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RADICAL CYCLIZATION TO THE TRIFLUOROMETHYL-SUBSTITUTED DOUBLE BOND: REGIOSELECTIVITY AND TANDEM CYCLIZATION

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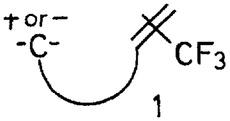
Summary: Regioselective radical cyclization to the trifluoromethyl-substituted double bond proceeds in good yield. Extension to tandem cyclization provides access to the angular trifluoromethyl group.

Recently, significant progress has been made in radical cyclization in synthetic chemistry.1) As an attractive feature of this process is that it may serve as a surrogate in synthetically inaccessible or restricted ionic processes. The ionic cyclization to trifluoromethyl-substituted double bond (CF_3-double bond, 1) involves unavoidable ploblems; electrophilic cyclization is uncommon due to the effect of the strongly electron-withdrawing CF_3 group (2) and nucleophilic cyclization to the carbon β to the CF_3 group induces β-elimination of the fluoride anion (3).2) To solve this inherent synthetic problem, radical cyclization to the CF_3-double bond (4) was attempted for the synthesis of CF_3-substituted cyclic componds.3) The regioselectivity (exo vs. endo) of radical cyclization to the CF_3-double bond still remains unclear with respect to the effects of CF_3 group, connecting chain length (formed ring size), and other substitutions in the system. This paper reports regioselective radical cyclization controlled by the CF_3 group and access to angular CF_3-substituted bicyclic compounds via tandem cyclization.



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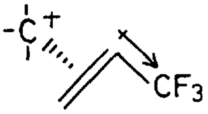

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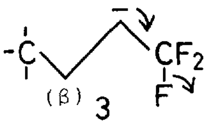

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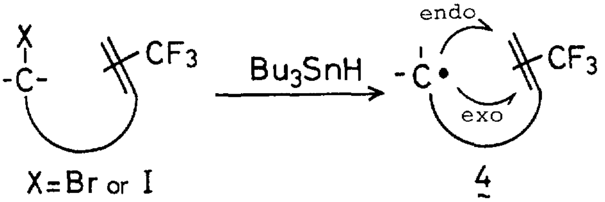

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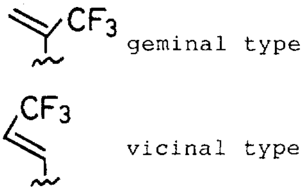
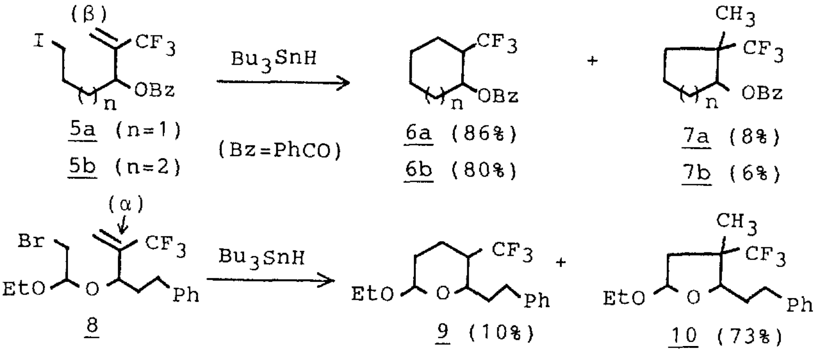
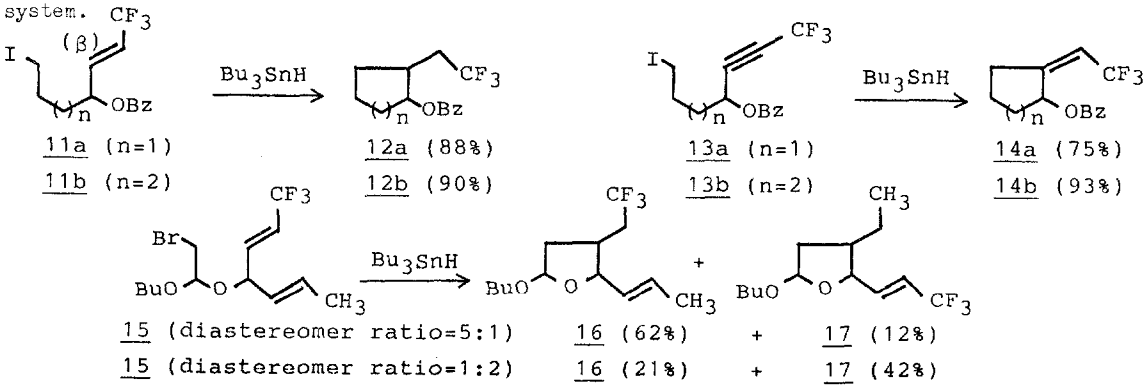


