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Accepted Article

Title: Direct Azidation of Phenols

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201900967

Link to VoR: http://dx.doi.org/10.1002/ejoc.201900967

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Direct Azidation of Phenols

Mitsuru Kitamura*,[a] Kento Murakami, Tatsuya Koga, Takashi Eto, Akihiro Ishikawa, Hirokazu Shimooka, Tatsuo Okauchi

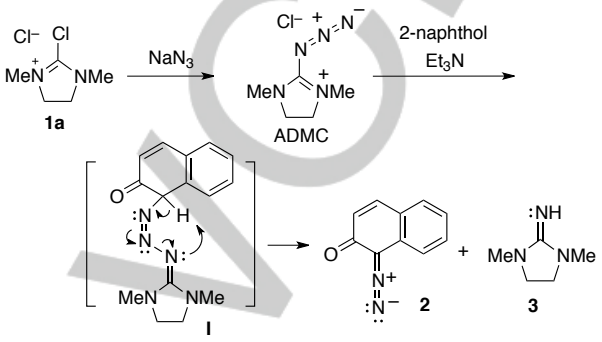
Abstract: Direct azidation of phenols was developed. By treating chloroimidazolinium chloride **1b** and sodium azide with phenol in the presence of a secondary amine in methoxyethanol, ortho-azidation of phenol was achieved.

Introduction

Aryl azides have often been used in organic syntheses as equivalents of protected aniline, and they have recently become increasingly important in biological chemistry.[1] Photoinduced nitrene formation from aryl azides is a common method of photoaffinity labeling to investigate the functions of enzymes and proteins.[2] 1,3-Dipole reactions of aryl azides and alkynes are indispensable for drug discovery and linking labeling groups to biomolecules.[3]

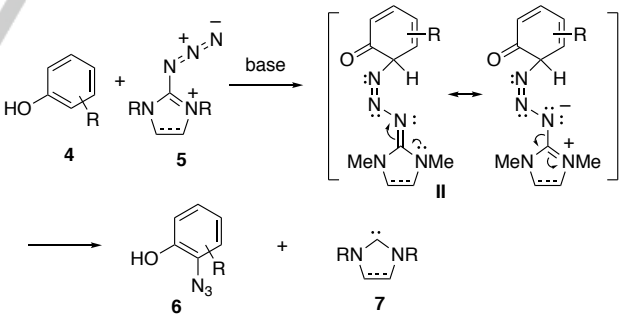
Various methods of synthesizing aryl azides have been reported.[4–9] Aryl azides are often prepared from aryl amines by i) diazotization and subsequent reaction of thus formed diazonium salts with nitrogen nucleophiles, such as azide ions,[4] or ii) diazo-transfer.[5,6] Aryl halides are also used as starting materials for synthesizing aryl azides. For example, aryl azides are synthesized by nucleophilic substitution (S_NAr reaction) of activated aryl halides with azide ions,[7] and substitution of sulfonyl azides with aryl magnesium or aryl lithium reagents formed from aryl halides.[8] Recently, metal-catalyzed coupling of aryl halides or aryl boronic acids with azide anions was developed.[9] Direct substitution of aromatic hydrogen with an electrophile by electrophilic aromatic substitution is a powerful method for synthesizing substituted arenes, and electron-rich aryl compounds such as phenols are efficient aryl donors in the reaction.[10] However, direct azidation of arenes has not been reported even for phenols.

We have been studying the reactions of 2-azido-1,3-dimethylimidazolinium salts, which showed efficient diazo-transfer ability;[11] 2-azido-1,3-dimethylimidazolinium chloride (ADMC), prepared from 2-chloro-1,3-dimethylimidazolinium chloride (**1a**) and sodium azide, reacted with naphthols in the presence of Et_3N to give diazonaphthoquinones **2**, which were formed via intermediate **I**, releasing guanidine **3** (Scheme 1).[12]



Scheme 1. Diazo-transfer of ADMC to naphthol.

Stable *N*-heterocyclic carbenes (NHC) are used as ligands of metal catalysts and organocatalysts in organic reactions.[13] Five-membered imidazole-derived NHC **7**, bearing a bulkier substituent R on its nitrogen, is commonly used for the reactions. We expected that direct introduction of the azide group to phenol could be achieved using azidoimidazolinium salt **5** when stable NHC **7** was released from adduct **II** of azidoimidazolinium salt **5** and phenol **4** (Scheme 2). We then began to investigate the direct azidation of phenol. Herein, we describe the results in detail.



Scheme 2. Plan of direct azidation of phenol.

