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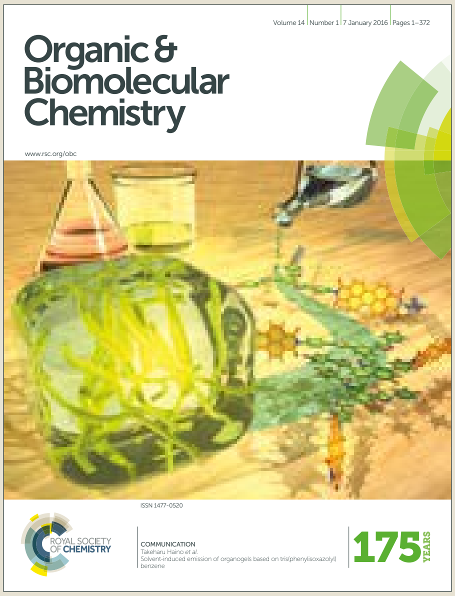

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Acid-induced chemoselective arylthiolations of electron-rich arenes in ionic liquids from sodium arylsulfinates: The reducibility of halide anions in [Hmim]Br

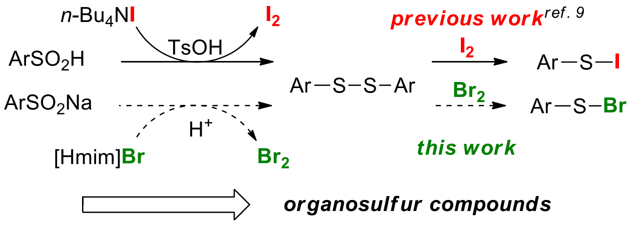
Zhu-bing Xu, Guo-ping Lu,* Chun Cai

An acid-induced protocol for the chemoselective arylthiolations of electron-rich arenes in ionic liquids from sodium arylsulfinates is introduced. The chemistry, in which [Hmim]Br (heaxylmethylimidazolium bromide) is applied as both a solvent and reducer, provides several advantages including odorless and simple operation, cheap reagents, recyclable solvent and gram-scale synthesis.

Introduction

Ionic liquids (ILs) as multipurpose materials have been widely applied in organic synthesis, catalysis, chemical separation, material and energy science, due to their unique chemical or biological properties.[1] Among them, the imidazolium-based ILs are one of the first to find applications in organic synthesis on an industrial scale.[2] These ILs have several unique properties, such as hydrogen bonding,[3] self-assemble[4] and outstanding solvation potential,[5] which may promote some transformations.[6] Several anions of ILs have been employed in organic synthesis as the reagents, such as nucleophilic halogenating reagents, nitrating reagents,[7] but no report notes that the potential reducibility of halide anions (Br^- and I^-) in these ILs, which may make them play a dual role (solvent and reducer) in some transformations.

Recently, sodium arylsulfinates are a kind of stable, odorless and easy-to-handle sulfur compounds that have been widely applied as the sulfur sources under reduction conditions for the construction of C-S bonds.[8] Arylsulfinic acid can be reduced by *n*-Bu_4NI to form the corresponding sulfenyl iodide.[9] Therefore, we envisioned that [Hmim]Br may serve as potential reducing agents to deoxidize sodium arylsulfinates for the synthesis of organosulfurs through *in situ* generation of thiyl cation species (Scheme 1). On the other hand, diaryl sulfides are a common structural motif in natural products, pharmacologically active compounds and organic materials.[10] Several attempts have been made to employ sodium arylsulfinates instead of smell thiols for the generation of diaryl sulfides from electron-rich arenes in water.[11]



Scheme 1 Work hypothesis: the potential reducibility of halide anions in ILs.

Nevertheless, stoichiometric toxic reducing agents (PPh_3 and HCOOH) and iodine are norm, and the reaction mediums are unrecyclable in these protocols. Although the environmental fate of ILs is a complex situation, such as their modes of toxicity, biodegradation pathways and behavior concerning biosorption,[12] the imidazolium-based ILs are still considered to be a greener solvent than other organic solvents owing to their negligible vapour pressure, non-flammability and recyclability.[2] Along this line, we disclose an acid-induced approach for the chemoselective arylthiolations of electron-rich arenes from sodium arylsulfinates in ILs. This chemistry, in which [Hmim]Br (heaxylmethylimidazolium bromide) is used as both a solvent and reducer and the reaction system can be recycled by simple extraction, is a simpler and greener route for the formation of diaryl sulfides.

