


Selective Oxidation of Aromatic Amines to Nitro Derivatives using Potassium Iodide-*tert*-Butyl Hydroperoxide Catalytic System

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Abstract: The direct oxidation of aromatic primary amines to the corresponding nitro compounds selectively in 47–98% yields has been achieved by using potassium iodide as catalyst and *tert*-butyl hydroperoxide as the external oxidant. The present catalytic system works well for both electron-rich and electron-poor substrates.

Keywords: amines; nitroarenes; oxidation; peroxides

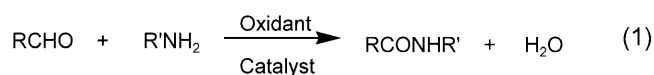
The oxidation of amines is a fundamental reaction for the synthesis of *O*-containing amine derivatives such as hydroxylamine, nitroso, nitro, oxime, azoxy and azo compounds. Among them, nitro compounds which were quoted as “ideal intermediates in organic synthesis” by Seebach,^[1] have many industrial applications, such as in the preparation of explosives, dyes, perfumes, pharmaceuticals and in the plastic industries.^[2] Aromatic nitro compounds also play an important role in evaluating many mechanistic concepts.^[3]

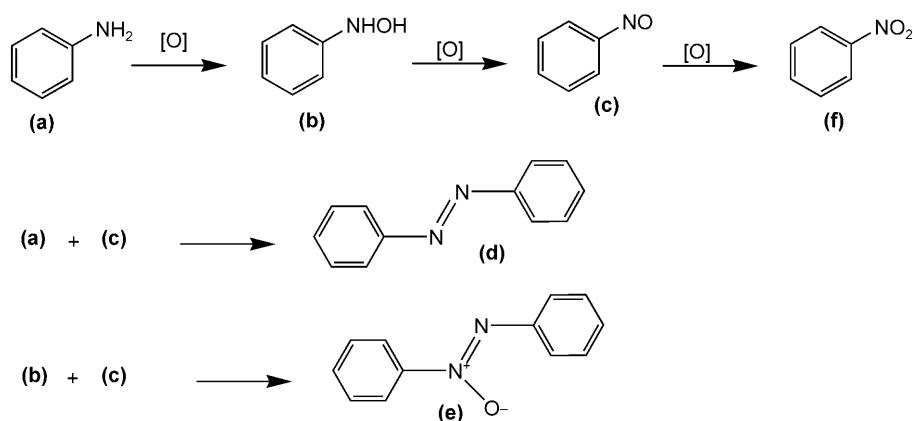
Classical methods for the preparation of aromatic nitro compounds involves direct nitration of the aromatic ring under harsh reaction conditions or through nitration of anionic intermediates originating from alkyl halides, alkenes or ketones.^[2–4] But many nitro compounds are difficult to synthesize by the above methods. Therefore indirect methods, such as oxidation of aromatic primary amines to nitro compounds, provide an alternative route. Several stoichiometric oxidants such as peracetic acid,^[5] MnO₂,^[6] Pb(OAc)₄,^[7] Hg(OAc)₂,^[8] and dioxirane.^[9] or with peroxides in combination with metal catalysts like Mo,^[10] W,^[11] Zr,^[12] Re,^[13] Ti silicates or Cr silicates,^[14] Fe(3+)

and Mn(3+) tetraarylporphyrins^[15] etc., are reported for the oxidation of aromatic amines. The nature of the oxidation products formed depends on the type of the oxidant, catalyst and reaction conditions. For example, oxidation of arylamines to nitro derivatives is generally complicated, since several products like azobenzenes, azoxybenzenes, nitrosoamines, and hydroxylamines are always formed as side products (Scheme 1). Therefore, a direct and selective oxidation of amines into nitro derivatives represent a greater necessity for chemists.