Results and Discussion

For the azidation, 2,4-dimethylphenol (*m*-xylenol, **4a**) was chosen as a model compound. First, chloroimidazolinium chloride **1** (1.2 equiv., Figure 1) and sodium azide (10 equiv.) were mixed at −30 °C in acetonitrile to prepare azide imidazolinium **5**, and *m*-xylenol (**4a**) and base were added to the reaction mixture (Method A) (Table 1, runs 1–4). Using chloroimidazolinium chloride **1b,** the expected azidation proceeded in the presence of various bases,[14] and azidophenol **6a** was obtained in the highest yield

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Supporting information for this article is given via a link at the end of the document. General methods, experimental procedure, physical data of **1**, **6**, **9a-PF$_6$**, **10**, and ^{1}H and ^{13}C NMR spectra of **1**, **6**, **9a-PF$_6$**, **10**.

(57%) when Et_2NH was used (Table 1, run 1). When **1c** was employed, **6a** was obtained in 38% yield (run 2). Although azidation proceeded using saturated chloroimidazolinium chloride **1c**, the yield of **6a** was lower than that using unsaturated **1b** (run 1 vs. run 3). ADMC, prepared from **1a**, did not work for the azidation of phenol **4a** (run 4).

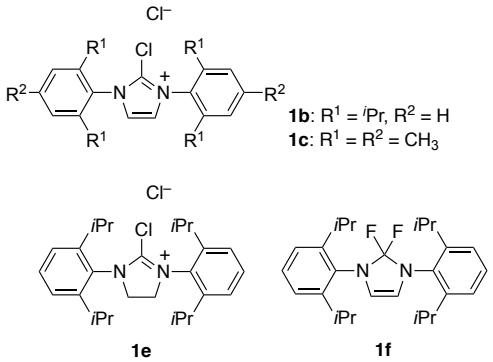


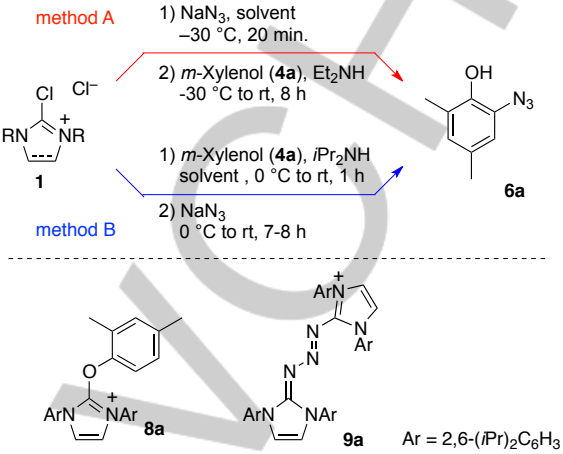
Figure 1. Imidazolinium chlorides **1b**–**1e** and related compound **1f**.

By changing the order of mixing reagents (**1b**, **4a**, base, and sodium azide), azidophenol **6a** was also obtained. That is, phenol **4a**, **1b**, and base were mixed first, and then sodium azide was added to the mixture (Method B). When phenol **4a** was treated with **1b** in the presence of Et_2NH in acetonitrile, phenol **4a** was gradually consumed and a new TLC spot was observed; this was consumed on adding sodium azide to form azidophenol **6a** in 46% yield (Table 1, run 5). Although we could not confirm the structure of the intermediate in the first step, this may be **8a**, similar to the adduct of phenol and **1f**, reported by Ritter *et al.*[15] When $^iPr_2NH$ was used, **6a** was obtained in the highest yield (62%) (run 6) among the bases we examined.[14]

In the reactions using methods A and B in acetonitrile, not all the sodium azide dissolved in the solvent, and the reaction mixture changed from colorless to reddish as the formation of **6a** progressed. For example, in the reactions using **1b** (runs 1, 5, and 6 in Table 1), the reaction mixtures became red as the reaction progressed. The red color was attributed to the formation of **9a**, by comparison with the ^1H NMR spectrum of the PF_6 salt of **9a** (**9a-PF$_6$**). Authentic **9a-PF$_6$** was synthesized as shown in Scheme 3. When **1b** and sodium azide were mixed in acetonitrile at room temperature, the reaction mixture became red. The red species was isolated as the PF_6 salt by treating the mixture with KPF_6, and its structure was confirmed by single crystal X-ray structure analysis (Figure 2).[16,17]

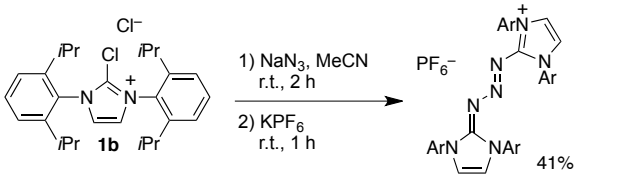
Further optimization of the azidation with **1b** and iPr_2NH was conducted using Method B. When protic solvents were used, the reaction mixture formed a single phase because sodium azide was dissolved in the solvents, and it did not change color (runs 7–12). Using ethylene glycol and ethylene glycol monomethyl ether increased the yield of **6a** to 87% and 90%, respectively (runs 11 and 12). The efficiency of ethylene glycol monomethyl ether was also confirmed in the reaction using Method A (run 13). The use of excess sodium azide was important in achieving a high yield in the azidation (runs 12, 14, 15). When trimethylsilyl azide was used instead of sodium azide, azidophenol **6a** was not formed at all (run 16).

