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Copper promoted synthesis of diaryl ethers†

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An efficient protocol using copper based reagents for the coupling of aryl halides with phenols to generate diaryl ethers is described. A copper(I) complex, $[Cu(CH_3CN)_4]ClO_4$, or the readily available copper(II) source, $CuCO_3 \cdot Cu(OH)_2 \cdot H_2O$ (in combination with potassium phosphate), can be used. Aryl halides and phenols with different steric and electronic demands have been used to assess the efficiency of the procedure. The latter source of copper gives better yields under all conditions.

Introduction

The preparation of diaryl ethers by coupling a phenol and aryl halide is an important reaction due to the number of medicinally important compounds such as combretastatin D-2 (antifungal), riccardin (cytotoxin), piperazinomycin (antifungal) and (−)-K-13 (ACE inhibitor) that contain the diaryl ether moiety.[1] These linkages are also present in commercially relevant polyphenylene polymers. Of the methods used for the preparation of diaryl ethers, the classic Ullmann method[2] is the most important,[3] but it is often limited by the need to employ harsh reaction conditions and stoichiometric or greater amounts of copper. A number of interesting and useful techniques for diaryl ether formation have been reported in recent years[4–6] based on Pd and Cu, of which Pd based reagents have shown greater promise.

The use of palladium catalysts for the combination of phenols and aryl halides or sulfonates permits the reaction to be carried out under relatively mild conditions but with the limitation that only electron-deficient aryl bromides can be used.[7] The more general method of coupling a wide range of electron-deficient, electronically neutral and electron-rich aryl halides with a variety of phenols using palladium catalysts suffers from the serious drawback that it requires the use of electron-rich, sterically bulky aryl dialkylphosphines as ligands.[8] There are a few reports where copper(I) has been employed as a catalyst. In one case, the catalyst is $[(CuOTf)_2 \cdot C_6H_6]$, which is unstable in air. It also requires the presence of a carboxylic acid to couple unactivated aryl halides and phenols containing electron-withdrawing groups.[9] Another report employing $[Cu(CH_3CN)_4]PF_6$[10] is limited to coupling aryl bromides with *o*-tertiary and secondary benzamides and sulfonamides. The most recent reports are with 50 mol % CuCl used along with 2,2,6,6-tetramethylheptane-3,5-dione and cesium carbonate to give the coupled product in reasonable yields[11] and with 10 mol % CuI and cesium carbonate in *N*-methylpyrrolidinone (NMP) at 195 °C under microwave irradiation.[12] There are a few studies that report the synthesis of diaryl ethers by the coupling of aryl boronic acids and phenols.[13] There appears to be ample scope for developing a general, inexpensive method for C–O coupling reactions.

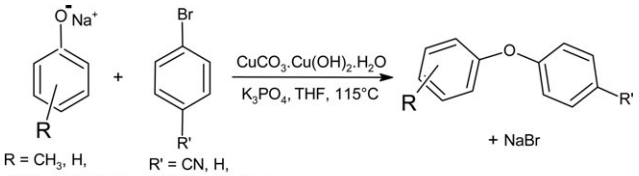
We report here the results from a study carried out with copper(I) complexes to couple a variety of electron-deficient or electron-rich aryl bromides with phenols ranging from the favorable electron-rich, to the difficult-to-couple electron-deficient, phenols. The aim was to find the most convenient copper reagent to carry out the Ullmann coupling. Malachite, the common copper source containing $CuCO_3 \cdot Cu(OH)_2 \cdot H_2O$, also known as basic copper carbonate, is shown to give very good to excellent yields under the conditions described here (Scheme 1).

Results and discussion

Based on our earlier success in mimicking Pd with Cu,[14] our initial studies involved the use of the stable tetrakis acetonitrile complex of copper(I) perchlorate, $[Cu(CH_3CN)_4]ClO_4$, in stoichiometric amounts. The results are summarized in Table 1. Reactions were carried out in refluxing toluene or THF. The reactions attempted in THF as a solvent, under reflux conditions, led to <1% product formation. But if the same reaction mixture was heated at 115 °C in a sealed vial with 25% of the catalyst, 86% yield was obtained (*cf.* entries 5 and 8).

