

# Regioselective preparation of functional aryl ethers and esters by stepwise nucleophilic aromatic substitution reaction



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## ABSTRACT

Functional aryl ethers bearing mono- and di-substituted azo compounds, allyl functionalities, vinyl phenyl moieties, trifluoromethyl ( $-\text{CF}_3$ ) groups, etc. were prepared by nucleophilic substitution reaction of 2,3,4,5,6-pentafluorobenzonitrile (PFBN) in a stepwise manner at room temperature in dipolar aprotic solvents in a regioselective manner. Mono substituted aryl ether further underwent two more substitutions at *ortho* and *ortho'* positions either with the same or different phenoxides. However, *para* substituted monoesters as well as *para*-ether-*ortho*-ester obtained by using carboxylates as (one of the) nucleophiles did not undergo any further displacement. The synthetic strategy described here is useful for making various functional materials such as lubricants, liquid crystals, curing agents, pigments and superhydrophobic materials.

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## 1. Introduction

Organic compounds containing multiple fluorine atoms are high performance materials and applied in many areas such as hydrophobic materials [1], lubricants [2], thermally stable materials [3], dielectric materials [4], liquid crystals [5], etc. Due to the unique properties of fluorinated compounds, these are also used widely as drugs in various therapeutic areas such as antifungal agents [6], antibiotics [7], antimalarial compounds [8], antidepressants [9], anti-inflammatory agents [10], anesthetics [11], and in biomedical research as drug delivery systems [12]. Quite apart from these applications, fluorinated compounds are also valuable intermediates for preparing a variety of materials such as contrast agents for bio-imaging applications [13], electronic applications [14] and high performance coatings [15].

In aromatic compounds containing fluorine atoms, these atoms are either present on the aromatic ring substituting H atoms or attached as a pendant group such as perfluoroalkyl (e.g.,  $-\text{CF}_3$  or higher homologues). These fluorinated aromatic compounds of the first category readily undergo nucleophilic substitution reactions, particularly if the compound contains multiple F atoms on the aromatic ring or if it possesses electron withdrawing groups

suitably positioned to activate the displacement of fluorine as fluoride ( $\text{F}^-$ ). Indeed this ability to undergo nucleophilic substitution has been made use of for making various high performance engineering thermoplastics such as poly(arylene ether)s viz., poly(ether ether ketone)s, (PEEK), poly(ether sulfone)s, poly(ether imide)s, etc. which are well known for excellent properties such as high temperature stability, high glass transition temperature, anti-flammable nature, solvent resistance, etc. [16]. Fluorinated aromatic compounds are also often used as building blocks in the preparation of macrocycles [17], glycosyl donors [18], and fused ring systems [19].

## 2. Results and discussion

Perfluoro and difluoro organic compounds such as 2,3,4,5,6-pentafluorobenzonitrile [20] (PFBN) and 2,6-difluorobenzonitrile [21] (DFBN) are valuable starting materials, because of its ability to undergo nucleophilic substitution under mild conditions yielding various organic compounds and functional polymers with highly polar cyano ( $-\text{CN}$ ) pendant groups [20d,21b].

The *para* F atom of PFBN readily undergoes nucleophilic substitution selectively even at room temperature or lower [20d]. This superior reactivity of *para* F atom as compared to those at *ortho*, *ortho'* positions enabled us to prepare linear poly(arylene ether)s with multiple pendant groups [20d]. As reported here, this reactivity difference has been exploited to prepare various symmetrically and unsymmetrically trisubstituted arylene ether and ester derivatives under mild reaction conditions. It is useful to

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note here that carboxylates have rarely been used as nucleophiles in nucleophilic aromatic substitution reactions. Previously we employed carboxylates as nucleophiles in nucleophilic aliphatic substitution reactions to make unsaturated poly(ether ester)s and polyesters [22].

