crystallized to a white solid: mp 30.8–31.2°; ir (neat) 5.50 (methylenecyclopropyl) and 6.05μ (C=C); nmr (CCl_4 with TMS standard on Varian A-60) τ 8.68 (rounded, 2 H, cyclopropyl), 8.52 (singlet with slight coupling, 6 H, CH_3), 8.13 (rounded singlet, 4 H, CH_2 adjacent to cyclopropane ring), 7.85 (sharp singlet, 4 H, CH_2 between ethylenes), and 4.16 (singlet, 2 H, vinyl protons).

Anal. Calcd for $C_{14}H_{18}$: C, 90.3; H, 9.7. Found: C, 90.3; H, 9.8.

Copper(I) Substitutions. Scope and Mechanism of Cuprous Acetylide Substitutions

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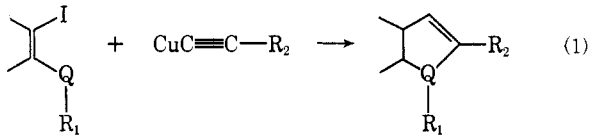
Abstract: Substitutions with cuprous acetylides provide a most convenient route to a wide variety of acetylenes and heterocyclic arrays. This summarizing work casts these reactions into a general pattern for copper(I) substitution. The reactivity of acetylides toward bond type, the kinetics of aromatic substitution, the geometry of allylic substitution, the nature and path of the heterocyclic synthesis, and some mechanistically instructive ring size experiments are presented. Additional heterocyclic syntheses are described. The mechanisms for reaction range from a four center process (aryl halide substitution) to homolytic scission (oxidation with N-bromosuccinimide). The stereochemistry of the cuprous chloride-catalyzed hydrolysis of allylic halides is portrayed and the reaction of these salts with halohydrins is described.

The reaction of cuprous acetylides with aryl halides has proven to be a most effective route to a wide variety of aromatic acetylenes.[1] Moreover, the substitution and cyclization of halides bearing a neighboring nucleophilic substituent is now the basis of a versatile heterocyclic synthesis (eq 1). Thus, indoles,



(1)

benzofurans, phthalides,[1a] thianaphthenes,[2] furans,[3] and a range of polynuclear multiheterocyclic arrays[4] are easily obtained in high yield. Indeed, the results at hand suggest an extremely broad scope for the reaction in this domain and some additional ring systems are reported herein.

The present summarizing work is intended to cast these reactions into a general pattern for Cu(I) substitutions. A general reactivity of the acetylides toward bond type, the kinetics of aromatic substitution, the stereochemistry of allylic substitution, and some mechanistically instructive ring-size experiments are presented. The characteristics of several compounds we have not previously reported are given in the experimental section.

(1) (a) C. E. Castro, E. J. Gaughn, and D. C. Owsley, *J. Org. Chem.*, 31, 471 (1966), and references therein; (b) M. D. Rausch, H. Siegel, and L. P. Kleman, *ibid.*, 31, 2703 (1966); (c) S. A. Kandil and R. E. Ressey, *J. Amer. Chem. Soc.*, 88, 3027 (1966); (d) R. E. Atkinson, R. F. Curtis, and J. A. Taylor, *J. Chem. Soc.*, 578 (1967); (e) R. E. Atkinson, R. F. Curtis, D. M. Jones, and J. A. Taylor, *Chem. Commun.*, 14, 718 (1967); (f) A. M. Sladkov and L. Yu. Ukhin, *Russ. Chem. Rev.*, 37, 1750 (1968), and references therein.

(2) A. M. Malte and C. E. Castro, *J. Amer. Chem. Soc.*, 89, 6770 (1967).

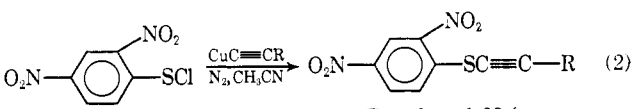
(3) K. Gump, S. W. Mojé, and C. E. Castro, *ibid.*, 89, 6770 (1967).

(4) S. A. Mladenovíc and C. E. Castro, *J. Heterocycl. Chem.*, 5, 227 (1968).

