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Graphical Abstract

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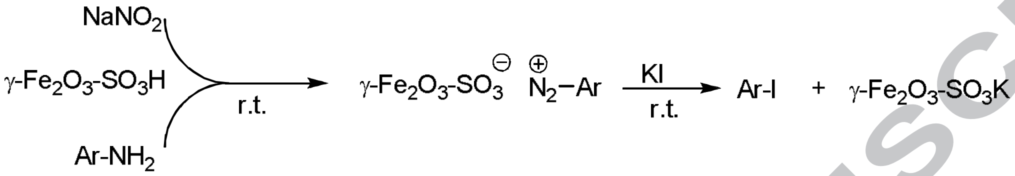

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Aryl diazonium nanomagnetic sulfate and potassium iodide: an iodination process

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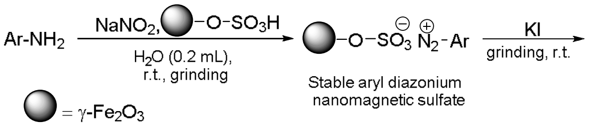
ABSTRACT

A simple and efficient procedure for the synthesis of iodoarenes is developed which involves the sequential diazotization–iodination of aromatic amines with sodium nitrite, nanomagnetic supported sulfonic acid and potassium iodide under solvent-free conditions at room temperature.

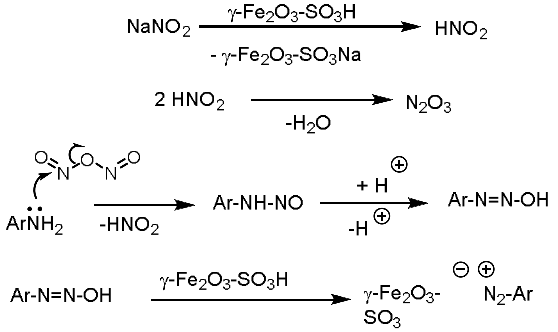
As the iodine atom is an excellent leaving group, iodo-substituted aromatic compounds have, for a long time, been recognized as valuable synthons or precursors in reactions such as the Heck arylation, and Stille, Negishi, Suzuki, Buchwald, and Sonogashira couplings. In addition, the iodoarene moiety is an important structural motif in biologically active molecules (e.g., thyroxine) and a synthetic intermediate for a variety of fine chemistry products (e.g., iso-vanillyl sweeteners[1]), radiopharmaceuticals,[2] and numerous bioactive compounds such as camptothecin,[3] cephalosporin derivatives,[4] dehydrotubifoline,[5] morphine,[6] sangliferine A,[7] and ecteinascidine.[8] Galanthamine is one example of a prescription drug synthesized from an iodoarene intermediate, which is used, for symptomatic treatment of dementia in Alzheimer patients.[9] Despite their utility, aryl iodides are more expensive, and fewer aryl iodides are commercially available than aryl bromides and aryl chlorides. Direct iodination of aromatic compounds with iodine is difficult due to the weak electrophilicity of molecular iodine. Also, the regioselectivity of direct iodination is poor and gives a mixture of isomers. Hence, the Sandmeyer reaction (reaction of arenediazonium salts with iodide)[10] is an effective alternative method for the preparation of aromatic iodides.[11-14] Although significant developments have been achieved in the synthesis of iodoarenes, their preparation *via* direct iodination has some limitations.[15-18]

The search for mild conditions for the synthesis of aryl iodides is important in organic chemistry. As aromatic amines are generally available, most methods for the preparation of substituted aromatic iodides have focused on improving the diazotization–iodination reaction. Diazotization reactions are usually carried out *via* protonation of nitrous acid in a strongly acidic medium (H_2SO_4, HCl).[19] The "green" approach to chemical processes has stimulated the use of recyclable strong solid acids as replacements for such unrecyclable "liquid acid" reagents. We have previously reported the synthesis of nanomagnetic-supported sulfonic acid and its applications in organic synthesis.[20] Magnetic nanoparticles[13] have emerged as viable alternatives to porous materials for use as robust, readily available, high surface area heterogeneous supports in organic transformations. They possess the added advantage of being magnetically recoverable, which facilitates reaction work-up and rapid sample processing, and most importantly, reduces solvent consumption. For these reasons, it is of interest to use nanomagnetic-supported sulfonic acid (γ-Fe_2O_3-SO_3H)[20] for the conversion of aryl amines into aryl iodides. Herein, we report an efficient, rapid, and convenient procedure for the synthesis of aryl iodides employing aryl diazonium nanomagnetic sulfates in the presence of potassium iodide at room temperature (Scheme 1).



