One-pot selective synthesis of azoxy compounds and imines via the photoredox reaction of nitroaromatic compounds and amines in water

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A facile one-pot two-stage photochemical synthesis of aromatic azoxy compounds and imines has been developed by coupling the selective reduction of nitroaromatic compounds with the selective oxidation of amines in an aqueous solution. In the first stage (light illumination, Ar atmosphere), the light excited nitroaromatic molecule abstract H from amine to form ArNO2H and amine radical, which then form nitrosoaromatic, hydroxylamine and imine compounds. Water acts as a green solvent for the dispersion of the reactants and facilitates the formation of nitrosoaromatic and hydroxylamine intermediate compounds. In the second stage (no light, air atmosphere), the condensation of nitrosoaromatic and hydroxylamine compounds yields aromatic azoxy product with the aid of molecular oxygen in air. This photochemical synthesis achieved both high conversion and high product selectivity (>99%) at room temperature.

The selective reduction of nitroaromatic compounds to azo/azoxy compounds and the selective oxidation of amines to imines are two important types of reactions. They are widely studied in the formation of molecules containing N=N or C=N bonds, which are important intermediates for the production of dyes and pharmaceuticals1–3. For the selective reduction of nitroaromatic compounds to azo and azoxy compounds, either reducing agent or catalytic routes are used. However, these processes normally generate hazardous by-products or require harsh reaction conditions such as high temperature and pressure4–6. Recently, it has been reported that Au/ZrO2 and Cu/graphene can reduce nitroaromatic compounds to azo compounds <100 °C with high product selectivity (>99%) under incandescent light irradiation7–9. On the other hand, the selective oxidation of an amine to the corresponding imine is a extensively studied acid-catalyzed reaction10. The direct oxidation of amines using molecular oxygen under light irradiation has drawn a lot of attention lately, with metal oxides such as TiNb2O711 and Nb2O512 or metal free photocatalyst such as carbazolic conjugated microporous polymer13 exhibiting good catalytic activity for the oxidation reaction. In both of the photocatalytic selective reduction and oxidation reactions, the photocatalysts absorb incident light and transfer the light energy to the substrate via photo-induced carriers, which are low efficient processes because the photo-induced carriers are prone to recombination in the transmission process14,15.

Recently, catalyst-free photochemical reactions have shown great promise in providing efficient routes to prepare fine chemicals, e.g. the conversion of cyclohexane to adipic acid using UV light and ozone16. We questioned whether the selective reduction and oxidation steps can be coupled without the need of a catalyst if at least one of...
the substrates can directly absorb incident light to become activated. Given the light absorption of nitroaromatic compounds in the near-UV and the H-donating ability of amines\textsuperscript{17}, it is possible that an amine can act as the reducing agent for the selective reduction of a nitroaromatic compound and itself is oxidized to its corresponding imine. If it works, both the reactants convert to valuable products without the need of a catalyst using a one-pot reaction. Evidently this process can reduce the use of reagents, simplify the separation steps and increase the yield\textsuperscript{18}. Furthermore, the mechanism of this type of process will advance our fundamental knowledge of photophysical reaction kinetics. Herein, we design a facile photochemical “one-pot” approach for the synthesis of imine and azoxybenzene from the aqueous solution of amine and nitrobenzene without the addition of any catalyst. The light was then turned off and air was introduced into the reaction. As expected, the reaction system worked effectively with high selectivity. Importantly, the reaction was conducted in a green solvent - water.

**Results and Discussion**

The reaction process between nitrobenzene (NB) and propylamine (PA) in aqueous solution can be divided into two main steps (Fig. 1a). The photoreaction process (1–5 h) and the exposure process (5–13 h). In the photoreaction process, more than 98% of NB can be converted at 5 h (the apparent quantum yield, AQY, is 0.25%, the calculation details are given in the ESI). Three main products from NB were detected with gas chromatography mass spectrometry (GC-MS) and high-performance liquid chromatography (HPLC) analysis, including nitroso-benzene (NSB), phenyl-hydroxylamine (PHA) and azoxybenzene (AOB). The proportion of the three products remained almost constant throughout the photoreaction process indicating that the reaction followed the equation Fig. 1b-1. In the exposure stage, the light was switched off and air was introduced into the reaction vessel. During the initial exposure stage (5–8 h), the condensation of PHA and NSB proceeded rapidly to yield AOB. The similar trend was observed when O\textsubscript{2} instead of air was purged into the vessel. These imply that O\textsubscript{2} in the air can promote the condensation reaction between NSB and PHA (Fig. 1b-2). It has been reported that the molecular oxygen in the air can destroy the nitrosobenzene radical anion formed during the reaction between NSB and
PHB, which is favorable for the condensation reaction. During the later stage (8–11 h), the PHA was not detected after 10 h, however, the NSB had disappeared until 11 h and the yield of AOB had increased from 92.6% to 98.2% when the reaction time was from 10 h to 11 h. It indicates there may exist a reaction pathway that can yield AOB from NSB, which is probably the rate-determining step. In a control experiment, PHA was detected by HPLC in the reaction between NSB and PA (Figure S1). When PA was replaced with toluene, AOB was not detected (Figure S2), indicating that PA plays an important role in converting NSB to AOB. To clarify whether PHA reacts in the presence of oxygen to yield AOB, pure PHA was exposed to air, and a mixture including NB, AOB and azobenzene was obtained. This indicates that AOB is yielded via the condensation between NSB and PHA and not via PHA reaction with O₂. The oxidation product of PA, N-propylpropanimine (NPPI), was identified by nuclear magnetic resonance (NMR) spectroscopy (Figure S3 a–c). Based on the above results, a rational reaction equation (Fig. 1b-5) was conjectured. The Gibbs free energy of the reaction is $\Delta G = -1.44 \text{ kJ mol}^{-1}$ (Table S1), indicating that the reaction was thermodynamically spontaneous.

