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Copper(I)-assisted Halogen-halogen Exchange as a Method to Improve Copper-promoted Biaryl Syntheses

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The reaction between 1,3-dinitrobenzene, iodoarenes, and copper(I) oxide in quinoline at about 220° affords 2,6-dinitrobiphenyls in fair yields. It is possible to extend this reaction to other haloarenes if copper(I) iodide is present in the reaction mixture, the iodoarene being generated *in situ* by halogen-halogen exchange.

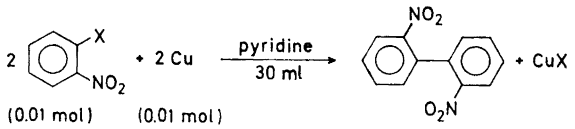
The use of halogen-halogen exchange with copper(I) iodide also allows bromoarenes to be used in the Ullmann reaction at temperatures where the reaction rate otherwise is too slow.

Copper and copper salts are used, both as catalysts and as reactants, in a variety of organic reactions of haloarenes. In this paper the possibilities of using less reactive halogenoarenes in two coupling reactions will be discussed. One is the Ullmann biaryl synthesis and the other is the copper-promoted coupling of 1,3-dinitrobenzene (or 1,3,5-trinitrobenzene) with iodoarenes [2,3] to give unsymmetrical nitrobiaryls.

Some cases of copper-promoted halogen-halogen exchange have previously been observed by Hardy and Fortenbaugh [4] and by Nilsson.[5] Bacon and Hill subsequently studied the copper(I)-assisted halogen-halogen exchange between haloarenes and copper(I) halides in various solvents.[6] They reported that such halogen-halogen exchanges take place at temperatures as low as 110° even for unactivated haloarenes. This reaction seemed to offer a possibility of converting bromoarenes to iodoarenes by using copper(I) iodide. The iodoarene thus formed would be expected to react more easily in subsequent coupling reactions.

The effect of adding copper(I) iodide in the Ullmann reaction has been studied in the formation of 2,2′-dinitrobiphenyl from 2-iodo- and 2-bromonitrobenzene and copper powder in pyridine. A fair yield of 2,2′-dinitrobiphenyl is obtained when 2-iodonitrobenzene is treated with copper at 80° (6 h) but only a few per cents' yield of biphenyl is formed when the 2-bromonitrobenzene is used (Table 1).

Table 1. Ullmann reactions with and without the addition of copper(I) iodide (80°, 6 h).

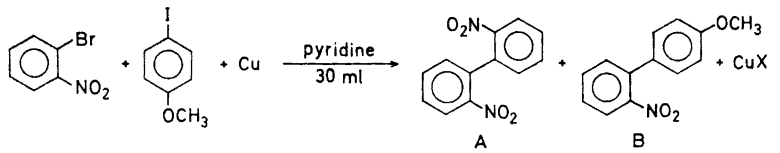


Experiment No.	X	CuI mol	Yield 2,2′-dinitrobiphenyl, %
1	I	–	46
2	I	0.01	52
3	Br	–	3
4	Br	0.01	12

The addition of copper(I) iodide in the reaction of 2-bromonitrobenzene with copper gives a significantly higher yield of biphenyl. The difference in the yields of 2,2′-dinitrobiphenyl obtained in the reactions of 2-iodonitrobenzene with and without copper(I) iodide present may not be significant. The reproducibility in heterogeneous, copper-promoted reactions is often moderate,[7] one complication being the reductive displacement of the halogen. This side reaction is often favoured by the presence of nitro or other unsaturated groups.[7] However, under the conditions used in the present experiments there was little reduction (a few per cents).

Since mixed Ullmann couplings offer a method of preparing unsymmetrical biaryls it was also of interest to examine the influence of copper(I) iodide in the competitive formation of symmetrical and unsymmetrical biaryls (Table 2).

Table 2. Mixed Ullmann couplings with and without the addition of copper(I) iodide (80°, 6 h, 0.01 mol scale).



Experiment No.	CuI mol	Yield A %	Yield B %
5	–	3	0.4
6	0.01	13	0.3

As is shown in Table 2 the addition of copper(I) iodide increases the amount of 2,2′-dinitrobiphenyl (A) only. 4,4′-Dimethoxybiphenyl was not formed.

The reaction between iodoarenes, nitroarenes, and copper(I) oxide in quinoline at about 220° offers convenient preparations of 2,6-dinitro- or 2,4,6-trinitrobiphenyls.[2,3] A limitation of the reaction is that in general only iodoarenes react at an acceptable rate. Copper-assisted halogen-halogen exchange could offer a possibility of increasing the production of nitrobiaryls.