The base used for carrying out the reaction appeared to be a critical factor in the reaction. In the presence of KO^{t}Bu, reasonable formation of the coupled product was achieved in toluene, which otherwise proved to be a poor choice as a solvent. Other bases such as K_2CO_3 or Na_3PO_4 led to zero percent or very poor yields of the product (entries 2 and 3). The hydrolysis reaction observed with the use of KO^{t}Bu (entry 7), could be avoided by using K_2CO_3 to give high yields of the coupled product (entries 8 and 9).

The use of phenoxide appeared to be an essential feature if only mild bases are used. The phenoxide was prepared by the reaction of the phenol with sodium hydride in tetrahydrofuran as the solvent. If the phenol was used in combination with K_2CO_3 no yield was obtained (entry 11). In a separate reaction,



Scheme 1 Reactions conditions for synthesis of diaryl ether.

† Electronic supplementary information (ESI) available: complete spectroscopic data for all the coupled diaryl ethers. See http://www.rsc.org/suppdata/nj/b4/b401179a/

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Table 1 Reaction conditions for coupling 4-methylphenol and 4-bromobenzonitrile using $[Cu(CH_3CN)_4]ClO_4$

Entry	Solvent	T/°C	Additional base	Catalyst/mol %	Time/h	Yield (%)
1	Toluene	110	KO^{t}Bu	100	24	60
2	Toluene	115	K_2CO_3	100	20	0
3	Toluene	115	Na_3PO_4	100	20	1
4	Toluene	115	K_2CO_3	25	24	4
5	THF	58	K_2CO_3	25	24	1
6	THF	115	K_2CO_3	100	18	17[a]
7	THF	115	KO^{t}Bu	25	18	0[b]
8	THF	115	K_2CO_3	25	18	86[a]
9	THF	115	K_2CO_3	10	18	93[a]
10[c]	THF	115	KO^{t}Bu	25	18	60[a]
11[c]	THF	115	K_2CO_3	25	18	0
12	THF	115	–	25	18	69[a]
13	THF	115	K_2CO_3	–	18	15

[a] About 5–8% of amide formation was observed. [b] Complete conversion to the amide was observed [eqn. (1)]. [c] The phenol was not converted to the sodium phenolate in these runs.

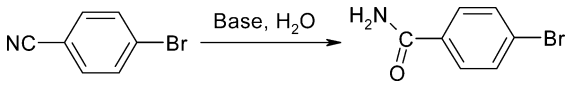
the phenoxide was used (2.2 equiv) in the absence of an additional base, leading to about 69% of the required product (entry 12).

Thus, reactions carried out with THF as a solvent proceeded efficiently with a combination of K_2CO_3 as a base and the sodium phenolate. Contrary to what is known about Ullmann coupling, the reaction proceeded in a catalytic fashion and was hindered by the presence of stoichiometric amounts of copper(I). Thus, when the quantity of $[Cu(CH_3CN)_4]ClO_4$ was reduced from 100 to 25 to 10 mol %, the yield of the product increased in both solvents: toluene (entries 2 and 4) and THF (entries 6, 8 and 9). However, the yield was significantly lower (56%) when 5 mol % catalyst was used. So the optimized conditions were identified as a combination of aryl bromide and 1.2 equiv of sodium aryl oxide, with 10 mol % of $[Cu(CH_3CN)_4]ClO_4$, and 1.5 equiv of pulverized K_2CO_3, in a sealed vial with THF as the solvent kept at 115 °C for 18 h. These conditions were then tested for the coupling of other substrates in a systematic fashion. Note that it is possible to avoid the sealed tube reaction by carrying out the reaction in diglyme at 115 °C.

In the absence of the catalyst, only 15% product is obtained, showing that copper is essential to promote the reaction (Table 1, entry 13). Activated aryl bromides gave excellent yields of the coupled product with a variety of phenols (Table 2). However, rather poor yields were obtained with unactivated aryl bromides such as bromobenzene. In these cases, surprisingly, an increase in the copper concentration to 25 mol % gave better results. In the case of unactivated aryl bromides, the coupled product was obtained in good yield except in the case of 4-chlorophenol and 4-methoxyphenol.

The different efficiencies with which 4-bromobenzonitrile and bromobenzene are converted suggest that the mechanism involves oxidative addition in the rate-determining step. In the case of the bromobenzene, the aryl halide is unactivated and oxidative addition occurs efficiently. After the catalytic cycle CuX is generated. Subsequent oxidative additions to the copper(I) intermediate will occur only if the halide is removed from the coordination sphere of copper (Scheme 2).