Results

Reactivity. A broad range of studies indicates the following pattern of reactivity of halogen (x) bond types toward substitution with cuprous acetylides in dimethyl formamide (DMF): ArSX, ArX > RCOX >> benzyl-X, allyl-X, phenacyl-X > alkyl-X, vinyl-X. The order of reactivity for halogen in all families of compounds is I > Br > Cl. Thus, aryl halides and sulfenyl halides are easily substituted in many solvents at 110° or less. The media of choice for these halides are pyridine and acetonitrile, respectively. An amplification of the influence of substituents upon the rates of substitution of aryl halides is given in the kinetic section. The insensitivity of the aryl halide substitution to solvent is illustrated in the conversion of *o*-iodophenol to 2-phenylbenzofuran. The reaction takes place in high yield in pyridine, dimethylformamide, dimethyl sulfoxide, ethylene glycol, and acetic acid.[5] Although acyl halides react in dimethylformamide slowly, best conversion conditions are mixing neat at room temperature. The benzylic, allylic, and phenacyl systems are loathe to react in DMF at 120°, but they may be substituted at higher temperatures.[3] In contrast, vinyl and saturated aliphatic halides are inert toward substitution at 220° neat or in N-methylpyrrolidone.

We have not previously described the relatively mild substitutions of sulfenyl or acyl halides. Best yield conditions are typified by eq 2 and 3. Moreover, halide



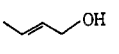
(2)

R = phenyl, 80%; *n*-propyl, 70%

substrates that are prone to homolytic scission do not

(5) R. D. Stephens and C. E. Castro, *J. Org. Chem.*, 28, 3313 (1963).

Table I. Comparison of Hydrolysis of *cis*- and *trans*-Crotyl Chloride and Isomerization of the Alcohols

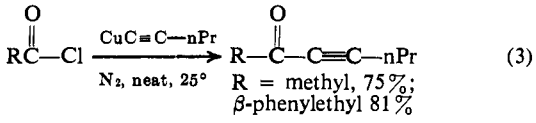
Crotyl halide	Conditions	% conversion	Product distribution,[a] % 		
cis	0.47 *N* HCl, 2 hr, 75°	80	53	39	8
trans	0.47 *N* HCl, 2 hr, 75°	63	63	0.5	36.5
cis	0.47 *N* HCl, 3.4×10^{-2} *M* CuCl, 2 hr, 75°	100	74.9	3.9	21.2
trans	0.47 *N* HCl, 3.4×10^{-2} *M* CuCl, 2 hr, 75°	100	76.1	2.5	21.4
cis-Crotyl alcohol	0.47 *N* HCl, 3.4×10^{-2} *M* CuCl, 2 hr, 75°		52.4	35.2	12.4
trans-Crotyl alcohol	0.47 *N* HCl, 3.4×10^{-2} *M* CuCl, 2 hr, 75°		72.5		22.5

[a] Analysis of reactants and products by gas chromatography on a 20% Carbowax column at 75°.

Table II. Attempted Cyclization of *o*-Aminophenylacetylenes

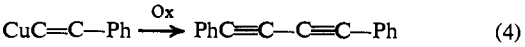
Acetylene, 2×10^{-2} *M* R	Copper salt	Medium	Temp, °C/time, hr	Yield of indole, %
Phenyl	CuI	Cyclohexane[a]	70, 15	100
Phenyl	CuCl	Cyclohexane[a]	70, 15	100
n-Propyl	CuI	Cyclohexane[a]	70, 15	100
n-Propyl	CuCl	Cyclohexane[a]	70, 15	100
Phenyl	CuCl	Homogeneous DMF[b]	100, 15	0
n-Propyl	CuCl	Homogeneous DMF[b]	100, 15	0
Phenyl	CuCl	Heterogeneous DMF[c]	100, 15	100
n-Propyl	CuCl	Heterogeneous DMF[c]	100, 15	100

[a] The cuprous salts are insoluble in cyclohexane. [b] A 2×10^{-2} *M* solution of copper salt, prepared by warming in DMF and carefully filtering was treated with an equimolar amount of acetylene. [c] A 2×10^{-2} *M* acetylene solution was treated with an equimolar amount of solid copper salt.