Results and discussion

As a representative example, the reaction of naphthalen-2-ol **1a** and sodium benzenesulfinate **2a** was chosen as the model reaction. Acid is necessary for the reaction (Table 1, entries 1 *vs* 2). After screening various acids, strong acids (entries 2, 6, 10) provided excellent yields, and HCl was the best option owing to its low price. Lower temperature proved to inhibit the reaction (entry 2). Compared with other solvents (entries 11, 14-21), [Hmim]Br resulted in the highest yield. Other bromides (NH_4Br and TBAB) were also added in water as

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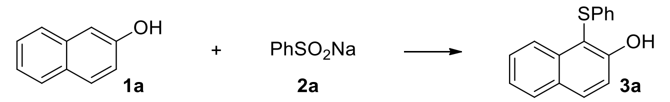
Table 1 Optimization of reaction conditions[a]

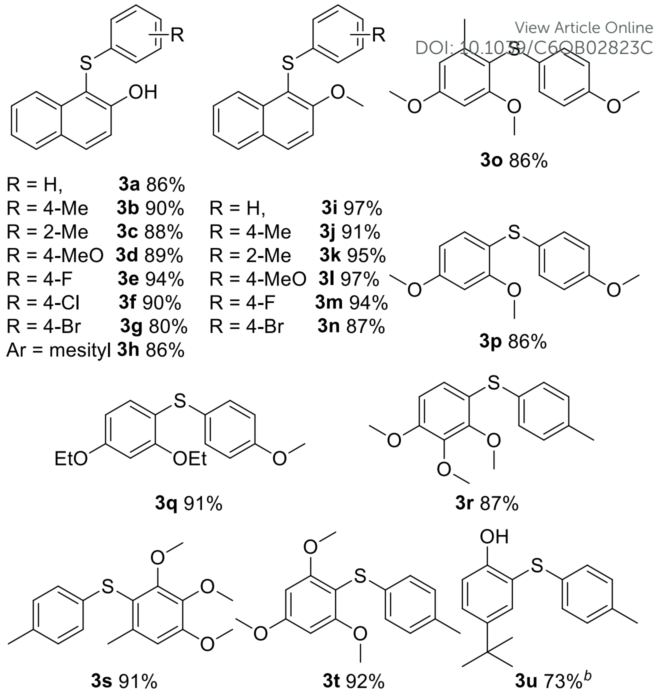


entry	additive	solvent	yield[b]
1	/	[Hmim]Br	0
2	HCl	[Hmim]Br	94, 11[c]
3	citric acid	[Hmim]Br	24
4	H_3BO_3	[Hmim]Br	trace
5	HCOOH	[Hmim]Br	trace
6	TsOH	[Hmim]Br	93
7	AcOH	[Hmim]Br	trace
8	lactic acid	[Hmim]Br	trace
9	$H_2C_2O_4•2H_2O$[d]	[Hmim]Br	43
10	H_2SO_4[d]	[Hmim]Br	91
11	HCl	H_2O	12
12	HCl/NH_4Br[e]	H_2O	15
13	HCl/TBAB[e]	H_2O	9
14	HCl	Toluene	27
15	HCl	THF	6
16	HCl	DMSO	0
17	HCl	DMF	trace
18	HCl	MeCN	12
19	HCl	Dioxane	23
20	HCl	DCE	40
21	HCl	EtOH	37
22	HCl	[Hmim]Cl	27
23	HCl	[Hmim]OAc	19
24	HCl	[Hmim]HSO_4	27
25	HCl	[Hmim][$MeSO_3$]	23
26	HCl	[Hmmim]Br	81
27	HCl	[Hmim]Br	95[f], 85[g], 82[h]
28	HCl	[Hmim]Br	93[f,i], 67[f,j]
29	HCl	[Hmim]I	92, 94[k]
30	HCl	[Hmim]Br	93[k]