Table 1. Direct azidation of *m*-xylenol (**4a**).[a]



Run	Method[a]	1	solvent	Yield [%]
1	A	**1b**	CH_3CN	57
2	A	**1c**	CH_3CN	38
3	A	**1d**	CH_3CN	13
4	A	**1a**	CH_3CN	0
5	B[b]	**1b**	CH_3CN	46
6	B	**1b**	CH_3CN	62
7	B	**1b**	CH_3OH	69
8	B	**1b**	EtOH	72
9	B	**1b**	*i*PrOH	71
10	B	**1b**	*t*BuOH	61
11	B	**1b**	$HO(CH_2)_2OH$	87
12	B	**1b**	$HO(CH_2)_2OCH_3$	90
13	A	**1b**	$HO(CH_2)_2OCH_3$	85
14[c]	B	**1b**	$HO(CH_2)_2OCH_3$	70
15[d]	B	**1b**	$HO(CH_2)_2OCH_3$	49
16[e]	B	**1b**	$HO(CH_2)_2OCH_3$	0

[a] Reaction conditions. Method A: i) **1** (1.2 equiv.), NaN_3 (10 equiv.), in solvent −40 °C, 10 min, ii) **4a** (1 equiv.), Et_2NH (2.0 equiv.), −40 °C to r.t., 8 h. Method B: i) **4a** (1 equiv.), **1b** (1.2 equiv.), iPr_2NH (2.0 equiv.), in solvent 0 °C to r.t., 1 h, ii) NaN_3 (10 equiv.), 0 °C to r.t., 7–8 h. [b] Et_2NH was used instead of iPr_2NH. [c] 5 equiv. of NaN_3 was used. [d] 2.5 equiv. of NaN_3 was used. [e] 10 equiv. of trimethylsilyl azide was used instead of NaN_3.



9a-PF$_6$ Ar = 2,6-(*i*Pr)$_2$C$_6$H$_3$

Scheme 3. Synthesis of **9a-PF$_6$**.

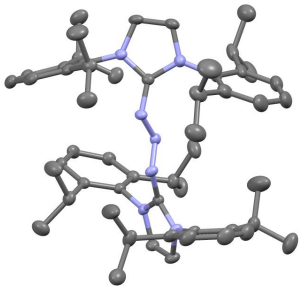
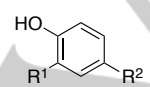
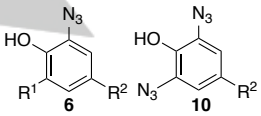
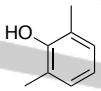
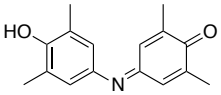


Figure 2. X-ray structure of **9a-PF$_6$** omitting hydrogen atoms and PF$_6$.

To explore the scope and limitations of the azidation, various phenols were examined under the optimal conditions for Method B (Table 2). In the reaction with 2,4-disubstituted phenol **4**, 6-azidophenol **6** was obtained in good yield when the substituents were electron-donating groups (runs 1 and 2). However, the yields of azide **6** were low when one substituent R in **4** was electron-withdrawing (runs 3 and 4). In the reaction with 4-monosubstituted phenol, monoazide **6** and diazide **10** were formed depending on the substituents (runs 5–9); 4-alkylphenol gave a mixture of **6** and **10** (runs 5 and 6). Conversely, 4-methoxycarbonylphenol (**4h**) gave monoazide **6h** in high yield (run 7). In the reactions with 4-methoxyphenol (**4i**) and 4-chlorophenol (**4j**), monoazides **6** were formed selectively, but the yields were low (runs 8 and 9). In the reaction with 2-methylphenol (**4k**), azide **6k** was obtained in 13% yield (run 10); 2,6-dimethylphenol (**4l**) did not give the corresponding azide but afforded quinoneimine **11** (run 11). The reaction with 2-naphthol was complex, and no compounds were identified (run 12).

