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Convenient Preparation of (Chlorodifluoromethyl)arenes. Useful Precursors for Aryldifluoromethyl Radicals

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Chlorodifluoromethyl group was introduced into aromatic rings using bis(chlorodifluoroacetyl) peroxide which was readily prepared from corresponding acid anhydride with 30% hydrogen peroxide, and the chlorine was successively replaced by hydrogen or allyl group in excellent yields under radical conditions.

There are many $ArCH_2$ branched natural and biological active compounds, and the replacement of the two hydrogen atoms on the benzylic carbon to fluorine atoms is expected to modify the properties and biological activities of these molecules. However, the general methods for the preparations of the $ArCF_2$ derivatives have not yet been well established.[1-3] Recently, we have developed the convenient method for the introduction of various perfluoroalkyl groups into aromatic rings using bis(perfluoroalkanoyl) peroxides,[4] which are readily prepared from corresponding acid chlorides or acid anhydrides with 30% hydrogen peroxide.[5,6] Thus, in connection with the interest in the development of new synthetic method for the molecules bearing $ArCF_2$ groups, we investigated the chlorodifluoromethylations of aromatic rings using commercially available chlorodifluoroacetic anhydride, followed by replacement of the chlorine with other functional groups.

Hydrogen peroxide (30% aq, 2.5 mL) and then Freon 113 (1,1,2,-trichloro-1,2,2,-trifluoroethane; 15 mL) were added to the solution of sodium carbonate (4.4 g) and sodium chloride (4.8 g) in water (80 mL). The heterogeneous solution was cooled to -3 °C, stirred vigorously, and chlorodifluoroacetic anhydride (4.5 g) in Freon 113 (5 mL) was added drop by drop. The Freon layer was separated, and the concentration of the thus prepared peroxide was determined by iodometry (Yield; 35%). To the Freon solution of the peroxide (0.1 mol/L) was added an aromatic compound (5 - 10 equivalents to the peroxide), and the resulting solution was degassed by freeze-pump-thaw cycle, sealed in an ampoule, and kept at 40 °C for 10 h to afford a chlorodifluoromethylated arene. The result is shown in Table 1.

$$(CF_2ClCO)_2O \xrightarrow[Freon113 - H_2O]{H_2O_2,\ Na_2CO_3} (CF_2ClCO_2)_2 \qquad (1)$$

$$(CF_2ClCO_2)_2 + ArH \longrightarrow ArCF_2Cl + CF_2ClCO_2H + CO_2 \qquad (2)$$

Table 1. Chlorodifluoromethylation of Aromatic Rings

ArH	equiv.	Yield of $ArCF_2Cl$ / % [a]
Anisole	5	90 (o;58, m;16, p;26)[b]
Toluene	5	91 (o;51, m;26, p;23)[b]
Benzene	10	63
Benzene	5	43
Chlorobenzene	10	24 (o;38, m;19, p;43)[b]
Naphthalene	5	53 (α;87, β;13)[c]
Thiophene	5	68 (α;100)
Furan	5	48 (α;100)

a) The yields were determined by GC based on the used peroxide.

b) Ortho and para isomers were isolated as almost pure forms and identified by ^{1}H- and ^{13}C-NMR. The ratios (o:m:p) were determined by ^{19}F-NMR.

c) The each isomers were isolated and identified by ^{1}H- and ^{13}C-NMR.

The chlorodifluoromethylation proceeded in good to moderate yields except for chlorobenzene. Previously, we proposed the electron transfer mechanism for perfluoroalkylations of arenes with bis(perfluoroalkanoyl) peroxides.[4] The present chlorodifluoromethylation is also accounted for by electron transfer from the substrates to the peroxide as shown in Scheme 1. Therefore the reaction effectively proceeded in electron-rich aromatic rings as shown in Table 1. Fluoroalkyl radical is very reactive species and usually difficult to control the reactions. However, in this reaction chlorodifluoromethy radical is produced as a radical pair in close proximity with the radical cation of the substrate in a solvent cage, so the chlorodifluoromethyl radical reacts with the radical cation selectively.

$$(CF_2ClCO_2)_2 + ArH \longrightarrow (CF_2ClCO_2)_2^{\cdot -} + [ArH]^{\cdot +}$$
$$\longrightarrow CF_2Cl\cdot + [ArH]^{+} + CO_2 + CF_2ClCO_2^{-}$$
$$\longrightarrow ArCF_2Cl + CF_2ClCO_2H + CO_2$$

Scheme 1.