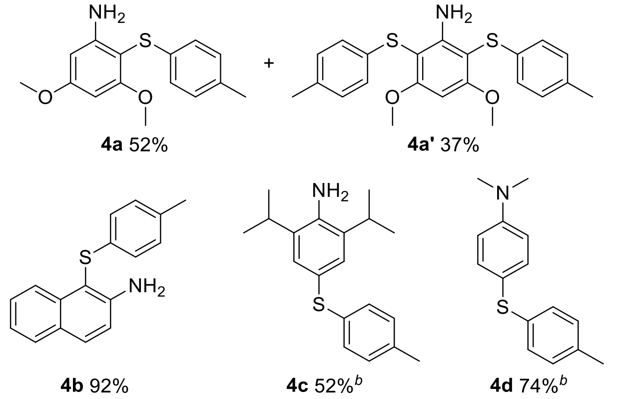
[a] Conditions: **1a** 0.50 mmol, **2a** 1.0 mmol, additive 1.50 mmol, solvent 0.5 mL, 80 °C, 6 h. [b] GC yields. [c] At 40 °C. [d] 1.5 equiv. [e] 3.0 equiv. [f] 1.5 equiv of **2a** was used. [g] 1.2 equiv of **2a** was used. [h] 1.0 equiv of **2a** was used. [i] 1.5 equiv of HCl was used. [j] 1.0 equiv of HCl was used. [k] Under N_2 atmosphere

the potential reducers, but no obvious promotion was observed indicating that both cation and anion of [Hmim]Br might be beneficial to the transformation.

Other ILs containing different anions were also tested in the reaction (entries 22-25, 29). Only [Hmim]Br and [Hmim]I could provide the excellent yields of **3a**. It could be concluded that the reductibility of anion play an important role in the reaction. [Hmimm]Br (1,2-dimethyl-3-octyl-1*H*-imidazol-3-ium bromide) was also employed as the solvent to confirm the effects of C-2 hydrogen of imidazole. The results suggested that a slight influence was found during the process (entries 2 *vs* 26). The amount of **2a** and HCl were also optimized, and the best option was using 1.5 equiv of **2a** and 1.5 equiv of HCl (entries 27, 28). The reaction can also take place under N_2 atmosphere (entries 29, 30), so sodium arylsulfinates (rather than air) are the oxidants, which have enough oxidizability to oxidize both Br^- and I^- to Br_2 and I_2 respectively under acidic conditions. Therefore, the reduction potential of I_2/I^- and Br_2/Br^- system are no obvious influence on the reaction.



Scheme 2 The reactions of sodium arylsulfinates with electron-rich arenes[a] [a] Conditions: **1** 0.50 mmol, **2** 0.75 mmol, HCl 0.75 mmol, [Hmim]Br 0.5 mL, 80 °C, 6 h. Isolated yields. [b] 120 °C.



Scheme 3 The reactions of sodium arylsulfinates with arylamines[a] [a] Conditions: **1** 0.50 mmol, **2** 0.75 mmol, HCl 0.75 mmol, [Hmim]Br 0.5 mL, 80 °C, 6 h. Isolated yields. [b] 120 °C.

With the optimized conditions in hands, a series of sodium arylsulfinates **2** and various electron-rich arenes **1** were applied in the reaction to establish the scope and generality of this protocol (Scheme 2). Both sodium arenesulfinates **2** with electron withdrawing and donating groups could react with naphthalen-2-ol or 2-methoxynaphthalene smoothly (**3a**-**3n**), and only 1-substituted products were detected in all cases. Aryl ethers were also afforded the desired products with excellent regioselectivity and yields (**3o**-**3t**). A moderate yield of **3u** was derived in the case of phenol with an electron donating group (*t*-butyl) by raising temperature to 120 °C, however phenol and phenol with electron withdrawing groups failed to yield the final products.