To confirm whether this one-pot synthesis can be scaled up, the gram scale reaction was conducted by mixing 1.2 g of NB with 7.2 of PA (10–50 times greater than the previous photocatalytic studies). As shown in Figure S4, conversion of 100% of NB is achieved by yielding the NSB, PHA and AOB products under irradiation for 28 h. After the mixture were exposed at air for 120 h, only AOB and NPPI were observed besides solvent and the yield of AOB and NPPI was 99% and 38%, respectively (AQY = 0.23%). While the theoretical yield of NPPI should be 24% based on the equation Fig. 1b-5. This indicates that a condensation reaction between PA and propanimine [C₂H₅CH=NH, the direct oxidation product of PA attacked by the excited NB (Fig. 1b-3)] occurred, which contributed to the production of NPPI (Fig. 1b-4).

Neither AOB nor NPPI was achieved in the absence of light. The conversion rate of NB increased from 21% to 57% in aqueous solution [Figure S5a (red line)] and from 35% to 86% in pure PA solution [Figure S5b (red line)] when the light intensity was increased from 40 to 200 mW cm⁻². These results indicate that the conversion of NB was driven by light. The conversion of NB was increased when the temperature was increased from 30 to 80 °C in aqueous solution while keeping other conditions identical (Figure S5a, blue line). However, in a pure PA or inert organic liquid solution, such as acetonitrile, toluene or cyclohexane (Figure S5b and c), the conversion rate remained constant with changing the reaction temperature. It leads us to further study the unique role of water. On one hand, the solubility of nitrobenzene is higher in an organic solvent than in an aqueous solution. A higher temperature can increase the solubility of nitrobenzene in H₂O. On the other hand, the ionization of water is endothermic. Therefore, higher temperatures will promote the dissociation of water and produce more OH⁻ and H⁺ ions which will be beneficial to the reaction.

The hydrogen donating ability of ammonia, amine and water was investigated (Table S2). Trace amounts of NB were converted when using H₂O (entry 1). In an NH₃·H₂O solution, 14% of NB was converted within 5 h (entry 2) and the main product was aniline, the over-reduced product. In a N₂H₄·H₂O solution, the product selectivity was the same as that observed in NH₃·H₂O, however, the conversion was higher. When the –NH₂ group is bonded to an alkyl group, such as methylamine or ethylamine, (entires 4 and 5), less than 5% of aniline and more AOB product was observed in the resulting products and the conversion rate was >97%. The alkyl group may affect the hydrogen donating ability of the –NH₂ group, the reduction pathway of NB and the selectivity for AOB. Therefore, the reducing ability of the amines was in the order of:

$$\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O} > \text{NH}_3 \cdot \text{H}_2\text{O} > \text{CH}_3\text{NH}_2 \cdot \text{H}_2\text{O} > \text{C}_2\text{H}_5\text{NH}_2 \cdot \text{H}_2\text{O}$$

and H₂O probably acts as a dispersant in the photoreaction process.