We examined the conversion of chlorodifluoromethylarenes to difluoromethylated ones by the reduction with tributyltin hydride under radical conditions. Tributyltin radical is expected to abstract the chlorine atom selectively from chlorodifluoromethylarenes to afford aryldifluoromethyl radicals, because C-F bond is much stronger than C-Cl bond. The reduction proceeded in excellent yields; typically, when a solution of 1-(chlorodifluoromethyl)naphthalene (1.0 mmol) and tributyltin hydride (1.2 mmol) in benzene (10 mL) was refluxed in the presence of AIBN (0.01 mmol) for 12 h, 1-(difluoromethyl)naphthalene was obtained in 87% yield.

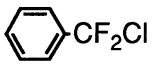
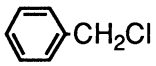
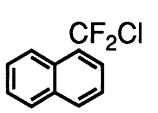
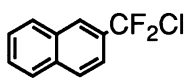
$$ArCF_2Cl \xrightarrow[\text{benzene}]{Bu_3SnH,\ AIBN} ArCF_2H \qquad (3)$$

Ar	Yield / %
Phenyl	82
1-Naphthyl	87
2-Naphthyl	88

We further demonstrated the conversion of chlorine into allyl group, which is useful functional group in organic synthesis, with allyltributyltin under radical conditions, and the results are shown in Table 2. Allylation of (chlorodifluoromethyl)benzene proceeded effectively; however, that of benzyl chloride did not take place (Table 2; runs 1, 3). Although benzyl-type radical is usually stable and does not react with a carbon-carbon double bond, α,α-difluorobenzyl radical smoothly reacted with carbon-carbon double bond of allyltributyltin to release tributyltin radical promoting radical chain reaction. When 1.2 equiv. of allyltributyltin was used, the radical chain reaction did not proceed

$$ArCF_2Cl \xrightarrow[\text{benzene}]{Bu_3SnCH_2CH=CH_2,\ AIBN} ArCF_2CH_2CH=CH_2 \qquad (4)$$

Table 2. Allylation of $ArCF_2Cl$ by Allyltributyltin

Run	Substrate	equiv.[a]	Initiator[b]	Yield / %[c]
1		1.2	AIBN	47[d]
2		5.0	AIBN	99[d]
3		1.2	AIBN	0
4		1.2	AIBN	33
5		1.2	BPO	36
6		1.2	AIBN, Bu_3SnH	44
7		5.0	AIBN	93
8		5.0	AIBN	96

a) $Bu_3SnCH_2CH=CH_2$ / Substrate. b) 0.01 equiv. of initiator was used. c) Determined by GC. d) Determined by ^{19}F-NMR.

completely: the allylated product was obtained in 47% yield with 40% recovery of chlorodifluoromethylbenzene (Table 2; run 1). Also in allylation of 1-(chlorodifluoromethyl)naphthalene, when 1.2 equiv. of allyltributyltin was used, the radical chain reactions terminated in 50 - 60% conversion regardless of the used initiators (Table 2; runs 4-6). By the use of 5.0 equiv of allyltributyltin, the allylated products were afforded in excellent yields (Table 2; runs 2, 7, 8). Thus, aryldifluoromethyl radicals are seemed to be moderately reactive and are expected to be useful species for the synthesis of $ArCF_2$ derivatives.

The fluorine-substituted carbocation intermediates are usually difficult to use in organic synthesis due to the strong electronegativity of fluorine. Further, α-fluorocarbanion is also unstable and tends to undergo defluorination due to the electrostatic repulsion between unshared electron pair of the carbanion and lone pair of fluorine. Therefore, radical species are likely to play an important role in the synthesis of organofluorine compounds. However, readily available (trifluoromethyl)arenes are inconvenient as precursors for aryldifluoromethyl radicals, since the C-F bond is too strong to abstract the fluorine.[7)]

In this study, (chlorodifluoromethyl)arenes were shown to be useful precursors for aryldifluoromethyl radicals. Since the convenient methods for the direct introduction of chlorodifluoromethyl group into aromatic rings have not been reported so far, the method described in this paper is novel and very promising for the synthesis of $ArCF_2$ derivatives.

References

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