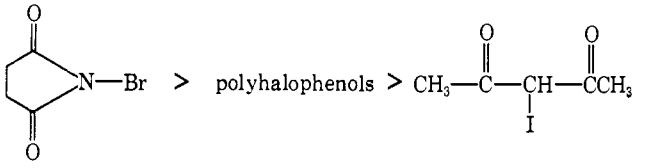
(3)

yield substitution products, but rather, like oxygen result in the oxidative coupling of the acetylide (eq 4).

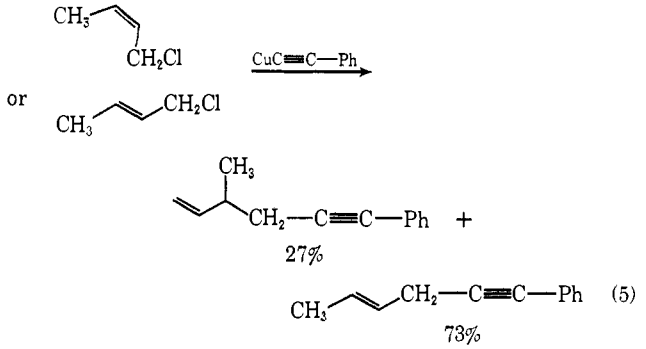


(4)

The order of reactivity for this process is



Stereochemistry. The results of the substitution of *cis*- and *trans*-crotyl chloride conducted neat at 75° or in dimethylformamide at 126° is given in eq 5. The



(5)

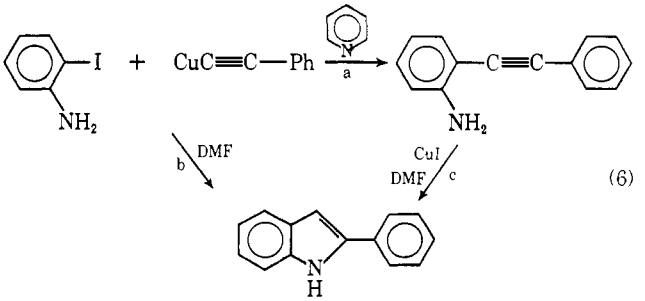
same isomer distribution is obtained from either substance, and neither the starting halides nor the products are isomerized under reaction conditions.

From considerations of mechanistic continuity we wished to compare the stereochemistry of the acetylide substitution with that of the cuprous chloride HCl-catalyzed hydrolysis of allylic halides.[6] The process could be a model for enzymatic hydrolysis[7,8] and its stereochemistry has not been described. Isomer distributions from the hydrolysis of *cis*- and *trans*-crotyl chloride in the presence and absence of CuCl are given in Table I.

The distribution of alcohols obtained in the cuprous chloride-catalyzed reaction is not the result of the initial substitution for the product alcohols are rapidly equilibrated in this milieu. The isomerization renders a mechanistic interpretation difficult.

Cyclization and Ring Size

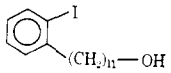
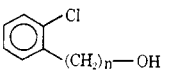
The Cyclization. We have previously reported the dominant influence of reaction medium upon the course of the substitution of *ortho*-haloanilines with cuprous acetylides. This reaction proceeds in excellent



(6)

(6) L. F. Hatch and R. R. Estes, *J. Amer. Chem. Soc.*, 67, 1730 (1945); L. F. Hatch, L. O. Morgan, and V. L. Tweedie, *ibid.*, 74, 1826 (1952).
(7) C. E. Castro and E. W. Bartnicki, *Biochim. Biophys. Acta*, 100, 384 (1965).
(8) C. E. Castro and E. W. Bartnicki, *Biochemistry*, 7, 3213 (1968).

