## PRELIMINARY NOTE

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

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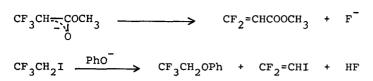
## SUMMARY

 $\alpha$ -Trifluoromethyl carbon radicals, generated by the tributyltin radical, added intramolecularly to oleginic double bonds to afford the trifluoromethyl-substituted five-membered ring compounds.

Much attention has been paid to trifluoromethylated compounds 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 trifluoromethyl-substituted carbon. In fact, lithium  $\alpha$ -CF<sub>3</sub>enolates are reported to be extremely labile and undergo facile defluorination prior to trapping [2], while for  $\beta$ ,  $\beta$ ,  $\beta$ -trifluoroethyl 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

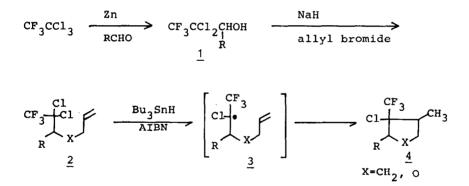
0022-1139/88/\$3.50

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the presence of various catalysts such as Cu(I)-salts [4]. From these reports, radical reactions may be considered to be the most promising methods for carbon-carbon bond formation on trifluoromethyl-substituted carbon without simultaneous defluorination.

In continuation of our study on radical cyclization [5] we report here a facile radical ring closure on trifluoromethylsubstituted carbon by use of the tributyltin radical, to afford a variety of  $3-CF_3$ -tetrahydrofurans and  $2-CF_3$ -cyclopentanol which have been difficult to obtain via earlier methodology.



Starting materials <u>1b-1e</u> were easily prepared by the modification of 2-trifluoromethyl alcohols which were prepared by the efficient method reported by Hiyama <u>et al.</u> [6]. Namely, to an ice-cooled solution of <u>1</u> in THF was added sodium hydride. After stirring for half an hour allyl bromide was added and the reaction mixture was stirred for 3 h at room temperature ( 48%-71% ). A typical radical cyclization procedure is

## TABLE

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	x	R	Reaction Condition	Yield <sup>a</sup> (%)	<sup>19</sup> Fnmr <sup>b</sup> (ratio)
a	<sup>СН</sup> 2	ОН	65°C / 5 h	78	+8.99, +9.25, +9.35
b	0	Ph	70°C / 5 h	82	+10.5, +8.41, +6.85 ( 70.0 : 17.3 : 12.7 )
с	0	p-C1-C <sub>6</sub> H <sub>4</sub>	70°C / 4 h	85	+10.4, +8.23, +6.77 ( 72.2 : 18.1 : 9.8 )
đ	o	с <sub>2</sub> н <sub>5</sub>	65°C / 4 h	76	+9.52, +7.81, +5.62 ( 68.7 : 18.3 : 13.0 )
e	0	PhC <sub>2</sub> H <sub>4</sub>	65°C / 5 h	88	+9.30, +7.74, +5.47 ( 70.1 : 16.4 : 13.5 )
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Cyclization of trifluoromethyl-substituted carbon radicals.

<sup>a</sup> Isolated yields. <sup>b</sup> In CDCl<sub>3</sub>: 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 (  $\underline{4b}-\underline{4e}$  ) and 2-CF3-cyclopentanol (  $\underline{4a}$  ) 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 trifluoromethyl group attached to the the 5-exo mode. 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 <sup>1</sup>H and <sup>19</sup>F nmr examination, the cyclization products 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. Extentional approaches to bio-active compounds using related intra or intermolecular reactions are now in progress.

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