The substrate scope of this one-pot coupling reaction was explored (Table 1). Reactions using nitrobenzene derivatives bearing electron-donating groups (–CH₃, –OCH₃) and electron-withdrawing groups (–Cl, –CN) were studied (entries 1–4). The substrates reacted with PA to give corresponding azoxy compounds and NPPI with high selectivity. We also investigated the reactions of NB with a series of amines. When butylamine or

| Entry | Substrate | Amines | tₚ/tₜ (h)⁴ | Con.ₐOB (%)⁵ | Sel.ₐOB (%)⁶ | Sel.ₐamine (%)⁷ |
|-------|-----------|--------|------------|--------------|-------------|----------------|
| 1     | H₃C–NO₂  | C₆H₅NH₂ | 5/48       | 99           | >99         | >99           |
| 2²    | H₂CO–NO₂ | C₆H₅NH₂ | 2/48       | 93           | >99         | >99           |
| 3³    | Cl–NO₂   | C₆H₅NH₂ | 2/48       | 97           | >99         | >99           |
| 4⁴    | NC–NO₂   | C₆H₅NH₂ | 2/48       | 98           | >99         | >99           |
| 5     | NO₂      | C₆H₅NH₂ | 5/48       | 99           | 99          | >99           |
| 6     | NO₂      | PbCH₃NH₂| 5/48       | 97           | 92          | >99           |

Table 1. The photochemical reaction between various nitrobenzene derivatives (N.D.) and different amines. ¹tₚ: the photochemical reaction time; tₜ: the time exposure to air in the absence of light. ²Conversion rate of nitro-derivatives bearing electron-donating groups (–CH₃, –OCH₃) and electron-withdrawing groups (–Cl, –CN) were studied (entries 1–4). The substrates reacted with PA to give corresponding azoxy compounds and NPPI with high selectivity. We also investigated the reactions of NB with a series of amines. When butylamine or
benzylamine reacted with NB, the resulting products were the corresponding imine and AOB (entries 5 and 6). The yield of corresponding azoxy- and imines compounds are shown in Table S3.

The absorption of light is the first step during a photochemical reaction. To understand how the coupled reaction was initiated, we compared the UV-Vis absorption spectra of the reactants and the output spectrum of the purple LED light (Fig. 2a). No absorption of PA was observed in the range >350 nm. The absorption of NB was in the wavelength range <440 nm, which was due to n–π* transitions of NB. It is obviously that the light absorption of NB range overlaps with the light output spectrum of the purple LED in the 370–440 nm range. No conversion of NB was observed when using blue LED light (~460 nm) as the light source, which indicates that light with a length between 370 and 440 nm induces the conversion of NB.

A photochemical reaction normally involves radical formation pathway. The radicals formed during the reaction were determined by electron paramagnetic resonance (EPR) spectroscopy. No EPR signal was observed when the mixture of NB and PA was analyzed in the dark. After the mixture was irradiated under UV light for 1 min, an EPR signal with a complicated hyperfine feature was recorded in situ (Fig. 2b). The signal can be assigned to the nitrogen-centered PrNH• radical. The results of the simulation show that the hyperfine constants from the coupled nitrogen and hydrogen in PrNH• are aN = 11.6 G, aH3 = 3.6 G and aH2 = 1.2 G. The EPR signals observed for the PrNH• radicals are rather stable at room temperature under illumination. However, the signal intensity decayed quickly when the light was turned off. No EPR signal was observed from PA or NB alone in the dark or after 1 min of light irradiation (Figure S6). The results confirm that PrNH• radicals were generated only under light irradiation in the presence of NB. It has been reported that the n–π* transitions of NB can remove hydrogen atoms from an amine. Therefore, it is sensible to infer that the purple light initiates the reaction between NB and PA by exciting the n–π* transitions of NB to produce radicals.

As stated earlier, NSB and PHA were gradually converted to AOB when exposed to air (Fig. 1). It has been reported that the reaction of NSB with an amine involves the initial nucleophilic attack of NSB by the alkylamine, which affords an intermediate state containing a N–N bond such as reported that the reaction of NSB with an amine involves the initial nucleophilic attack of NSB by the alkylamine molecule participates in the nucleophilic attack of RCH = NH and eliminates an ammonia to form the final coupled imine product (1). The latter was subsequently converted to a carbon radical (2) by means of a rearrangement and the radical loses a hydrogen atom to form RCH = NH (3). Then, the lone pair of electrons in a second amine molecule participates in the nucleophilic attack of RCH = NH and eliminates an ammonia to form the final coupled imine product (4). The PhNO3 radical further give NSB via a PhN(OH)2 intermediate. Under the synergistic effect of water and amines, NSB can be converted to PHA. Finally, NSB reacts with PHA and yields AOB through a condensation reaction, where O2 molecules in the air facilitate the process.

![Figure 2.](https://example.com/image.png)

**Figure 2.** (a) The UV-Vis spectra of the reactants (PA and NB) and the output spectrum of the purple LED light. (b) The EPR spectra of the mixed solution of NB and PA in the presence and absence of light irradiation.
Conclusions
In conclusion, the photochemical protocol reported in the present study provides a facile and effective route for the preparation of high value azoxy compounds and imines. It reveals that the photochemical properties of nitroaromatic compounds, including their excitation by light and the ability of the light excited molecules to generate radicals, can be utilized for synthesis of fine chemicals under mild conditions with high selectivity if the reaction conditions are well controlled (e.g. light wavelength, solvent, atmosphere). These photochemical properties should also be taken into account in studies of photocatalytic reactions involving nitroaromatic compounds.