Table III. Internal Substitution of Iodoaryl Alcohols with Cuprous Salts

Alcohol 	Cu(I)L[a]	Medium[b]	% conversion	Yield, % 	
$n = 2$	CuC≡CPh	DMF	20	100	
		Pyridine	100	100	
	CuC≡C-*n*Pr	DMF	42	100	
		Pyridine	90	100	
	CuCl	DMF	83	9	91
		Pyridine	53	21	79
$n = 3$	CuC≡C—Ph	DMF	20	100	
		Pyridine	85	100	
	CuC≡C—*n*Pr	DMF	20	100	
		Pyridine	54	100	
	CuCl	DMF	100	5	95
		Pyridine	35	32	

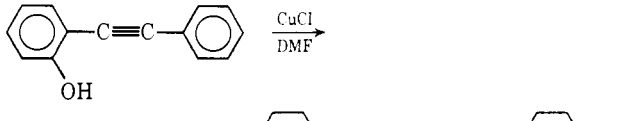
[a] 1.5 mmol of Cu(I)L and 1 mmol of alcohol in 2 ml of solvent at 100° for 21 hr. [b] All DMF reactions were heterogeneous, all pyridine reactions homogeneous.

yield to either indole (eq 6b) or tolan (eq 6a). In an effort to discern the kinetics of the cyclization process (eq 6c) we have found it to be a *heterogeneous* transformation.

Attempts to cyclize *o*-pentynylaniline and *o*-phenylethynylaniline under a variety of conditions are presented in Table II. The cuprous salts are slow to dissolve in DMF and the latter two sets of data are particularly informative in that the conditions are identical except that the cuprous chloride was not dissolved in the heterogeneous runs.

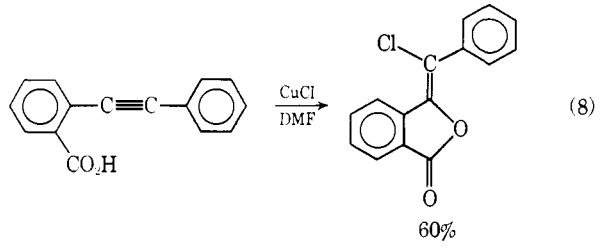
In addition to the cuprous salts given in Table II, a qualitative scan for the cyclizations of *o*-pentynylaniline (λ_{max} 315 mμ) to 2-*n*-propylindole (λ_{max} 278 mμ) was made spectrophotometrically. The following salts do catalyze the cyclization (0.1 equiv of salt, 0.1 *M* acetylene in DMF at 80° for 20 hr): HgI_2, $AgNO_3$, Hg_2Cl_2, $PdCl_2$, and PtI_2. The following salts do not: $CoCl_2$, $CrCl_3$, $FeCl_2$, $FeCl_3$, $NiCl_2$, $MnCl_2$, $CuBr_2$, and $CaCl_2$.

The heterogeneous character of the cyclization in the heterocyclic synthesis is further emphasized by the conversion of the acetylenic intermediates for the benzofuran and phthalide syntheses to other products when the reactions are run homogeneously. These striking reactions (eq 7, 8) afford no benzofuran or



(7)

100%



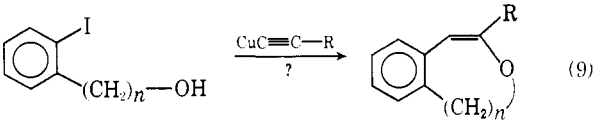
(8)

60%

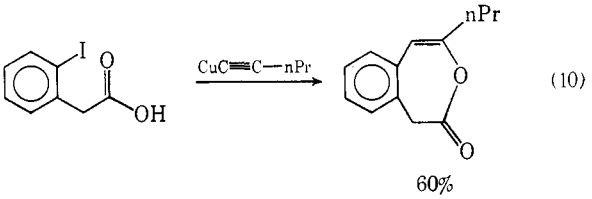
3-benzylidene phthalide, respectively, although these are the exclusive products obtained with undissolved cuprous salts.

Indeed these findings have led to an improved synthetic procedure for effecting cyclization. Cyclization is best achieved by mixing *ortho*-substituted acetylene with cuprous salts neat and allowing to stand at room temperature. Thus, the general heterocyclic synthesis (eq 1) is best performed by allowing the concentrated product mixture to stand in the presence of the generated cuprous salts or by adding cuprous halide to the concentrate. The unpredictable yields of aminotolans and indoles obtained from the iodoanilines[1a] reflect these observations.

