Preliminary Note

Substituent modulation of mild fluorination of aromatic molecules with caesium fluoroxysulphate

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Abstract

Functionalization of mono- and di-substituted benzene derivative with $CsSO_4F$ has been modulated by substituents on the benzene ring. α-Hydroxyalkylbenzenes, with a deactivated ring, were oxidized to phenones, while fluorodealkylation was achieved in high yield when electron-donating groups were present in a *para* position. Electron-withdrawing substituents favoured chain fluorofunctionalization in alkylbenzenes, while ring fluorination was found exclusively in acylamino-derivatized alkylbenzenes; fluoro-addition products were formed in the case of *p*-alkoxy-substituted alkylbenzene derivatives.

Direct introduction of fluorine atoms into aromatic molecules is still a partially solved problem [1], and only a few examples of high-yield direct fluorination of benzene or other aromatics are known [2]. The problem is not only connected with the use of an appropriate reagent (F_2, XeF_2, $CsSO_4F$, CF_3OF, CH_3COOF, etc.) and reaction conditions, but also with the regioselectivity of fluorination and side-reactions (addition and polymerization processes). It appears, that the well-known Balz–Schiemann reaction, where the above-mentioned problems are not so defined, is still the most widely used method for the preparation of fluoroaromatic compounds [3].

We now report our investigation of the effect of benzene ring substituents on the reactions of benzene derivatives with $CsSO_4F$ [4] and, as evident from Scheme 1, five different types of transformations can be selectively achieved by choosing appropriate substituents.

In a typical experiment, 1 mmol 4-methyl-α-methylbenzyl alcohol was dissolved in 2 ml CH_3CN and, after the addition of 1.4 mmol $CsSO_4F$, the reaction suspension was stirred at room temperature for 1 h and then diluted with 20 ml CH_2Cl_2. The insoluble residue was filtered off, the filtrate washed with 20 ml water, dried (Na_2SO_4) and evaporated under reduced pressure. Nearly quantitative amounts (95%) of 4′-methylacetophenone were isolated. Numerous benzyl alcohols with unsubstituted (α-methyl-; α-ethyl-; α-cyclo-

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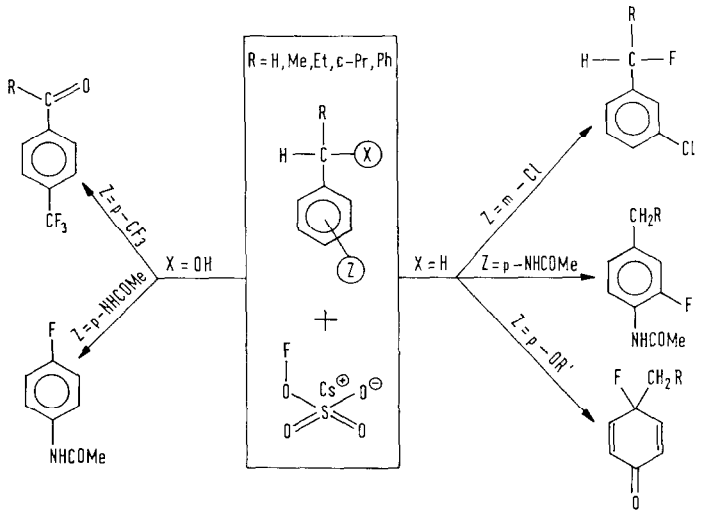

Scheme 1.

propylbenzyl alcohol; benzhydrol) or deactivated (3-trifluoromethyl-; 3-chloro-; 4-fluoro-; 4-nitrobenzhydrol) benzene rings were readily oxidized to the corresponding phenones under the same reaction conditions (Scheme 1, Table 1). Contrary to the above mentioned oxidation process, a fluoro-dealkylation reaction forming fluorobenzene derivatives in over 80% yield took place when α-hydroxyalkylbenzene derivatives with an electron-donating group in the *para* position were treated with $CsSO_4F$ in a CH_3CN suspension. 4-Acetylaminofluorobenzene was isolated as the sole product in the fluorination of 4-acetylamino-α-methylbenzyl alcohol, while 4-hydroxy- or 4-alkoxy-fluorobenzenes were selectively obtained by the reaction of 4-hydroxy- or 4-alkoxy-substituted α-hydroxyalkylbenzene derivatives (Scheme 1, Table 1).