Molecular halogens and related reagents are well known for oxidations due to their simple operation and low cost.^[16] Among them molecular iodine is an attractive candidate as it is cheap, readily available and less toxic than molecular bromine or chlorine. Several reports appeared recently on the use of iodine-based reagents for various organic transformations.^[17] To the best of our knowledge, there are no reports on the direct oxidation of aromatic primary amines to corresponding nitro compounds using iodine reagents. In the cases of other halogen reagents, Rozen and co-workers reported the use of the HOF-CH₃CN system, which was generated *in situ* by passing molecular fluorine through aqueous acetonitrile for the direct oxidation of amines to nitro derivatives.^[18]

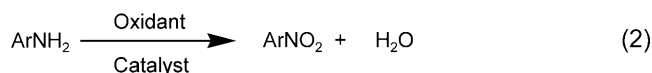
As a part of our study on iodine/iodide-mediated catalytic oxidative functionalizations of various functional groups, we have recently shown the use of a catalytic amount of KI and molecular iodine for the facile oxidative amidation of aldehydes and alcohols using TBHP as an external oxidant [Eq. (1)].^[19]





Scheme 1. Possible products obtained in the conversion of primary aromatic amines to nitro derivatives.

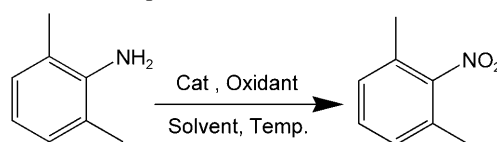
Herein, we would like to present a mild and selective oxidation of arylamines to their corresponding nitro derivatives using potassium iodide as catalyst and TBHP as the external oxidant [Eq. (2)].



For our initial optimization studies, we have chosen 2,6-dimethylaniline as our model substrate. A mixture of 2,6-dimethylaniline and solvent was stirred under different conditions and the results are summarized in Table 1. Control reactions without either oxidant or catalyst do not produce any product (Table 1, entries 1 and 2). Reaction at room temperature provided 62% of the nitro product. Among the various solvents screened CH_3CN provided the highest conversion (Table 1, entries 3–8). Under the same reaction conditions molecular iodine shows a lower activity over KI (Table 1, entries 10 and 11). By increasing the temperature (80°C) and decreasing the catalyst loading (5 mol%), the reaction proceeded to completion within 6 h ($\text{ArNH}_2:\text{KI}:\text{TBHP} = 1.0:0.05:3.8$). We have also examined the role of other commercially available oxidants such as 30% H_2O_2 on the model reaction using $\text{ArNH}_2:\text{KI}:\text{H}_2\text{O}_2$ in the ratio of 1.0:0.2:3.8, where we could not observe any conversion. It is expected that 3 equiv. of oxidant is required for the conversion of amines to nitro compounds and any decrease from this theoretical amount results in lower conversion (Table 1, entry 13).^[12b]

The general applicability of this method was further evaluated for structurally diverse aniline derivatives under optimized reaction conditions and the results are shown in Table 2. The reactivity depends on the aniline derivative used, thus aromatic amines having electron-donating groups are smoothly converted to their corresponding nitro compounds in good yields

Table 1. Optimization of conditions for the conversion of amines to nitro compounds.^[a]



| No. | Catalyst [mmol] | Oxidant [mmol] | Temp. [$^\circ\text{C}$] | Solvent | Yield [%] ^[b] |
|-----|--------------------|------------------------------|----------------------------|------------------------|--------------------------|
| 1 | – | TBHP [3.8] | r.t. | CH_3CN | 3 |
| 2 | KI (0.2) | – | r.t. | CH_3CN | – |
| 3 | KI (0.2) | TBHP [3.8] | r.t. | CH_3CN | 62 |
| 4 | KI (0.2) | TBHP [3.8] | r.t. | THF | 36 |
| 5 | KI (0.2) | TBHP [3.8] | r.t. | H_2O | 38 |
| 6 | KI (0.2) | TBHP [3.8] | r.t. | CHCl_3 | 42 |
| 7 | KI (0.2) | TBHP [3.8] | r.t. | Toluene | 13 |
| 8 | KI (0.2) | TBHP [3.8] | r.t. | DMSO | NR |
| 9 | KI (0.2) | H_2O_2 [3.8] | r.t. | CH_3CN | NR |
| 10 | KI (0.1) | TBHP [3.8] | 80 | CH_3CN | 83 |
| 11 | I_2 (0.1) | TBHP [3.8] | 80 | CH_3CN | 14 |
| 12 | KI (0.05) | TBHP [3.8] | 80 | CH_3CN | 90 ^[c] |
| 13 | KI (0.05) | TBHP [2.0] | 80 | CH_3CN | 64 |

