



Copper(0) in the Ullmann heterocycle-aryl ether synthesis of 4-phenoxy pyridine using multimode microwave heating

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ABSTRACT

The action of nanoparticulate copper catalysts with a mean particle size of 10 nm in the Ullmann ether synthesis is reported using multimode microwave heating and employing stable chloropyridine salts and unactivated phenol, with stabilized copper nanoparticles outperforming other copper catalysts in terms of stability and reusability.

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The Ullmann ether synthesis has been a topic of intense interest since it was first reported by Ullmann and Goldberg in 1905,¹ with many Ullmann reaction products acting as precursors for fine chemicals and pharmaceuticals.² Many refinements have been made, leading to a better understanding of the beneficial ligand effects to be had by tailoring homogeneous copper³ and palladium⁴ catalysts. Moreover, solvent effects in the synthesis have been intensively investigated by Cherng.⁵ Recently, the industrial solvents DMF and DMA have attracted particular attention, being successfully used in conjunction with microwave heating.⁶ These solvents possess strong polar moments and so rapidly heat up when microwaves are applied suggesting green chemical benefits through enhanced yields and decreased energy consumption by selective heating. Hence, for example, the single mode microwave-assisted synthesis of phenoxy pyridines using chloroheterocycles has resulted in higher yields than those that could be achieved with conventional heating, albeit on a small scale.⁷ These heating effects can be amplified, allowing less harsh bulk temperatures, when microwave-absorbing materials are used in conjunction with the catalyst, through hotspot formation at the solid surface.⁸

While it has been used as a catalyst in organic synthesis at the molecular level for many decades, nanoparticulate copper has only recently been deployed. This represents part of a recent research trend towards the use of nanoparticles in process intensification. In this context, exploitable methods now exist for the fabrication of the copper-based nanomaterials Cu(0), CuO and Cu₂O.^{3a} These have been tested in fine chemical syntheses, including C–H (N–H) activation reactions in the quantitative preparation of propargylamines, bis-(4-hydroxy-2-oxothiazolyl)methanes in ionic liquids and the selective aza-Michael reaction of *N*-alkyl- and *N*-arylpiperazines in the presence of aromatic amino or aliphatic hydroxy groups.^{3b} Proof-of-concept has been achieved for the use of nanoparticulate Cu, with nano-Cu₂O-catalyzed Ullmann-type amination using aryl chlorides and very long reaction times,⁹ and nano-Cu-catalyzed etherification using expensive aryl iodides¹⁰ described. Although this use of nanocatalysts offers new opportunities in terms of economic and sustainable processes where homogeneously catalyzed reactions suffer from major drawbacks such as an inability to easily recover the catalyst, product contamination and space-time yield limitations, the sensitivity of nanoparticulate copper towards oxidation has previously limited applications.

We report here what is, to the best of our knowledge, the first use of nanoparticulate Cu in a microwave-assisted Ullmann ether synthesis. We varied both the metal oxidation state and particle size in combination with multimode microwave irradiation. The use of microwave methods was shown to result in a near 20-fold

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increase in heating rate relative to that achievable using an oil bath (Fig. 1) and we compared catalyst effectiveness using both microwave and oil bath heating in the synthesis of 4-phenoxy pyridine from chloropyridine salts and unactivated phenol (Scheme 1).

Rapid microwave heating can be attributed to the uniform volumetric heating effect, which cannot be attained by surface heating using an oil bath. As a consequence, microwave heating offers much higher efficiencies with respect to energy consumption. From the heating profiles it was found that the initial energy consumption for microwave heating was 14.1 kJ in 60 s, while for an oil-bath this was 1.4 MJ in 20 min for the same reaction volume. The use of copper nanocatalysts has been made possible by the development of catalytically stable, zero-valent copper nanoparticles that exhibit long-term oxidation stability. The results indicate a reproducible route to the large-scale application of Ullmann-type chemistry with previously unachievable yields and excellent selectivity. Only after reaction times of more than 5 h could mass spectrometry detect 1-(pyridin-4-yl)pyridin-4(1H)-one as a side-product upon neutralization of the product solution. The results also suggest large-scale reusability of the catalyst in a multimode

microwave set-up. The data are given in Table 1 (and more details are supplied in the Supplementary data).

