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The Use of Dimethylformamide in the Ullmann Reaction

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When a relatively reactive aryl halide is heated with copper powder in the absence of a solvent a vigorous, exothermic reaction may occur. In many instances it has, therefore, proved advantageous to add a diluent and for this purpose nitrobenzene has most often been used, although toluene, *p*-cymene, naphthalene, biphenyl and anthracene have also been employed.[2]

TABLE I

PREPARATION OF BIARYLS

Halide	Biaryl	Reaction time, hr.	M.p., °C.[a]	Yield, %[b]	Previous yield, %
2-Chloro-3-methoxynitrobenzene	2,2′-Dimethoxy-6,6′-dinitrobiphenyl	8	231–232	84[c]	70[d]
o-Chloronitrobenzene	2,2′-Dinitrobiphenyl	8	125.5–126	80	52–61[e]
2,5-Dichloronitrobenzene	4,4′-Dichloro-2,2′-dinitrobiphenyl	8	138–139	75	42[f]
m-Iodotoluene	3,3′-Dimethylbiphenyl	72	[g]	55	35[h]
p-Iodotoluene	4,4′-Dimethylbiphenyl	72	122–122.5	68	54[i]
Methyl *p*-iodobenzoate	4,4′-Dicarbomethoxybiphenyl	24	212–214	74[j]	70[k]
Methyl *m*-iodobenzoate	3,3′-Dicarbomethoxybiphenyl	72	103–104	89	60[l]
p-Iodophenetole	4,4′-Diethoxybiphenyl	72	176–177	77	72[m]
α-Iodonaphthalene	1,1′-Binaphthyl	24	159–159.5	76	68[n]

[a] All m.ps. determined on a Fisher–Johns hot-stage. [b] These are the yields of products which have been recrystallized to the melting points given in this Table. [c] Average of four runs. [d] R. Adams and G. C. Finger [THIS JOURNAL, **61**, 2828 (1939)]; m.p. 226–228° (uncor.). [e] R. C. Fuson and E. A. Cleveland [*Org. Syntheses*, **20**, 45 (1940)]; m.p. 123.5–124.5° (cor.). [f] F. Ullmann and J. Bielecki [*Ber.*, **34**, 2174 (1901)]; m.p. 136°. [g] B.p. 135° at 3 mm., $n^{20}\mathrm{D}$ 1.5925; O. S. Mills [*Nature*, **167**, 726 (1951)] reports b.p. 130° at 1 mm., $n^{20}\mathrm{D}$ 1.5962; N. Kornblum [*Org. Syntheses*, **21**, 30 (1941)] gives b.p. 115° at 3 mm., $n^{20}\mathrm{D}$ 1.5945. [h] F. Ullmann [*Ann.*, **332**, 38 (1904)]. [i] F. Ullmann, *ibid.*; m.p. 122°. [j] When account is taken of the starting material which is recovered the yield rises to 93%; presumably a longer reaction time would be beneficial. [k] F. Ullmann, *ibid.;* m.p. 214°. [l] F. Ullmann, *ibid.;* m.p. 104°. [m] F. Ullmann, *ibid.;* m.p. 176°. [n] K. Brass and R. Patzelt [*Ber.*, **70,** 1349 (1937)]; m.p. 154°. C. Willgerodt and P. Schlosser [*Ber.*, **33**, 698 (1900)], report m.p. 160.5° (cor.).

Incidental to another investigation, it has now been found that dimethylformamide is a good solvent for the Ullmann reaction, in spite of the fact that its boiling point, 153°, is lower than that of most of the diluents previously used. Among other things, dimethylformamide has the considerable advantage over the previously employed diluents of being water soluble; hence it can easily be removed from the reaction product. Not only does this simplify the isolation procedure but, as can be seen from Table I, the yields are significantly higher than those obtained previously.

It should be emphasized that with those halides which are inert under the usual Ullmann conditions the present procedure offers no advantage. Thus, after 24 hours in refluxing dimethylformamide the following halides had undergone little or no reaction with copper powder: *p*-bromophenetole, *m*-chloronitrobenzene, *p*-chloronitrobenzene, *p*-bromonitrobenzene[3] and *α*-bromonaphthalene.

Experimental

The copper powder used was Natural Copper 44F (United States Bronze Powder Works) pretreated according to Kleiderer and Adams.[4] Dimethylformamide[5] (du Pont) was stored over calcium hydride at least 12 hours; very possibly no drying is necessary but this point was not investigated. The 2-chloro-3-methoxynitrobenzene (m.p. 94°) was prepared according to Finger.[6] *o*-Chloronitrobenzene was obtained from Monsanto and the other starting halides were Eastman Kodak Co. "white label" products.

The following preparation of 2,2′-dimethoxy-6,6′-dinitrobiphenyl is typical. In the other runs the only changes were in the time of reaction (*cf.* Table I) and the solvent used for recrystallizing the product. With a given biaryl the same solvent was employed as had been used by the workers cited in Table I.

Preparation of 2,2′-Dimethoxy-6,6′-dinitrobiphenyl.—Twenty grams of 2-chloro-3-methoxynitrobenzene and 100 ml. of dimethylformamide were placed in a 200-ml., 3-neck flask equipped with reflux condenser and a tantalum Hershberg-type stirrer. The solution was heated to reflux and then 20 g. of copper powder was added in one portion. Heating at reflux was continued for four hours after which another 20-g. portion of copper powder was added; refluxing was continued for a second four-hour period. On cooling, the reaction mixture was poured into two liters of water and then filtered. The solids were extracted with a total of two liters of boiling acetone. Concentration of the acetone extracts gave 11.1 g. of yellow crystals melting at 231–232° (uncor.); further evaporation of the acetone, followed by the addition of absolute ethanol, gave another 2.8 g., m.p. 228–229°. The 2.8 g. was digested for 10 minutes on the steam-bath with about 5 ml. of glacial acetic acid. After cooling to room temperature the crystals were isolated by filtration and then washed with a little glacial acetic acid. In this way a small amount of copper salts was removed leaving 2.4 g. of the dimethoxydinitrobiphenyl, m.p. 231–232° (uncor.), total yield 13.5 g. (84%).

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[2] P. E. Fanta, *Chem. Revs.*, **38**, 149 (1946).

[3] W. Davey and R. W. Latter (*J. Chem. Soc.*, 264 (1948)) obtained no dinitrobiphenyl on treating *m*- or *p*-chloronitrobenzene with copper powder either in the absence of solvent (at 200–220°) or in refluxing nitrobenzene. With *p*-bromonitrobenzene a 15% yield of 4,4′-dinitrobiphenyl was obtained after nine hours in refluxing nitrobenzene. In the absence of a solvent *p*-bromonitrobenzene gave the biaryl in 36% yield after 40 minutes at 200–220°.

[4] E. C. Kleiderer and R. Adams, THIS JOURNAL, **55**, 4219 (1933).

[5] We wish to thank the Grasselli Division of E. I. du Pont de Nemours & Co., Inc., for a generous supply of dimethylformamide.

[6] G. C. Finger, Ph.D. Thesis, University of Illinois, 1938, p. 56.