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CATALYTIC EFFECTS IN THE COUPLING OF ARYL HALIDES BY CUPROUS OXIDE

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Copper-promoted organic reactions of more than one kind (1) are liable to occur simultaneously, as when, for example, aryl halides and nucleophilic reagents are heated in a solvent with a suspension of cuprous oxide. Using a system of this type with the object of preparing diaryl ethers (2), we frequently observed competition between the desired nucleophilic substitution by a phenol (A), and substitutive reduction (B), also due to the phenol; coupling of the halide (C) occurred exceptionally, as a minor reaction, when o-bromonitrobenzene was used:

$$2\mathrm{ArHal} + 2\mathrm{Ar'OH} + \mathrm{Cu_2O} \longrightarrow 2\mathrm{ArOAr'} + 2\mathrm{CuHal} + \mathrm{H_2O} \qquad (A)$$

$$2\mathrm{ArHal} + x\mathrm{Ar'OH} + \mathrm{Cu_2O} \longrightarrow 2\mathrm{ArH} + 2\mathrm{CuHal} + \mathrm{H_2O} + \text{dehydrogenation products of Ar'OH} \qquad (B)$$

$$2\mathrm{ArHal} + \mathrm{Cu_2O} \longrightarrow \mathrm{Ar{\cdot}Ar} + \mathrm{CuO} + \mathrm{CuHal_2} \qquad (C)$$

Other investigations have been carried out (3), with a variety of potential hydrogen donors, to discover whether reduction of the halide, similar in type to (B), could be achieved as the principal reaction. Because o-bromonitrobenzene is relatively easily thus reduced (giving nitrobenzene), it was convenient to use this halide to test the reducing capacity of reagents. and in such experiments it regularly afforded the biaryl (2,2'-dinitrobiphenyl) as a by-product. Among the other halides then under examination, only p-bromonitrobenzene behaved similarly.

We have looked more closely at the possibility of preparing biaryls with the aid of cuprous oxide, partly because it is unusual for copper(I) species to act as reductants in Ullmann-type coupling reactions, and partly because the reaction shows considerable sensitivity to catalytic and solvent influences.

Thus, when the reduction experiments were performed with boiling dimethylacetamide (at 166°) as solvent, the yield of by-product (2,2'-dinitrobiphenyl) was only 1-8% (average, 5%)

in 19 cases, but there was unexpectedly a significant increase (to 11-17%) when phenylhydrazine or benzalaniline happened to be used as hydrogen donors. Likewise, when the solvent was boiling 2,4,6-collidine (at 170°), the yield of the biaryl was 2-5% in 8 cases, but increased significantly (to 16-20%) in the presence of a particular donor, 2,6-di-t-butyl-4-methylphenol. Experiments which happened to be carried out in boiling pyridine (at 115°), in the absence of a hydrogen donor, afforded the biaryl in 30-35% yield. By contrast, the yield was only 8-15% when o-bromonitrobenzene was treated with cuprous oxide at ~195°, without either a solvent or a hydrogen donor being present, i.e., under conditions similar to those conventionally used for the Ullmann coupling of halides (4) with copper metal.

From these incidental observations it could be concluded that for particular halides, in particular solvents, cuprous oxide is capable of effecting a reasonable degree of coupling, and that the reaction may be catalysed. Subsequent results substantiate these views. Pyridine is the best solvent so far discovered, and in this medium coupling appears to be a general reaction of o-nitroaryl bromides or iodides, with a varying amount of competition from reduction (giving the dehalogenated nitro-compound) or from nucleophilic substitution (giving, e.g., nitrophenols).

Even when particular compounds had not been added to the reaction system, the possibility of catalysis was indicated by observations that the rate of coupling varied with the sample of pyridine used, and that reaction rates were slower in the purer samples. For example, after 24 hr. at the boiling point, the yield of 2,2'-dinitrobiphenyl was 75% in one sample of pyridine, but attained only about 30% in this period of time when purer grades were used. The higher yields could be attributed to adventitious catalysts, since the addition of small amounts of certain substances, such as n-octylamine or phenylhydrazine, was found to stimulate coupling in the purer samples of pyridine. The amount of catalyst to be added is somewhat critical, probably because it may also participate in the competing reactions.

Cohen and his co-workers (5) have recently observed catalytic effects by pretreatment of copper metal, which was then used for the Ullmann coupling of p-iodotoluene, carried out without solvent. The characteristics of our reaction system seem to be different from theirs, since we find catalysts to be effective in the liquid reaction medium, but not when used in prior treatment of the copper species. Also, the effect of oxygen appears to be different in the two systems.

Some conclusions may be drawn:

(a) Our observations, considered in conjunction with others which have recently been reported (6) for the related process of biphenylene production from halides, demonstrate a need to modify the traditional view that Ullmann coupling (4) necessarily requires copper metal, whereas the biphenylene synthesis (7) necessarily requires cuprous oxide.

(b) The demonstrated susceptibility to catalysis may be at least part of the explanation for the poor degree of reproducibility which frequently attends both biaryl and biphenylene preparations (8).

(c) Although certain favourable effects of a solvent or catalyst in Ullmann reactions, when previously observed, have been attributed to cleansing of the surface of the copper (5,9), we suggest that these species could also be more intimately involved, e.g, as participants in induced reactions or as ligands in intermediate copper complexes. Some mechanistic aspects of Ullmann-type coupling (1,4,10) are at present being studied here.

REFERENCES

1. R. G. R. Bacon and H. A. O. Hill, Quart. Rev., **19**, 95 (1965).
2. R. G. R. Bacon and O. J. Stewart, J. Chem. Soc., 4953 (1965).
3. R. G. R. Bacon, S. C. Rennison, and O. J. Stewart, Proc. Chem. Soc., 409 (1964);
   R. G. R. Bacon and O. J. Stewart, in the press.
4. P. E. Fanta, Chem. Rev., **38**, 139 (1946); **64**, 613 (1964).
5. A. H. Lewin, M. J. Zovko, W. H. Rosewater, and T. Cohen, Chem. Comm., 80 (1967).
6. J. C. Salfeld and E. Baume, Tetrahedron Letters, No. **28**, 3365 (1966).
7. W. Baker, J. F. W. McOmie, *et al.*, J. Chem. Soc., 1476 (1954), and later papers.
8. E.g., P. H. Gore and G. K. Hughes, J. Chem. Soc., 1615 (1959); C. R. Harrison, J. F. W. McOmie, J. B. Searle, J. P. Smith, J. O. Jenkins, and J. W. Smith, J. Chem. Soc., C, 1769 (1966); see also comments in Refs. 4 and 1.
9. R. S. W. Braithwaite and P. F. Holt, J. Chem. Soc., 3025 (1959).
10. A. H. Lewin and T. Cohen, Tetrahedron Letters, No. **50**, 4531 (1965).