Two types of CF_3-double bonds (geminally and vicinally substituted) are incorporated into the substrate as the radical acceptor.4) The reaction was carried out by treating the substrate with tributyltin hydride (Bu_3SnH, 1.1 equiv.) and azobisisobutyronitrile (AIBN, catalytic amount) in benzene (0.02 M) at reflux temperature for 2 hr.5)

In reactions of geminal types (5a and 5b), the carbon radical predominantly attacked the carbon atom β to the CF_3 group (β-attack) via an endo closure to form 6a and 6b in 86% and 80% yields, respectively.[6) The α-attacked product (7a and 7b) via an exo closure was isolated in each case as a minor component (8% and 6% yields, respectively).[7,8) In contrast to the cyclization of the 5-methyl-5-hexenyl radical (endo : exo = 2 : 1),[9) a CF_3 group on the acceptor significantly enhanced the endo selectivity (β-attack) in the cyclization of 5a (endo : exo = 11 : 1). An oxygen atom in the connecting chain overrode this preference. Thus, radical cyclization of acetal (8) proceeded mainly via the exo closure (α-attack) to give 10. While the formation of 10 can be explained on the basis of acceleration of the 5-exo closure owing to the location of the oxygen atom in the chain,[10) the competitive 6-endo closure via β-attack leading to 9 should be directed by the CF_3 group.

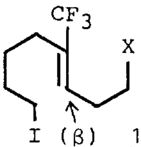
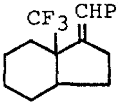
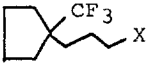
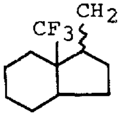
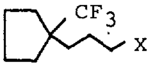
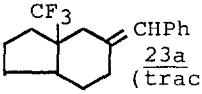
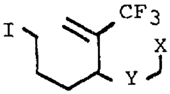
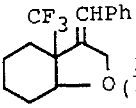
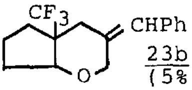
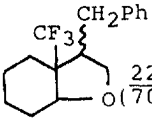
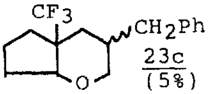


Highly selective β-attack on the CF_3-substituted unsaturated bond leading to the exo closure was observed in the cyclization of vicinal types (11 and 13), and five- and six-membered rings (12[6) and 14) were obtained exclusively in high yields. Compared with the case of 5, β-attack on the CF_3-double bond and exo closure positively dominate the high regioselectivity of the cyclization of 11. The CF_3-substituted triple bond can also serve as a radical acceptor. In the reaction of the acetal (15), it was noted with surprise that the product distribution (16 and 17) was in agreement with the diastereomer ratio of the substrate used. Thus possibly, the geometric constraint between the radical center and acceptor site imposed by the substituted connecting chain is a dominant factor determing the ring closure course, and substituents (CF_3 and CH_3) on the acceptor exert no effect in this system.



An intermediary carbon radical bearing a CF$_3$ group ($\mathrm{CF_3}\text{-}\overset{|}{\underset{|}{\mathrm{C}}}\bullet$) derived from β-attack of the initial carbon radical on the CF$_3$-double bond may possibly contribute to C-C bond formation, since synthetic use of ionic counterparts ($\mathrm{CF_3}\text{-}\overset{|}{\underset{|}{\mathrm{C}}}^{+}$ and $\mathrm{CF_3}\text{-}\overset{|}{\underset{|}{\mathrm{C}}}^{-}$) is difficult.[11]) Thus, tandem cyclization mediated by CF$_3$-double bond was carried out for confirmation of this point. Substrates (18 and 21)[4]) were prepared so as to affect initial cyclization by β-attack on the CF$_3$-double bond, followed by a second cyclization via the preferential 5-exo

Table. Tandem cyclization mediated by CF$_3$-double bond

Substrate		Products (Yield)	
 18	18a (X=PhC≡C-)	 19a (33%) +	 20a (55%)
	18b (X=PhCH=CH-)	 19b (25%) +	 20b (48%)
	21a (X=PhC≡C-, Y=CH$_2$)	19a (71%) +	 23a (trace)
 21	21b (X=PhC≡C-, Y=O)	 22b (81%) +	 23b (5%)
	21c (X=PhCH=CH-, Y=O)	 22c (70%) +	 23c (5%)

closure. Tin hydride mediated cyclization of 18 containing trisubstituted CF$_3$-double bond resulted in a low yield of the desired 19.[12,13]) The competitive formation of 20 may be ascribed to the introduction of a β-alkyl chain which sterically hindered β-attack of the initial radical in the first stage. However, the reaction of 21 mediated by the CF$_3$-double bond of geminal type proceeded smoothly via 6-endo followed by 5-exo closure to produce a bicyclic compound (19a, 22b and 22c)[12,13]) with an angular CF$_3$ group in good yield. A trace amount of 23 (<5%) was isolated as a by-product. The success of tandem cyclization without termination at the first stage demonstrates the CF$_3$-substituted carbon radical ($\mathrm{CF_3}\text{-}\overset{|}{\underset{|}{\mathrm{C}}}\bullet$) to possibly also be applicable to the synthesis of CF$_3$-substituted cyclic compounds, if it could be selectively generated.