To prepare 4-phenoxy pyridine, chloropyridine (6 mmol), phenol (9 mmol), Cs₂CO₃ (18 mmol) and DMA (15 ml) were stirred with the corresponding amounts of catalyst (Table 1) in a baffled glass reactor in an oil bath or in the microwave apparatus. Yields were determined by ¹H NMR spectroscopy and the bulk temperatures during the reaction measured with a fibre optic probe and an infrared sensor (Fig. 1).^{11,12} Metallic Cu and Cu(I) and Cu(II) chlorides were obtained commercially, while Cu wire was fabricated mechanically. Poly(*N*-vinylpyrrolidone) (PVP)-capped Cu nanoparticles were made by treating a PVP/ethylene glycol mixture containing Cu(OAc)₂ and sodium hypophosphite coreductant. Purification of the crude suspension with acetone yielded particles with a mean diameter of 9.6 ± 1.0 nm. These were characterized using high-resolution transmission electron microscopy (HRTEM), energy dispersive X-ray spectroscopy (EDS) and powder X-ray diffractometry (PXRD, Fig. 2).¹³

Entries 1–3 (Table 1) reveal that, for metallic Cu, decreasing the particle size (by a factor of 25) enhances the yield of 4-phenoxy pyridine, underlining surface area/turnover relationships for heterogeneous copper catalysts in solid-liquid-type reactions. However, although the experiments were performed under an argon atmosphere, the observation that the solid catalyst changed colour from brown to green suggested copper oxidation in the case of non-nanodimensional catalysts. Further, a trial to recover copper by filtration and washing resulted in <30% recovery. In contrast, nanoparticles sterically protected by PVP as a coordinative capping agent proved very stable to oxidation (entries 4 and 5), giving excellent yields of 4-phenoxy pyridine after 240 min, with 72% catalyst recovery. Importantly, the PVP coating on the surface provides long-term stability not only against nanoparticle agglomeration, but also against oxidation, and it is noteworthy that, after 30 days, EDS and HRTEM confirmed no change in either particle size or oxidation state. It has been previously noted that the use of *N,O*-chelating ligands, such as amides, exhibit a ‘promotional effect’ on Cu(I) catalysts by inhibiting oxidation to Cu(II),¹⁴ with such effects also

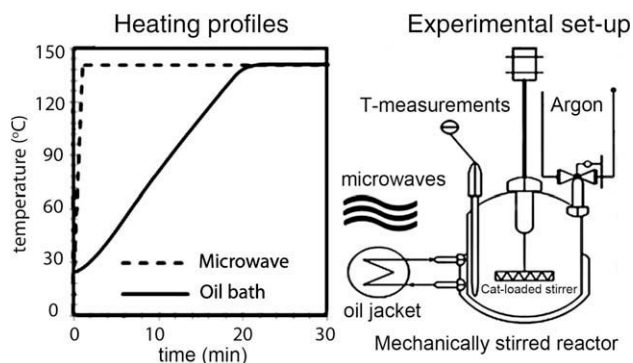
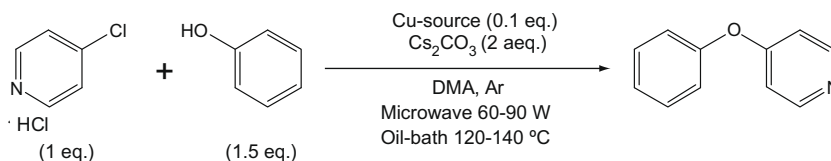


Figure 1. Heating profiles and set-up of microwave and oil bath experiments.



Scheme 1. The Ullmann ether synthesis of 4-phenoxy pyridine.

Table 1
Cu-catalyzed formation of 4-phenoxy pyridine

Entry	Cu-source ^a	Particle size (μm)	T (°C)	Heating method ^b	Time (min)	Yield (%)
1	Metallic Cu	75	120	MW	90	Trace
2	Metallic Cu	45	120	MW	90	3
3	Metallic Cu	3	120	MW	90	20
4	Nano-Cu ^c	9.6 × 10 ⁻³	140	MW	120	63
5	Nano-Cu ^c	9.6 × 10 ⁻³	140	MW	240	80
6	Cu(I)Cl	—	120	MW	40	5
7	Cu(II)Cl ₂	—	120	MW	40	4
8	Cu(I)Cl	—	120	O.B.	90	11
9	Cu(II)Cl ₂	—	120	O.B.	90	Trace
10	Cu-wire	50	140	MW	90	Trace
11	Cu-wire	20	140	MW	90	Trace
12	Cu-wire	50	140	O.B.	90	55
13	Cu-wire	20	140	O.B.	90	90

^a 10 mol %.

