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An Efficient O-Monoalkylation of Dimethyl L-Tartrate via O-Stannylene Acetal with Alkyl Halides in the Presence of Cesium Fluoride

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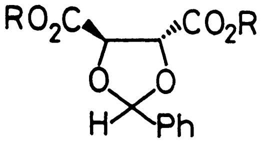
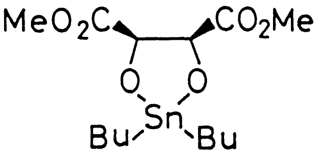
Selective O-monoalkylation of the vic-glycol of dimethyl L-tartrate with alkyl halides has been found to take place smoothly under mild conditions in the presence of cesium fluoride.

Dialkyl tartrates have been used as chiral synthons for the synthesis of various biologically active compounds or enantiomerically pure compounds.$^{1)}$ The selective O-monosubstitution is the key reaction of the synthetic strategy using the optically active$^{2)}$ or meso$^{3)}$-tartaric acid. However, direct monoacetylation$^{2a)}$ (61%), -tosylation$^{2b)}$ (34%), and -benzylation$^{2c)}$ (37%) are not satisfactory in the yields. Therefore, recent study is mainly focused on the monosubstitution of the esters of tartaric acids which include reductive opening of O-benzylidene tartrate (1) with $LiAlH_4$-$AlCl_3$$^{1,4)}$ (99%) or $NaBH_3CN$-HCl$^{5)}$ (85%), monomethylation (75%) with CH_2N_2-$SnCl_2$$^{5)}$ or asymmetric acylation through O-stannylene acetal (**2**) with d-ketopinic acid chloride$^{3)}$ (80%), and we wish to report here an efficient O-monoalkylation of the vicinal glycol of dimethyl L-tartrate through O-stannylene acetal (**3**) in the presence of CsF. Treatment of usual alkyl halides such as benzyl bromide, allyl iodide and methyl iodide with O-stannylene acetal (**3**) of dimethyl L-tartrate gave the desired monoalkylation products in poor yields. For example, the reaction of benzyl bromide with **3** gave only 41% yield of the expected monobenzylated product under the reaction conditions reported by Moffatt et al.$^{6)}$ (Entries 2 and 4 in Table 1). Therefore, we investigated about the effect of additives favorable for the reaction and found that cesium fluoride remarkably increased the yield of the selective monoalkylation products (Entries 1, 7 to 13 in Table 1) of the vicinal glycol of the tartrate. Other fluorides were found to be also effective to some extent (Entries 5 and 6 in Table 1).



1 R=Me, Et



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The following example is representative: (Entry 1 in Table 1) A mixture of

Table 1. Fluoride Anion Promoted O-Monoalkylation of O-Stannylene Acetal of Dimethyl L-Tartrate (**3**)a)

Entry	Halideb)	Fluoride saltb)	Temperature °C	Time	Yield/%c) of **4**
1	$PhCH_2I$(2.84)	CsF(1.93)	rt	1 h	99
2	$PhCH_2I$(1.11)	no salt	100	2 h	13>
3	$PhCH_2Br$(2.19)	CsF(1.22)	rt	2 h	85
4	$PhCH_2Br$(2.04)	no salt	100	3 h	41
5	$PhCH_2I$(1.71)	KF(1.53)	50 → rt	2 h → 11.5 h	55
6	$PhCH_2I$(2.11)	$n\text{-}Bu_4NF$(1.60)	rt	24 h	67
7	$p\text{-}NO_2C_6H_4CH_2I$(2.00)	CsF(1.29)	rt	3.5 h	84
8	$p\text{-}NO_2C_6H_4CH_2Br$(1.50)	CsF(1.90)	rt	46 h	93
9	$p\text{-}MeOC_6H_4CH_2Cl$(1.35)d)	CsF(1.19)	0 → rt	20 min → 1 h	67
10	$p\text{-}MeOC_6H_4CH_2I$(2.10)	CsF(2.05)	0 → rt	20 min → 20 min	72
11	$CH_2=CHCH_2I$(1.53)	CsF(1.62)	rt	6 h	98
12	$CH_2=CHCH_2Br$(1.26)	CsF(1.39)	rt	20 h	83
13	MeI(4.29)	CsF(1.26)	rt	21 h	72

a) All reactions were carried out on 0.5 - 0.8 mmol scales as shown in Entry 1. b) Numbers in parentheses show the equivalent of halides and fluoride salts. c) Isolated yields after chromatography on silica gel. d) The addition of potassium iodide (1.33 equiv.) was necessary for the conversion.