Likewise, aromatic amines underwent arylthiolation smoothly, giving moderate to excellent yields (Scheme 3). Both 2-sulfanyl product **4a** and 2,6-disulfanyl product **4a'** are

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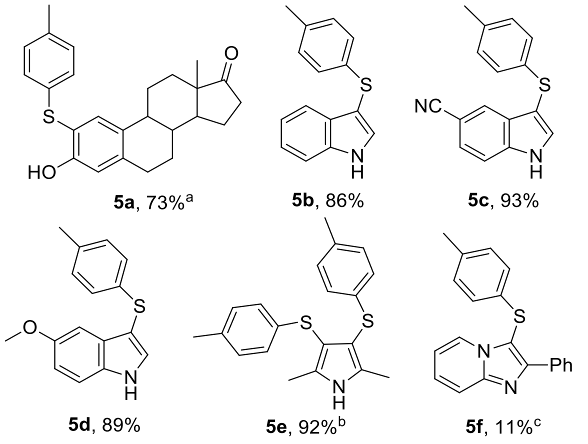
obtained in the coupling of sodium *p*-tolylsulfinate with 3,5-dimethoxyaniline. As expect, anilines with electron-withdrawing groups failed to yield the desired products in the approach. Higher temperature was needed in the case of *N*,*N*-dimethylaniline and 2,6-diisopropylaniline to produce **4c** and **4d**. To further demonstrate the potential of the strategy, the sulfanylations of a more complex arenol (estrone) and heteroarenes also worked under similar conditions (Scheme 4). However, coumarin, benzofuran and benzothiophene failed to yield the desired products in the protocol.

Further investigations were also conducted to assess the potential for recycling of [Hmim]Br in the model reaction. Meanwhile, we scaled up the reaction to 10 mmol to show the possibility for large-scale operation. After completion of the reaction, the product underwent in-flask extraction with minimum amounts of an organic solvent (MTBE). The phase of [Hmim]Br was separated by simple extraction and reuse for next run. The process could be repeated 10 times without an obvious change in yields, but an additional distillation process was required for the dehydration of [Hmim]Br after reusing five times (in 4th run and 9th run) (Figure 1).



Scheme 4 The arylsulfanyltion of estrone and heteroarenes in [Hmim]Br. Conditions: 1.0 mmol estrone or heteroarene, 1.5 mmol **2b**, 1.5 mmol HCl, 0.5 mL [Hmim]Br, 80 °C, 6 h, isolated yields. [a] 120 °C, 12 h. [b] 3.0 mmol **2b** and 3.0 mmol HCl were used. [c] GC yield.

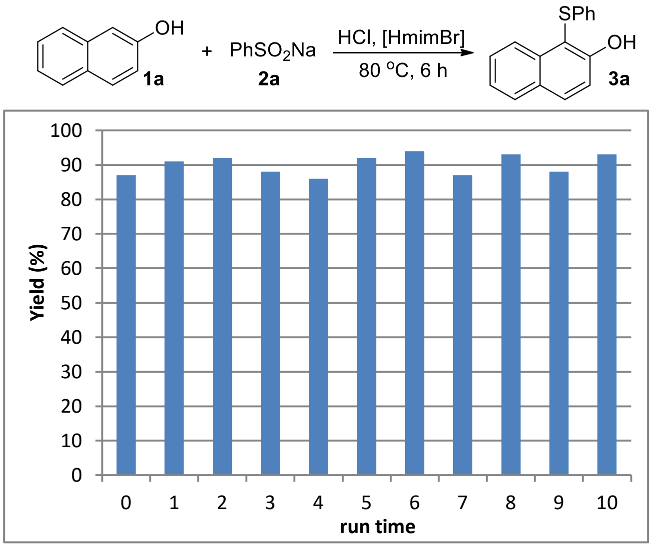
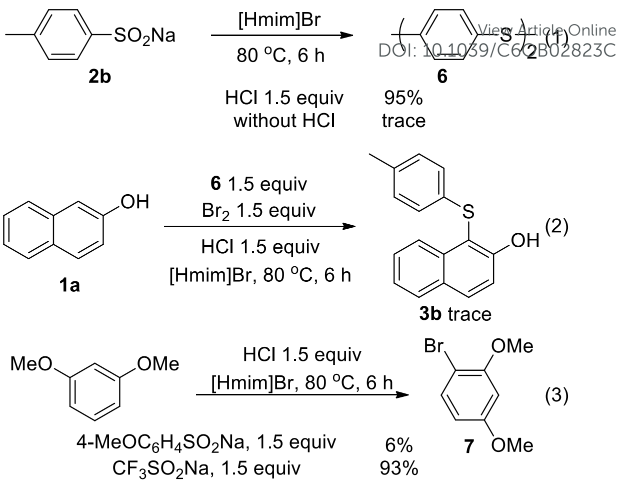
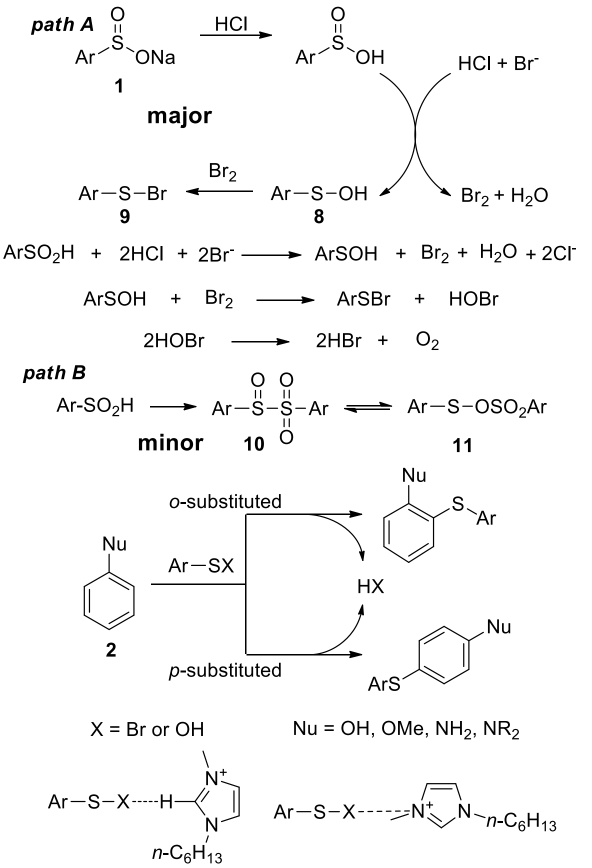


