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Iodine(III)-Catalyzed Electrophilic Nitration of Phenols via Non-Brønsted Acidic NO₂⁺ Generation

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Supporting Information

ABSTRACT: The first catalytic procedure for the electrophilic nitration of phenols was developed using iodosylbenzene as an organocatalyst based on iodine(III) and aluminum nitrate as a nitro group source. This atom-economic protocol occurs under mild, non-Brønsted acidic and open-flask reaction conditions with a broad functional-group tolerance including several heterocycles. Density functional theory (DFT) calculations at the (SMD:MeCN)Mo8-HX/(LANLo8+f,6-311+G*) level indicated that the reaction proceeds through a cationic pathway that efficiently generates the NO_2^+ ion, which is the nitrating species under neutral conditions.

T itroaryl derivatives including the nitrophenol core are very important nuclei in life and organic chemistry.¹ Their presence is ubiquitous in naturally occurring compounds,² antibiotics,³ organic dyes,⁴ explosives,⁵ pesticides,⁶ as well as in the plastics⁷ and pharmaceutical⁸ industries. They have also been used as solvents9 and key intermediates in the synthesis of amines¹⁰ (Figure 1).



Figure 1. Relevance of the nitroaryl core.

To date, several procedures have been described for the introduction of nitro groups into the aryl moiety.¹¹ Of these, concentrated nitric acid is the simplest nitrating reagent used.¹ Harsh acidic mixtures of HNO3 with H2SO4,13 TfOH14 or Ac_2O^{15} have also been described. Less-aggressive nitration conditions are provided by ${}^{16}BuNO_2{}^{16}$ or the Crivello reagent (NH_4NO_3-TFAA) .¹⁷ A broadly used strategy consists of the combination of NaNO₂ with different Brønsted acids such as HCl,¹⁸ HClO₄,¹⁹ or KHSO₄.²⁰ On the other hand, the nitrating systems melamine–NO₃,²¹ TCT–Zn(NO)₃,²² [BnPh₃P⁺]-[$^{-}S_{2}O_{8}$]–NO₃,²³ and H₂SO₄ with Sr(NO₃)2²⁴ or Bi(NO₃)3²⁵



have also been reported to perform the nitration of arenes. Regarding transition-metal-catalyzed nitration procedures, those involving Rh²⁶ and Pd²⁷ are the most commonly encountered; however, nitrates from Zr,²⁸ Ce,²⁹ Bi, or Fe³⁰ can introduce a nitro group simply by using stoichiometric amounts of these salts. Generally, the aforementioned procedures lack functional-group compatibility, mainly because of the extreme Brønsted or Lewis acidic conditions. Finally, in the context of this work, various procedures for aryl nitration involving iodine(III) as the oxidant have been described with PIFA³¹ or diaryliodonium salts.³² However, they require at least 1 equiv of oxidant and an excess of the nitro group source. In this regard, Olofsson³³ described a nitration protocol based on the in situ formation of the diaryliodonium salts, which, after the nitration reaction, allows reoxidation of the iodobenzene byproducts to be reused. According to the authors' mechanistic calculations, this pericyclic reaction proceeds by an ONO-IPh2 intermediate, followed by an unusual [2,2] ligand coupling.

In light of the relevance of the nitrophenol core and the predominance of strongly acidic nitration procedures as described above, we were interested in the development of a mild, non-Brønsted acidic and cost-economic nitration protocol, based on the use of iodine(III) reagents and aluminum nitrate. Herein, we describe the first catalytic³⁴ nitration procedure, which occurs under neutral conditions via a cationic route in the presence of iodosylbenzene and aluminum nitrate (Scheme 1).

We initially sought validation of our hypothesis using 2naphthol as a model system. The representative optimization assays are described in Table 1.

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Scheme 1. Representative Procedures for Nitration of Arenes Using Iodine(III) Reagents

Olofsson (pericyclic pathway)³³





Table 1. Optimization of the Iodine(III)-CatalyzedElectrophilic Nitration of 2-Naphthol a