^[a] Reaction conditions: amine (1 mmol), solvent (3 mL), 15 h.

^[b] Yields based on GC.

^[c] Yield after 6 h.

(Table 2, entries 1–9). In the cases of 2,6-diethyl-, 2-benzyl and 2-methoxy-6-methylaniline derivatives, the lower yields may be due to steric factors (Table 2, entries 7–9). Aromatic amines with electron-withdrawing groups have shown lower conversions (Table 2, entries 11–17). The reaction with 4-nitroaniline resulted in the formation of 2,4-dinitrobenzene in 67% yield. In the case of 3-chloroaniline (Table 2, entry 14) we have observed a very low conversion (21%), however increasing the catalyst loading to 20 mol% led to an improvement (75%) in product formation. In all the cases, nitro derivatives are found to be the sole

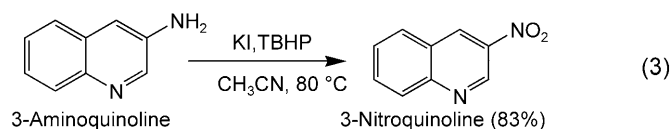
Table 2. KI-TBHP-catalyzed oxidative conversion of amines to nitro products.^[a]

| Entry | Reactant | Product | Yield [%] | |
|-------|---|---|------------------------|-------------------|
| | | | GC | Isolated |
| 1 | 2,6-di-Me-C ₆ H ₃ -NH ₂ | 2,4-di-Me-C ₆ H ₃ -NO ₂ | 98 | 93 |
| 2 | 2,4-di-Me-C ₆ H ₃ -NH ₂ | 2,4-di-Me-C ₆ H ₃ -NO ₂ | 90 | 86 |
| 3 | 2-ethyl-C ₆ H ₄ -NH ₂ | 2-ethyl-C ₆ H ₄ -NO ₂ | 82 | 80 |
| 4 | 4-isopropyl-C ₆ H ₄ -NH ₂ | 4-isopropyl-C ₆ H ₄ -NO ₂ | 80 | 74 |
| 5 | 2-isopropyl-C ₆ H ₄ -NH ₂ | 2-isopropyl-C ₆ H ₄ -NH ₂ | 76 | 73 |
| 6 | 2,6-di-ethyl-C ₆ H ₃ -NH ₂ | 2,6-di-ethyl-C ₆ H ₃ -NO ₂ | 68 | 62 |
| 7 | 2-benzyl-C ₆ H ₄ -NH ₂ | 2-benzyl-C ₆ H ₄ -NO ₂ | 60 | 55 |
| 8 | 2-OMe,6-Me-C ₆ H ₃ -NH ₂ | 2-OMe,6-Me-C ₆ H ₃ -NO ₂ | 71 | 69 |
| 9 | C ₆ H ₅ -NH ₂ | C ₆ H ₅ -NO ₂ | 99 | 93 |
| 10 | 4-NO ₂ -C ₆ H ₄ -NH ₂ | 4-NO ₂ -C ₆ H ₄ -NO ₂ | 72 | 67 |
| 11 | 4-Cl-C ₆ H ₄ -NH ₂ | 4-Cl-C ₆ H ₄ -NO ₂ | 54 | 51 |
| 12 | 2-Cl-C ₆ H ₄ -NH ₂ | 2-Cl-C ₆ H ₄ -NO ₂ | 47 | 44 |
| 13 | 3-Cl-C ₆ H ₄ -NH ₂ | 3-Cl-C ₆ H ₄ -NO ₂ | 21 (75) ^[b] | 70 ^[b] |
| 14 | 2,4-di-Cl-C ₆ H ₃ -NH ₂ | 2,4-di-Cl-C ₆ H ₃ -NO ₂ | 54 | 52 |
| 15 | 4-Br-C ₆ H ₄ -NH ₂ | 4-Br-C ₆ H ₄ -NO ₂ | 65 | 54 |
| 16 | 4-F ₃ C-C ₆ H ₄ -NH ₂ | 4-F ₃ C-C ₆ H ₄ -NO ₂ | 52 | 48 |
| 17 | 2,6-dibromo,4-F-C ₆ H ₂ -NH ₂ | 2,6-dibromo,4-F-C ₆ H ₂ -NO ₂ | 30 | -- |