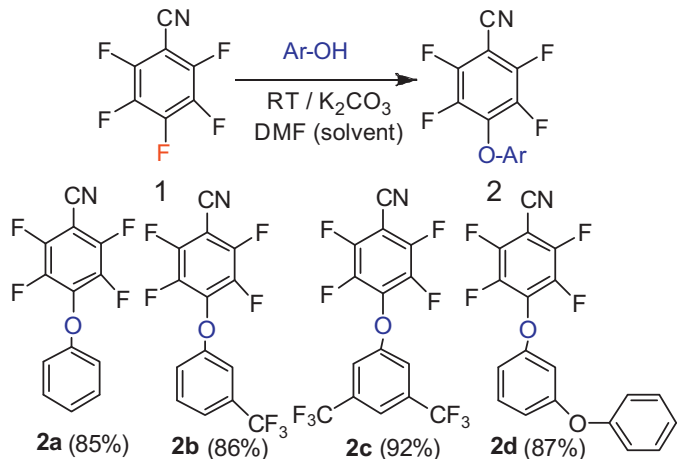
In the first step of nucleophilic substitution reaction, the *para* fluorine atom was selectively displaced with one equivalent of (substituted) phenol in presence of base at room temperature or below, quantitatively. Subsequent reaction(s) with two more equivalents of similar or dissimilar nucleophiles displaces F atoms at *ortho* and *ortho'* positions as well. Thus this methodology offers a unique advantage of making symmetrical or differently trisubstituted benzonitriles in a facile manner.

In this study, we used four different phenols viz., phenol, 3-(trifluoromethyl)phenol, 3,5-bis(trifluoromethyl)phenol and 3-phenoxyphenol as nucleophile to displace the *para*-fluorine atom of PFBN. The nucleophilic aromatic substitution reaction proceeded smoothly in dipolar aprotic solvents in presence of base such as potassium carbonate at room temperature for 24 h. The preparation of various 4-phenoxy-2,3,5,6-tetrafluorobenzonitrile (PTFBN) is shown in Scheme 1.

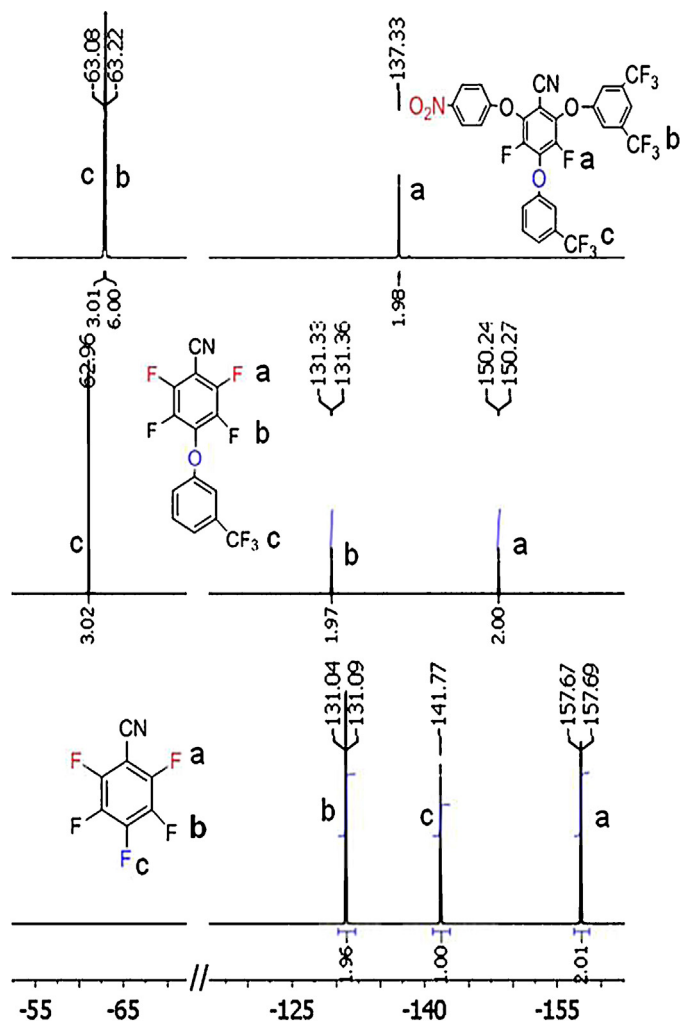
The nuclear magnetic resonance spectrum of F nuclei,  $^{19}\text{F}$  NMR spectra, of PTFBN clearly indicate that the complete disappearance of signal corresponding to the *para* fluorine atom at  $-141.75$  ppm. Also, the  $^{19}\text{F}$  NMR spectroscopic analysis of **2b** (Figs. 1 and S1) showed signals at  $-62.96$  ppm,  $-131.5$  ppm, and  $-150.42$  ppm corresponding to  $-\text{CF}_3$  group, *meta* and *ortho* F atoms respectively with the intensity ratio of 3:2:2, as expected. The facile mono substitution yielded analytically pure compounds as established by elemental analysis. The nature of compounds varied from solid to viscous liquid depending on the type of phenol used for nucleophilic substitution reaction. The mono substituted PTFBN were obtained in high yields (85–92%) after purification.