Scheme 1. One-pot iodination of aryl amines via an aryl diazonium nanomagnetic sulfate.

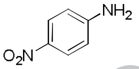
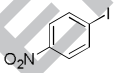
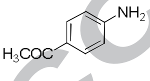
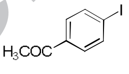
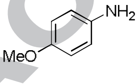
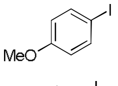
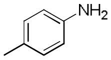
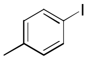
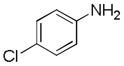
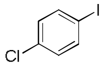
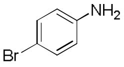
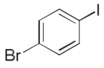
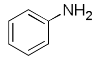
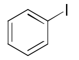
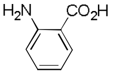
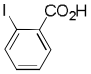
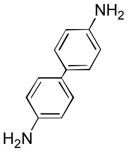
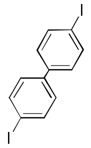
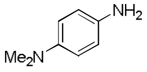
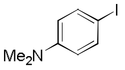
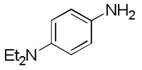
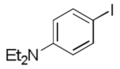
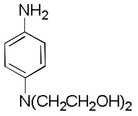
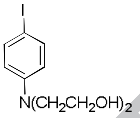
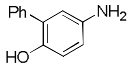
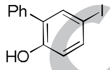
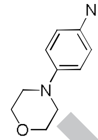
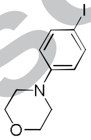
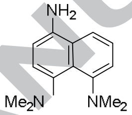
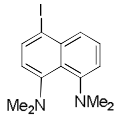
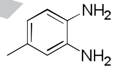
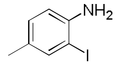
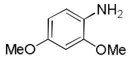
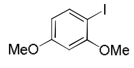
The remarkable leaving group ability of -N_2^+ enables high-energy reactive aryl cation intermediates to be generated *via* diazoniation (Scheme 2).



Scheme 2. Diazotization process for the generation of aryl diazonium nanomagnetic sulfate.

However, the intrinsic instability and explosive nature of diazonium compounds limits the applications of these derivatives. Usually, these compounds are synthesized around 10 °C, and to avoid their decomposition, they are handled below 0 °C. In this new method, iodination of various aromatic amines, with electron-withdrawing groups as well as electron-donating groups, can be successfully carried out in good yields under solvent-free conditions at room temperature (Table 1). The process was carried out in two steps:[21] the amine, nanomagnetic-supported sulfonic acid, sodium nitrite and 0.2 mL of water were homogenized by grinding in a mortar with a pestle for a few minutes. The diazotization proceeded in 5–30 min. During this time, the starting amine was consumed. Next, potassium iodide was added to the diazonium salt and grinding continued until the intermediate aryl diazonium nanomagnetic sulfate was exhausted; this was determined simply by the negative probe with β-naphthol. As is indicated in Table 1, the diazotization-iodination process took 20–60 minutes. The crude product was extracted with ethyl acetate, and after evaporation of the solvent, the crude product was purified by recrystallization or short column chromatography. This new, simple method was applied successfully with aryldiazonium nanomagnetic sulfates possessing electron-deficient or electron-rich groups.

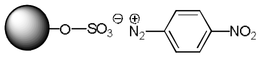
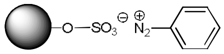
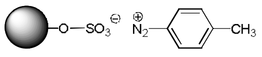
Table 1 Synthesis of aryl iodides by means of the diazotization–iodination of aromatic amines under solvent-free conditions at room temperature (substrate: Ar-NH_2/$NaNO_2$/KI = 1:2:2.5 molar ratio, 0.65 g of γ-Fe_2O_3-SO_3H) and 0.2 ml of water.

