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Room Temperature Regioselective Iodination of Aromatic Ethers Mediated by Selectfluor^{TM} Reagent F-TEDA-BF$_4$

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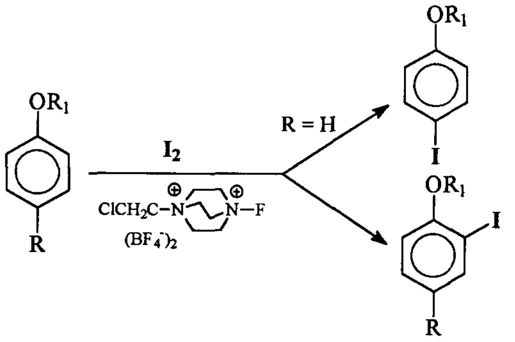
Abstract: Monosubstituted phenyl ethers were regioselectively iodinated with a mixture of iodine and F-TEDA in acetonitrile at room temperature at the para position, while 1-methoxy-4-substituted benzene derivatives were converted to 2-iodo products in high yield. © 1997 Elsevier Science Ltd.

Mild introduction of iodine into aromatic molecules has been a subject of broad interest[1]. A variety of reagents bearing positive iodine[2] were developed and new oxidizers for conversion of iodide or iodine to active iodinating species have been successfully promoted[3]. In recent years it has been demonstrated that F-N type of reagents, besides being able to introduce fluorine selectively into aromatic molecules[4] under mild reaction conditions, also possess oxidizing properties. The commercial availability of various types of F-N reagents[5] allows the broader application of this class of compounds and we report now that 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo [2.2.2]octane bis(tetrafluoroborate) (F-TEDA) could be an excellent mediator for mild introduction of iodine into an activated phenyl ring.

In a typical experiment to a solution of 1.0 mmol of F-TEDA and 0.5 mmol of iodine in 10 ml of CH_3CN, 1.0 mmol of anisole was added and a reaction mixture stirred for 3 hours at 22°C. The dark colour of iodine almost disappeared after half an hour and after a work-up procedure, the formation of 4-iodoanisole as the sole product was established. Reduction of the amount of F-TEDA to 0.5 mmol has no appreciable effect on a yield of the iodination process. In a blank experiment, under the above mentioned conditions, no reaction between anisole and F-TEDA, iodine and F-TEDA or iodine and anisole was observed. Conversion of anisole was not affected by the presence of nitrobenzene usually used as a radical scavenger, while solvent polarity played an important role in iodination, where longer reaction times were needed for complete conversion (7 hours in mixture of CH_3CN and 25% of CH_2Cl_2, H_2O or CH_3COOH). Finally we investigated the role of the source of iodine on iodination and potassium iodide was also found to be convenient but a larger amount of F-TEDA (1.0 mmol) was required. In this case the presence of water enhanced reactivity and complete conversion of anisole was acchieved in two hours at room temperature. Quantitative conversion was also observed after 4 hours reaction in the presence of Me_3SiI, while only 84% conversion was found after 24 hours at room temperature when MeI was used.

Scheme. Iodination of Aromatic Ethers with I_2 and F-TEDA in CH_3CN at 22°C



R	R_1	React. time[a]	Yield[b] (%)
H	CH_3	3h	89
H	CH_2Ph	3h	90
H	Ph	3h	80
F	CH_3	24h	87
Cl	CH_3	24h	89
Br	CH_3	26h	91
I	CH_3	30h	88
$COCH_3$	CH_3	10h	90
CHO	CH_3	10h	85
$C(CH_3)_3$	CH_3	3h	92

[a] 0.51 mmol of I_2 and 1.0 mmol of F-TEDA, 1.0 mmol of substrate in 10 ml of CH_3CN and stirred at 22°C. [b]Yields of purified compounds.

We further investigated the role of the aromatic molecule in this new iodination procedure and by using a two percent excess of iodine and a one to one molar ratio of substrate and F-TEDA, the complete conversion of starting material was achieved (Scheme). We established that a larger substituent on the ether function did not affect the iodination procedure since phenylbenzyl ether and diphenyl ether were quantitatively transformed to 4-substituted isomers at 22°C. Introduction of a halogen atom at the para position in anisole reduced the reactivity and a longer reaction time (24-30h) for almost quantitative conversion to the 2-iodosubstituted product was required. Para-methoxyacetophenone and 4-methoxyaldehyde were converted after 10 hours to 2-iodo derivatives and no side reactions on the carbonyl functional group took place. Introduction of a large group did not effect the iodination process and after 3 hours 2-iodo-4-t-butylanisole was isolated in excellent yield.

On the basis of these reported results we can conclude that by using F-TEDA and various iodine sources regioselective iodination could be achieved. The mechanism of the reaction and the applicability of this new method to other aromatics, olefins and ketones, as well as its convenience for radiolabeling of organic molecules[6] is now under further investigation.

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