Table 2. Direct azidation of various phenols.[a]

Run	Substrate	Product (Yield [%])		Rec. of **4** [%][b]
				
1	**4b** (R^1 = *t*Bu, R^2 = CH$_3$)	**6b** (71)		22
2	**4c** (R^1 = OCH$_3$, R^2 = CH$_3$)	**6c** (65)		8
3	**4d** (R^1 = CHO, R^2 = CH$_3$	**6d** (30)		61
4	**4e** (R^1 = CH$_3$, R^2 = Cl)	**6e**(28)		35
5	**4f** (R^1 = H, R^2 = *t*Bu)	**6f** (26)	**10f** (30)	40
6	**4g** (R^1 = H, R^2 = CH$_3$)	**6g** (29)	**10g** (13)	52
7	**4h** (R^1 = H, R^2 = CO$_2$CH$_3$)	**6h** (74)		0
8	**4i** (R^1 = H, R^2 = OCH$_3$)	**6i** (30)		66
9	**4j** (R^1 = H, R^2 = Cl)	**6j** (10)		56
10	**4k** (R^1 = CH$_3$, R^2 = H)	**6k** (13)		26
11	 **4l**	 **11** (37)		0
12	2-naphthol	-[c]		-

[a] Reaction conditions: i) substrate (phenol, 1 equiv.), **1b** (1.2 equiv.), *i*Pr$_2$NH (2.0 equiv.), HO(CH$_2$)$_2$OCH$_3$, r.t., 1 h, ii) NaN$_3$ (10 equiv.), r.t., 7-8 h. [b] Recovery of substrate. [c] Complex mixture.

Conclusion

We have developed a new synthetic method for direct azidation of phenols. Although azidophenols have been prepared from phenol by several steps via aminophenols, generally, our method offers one-step transformation of phenol to azidophenol. The drawbacks of this reaction are the requirement for an equimolar amount of a large leaving group and excess sodium azide, which are under consideration for improvement.

Experimental Section

Typical procedure for Method A: To a solution of imidazolium chloride **1** (1.2 mmol) in acetonitrile (2.5 mL) at -40 °C, sodium azide (10 mmol) was added, and the mixture was stirred at -40 °C for 10 min. Phenol **4** (1.0 mmol) and diethylamine (2.0 mmol) in acetonitrile (2.5 mL) was added to the mixture at -40 °C. The reaction mixture was warmed to room temperature, and was stirred for 8 h. Then, the reaction was quenched by adding water. The organic materials ware extracted with ethyl acetate three times. The combined extracts ware washed with brine and then dried over anhydrous Na$_2$SO$_4$. The solvent was removed in vacuo to afford crude compounds, which was purified by silica gel column chromatography (hexane/ethyl acetate) to give pure azidophenol **6**.

Typical procedure for Method B: To a solution of imidazolium chloride **1** (0.80 mmol) in ethylene glycol mono methyl ether (5 mL) at room temperature, phenol **4** (0.67 mmol) and diisopropylamine (1.3 mmol) were added. After stirring the mixture for 1 h at room temperature, sodium azide

(6.7 mmol) was added. The reaction mixture was stirred for 7-8 hour at this temperature, then the reaction was quenched by adding water. The organic materials ware extracted with ethyl acetate three times. The combined extracts ware washed with brine and then dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to afford crude compounds, which ware purified by silica gel column chromatography (hexane/ethyl acetate) to give pure azidophenols **6** and **10**.

Acknowledgments

This work was supported by JSPS KAKENHI Grant Number 17K19125. This work was performed under the Cooperative Research Program of "Network Joint Research Center for Materials and Devices.".

Keywords: azidation • azides • phenols

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[14] Various bases were examined for the reactions, such as $^{n}BuNH_2$, Et_2NH, $^{i}Pr_2NH$, $^{i}Pr_2NEt$, Et_3N, 1,8-Diazabicyclo[5.4.0]-7-undecene (DBU), pyridine, 4-dimethylaminopyridine (DMAP), imidazole, and 1,2,4-triazole.

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10.1002/ejoc.201900967

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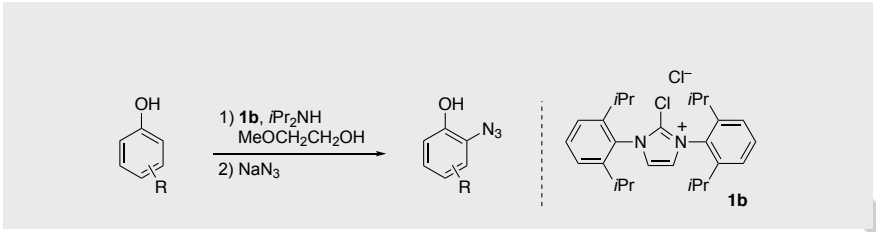

Direct azidation to phenol was archived by the treatment of chloroimidazolinium cloride **1b**, secondary amine, and sodium azide in methoxyethanol.

Azidation

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