| | OH I(III), AI(NO ₃) ₃ .9H ₂ | | ж , г∕ | NO₂ ↓ OH | 0° 0-N-0H |
|-----------------|---|--|------------------|-------------|---------------------------------|
| | solvent, T (°C) | | O ₂ N | / | |
| | | 1 | 2 | | 3 |
| entry | iodine(III) ^b (equiv) | Al(NO ₃) ₃ (equiv) | solvent | t (°C) | yield (%) ^c 1/2/3 |
| 1^d | PIDA (1.2) | 2.4 | MeCN | 23 | 0/91/0 |
| 2 | PIDA (1.2) | 2.4 | MeCN | 23 | 0/88/0 |
| 3 ^e | PIDA (1.2) | 2.4 | MeCN | 23 | <5/71/0 |
| 4 ^e | PIDA (0.5) | 0.35 | MeCN | 23 | 68/<5/0 |
| 5 ^e | PIDA (0.3) | 0.35 | MeCN | 23 | 77/<5/0 |
| 6 ^f | PhIO (0.1) | 0.35 | MeCN | 0 | 34/8/<5 |
| 7 ^f | PhIO (0.15) | 0.35 | MeCN | 0 | 34/10/<5 |
| 8 | PhIO (0.2) | 0.35 | MeCN | 0 | 72/5/0 |
| 9 | PhIO (0.25) | 0.35 | MeCN | 0 | 78/7/0 |
| 10 | PhIO (0.30) | 0.35 | MeCN | 0 | 42/5/27 |
| 11 | PhIO (0.35) | 0.35 | MeCN | 0 | 46/7/27 |
| 12 | PhIO (0.25) | 0.35 | DCM | 0 | c.r.m. ^g |
| 13 | PhIO (0.25) | 0.35 | TFE | 0 | c.r.m. ^g |
| 14 | PhIO (0.25) | 0.35 | MeOH | 0 | c.r.m. ^g |
| 15 ^f | PhIO (0.25) | 0.35 | THF | 0 | 48/0/0 |
| 16 ^f | PhIO (0.25) | 0.35 | H_2O | 0 | 0/12/0 |
| 17 ^f | PhIO (0.25) | 0.35 | DMSO | 0 | 25/0/0 |
| 18 | PIDA (0.25) | - | MeCN | 0 | n.r. ^h |
| 19 | PhIO (0.25) | _ | MeCN | 0 | n.r. ^h |
| 20 | _ | 0.35 | MeCN | 0 | n.r. ^h |
| | | | | | |

"Reaction conditions: 2-naphthol (0.5 mmol), solvent (0.3 M), open flask. b



^cIsolated yields. ^d4 Å molecular sieves were used. ^eThe reaction started at 0 °C and was progressively warmed to 23 °C. ^fThe reaction was not complete after 10 h. ^gc.r.m. = complex reaction mixture. ^hn.r. = no reaction observed.

Initial attempts to induce the nitration of 2-naphthol were performed based on our previously developed conditions for iodine(III)-mediated chlorination³⁵ and bromination.³⁶ Thus, the reaction of 1 equiv of PIDA and 2.4 equiv of nonahydrate aluminum nitrate was tested at 23 °C in acetonitrile, leading only to the bis-nitration product 2 (Table 1, entries 1 and 2). These results validated the proposed hypothesis and confirmed that a carbon-selective nitration had occurred, since no reaction at the

phenolic oxygen was observed. The reaction was water-tolerant, displaying yields of 91% and 88% with and without the use of 4 Å molecular sieves, respectively. The mononitration product 1 was obtained selectively after some modifications of the reaction conditions. Thus, starting the reaction at 0 °C and warming to 23 $^{\circ}$ C, only small amounts of 1 (<5%) and large quantities of 2 were found (Table 1, entry 3). By decreasing the number of equiv of PIDA to 0.5 and 0.3 equiv, as well as the aluminum nitrate to 0.35 equiv, the reaction afforded 1 in 68% and 77% yields, with <5% of 2 (Table 1, entries 4 and 5). These results indicate that a substoichiometric amount of the iodine(III) reagent is acting as a catalyst. Therefore, a plausible mechanism for this catalytic transformation was developed involving aluminum coordination and cleavage of the acetoxy group in PIDA (A), followed by bond formation between a nitrate group and the iodine(III) center (B). Then, after the attack of the phenol at the nitrogen, the nitrated product would be released concomitant with iodosylbenzene (PhIO) formation. This could react again with the nitrate salt, giving rise to intermediate C, which is attacked by a second molecule of 2-naphtol. Thereafter, the nitration occurs and the iodosylbenzene is released to continue the catalytic cycle (Scheme 2).





