered ring compounds (6e, 6f, and 6g) were obtained in 25% - 48% yield. A competitive reaction leading to the reduction product (7) reduced the yield of the cyclized product in these 6-exo mode closures.

Table 1. The Reaction of O-Thiocarbonylimidazolides (5) with Bu$_3$SnH a)

Starting material b)		Time/h	Product(s) (Yield/%) c), d)	
	5a R=n-C$_9$H$_{19}$	4.5	 6a-d	6a (83)
	5b R=n-C$_6$H$_{13}$	3		6b (66)
	5c R=CH$_2$OCOPh	3		6c (81)
	5d R=Ph	2		6d (69)
	5e R=Ph	4.5		6e (48), 7e (8)
	5f R=CH$_2$OCOPh	3.5		6f (48) e), f)
	5g R=Ph	7		6g (25), 7g (34)

a) Reactions were carried out in 0.015 - 0.085 mol dm^{-3} solutions except for the case of 5f. b) A mixture of E- and Z-isomers. c) All the products obtained gave satisfactory spectral data. d) The ratios of stereoisomers were determined by GLC: 6a (1 : 1), 6b (1 : 1), 6c (1 : 1), 6d (1.1 : 1), 6e (3 : 1), 6f (1.4 : 1), 6g (1.5 : 1). e) The yield of 7f was not determined. f) High dilution method (0.002 mol dm^{-3}) using the syringe pump technique was employed.

The present method for generating the carbon radical (3) is synthetically useful since the α-trifluoromethyl alcohol moiety can be easily prepared by hydride reduction of the trifluoromethyl ketone (CF$_3$CO-) or Grignard reaction with trifluoroacetaldehyde (CF$_3$CHO). This work demonstrates the synthetic potential of the CF$_3$-substituted carbon radical for intramolecular C-C bond formation.

References

1) Recent reviews: B. Giese, "Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds," Pergamon Press, Oxford (1986); M. Ramaiah, Tetrahedron, 43, 3541 (1987); D. P. Curran, Synthesis, 1988, 417 and 489.

2) During the course of the present work, a related radical cyclization of a carbon radical bearing both CF$_3$- and Cl-substituents was reported. Y. Watanabe, T. Yokozawa, T. Takata, and T. Endo, J. Fluorine Chem., 39, 431 (1988).

3) D. H. R. Barton, R. S. H. Motherwell, and W. B. Motherwell, J. Chem. Soc., Perkin Trans. 1, 1981, 2363.

(Received January 28, 1989)