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Heterogeneous copper ferrite nanoparticles for catalytic synthesis of tetrahydroquinolines

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ABSTRACT

Methods for using commercially available copper ferrite nanoparticles for organic transformations have witnessed emerging development. Herein we expand the application of such material for heterogeneously catalytic annulation of *N*,*N*-dimethylaniline and maleimides to yield tetrahydroquinolines. Using the developed conditions, a 73% yield of tetrahydroquinoline derived from *N*-benzylmaleimide and 4,*N*,*N*-trimethylaniline was isolated. Derivatives bearing fluoro, thiophenyl, and alpha-methylbenzyl groups were also obtained with yields varying from 54% to 80%. The copper ferrite nanoparticles could be easily separated after the reaction and showed nearly identical XRD result compare to that of the fresh material.

1. Introduction

Tetrahydroquinolines are prominent scaffolds often found in an array of biologically active molecules [1,2]. Emerging methods to construct tetrahydroquinolines are focusing on the oxidative [4+2] cycloaddition of *N*-alkylanilines and electron-poor alkenes such as maleimides [3-7]. Notably, successes often rely on the use of transition metal complexes. For example, Hirano and Miura reported a praiseworthy method for copper-catalyzed coupling of *N*,*N*-dialkylanilines and maleimides to yield tetrahydroquinolines [3]. Annulation of alkenes with *N*,*N*-dialkylanilines triggered by the combination of an organocatalyst and visible light was revealed by Sundén and Runemark [8]. Excess amount of strong oxidants such as $K_2S_2O_8$ could also be utilized to facilitate such transformation [9]. Until now, it is often that the known methods utilize non-recyclable catalyst and/or harsh conditions. As such, more examples with respect to using heterogeneous, reusable catalysts in combination with mild reaction conditions should be of worthy consideration.

Copper ferrite nanoparticles ($CuFe_2O_4$) are among rare commercial solid catalyst that are widely used for organic transformations. Our group and others have utilized copper ferrite nanoparticles in oxidative coupling reactions [10-12]. Herein we would like to develop a method for synthesis of tetrahydroquinolines from *N*,*N*-dimethylaniline and *N*-benzyl maleimides promoted by $CuFe_2O_4$. The reaction conditions were tolerant of oxidation-prone benzylic C−H bonds. The material could be recovered without structural change as shown by XRD results.

2. Experimental

Chemicals were obtained from Sigma-Aldrich and used as received unless otherwise stated. Copper ferrite ($CuFe_2O_4$) nanoparticles were directly used as received from Sigma-Aldrich as nanopowder (particle size is

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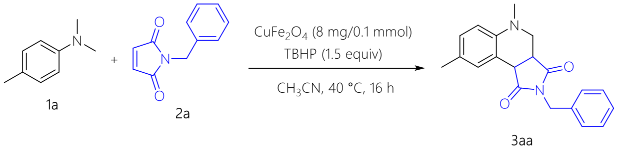
smaller than 100 nm). Derivatives of *N*-benzylmaleimide **1a** were prepared following the known procedure [13]. Progress of annulation of **1a** and 4,*N*,*N*-trimethylaniline **2a** was studied by thin layer chromatography (TLC) and gas chromatography (GC). Results of GC were obtained from experiments on a Shimadzu GC 2010-Plus equipped with a flame ionization detector (FID) and an SPB-5 column (inner diameter = 0.25 mm, film thickness = 0.25 µm). Characterization by X-ray diffraction (XRD) was performed on a D8 Advance Bruker powder diffractometer equipped with a Cu Kα radiation source. Results of nuclear magnetic resonance (NMR) spectroscopy were recorded on Bruker AV 600 spectrometer.