^b Microwave (MW) or oil bath (O.B.).

^c Protected by poly(*N*-vinylpyrrolidone).

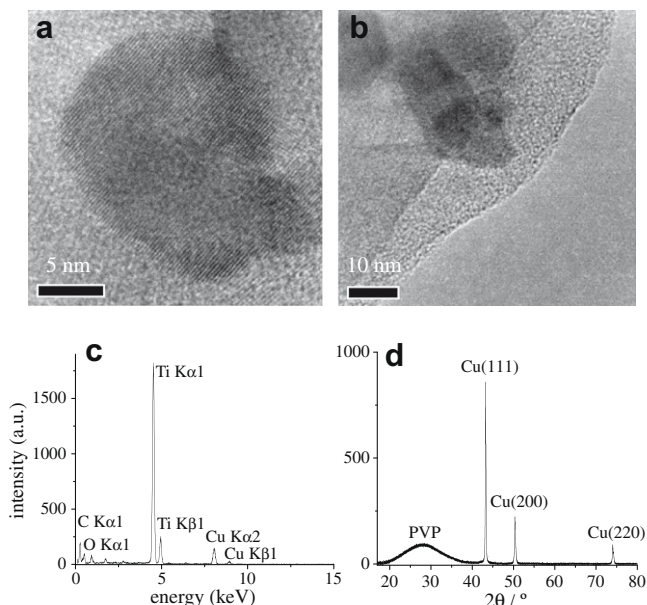


Figure 2. Cu nanoparticles. (a, b) Representative HRTEM images, (c) EDS data (4 nm beam width; C, O and Ti lines from carrier grid material), (d) PXRD data (see also Supplementary data).

reported in studies on the stabilization of nanoparticulate Cu(0) against cuprite formation.¹⁵ Thus, we believe that complex formation between heterogeneous, nanoscale Cu(0) and the keto-functions in PVP stabilizes our nanocatalysts with respect to oxidation. This is underlined by the observations of Gedanken, who in the case of unprotected 50–70 nm particles noted rapid oxidation to Cu(I) in the Ullmann coupling reaction of iodobenzene.¹⁶ Furthermore, the synthesis of Cu₂O-coated Cu nanoparticles for Ullmann-type chloroheterocyclic aromatic substitutions revealed excellent catalytic performance of the uncapped particles, with the protecting oxide layer apparently preventing further oxidation.⁹ Of course, the same protecting property of both Cu₂O and PVP has the drawback that it limits the accessibility of the catalyst surface for the reagents, incurring a diffusion limited reaction rate. Nevertheless, whereas for Cu₂O-coated catalysts, reaction times of 18 h were necessary for Ullmann-type substitutions, our PVP-coated nanocatalysts delivered good-to-excellent yields in only 4 h.

The data clearly reveal that for this type of Ullmann coupling, the most active copper species was Cu(0) (entries 6–9) for both oil bath and microwave-heated systems. Lastly, Ullmann C–O, C–C, C–N and C–S coupling reactions have been extensively surveyed,^{3d} with the use of catalytic amounts of metals generally being successful only with the deployment of noble metal catalysts (e.g., Pd). Plainly, the data presented here allow the conclusion to be drawn that superior results are achievable using relatively inexpensive Cu(0).

Loss of copper over time was examined using copper wires fixed to the mechanical stirrer (Fig. 1). The mass of the wire was determined for each run after washing and drying. Interestingly, oil bath experiments gave good-to-excellent yields (entries 12 and 13) with weight losses of <20%. Moreover, the impact of increased surface area on the yield was clearly demonstrated by using 20 micron wire (entry 13). These data are consistent with the earlier observations using Cu particles (entries 1–3). However, the same procedure was ineffective in microwave experiments, with the wires being undetectable as copper. Instead, black foams were noted, which, based on previous work with Zn and Mg wires and Fe particles,¹⁷ we attribute to Cu carbide species. The origins of their formation are still under investiga-

tion, though it seems probable that the wires act as antennae in the microwave field, carrying high electric loads. When discharges occur, plasma temperatures destroy the wire surface giving carbide-coated copper due to solvent combustion. This process is similar to the concept of electric discharge machining (EDM) by which method metals can be etched using electric discharges.¹⁸

In summary, nanoscopic Cu catalysts have been used to achieve excellent selectivity in the microwave-assisted Ullmann ether synthesis of 4-phenoxy pyridine. This has been enabled using oxidation-resistant nanoparticle catalysts stabilized by a protective anti-agglomerant coating of PVP to deliver good-to-excellent yields in 4 h. Studies are now focusing on the influence of PVP and other capping agents on reaction rate and on the systematic variation of nanoparticle size. Concurrently, we are supporting Cu nanoparticles on glass beads packed into fused silica capillaries as microwave-assisted continuous flow capillary microreactors in which the beads provide the extra surface area required for efficient microreactor activity, and may also accelerate the reaction through hotspot formation. Lastly, microwires have proved excellent catalysts in oil bath-heated systems, and the methods for the synthesis of protected nanowires for microwave applications are being developed.