Fig. 1 Recycle studies. Conditions: 10 mmol **1a**, 15 mmol **2a**, 15 mmol HCl, 10 mL [Hmim]Br, 80 °C, 6 h. Isolated yields.



Scheme 5 Control experiments



Scheme 6 A tentative pathway for the arylthiolation of electron-rich arenes in [Hmim]Br

To probe the mechanism, further control experiments were also performed (Scheme 5). A disulfide **5** was generated from sodium *p*-toluenesulfinate **2b** under optimized conditions, and only trace of disulfide **5** was detected in the absence of HCl, suggesting that the acid play a curial role in the reduction of **2b** (eq. 1). However, **6** fail to react with **1a** to yield the final product in presence of bromine (eq. 2), so the reaction

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pathway was not including the formation of sulfenyl bromide from disulfide. A bromide **7** was also observed as a by-product in the reaction of 1,3-dimethoxybenzene and sodium 4-methoxybenzenesulfinate (eq. 3), and an excellent yield of **7** could be obtained when sodium trifluoromethanesulfinate instead of sodium 4-methoxybenzenesulfinate was employ. The result was an evidence for the generation of bromine during the process.

Based on these results, a tentative mechanism was proposed (Scheme 6). Firstly, arylsulfinic acid derived from **1** under acidic conditions, is further reduced by acid and bromide anion to yield **8**.[9,13] The arylsulfanol **8** may also react with bromine to produce **9** (***path A***). Both **8** and **9** may undergo the aromatic electrophilic substitution with arenes to form the *p*-arylsulfanyl arene (or *o*-arylsulfanyl arene) as the major path. The enhancement of [Hmim]Br's cation on the pathway may be attributed to the formation of Hydrogen bonds between the C-2 hydrogen and X (X = OH, Br), and the charge-charge interaction of the quaternary nitrogen atom and X, resulting in an electrophilic activation of the S-X bond's sulfur.[6,14]

The chemoselectivity of the arylthiolation can be explained by resonance theory. The transition states are the most stable when the electrophilic sulfur intermediates (**8** and **9**) attack 2 or 4 position of electron-rich arenes, so the reaction has high chemoselectivity (Scheme 6).[8,11] Moreover, arylsulfinic acid can also afford the electrophilic sulfur intermediate **11** through dehydration condensation and tautomerizm (***path B***),[13] which can also react with electron-rich arenes to form the desired product as the minor path. This can explain that the arylthiolation still occur in other organic solvents with poor yields.