Entry	Substrate	Product	Time (min)	Yield (%)	Mp (°C)
1			20	83	172-3[19]
2			45	80	84-5[19]
3			30	80	51-2[19]
4			60	78	35-7[19]
5			40	88	55-6[19]
6			30	79	40-2[19]
7			25	70	oil[20]
8			50	55	162[19]
9			40	78	203-4[19]
10			35	82	67-71
11			45	74	oil
12			40	84	oil
13			40	72	oil
14			30	80	151-4
15			50	81	197-200
16			50	67	39-41
17			55	70	37-39

In comparison with electron-withdrawing groups, aryldiazonium nanomagnetic sulfates with electron-donating groups reacted more slowly (Table 1, entry 4). The steric effects of *ortho* substituents had relatively little influence on the yields and reaction times (Table 1, entries 8, 16 and 17). It should be emphasized that the reaction required a small amount of water for the formation of a paste and had to be carried out in a stepwise fashion for a successful outcome. When KI was added together with $NaNO_2$, a complex product mixture was produced with much lower yields of the aryl iodides. This indicates that the iodination reaction in the water-paste occurs differently than the diazotization–iodination in an aprotic solvent, where sodium nitrite and KI are treated together with aromatic amines.[22] Furthermore, neat reactions with dry diazonium salts may be more dangerous and explosive than wet reactions, or those that take place in solution. Our diazotization–iodination method is safer in this sense, as the reactions were carried out in a water-paste. It should be noted that the aryldiazonium salts supported on nanomagnetic-supported sulfonic acid were relatively stable and could be kept at room temperature in a desiccator without any loss of activity. After the times specified in Table 2, the addition of KI to the stored sulfate salt provided almost the same yield of product as that from freshly-prepared salt. As shown in Table 2, aryl diazonium nanomagnetic sulfates with electron-withdrawing groups on the aromatic rings were more stable than those with electron-donating groups because of the instability of the resulting aryl cation.[23]

Table 2 The stability of some examples of aryl diazonium nanomagnetic sulfates at room temperature[a,b]

Diazonium salt	After 6 h	After 24 h	After 48 h

	(%)	(%)	(%)
	85	76	70
	73	61	50
	77	65	55

[a] The yields refer to isolated pure products after adding KI to the diazonium salts within the specified times.

[b] Each product yield was compared with that obtained using fresh diazonium salt.

To summarize, we have described a new, rapid, efficient and experimentally simple method for the diazotization–iodination of aromatic amines on nanomagnetic-supported sulfonic acid at room temperature. The resulting diazonium salts are stable and react rapidly with potassium iodide to produce iodoarenes in good yields. Our new method offers several advantages including short reaction times, the use of mild reaction conditions, avoids the use of harmful acids and involves a simple work-up procedure. Further investigations on the new applications of this method are ongoing in our laboratory.

Acknowledgment

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21. *Diazotization–Iodination of Aromatic Amines; General Procedure:* An aromatic amine (1 mmol), nanomagnetic-supported sulfonic acid (γ-Fe_2O_3-SO_3H) (0.65 g), $NaNO_2$ (2 mmol, 0.138 g) and 0.2 mL of H_2O were homogenized by grinding in a mortar with a pestle for a few minutes. Formation of a reddish-brown gas was observed as soon as H_2O was added. The diazotization reaction lasted approximately 5-30 min. Next, KI (2.5 mmol, 0.415 g) was added to the diazonium salt and grinding was continued for 10–20 min. After completion of the reaction, the mixture was triturated with EtOAc (5 mL). The γ-Fe_2O_3-SO_3K was separated from the solution using a magnetic bar. The organic layer was treated with aq. 10% Na_2SO_3 (15mL), then dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was afforded. Purified products were obtained by recrystallization from ethanol or by flash chromatography (*n*-hexane-EtOAc, 95:5). **CAUTION!** Although we did not experience any problems, diazonium salts are known to be explosive. Care must be exercised in handling them, especially when they are subjected to grinding.
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