立体位阻效应导致的苯酚的区域选择性溴化

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摘要 报道了苯酚与廉价易得的氢溴酸的区域选择性溴化反应。研究发现使用含有较大取代基的亚砷取代广为使用的二甲亚砷作为氧化剂,可以极大地提高反应的区域选择性,以中等至优秀的收率、高达 99/1 的区域选择性得到预期的溴代苯酚产物。该方法可以很容易放大到 50 mmol 级别,并且通过萃取与重结晶分离技术即可得到预期的溴代苯酚产物。

关键词 苯酚; 区域选择性溴化; 氢溴酸; 亚砷; 位阻效应

Steric Hindrance Effect Leading to Regioselective Bromination of Phenols with HBr

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Abstract A mild and regioselective bromination of phenols with the cheap and easily-available HBr is developed. By replacing the common used dimethyl sulfoxide (DMSO) with sulfoxides bearing sterically hindered substituents, the desired brominated phenols could be obtained in moderate to high yields with up to 99/1 regioselectivity. This method could be easily scaled up to 50 mmol scale and has the potential to isolate the desired product by simple extraction and recrystallization, showing great practicality of this new method.

Keywords phenol; regioselective bromination; HBr; sulfoxide; steric hindrance effect

1 Introduction

Bromated phenols are important synthetic intermediates of some natural products and biologically active compounds.^[1] While the toxic and corrosive molecular bromine was frequently used in bromination of phenols via electrophilic aromatic substitution (EAS), despite the drawbacks of low regioselectivity and poor functional group tolerance.^[2] Then *N*-bromosuccinimide (NBS) and the analogues were developed as more preferable alternatives and widely used in organic synthesis, however, these brominating reagents are usually expensive.^[3]

Inspired by the enzyme-catalyzed oxidative halogenation in nature,^[4] the slow release of brominating reagent by oxidation of bromide has recently received much attention.^[5] HBr is the byproduct of Br₂-based bromination in ton scale every year, which is readily available, inexpen-

sive, easy to store and handle.^[6] therefore, it would be worthwhile to develop practical methods to utilize HBr efficiently. The combination of HBr with an oxidant such as selectfluor, persulfates, hypervalent iodine, H₂O₂, air and dimethyl sulfoxide (DMSO), was then developed for oxidative bromination.^[5a,5b,7] However, the use of selectfluor, persulfates, or hypervalent iodine as the oxidant has obvious drawbacks of expensive price and/or generation of many wastes, while the reaction with the greener H₂O₂ or air generally required metal catalysts and/or harsh reaction conditions. In contrast, using the cheap and easily available DMSO seems much attractive, due to the advantages of safety, high atom economy, mild and metal-free conditions.

In 2015, Jiao and coworkers^[8] found that the use of stoichiometric DMSO as the oxidant instead of the solvent can greatly improve the reaction efficiency and selectivity,

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leading to an efficient and practical halogenation of arenes. However, owing to the negligibly electronic differences between *para*- and *ortho*-position of phenols, obtaining high selectivity at *para*-position of phenols remains challenging at present.^[9] Therefore, it is still highly desired to develop a mild, regioselective and waster-free bromination of phenols.

With our continuous interest in regioselective halogenation,^[10] we recently observed an unexpected steric hindrance effect from byproduct leading to a mild and regioselective bromination of phenols with TMSBr.^[10b] However, the use of the expensive and water-sensitive TMSBr narrowed the wide applications of this new method. Herein, we wish to report a mild, efficient and regioselective bromination of phenols with the cheap and easily-available HBr, and by replacing the common used DMSO with sulfoxides bearing sterically hindered substituents. The desired brominated phenols could be obtained in high selectivity (*p/o* up to 99/1). Notably, this new method could be easily scaled up to 50 mmol scale without reduction in reaction selectivity and has the potential to isolate the desired product and recycle the byproduct thioether by simple extraction and recrystallization. Moreover, water is the sole byproduct, making the method much greener and practical.