To test this new hypothesis, a catalytic amount of PhIO (10 mol %) and 0.35 equiv of aluminum nitrate were combined at 0 °C in acetonitrile. To our delight, we found the desired nitration product 1 in 34% of yield in addition to 2 and 2-hydroxynaphtho-[1,2-d][1,3,2]dioxazole-2-oxide 3 (Table 1, entry 6). The starting 2-naphthol was not fully consumed, even after 10 h. However, we were able to identify iodosylbenzene as the organocatalyst in this nitration protocol. Subsequently, the optimization proceeded by progressively increasing the catalyst loading in 5 mol % increments (Table 1, entries 7-12). Thereby, the full consumption of the starting material was observed with 20 mol % of catalyst (Table 1, entry 8), while the best yield and 1:2:3 ratio was achieved using 25 mol % of PhIO (Table 1, entry 9). This indicated that, since we used only 0.35 equiv of aluminum nitrate, the three nitrate groups were introduced as the nitro group in the phenol. Continued increases of the catalyst loading provided only poorer product ratios (Table 1, entries 10 and 11). Optimization of the reaction solvent did not improve the results. Reactions in DCM, TFE, or MeOH produced only complex reaction mixtures (Table 1, entries 12-14), while the use of THF and DMSO gave low yields of 1 (Table 1, entries 15 and 17). Interestingly, the reaction in water selectively produced 2, but in a poor 12% yield (Table 1, entry 16). To conclude, several control experiments were performed. These consisted of the use of PIDA or PhIO in the absence of the nitrate salt (Table 1, entries 18 and 19) and the use of aluminum nitrate³⁷ without

iodine(III) reagent (Table 1, entry 20). In all of these tests, no reaction was observed, thus confirming the necessity of each reagent in the procedure.

With the optimized conditions at hand, we proceeded to explore the scope of the protocol (Scheme 3).





^{*a*}Reaction conditions: phenol (0.5 mmol), MeCN (0.3 M), open flask. ^{*b*}Isolated yields. ^{*c*}Use of PhIO (1.2 equiv) and Al(NO₃)₃ (2.4 equiv).

Several mono- and bis-annular phenols were assayed to determine the scope of the reaction when varying the electronic nature at the aryl moiety. Therefore, electron-rich (1, 7-9), and electron-deficient (4-6) naphthol derivatives were applied to our optimized catalytic nitration conditions, providing yields ranging from 26% to 78%.³⁸ Additionally, monosubstituted monoannular phenols containing electron-deficient groups such as halogens F, Cl, Br, I (10–13), Cl, Br (16), and F, F (17), nitrile (14), and nitro (15) were successfully nitrated in modest to good yields (31%-72%).³⁸ On the other hand, electron-rich derivatives containing a phenyl (18), alkyl (19–22) or bicycloalkyl groups (28) as well as one or two methoxy (23)

and 24) or methyl groups (25) were generally tolerated in modest³⁹ to excellent yields (35%-89%). Remarkably, two gram-scale reactions were achieved, providing 11 and 22 in 70% and 73% yield, respectively. The known o- or p- regioselectivity dictated by the more electron-donating group was observed. Interestingly, the regioselective *o*-nitration of phenol yields **29** in 64%.⁴⁰ Another aspect of potential relevance to the reaction is the effect of steric hindrance. To evaluate this, the nitration of 3,5and 2,6-di-tert-butylphenols was performed. Gratifyingly, we obtained the desired nitroaryl derivatives 26 and 27 in 25% yield⁴¹ and 57% yield, respectively. In this case, the observed *o*- or *p*-regioselectivity was directed by the bulky group. A last point to be explored was the introduction of two nitro groups to afford bisnitrated derivatives. Thus, dinitro phenols containing methoxy (30) and alkyl groups (31-35), as well as 1,6-dinitro-2-naphthol (2), were obtained in moderate to excellent yields (52%-91%).

The previous set of experiments described a wide scope in the electronic nature of the phenolic nucleus. The next step was to determine the functional-group tolerance of the reaction (Scheme 4).

Scheme 4. Scope of the Phenol Functional Groups for the PhIO-Catalyzed Electrophilic Nitration a,b



^aReaction conditions: phenol (0.5 mmol), MeCN (0.3 M) open flask. ^bIsolated yields. ^cReaction performed at 23 ^oC.

In these reactions, the temperature had to be increased to 50 $^{\circ}$ C to obtain the products. Here, distinct functional groups such as methyl- (36 and 37) or methylthio-ethers (39), allyl (38), aldehyde (40) and ketones (41 and 42) were tolerated by our nitration procedure. Furthermore, nitrogen-containing functional groups such as amides (43) and anilines (44 and 45) were

also tolerated by the reaction. Interestingly, the substrate 2allylphenol did not undergo cationic π -cyclization, and only the nitration product 38 was solely isolated. In the case of ketones and amides, the bulk of tert-butyl group was key for their nitration, insomuch as smaller groups such as methyl or isopropyl did not produce any observable reaction (cf, 42 and 43), presumably because of interactions of the nitrogen atoms with the catalyst or the nitrating species. Aside from the derivatives 39 and 40^{42} , the rest of the reactions proceeded in modest to good yields (42%-77%).³⁸ Finally, heterocycles including pyridines (46 and 47), quinolone (48), quinoxaline (49), or carbazole (50) were nitrated in good to excellent yields (57%-83%). The exception in this group of heterocycles was the quinolone, which gave a low yield (11%). Note that the acid-sensitive groups such as allyl, pyridines, and quinoxaline, which contain centers prone to react with Lewis or Brønsted acids, were tolerated. This supports the neutral conditions for the NO_2^+ formation.

