Hypervalent iodine reagents in organic synthesis: Nucleophilic substitution of *p*-substituted phenol ethers

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Abstract: The novel hypervalent iodine-induced nucleophilic substitution of *p*-substituted phenol ethers in the presence of a variety of nucleophiles and the direct alkyl azidation of *p*-alkyl phenol ethers are described. UV and ESR spectroscopic studies indicate that these reactions proceed via radical species; one is $[ArH^{+\cdot}]$ and the other is $[ArC^{\cdot}R^1R^2]$ as reactive intermediates.

Introduction

There is an increasing interest in the hypervalent iodine oxidation of phenols and related compounds (1). Although the reaction of phenols themselves with phenyliodine(III) diacetate (PIDA) or phenyliodine(III) bis(trifluoroacetate) (PIFA) frequently leads to resinous products (2), phenols bearing electron-withdrawing *o*-nitro and *o,p*-dinitro groups react with PIDA to give the corresponding iodonium salts (3). Hypervalent iodine reagents have also been used for the oxidative cyclization of binaphthols to spiro compounds (4), for intramolecular oxidative aryl-aryl coupling (5), and for carbon-carbon bond cleavage of NH_2-tyrosine dipeptides (6). As part of our continuing studies concerning hypervalent iodine chemistry (7), we have reported the oxidation of *p*-substituted phenol derivatives leading to *p*-benzoquinone monoacetals (8), spiro compounds (9), *p*-benzoquinones (10), and azacarbocyclic spirodienones (11, 12) using PIFA. In most cases, the reactions of phenol derivatives with PIFA first proceed via the reaction of the phenolic OH group with an iodine center. On the other hand, it is well-known that diaryliodonium salts (13, 14) are obtained by the reaction of unsubstituted or *m*-substituted phenol ethers with hypervalent iodine species.

In the case of *p*-substituted phenol ethers with PIFA, however, diaryliodonium salts were not obtained, but a nucleophilic substitution reaction occurred. We now describe the generality of the hypervalent iodine-induced nucleophilic substitution of *p*-substituted phenol ethers with various nucleophiles (N_3^-, OAc^-, β-dicarbonyl compounds and SAr^-) in 1,1,1,3,3,3-hexafluoro-2-propanol ($(CF_3)_2CHOH$) and the direct alkyl azidation of *p*-alkyl phenol ethers in CH_3CN and discuss the reaction mechanism.

1. Oxidative Nucleophilic Substitution of *p*-Substituted Phenol Ethers

The oxidative nucleophilic substitution reaction of *p*-substituted phenol ethers (**1**) with PIFA proceeded clearly in poorly nucleophilic polar solvent, $(CF_3)_2CHOH$. This reaction was found to be useful for the introduction of various types of oxygen, nitrogen, carbon, and sulfur nucleophiles to *p*-substituted phenol ethers as described below.

1.1. Introduction of Azido Group (15, 16)

The combination of the hypervalent iodine reagent and trimethylsilyl azide ($TMSN_3$) has been known to generate hypervalent azidoiodine(III) species (17) and used for the oxidative azidation of olefins into α-azido ketones (18) and vicinal diazides, of β-dicarbonyl compounds into α-azido-β-dicarbonyl compounds (19), of 2-(trimethyl-silyloxy)furan into 5-azido-2(5H)-furanone (20), and of triisopropylsilyl enol ether into β-azido triisopropylsilyl enol ether (21). These hypervalent azidoiodine(III) species, however, may not be active enough for the oxidative azidation of aromatic carbons and there is no report on these types of reactions. We found a novel and useful oxidative azidation of aromatic compounds using the hypervalent iodine reagent, PIFA and $TMSN_3$ in $(CF_3)_2CHOH$ (Chart 1).

R=OMe, Me, *i*-Pr, Br, Cl,
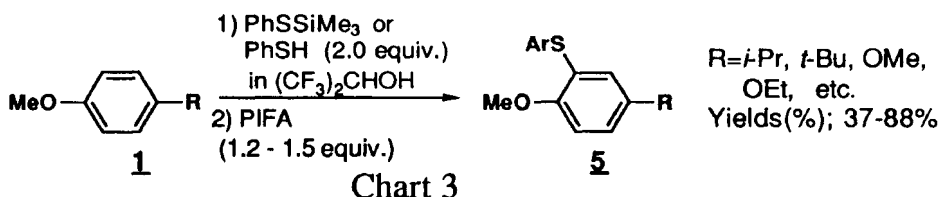*t*-Bu, CH_2CO_2Me, CH_2CN, etc.

