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PRELIMINARY NOTE

# Selective Fluorination of Substituted Methanols with Methanesulfonyl Fluoride and Cesium Fluoride as Modified with Crown Ethers

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SUMMARY

A new combination of methanesulfonyl fluoride and cesium fluoride as modified with 18-crown-6 was demonstrated to be the best for selective fluorination of various benzyl alcohols via nucleophilic substitution. As extended applications of this procedure, ethyl 1-fluoromethylpyrazole-4-carboxylate (6) and N-fluoromethylphthalimide (12) have been synthesized in high yields from the corresponding alcohol (4) and chloride (11) respectively.

Although there are many potential synthons containing a monofluoromethyl group appearing to be of particular interest in the light of newer drug designs, they have seldom materialized to date owing to synthetic drawbacks associated with low selectivity or

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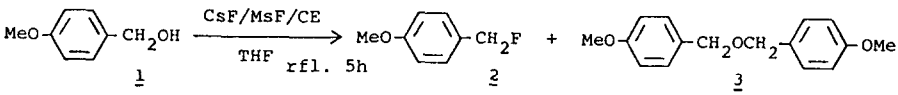
the unsatisfactory nature of existing reagents for fluorinations of primary alcohols, chlorides or bromides as usually the most accessible substrates. For example, fluorinations with alkali metal fluorides, even with the ones specifically prepared for activation, generally require 'forcing conditions' under severe heating in a strongly polar media, that often results in decomposition of unstable substrates. A quarternary ammonium fluoride, or our recent modification with methanesulfonyl fluoride (MsF) [1] can be a superior option in most cases, but we have now found this to be inapplicable to certain substrates containing the N-$CH_2$OH group, which were easily destroyed by the strong basicity of the ammonium fluoride. In this respect, cesium fluoride (CsF) is known to be useful for nucleophilic substitution, but it also demands the sort of forcing conditions as described above. The efficiency in conversion with CsF is improved when it is coupled with crown ethers, though this has been limited so far to a single example of polychlorinated aromatics in acetonitrile [2]. We now report briefly a new facile fluorination of benzyl alcohols with CsF as coupled with a crown ether, following esterification by MsF, and its extended application to N-$CH_2$OH and N-$CH_2$Cl groups on heterocyclic rings.

Firstly, 4-methoxybenzyl alcohol (1) was chosen as a substrate and various crown ethers were screened in combination with CsF and MsF in THF under reflux (Table 1). We found that the promoting effect of crown ether for the fluorination increased in the following order: 12-crown-4 < dibenzo-24-crown-8 < 15-crown-5 < dicyclohexyl-18-crown-6 < TDA-1 < 18-crown-6. The selectivity of the fluorination was quite dependent on the species of crown ethers. The effect of crown ether was best demonstrated in Run 3, where the yield as well as the selectivity was maximized in sharp contrast to the Run 9 without crown ether, but the etherification of 1 became dominant in the latter case.

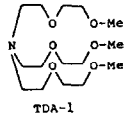
TABLE 1

Fluorination of 4-Methoxybenzyl Alcohol with Cesium Fluoride - Methanesulfonyl Fluoride(MsF) - Crown Ether(CE)




1 2 3

| Run | CsF (eq) | MsF (eq) | CE (eq) | Yield(%) 2 | Yield(%) 3 |
|---|---|---|---|---|---|
| 1 | 4 | 2 | 12-CE-4(1) | 16 | 32 |
| 2 | 4 | 2 | 15-CE-5(1) | 47 | 22 |
| 3 | 4 | 2 | 18-CE-6(1) | 80 | Trace |
| 4 | 4 | 2 | 18-CE-6(0.1) | 66 | 7 |
| 5 | 2.2 | 1.2 | 18-CE-6(0.3) | 75 | 7 |
| 6 | 4 | 2 | Dicyc.hexyl-18-CE-6(0.1) | 28 | 26 |
| 7 | 4 | 2 | Dibenzo-24-CE-8(0.1) | 9 | 32 |
| 8 | 4 | 2 | TDA-1(0.1) | 38 | 23 |
| 9 | 4 | 2 | - | 0 | 40 |

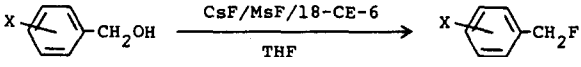



TDA-1

A variety of benzyl fluorides could be prepared by the current procedure in good or moderate yields (Table 2), among which the fluorides with an electron-donating group on the o-position or the p-position were found to be rather unstable, undergoing an auto-decomposition on standing.

