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Facile and efficient synthesis of fluoroalkyl aryl ethers

Ahmed Kamal,* T. B. Pratap, K. Venkata Ramana, A. V. Ramana and A. Hari Babu

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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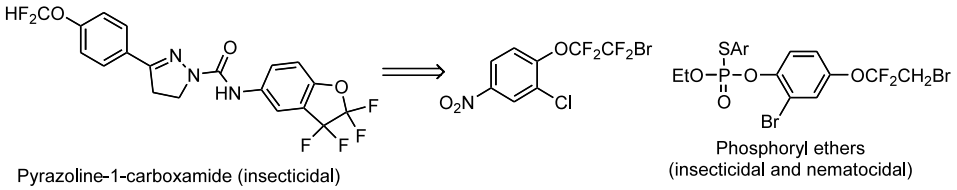
Abstract—A convenient and practical method for the preparation of fluoroalkyl aryl ethers via substitution of iodoalkyl fluorides is described. This method involves KF complexation of the phenol, which increases the nucleophilicity of oxygen for the formation of the ether linkage.

It is well known that the substitution of hydrogen with fluorine in organic compounds can sometimes dramatically change physical, chemical and biological properties.[1] Therefore, the synthesis of organofluorine compounds has become an important area of chemistry both in academia and in industry. A large number of methods have been developed for the introduction of fluorine into different organic compounds.[2] Recently, enantioselective fluorination[3] to obtain chiral fluorinated molecules has attracted considerable interest due to the unique properties of the C–F bond, and the importance of the fluorine moiety in molecules of pharmaceutical and biological interest is undisputed.[4] Amongst fluorinated organic materials, fluoroalkyl aromatics and, more precisely, fluoroalkyl aryl ethers have been found useful as insecticides,[5] fungicides,[6] herbicides,[7] dyes,[8] and as intermediates for antiulcer agents,[9] and some examples are shown below.

The majority of reported synthetic procedures[10] for fluoroalkyl aryl ethers involve the reaction of an electrophilic iodo/bromoalkylfluoride or fluoroalkene or fluoroalkyl sulfonate with a nucleophilic phenol. A single vessel process for the preparation of trifluoromethyl aryl ethers employing HF has also been reported.[11] However, most of the methods employed for the preparation of fluoroalkyl aromatic components generally involve the use of strongly basic conditions, and, moreover, they do not offer practical convenience and simplicity. For example, aromatic fluoroalkoxylation has been carried out by aromatic nucleophilic substitution with fluorinated alkoxide anions in solvents such as HMPA at temperatures of 90–150°C. This route is useful for trifluoroethoxylation, whereas tetrafluoroethoxylations have not been attempted by this approach. In connection with a programme directed towards the preparation of fluorinated alkylaryl ethers, our earlier attempts to displace the iodo functionality of alkyl halides by employing different bases such as K_2CO_3 and NaOH, and also involving techniques like sonification and phase transfer conditions did not yield the desired results.

In this communication, we wish to report an easy and efficient procedure for the preparation of fluoro alkyl aryl ethers by the direct iodine displacement of alkyl halides employing KF (Scheme 1). The etherification of 4-substituted phenols with iodofluoro alkanes proceeds smoothly to afford the corresponding fluoro substituted alkyl aryl ethers as illustrated in Table 1. It is observed that the yields are excellent for entries **a**–**h** and good to moderate in case of **i**–**n**. These etherification reactions are generally completed within 3–7 hours and no significant amounts of any side-products have been observed suggesting that the nucleophilicity of fluoride is effectively suppressed by complexation with phenolic -OH.



Pyrazoline-1-carboxamide (insecticidal)

Phosphoryl ethers
(insecticidal and nematocidal)

* Corresponding author. Tel.: +91-40-7193157; fax: 91-40-7160512; e-mail: ahmedkamal@iict.ap.nic.in

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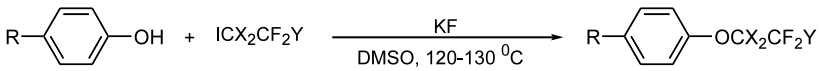

R = CN, NO_2, CF_3, CH_3, C_2H_5O X = H, F Y = F, Cl, H

Scheme 1.