Ring Size. Because of the ease of the phthalide and benzofuran syntheses and the availability of the alcohols, we sought to determine the size of heterocyclic rings that can be constructed by acetylide substitution and cyclization (eq 9). *o*-Iodophenylacetic acid and *o*-iodobenzyl alcohol react smoothly to the products indicated (eq 10–12). In contrast, the alcohols with $n = 2$ and 3 (eq 9) allow no acetylide substitution and yield the



(9)



(10)

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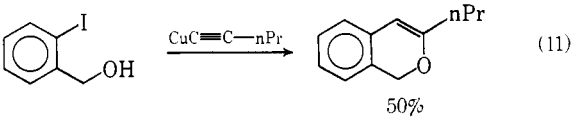
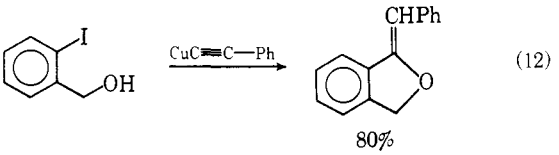


(11)

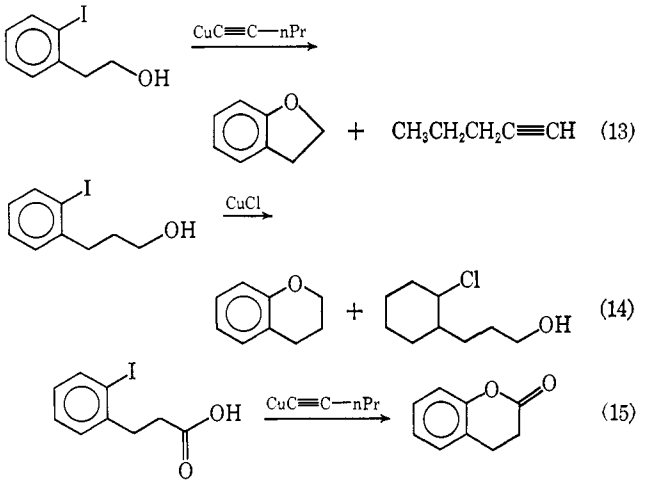
50%



(12)

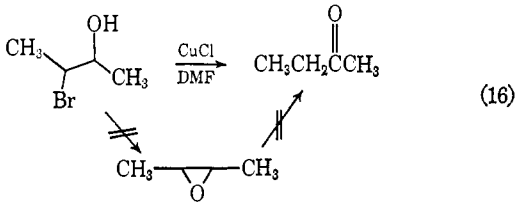
80%

internal substitution product only (eq 13, 14). Similarly, *β-o*-iodophenylproprionic acid yields dihydrocoumarin (eq 15). With cuprous chloride, in addition to dihydrobenzofuran and dihydrobenzopyran, the

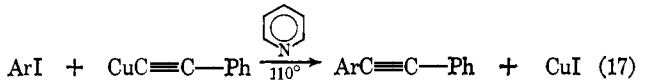


iodo alcohols are converted to the corresponding chlorides. Reaction 14 is illustrative. The efficiency of the copper salts to catalyze the internal cyclization is illustrated in Table III. Thus, the qualitative order of substitution of carbon–aryliodide bonds by copper(I) ligands is Cl > internal OH > C≡C—R.

The facility of the internal cyclization of the halo alcohols promoted by cuprous salts led us to consider the synthesis of smaller rings and in particular the generation of epoxides from halohydrins. Ring strain would be diminished in the aliphatic system and the reaction could provide a model for the rapid enzymatic ring closure of these substrates.[8] Both *threo*- and *erythro*-2-bromo-3-butanol do react with cuprous chloride in acetonitrile, and 2-butanone is obtained in good yield (eq 16). However, the epoxides *are not* intermediates for they are inert under reaction conditions.



