121. *The Ullmann Biaryl Synthesis. Part V.*[1] *The Influence of Ring Substituents on the Rate of Self-condensation of an Aryl Halide.*

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A series of aryl halides has been treated with copper under comparable conditions.

IN this investigation of the Ullmann biaryl synthesis,[1] the relative reactivities of certain aryl halides towards copper seemingly diverged to some extent from the conventional pattern.[2] In attempt to clarify the position this communication reports comparable Ullmann self-condensations of a short series of readily available aryl halides.

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[1] Part IV, preceding paper.

[2] Fanta, *Chem. Rev.*, 1946, **38**, 139.

It is clear that the rate of the apparent aryl halide–copper reaction, as measured by self-condensation, does not necessarily represent accurately the true reaction rate, particularly should biaryl formation be a multistage reaction. On the other hand, no diluent has been found which could react with a presumed intermediate to the exclusion of self-condensation without radically altering the apparent rate of the original halide–copper reaction. Phenols and carboxylic acids, which respectively suppress and promote the interaction,[3] were impracticable reagents for that reason. The undiluted reaction was therefore selected as the best available means of approximate assessment.

Comparative reactivities of aryl halides at 190—195° (1·5 *hr.*).

	Reaction (%)				Reaction (%)		
Aryl halide	by hal. recovery	by Cu halide	Biaryl (%)	Aryl halide	by hal. recovery	by Cu halide	Biaryl (%)
C_6H_5I	40	35	30	$C_6H_4Cl{\cdot}NO_2$	55	55	50
o-C_6H_4MeI	40	35	25	1,2,4-$C_6H_3Cl(NO_2)_2$	65	65	—
m-C_6H_4MeI	60	55	50	o-$C_6H_4Br{\cdot}NO_2$	95	95	75
p-C_6H_4McI	—	55	45	m-$C_6H_4Br{\cdot}NO_2$	2·5	2·5	2·5
o-C_6H_4ClI	50	45	35	p-$C_6H_4Br{\cdot}NO_2$	2·5	2·5	2·5
m-C_6H_4ClI	60	55	40	m-$C_6H_4I{\cdot}NO_2$	55	55	30
p-C_6H_4ClI	60	55	40	p-$C_6H_4I{\cdot}NO_2$	—	50	25
o-$C_6H_4I{\cdot}OMe$	75	75	70	o-$C_6H_4Cl{\cdot}CO_2Me$	0	0	0
m-$C_6H_4I{\cdot}OMe$	70	70	65	o-$C_6H_4Br{\cdot}CO_2Me$	90	90	80
p-$C_6H_4I{\cdot}OMe$	—	75	70	m-$C_6H_4I{\cdot}CO_2Me$	35	30	25
o-$C_6H_4Br{\cdot}OMe$	0	0	0	p-$C_6H_4I{\cdot}CO_2Me$	30	25	15
p-$C_6H_4Br{\cdot}OMe$	0	0	0	o-$C_6H_4Br{\cdot}CHO$	45	35	—
1,3,4-$C_6H_3I(OMe)_2$	75	80	55	o-$C_6H_4Br{\cdot}CN$	30	25	2·5
1,2,4-$C_6H_3I(OMe)_2$	80	80	65				

Little work has been done on the relative reactivities of aryl halides in the Ullmann reaction. Apart from observations on individual halides in specific reactions, the major work of this kind, an extensive series of reaction rate studies by Mascarelli *et al.*,[4] divided aryl halides into several groups according to the visible changes and evolution of heat at reaction temperatures which varied for individual halides. This work, however, is no guide either to the minimal reaction temperature of a specific halide or to its reactivity relative to that of a second halide. For example, 1-chloro-2,4-dinitrobenzene is classed solely as very reactive at 295°, whereas a slower but smooth reaction with copper takes place under 200°; [5] iodobenzene is erroneously stated to be unattacked by the metal at 190°. Later, the greater activation of an *o*-nitro-halide than of the other isomers, in studies on the rate of self-condensation of some halogenonitrobenzenes, was disclosed by Davey and Latter.[6]

In the present work the relatively slowly reacting iodobenzene was conveniently used as a standard. In consequence the temperature of the condensations was restricted to 190—195°.

As shown in the Table, the effect of an electronegative substituent on the reactivity of the halogen atom was apparently more complex than hitherto realised. The nitro-group, as has been reported, predominantly activated an *o*-halogen atom. In fact, under the conditions of reaction, iodo-compounds with less powerful electronegative substituents, such as the cyano-group, in the *ortho*-position, reacted strongly exothermally; they were therefore omitted from the present study. Surprisingly, in positions other than *ortho* the nitro-group had little effect on the reaction rate of the halide. For example, both *m*- and *p*-iodonitrobenzene were comparatively little more reactive than iodobenzene alone, and the reactivity of *o*-chloronitrobenzene was not materially enhanced by an additional nitro-group *para* to the halogen atom. Moreover, it is difficult to distinguish between the relative stimulation of a halogen atom by a nitro-group in the *meta*- or *para*-position.

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[3] Part III, *J.*, 1960, 581.

[4] Mascarelli, Longo, and Ravera, *Gazzetta*, 1938, **68**, 33.

[5] Part I, *J.*, 1960, 566.

[6] Davey and Latter, *J.*, 1948, 264.

This contrasts with the recognised concept of *o*/*p* activation of an aryl halide in the Ullmann reaction by an electronegative group.[2] A similar but less powerful halide activation pattern was shown by a carboxylic ester substituent. Under the reaction conditions methyl *o*-chlorobenzoate was unattacked by copper. The *o*-bromo-analogue reacted readily, whereas the corresponding *meta*- and *para*-isomers were practically inert. On similar treatment methyl *m*- and *p*-iodobenzoate reacted slowly with copper at approximately equivalent rates although both were slightly less readily attacked than iodobenzene itself.

As indicated by reported work,[4] further substitution of iodobenzene by chloro-, methoxy-, or methyl groups increased the activity of the halogen atom irrespective of orientation. Of these, the methoxyl group was the most powerful stimulant, the effect of the others being of the same order, but less marked, particularly in the case of *ortho*-substitution. The influence of further substitution by methoxyl groups appeared to be complementary. Thus both 4-iodoresorcinol dimethyl ether and 4-iodoveratrole reacted exothermally under comparable conditions.

EXPERIMENTAL

Copper bronze (from B.D.H) was used without pretreatment as the condensing agent.

General Procedure.—The halide (0·05—0·1 mol.) and copper (in 50% excess) were heated at 190—195° (metal bath) for 1·5 hr. Thermometers were placed in the bath and reagents. The product was treated as described in Part I of this series. Where the biaryl was a relatively high-melting insoluble material such as 4,4′-dimethoxy- or 4,4′-dimethoxycarbonyl-biphenyl, the product was initially crystallised as far as possible, then the mother-liquors were fractionally distilled. Certain reactions were exothermic. This effect was confined to *o*-bromonitrobenzene, methyl *o*-bromobenzoate, and the isomeric iododimethoxybenzenes, and was controlled by the removal of the reaction mixture from the metal-bath before the temperature had exceeded 200°, followed by external cooling if necessary, after which the reaction was completed in the usual way.

The proportion of aryl halide attacked was estimated from the increase in weight of the inorganic product, and, when convenient, by calculation from the aryl halide recovered. Normally the latter figure was somewhat higher, probably owing to loss of volatile material. The yield of biaryl, whilst of secondary importance, was normally determined, except in condensations in which the simultaneous formation of resinous by-products made isolation difficult. Details of the physical characteristics of the aryl halides or of the biaryls, which are all known compounds, are not included.

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