

Received: March 7, 1988; accepted: May 11, 1988

PRELIMINARY NOTE

Radical Cyclization on Trifluoromethyl-substituted Carbon:
A Facile Preparation of Trifluoromethylated Five-membered Ring
Compounds

YOSHIHIKO WATANABE, TSUTOMU YOKOZAWA, TOSHIKAZU TAKATA AND
TAKESHI ENDO

Research Laboratory of Resources Utilization, Tokyo Institute
of Technology, Nagatsuta, Midori-ku, Yokohama 227 (Japan)

SUMMARY

α -Trifluoromethyl carbon radicals, generated by the tri-
butyltin radical, added intramolecularly to olefinic double
bonds to afford the trifluoromethyl-substituted five-membered
ring compounds.

Much attention has been paid to trifluoromethylated com-
pounds because of their remarkable biological activities [1].
In the synthesis of such compounds, however, there is a serious
problem, the difficulty of carbon-carbon bond formation with
trifluoromethylated synthons, especially bond formation on tri-
fluoromethyl-substituted carbon. In fact, lithium α -CF₃-
enolates are reported to be extremely labile and undergo facile
defluorination prior to trapping [2], while for β,β,β -trifluoro-
ethyl iodide even reaction with sodium phenolate proceeded in
competition with elimination of hydrogen fluoride [3]. On the
other hand, organic polyhalides are known to add to olefins in

TABLE

Cyclization of trifluoromethyl-substituted carbon radicals.

	X	R	Reaction Condition	Yield ^a (%)	¹⁹ F nmr ^b (ratio)
a	CH ₂	OH	65°C / 5 h	78	+8.99, +9.25, +9.35
b	O	Ph	70°C / 5 h	82	+10.5, +8.41, +6.85 (70.0 : 17.3 : 12.7)
c	O	p-Cl-C ₆ H ₄	70°C / 4 h	85	+10.4, +8.23, +6.77 (72.2 : 18.1 : 9.8)
d	O	C ₂ H ₅	65°C / 4 h	76	+9.52, +7.81, +5.62 (68.7 : 18.3 : 13.0)
e	O	PhC ₂ H ₄	65°C / 5 h	88	+9.30, +7.74, +5.47 (70.1 : 16.4 : 13.5)

^a Isolated yields. ^b In CDCl₃: external standard; trifluoroacetic acid.

as follows: To a mixture of 1.40 g (4.68 mmol) of 2b and a catalytic amount of azobisisobutyronitrile (AIBN) in benzene (10 ml) was added dropwise an equimolar solution of tributyltin hydride in benzene (10 ml) over a period of half an hour at 70°C and the mixture was stirred for 5 h. 4b was obtained in 85% yield by column chromatography on silica gel eluted with a mixed solvent of hexane and ether (95 : 5). As is shown in the table, 3-CF₃-tetrahydrofurans (4b-4e) and 2-CF₃-cyclopentanol (4a) were obtained in excellent yields and 6-membered products via a 6-endo cyclization mode could not be detected at all. In all cases, ring closure of the radical 3 was regioselective and by the 5-exo mode. The trifluoromethyl group attached to the radical site had no effect on the regioselectivity in the ring closure step. It is noteworthy that no elimination of fluorine was observed in the cyclization, because the trifluoromethyl group was inert toward tributyltin hydride under radical conditions. From ¹H and ¹⁹F nmr examination, the cyclization pro-

ducts proved to be mixtures of three stereoisomers. Although further study is necessary to establish definitive conformations, in the major isomers the substituent at the 2-position and the methyl group seem to have the cis-relationship, and the other two isomers are trans-forms, from comparison with the cyclization modes of allyl-1-phenyl-2,2,2-trichloroethylethers or amines [5].

The present method offers an example of radical cyclization on trifluoromethyl-substituted carbon using the tributyltin radical, and could serve as a model for facile synthetic methods for otherwise difficult preparations of a variety of trifluoromethyl-containing five membered ring compounds. Experimental approaches to bio-active compounds using related intra or intermolecular reactions are now in progress.

- 1 Chiba Foundation, 'Carbon-Fluorine Compounds—Chemistry, Biochemistry, and Biological Activities', Elsevier, Amsterdam 1971.; R. Fillar, 'Biochemistry Involving Carbon-Fluorine Bonds', Am. Chem. Soc., Washington 1976.; M. Hudlicky, 'Chemistry of Organic Fluorine Compounds', 2nd edn., Wiley, New York, 1976.
- 2 T. Yokozawa, T. Nakai and N. Ishikawa, *Tetrahedron Lett.*, 25, (1984) 3987.
- 3 T. Nakai, K. Tanaka and N. Ishikawa, *J. Fluorine Chem.*, 9 (1977) 89.
- 4 P. Martin, J. Streith, G. Rihs, T. Winkler and D. Bellus, *Tetrahedron Lett.*, 26 (1985) 3947.
- 5 Y. Watanabe, Y. Ueno, C. Tanaka, M. Okawara and T. Endo, *Tetrahedron Lett.*, 26 (1987) 3953.; Y. Watanabe and T. Endo, *ibid.*, 29 (1988) 321.
- 6 M. Fujita, T. Morita and T. Hiyama, *Tetrahedron Lett.*, 27 (1986) 2135.