For the general procedure to obtain tetrahydroquinololines, a typical example was as follows: to a dried 12-mL vial equipped with a magnetic stir bar was added *N*-benzylmaleimide **1a** (0.1 mmol, 18.7 mg), 4,*N*,*N*-trimethylaniline **2a** (0.3 mmol, 40.6 mg), $CuFe_2O_4$ nanoparticles (8 mg), *tert*-butylhydro peroxide (TBHP, 70% aqueous solution, 0.15 mmol, 19.3 mg), and CH_3CN (1 mL). The mixture was stirred at 40 °C for 16 h. For GC determination, the crude mixture was added diphenyl ether (0.1 mmol, 17.0 mg) as internal standard after the reaction completed. Aliquots of the mixture were added to a test tube containing brine (2 mL), followed by extraction with ethyl acetate (EtOAc, 3 x 2 mL). Combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated. For isolated yield, the crude reaction mixture was purified by column chromatography (eluent hexanes/EtOAc 5:1) to yield a yellow solid as the desired product **3aa**.

3. Results and discussion

Our study started with investigation of reaction between **1a** and **2a**. As we did perform a thorough study of reaction conditions on a nearly identical reaction between *N*-phenylmaleimide and **2a** [14], only some control experiments were performed herein. The results are shown in Table 1. Following the general procedure, tetrahydroquinoline **3aa** was isolated in 73% yield (entry 1). Omitting the presence of $CuFe_2O_4$ nanoparticles did not furnish **3aa**, confirming the pivotal role of copper catalyst (entry 2). Running the annulation with air as the sole oxidant afforded **3aa** in 24% yield (entry 3). This result indicated that TBHP should be the co-oxidant for this reaction. If the annulation was carried out at room temperature, a 36% yield of **3aa** was obtained (entry 4). Addition of a radical quencher such as TEMPO shut down the annulation (entry 5), which was indicative of a radical-based mechanism.

Table 1: Control experiments



Entry	Variation from standard conditions	Yield of **3aa** (%)
1	none	73^a
2	no $CuFe_2O_4$	$< 5^b$
3	without TBHP	24^b
4	reaction at room temperature	36^b
5	TEMPO (1 equiv) was added	trace

Reaction condition: ***1a*** *(0.1 mmol),* ***2a*** *(0.3 mmol),* $CuFe_2O_4$ *nanoparticles (8 mg), TBHP (70% aqueous solution, 0.15 mmol),* CH_3CN *(1 mL).* ^{a} *Isolated yield.* ^{b} *GC yield.*

It should be noted that $CuFe_2O_4$ nanoparticles were not soluble, thus recoverable after the reaction. Results of XRD characterization of the reused material compared to that of fresh material are shown in Fig 1. Characteristic peaks were still remained, together with results of SEM images (Fig. 2), somewhat confirming that the structure of $CuFe_2O_4$ nanoparticles did not change during the course of the annulation. In fact, using the reused $CuFe_2O_4$ for another catalytic run afforded **3aa** in 67% yield.

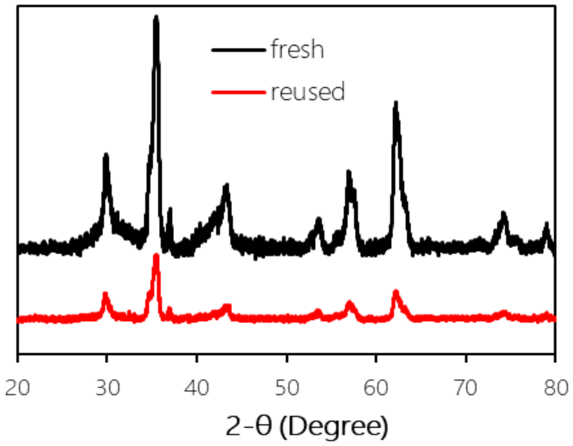


Fig. 1: XRD characterization of fresh and reused $CuFe_2O_4$ nanoparticles

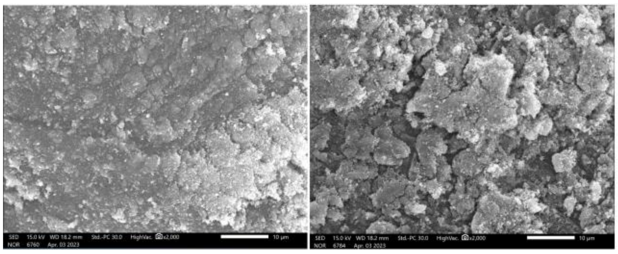


Fig. 2: SEM images of the fresh (left) and reused (right) $CuFe_2O_4$ nanoparticles

