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Abstract: A transition-metal-free, mild, and highly regioselective synthesis of nitroarenes from arenes has been developed. The products are obtained in a sequential one-pot reaction by nitration of iodine(III) reagents with two carbon ligands, which are formed in situ from iodine(I). This novel concept has been extended to formation of aryl azides and constitutes an important step towards catalytic reactions with these hypervalent iodine reagents. An efficient nitration of isolated diaryliodonium salts has also been developed, and the mechanism is proposed to proceed by a [2,2]ligand coupling pathway.

Hypervalent iodine compounds have become important reagents for a wide variety of transformations, as they have a valuable combination of properties including high reactivity, high functional-group tolerance, and low toxicity.[3] The main drawback with hypervalent iodine reagents is the stoichiometric formation of either an iodine(I) or iodine(III) compound as waste, depending on the oxidation state (III or V) of the starting reagent. This aspect lowers the atom efficiency and may lead to product purification problems. The groups of Ochiai and Kita reported the first catalytic uses of hypervalent iodine reagents in 2005 (Scheme 1a).[2] Since then many other systems have appeared, where a catalytic amount of iodoarene is combined with a stoichiometric amount of an oxidant.[3]

Iodonium salts and their cyclic counterparts benziodoxolones (e.g. EBX and Togni’s reagent) are important iodine(III) reagents for the transfer of carbon ligands (aryl, alkynyl, vinyl, CF3, or CN groups) to a wide range of nucleophiles.[4] These reagents are generally synthesized in one or more steps, isolated, and subsequently reacted with a nucleophile. Kita and co-workers have demonstrated the efficient in situ formation of diaryliodonium salts from other iodine(III) reagents in metal-free arylations (Scheme 1b),[5] and the group of Suna has utilized the same strategy in metal-catalyzed arylations.[6] However, to the best of our knowledge, catalytic reactions with iodonium salts or benziodoxolones remain unknown.[4,7]

In our long-term quest for catalytic arylation conditions, we reasoned that in situ formation of diaryliodonium salts from arenes and iodoarenes in the presence of an oxidant, followed by arylation of a suitable nucleophile under metal-free conditions, would constitute an important step towards this difficult goal. Herein we present our results of an efficient arylation of sodium nitrite with diaryliodonium salts, which can be formed in situ from arenes and iodoarenes under oxidative conditions (Scheme 1c). The methodology compares well to previous routes to nitroarenes, concerning regioselectivity, functional-group tolerance, and ease of handling.[8]

Synthetic routes to aromatic nitro compounds are important, as nitroarenes are key intermediates in the preparation of many dyes, plastics, and explosives.[9] They can be synthesized from arenes under harsh acidic conditions,[10] by treatment with [bis(trifluoroacetoxy)iodo]benzene (PIFA)[11] and by rhodium-catalyzed oxidative C–H activation,[12] all of which give regioisomeric mixtures. Regioselective transformations include palladium-catalyzed nitration of aryl chlorides,[12] and either metal-mediated or metal-free conversion of arylboronic acids.[13] Nitroarenes have also been obtained from diaryliodonium salts,[14] thus making this transformation suitable for our envisioned one-pot reaction.

The nitration reaction was first investigated using isolated diaryliodonium salts, as a stepwise and general methodology to nitroarenes could be preferable with advanced diaryliodonium salts carrying sensitive functional groups. Various nitrite sources, solvents, and temperatures were screened, and high yields of nitroarenes were obtained with NaN3, in either DME or EtOAc at 70 °C,[15] the latter solvent being preferable from an environmental perspective. The nitration proved insensitive to moisture and air, and can be conveniently carried out without special precautions.

Interestingly, the diaryliodonium counterion had a major impact on the reaction, as shown in Table 1. Diphenyliodonium...
nium triflate (X = OTf) and hexafluorophosphate (X = PF₆) gave nitrobenzene (2a) in excellent yields, whereas the corresponding tetrafluoroborate (X = BF₄) and tosylate (X = OTs) resulted in poor conversion into 2a. This result was surprising as tetrafluoroborate salts are usually efficient in both metal-free and metal-catalyzed reactions.[4–6] We hypothesized that addition of sodium triflate might improve the outcome, and discovered that 1 equivalent of NaOTf was indeed sufficient to provide 2a in 94% yield. The tosylate salt could also be efficiently utilized upon addition of NaOTf, and the trend was verified with other tetrafluoroborate salts.[8] This finding is important, as anion exchange of diaryliodonium salts can be tedious and waste producing. While the exact role of NaOTf remains unknown, the additive effect could be useful in other arylation where the counterion influences the reaction.