Kinetics. The rates for the homogeneous substitution of aryl iodides with cuprous phenylacetylide in pyridine (eq 17) were monitored by following cuprous



iodide potentiometrically (*cf.* Experimental Section). In addition, the reaction of *o*-iodoaniline with the acetylide was followed by gas chromatographic analysis. Initial concentrations were in the range 2×10^{-2} *M* to 0.5×10^{-2} *M* for aryl halide and 2×10^{-2} *M* to 0.5×10^{-2} *M* for acetylide. The rate law for the process is

$$-\frac{d(ArI)}{dt} = \frac{d(CuI)}{dt} = k_2(ArI)(CuC{\equiv}C{-}R)$$

The values reported for k_2 in Table IV are the average of three separate determinations and were calculated from general second-order plots of the data.

Table IV. Rates for the Substitution of Iodobenzenes with Cuprous Phenylacetylide in Pyridine at 100°

R substituent	Position, k_2, l./mol/sec *ortho*	*meta*	*para*
CO_2H	7.0×10^{-2}	2.9×10^{-5}	4.6×10^{-5}
OH	8.6×10^{-3}	1.3×10^{-5}	2.0×10^{-5}
NO_2	2.0×10^{-3}	9.1×10^{-5}	1.4×10^{-4}
OCH_3	1.7×10^{-5}	1.4×10^{-5}	0.85×10^{-5}
NH_2	3.4×10^{-5}	1.0×10^{-5}	1.4×10^{-5}
H	0.80×10^{-5}		

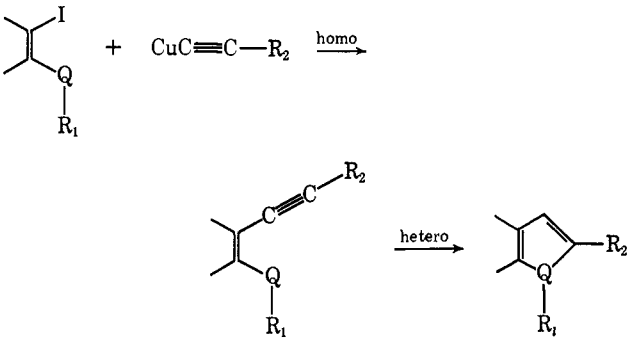
In the case of *p*-iodobenzoic acid it is important to note that a 1:1 molar ratio of reactants gave the same pale green solution as its isomers, but no substitution occurred. The corresponding activation parameters for iodobenzene and the nitro-substituted compounds are presented in Table V.

Table V. Activation Parameters for Substitutions with Cuprous Phenylacetylide in Pyridine, Calculated at 25°

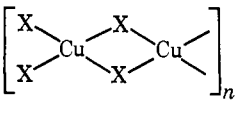
Halide	$\Delta F^{\ddagger}$, kcal	$\Delta H^{\ddagger}$, kcal	$\Delta S^{\ddagger}$, eu
Iodobenzene	26	7.2	−63
o-Nitroiodobenzene	26	16	−29
m-Nitroiodobenzene	27	15	−36
p-Nitroiodobenzene	26	13	−41

Discussion

Taken together with earlier work, these studies fix the over-all heterocyclic synthesis as a two-step process entailing a homogeneous substitution followed by a heterogeneous Cu(I) catalyzed addition to the triple bond. Of the heterogeneous cyclization it can only be



said that apparently a Cu(I) polymer of the form



is essential for catalysis. The monomer or other low molecular weight aggregates that are obtained in warm pyridine or upon prolonged warming in DMF are not capable of rapid catalysis.

Although telomeric cuprous acetylides are likely to be present under our reaction conditions,[9] it is apparent from the kinetics that a monomer is the reactive species. Moreover, the reactivity of bond types and the kinetics