The mono substituted PTFBNs possess two more displaceable F atoms of equal reactivity at *ortho*, *ortho'* positions. Thus, trisubstituted arylene ethers were prepared by employing two equivalents of same or different phenols in a one or two step reaction at room temperature respectively.

The disubstituted phenoxy benzonitriles, TriFBNs were obtained by reacting PTFBN with one equivalent of phenol such as 3-(trifluoromethyl)phenol, and 3,5-bis(trifluoromethyl)phenol as shown in Scheme 2. These reactions usually yielded some impurities such as trisubstituted compounds because of the equal reactivity of fluorine atoms at *ortho*, *ortho'* positions. In spite of this side reaction, disubstituted compounds were obtained in high to very high yields depending on the reactivity of monohydroxy

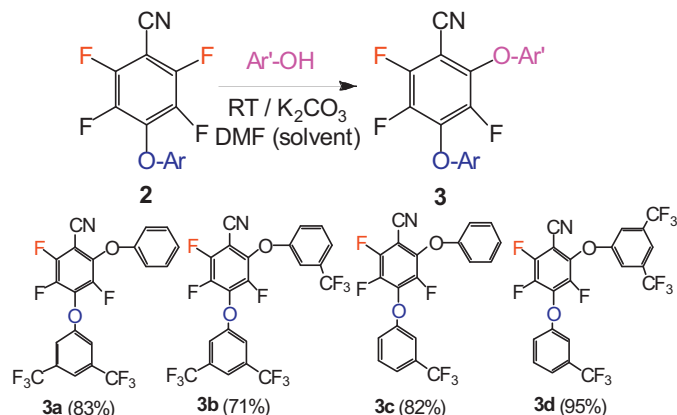


**Scheme 1.** Regioselective synthesis of 4-phenoxy(substituted)-2,3,5,6-tetrafluorobenzonitriles (PTFBN).



**Fig. 1.** Stacked  $^{19}\text{F}$  NMR spectra of 2,3,4,5,6-pentafluorobenzonitrile (PFBN), 4-phenoxy-3-(trifluoromethyl)-2,3,5,6-tetrafluorobenzonitrile (**2b**) and 2-[3,5-bis(trifluoromethyl)phenoxy]-3,5-difluoro-6-(4-nitrophenoxy)-4-[3-(trifluoromethyl)phenoxy]benzonitrile (**4e**).

phenol moiety. The formation of trisubstituted product occurred even when the reaction was carried out at lower temperatures ( $5\text{--}10^\circ\text{C}$ ) and with lower base concentration (0.75 equivalents). Surprisingly the reactions with 3,5-bis(trifluoromethyl)phenol proceeded with high yields for both mono (Scheme 1, **2c**) as well as disubstitution (Scheme 2, **3d**). Earlier we noticed that the PTFBN



**Scheme 2.** Regioselective synthesis of disubstituted trifluorobenzonitrile ethers.

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