Light-emitting diode light–enabled denitrative etherification of 4-nitrobenzonitrile under catalyst-free conditions at room temperature

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Abstract
In this study, we have developed a catalyst-free procedure for denitrative etherification of electron-deficient nitroarenes. In this method, the reaction failed in the dark but was enabled by white light-emitting diode light (6 W) in the presence of NaOH/dimethylformamide at room temperature with short reaction times. Interestingly, the reaction in the dark is completed almost immediately once a small quantity of water is added to the reaction mixture. Ultraviolet irradiation ($\lambda = 254 \text{ nm}$) was not effective for this reaction to proceed.

Keywords
catalyst-free, C–O bond formation, denitration, photoetherification, white light-emitting diode light

Introduction
In recent years, nitroarenes have been used in cross-coupling reactions as alternatives to aryl halides. Using these compounds as the starting materials, we have developed three efficient approaches for the synthesis of aromatic sulfides under copper catalysis. In addition to this report, conditions have been developed by our group and others for construction of C–O, C–N, C–C, and C–S bonds in the presence of transition-metal catalysts. Apart from these metal-catalyzed reactions, some metal-free procedures are also available in the literature.

Results and discussion
We started our studies on the reaction of 4-nitrobenzonitrile with ethanol under white light-emitting diode (LED; 6 W) irradiation at room temperature (Table 1). The reaction failed in the presence of either 1,8-diazabicyclo(5.4.0)undec-7-ene DBU, nPr$_3$N, KF, or K$_2$CO$_3$ as the base in dimethylformamide after 24 h (entries 1–4). A low yield of the product was obtained in the presence of K$_3$PO$_4$ as the base (entry 5). Interestingly, by switching the base to KOH, the yield of the desired product increased drastically to 80% within 20 min (entry 6). A further increase in the yield up to 97% was observed when using NaOH as the base with a 10-min reaction time, and we selected these as the optimal conditions.

Herein, we wish to report an effective procedure for denitrative photoetherification of 4-nitrobenzonitrile under catalyst-free conditions.
the optimized conditions (entry 7). Dimethyl sulfoxide (DMSO) was also found to be an effective solvent for this reaction (entry 8). However, polyethylene glycol (PEG), EtOH, CH$_3$CN, and water were not suitable solvents (entries 9–12). To our surprise, when we added CuI and 1,10-phenanthroline to the standard conditions and raised the temperature up to 100 °C, the reaction failed even after a 24-h reaction time (entry 13). In addition, when the optimized conditions (entry 7) were carried out in the absence of LED light, no product was obtained after 24-h reaction time (entry 14). This observation shows the importance of the white LED irradiation in this reaction. When we increased the temperature to 100 °C, the reaction gave the desired product in 80% yield in the dark within 12 h (entry 15). We were surprised to observe that the reaction in the dark using 96% EtOH instead of absolute EtOH proceeded very quickly, giving a yield comparable to the optimized conditions (entry 16). To clarify the effect of water, we conducted the standard reaction using absolute ethanol and we added 2 mmol of water to the reaction. Again, a 97% of the desired product was isolated from the reaction mixture within 10 min (entry 17). The reaction failed under ultraviolet (UV) irradiation ($\lambda = 254$ nm) after a 30-min reaction time (entry 18). In the next experiment, we mixed all the starting materials in a flask and exposed it to sunshine. When we carried out the reaction under these conditions, the product was obtained in a 80% yield within a 60-min reaction time (entry 19). Hence, the best conditions for the reaction of 4-nitrobenzonitrile with absolute ethanol were using NaOH as the base, DMF as the solvent under white LED irradiation at room temperature (entry 7).

Having optimized conditions in hand, we used different alcohols for denitrative etherification reactions (Scheme 1). Primary (3a and 3b) as well as secondary alcohols (entries 3c–e) gave the corresponding products in excellent yields within short reaction times. However, when propargyl alcohol was used, the desired product 3f was obtained in only a 48% yield. Likewise, only a moderate yield of the product 3g was separated from the reaction mixture when phenol was employed as the coupling partner. The reaction of 4-nitrobenzonitrile with tetraethyl orthosilicate was also studied, giving an excellent yield of the desired product 3a. However, only a moderate yield of 3h was obtained for the reaction of ethyl 4-nitrobenzoate with tetraethyl orthosilicate.

To obtain some information about the reaction pathway, we determined the UV-Vis spectrum of 4-nitrobenzonitrile, a potential chromophore for the reaction (Figure S1). No significant peak was observed in the visible region of the spectrum. This suggests that the utilized LED might cover some area in the near UV region. Alternatively, the visible LED light can be absorbed by the intermediates produced during the course of the reaction.

Although the mechanism of the reaction is not clear to us yet, but based on our experiments and related reports in literature, we proposed a mechanism as shown in Scheme 2. In the first step, ethanol is converted to ethoxide. The presence of water can help NaOH and sodium ethoxide to dissolve in the DMSO solution. Then, ethoxide attacks to 4-nitrobenzonitrile to form intermediate I. This intermediate can absorb energy from white LED causing the electronic excitation from highest occupied molecular orbital (HOMO) to lowest unoccupied molecular orbital (LUMO) of intermediate I producing intermediate II. Finally, the nitro group is removed and the desired product is obtained.

### Conclusion

In summary, we report a novel procedure for the synthesis of ethers using activated nitroarenes as the coupling partners. In this approach, a transition metal-free denitrative etherification of 4-nitrobenzonitrile or ethyl 4-nitrobenzoate is reported in the presence of NaOH under white LED irradiation at room temperature.