Methods
Photoreaction test. In general, all chemicals were used as received without further purification. The reduction of nitrobenzene was conducted under an Ar atmosphere (1 atm) in a 10 mL (25 mL for gram scale) round-bottomed pyrex glass flask with a sealed spigot and a magnetic stirrer. A purple LED lamp (~400 nm) was used as the light source. In the reaction, the concentration of nitrobenzene was 0.02 mol/L, unless specified otherwise, dissolved in an aqueous solution of PA at a volume ratio of 3:1. The concentration of nitrobenzene was increased 50–fold for the large-scale experiment. The product compositions were analyzed and determined by means of an Agilent HP5973 mass spectrometer and Agilent 1260 high efficiency liquid chromatography. The Agilent Series are equipped with a vacuum degasser, a quaternary pump, an autosampler and a DAD system, connected to a Agilent ChemStation software. A C18 column (250 × 4.6 mm i.d., 5 μm) were used. Flow rate was 1 mL min−1. Detection wavelength was at 280 nm. Solvents that constituted the mobile phase were (A) methanol and (B) water with the volume ratio 50:50.

N-propylpropanimine (NPPI). 1.2 g nitrobenzene and 7.2 g propylamine was mixed. After the reaction (the total weight is about 8 g), the mixture was distilled at 85 °C to separate the imine/propylamine and azo compounds. About 5 g of imine and propylamine transparent mixture was collected: 1H NMR (400 MHz, CDCl3, 25 °C, TMS) δ = 0.88 (t, J = 7.4 Hz, 2 H); δ = 1.09 (td, J = 7.6, 1.2 Hz, 3 H); δ = 1.61 (qd, J = 7.2, 1.2 Hz, 2 H); δ = 2.32–2.19 (m, 1 H); δ = 3.32 (tt, J = 7.6, 1.2 Hz, 2 H); δ = 7.64 (td, J = 4.6, 1.3 Hz, 1 H). 13C NMR spectrum of imine (100 MHz, CDCl3): δ 10.25, 11.57, 23.76, 28.90, 63.01, 165.62.

Characterization. EPR in situ photochemical experiments: The formation of paramagnetic intermediates upon irradiation of solutions was monitored in situ using an EPR X-band spectrometer (Bruker Empxplus-10/12) at RT. The irradiation source was a 100 W Hg Arc lamp power supply (LOT, LSN161). Typical EPR spectrometer settings in a standard photochemical experiment were: microwave power, 10.02 Mw; microwave frequency, ca 9.863 GHz; center field, 348.0 mT; sweep width, 50 mT; scan, 60 s; time constant, 0.01 ms; modulation amplitude, 0.6 mT. In the water added measurement, 1 mL of nitrobenzene mixed with 100 µL deionized water and ultrasonication for 5 min.

Diffuse-reflectance UV-vis spectra were measured on a UV-vis spectrophotometer (Shimadzu UV-3600 - spectrometer). NMR spectra were acquired on a Bruker AV-III 400 MHz NMR spectrometer (9.39 T) equipped with a 5 mm PABBO BB/19F-1H/D Z-GRD probe and autosampler at room temperature. 1H and 13C NMR were obtained at frequencies of 400.13 MHz and 100.61 MHz respectively. The chemical shifts for 1H NMR and 13C NMR were referenced of the residual protons of CDCl3 (7.262 for 1H, 77.01 for 13C). When peak multiplicities were reported, the following abbreviations were used: s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet, br-broadened. The pulse programs for COSY and HSQC acquisition are “cosypppapl” and “hsqctgpsi2”, respectively. The collected 1D and 2D NMR data were processed using Bruker Topspin 3.1 software.

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Acknowledgements

We would like to thank the National Natural Science Foundation of China (No. 21503258, 21773284, 51401233), the Shanxi Science and Technology Department (No. 201601D021032, 2015081044), the Foundation of State Key Laboratory of Coal Conversion (No. J17-18-605) and the Hundred Talents Program of the Chinese Academy of Sciences and Shanxi Province.

Author Contributions

Z.F. Zheng and X.M. Gu conceived the experiment idea and designed the research. H. Tan carried out the experiment and did most measurement and wrote the manuscript. J.H. Su analyzed the EPR data; Y.X. Wang analyzed the NMR data, X.C. Liu carried out the DFT calculation. D.J. Yang, Eric R. Waclawik and H.Y. Zhu give constructive suggestions during the article modification. All authors reviewed the manuscript.

Additional Information

Supplementary information accompanies this paper at https://doi.org/10.1038/s41598-018-38100-6.

Competing Interests: The authors declare no competing interests.

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