2 Results and discussion

The mixture of phenol (**1a**) and HBr was initially stirred in a solvent of DMSO at 25 °C, and the target **3a** could be obtained in 25% yield with a poor selectivity of 65/35 (**3a/4a**) (Table 1, Entry 1).^[11] The reaction at 40 °C gave target **3a** in 55% yield with *p/o* selectivity of 72/28 (Entry

Table 1 Conditions screening for regioselective bromination of phenol with HBr^a

Entry	R (2)	Solvent	3a ^b /%	3a/4a ^c
1 ^d	Me (2a)	DMSO	25	61/39
2	Me (2a)	DMSO	55	69/31
3	Me (2a)	MeCN	80	89/11
4	<i>n</i> -Bu (2b)	MeCN	75	93/7
5	Bn (2c)	MeCN	82	98/2
6	Ph (2d)	MeCN	86	95/5
7	4-MeC ₆ H ₄ (2e)	MeCN	87	96/4
8	4-ClC ₆ H ₄ (2f)	MeCN	91	97/3
9	4-ClC ₆ H ₄ (2f)	EtOAc	84	94/6
10	4-ClC ₆ H ₄ (2f)	DMF	0	—
11	4-ClC ₆ H ₄ (2f)	CHCl ₃	41	62/38

^a Unless otherwise noted, a mixture of **1a** (0.50 mmol), HBr (0.525 mmol), sulfoxide **2** (0.50 mmol) and a solvent (2.0 mL) was directly sealed under air in a Schlenk tube, and stirred at 40 °C for 12 h, then monitored by thin-layer chromatography (TLC) and/or GC-MS. ^b Isolated yield based on **1a**. ^c Determined by GC-MS. ^d 25 °C.

2). To our delight, using stoichiometric DMSO as the oxidant greatly promoted the reaction, affording the target **3a** in a much higher yield (80%) with a higher selectivity of 89/11 (Entry 3).^[12] Inspired by our previous regioselective bromination of phenols with TMSBr,^[10b] various sulfoxide surrogates such as di-butyl-, di-benzyl-, di-phenyl-, di-4-tolyl- and di-4-chlorophenyl-sulfoxide were then screened to further improve the reaction selectivity (Entries 4~8). As shown in Table 1, the reaction with sulfoxide surrogate bearing sterically hindered group, generally gave target **3a** in high selectivity (Entries 3~8).^[13] The reaction with di-benzyl sulfoxide gave target **3a** in 82% yield with the highest selectivity (98/2) (Entry 5), while the reaction with di-4-chlorophenyl sulfoxide gave target **3a** in 91% yield with a comparable selectivity (97/3) (Entry 8). Therefore, di-4-chlorophenyl sulfoxide was chosen as the best sulfoxide surrogate. The reaction solvents were finally screened to further improve the reaction yield, but no better results were obtained (Entries 9~11).

With the optimized conditions (Table 1, Entry 8) in hand, various phenols were then tested to extend the scope of the method. As shown in Table 2, like the model reaction, both electron-rich and electron-deficient phenols and even naphthols reacted effectively with HBr, affording the desired products **3a**~**3m** in moderate to high yields (Table 2, Entries 1~14). A series of functional groups such as reactive methoxyl, fluoro, chloro, bromo, aldehyde, and ester groups could be tolerated by this method (Entries 3~8). The reactions of *ortho*- or *meta*-substituted of phenols successfully gave *para*-brominated products with high selectivity (Entries 2~10). As to *para*-substituted phenols, *ortho*-brominated products were obtained in good yields with high selectivity (Entries 11~13). The method can also be extended to oxidative chlorination with concentrated HCl, but the chlorinated product was obtained with poor *p/o* selectivity (Entry 15). Unfortunately, the method is not suitable for the synthesis of *para*-iodinated phenols (Entry 16). Then the method was extended to other electron-rich arenes such as anisole and anilines. To our delight, the target *para*-brominated products were obtained in moderate to high yields with high selectivity (Entries 17~19).