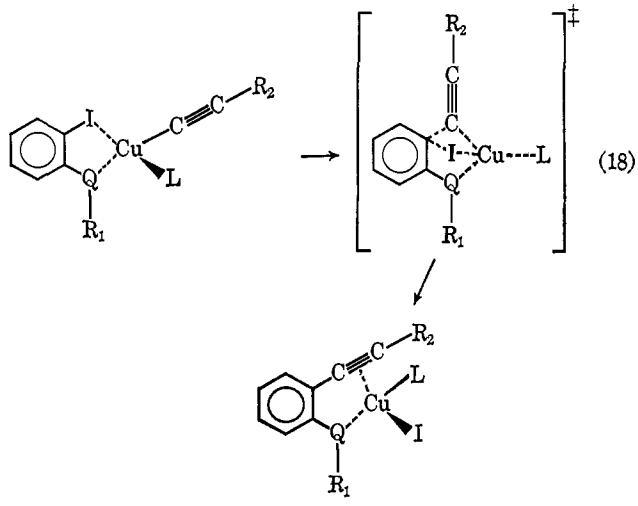
(9) G. E. Coates and C. Parkin, *J. Inorg. Nucl. Chem.*, 22, 59 (1961).

bespeak a four-center transition state for the substitution of aryl halides. Indeed the mild pattern of substituent influence upon the rates of substitution of iodobenzenes is broken only by CO_2H, OH, and NO_2. The only really large differences occur when these groupings are in the *ortho* position. The negative entropies of activation indicate a high degree of order for the bond-making process, and the enhanced rate for the *ortho*-nitro compound is clearly the result of a more favorable entropy for that reaction. This result is in accord with the beneficial coordination of copper by a substituent near the substitution site. This view is supported by the lack of substitution of *p*-iodobenzoic acid when reactants are mixed in equimolar amounts. That is, of the substituents examined, carboxyl is most effective in coordinating the metal and its acetylenic ligand in the most favorable way for substitution to ensue. Thus, with carboxyl in the *para* position, the acetylide is held away from the substitution site. Hence, we formulate the following mechanism for substitution.

$$\mathrm{ArI} + \mathrm{CuC{\equiv}C{-}R} \rightleftharpoons \underset{\mathrm{I}}{\mathrm{Complex}} \longrightarrow \mathrm{ArC{\equiv}C{-}R} + \mathrm{CuI}$$

For *ortho*-coordinating substituents the complex (I) and its dissipation to products may be portrayed as eq 18.

When the substituent, QR, is on a long enough side chain such that it can sterically reach the carbon bearing halogen *as a ligand of copper*, it is preferably transferred. This is the case for the β-(*o*-iodophenyl)ethanol, γ-(*o*-iodophenyl)propanol, and for β-(*o*-iodophenyl)propionic acid (eq 13–15). A chloride ligand would substitute in similar fashion and the kinetics of that process are in harmony with this description.[10]



(18)

It was noted (*vide supra*) that those bonds prone to homolytic scission yield diphenylbutadiyne upon even mild treatment with cuprous phenylacetylide. We believe these oxidations are the result of an initial cleavage to radicals (eq 19). The dimerization of the

$$\mathrm{Z{-}X} + \mathrm{CuC{\equiv}CR} \longrightarrow \mathrm{Z\cdot} + \mathrm{XCu(II)C{\equiv}CR} \qquad (19)$$

$$\downarrow$$

$$\mathrm{RC{\equiv}C{-}C{\equiv}CR}$$

alkynyl moiety of the Cu(II) species is akin to the generation of cyanogen from cupric salts and CN^-, and the initial scission is analogous to cleavages effected by Cr(II).[11] Moreover, the scrambling in the butenyl halide substitution is in accord with a radical character of the transition state for the forcing allylic substitutions. However, the lack of crotyl halide isomerization or diphenylbutadiyne generation in reaction 5 suggest a free radical is not obtained.

Thus, a gradation of mechanisms ranging from a four-center process to homolytic scission are operative in substitutions with cuprous acetylides. The former is typified by the homogeneous reaction of aryl halides in pyridine and the latter by the oxidations that occur with some iodo ketones and N-bromosuccinimide. The butenyl halide substitutions are representative of a class of aliphatic reactions intermediate between these extremes.

Since phenols will oxidize cuprous acetylides,[1a] the remarkable homogeneous reaction of *o*-hydroxytolan with cuprous chloride (eq 7) can be rationalized by the reverse of eq 18. That is, it is a case for the converse substitution of chloride for acetylide (eq 20). Oxidation of the acetylide by the chlorophenol would result in diphenylbutadiyne.

$$\mathrm{ArC{\equiv}CR} + \mathrm{CuCl} \longrightarrow \mathrm{ArCl} + \mathrm{CuC{\equiv}CR} \qquad (20)$$

Experimental Section

Materials. All substances were purified before use and had physical properties and spectra which checked with the literature.