Bacon and Hill showed that exchange of halogens in unactivated haloarenes takes place at temperatures as low as 110 – 115°. They found the second order rate constant for the conversion of 1-bromonaphthalene to 1-chloronaphthalene to be $3.3 - 6.2 \times 10^{-5}$ l/mol sec at 115° in pyridine. The rate "constant" was slightly higher at lower concentrations. Since the coupling reaction of 1,3-dinitrobenzene and 4-iodotoluene usually is run at about 220° the rate of copper(I)-assisted halogen-halogen exchange between 4-bromotoluene and copper(I) iodide was studied at this temperature. Although Bacon and Hill found the highest rate of reaction for the halogen-halogen exchange in pyridine *N*-oxide or in dimethyl sulphoxide the reaction, in this case, has to be run in quinoline which is the best solvent for the coupling reaction.[2]

The exchange was found to be reversible and the rate expression was first order in each reactant (eqn. 1). Fig. 1 illustrates the second-order reaction-rate plot which was obtained.

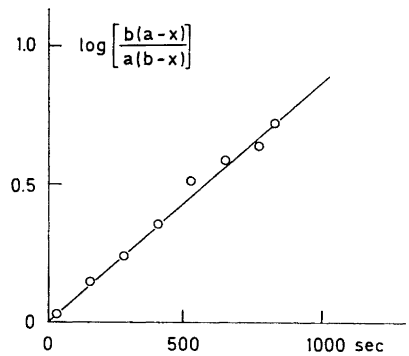
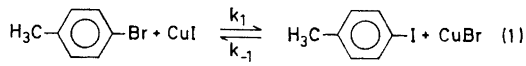


Fig. 1. Second-order plot for halogen exchange between *p*-iodotoluene and copper(I) bromide in quinoline at 220° (for details see Experimental part).



$k_1 \times 10^3 = 1.4 \pm 0.1$ l/mol sec

$k_{-1} \times 10^3 = 8.7 \pm 0.6 \pm$ l/mol sec

From a practical point of view, the approximate rate constants show that in the reaction between equimolar amounts of 4-bromotoluene and copper(I) iodide 90 % equilibration is reached within 20 min.

Table 3 shows the results from the reaction of 1,3-dinitrobenzene, 4-bromotoluene and copper(I) oxide in quinoline with and without copper(I)

iodide present. For comparison the same coupling reaction was run with 4-iodotoluene both with and without the addition of copper(I) iodide and also with 4-bromotoluene and copper(I) bromide. The variations in yield are probably within ± 5 %.

The presence of copper(I) iodide obviously accounts for the much higher yield of 4-methyl-2′,6′-dinitrobiphenyl in experiments 13 and 14 as compared to that obtained in experiments 15 and 16. The differences in yield between the experiments 9, 10 and 11, 12 are well within the experimental error. Coupling of 4-bromotoluene in presence of copper(I) bromide gave a somewhat higher yield. Similarly copper(I) iodide seemed to increase the yield in the reaction between the iodoarene and the nitroarene. This is similar to the results shown in Table 1.

In the present communication it is not intended to comment upon the mechanism of the reactions involved. Although the mechanisms are not finally clarified [2,6,8,9] the reactions are important from the view of synthesis. The reported combination of methods offers a way of using less reactive bromoarenes instead of iodoarenes in some coupling reactions. The possibility to extend the *in situ* generation of haloarenes to other copper-promoted reactions is under study.

EXPERIMENTAL

Gas chromatographic analyses were run on an Aerograph 204 – 1B fitted with a hydrogen flame ionization detector (Column: SE – 30, 5 %, on Chromosorb W, 6 ft, operated at 225°) in combination with an Aerograph 480 digital integrator. Mass spectra were run on an LKB-9000 mass spectrometer. Thin-layer chromatograms (TLC) were run on fluorescent silica gel and developed with chloroform/carbon tetrachloride (1:4).

General procedure for experiments 1 – 6 (*cf.* Tables 1 and 2). The copper powder used was of electrolytical grade. The pyridine (analytical grade) was distilled before use. The reactions (0.01 mol scale) were run in a three-necked flask fitted with a stirrer and a condenser; the flask was heated in a silicone oil bath (80 ± 0.5°).

After the reaction, the solution was allowed to cool and ether (70 ml) and an internal reference for the gas chromatographic analysis (4-methoxybiphenyl, 0.300 g) were added. The mixture was then extracted with hydrochloric acid (2 M), the ether phase was filtered, washed with water and dried (Na_2SO_4). The ether solution was used for gas chromatographic analysis.