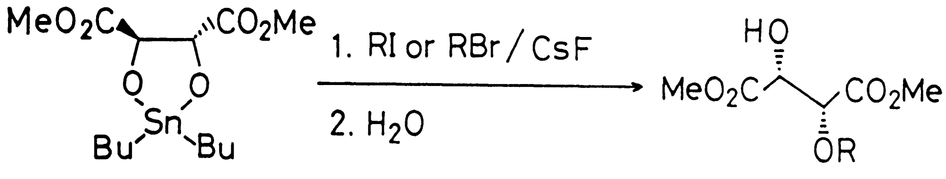
Table 2. O-Monosubstitution of O-Stannylene Acetal of Dimethyl L-Tartrate (**3**)a)

Entry	Halideb)	Solvent	Temperature	Time/h	Yield/%c) of **4**
1	t-BuCOCl(1.06)	$CHCl_3$	rt	7	quant.
2	$PhCH_2OCOCl$(1.05)	$CHCl_3$	rt	20	85
3	$MeOCH_2Cl$(1.59)	$CHCl_3$	rt	5.5	86
4	$PhCH_2OCH_2Cl$(2.01)	$CHCl_3$	rt	5	73
5	$t\text{-}BuMe_2SiCl$(1.13)	DMF	rt	18	79
6	$p\text{-}MeC_6H_4SO_2Cl$(1.00)	$CHCl_3$	rt	69	94

a) All reactions except in the case of the tosylation reaction (5 mmol scale) were carried out on a 0.5 mmol scale. b) Numbers in parentheses show the equivalent of halides. c) Isolated yields after chromatography on silica gel.

dimethyl L-tartrate (90 mg, 0.506 mmol) and di-n-butyltin oxide (126 mg, 0.506 mmol) in 3 ml of toluene was heated under reflux for 2 h, while removing water formed as the azeotropic mixture. The solution was evaporated to complete dryness *in vacuo*. Cesium fluoride (148 mg, 0.976 mmol) was added to the resulting white solid and the mixture was further dried *in vacuo* for 1.5 h, and then suspended in 3 ml of DMF containing benzyl iodide (314 mg, 1.44 mmol) under argon atmosphere with vigorous stirring at room temperature for 1 h. After removal of the DMF *in vacuo*, the residue was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4. After removal of the solvent, the oily residue was subjected to column chromatography on silica gel. O-Monobenzyl product (134 mg, 99%) was obtained as a colorless solid, showing mp 69 - 70 °C after recrystallization from a mixed solvent of ether and n-hexane. The results of the reaction with other halides are shown in Table 1.

The characteristic features of the present methodology are the mild reaction conditions, the excellent yields of the products, and a new application of CsF to organic synthesis.7,8)



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It should be mentioned here about the role of cesium fluoride in the reaction. Since the high reactivity of **3** activated by Sn-O bonds6) is not enough (Entries 2 and 4 in Table 1), it may be most reasonable to assume that alkyl halides are activated first by cesium fluoride through the interaction of cesium cation with the halogen atoms. Furthermore, the activation of Sn-O bonds in **3** may be caused by the formation of a pentaco-ordinate complex,9,10) because the maximum yield of Entry 1 in Table 1 was obtained by the use of almost 2 mol equivalents of CsF. The selective and efficient O-monoalkylation is likely to take place smoothly as the two combined consequences.

On the other hand, O-monosubstitution 3,6,11) of **3** with other halides are also efficiently achieved as shown in Table 2.

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8) All new compounds were well characterized and gave satisfactory spectra and the elemental analysis. The optical rotations of **4** are shown below. R=Me, $[\alpha]_D^{21.0}$ +39.0° (c 1.07, $CHCl_3$); R=CH_2=$CHCH_2$, $[\alpha]_D^{22.5}$ +34.1° (c 1.28, $CHCl_3$); R=p-$MeOC_6H_4CH_2$, $[\alpha]_D^{23.0}$ +84.0° (c 1.72, $CHCl_3$); R=p-$NO_2C_6H_4CH_2$, $[\alpha]_D^{24.0}$ +68.1° (c 1.03, $CHCl_3$); R=$PhCH_2$[2c], $[\alpha]_D^{22.0}$ +87.5° (c 1.17, $CHCl_3$); R=t-BuCO, $[\alpha]_D^{23.0}$ -12.1° (c 1.76, $CHCl_3$); R=$PhCH_2OCO$, $[\alpha]_D^{22.0}$ -0.6° (c 1.12, $CHCl_3$); R=$MeOCH_2$, $[\alpha]_D^{22.0}$ +102.6° (c 1.28, $CHCl_3$); R=$PhCH_2OCH_2$, $[\alpha]_D^{22.0}$ +81.6° (c 0.79, $CHCl_3$); R=t-$BuMe_2Si$, $[\alpha]_D^{22.5}$ +31.6° (c 1.32, $CHCl_3$); R=p-$MeC_6H_4SO_2$[2b], $[\alpha]_D^{23.0}$ +13.7° (c 1.23, $CHCl_3$)

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