With the scope of the reaction regarding the electronic nature and functional group tolerance having been established, the synthetic utility of our nitration reaction is demonstrated (Scheme 5).

Scheme 5. Synthetic Utility of the PhIO-Catalyzed Electrophilic Nitration Procedure



In such a way, the nitrophenol **25** was efficiently reduced via a Ni-catalyzed procedure,⁴³ giving rise to **51** in 91% yield. In addition, the naturally occurring nitrophenols **52–54**, which were isolated from bacteria, bryozoans, and deuteromycetes *Salegentibacter sp*,⁴⁴ *Phidolophora pacifica*,⁴⁵ and *Pyricularia oryzae*⁴⁶ were obtained in yields of 94% (**52**) and 73% (**53**), respectively, under our standard nitration conditions. The benzylic methylation of **53** afforded **54** in 28% yield. In addition, the *o*-nitration of estrone proceeded successfully, giving rise to **55** in 26% of yield.

Finally, DFT calculations at the (SMD:MeCN)Mo8-HX/ (LANLo8+f,6-311+G*) level suggest that the reaction mechanism proceeds via the generation of NO_2^+ , which acts as the nitrating species (Scheme 6).

The mechanism starts with the coordination of iodosylbenzene (PhIO) to aluminum nitrate to obtain I (see the Supporting Information for further details). The following [3,3] pericyclic reaction leads to the formation of II, which contains the iodine(III)-nitrate bond. This key intermediate undergoes a decomposition to form the nitrating species NO_2^+ , the Scheme 6. Plausible Reaction Mechanism for the PhIO-Catalyzed Electrophilic Nitration^{*a*}



^aGibbs free energies and enthalpies are shown in units of kcal mol⁻¹.

bis(nitrooxy)aluminum oxide III in resonance with IIIa, and concomitant iodosylbenzene regeneration. This reaction step is endergonic by 15 kcal mol⁻¹. However, the NO₂⁺ readily attacks to the naphthol, transferring a proton to the OAl(NO₃)₂ anion, thus affording the nitrated product, which is highly exergonic (total reaction energy: -51.6 kcal mol⁻¹). The iodosylbenzene continues its catalytic role in a new cycle, while HOAl(NO₃)₂ will continue in two more cycles, efficiently generating nitronium cations and ultimately being transformed to aluminum trioxide.

In summary, we have developed the first electrophilic nitration procedure of phenols catalyzed by iodosylbenzene, which acts as a nontoxic and iodine(III)-based organocatalyst. The source of the nitro group was the inexpensive aluminum nitrate nonahydrate. This novel reaction proved to be scalable and conducted under mild,⁴⁷ open-flask, and operationally simple conditions. The remarkably non-Brønsted acidic and cationic generation of the NO₂⁺ ion as the active nitrating species was demonstrated by theoretical calculations, and efficiently provided access to valuable nitrophenols and nitroheterocycles.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b04141.

Experimental procedures, characterization data, copies of 1 H and 13 C for compounds 1–55 and mechanic calculation details (PDF)

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Notes

The authors declare no competing financial interest.

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(37) Some other metallic nitrates (Na, Sr, Fe, Bi and Ag) were assayed; however, $Al(NO_3)_3$ showed the best results. See the SI for complete details.

(38) In each example, the bis-nitration product was not observed.

(39) The modest to low yields obtained are attributed to (a) water solubilization of the nitrophenol obtained after reaction quench, and (b) side-oxidation reactions at the phenolic ring promoted by the iodine(III) reagent.

(40) This result may indicate an interaction of the Ph-OH with a key intermediate of the reaction between PhIO and $Al(NO_3)_3$ but previous to the NO_2^+ formation. However, is not possible to generalize this interaction, since the nitrated *p*-products cannot be explained with this argument. In consequence, more than one reaction pathway could be operative.

(41) Some derivatives such as 5, 6, 7, 23 and 39 were assayed with different conditions for example, starting the reaction at room temperature instead to 0 °C; or different stoichiometries at PhIO or Al(NO₃)₃; or even quenching the reaction with 5% HCl. However, we could just increase the yield by 2%-4%.

(42) The low yields for **39** and **40** are attributable to direct interactions of the sulfur (**39**) and oxygen at formyl group (**40**) with either aluminum or iodine(III) center, diminishing the performance of the NO_2^+ formation and, as a consequence, the yield.

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(47) During the course of the reaction, the pH oscillates between 5.6 and 6.5.