The potential of this new method in large scale synthesis was also investigated. As shown in Scheme 1, the model reaction of phenol (**1a**) with HBr could be easily scaled up in 50 mmol scale, affording the desired product **3a** in 84% isolated yield (7.23 g) only by extraction and recrystallization. Moreover, the byproduct **5f** could be recycled by only extraction, and then be readily oxidized into sulfoxide **2f** with H₂O₂,^[13] with a totally >80% recovery.^[12] These experimental results showed great practicality of this new method.

According to our experimental results and the literature reports,^[8,10b,14] the possible reaction mechanism for this regioselective bromination of phenols is depicted in Scheme 2. HBr is initially oxidized by sulfoxide **2** to

Table 2 Regioselective bromination of phenols with HBr^a

 3a: 91% (97/3)	 3b: 91% (99/1) ^c
 3c: 90% (95/5) ^c	 3d: 73% (99/1)
 3e: 84% (99/1)	 3f: 81% (92/8)
 3h: 81% (96/4) ^c	 3i: 92% (98/2)
 3j: 73% (85/15)	 3k: 90% (99/1) ^{c,d}
 3l: 85% (97/3) ^{c,d}	 3m: 87% (99/1) ^e
 3n: 57% (65/35) ^f	 3o: trace ^f
 3p: 73% (99/1) ^c	 3q: 46% (95/5) ^c
 3r: 84% (99/1) ^c	

^a Unless otherwise noted, see Entry 8 of Table 1 for details, isolated yield based on **1**, and the ratio of **3/4** in parenthesis was determined by GC-MS; ^b 6 h; ^c 60 °C, 12 h; ^d For **3k**~**3f**, *ortho*-brominated products were obtained, the regioselectivity was listed in parenthesis; ^e 4 h; ^f GC yield, 80 °C, HX (for **3n**, X=Cl; **3o**, X=I) was used instead of HBr.

Scheme 1 50 mmol of scale synthesis of **3a**

of R group of intermediate **7**, the electrophilic bromination at the *para*-position of phenols is much favorable.^[10b]

3 Conclusions

A practical and regioselective bromination of phenols with the cheap and easily-available HBr was developed. The desired brominated phenols could be obtained with high regioselectivity by replacing the common used DMSO with a sulfoxide bearing sterically hindered substituents. A series of functional groups such as the reactive methoxyl, fluoro, chloro, bromo, aldehyde and ester groups can be tolerated by this method. Moreover, this method could be easily scaled up to 50 mmol and has the potential to isolate the desired product and recycle the byproduct thioether by simple extraction and recrystallization.

$R_2S \cdot Br_2$.^[8] Then a EAS bromination of phenols leads to the target product **3**, meanwhile liberating a molecule of HBr which could be reoxidized by sulfoxide **2** for the next oxidative cycle. Possibly owing to the steric hindrance effect

stallization, showing great practicality of this new method. Further application of this novel method for the regioselective functionalization of phenols is under way.

4 Experimental section

4.1 General information

^1H NMR and ^{13}C NMR spectra were recorded on a JNM-ECZ600R/S3 (Jeol, Japan) (600 MHz and 150 MHz, respectively) using tetramethylsilane as an internal reference. Mass spectra were measured on an Agilent GC-MS-5890A/5975C Plus spectrometer (EI).

All reactions were conducted in a sealed tube under air atmosphere. All the chemicals were purchased from the Energy, Alfa Aesar, and Tansoole Chemical Reagent Co., and used as received.

4.2 Experimental

4.2.1 General procedure for regioselective bromination of phenols with HBr

A mixture of phenol **1a** (47.0 mg, 0.50 mmol), HBr ($w=33\%$, in HOAc, 130 mg, 0.525 mmol), di-4-chlorophenyl-sulfoxide (135.5 mg, 0.50 mmol) and acetonitrile (2.0 mL) was directly sealed and stirred in a 20 mL tube at 40 °C for 12 h. Then the solvent was evaporated and the residue was purified by silica gel chromatography, eluting with ethyl acetate/petroleum ether ($V/V=0/100\sim 1/10$), to give compound **3a**.