Yields (%); 31-82%
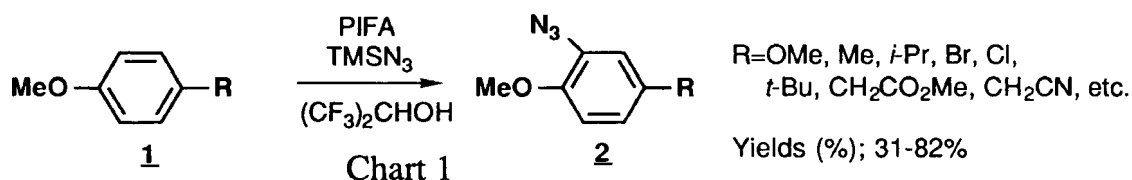
Chart 1

1.2. Introduction of Acetoxy and β-Dicarbonyl Groups (16)

Other nucleophiles (OAc⁻, and β-dicarbonyl compounds) could be introduced in moderate yields under similar conditions for aromatic azidation (Chart 2).

R=OMe, *i*-Pr, etc. Yields (%); 43-67%

Nu(C)

R=OMe, OEt, *i*-Pr, etc.

Yields (%); 39-83%

Chart 2
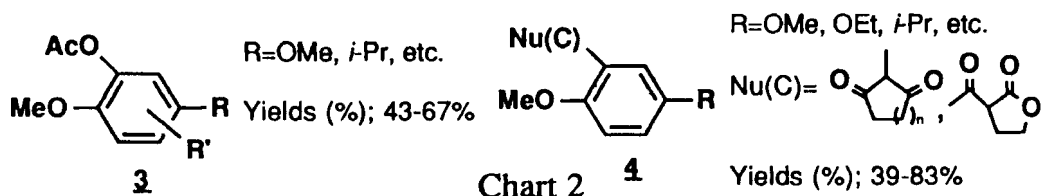
1.3. Introduction of Sulfenyl Group (22)

Several types of sulfenylation methods for aryl compounds have been reported (23). Most of these reactions, however, require high temperature, metals or drastic catalysts, and usually a long reaction time. We found a mild and efficient sulfenylation method for phenol ethers using PIFA and various types of thiophenols (Chart 3).

1) PhSSiMe₃ or
   PhSH (2.0 equiv.)
   in (CF₃)₂CHOH
2) PIFA
   (1.2 - 1.5 equiv.)

R=*i*-Pr, *t*-Bu, OMe, OEt, etc.
Yields(%); 37-88%

Chart 3

1.4. Reaction Mechanism (16)

According to the extensive UV and ESR spectroscopic studies for this type of reaction, we now propose the following plausible reaction mechanism (Chart 4).

SET: Single Electron Transfer

Nu=N₃, OAc, SAr,

Chart 4
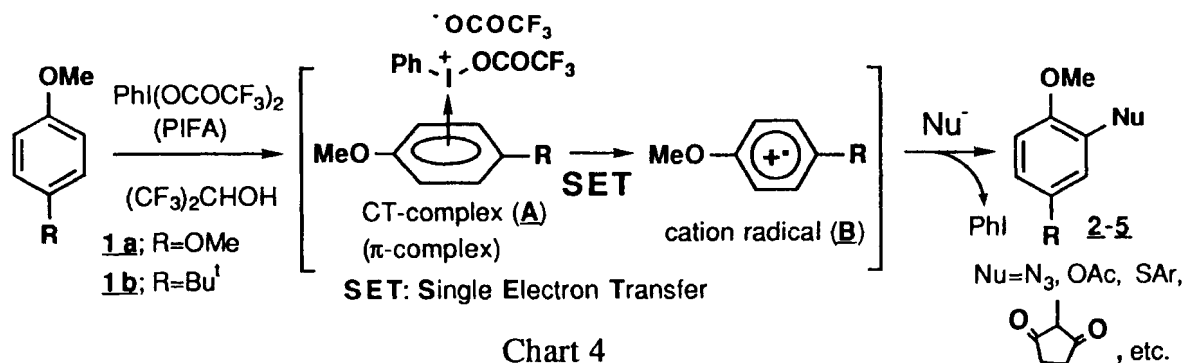
That is, the reaction proceeds via cation radicals [ArH⁺·] (**B**) as reactive intermediates generated by SET from the CT-complex (**A**) of phenol ethers with PIFA. The electron spin density for the cation radical of **1b** was calculated using the Hückel molecular orbital calculation method and from the ESR spectrum for **6** (Fig. 2). The results are summarized in Fig. 1, in which the values from both methods were found to be almost identical. The result of the calculation rationalized the regiospecificity during the nucleophilic substitution of **1b**; the cation radical of **1b** is concentrated at the *ortho* position relative to the methoxy group.
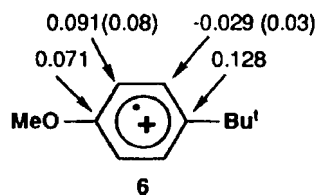