Three other types of transformations were observed during the reactions of $CsSO_4F$ in acetonitrile suspension at 35 °C with alkyl-substituted aromatic molecules. Unsubstituted or ring-deactivated alkylbenzenes were regioselectively fluorofunctionalized on the benzylic position. Ethylbenzene was transformed into 1-fluoro-1-phenylethane and isopropylbenzene into 2-fluoro-2-phenylpropane in over 70% yield. The corresponding benzyl fluorides were selectively obtained from *m*- and *p*-chloro-,*m*- and *p*-methylcarboxy-, or *m*-fluorotoluene. On the other hand, the introduction of an electron-donating group into the benzene ring changed the direction of functionalization and only ring fluorination was observed. *p*-Acetylaminotoluene was regioselectively transformed into 3-fluoro-4-acetylaminotoluene, while the ring-substitution reaction was also accompanied by a fluoro-addition process resulting in 4-fluoro-4-methyl-2,5-cyclohexadienone formation in the fluorination of *p*-alkoxy-substituted toluenes (Scheme 1). The ratio between both processes depended strongly on the structure of the alkoxy substituent and varied from

TABLE 1

Substituent modulation of reactions of substituted benzene derivatives with caesium fluoroxysulphate[a]

Substituent			Product[b]	Yield (%)[c]
X	Z	R		
OH	H	Me	acetophenone	95
OH	H	Et	propiophenone	94
OH	H	c-Pr	c-propyl phenyl ketone	95
OH	H	Ph	benzophenone	92
OH	*p*-ME	Me	4'-methylacetophenone	95
OH	*m*-CF_3	Ph	3'-trifluoromethylbenzophenone	90
OH	*m*-Cl	Ph	3'-chlorobenzophenone	88
OH	*p*-F	Ph	4'-fluorobenzophenone	87
OH	*p*-NO_2	Ph	4'-nitrobenzophenone	82
OH	*p*-OH	Me	4-hydroxyfluorobenzene	82
OH	*p*-OMe	Me	4-methoxyfluorobenzene	85
OH	*p*-NHCOMe	Me	4-acetylaminofluorobenzene	86
H	H	Me	1-fluoro-1-phenylethane	73
Me	H	Me	2-fluoro-2-phenylpropane	70
H	*m*-Cl	H	3-chlorobenzyl fluoride	68
H	*p*-Cl	H	4-chlorobenzyl fluoride	69
H	*p*-COOMe	H	4-methylcarboxybenzyl fluoride	62
H	*m*-COOMe	H	3-methylcarboxybenzyl fluoride	60
H	*m*-F	H	3-fluorobenzyl fluoride	64
H	*p*-NHCOMe	H	3-fluoro-4-acetylaminotoluene	78
H	*p*-OMe	H	3-fluoro-4-methoxytoluene and 4-fluoro-4-methyl-2,5-cyclohexadienone (1.4:1)[d]	65
H	*p*-OBu^t	H	3-fluoro-4-t-butoxytoluene and 4-fluoro-4-methyl-2,5-cyclohexadienone (0.5:1)	64

[a]1 mmol substrate, 1.4–1.6 mmol $CsSO_4F$, 2 ml CH_3CN, temp. = 22–35 °C.
[b]Purified with column chromatography (SiO_2) or TLC, and identified on the basis of spectroscopical data for pure compounds by comparison with authentic samples or with literature values.
[c]Calcd. on basis of starting material.
[d]Ratios determined from ^{19}F NMR spectra of crude reaction mixtures.

1.4:1 to 0.5:1, when *p*-methoxy- or *p*-t-butoxytoluene were fluorinated by $CsSO_4F$.

The present study shows that with an appropriate change of substituents on the benzene ring, various types of transformations can be achieved selectively via reaction with $CsSO_4F$. Further research is in progress in order to evaluate more completely the results reported to date.

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