4-Bromophenol (**3a**): Colorless solid. m.p. 65~66 °C (lit.^[3d] 66~68 °C); ^1H NMR (600 MHz, CDCl_3) δ : 7.42~7.30 (m, 2H), 6.81~6.66 (m, 2H), 4.97 (br s, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ : 154.72, 132.56, 117.27, 112.94; MS (EI) m/z : 174, 172, 155, 143, 128, 117, 93, 79, 74, 65.

4-Bromo-2-methylphenol (**3b**): Colorless solid. m.p. 62~63 °C (lit.^[15] 63~65 °C); ^1H NMR (600 MHz, CDCl_3) δ : 7.23 (d, $J=1.8$ Hz, 1H), 7.16 (dd, $J=8.4$, 2.4 Hz, 1H), 6.64 (d, $J=8.4$ Hz, 1H), 4.83 (br s, 1H), 2.21 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ : 153.01, 133.61, 129.82, 126.32, 116.60, 112.61, 15.75; MS (EI) m/z : 188, 186, 168, 141, 117, 107, 89, 77, 63.

4-Bromo-2-methoxyphenol (**3c**):^[16] Colorless oil. ^1H NMR (600 MHz, CDCl_3) δ : 7.05~6.88 (m, 2H), 6.79 (d, $J=8.4$ Hz, 1H), 5.54 (br s, 1H), 3.87 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ : 147.32, 144.91, 124.23, 115.87, 114.24, 111.68, 56.23; MS (EI) m/z : 204, 202, 189, 187, 161, 159, 145, 143, 133, 131, 117, 108, 94, 79, 63.

4-Bromo-2-fluorophenol (**3d**):^[17] Colorless oil. ^1H NMR (600 MHz, CDCl_3) δ : 7.20 (dd, $J=9.6$, 2.4 Hz, 1H), 7.15~7.07 (m, 1H), 6.87 (t, $J=9.0$ Hz, 1H), 5.96 (br s, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ : 151.00 (d, $J=242.6$ Hz), 142.67 (d, $J=13.6$ Hz), 128.05 (d, $J=3.7$ Hz), 119.22 (d, $J=21.4$ Hz), 118.74 (s), 111.96 (d, $J=8.3$ Hz); MS (EI) m/z : 192, 190, 172, 163, 161, 144, 142, 111, 95, 83, 63.

4-Bromo-2-chlorophenol (**3e**):^[18] Colorless oil. ^1H NMR (600 MHz, CDCl_3) δ : 7.59 (d, $J=2.4$ Hz, 1H), 7.32 (dd, $J=8.4$, 2.4 Hz, 1H), 6.90 (d, $J=8.4$ Hz, 1H), 5.51 (br s,

1H); ^{13}C NMR (150 MHz, CDCl_3) δ : 150.75, 131.52, 131.40, 120.89, 117.71, 112.40; MS (EI) m/z : 210, 208, 206, 179, 177, 172, 170, 153, 144, 142, 127, 117, 99, 91, 73, 63.

2,4-Dibromophenol (**3f**):^[15] Colorless oil. ^1H NMR (600 MHz, CDCl_3) δ : 7.59 (d, $J=2.4$ Hz, 1H), 7.32 (dd, $J=8.4$, 2.4 Hz, 1H), 6.90 (d, $J=8.4$ Hz, 1H), 5.51 (br, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ : 151.70, 134.13, 132.21, 117.53, 112.73, 110.94; MS (EI) m/z : 252, 251, 223, 197, 173, 143, 117, 92, 74, 63.