Next scope of *N*-benzylmaleimides was investigated. The results are shown in Fig. 3. Fluoro-substituted *N*-benzylmaleimide afforded the product **3ab** in 62% yield, showing that electron-poor arenes should be compatible with reaction conditions. Heteroarenes such as thiophene were also competent substrates, as **3ac** was isolated in 54% yield. Use of alpha-methylbenzyl amine derived maleimide afforded the annulation production **3ad** in 80% yield as a 1:1 mixture of diastereomers.

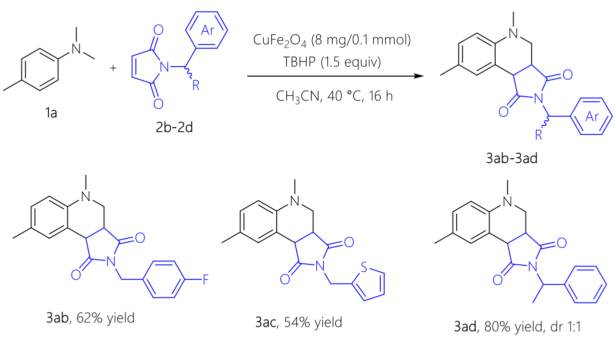


Fig. 3: Scope of maleimides. Reaction conditions: 1a (0.1 mmol), 2b-2d (0.3 mmol), $CuFe_2O_4$ (8 mg), TBHP (70% aqueous solution, 0.15 mmol), CH_3CN (1 mL). Yields are isolated yields

The NMR results of the annulation products were as follows:

2-Benzyl-5,8-dimethyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (**3aa**): ^1H NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.21 (m, 6H), 7.01 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.61 (d, *J* = 8.3 Hz, 1H), 4.68 (d, *J* = 14.4 Hz, 1H), 4.61 (d, *J* = 14.4 Hz, 1H), 3.94 (d, *J* = 9.4 Hz, 1H), 3.46 (dd, *J* = 11.4, 2.7 Hz, 1H), 3.33 (ddd, *J* = 9.4, 4.5, 2.7 Hz, 1H), 2.98 (dd, *J* = 11.4, 4.5 Hz, 1H), 2.76 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.4, 176.5, 146.3, 135.6, 130.7, 129.1, 129.0, 128.5, 128.3, 127.7, 118.8, 112.4, 51.1, 43.6, 42.8, 42.1, 39.4, 20.4.

2-(4-Fluorobenzyl)-5,8-dimethyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (**3ab**): ^1H NMR (600 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 3H), 7.01 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.96 – 6.91 (m, 2H), 6.61 (d, *J* = 8.3 Hz, 1H), 4.64 (d, *J* = 14.3 Hz, 1H), 4.57 (d, *J* = 14.3 Hz, 1H), 3.94 (d, *J* = 9.4 Hz, 1H), 3.45 (dd, *J* = 11.4, 2.7 Hz, 1H), 3.33 (ddd, *J* = 9.3, 4.5, 2.7 Hz, 1H), 2.97 (dd, *J* = 11.4, 4.5 Hz, 1H), 2.75 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.4, 176.4, 162.3 (d, *J* = 246.1 Hz), 146.3, 131.4 (d, *J* = 2.9 Hz), 130.7, 130.2 (d, *J* = 8.3 Hz), 129.2, 129.0, 118.7, 115.4 (d, *J* = 21.3 Hz), 112.4, 51.1, 43.7, 42.1, 42.0, 39.4, 20.4.

