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# C-C Bond Formation at α to a Trifluoromethyl Group. Cyanation and Allylation of α-Trifluoromethylated N,O-Acetals[1)]

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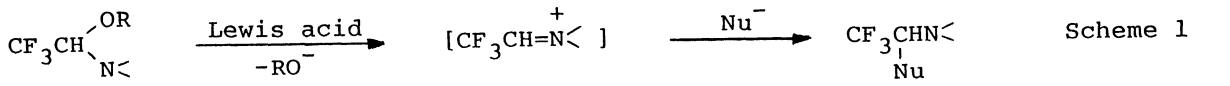
α-Trifluoromethylated N,O-acetals, N-(1-methoxy-2,2,2-trifluoroethyl)anilines readily reacted with cyanosilane and allylsilane in the presence of a Lewis acid to efficiently provide the corresponding trifluoromethylated α-aminonitrile and homoallylamine derivatives, respectively. α-Difluoromethyl-α-aminonitriles were also similarly prepared in high yields using α-difluoromethylated N,O-acetals.

Recently, much interest has been focused on trifluoromethylated compounds because of their potential biological activity.[2)] However, their preparative methods are limited in many cases.[3)] Particularly, substitution with carbon-nucleophiles at the α-position toward a trifluoromethyl group is quite difficult due to its strong electron-withdrawing effect.[4,5)] Therefore, development of efficient methods for C-C bond formation at the α-position is required in modern organofluorine chemistry.

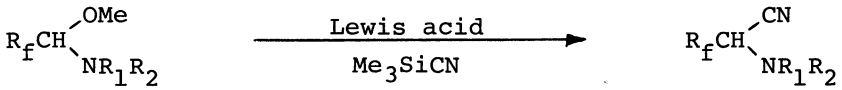
On the other hand, Lewis acid mediated reactions of acetals with organosilicon compounds as carbon nucleophiles are well-known versatile methods for the C-C bond formation.[6)] From this point, α-trifluoromethylated N,O-acetals seem to be one of promising building blocks for the construction of such a C-C bond since trifluoromethylated iminium cations would be easily generated by treatment with a Lewis acid as shown in Scheme 1.




Scheme 1

In this paper, we wish to report efficient cyanation and allylation of α-trifluoromethylated N,O-acetals 1[1)] by the reaction with cyanosilane and allylsilane as shown in Schemes 2 and 3.

Cyanation of 1 was carried out in dichloromethane at ca. -78 °C. As shown in Table 1, the reaction in the presence of $TiCl_4$ did not provide the desired α-cyanation product 3 efficiently due to the formation of many by-products. It was found that the yield was remarkably increased using a less active Lewis acid such as $BF_3 \cdot OEt_2$. Next, we successfully extended this cyanation reaction to α-difluoromethylated N,O-acetals 2, which were easily prepared by anodic methoxylation of N-(2,2-difluoroethyl)anilines similarly to the preparation of 1.[1)]




Scheme 2.

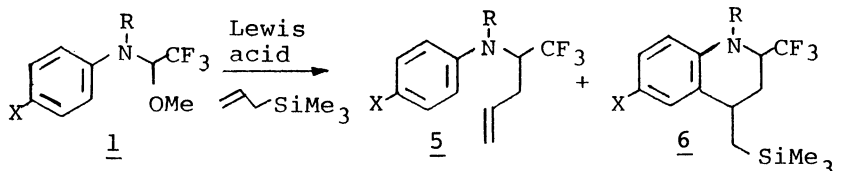
1: $R_f=CF_3$, 2: $R_f=CHF_2$ 3, 4

Table 1. Synthesis of α-fluoromethyl α-aminonitriles (3, 4)

| Starting N,O-acetal | | | | Lewis acid | Yield/% |
|---|---|---|---|---|---|
| No | $R_f$ | $R_1$ | $R_2$ | | |
| 1a | $CF_3$ | Ph | Et | $TiCl_4$ | 49 (3a) |
| 1a | $CF_3$ | Ph | Et | $BF_3\cdot OEt_2$ | 73 (3a) |
| 1b | $CF_3$ | p-Tol | Et | $BF_3\cdot OEt_2$ | 94 (3b) |
| 1c | $CF_3$ | Ph | Ph | $BF_3\cdot OEt_2$ | 71 (3c) |
| 2a | $CHF_2$ | Ph | Et | $BF_3\cdot OEt_2$ | 90 (4a) |
| 2b | $CHF_2$ | m-Tol | Et | $BF_3\cdot OEt_2$ | 92 (4b) |

Trifluoromethylated and difluoromethylated α-aminonitriles, 3 and 4 thus obtained seem to be versatile building blocks and they are also useful precursors to the corresponding fluorinated α-amino acids, which are currently receiving biological interst.[7)]

Furthermore, α-allylation of 1 was also attempted using allylsilane(Scheme 3). However, the reaction resulted in the formation of a mixture of allylation and cyclization products, 5 and 6. After many attempts, the efficient allylation was achieved using $TiCl_4$ or $BF_3\cdot OEt_2$ to provide the corresponding homoallylamines 5, which are difficult to prepare by other methods.[8)]




Scheme 3.

| 1 | Lewis acid | Yield/% 5 | 6 |
|---|---|---|---|
| 1a(X=H) | $TiCl_4$ | 64 | 8 |
| 1b(X=Me) | $BF_3\cdot OEt_2$ | 72 | 22 |

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References

1) Electrolytic Transformation of Fluoroorganic Compounds. Part 4. Part 3: T. Fuchigami, Y. Nakagawa, and T. Nonaka, J. Org. Chem., 52, 5489 (1987).
2) "Biomedical Aspects of Fluorine Chemistry," ed by R. Filler and Y. Kobayashi, Kodansha & Elsevier Biomedical, Tokyo (1983).
3) For example, M. Hudlicky, "Chemistry of Organic Fluorine Compounds," 2nd ed, John Wiley & Sons, New York (1976).
4) T. Umemoto, Yuki Gosei Kagaku Kyokai Shi , 41, 251 (1983); T. Umemoto and Y. Goto, J. Fluorine Chem., 31, 231 (1986).
5) T. Morikawa, M. Uejima, and Y. Kobayashi, Chem. Lett., 1989, 623.
6) T. Mukaiyama, "Yuki Gosei Hanno," Tokyo Kagaku Dojin, Tokyo (1987), Chap. 9.
7) K. Kawada and T. Tsushima, Chemical Industry, 38, 164 (1987).
8) The reaction was carried out as follows: a Lewis acid was added to a solution of 1 and allylsilane in dichloromethane at ca. -78 °C.

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