Since copper in the +2 state can be reduced *in situ* by the phenoxide to copper(I), we attempted a reaction with catalytic amounts of $CuCO_3 \cdot Cu(OH)_2 \cdot H_2O$, which is readily available. In this case, some amount of the hydrolysis product identified as the amide was obtained. It is well-documented that nitriles can be easily converted to the amide in the presence of base and water [eqn. (1)]:[15]



(1)

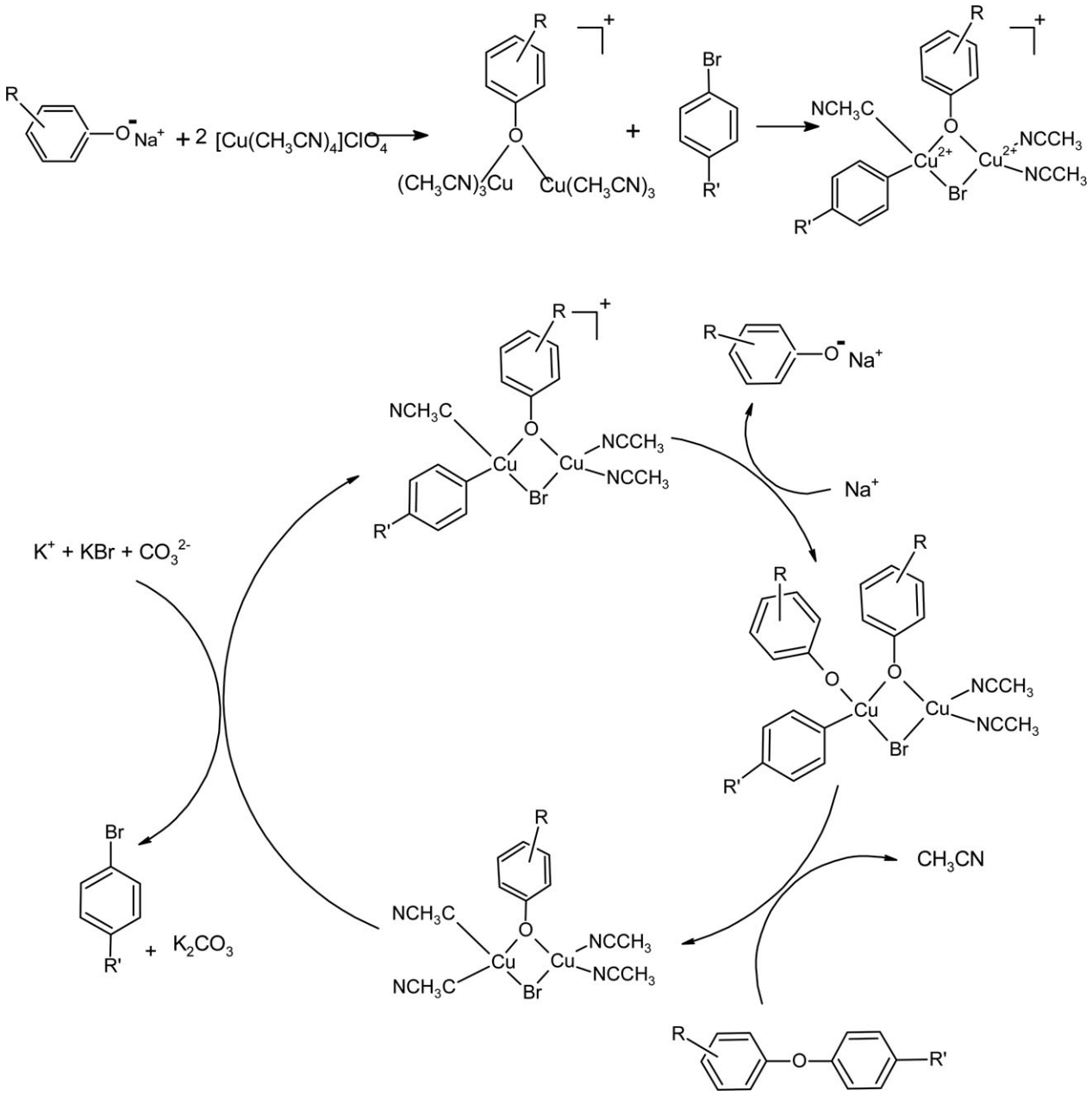
A strong base is required for this reaction to take place. The water required for this reaction could probably be from the catalyst, which contains one molecule of water. However, hydrolysis could be suppressed with K_3PO_4 as the base instead of K_2CO_3. Hence K_3PO_4 was retained as the reagent of choice in subsequent reactions. Where hydrolysis reduced the yield in reactions promoted by $[Cu(CH_3CN)_4]ClO_4$, as in entry 4 of Table 2, the use of K_3PO_4 was found to be beneficial.

