



An efficient and regioselective iodination of electron-rich aromatic compounds using *N*-chlorosuccinimide and sodium iodide

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ABSTRACT

An efficient and regioselective method for iodination of electron-rich aromatic compounds was found using *N*-chlorosuccinimide and sodium iodide in AcOH with short reaction times. This method is also applicable to non-benzenoid aromatic or heteroaromatic compounds.

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Iodoarenes are one of the most important species in organic synthesis, because they are more reactive than the corresponding bromides and chlorides. For example, they are used in metal-catalyzed coupling¹ reactions such as Heck–Mizoroki,² Negishi,³ Stille,⁴ and Suzuki reactions.⁵ Iodination of aromatic compounds is carried out normally by using reagents such as I₂,⁶ benzyltriethylammonium dichloriodate–NaHCO₃,⁷ ICl,⁸ ICl–Cp₂FeB[3,5-(CF₃)₂C₆H₃]₄,⁹ *N*-iodosuccinimide (NIS),¹⁰ NIS–CF₃SO₃H,¹¹ NIS–CF₃CO₂H,¹² NaOCl–NaI.¹³ However, most of these methods require toxic reagents or hard conditions. In addition, NIS is expensive than *N*-chloro (NCS) and *N*-bromosuccinimide (NBS).¹⁴

Thus, it is useful to use iodide salts such as sodium iodide compared with using I₂, NIS, or other reactive reagents. Recently, Ogivie et al. reported the iodochlorination of alkynes and alkenes using NCS in the presence of tetrabutylammonium iodide,¹⁵ but iodination of aromatic compounds were not carried out. Iodination of aromatic compounds using NCS in the presence of iodide ion is of interest.

Here we report the iodination of activated aromatic compounds with NCS and NaI under mild conditions.

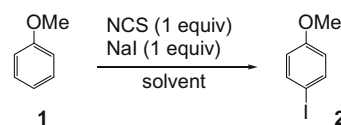
Our initial exploration was focused on the reaction of anisole (**1**) with NCS and NaI in AcOH at room temperature, which proceeded to afford **2** in 54% yield (Table 1, entry 1). Efficient iodination was realized at 50 °C for 2 h in 93% yield (entry 2). The other additives such as KI and tetrabutylammonium iodide did not give satisfac-

tory results (entries 3 and 4). Other solvents were screened, and acetic acid was found to be the best one (entries 5 and 6).

We next explored the iodination of several aromatic compounds with NCS and NaI under the optimized conditions. The results are summarized in Table 2.¹⁶ Methoxy aromatic derivatives gave the excellent yields of the corresponding iodoarenes with good selectivity (entries 1–4). The reaction of 1,3,5-triethylbenzene¹⁷ proceeded at 100 °C in the modest yield (entry 5). Iodination of *N,N*-dimethylaniline produced *p*-iodo-*N,N*-dimethylaniline (**7**) (entry 6). The reaction of azulene as a non-benzenoid aromatic compound with 2 equiv of reagents also afforded the expected iodination product **8** (entry 7).

Table 1

Optimization of the reaction conditions of **1**^a



| Entry | Additive | Solvent | Condition | Yield ^b (%) |
|-------|------------------------------|---------|--------------|------------------------|
| 1 | NaI | AcOH | rt, 3 h | 54 |
| 2 | NaI | AcOH | 50 °C, 2 h | 93 |
| 3 | KI | AcOH | 50 °C, 2 h | 65 |
| 4 | <i>n</i> -Bu ₄ NI | AcOH | Reflux, 2 h | 67 |
| 5 | NaI | MeOH | Reflux, 2 h | NR |
| 6 | NaI | MeCN | Reflux, 12 h | 25 |

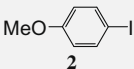
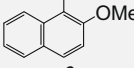
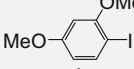
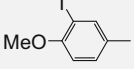
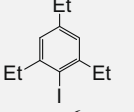
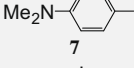
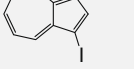
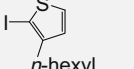
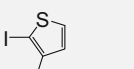
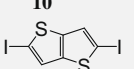
^a Concentration was 0.1 M.

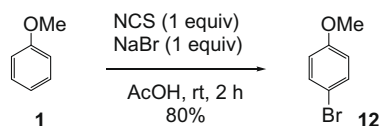
^b Isolated yield.