TABLE 2

Fluorination of Substituted Benzyl Alcohols

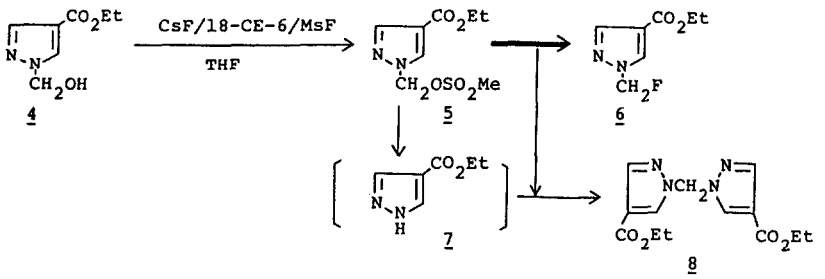



| Run | X | React. time(h) | Yield (%) | Chemical shift(ppm) | Coupling const(Hz) |
|---|---|---|---|---|---|
| 1 | 4-OMe | 5 | 80 | 5.26 | 48.6 |
| 2 | 3-OMe | 5 | 40 | 5.34 | 47.7 |
| 3 | 2-OMe | 5 | 23 | 5.44 | 47.9 |
| 4 | 4-$OCH_2\phi$ | 5 | 74 | 5.29 | 48.6 |
| 5 | 2,5-diOMe | 5 | 35 | 5.41 | 47.7 |
| 6 | 4-Me | 15 | 55 | 5.32 | 48.1 |
| 7 | 4-Cl | 15 | 72 | 5.31 | 47.7 |
| 8 | 4-$CF_3$ | 5 | 70 | 5.44 | 47.0 |

Next, we found that this method could be extended to certain heterocycles bearing a N-$CH_2OH$ group. For example, ethyl 1-hydroxymethylpyrazole-4-carboxylate (4) could be readily converted into ethyl 1-fluoromethylpyrazole-4-carboxylate (6) [A] in 76% yield with CsF (4 eq) as coupled with MsF (2 eq) and 18-crown-6 (1 eq) (Table 3). The formation of bis(4-ethoxycarbonylpyrazol-1-yl)methane (8) [B] as a result of cleavage of the C-N bond was virtually negligible, as indicated in Table 3. Potassium fluoride and tetra-n-butylammonium fluoride were respectively applied in this procedure in place of CsF, and it was found that the reaction did not proceed with the former and the application of the latter resulted in a total decomposition of the substrate (4) affording a mixture of ethyl pyrazole-4-carboxylate (7) and 8.

TABLE 3

Fluorination of Ethyl 1-Hydroxymethylpyrazole-4-carboxylate




| Run | CsF (eq) | MsF (eq) | 18-CE-6 (eq) | React. temp. | React. time(h) | Yield(%) 5 | 6 | 8 |
|---|---|---|---|---|---|---|---|---|
| 1 | 4 | 2 | 1 | r.t. | 20 | 23 | 60 | 0 |
| 2 | 4 | 2 | 1 | rfl. | 4 | 0 | 76 | 2-3 |
| 3 | 4 | 2 | 0.3 | rfl. | 4 | 8 | 65 | 3-4 |
| 4 | 2.2 | 1.2 | 0.3 | rfl. | 4 | 18 | 61 | 3-4 |

The current procedure was similarly applied to a fluorination of N-hydroxymethylphthalimide (9), but we found that bis(N-phthalimidyl)-methane (10) [C] was a major product though accompanied by a trace of N-fluoromethylphthalimide (12). Hence, we turned to the fluorination of N-chloromethylphthalimide (11). The reaction proceeded smoothly with CsF (1.2 eq) as modified with 18-crown-6 (0.3 eq) at room temperature and afforded 12 [D] in 76% yield (Table 4).

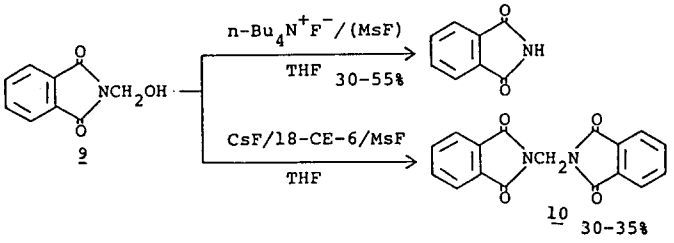
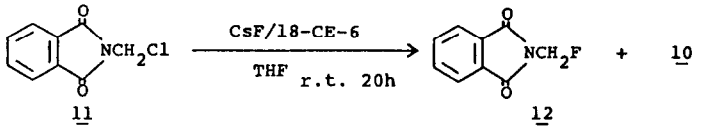