Experimental

General

All chemical reagents were obtained from commercial suppliers and used without further purification. Melting points were determined uncorrected. All known compounds were identified by appropriate technique such as such as ^{1}H NMR and ^{13}C NMR and compared with previously reported data. All unknown compounds were characterized by ^{1}H NMR, ^{13}C NMR, GC-MS (or MS) and elemental analyses. Analytical thin-layer chromatography was performed on glass plates pre-coated with silica gel impregnated with a fluorescent indicator (254 nm), and the plates were visualized by exposure to ultraviolet light. ^{1}H NMR and ^{13}C NMR spectra were recorded on an AVANCE 500 Bruker spectrometer operating at 500 MHz and 125 MHz and chemical shifts were reported in ppm. GC analyses were performed on an Agilent 7890A instrument (Column: Agilent HP-5: 30 m × 320 μm × 0.25 μm, carrier gas: H_2, FID detection). GC-MS analyses were performed on a Thermo Trace 1300 and ISQLT instrument (Column: TR-35 MS: 30 m X 0.25 mm X 0.25 μm, ionization mode: EI, carrier gas: He). Elemental analyses were performed on a Yanagimoto MT3CHN recorder.

Synthesis of imidazolium-based ILs

N-Methylimidazole 40 mmol, 1-halohexane 48 mmol and ethyl acetate 10 mL were heated under reflux for 24 h. The biphasic system obtained was separated and the upper organic phase discharged. The bottom product phase was washed with ethyl acetate (3 × 20 mL), and dried under vacuum to give 1-hexyl-3-methylimidazolium halide (Cl, Br and I) as a colourless liquid. [Hmim]OAc, [Hmim][CH_3SO_3] and [Hmim]HSO_4 were synthesized by exchanging the bromide ion of [Hmim]Br with AcO^-, $CH_3SO_3^-$ and HSO_4^- with NaOAc, CH_3SO_3Na and H_2SO_4 respectively.

General procedures for the direct sulfenylation reactions of electron-rich arenes

A 15 mL oven-dried reaction vessel was charged with sodium benzenesulfinate (0.75 mmol), arene (0.50 mmol) and [Hmim]Br (0.5 mL). Concentrated HCl (as a 37wt.% HCl aqueous solution, 0.75 mmol) was added to the mixture and the resulting mixture was stirred at 80 °C for 6 h. After completion, the mixture was extracted with MTBE. The organic phase was collected and filtered through a bed of silica gel layered over Celite to dry the organic layer and remove inorganic salts or other undissolved substances in the organic layer. The volatiles were removed in *vacuo* to afford the crude product. Further column chromatography on silica gel (EtOAc/petroleum ether, v/v = 1/19 or 1/9) or recrystallization was needed to afford the pure product. In the cases of aromatic amines, an additional neutralization step was required.

The procedure of recycling [Hmim]Br

After reaction completion, the mixture was then extracted with MTBE (3×10 mL). The organic layer was collected and filtered through a bed of silica gel layered over Celite to dry the organic layer and remove inorganic salts or other undissolved substances in the organic layer. The volatiles were removed in *vacuo* to afford the crude product **3a**. To the phase of IL, HCl 15.0 mmol was added, followed by **1a** 10.0 mmol and **2a** 15.0 mmol at room temperature and the reaction stirred for 6 h at 80 ^{o}C. The extraction cycle was then repeated for the separation of **3a**.

Conclusions

In summary, we develop a practical strategy for the chemoselective synthesis of diaryl sulfides under acidic conditions, in which odorless, easy-to-handle sodium arylsulfinates and recyclable IL are used as the sulfur source and solvent respectively. The reducibility of Br^- in [Hmim]Br is found, so no additional reducing agent is needed in the process. The chemistry features simple operation, gram-scale synthesis, inexpensive reagents and recyclable solvent, thereby making it more environmentally friendly and suitable for large-scale operations. Other transformations in ILs are ongoing in our group.

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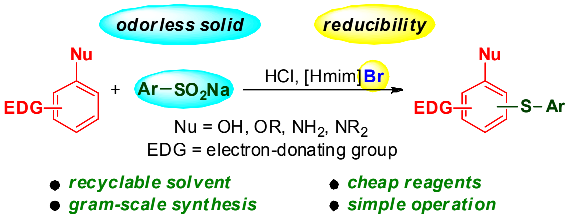

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