Fig. 1: Electron Spin Density of Cation Radical (**6**): The value in the parentheses were obtained from the ESR spectrum (Fig. 2).
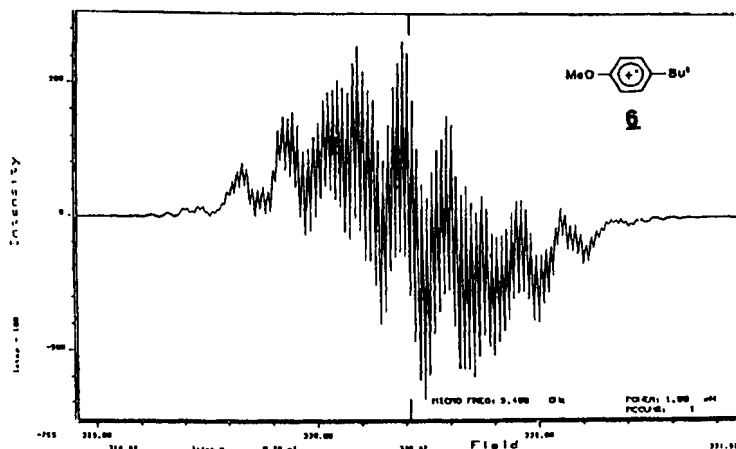
Fig. 2

This is the first case in which a radical intermediate was detected during hypervalent iodine oxidations. Thus, this type of reaction was found to be mild and quite effective for the introductions of azido, acetoxy, β-dicarbonyl and aryl thio groups to *p*-substituted phenol ethers.

2. Direct Alkyl Azidation of *p*-Alkylphenol Ethers (24)

Azidation is an important reaction in organic synthesis, since the azido group is readily converted to a variety of other functional groups through the amino group and the diazonium salt. Direct alkyl azidation seems to be a convenient method for the preparation of alkyl azido compounds, but it is not a widely used method. Generally, alkyl azides are prepared by the nucleophilic substitution of alkyl halides or sulfonates using the azido anion. As previously described, the aromatic azidation of *p*-substituted phenol ethers using PIFA and TMSN$_3$ proceeds in (CF$_3$)$_2$CHOH. On the other hand, the direct alkyl azidation of *p*-alkyl phenol ethers bearing benzylic protons using the reagent combination of PIFA and TMSN$_3$ occurred in CH$_3$CN (Chart 5).

Chart 5

R=Me, ^{t}BuMe$_2$Si, etc.
R^1, R^2=H, Me, Et, CN,
SMe, CO$_2$Me, etc.
Yields (%); 24-79%
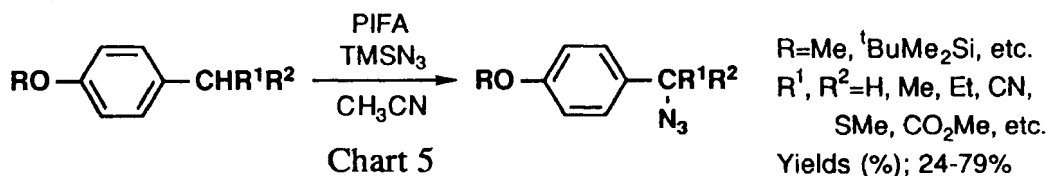
We assume that the present direct alkyl azidation proceeds via a homolytic pathway as shown in Chart 6 partly because the generation of the azido radical from PIDA and NaN$_3$ in several organic solvents such as alcohols, ethers, formamide, and aldehydes has been postulated by Fontana *et al.*(17)(Chart 6).

Chart 6
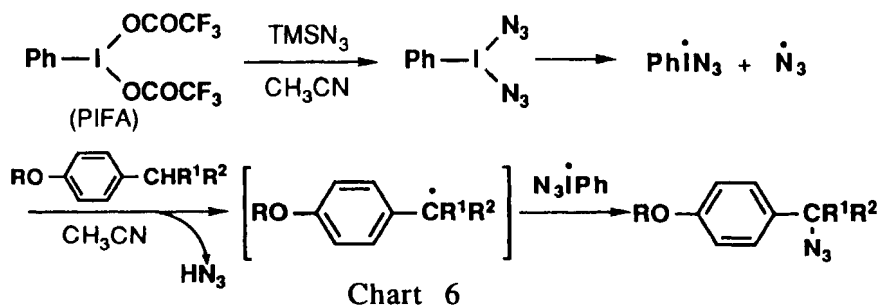
Conclusions

The nucleophilic substitution of *p*-substituted phenol ethers has been found to proceed via cation radicals as reactive intermediates by SET from the CT-complex of **1** and PIFA. The mechanism was confirmed by UV and ESR spectroscopic studies. This is the first case that does not involve diaryliodonium salts but cation radicals in the reaction of aromatic compounds with hypervalent iodine reagents. Furthermore, we have found that the novel and general direct azidation of *p*-alkylphenol ethers at the benzylic positions has been developed.

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