5,8-Dimethyl-2-(thiophen-2-ylmethyl)-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (**3ac**): ^1H NMR (600 MHz, $CDCl_3$) δ 7.28 (s, 1H), 7.18 (d, *J* = 5.1 Hz, 1H), 7.03 (d, *J* = 3.2 Hz, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.91 – 6.87 (m, 1H), 6.60 (d, *J* = 8.3 Hz, 1H), 4.84 (d, *J* = 14.8 Hz, 1H), 4.76 (d, *J* = 14.8 Hz, 1H), 3.93 (d, *J* = 9.4 Hz, 1H), 3.45 (dd, *J* = 11.4, 2.6 Hz, 1H), 3.32 (m, 1H), 2.98 (dd, *J* = 11.4, 4.5 Hz, 1H), 2.75 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.9, 176.0, 146.2, 137.2, 130.7, 129.1, 128.9, 127.7, 126.7, 125.8, 118.5, 112.4, 50.9, 43.6, 42.0, 39.4, 37.0, 20.4.

5,8-Dimethyl-2-(1-phenylethyl)-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (**3ad**, mixture of two diastereomers): ^1H NMR (600 MHz, $CDCl_3$) due to overlapping, only one isomer and possible coupling constants are listed δ 7.34 (t, *J* = 7.1 Hz, 2H), 7.29 – 7.18 (m, 4H), 7.03 – 6.98 (m, 1H), 6.61 (dd, *J* = 8.3, 3.0 Hz, 1H), 5.39 (dq, *J* = 21.2, 7.3 Hz, 1H), 3.86 (dd, *J* = 16.8, 9.4 Hz, 1H), 3.39 (td, *J* = 11.6, 3.0 Hz, 1H), 3.26 (dddd, *J* = 16.7, 9.3, 4.6, 3.0 Hz, 1H), 2.96 (ddd, *J* = 11.3, 10.2, 4.6 Hz, 1H), 2.75 (d, *J* = 18.2 Hz, 3H), 2.28 (d, *J* = 8.1 Hz, 3H), 1.76 (dd, *J* = 22.9, 7.3 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) due to complexity, only possible peaks are listed δ 178.5, 178.5, 176.6, 176.5, 146.3, 139.5, 130.7, 129.0, 129.0, 128.9, 128.8, 128.3, 128.3, 127.5, 127.1, 127.0, 119.1, 118.9, 112.4, 112.3, 51.4, 51.3, 50.5, 50.5, 43.3, 43.3, 42.0, 41.9, 39.4, 39.3, 20.4, 20.4, 16.7.

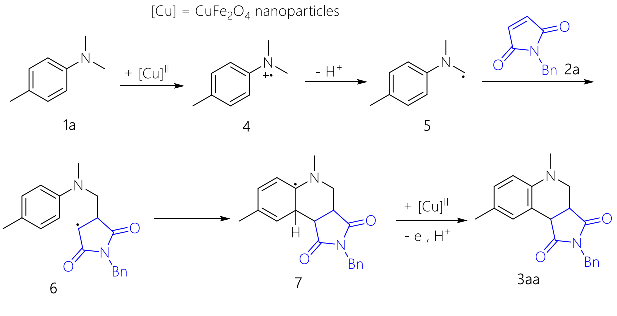


Fig. 4: Mechanistic consideration. Bn = benzyl

Based on results obtained from previous studies [3,6], we next proposed a possible mechanism for this transformation as that shown in Fig. 4. A single electron transfer from **1a** to $CuFe_2O_4$ nanoparticles followed by deprotonation would afford an alphaamino radical (1a → 4 → 5). Addition of the ensuing radical into maleimide 2a followed by cyclization and oxidation (5 → 6 → 7) would afford the desired product 3aa. Given that the annulation of 1a and 2a did not furnish the product 3aa in the presence of a typically used radical scavenger TEMPO (1 equiv) perhaps confirmed such radical-based mechanism.

4. Conclusion

In conclusion we have developed a method for synthesis of tetrahydroquinolines derived from 4,*N*,*N*-trimethylaniline and derivatives of *N*-benzylmaleimides. The reaction progressed feasibly in the presence of heterogeneous, commecially available $CuFe_2O_4$ nanoparticles. A 73% yield of the corresponding product was isolated. Three more examples of tetrahydroquinolines substituted with fluoro, thiophenyl, and alpha-methylbenzyl groups were also obtained in good yields. The XRD and SEM characterization confirmed that the material still remained the structure after being treated under reaction conditions. Early mechanistic thoughts proposed a radical-based mechanism.

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