### Experimental

#### General

All chemicals were purchased from Merck and Aldrich chemical companies and used as received without further purification. All experiments were run under white LED light and air atmosphere unless stated otherwise. Nuclear
magnetic resonance (NMR) data were determined in the Bruker instrument (300 MHz) using CDCl₃ as the solvent.

**Typical procedure for the denitrative etherification of 4-nitrobenzonitrile**

A mixture of 4-nitrobenzonitrile (0.5 mmol), NaOH (4 mmol), DMF (3 mL), room temperature, under white LED irradiation; b Si(OEt)₄ was used as the ethoxide source.

**Scheme 1.** The reaction scope for denitrative functionalization of nitroarenes. Reaction conditions: nitrobenzene derivative (0.5 mmol), nucleophile (2 mmol), NaOH (4 mmol), DMF (3 mL), under white LED irradiation in air atmosphere at 25 °C. The progress of reaction was monitored by thin layer chromatography (TLC). After the completion of reaction, the product was extracted with ethylacetate/water. The layer chromatography (TLC) was purified by column chromatography over silica gel using n-hexane/ethylacetate (8:2) as the eluent.

**Scheme 2.** The reaction pathway for denitrative etherification of 4-nitrobenzonitrile.

(q, J = 6.7 Hz, 2 H), 1.69–1.81 (m, 1 H), 3.95 (t, J = 6.6 Hz, 2 H), 4.78 (d, J = 8.8 Hz, 2 H); 13C NMR (75 MHz, CDCl₃) δ; 22.52, 25.01, 37.65, 66.82, 103.64, 115.20, 119.33, 133.95, 162.46.

4-Isopropoxybenzonitrile (3e):²⁵ Yellow liquid, 1H NMR (300 MHz, CDCl₃) δ; 1.27 (t, J = 6.1 Hz, 6 H), 4.53 (sept, J = 6.0 Hz, 1 H), 6.83 (d, J = 7.4 Hz, 2 H), 7.47 (d, J = 7.2 Hz, 2 H); 13C NMR (75 MHz, CDCl₃) δ; 21.79, 70.38, 103.35, 116.06, 119.34, 133.98, 161.37.

4-sec-butoxybenzonitrile (3d):²⁵ Yellow liquid, 1H NMR (300 MHz, CDCl₃) δ; 0.89 (t, J = 7.4 Hz, 3 H), 1.23 (d, J = 6.1 Hz, 3 H), 1.52–1.73 (m, 2 H), 4.29 (sex, J = 6.0 Hz, 1 H), 6.83 (d, J = 8.9 Hz, 2 H), 7.47 (d, J = 8.9 Hz, 2 H); 13C NMR (75 MHz, CDCl₃) δ; 9.65, 19.00, 29.72, 75.46, 103.30, 116.08, 113.96, 133.99, 161.72.

4-Cyclohexyloxybenzonitrile (3f):²⁶ Pale yellow oil; 1H NMR (300 MHz, CDCl₃) δ; 1.25–1.51 (m, 6 H), 1.70–1.72 (m, 2 H), 1.86–1.90 (m, 2 H), 4.20–4.28 (m, 1 H), 6.83 (d, J = 8.8 Hz, 2 H), 7.45 (d, J = 8.6 Hz, 2 H); 13C NMR (75 MHz, CDCl₃) δ; 23.54, 25.43, 31.45, 75.65, 103.24, 116.17, 119.38, 133.94, 161.31.

4-(Prop-2-nyloxybenzonitrile (3g):²⁷ Yellow liquid, 1H NMR (300 MHz, CDCl₃) δ; 2.61 (t, J = 2.3 Hz, 1 H), 4.79 (d, J = 2.3 Hz, 2 H), 7.08 (d, J = 8.9 Hz, 2 H), 7.65 (d, J = 8.9 Hz, 2 H); 13C NMR (75 MHz, CDCl₃) δ; 55.97, 68.11, 86.26, 104.99, 115.67, 119.00, 134.00, 160.69.

4-Phenoxybenzonitrile (3h):²⁷ Yellow solid; 1H NMR (300 MHz, DMSO-d₆) δ; 7.11 (d, J = 8.9 Hz, 2 H), 7.16 (d, J = 8.3 Hz, 2 H), 7.30 (t, J = 7.5 Hz, 1 H), 7.50 (t, J = 8.0 Hz, 2 H), 7.86 (d, J = 8.9 Hz, 2 H); 13C NMR (75 MHz, DMSO-d₆) δ; 105.52, 118.47, 119.21, 120.76, 125.69, 130.95, 135.13, 154.90, 161.62.

Ethyl 4-ethoxybenzoate (3i):²⁷ Yellow liquid, 1H NMR (300 MHz, CDCl₃) δ; 1.30 (t, J = 7.13 Hz, 3 H), 1.36 (t, J = 7.0 Hz, 3 H), 4.01 (q, J = 7.0 Hz, 2 H), 4.27 (q, J = 7.1 Hz, 2 H), 6.82 (d, J = 8.9 Hz, 2 H), 7.91 (d, J = 8.9 Hz, 2 H); 13C NMR (75 MHz, CDCl₃) δ; 14.41, 14.70, 60.61, 63.67, 114.00, 122.76, 131.54, 162.69, 166.46.

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Supplemental material

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