Table 1. Potassium fluoride-mediated preparation of fluoroalkyl aryl ethers

Entry	Phenol (**1**)	Iodoalkyl halide (**2**)	Product (**3**)	Reaction time (h)	Yield (%)
a	4-NCC_6H_4OH	ICH_2CF_3	4-$NCC_6H_4OCH_2CF_3$	4	85
b	4-NCC_6H_4OH	ICF_2CF_2Cl	4-$NCC_6H_4OCF_2CF_2Cl$	5	75
c	4-$O_2NC_6H_4OH$	ICF_2CF_2H	4-$O_2NC_6H_4OCF_2CF_2H$	4	90
d	4-$O_2NC_6H_4OH$	ICH_2CF_3	4-$O_2NC_6H_4OCH_2CF_3$	4	90
e	4-$O_2NC_6H_4OH$	ICF_2CF_2Cl	4-$O_2NC_6H_4OCF_2CF_2Cl$	6	80
f	4-$F_3CC_6H_4OH$	ICF_2CF_2H	4-$F_3CC_6H_4OCF_2CF_2H$	4	85
g	4-$F_3CC_6H_4OH$	ICH_2CF_3	4-$F_3CC_6H_4OCH_2CF_3$	3	80
h	4-$F_3CC_6H_4OH$	ICF_2CF_2Cl	4-$F_3CC_6H_4OCF_2CF_2Cl$	5	75
i	4-$H_3CC_6H_4OH$	ICF_2CF_2H	4-$H_3CC_6H_4OCF_2CF_2H$	5	50
j	4-$H_3CC_6H_4OH$	ICH_2CF_3	4-$H_3CC_6H_4OCH_2CF_3$	4	50
k	4-$H_3CC_6H_4OH$	ICF_2CF_2Cl	4-$H_3CC_6H_4OCF_2CF_2Cl$	6	35
l	4-$C_2H_5O_2CC_6H_4OH$	ICF_2CF_2H	4-$C_2H_5O_2CC_6H_4OCF_2CF_2$	6	50
m	4-$C_2H_5O_2CC_6H_4OH$	ICH_2CF_3	4-$C_2H_5O_2CC_6H_4OCH_2CF_3$	6	40
n	4-$C_2H_5O_2CC_6H_4OH$	ICF_2CF_2Cl	4-$H_5C_2O_2CC_6H_4OCF_2CF_2Cl$	7	30

In the literature, a report[12] regarding the synthesis of biaryl ethers claimed that KF forms a complex with 4-cyanophenol thereby localizing the charge on oxygen. This complex was analyzed by thermogravimetric analysis and infrared spectroscopy. Based on this finding, it is considered that in the present method a similar mechanism may be operating for the formation of fluoroalkyl aryl ethers.

In a typical experiment, the 4-substituted phenol (1 mmol) and KF (1 mmol) were dissolved in methanol (10 ml) and the methanol was gradually distilled off. The solid obtained was washed with dry ether (3×10 ml) and dried under vacuum to obtain a nonhygroscopic white solid (unlike KF, which is hygroscopic). This complex was dissolved in DMSO (15 ml) and to this was added to a solution of the iodofluoroalkane (3 mmol) in DMSO (3 ml). The mixture was heated at 120°C in a sealed reactor and the reaction was monitored by TLC. The reaction mixture was diluted with ice-cold water and subsequently extracted with ethyl acetate (3×20 ml). The combined ethyl acetate layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain an oily residue. This was purified by column chromatography (silica gel, hexane/EtOAc, 9:1) to obtain the pure fluoroalkyl aryl ether. These compounds were characterized by IR, ^1H NMR and mass spectral analysis.[13]

In conclusion, we have described an easy and efficient procedure for the etherification of 4-substituted phenols with fluoroalkyl iodides to afford α,α,β,β-tetrafluoroalkyl-aryl ethers and β,β,β-trifluoroalkyl-arylethers using KF. The present method offers several advantages such as nearly neutral reaction conditions, high yields, short reaction times and a simple work-up procedure. Further, this method is devoid of the use of corrosive starting materials like tetrafluoroethylene and strong bases.

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13. Selected spectral data of some representative compounds: **3a**: IR (neat): 1180 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$): δ 7.7 (2H, d, $J=6.3$ Hz), δ 7.1 (2H, d, $J=6.3$ Hz), δ 4.5 (2H, m) MS: m/z 201 (M^+, 100%). **3c**: IR (neat): 1110 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$): δ 8.3 (2H, d, $J=6.5$ Hz), δ 7.4 (2H, d, $J=6.5$ Hz), δ 5.9 (1H, m) MS: m/z 239 (M^+, 100%).