The catalytic transformation was attempted with different phenols having electron-donating and -withdrawing substituents such as 4-methylphenol, phenol, 4-methoxyphenol and 4-chlorophenol. Excellent yields were obtained for the 4-bromobenzonitrile and good yields for the bromobenzene reactions with $CuCO_3 \cdot Cu(OH)_2 \cdot H_2O$ as the copper catalyst. 4-Bromoacetophenone also performed satisfactorily. However, 4-bromobenzaldehyde gave a mixture of the desired diaryl

Table 2 Results with catalytic $[Cu(CH_3CN)_4]ClO_4$ under optimized conditions[a]

Entry	Aryl halide	Phenol	Catalyst/mol %	Yield (%)
1	4-Bromobenzonitrile	4-Methylphenol	10	89
2	4-Bromobenzonitrile	Phenol	10	96
3	4-Bromobenzonitrile	4-Methoxyphenol	10	92
4	4-Bromobenzonitrile	4-Chlorophenol	10	83
5	Bromobenzene	4-Methylphenol	–	7
6	Bromobenzene	4-Methylphenol	10	73
7	Bromobenzene	4-Methylphenol	25	84
8	Bromobenzene	Phenol	10	40
9	Bromobenzene	Phenol	25	83
10	Bromobenzene	4-Methoxyphenol	10	51
11	Bromobenzene	4-Methoxyphenol	25	29
12	Bromobenzene	4-Chlorophenol	10	16
13	Bromobenzene	4-Chlorophenol	25	20

[a] Reaction was carried out for 18 h in a sealed vial with 1.0 ml of THF as solvent with indicated mol % of $[Cu(CH_3CN)_4]ClO_4$, 1.5 equiv K_2CO_3, 1.2 equiv sodium salt of the phenoxide and 1 equiv of the aryl bromide.



Scheme 2 Mechanism of diaryl ether formation.

ether along with 4′-bromo-2-hydroxybenzophenone, a result of Friedel–Crafts reaction followed by benzylic alcohol oxidation; this is being investigated further. The results obtained are shown in Table 3.

Conclusion

An efficient method using low amounts of solvent and an inexpensive, readily available reagent, $CuCO_3 \cdot Cu(OH)_2 \cdot H_2O$, has been devised for the coupling of various aryl bromides with different phenols. The circumstances under which copper, either copper(II) or copper(I) sources, acts as a catalyst and the conditions under which it functions in a stoichiometric fashion have been highlighted. The method eliminates the need to make unstable copper(I) precursors for these reactions. The reaction works effectively even for substrates like 4-bromobenzyl alcohol, which is an electron-rich halide. Moderate yields are seen for its reaction with electron-deficient phenols like 4-chlorophenol. Aldehyde groups do not seem to be compatible with these reaction conditions, for 4-bromobenzaldehyde could not be used to get the coupled diaryl ether using this procedure.

Experimental

General remarks

The tetrahydrofuran solvent for the reaction was dried under sodium ketyl radical. 4-Bromobenzonitrile and potassium phosphate were obtained from Lancaster and bromobenzene and malachite were obtained from BDH; phenol, 4-methylphenol, 4-chlorophenol were obtained from S.D.Fine-Chem. Ltd.; 4-methoxyphenol was obtained from Sisco Chem Pvt. Ltd.; K_2CO_3 was obtained from Ranbaxy; sodium hydride (60% in mineral oil) from Aldrich, USA, was analysed using standard procedures prior to use and potassium *t*-butoxide (Aldrich, USA) was used as received. $[Cu(CH_3CN)_4]ClO_4$[16] and 4-bromobenzyl alcohol[17] were prepared by literature procedures.