The observed regioselectivity of the radical cyclization, preferential attack of the carbon radical on the carbon β to the CF$_3$ group irrespective of the ring closure mode, may be attributable to the steric and/or electronic effects of the CF$_3$ group in the transition state. The present radical cyclization to the CF$_3$-double bond provides a useful alternative to the inaccessible ionic process for preparation of CF$_3$-substituted cyclic compounds and can be extended to angular CF$_3$-substituted bicyclic compounds.[14])

References and Notes

1) For reviews: a) D. J. Hart, Science, 223, 883 (1984); b) B. Giese, Angew. Chem., Int. Ed. Eng., 24, 553 (1985); c) B. Giese, Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds, Pergamon Press, Oxford (1986); d) M. Ramaiah, Tetrahedron, 43, 3541 (1987); e) D. P. Curran, Synthesis, 1988, 417 and 489.

2) D. E. Bergstrom, M. W. Ng and J. J. Wong, J. Org. Chem., 48, 1902 (1983).

3) The CF_3 group is attracting considerable interest as a characteristic substituent in bioactive molecules. a) Carbon-Fluorine Compounds; A CIBA Foundation Synposium; Elsevier: Amsterdam (1972); b) M. Schlosser, Tetrahedron, 34, 3 (1978); c) R. Filler and Y. Kobayashi, Biomedicinal Aspects of Fluorine Chemistry, Kodansha Ltd. (Tokyo) and Elsevier Biomedical Press (1982); d) J. T. Welch, Tetrahedron, 43, 3123 (1987).

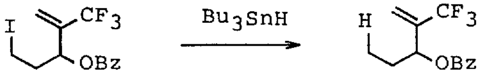
4) Synthesis of the substrates used in this study will be reported elsewhere.

5) The work-up is as follows. The solvent was removed in vacuo, and the residue was dissolved in ether. The ethereal solution was treated with 10% aqueous potassium fluoride with stirring, and the precipitate thus formed was filtered off through celite. Extraction with ether, drying over $MgSO_4$, and purification by column chromatography on silica gel gave the product. Satisfactory spectral data (^{1}H-NMR, ^{19}F-NMR, IR and Mass) was obtained for products.

6) Mixtures of stereoisomers: 6a (3.1:1), 6b (1.3:1), 12a (1.7:1), 12b (1:1).

7) The recovery of the reduction product of 5b without cyclization was only 3%.

8) No cyclization product via 5-endo closure was obtained in the reaction of 24. (According to the Baldwin's rules, 5-endo closure is disfavored.)



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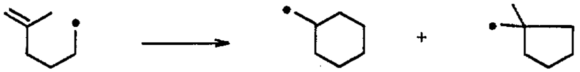
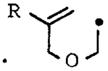
9) See Ref. 1c), p 146.



(2 : 1)

10) Oxygen-substituted 5-hexenyl radicals (25) undergo cyclization much more rapidly in greater preference for the 5-exo closure than their parent (carbon-chain) hexenyl radicals. a) A. L. J. Beckwith, Tetrahedron, 37, 3073 (1981); b) Ref. 1e), p 422 and references cited therein.



25 (R=H, CH_3)

11) a) T. Yokozawa, T. Nakai and N. Ishikawa, Tetrahedron Lett., 25, 3987 and 3991 (1984); b) T. Fuchigami and Y. Nakagawa, J. Org. Chem., 52, 5276 (1987); c) T. Fuchigami, Y. Nakagawa and T. Nonaka, ibid., 52, 5489 (1987); d) Y. Watanabe, T. Yokozawa, T. Takata and T. Endo, J. Fluorine Chem. 39, 432 (1988).

12) In these tandem cyclizations, the high stereoselectivity of ring junction was observed. Tentatively, it is assigned to be cis as observed in the related tandem cyclization.

13) 19a and 22b were mixtures of olefinic isomers: 19a (23:1 from 18a, 13:1 from 21a), 22b (1.8:1). 19b and 22c were mixtures of diastereoisomers: 19b (1.4:1), 22c (3.4:1).

14) For the angular CF_3 group in some steroids: J. C. Blazejewski, R. Dorm and C. Wakselman, J. Chem. Soc., Perkin Trans. 1, 1986, 337.

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