Non-phenolic oxidative coupling of phenol ether derivatives using phenyliodine(III) bis(trifluoroacetate)

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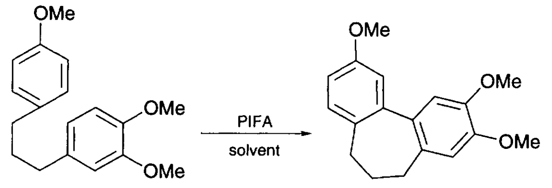
Phenol ether derivatives (non-phenolic derivatives), 1,3-diarylpropanes 1a–e, *N*-benzyl-*N*-phenethylamines 2a–c and *N*,*N*-dibenzylamines 3a–e react with a hypervalent iodine reagent, phenyliodine(III) bis(trifluoroacetate) (PIFA), containing $BF_3{\cdot}Et_2O$ in CH_2Cl_2 to give the biaryl coupling products 4a–e, 5a–c and 6a–e in good yields.

Intramolecular oxidative phenolic coupling reactions are important key steps in the biosynthesis of many natural products.[1] A number of biogenetic-type phenolic coupling reactions have been investigated using heavy metallic oxidizing reagents such as Tl^{III} or V^{V} salts.[2,3] These reagents are, however, highly toxic and care must be taken in handling them. To solve these problems, oxidative phenolic coupling reactions using hypervalent iodine(III) reagents, which are safe and useful synthetic reagents,[4] were examined. These methods using iodine(III) reagents could also be applied to substrates having free OH groups on the aromatic ring.[5] However, probably due to the lower reactivity of the phenol ethers towards iodine(III) reagents, the biaryl coupling reaction of non-phenolic type substrates has not been reported.

Recently, we reported the novel and direct nucleophilic substitution of phenol ethers by nitrogen, carbon, oxygen and sulfur nucleophiles using PIFA in 1,1,1,3,3,3-hexafluoropropan-2-ol [$(CF_3)_2CHOH$] or 2,2,2-trifluoroethanol (CF_3CH_2OH).[6,7] In our continuing effort to develop this nucleophilic substitution of phenol ethers, we now report the intramolecular oxidative phenolic coupling of various phenol ether derivatives (non-phenolic substrates) using PIFA.

At first, the biaryl coupling of 1,3-diarylpropanes **1** using PIFA was investigated. Treatment of 1-(3,4-dimethoxyphenyl)-3-(3-methoxyphenyl)propane **1a** with PIFA in $(CF_3)_2CHOH$ at room temperature gave a biaryl coupling product **4a** in 63% yield. The reaction in other solvents, such as CF_3CH_2OH, MeCN and CH_2Cl_2 also gave **4a** in 65, 46 and 25% yields, respectively. When the coupling reaction was carried out in the presence of $BF_3{\cdot}Et_2O$, which activates PIFA, the yield was dramatically improved. Thus, the coupling reaction proceeded smoothly at low temperature to give **4a** in good yields. In CH_2Cl_2, the yield of **4a** from **1a** increased to 91%† (Table 1).

Table 1 Intramolecular cyclization of **1a** in various solvents



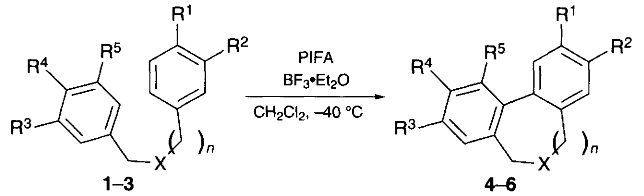
1a **4a**

Solvent	Yield of 4a (%) None	Yield of 4a (%) Containing $BF_3.Et_2O$
$(CF_3)_2CHOH$	63	63
CF_3CH_2OH	65	84
MeCN	46	73
CH_2Cl_2	25	91

Other 1,3-diarylpropanes **1b–e**, *N*-benzyl-*N*-phenethylamine derivatives **2a–c** and *N*,*N*-dibenzylamine derivatives **3a–e** similarly reacted with PIFA containing $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −40 °C to give the corresponding biaryl coupling products, **4b–e**, **5a–c**, **6a–e**, in good yields.‡ The results are summarized in Table 2.

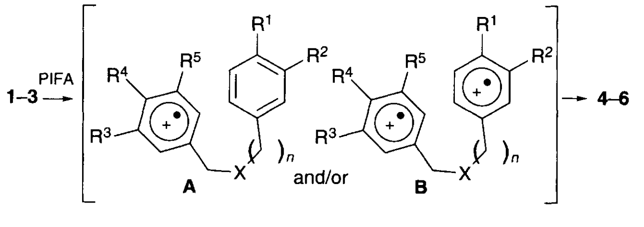
The mechanism for the biaryl coupling of phenol ether **A** or a dication radical intermediate **B** generated by the one-electron oxidation of an electron-rich aromatic ring with PIFA. The nucleophilic attack by the other aromatic rings on the cation radical **A** or a radical coupling reaction of the dication radical intermediate **B** then occurs to give the biaryl product (Scheme 1).

Table 2 Biaryl coupling of **1–3** with PIFA



1–3 **4–6**

1–3	R^1	R^2	R^3	R^4	R^5	*n*	X	4–6	Yield (%)
1a	OMe	H	OMe	OMe	H	1	CH_2	**4a**	91
b	$-OCH_2O-$		$-OCH_2O-$		H	1	CH_2	**b**	91
c	OMe	OMe	OMe	OMe	H	1	CH_2	**c**	99
d	OMe	OMe	OMe	OMe	OMe	1	CH_2	**d**	92
e	OMe	OMe	OMe	OTBS	H	1	CH_2	**e**	75
2a	OMe	H	OMe	OMe	H	2	$NCOCF_3$	**5a**	89
b	OMe	OMe	OMe	OMe	H	2	$NCOCF_3$	**b**	68
c	OMe	OMe	OMe	OMe	OMe	2	$NCOCF_3$	**c**	52
3a	$-OCH_2O-$		$-OCH_2O-$		H	1	$NCOCF_3$	**6a**	94
b	OMe	OMe	OMe	OMe	H	1	$NCOCF_3$	**b**	85
c	OMe	OMe	OMe	OMe	OMe	1	$NCOCF_3$	**c**	85
d	OMe	OMe	OMe	OTBS	H	1	$NCOCF_3$	**d**	64
e	OMe	OMe	OMe	OAc	H	1	$NCOCF_3$	**e**	60



Scheme 1 Possible reaction mechanism of biaryl coupling of non-phenolic substrates

Footnotes

† *Preparation of* **4a**: To a stirred solution of **1a** (14.2 mg, 0.050 mmol) in CH_2Cl_2 (1.0 cm^3) was added a solution of PIFA (21.4 mg, 0.050 mmol) and $BF_3 \cdot Et_2O$ (14.1 mg, 0.100 mmol) in CH_2Cl_2 (1.0 cm^3) at −40 °C under a nitrogen atmosphere. The reaction mixture was then stirred at −40 °C for 1.5 h and then evaporated *in vacuo*. Purification of the residue on silica gel (hexane–ethyl acetate) gave pure **4a** (12.8 mg, 91%) as a colourless oil.

‡ All compounds were characterized by ^1H NMR spectroscopy and mass spectral analysis.

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