The scope of the arene nitration was subsequently investigated with diaryliodonium salts 1 (Scheme 2).[15] Tri-flate, tetrafluoroborate, and tosylate salts could all be employed, using NaOTf as an additive with the two latter anions. Nitrobenzene (2a) and the halide-substituted products 2b–e were all isolated in high to excellent yields. The reaction showed great tolerance for steric hindrance in the ortho-position, as exemplified with the halide products 2d and 2e, and with the high-yielding synthesis of the di-ortho-alkyl-substituted nitroarenes 2f and 2g. While the electron-rich products 2h and 2i were obtained in moderate yields despite addition of 3 equivalents of NaNO₂, the synthesis of 2h was improved to 79% yield by changing the solvent. Moderately electron-donating substituents were still well tolerated, and alkyl-substituted salts were efficiently transformed into 2f, 2g, 2j, and 2k. The synthesis of 2k was easily scaled up to 7 mmol, thus displaying the robustness of the reaction. Likewise, products with electron-withdrawing substituents were obtained in high yields (2l–o). More elaborate diaryliodonium salts could also be utilized, as demonstrated in the synthesis of the carbonyl-substituted products 2p–q, and in the reactions with pyridyl iodonium salts to provide the heterocycles 2r and 2s in 78 and 88% yield, respectively.

Unsymmetric diaryliodonium salts were utilized in several reactions,[9] and the phenyl group was an efficient “dummy” group in the nitration of electron-deficient ary moieties (21).

| Table 1: Counterion effect under optimized reaction conditions. |  |
|---|---|
| [a] Reaction conditions: NaNO₂ (0.16 mmol) was added to 1 (0.14 mmol) and NaOTf (0–1 equiv) in EtOAc (1 mL). The suspension was stirred at 70°C for 16 hours. |  |
| Yield [%] |  |
| X = OTf | X = PF₆ | X = BF₄ | X = OTs |
| NaOTf (equiv) | 0 | 94 | 91 | 18 | 18 |
| 0.5 | 68 | 68 | 68 | 68 | 68 |
| 1.0 | 86 | 94 | 87 | 87 | 87 |

Scheme 2. Scope for the nitration with isolated salts 1. Reaction conditions as in Table 1 with 1 (0.5 mmol). Yields are those of isolated products. [a] NaOTf (1 equiv) was added. [b] NaNO₂ (3 equiv) was used. [c] In CH₂Cl₂/H₂O 1:1. [d] 7 mmol scale.

2m, 2p. A strong ortho-effect[16–17] was observed in reactions with ortho-substituted iodonium salts, which proceeded with excellent chemoselectivities (2e, 2g, 2b) despite competing electronic preferences (2g). p-Methoxyphenyl (anisyl) or 2,4,6-trimethoxyphenyl (TMP)[17a,18] dummy groups were efficiently utilized in reactions yielding 2h, 2o, 2r, and 2s.

The envisioned one-pot sequence was next investigated. Unfortunately, synthesis of the diaryliodonium salts in either EtOAc or DME was low yielding, hence the one-pot sequence was further studied in dichloromethane using our established methodology.[15] Bromobenzene (3b) and 4-bromoiodobenzene (4b) were treated with mCPBA and TiOH to yield the symmetric 4-bromophenyl iodonium salt 1b in situ (Scheme 3a). Sodium nitrite and NaHCO₃[19] were then added, thus providing nitroarene 2b and unreacted diaryliodonium salt as the major components. Addition of water[20] and adjustment of the pH value improved the outcome, and delivered 2b in 58% yield with 3 equivalents of NaNO₂ within 3 hours.[21] Only the p-substituted product 2b was observed, and the complete regioselectivity can be attributed to the known, highly p-selective formation of diaryliodonium salts.[4c,15]

Considering the three steps involved in this sequential one-pot reaction (oxidation, formation of 1b, and nitration to 2b), this metal-free C–H nitration of bromobenzene is quite efficient (Scheme 3a). The resulting iodoarene 4b was
was obtained with excellent efficiency, thus illustrating that electron-donating substituents are well tolerated. The p-azido product 2o was obtained in an unsatisfactory yield, which is likely due to the moderate-yielding salt synthesis.\[8\] Heterocyclic products could also be obtained in a one-pot manner, as exemplified by the synthesis of 3-nitropyridine (2r).

The application of this novel one-pot concept to other nucleophiles is currently underway in our laboratory, and preliminary results with sodium azide are promising (Scheme 4).