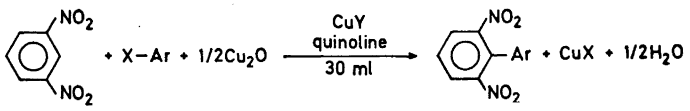
Identification of products. The solution from experiment 4 was analysed by mass spectrometry and the product proved to be the expected 2,2′-dinitrobiphenyl (parent ion at *m/e* 244, fragmentation in agreement with that given by authentic 2,2′-nitrobiphenyl). The small amounts of 4-methoxy-2′-nitrobiphenyl (B) proposed to be formed in experiments 5 and 6 gave the same retention time as did authentic 4-methoxy-2′-nitrobiphenyl on gas chromatograms. TLC on the ether solutions from experiments 1 – 6 showed the presence of 2,2′-dinitrobiphenyl.

General procedure for experiments 7 – 22 (*cf.* Table 3). The quinoline (Merck) used as solvent was dissolved in hydrochloric acid and extracted with ether to remove hydrocarbon impurities (mainly 2-methylnaphthalene). The quinoline recovered after alkalisation was distilled through a Vigreux column and redistilled immediately before use.

The reactions (0.01 mol scale) were run in a three-necked flask (100 ml) fitted with a stirrer and a condenser under dry, oxygen-free nitrogen (40 ml/min). The flask was heated in a silicone oil bath at 220 ± 0.5°. In each run the quinoline (30 ml) was heated to the reaction temperature before the other reactants and an internal reference for the gas chromatographic analysis (4-methoxybiphenyl, 0.300 g) were added.

In experiments 7 and 8 samples (0.20 ml) were taken with a syringe and mixed with hydrochloric acid (2 M, 1.5 ml) and benzene (0.5 ml) in test-tubes. After the test-tubes

Table 3. Copper-promoted coupling of nitroarene and haloarene in quinoline solution at 220° (0.01 mol scale).



Experiment No.	X–Ar	Reaction time, h	CuY, mol		Yield % 4-methyl-2′,6′-dinitrobiphenyl
9,10	*p*-iodotoluene	6	–	–	57
11,12	*p*-iodotoluene	6	CuI	0.01	59
13,14	*p*-bromotoluene	6	CuI	0.01	32
15,16	*p*-bromotoluene	6	CuBr	0.01	6
17,18	*p*-bromotoluene	6	–	–	2
19	*p*-bromotoluene	6	CuI	0.001	24
20	*p*-chlorotoluene	24	–	–	< 0.1
21	*p*-chlorotoluene	6	CuI	0.01	< 0.1
22	*p*-bromotoluene	24	–	–	9

had been shaken and centrifuged, the benzene phases were analyzed by gas chromatography.

Experiment 7. The reaction between *p*-iodotoluene (0.01 mol) and copper(I) bromide (0.01 mol) in quinoline was followed until no further change in composition (71 % conversion of *p*-iodotoluene to *p*-bromotoluene, equilibrium constant 0.17 (eqn. 1), initial concentration of reactants *ca.* 0.28 M).

Experiment 8. The reaction between *p*-bromotoluene (0.01 mol) and copper(I) iodide (0.03 mol) in quinoline gave 47 % conversion of *p*-bromotoluene to *p*-iodotoluene at equilibrium.

Experiment 9–22. The reaction mixture was allowed to cool and ether (150 ml) was added. The solid copper(I) iodide-quinoline complex was filtered off and the filtrate extracted with hyhrochloric acid (2 M), washed with water and dried (Na_2SO_4). After evaporation of the ether, the residue was dissolved in acetone and diluted to 25 ml. The acetone solution was used in the gas chromatographic analysis.

Identification of products. The formation of 4-methyl-2′,6′-dinitrobiphenyl in experiments 9 and 10 has previously been demonstrated.[10] The products from experiments 13 and 14 were shown to be identical with 4-methyl-2′,6′-dinitrobiphenyl (prepared as in experiments 9 and 10 [2]) by identical GLC-retention times, identical IR spectra, and identical mass spectra (parent ion at *m/e* 258, fragmentation as expected for nitrobiphenyls).

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REFERENCES

1. Fanta, P. E. *Chem. Rev.* **64** (1964) 613.
2. Björklund, C. and Nilsson, M. *Acta Chem. Scand.* **22** (1968) 2338.
3. Björklund, C. and Nilsson, M. *Acta Chem. Scand.* **22** (1968) 2581.
4. Hardy, W. B. and Fortenbaugh, R. B. *J. Am. Chem. Soc.* **80** (1958) 1716.
5. Nilsson, M. *Acta Chem. Scand.* **12** (1958) 537.

6. Bacon, R. G. R. and Hill, H. A. O. *J. Chem. Soc.* **1964** 1097.
7. Bacon, R. G. R. and Stewart, O. J. *J. Chem. Soc.* **C 1969** 301.
8. Björklund, C., Nilsson, M. and Wennerström, O. *Acta Chem. Scand.* **24** (1970) 3599.
9. Lewin, A. H. and Cohen, Th. *Tetrahedron Letters* **1965** 4531.
10. Forrest, J. *J. Chem. Soc.* **1960** 574.

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