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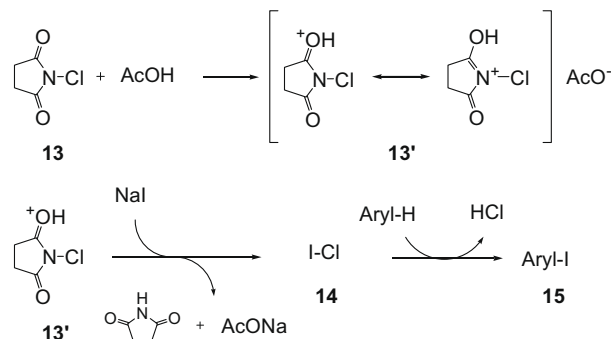
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Table 2
Iodination of various aromatic compounds with NCS and NaI^a

| Entry | Condition | Product | Yield ^b (%) |
|------------------|--------------|---|------------------------|
| 1 | 50 °C, 2 h |  | 93 ^c |
| 2 | 50 °C, 2 h |  | 91 |
| 3 | rt, 1.5 h |  | 87 |
| 4 | 50 °C, 2 h |  | 84 |
| 5 | 100 °C, 12 h |  | 49 ^d |
| 6 | rt, 1 h |  | 80 |
| 7 ^e | rt, 1 h |  | 89 |
| 8 ^{f,g} | rt, 2 h |  | 97 |
| 9 ^f | 50 °C, 3 h |  | 92 |
| 10 ^e | rt, 2 h |  | 92 |

^a NCS (1 equiv), NaI (1 equiv), AcOH (0.1 M).^b Isolated yield.^c Trace amount of *o*-iodoanisole was observed.^d Starting material was 49% recovery.^e NCS (2 equiv), NaI (2 equiv).^f NCS (1.5 equiv), NaI (1.5 equiv).^g A mixture of AcOH and MeCN (1:1) was used as a solvent.**Scheme 1.** Bromination of anisole (1).

Furthermore, this method is applicable to the heteroaromatic compounds (entries 8–10). Exclusive regioselective¹⁸ iodination¹⁹ was performed using AcOH/MeCN = 1:1 as a solvent (entry 8). It should be noted that the reaction of 3-hexylthiophene with NCS and NaI in AcOH formed 2-chloro-3-hexylthiophene as a by-product along with **9**.²⁰ 3-phenylthiophene gave 2-iodo-3-phenylthiophene (**10**) in an excellent yield (entry 9). Treatment of thieno[3,2-*b*]thiophene²¹ with 2 equiv of NCS and NaI afforded the disubstituted product **11** (entry 10).

**Scheme 2.** Plausible mechanism.

Although NCS/NaI system was highly selective for the iodination of thiophene rings, a reaction of 3-phenylthiophene with 1 equiv of ICl gave a mixture of products in our hands. The NCS/NaI system appeared to be moderately reactive, compared with the case of the reaction of ICl.

Furthermore, we investigated the bromination reaction (Scheme 1). The reaction of anisole (**1**) with 1 equiv of NCS and NaBr gave *p*-bromoanisole (**12**) (rt, 2 h, 80%).

A possible mechanism of iodination of aromatic compounds is shown in Scheme 2. NCS is activated by AcOH. The iodide ion attacks on the electrophilic chlorine atom of the intermediate **13'**, which would generate ICl **14**.¹⁵ Then, aromatic compounds react with the electrophilic iodine to generate iodoarenes **15**.

In conclusion, an efficient and mild method for the iodination of electron-rich aromatic compounds using NCS and NaI was accomplished. The reagents for iodination are superior in easy handling as well as availability and cost performance.

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- A typical experimental procedure is as follows: To a mixture of NCS (0.93 mmol) and NaI (0.93 mmol) in AcOH (4.0 mL) was added a solution of aromatic compound (0.93 mmol) in AcOH (5.3 mL). The reaction mixture was stirred at room temperature for several hours. Upon completion, the mixture was poured into satd aq NaHCO₃, and extracted with AcOEt. The organic layer was washed with brine and dried over MgSO₄. The filtrate was concentrated under reduced pressure, and purified by silica gel chromatography to give the iodoarene derivative.
- The reaction of toluene with 1 equiv of NCS and NaI did not proceed.

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20. The yields of 3-hexyl-2-iodothiophene (**9**) and 2-chloro-3-hexylthiophene in AcOH were 81% and 16%, respectively.
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