^{1}H NMR spectra were recorded on a Bruker ACF 200 MHz instrument and ^{13}C NMR on a Bruker AMX 400; high resolution electrospray ionisation mass spectra (HRESMS) were acquired on a Micromass Q-Tof micro. All the compounds prepared were characterised by ^{1}H NMR and proton decoupled ^{13}C NMR spectra in $CDCl_3$ as the solvent with tetramethylsilane (TMS) as the internal reference (Details are available in the

Table 3 Results with $CuCO_3 \cdot Cu(OH)_2 \cdot H_2O$ (5 mol %) under optimized conditions[a]

Entry	Aryl halide	Phenol	Yield (%)
1	4-Bromobenzonitrile	4-Methylphenol	>99
2	4-Bromobenzonitrile	4-Methoxyphenol	>99
3	4-Bromobenzonitrile	Phenol	>99
4	4-Bromobenzonitrile	4-Chlorophenol	>99
5	4-Bromobenzonitrile	2,4-Dimethylphenol	72
6	4-Bromobenzonitrile	2,6-Dimethylphenol	77
7	Bromobenzene	4-Methylphenol	79
8	Bromobenzene	4-Methoxyphenol	81
9	Bromobenzene	Phenol	91
10	Bromobenzene	4-Chlorophenol	78
11	Bromobenzene	2,4-Dimethylphenol	48
12	Bromobenzene	2,6-Dimethylphenol	53
13	4-Bromoacetophenone	4-Methylphenol	74
14	4-Bromoacetophenone	4-Methoxyphenol	80
15	4-Bromoacetophenone	Phenol	79
16	4-Bromoacetophenone	4-Chlorophenol	69
17	4-Bromoacetophenone	2,4-Dimethylphenol	70
18	4-Bromoacetophenone	2,6-Dimethylphenol	80
19	4-Bromobenzyl alcohol	4-Methoxyphenol	56
20	4-Bromobenzyl alcohol	4-Chlorophenol	45

[a] Reaction was carried out for 18 h in a sealed vial with 0.8 ml of THF as solvent with 5 mol % $CuCO_3 \cdot Cu(OH)_2$ H_2O, 1.5 equiv K_3PO_4, 1.2 equiv sodium salt of the phenoxide and 1 equiv of the aryl bromide.

supporting information). Gas chromatographic analysis was carried out on a Chemito GC 7610 using FID for detection. The yields obtained from the GC analysis were corrected by obtaining response factors for the isolated product and the starting aryl bromides and are averages of 2–4 runs.

General procedure for the reaction using $[Cu(CH_3CN)_4]ClO_4$

Finely powdered K_2CO_3 (0.2 g, 1.45 mmol), 4-bromobenzonitrile (0.182 g, 1 mmol) and $[Cu(CH_3CN)_4]ClO_4$ (0.033 g, 0.1 mmol), along with a magnetic stir bar, are loaded into a vial capped with a septum and fitted with a side arm attached to a double manifold. The aryl oxide is prepared in a two necked round bottom flask under nitrogen from 4-methylphenol (0.12 ml, 1.2 mmol.) dissolved in about 1.2–1.5 ml of tetrahydrofuran stirred with sodium hydride (0.056 g, 1.2 mmol) until a clear solution of the sodium aryl oxide is formed. The aryl oxide is then transferred to the vial through a syringe. The vial is then purged with nitrogen, cooled with liquid nitrogen and sealed after evacuating. The sealed vial is then immersed in an oil bath maintained at 115 °C and the contents stirred for the required time. At the end of the reaction, the vial is cooled, broken and the contents filtered through a short silica column with ethyl acetate. The eluent is collected and concentrated to 4 ml and analysed by GC.

General procedure for the reaction using $CuCO_3 \cdot Cu(OH)_2 \cdot H_2O$

Finely powdered K_3PO_4 (0.25 g, 1.2 mmol), 4-bromobenzonitrile (0.182 g, 1 mmol) and $CuCO_3 \cdot Cu(OH)_2 \cdot H_2O$ (0.012 g, 0.05 mmol) are reacted using a procedure similar to the one given above except that the solvent used is reduced to 0.8 ml of tetrahydrofuran. At the end of the reaction, the vial is cooled, broken and the contents filtered through a short silica column with ethyl acetate. The eluent is collected and concentrated to 4 ml and analysed by GC. The maximum scale attempted for a sealed tube reaction was 5 times the amount given in this reaction.

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