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Supplementary data

Supplementary data (synthetic and analytical procedures, HRTEM, EDS, PXRD data, nanoparticle size distribution analysis) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.126.

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11. Cu wire was fabricated mechanically by specialized equipment providing an accuracy of 3%. Uniform size distribution according to the suppliers' specifications was subsequently confirmed by optical microscopy.
12. *Synthesis and characterization of 4-phenoxyppyridine*: A mixture of chloropyridine (6 mmol), phenol (9 mmol), Cs₂CO₃ (18 mmol) and DMA (15 ml) in a baffled glass reactor was treated with an appropriate amount of catalyst and the resulting slurry was heated in either a circulating oil bath (Lauda Ecoline steredition 012, type E312, 2.3 kW) or a microwave (Milestones Multimode Microwave, type ETHOS 2450 MHz, 2.5 kW) (120–140 °C for 40–240 min). Bulk temperatures during the reaction were measured using a fibre optic probe and an infrared sensor. The yield of 4-phenoxyppyridine was determined by measuring the ¹H NMR spectra of reaction aliquots against unreacted material. The ¹H NMR data were compared with those in the literature and additional qualitative GC–MS measurements (Shimadzu QP 5000, zebtron column ZB35).
13. *Cu nanoparticle synthesis and characterization*: Copper(II) acetate (0.182 g, 1 mmol) and 0.8 g of poly(*N*-vinylpyrrolidone) (PVP, M(average) = 24000) were added to anhydrous ethylene glycol (120 ml) in a two-necked round-bottomed flask. The resulting mixture was heated to 80 °C and stirred for 2 h. Subsequently, the resulting blue solution was cooled to 0 °C and a solution of sodium hypophosphite monohydrate (0.213 g, 2 mmol) in H₂O (5 ml, millipore) was added promptly. After adjusting the pH value to 9–11 by adding 5 ml of 1 M NaOH (aq, millipore), the reaction mixture was stirred for 1 h at 140 °C to yield a brownish-red colloidal suspension. Aliquots of nanoparticle product were purified for analysis by extracting 50 ml suspensions using excess acetone. After sedimentation of the particles overnight, ca. 90% of the supernatant was decanted and the remaining suspension was centrifuged for 5 min. Upon removal of the acetone layer, the colloidal precipitate was resuspended in DMA (50 ml). Samples for electron microscopy were prepared by droplet coating of DMA suspensions on both Ti and carbon holey film-coated Ni grids and examined using a JEOL JEM-3011 high-resolution transmission electron microscope at nominal magnifications in the range 300,000–800,000. The exact magnification was previously characterized using images of lattice fringes in large (>10 nm) particles of colloidal gold. The electron optical parameters were C_s = 0.6 mm, C_c = 1.2 mm, electron energy spread = 1.5 eV and beam divergence semi-angle = 1 mrad. The mean particle size was calculated to be 9.6 ± 1.0 nm by counting the diameters of 100 particles in the lower magnification images. Data processing/calculation of standard deviation used Origin Pro. 8.0. Elemental composition was elucidated by energy dispersive X-ray emission spectroscopy (EDS, nominal beam width = 4 nm) using a PGT prism Si/Li detector and an Avalon 2000 analytical system. PXRD data were collected on a Roentgen PW3040/60 XPert PRO powder X-ray diffractometer with a high resolution PW3373/00 Cu LFF (unmonochromated) tube at λ = 1.5404 Å (Cu Kα). The powder sample was prepared by solvent evaporation from the colloidal suspensions deposited on the 0.5 mm deep ground area of a glass flatplate sample holder using a microscope slide so that the powder sample was smooth, flat and flush with the sample holder surface. The sample holder was inserted onto the sample stage (PW3071/60 Bracket) such that the sample material was just free of the reference plane of the sample stage.
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