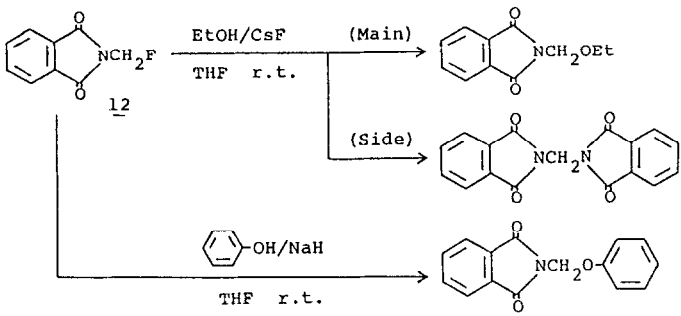

TABLE 4

Fluorination of N-Chloromethylphthalimide




| Run | CsF (eq) | 18-CE-6 (eq) | Yield(%) 12 | Yield(%) 10 |
|---|---|---|---|---|
| 1 | 4 | 1 | 37 | 22 |
| 2 | 4 | 0.3 | 64 | 5 |
| 3 | 1.2 | 0.3 | 76 | 4 |
| 4 | 1.2 | - | 21 | 0 |

Since little has been published to date about characteristic properties of the N-$CH_2F$ group on N-heterocycles, it is noteworthy that the fluorine atom in 12 was shown to be nucleophilically as active as the chlorine atom in 11, while the one in 6 was stable enough to remain intact on every treatment as applied to 12.




In conclusion, this method would be of wide applicability to the fluorination of various primary alcohols or its transient groups on N-heterocycles.

FOOTNOTES

A A typical reaction procedure is described for the synthesis of 6: To a suspension of CsF (712 mg, 4.69 mmol) and molecular sieves 4A (1.5 g) in 5 ml of dry THF, was added 18-crown-6 (310 mg, 1.17 mmol) at room temperature under stirring in nitrogen. After stirring for 1 h, MsF (230 mg, 2.35 mmol) and 4 (200 mg, 1.18 mmol) was added at room temperature and refluxed for 4 h. After celite-filtration of the mixture using a small amount of THF, the solvent was evaporated and ethyl acetate was added. The ethyl acetate solution was washed with water and dried on anhydrous

sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel with chloroform as an eluent to obtain 154 mg (76%) of 6, mp 44-45 °C. ir(KBr): 3415, 1698, 1560, 1449, 1410, 1250, 1224, 1189, 1136, 1028, 992, 962, and 770 $cm^{-1}$. pmr($CDCl_3$) δ 1.36(3H, t, J=7.1 Hz), 4.32(2H, q, J=7.1 Hz), 6.02(2H, d, J=52.1 Hz), 8.02(1H, s), and 8.14(1H, s). cmr($CDCl_3$) δ 14.33(q), 60.61(t), 83.18(t), 92.30(t), 117.80(s), 134.42(d), 143.05(d), and 162.31(s). ms m/z 172($M^+$), 144(base peak), and 127.

B 8; mp 145-146 °C. ir(KBr): 3400, 1723, 1705, 1555, 1382, 1290, 1248, 1231, 1029, and 764 $cm^{-1}$. pmr($CDCl_3$) δ 1.33(6H, t, J=7.1 Hz), 4.28(4H, q, J=7.1 Hz), 6.29(2H, s), 7.94(2H, s), and 8.16(2H, s). ms m/z 292($M^+$), 264, 247(base peak), 236, 153, and 108.

C 10; mp 239-240 °C. ir(KBr): 3425, 1769, 1719, 1432, 1390, 1311, 1212, 951, 730, and 708 $cm^{-1}$. pmr($CDCl_3$) δ 5.64(2H, s), and 7.60-8.00(8H, m). ms m/z 306($M^+$, base peak), 250, 222, 160, 132, and 104.

D 12; mp 83-84 °C. ir(KBr): 3480, 1780, 1722, 1468, 1418, 1364, 1328, 1290, 972, 722, and 708 $cm^{-1}$. pmr($CDCl_3$) δ 5.77(2H, d, J=52.1 Hz), and 7.60-8.10(4H, m). cmr($CDCl_3$) δ 70.55(t), 79.33(t), 124.14(d), 131.69(s), 134.91(d), 166.36(s), and 166.46(s). ms m/z 179($M^+$, base peak), 160, 151, 135, 132, 123, and 104.

1 M. Shimizu, Y. Nakahara, and H. Yoshioka, Tetrahedron Lett., 26 (1985) 4207.

2 V. V. Aksenov, V. M. Vlasov, I. M. Moryakina, P. P. Rodionov, V. P. Fadeeva, V. S. Chertok, and G. G. Yakobson, J. Fluorine Chem., 28 (1985) 73.