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CATIONIC POLAR CYCLOADDITION WITH ANODICALLY PREPARED α-TRI- and α-DIFLUOROMETHYLATED N,O-ACETALS: PREPARATION OF FLUOROMETHYLATED TETRA- and DIHYDROQUINOLINE DERIVATIVES [1]

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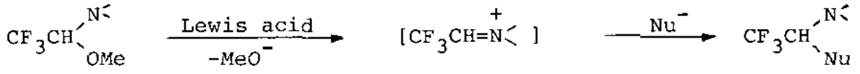
Abstract— *Anodically prepared α-tri- and α-difluoromethylated* N,O-acetals readily underwent $[4^{+}+2]$ type polar cycloadditions with styrenes and phenylacetylene in the presence of a Lewis acid to provide the corresponding fluoromethylated tetra- and dihydroquinoline derivatives.

In recent year, great interest has been paid to fluoro organic compounds, particularly tri- and difluoromethylated heterocyclic compounds because of their unique biological activities.[2] However, their synthetic methods are limited in many cases. For example, substitution with carbon-nucleophiles at α to a trifluoromethyl or difluoromethyl group is quite difficult mainly due to their strong electron-withdrawing effects.[3,4] Therefore, development of new efficient methods for carbon-carbon bond formation at the α-position is required in modern organo fluorine chemistry.

In our previous paper,[5] we have shown that anodically prepared α-trifluoromethylated N,O-acetals are useful building blocks for the construction of a carbon-carbon bond at α to the trifluoromethyl group (Scheme 1).



$$CF_3CH\begin{smallmatrix}N<\\ OMe\end{smallmatrix} \xrightarrow[-MeO^-]{\text{Lewis acid}} [CF_3CH=\overset{+}{N}<] \xrightarrow{Nu^-} CF_3CH\begin{smallmatrix}N<\\ Nu\end{smallmatrix}$$

(Scheme 1)

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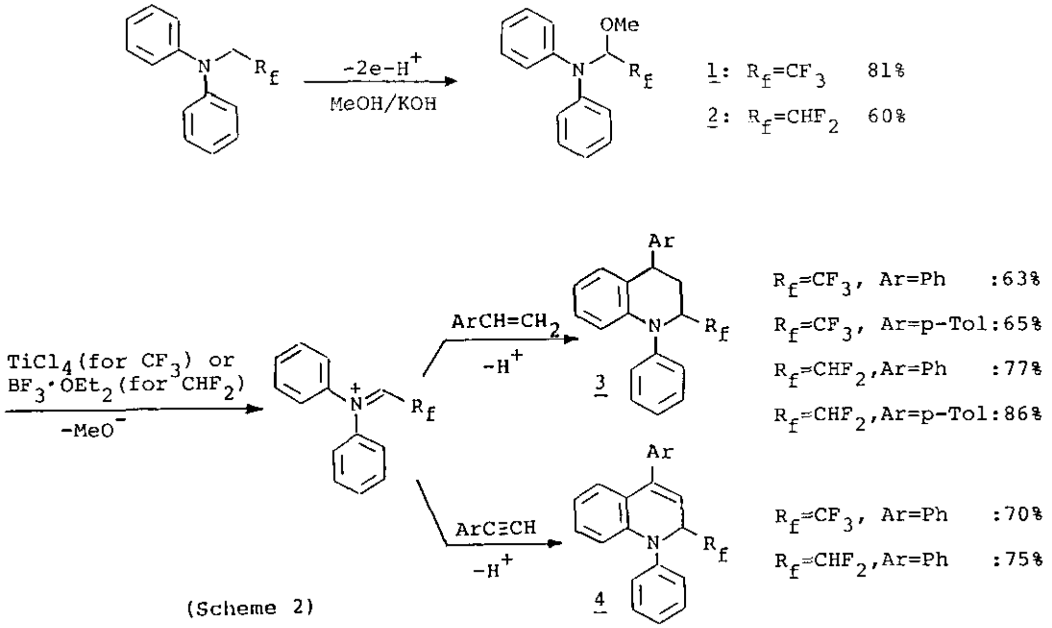
Now, we wish to report herein highly efficient cationic polar cycloaddition of α-tri- and α-difluoromethylated N,O-acetals 1[6] and 2[6] with nucleophilic unsaturated compounds in the presence of a Lewis acid to provide the corresponding α-fluoromethylated tetra- and dihydroquinolines, 3 and 4 as shown in Scheme 2. Although polar cycloaddition of aryliminium salts has been extensively studied,[7] the cycloaddition with the polar systems containing nitrogen-stabilized α-tri- and α-difluoromethylated carbocations has not been reported so far.

The cycloaddition of 1 and 2 with styrene (1.1 eq.) was successfully carried out in dichloromethane at −78 °C in the presence of $TiCl_4$ (1.1 eq.) to provide the corresponding tri- and difluoromethylated tetrahydroquinoline derivatives 3, respectively in good yields. The product 3 mainly consists of trans form, and a trace of cis isomer was observed in its ^{19}F nmr spectrum.[8]
Next, the cycloaddition with phenylacetylene was similarly attempted. However, the reaction resulted in a low yield (22%) due to the formation of many by-products. It was found that the yield of 4 was markedly increased using a less reactive Lewis acid such as $BF_3 \cdot OEt_2$.



(Scheme 2)

α-Difluoromethylated N,O-acetal 2 provided better yields than α-trifluoromethylated one 1. This result seems to be attributable to a weaker inductive effect of the difluoromethyl group.

The scope of this polar cycloaddition and biological activities of these products are currently under investigation.

ACKNOWLEDGMENT

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3. T. Umemoto and Y. Goto, J. Fluorine Chem., 1986, **31**, 231.
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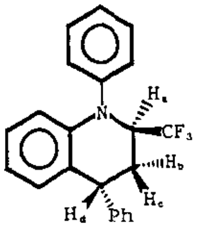
6. N,O-Acetals 1 and 2 are easily prepared by constant-current anodic oxidation at a graphite anode in methanol containing KOH as shown in Scheme 2.[5]
7. C. K. Bradsher, "Advances in Heterocyclic Chemistry," Vol. 16, ed. by A. R. Katritzky and A. J. Bouiton, Akademic Press, New York, 1974, pp. 289-324.
8. For example, trans 3 ($R_f=CF_3$, Ar=Ph) shows the following nmr spectra: ^1H nmr(270 MHz, $CDCl_3$), $\delta=2.30$ (ddd, $J_{H^b-H^c}=13.2$ Hz, $J_{H^b-H^d}=13.2$ Hz, $J_{H^a-H^b}=8.8$ Hz, 1H, $\underline{H}^b$), 2.62 (ddd, $J_{H^b-H^c}=13.2$ Hz, $J_{H^c-H^d}=4.00$ Hz, $J_{H^a-H^c}=8.60$ Hz, 1H, $\underline{H}^c$), 3.78 (dd, $J_{H^b-H^d}=13.2$ Hz, $J_{H^c-H^d}=4.00$ Hz, 1H, $\underline{H}^d$), 4.47 (ddt, $J_{H^a-H^b}=8.80$ Hz, $J_{H^a-H^c}=8.60$ Hz, $J_{CF_3-H^a}=6.80$ Hz, 1H, H^a), 6.52-7.44 (m, 14H, $C_6\underline{H}_5$, $C_6\underline{H}_4$). ^{19}F nmr($CDCl_3$, ext CF_3COOH), $\delta=-4.92$ (d, $J_{CF_3-H^a}=6.80$ Hz).



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