A radical mechanism is unlikely, as addition of the radical scavengers, 1,1-diphenylethylene and TEMPO, to the nitration in EtOAc did not hamper the reaction significantly.\[8\] Hence, we suggest that the reaction proceeds by formation of a T-shaped intermediate containing a Nu–I bond (Scheme 5). The nitrite nucleophile could either form an N–I or O–I intermediate (A and B), followed by ligand coupling to provide the N-arylated product 2a or O-arylated product 6 (not observed). While ligand coupling by the [1,2] pathway is the only possibility with some nucleophiles, recent computational studies have found that four- or five-membered transition states can be favored.\[17a,b,24\]

The suggested pathways were studied by DFT computations (Figure 1).\[8\] Ligand exchange by a dissociative pathway leads to a large increase in energy, whereas the associative pathway via four-coordinated complexes, to give the intermediates B1 and B2, is energetically favorable by 13 and 25 kJ mol\(^{-1}\), respectively. Ligand coupling via the three-membered TS1 would give N-arylation, whereas coupling via the three-membered TS2 or five-membered TS3 would result in O-arylation. These pathways are, however, all too high in energy to be plausible. The reaction is suggested to give the N-arylated product 2a via the four-membered TS5 (\(\Delta G^\ddagger = 73 \text{ kJ mol}^{-1}\)), which has a lower energy barrier than TS4 (\(\Delta G^\ddagger = 87 \text{ kJ mol}^{-1}\)). The energy difference corresponds to a 135:1 ratio in favor of 2a at 70 \(^\circ\)C, thus explaining why 6 is not observed.\[8\]

To conclude, nitroarenes have been efficiently synthesized by a transition-metal-free arylation of sodium nitrite with diaryliodonium salts. An interesting counterion effect was observed, and the unprecedented use of NaOTf as an additive enabled efficient arylation with such salts. The mechanism is

isolated in 72\%, thus showing the recyclability of this component. In the same fashion, chlorobenzene was converted into 2c in 55\% with recovery of the iodoarene 4c in similar yield, and benzene was transformed into nitrobenzene (2a). One-pot C–H nitration of alkyl benzenes proved more difficult, and the three-step reaction provided 2k in poor yield, which gracefully was considerably improved at higher temperature.\[20\]

The synthesis of unsymmetric diaryliodonium salts (Ar\(^{1} \neq\) Ar\(^{2}\)) is often high yielding,\[8\] hence we investigated the nitration of mesitylene by in situ formation of a mesityl- (phenyl)iodonium salt (Scheme 3a). To our delight, the sterically hindered product 2f was obtained with excellent chemoselectivity (2a not observed). In all cases the iodoarenes 4 could be recovered in at least equivalent amounts from the one-pot reactions, thus allowing reuse in subsequent reactions.\[21\]

The scope investigation was continued with a range of unsymmetric diaryliodonium salts, thus delivering functionalyzed nitroarenes in good yields with complete regioselectivity (Scheme 3b).\[22\] Nitroarenes with electron-withdrawing substituents were formed in excellent yields over the three steps (2l, 2m). 1-Nitroanthalene (2h), and the ortho-halogenated products 2d and 2e were also obtained with high efficiency, thus illustrating that electron-donating substituents

**Scheme 3.** One-pot nitration using 4 (0.5 mmol), 3 (1.1 equiv), mCPBA (1.1 equiv), TFO (2–3 equiv), and NaNO\(_2\) (3 equiv). Yields are those of isolated products. [a] Nitration at 80\(^\circ\)C, with < 5\% impurity. [b] TsOH·H\(_2\)O (1 equiv) used instead of TFOH. [c] 2d/21 > 20:1. [d] Anisole (5 equiv) used.

**Scheme 4.** Preliminary investigation with azide as a nucleophile (\(^1\)H NMR yield).

**Scheme 5.** Mechanistic possibilities.

The suggested pathways were studied by DFT computations (Figure 1).\[8\] Ligand exchange by a dissociative pathway leads to a large increase in energy, whereas the associative pathway via four-coordinated complexes, to give the intermediates B1 and B2, is energetically favorable by 13 and 25 kJ mol\(^{-1}\), respectively. Ligand coupling via the three-membered TS1 would give N-arylation, whereas coupling via the three-membered TS2 or five-membered TS3 would result in O-arylation. These pathways are, however, all too high in energy to be plausible. The reaction is suggested to give the N-arylated product 2a via the four-membered TS5 (\(\Delta G^\ddagger = 73 \text{ kJ mol}^{-1}\)), which has a lower energy barrier than TS4 (\(\Delta G^\ddagger = 87 \text{ kJ mol}^{-1}\)). The energy difference corresponds to a 135:1 ratio in favor of 2a at 70 \(^\circ\)C, thus explaining why 6 is not observed.\[8\]

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Figure 1. DFT calculated potential energy surfaces for the reaction between 1a(OTf) and nitrite. Energies are measured in kJ mol⁻¹. OTf omitted for clarity in B1 and B2, TS1–TS5, and C1 and C2.

suggested to proceed via an O–I intermediate followed by an unusual [2,2] ligand coupling. The reaction has been extended to a sequential one-pot transformation, where diarylidonium intermediates are generated from amines and iodoarenes in a highly regioselective fashion, and subsequently nitrated with recovery of the iodoarene. Azidation also proved possible using the same novel concept, where iodine(III) reagents with two carbon ligands are formed in situ from iodine(I) and subsequently intermolecularly reacted with nucleophiles. This feature constitutes an important step towards catalytic reactions with such hypervalent iodine reagents.

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