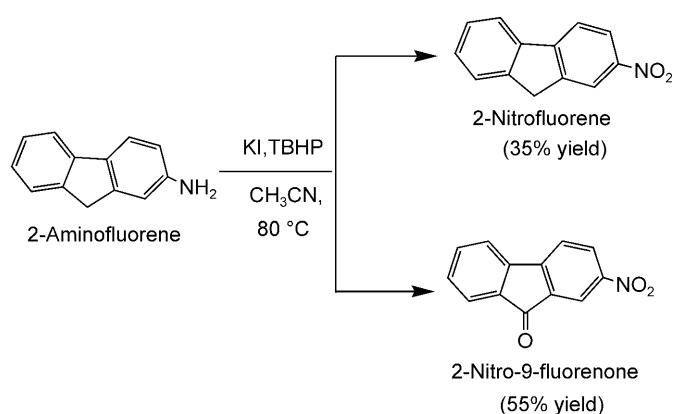
^[a] Reaction conditions: aromatic amine (1 mmol), CH₃CN (3 mL), KI (5 mol%), TBHP (3.8 equiv.), 80 °C, 15 h.

^[b] Reaction with 20 mol% KI as catalyst.

products. None of the side products, which are formed with other catalysts, were observed under the present reaction conditions. In the reaction with 2-aminofluorene, apart from desired nitro product (35%), a substantial amount (55%) of the further oxidized 2-nitrofluoren-9-one product was observed (Scheme 2). This methodology has been applied to heterocyclic compounds taking 3-aminoquinoline as an example. The reaction is very fast and proceeds to completion within 6 h [Eq. (3)].



In summary, a simple and convenient method has been developed for the direct oxidation of aromatic primary amines to the corresponding nitro compounds selectively in good yields, using a catalytic



Scheme 2. Products observed with 2-aminofluorene.

amount of KI in the presence of TBHP as the external oxidant. Compared to the established methods, the present catalytic system is highly selective towards the nitro compounds and works well for both electron-rich and electron-poor substrates. Moreover, this non-transition metal catalytic system avoids the use of expensive metal catalysts and toxic oxidants and provides an easy separation protocol.

Experimental Section

General Procedure for the Synthesis of Nitro Compounds from Amines

To a solution of amine (1.0 mmol) and potassium iodide (0.05 mmol) in 3 mL of CH₃CN was added a solution of 70% aqueous TBHP (3.8 mmol) dropwise over a period of 30 min and the mixture was stirred at 80 °C. The mixture was quenched with saturated aqueous Na₂S₂O₃ after 15 h, washed with brine, extracted with ethyl acetate and dried over anhydrous Na₂SO₄. Removal of the solvent under vacuum afforded the crude product, which was purified by column chromatography using hexane/ethyl acetate mixture and then analyzed by ¹H NMR, GC and GC-MS.

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