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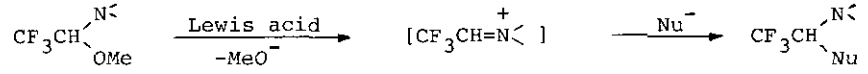
Abstract— *Anodically prepared α-tri- and α-difluoromethylated N,O-acetals readily underwent [4⁺+2] type polar cycloadditions with styrenes and phenylacetylene in the presence of a Lewis acid to provide the corresponding fluoromethylated tetra- and dihydroquinoline derivatives.*

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).



(Scheme 1)

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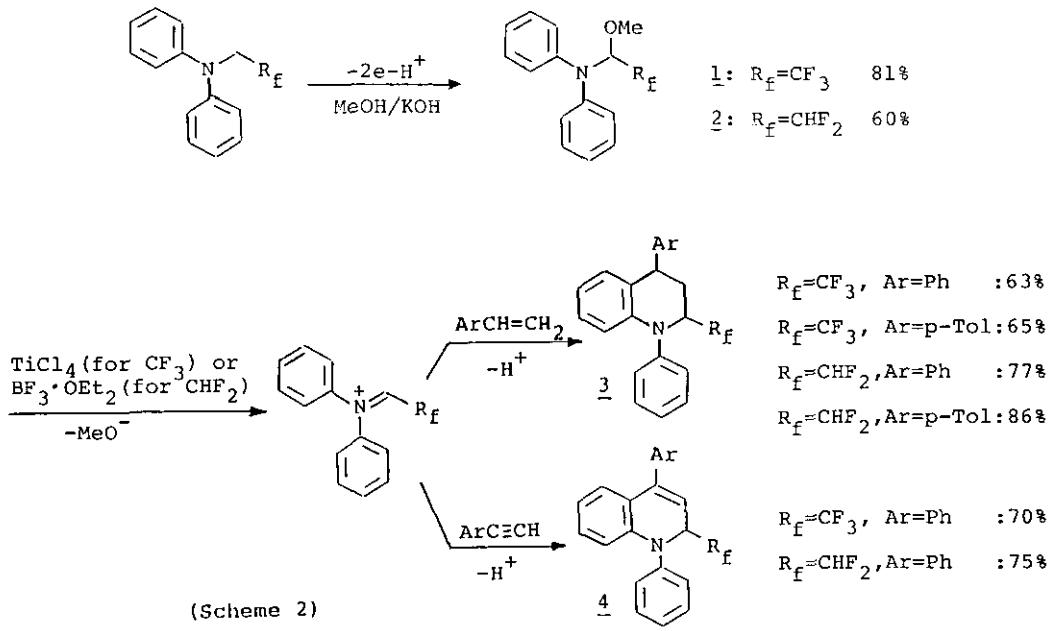
Now, we wish to report herein highly efficient cationic polar cycloaddition of α-tri- and α-difluoromethylated N,O-acetals 1[6] and 2[6] with nucleophilic unsaturated compounds in the presence of a Lewis acid to provide the corresponding α-fluoromethylated tetra- and dihydroquinolines, 3 and 4 as shown 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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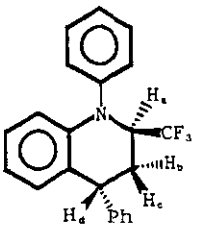
REFERENCES

1. Electrolytic Transformation of Fluoro Organic Compounds. Part 6. Part 5: A. Konno, T. Fuchigami, Y. Fujita, and T. Nonaka, J. Org. Chem., in press.
2. "Biomedicinal Aspects of Fluorine Chemistry," ed. by R. Filler and Y. Kobayashi, Kodansha & Elsevier Biomedical, Tokyo, 1983: K. Tanaka and K. Mitsuhashi, J. Syn. Org. Chem. Jpn., 1987, 45, 269.
3. T. Umemoto and Y. Goto, J. Fluorine Chem., 1986, 31, 231.
4. T. Morikawa, M. Uejima, and Y. Kobayashi, Chemistry Lett., 1989, 623.
5. T. Fuchigami, Y. Nakagawa, and T. Nonaka, J. Org. Chem., 1987, 52, 5489.
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, $CDCl_3$), δ=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, 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, H^c), 3.78 (dd, $J_{H^b-H}{}^d$=13.2 Hz, $J_{H^c-H}{}^d$=4.00 Hz, 1H, 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_6H_5, C_6H_4). ^{19}F nmr($CDCl_3$, ext CF_3COOH), δ=-4.92 (d, $J_{CF_3-H}{}^a$=6.80 Hz).



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