5-Bromo-2-hydroxybenzaldehyde (**3g**): Colorless solid. m.p. 104~105 °C (lit.^[19] 102~106 °C); ^1H NMR (600 MHz, CDCl_3) δ : 10.93 (br s, 1H), 9.83 (br s, 1H), 7.67 (d, $J=2.4$ Hz, 1H), 7.59 (dd, $J=9.0$, 2.4 Hz, 1H), 6.90 (d, $J=9.0$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ : 195.55, 160.64, 139.81, 135.73, 121.82, 119.91, 111.46; MS (EI) m/z : 202, 200, 184, 182, 173, 171, 145, 143, 117, 107, 92, 77, 63.

Ethyl 5-bromo-2-hydroxybenzoate (**3h**):^[20] Colorless oil. ^1H NMR (600 MHz, CDCl_3) δ : 10.79 (br s, 1H), 7.95 (d, $J=2.4$ Hz, 1H), 7.51 (dd, $J=9.0$, 2.4 Hz, 1H), 6.87 (d, $J=9.0$ Hz, 1H), 4.40 (q, $J=7.2$ Hz, 2H), 1.41 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ : 169.21, 160.73, 138.39, 132.26, 119.64, 114.17, 110.82, 62.01, 14.25; MS (EI) m/z : 246, 244, 218, 216, 200, 198, 172, 170, 159, 143, 119, 91, 81, 63.

4-Bromo-3-methylphenol (**3i**):^[3d] Colorless solid. m.p. 59~60 °C; ^1H NMR (600 MHz, CDCl_3) δ : 7.33 (d, $J=8.4$ Hz, 1H), 6.73 (d, $J=3.0$ Hz, 1H), 6.54 (dd, $J=8.4$, 3.0 Hz, 1H), 5.12 (br s, 1H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ : 154.93, 139.19, 133.09, 117.89, 115.37, 114.59, 23.07; MS (EI) m/z : 188, 186, 168, 141, 117, 107, 89, 77, 63.

3,4-Dibromophenol (**3j**):^[21] Colorless oil. ^1H NMR (600 MHz, CDCl_3) δ : 7.43 (d, $J=8.4$ Hz, 1H), 7.13 (d, $J=3.0$ Hz, 1H), 6.67 (dd, $J=8.4$, 3.0 Hz, 1H), 5.35 (br s, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ : 155.41, 134.08, 125.04, 120.82, 116.32, 115.35; MS (EI) m/z : 252, 251, 223, 197, 173, 143, 117, 92, 74, 63.

2-bromo-4-methylphenol (**3k**):^[22] Colorless oil. ^1H NMR (600 MHz, CDCl_3) δ : 7.27 (d, $J=1.2$ Hz, 1H), 7.00 (dd, $J=8.4$, 1.2 Hz, 1H), 6.91 (d, $J=8.4$ Hz, 1H), 5.46 (br s, 1H), 2.26 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ : 150.07, 132.26, 131.54, 129.87, 115.86, 109.92, 20.32; MS (EI) m/z : 188, 186, 168, 141, 117, 107, 89, 77, 63.

2-Bromo-4-methoxyphenol (**3l**):^[23] Colorless oil. ^1H NMR (600 MHz, CDCl_3) δ : 7.00 (d, $J=3.0$ Hz, 1H), 6.93 (d, $J=9.0$ Hz, 1H), 6.79 (dd, $J=9.0$, 3.0 Hz, 1H), 5.13 (br s, 1H), 3.74 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ : 153.85, 146.56, 116.88, 116.42, 115.40, 110.00, 56.06; MS (EI) m/z : 204, 202, 189, 187, 161, 159, 145, 143, 133, 131, 117, 108, 94, 79, 63.

