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THE MECHANISM OF THE ULLMANN REACTION.
DETECTION OF AN ORGANOCOPPER INTERMEDIATE.

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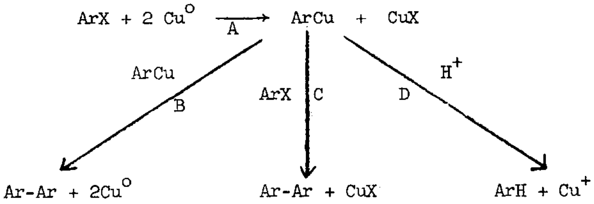
We wish to present evidence for an organocopper intermediate in the Ullmann biaryl synthesis (1) and to report results which suggest the possibility of direct preparation of otherwise unstable (2) organocopper compounds by the use of suitable complexing agents (3,4).

Although many data are available concerning the scope and applications of the copper induced coupling of aryl halides, the main mechanistic features remain obscure. Any satisfactory mechanism should be capable of explaining the following observations (1). [1] An electron withdrawing group in the <u>ortho</u> position activates an aryl halide in this reaction. [2] A good yield of an unsymmetrical biaryl can be obtained from the reaction of an activated and an unactivated aryl halide at a temperature too low for the latter halide alone to react. [3] Triphenylamine is formed when the Ullmann reaction of iodobenzene is performed in nitrobenzene. [4] 2,6-Dinitrobiphenyls are produced in the Ullmann reaction of iodobenzene in the presence of <u>m</u>-dinitrobenzenes (5). [5] Proton sources suppress the Ullmann reaction and lead to reductive dehalogenation of the aryl halide (6).

All of these observations can be explained if an organometallic is postulated as a reaction intermediate.* Since the formation of the intermediate, step A, would involve the donation of electrons from the copper to the aryl compound, electron withdrawing groups should stabilize the transition state. The particular effectiveness of ortho substituents such as nitro might further be due to stabilization by chelation (1a). The formation of triphenylamine by the reaction of phenylcopper (perhaps the most likely organometallic intermediate) with nitrobenzene is certainly a likely reaction (1a). Excellent analogies are available for the reaction of nucleophiles with m-dinitrobenzenes to form 2,6-dinitrosubstituted benzenes (8). Finally, the reaction of phenylcopper with protons to give benzene is an expected and known (2) reaction and on this basis observation [5] must be considered the most suggestive evidence for the intermediacy of an organocopper.



It appears likely from observations [1] and [2] that the formation of the organometallic, step A, is rate determining, at least in the case of non-activated aryl halides,** and that it would therefore not

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[*] Organometallics have been mentioned in review articles (1) and in one special case (7) as possible intermediates in this reaction, but such a mechanism has not been generally accepted (1a).

[**] It is possible that the rate of formation of the intermediate is increased sufficiently in the reaction of activated halides for product formation to become the rate determining step.

accumulate during the reaction. That this is the case was verified by the detection of only a trace of toluene when the Ullmann reaction of p-iodotoluene (neat) was quenched with aqueous acid (step D) prior to completion.

In order to detect the intermediate it seemed desirable to effect its accumulation during the reaction. This was accomplished by taking advantage of the expected stabilization of an organocopper compound by coordination with organic bases. Copper salts are known to form stable complexes with nitrogen heterocycles (9) and the reported (2b) solubility of phenylcopper in pyridine is probably a result of such interaction. When the reaction of p-iodotoluene with copper was carried out in quinoline or in 8-methylquinoline, the accumulation of an intermediate, capturable by protonation (step D), was evident. The reaction was followed by withdrawing aliquots periodically and quenching with aqueous acid. The results (Table I) provide strong evidence for the relatively rapid generation and slow destruction of an organocopper intermediate. It is clear that the toluene which is produced is not a permanent product of the unquenched reaction for its yield, although as high as 43% at the end of 95 hr., decreases almost to zero at the end of 373 hr. No intermediate could be detected by similar experiments when the same reaction was performed in the noncomplexing diluent 1-methylnaphthalene.

Since the iodotoluene is depleted early in the reaction, it is likely that much of the bitolyl is produced by self-coupling of the organometallic intermediate (step B). This supports the hypothesis that tolylcopper is the intermediate which is being trapped, for phenylcopper is known (2a) to undergo self-coupling with the deposition of a copper mirror. In our experiments, the deposition of copper was suggested by the fusing together of the fine copper powder during the reaction.

TABLE I

The Course of the Ullmann Reaction of p-Iodotoluene in 8-Methylquinoline at 190°

Time Interval (hr.)	% Unreacted [a] p-iodotoluene	% Yield [a]	
		Toluene	Bitolyl
3	100	trace	nil
$10\frac{1}{2}$	86	8	6
23	64	15	21
47	30	26	28
71	9	32	44
95	nil	43	41
167	nil	39	47
253	nil	12	73
373	nil	3	81

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[a] Determined by v.p.c.

In order to account for observation [2], it is necessary to postulate in some cases a second mode of product formation which involves reaction of the organocopper intermediate with aryl halide (step C). The driving force for this reaction, which presumably proceeds through a four-center transition state, would be the establishment of a strong cuprous halide bond in addition to the carbon-carbon bond. The reactions of cuprous acetylides with organic halides (3,10) might well be of the same type.

It is of interest that the rates of consumption of p-iodotoluene in the three solvents, at 190°, are in the order quinoline (half-life ca. 8 hr.) > 8-methylquinoline (half-life ca. 32 hr.) > 1-methylnaphthalene (half-life ca. 40 hr.). This is also the expected order of effectiveness of these solvents in stabilizing the products of step A by coordination[*] although this order could also be due to the varying effectiveness of these solvents in cleansing (particularly by dissolution of cuprous iodide) or otherwise activating the metal surface.

Unexpectedly, the rate of self-coupling of the intermediate, step B, (determined after the p-iodotoluene had been completely consumed), is considerably greater in quinoline than in 8-methylquinoline. This might be a reflection of the steric difficulty involved in bringing together molecules of organometallic bearing bulky ligands.[‡] This interesting phenomenon suggests further investigation.

Additional information is being sought concerning the nature and reactions of this Ullmann intermediate and the utility of this method for the direct preparation of stabilized organocopper compounds.

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[*] The 8-methyl group, because of steric compression, should cause the complexes of the substituted quinoline to be of higher energy than those of quinoline (11). In order for this explanation to be correct, the coordination would have to be manifested in the transition state for step A.

[‡] Implicit in this concept is the assumption that coupling occurs in the complex. This is not unreasonable in view of the powerful complexing ability of heterocyclic bases for Cu(I).

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