1-Bromonaphthalen-2-ol (**3m**): Colorless solid. m.p. 80~81 °C (lit.^[22] 80~82 °C); ^1H NMR (600 MHz, CDCl_3) δ : 8.02 (d, $J=8.4$ Hz, 1H), 7.78 (d, $J=8.4$ Hz, 2H), 7.72 (d, $J=8.4$ Hz, 1H), 7.61~7.52 (m, 1H), 7.41~7.36 (m, 1H), 7.26 (d, $J=8.4$ Hz, 1H), 5.94 (br s, 1H); ^{13}C

NMR (150 MHz, CDCl₃) δ : 150.67, 132.37, 129.76, 129.42, 128.31, 127.94, 125.42, 124.23, 117.25, 106.21; MS (EI) m/z : 224, 222, 195, 193, 167, 143, 115, 89, 74, 63.

1-Bromo-4-methoxybenzene (**3o**):^[22] Colorless oil. ¹H NMR (600 MHz, CDCl₃) δ : 7.52~7.29 (m, 2H), 6.90~6.66 (m, 2H), 3.77 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ : 158.78, 132.33, 115.82, 112.89, 55.51; MS (EI) m/z : 188, 186, 173, 171, 145, 143, 129, 117, 107, 92, 77, 63.

4-Bromoaniline (**3q**):^[22] Colorless oil. ¹H NMR (600 MHz, CDCl₃) δ : 7.24~7.19 (m, 2H), 6.61~6.48 (m, 2H), 3.65 (br, 2H); ¹³C NMR (150 MHz, CDCl₃) δ : 145.49, 132.10, 116.79, 110.29; MS (EI) m/z : 173, 171, 154, 143, 128, 117, 104, 92, 85, 79, 65, 52.

4-Bromo-*N,N*-dimethylaniline (**3r**):^[22] Colorless oil. ¹H NMR (600 MHz, CDCl₃) δ : 7.32~7.27 (m, 2H), 6.60~6.55 (m, 2H), 2.91 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ : 149.57, 131.76, 114.17, 108.57, 40.68; MS (EI) m/z : 201, 200, 199, 198, 185, 184, 183, 182, 168, 155, 141, 128, 118, 104, 91, 77, 63, 51.

4.2.2 General procedure for large scale synthesis

To a stirred mixture of phenol (**1a**) (4.70 g, 50 mmol), di-4-chlorophenyl-sulfoxide (**2f**) (13.50 g, 50 mmol) and acetonitrile (200 mL), HBr ($w=33\%$, in HOAc, 13.0 g, 52.5 mmol, 1.05 equiv.) was slowly added at room temperature, then the mixture was allowed to stirred at 40 °C for 18 h. The solvent was evaporated and the residue was alkaliified with 1 mol/L sodium hydroxide solution. The mixture was then extracted with ethyl acetate (100 mL $\times$ 3) and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and ethyl acetate was evaporated by a rotary evaporator to recover di-4-chlorophenylsulfoxide (**2f**) and di-4-chlorophenyl thioether (**5f**), which were then oxidized to regenerate di-4-chlorophenyl-sulfoxide (**2f**) (totally >80% recovery of **2f**). The aqueous phase was then acidized with 1 mol/L HCl to pH=1, then extracted with ethyl acetate (200 mL $\times$ 3) and the organic phases were combined, dried with anhydrous sodium sulfate, and filtered, and ethyl acetate was evaporated by a rotary evaporator to give the crude **3a** (8.05 g, $p/o=97/3$). Finally, the crude **3a** was recrystallized with EtOAc/PE ($V:V=10:1$) to give the pure product (7.23 g, 84% yield).

Bis(4-chlorophenyl)sulfane (**5f**): colorless solid; m.p. 93~94 °C (lit.^[24] 95~98 °C); ¹H NMR (600 MHz, CDCl₃) δ : 7.29~7.21 (m, 8H); ¹³C NMR (150 MHz, CDCl₃) δ : 134.0, 133.6, 132.4, 129.6; MS (EI) m/z : 228, 213, 195, 185, 171, 153, 143, 141, 128, 117, 102, 91, 77, 65.

Supporting Information Control experiments and copies of ¹H NMR and ¹³C NMR spectra of products. The Supporting Information is available free of charge via the Internet at <http://sioc-journal.cn>.

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