β-*o*-Iodophenylacetic acid was prepared from *o*-iodobenzyl bromide *via* the nitrile (60%, bp 104° (0.6 mm)) and acid hydrolysis (53%, mp 112°).

β-*o*-Iodophenylethanol was obtained from the above acid by conversion to the acid halide with thionyl chloride and reduction of the crude acid chloride with lithium aluminum hydride in ether (58%, bp 100° (0.5 mm)).

γ-*o*-Iodophenylpropionic acid was produced from the above alcohol *via* conversion to the bromide (PBr_3) and thence with KCN in ethanol to the nitrile, bp 110–115° (0.2 mm). Hydrolysis of the nitrile at 165° in 1:1 H_2SO_4–H_2O and recrystallization from chloroform–petroleum ether afforded the acid (over-all 50%, mp 87–88°).

γ-*o*-Iodophenylpropanol was prepared from the above acid *via* the acid chloride and reduction with lithium aluminum hydride in ether (64%, bp 95–101° (0.05 mm)).

The Cu(I) Substitutions. Only typical reactions are presented. Other essential features of compounds prepared during this work along with some we have not previously described are presented in Table VI.

2,4-Dinitrophenylethynyl Sulfide. A reaction mixture composed of 2.35 g (0.01 mol) of 2,4-dinitrobenzenesulfenyl chloride and cuprous phenylacetylide, 1.97 g (0.012 mol), in 300 ml of acetonitrile was stirred and gently refluxed under nitrogen for 48 hr. The solvent was evaporated *in vacuo*. The concentrate was treated with ether (300 ml) and undissolved copper salts filtered. The ether solution was dried over sodium sulfate, filtered, and evaporated. The crystallized residue of the product (2.4 g, 80%) was recrystallized from a 1:1:1 petroleum ether–benzene–ethanol mixture to yield pure 2,4-dinitrophenylphenylethynyl sulfide with mp 162°.

Anal. Calcd for $C_{14}H_8N_2O_4S$: C, 56.0; H, 2.66; N, 9.3; S, 10.6. Found: C, 56.29; H, 2.97; N, 9.05; S, 10.18. The nmr spectrum showed only aromatic protons.

1-Benzylidenedihydroisobenzofuran. A mixture of cuprous phenylacetylide (3.95 g, 0.022 mol) and *o*-iodobenzyl alcohol (4.68 g, 0.02 mol) in pyridine (200 ml) was stirred and warmed to reflux for 48 hr. The solvent was stripped *in vacuo* and the residue allowed to stand another 48 hr. Ether was added and the insoluble copper salts were removed. The dried (Na_2SO_4) filtered ether solution was concentrated. The residue was thrice recrystallized from petroleum ether to yield pure product (3.3 g, 80%), with mp 100°. The nmr showed singlets at δ 5.5 (2 H) and 5.95 (1 H) and a multiplet at δ 7.3 (9 H).

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Table VI

Compound	Yield, %	Elemental analysis, calcd (found) C	H	N	S	Bp or mp, °C (recryst solv)	Ir, cm^{-1}	Nmr, δ	Reference to method
2,4-Dinitrophenyl *n*-propylethynyl sulfide[a]	70	49.6 (49.88)	3.76 (3.91)	10.53 (10.44)	12.03 (11.74)	50 (pet. ether)	2180	8.85s (1 H), 8.48 (2 H), 2.62t (2 H), 1.72m (2 H), 1.13t (3 H)	This work
Acetyl-*n*-propylacetylene[a]	75	76.32 (76.24)	9.15 (9.57)			*c*	1665, 2210	2.32t (2 H), 2.2s (3 H), 1.65m (2 H), 1.05t (3 H)	This work
2-*n*-Propyl-4,5-dihydro-4-keto-3-benzoxepin[a]	60	77.22 (77.34)	6.93 (7.32)			155 (0.3 mm)	1740	7.3d (4 H), 6.32s (1 H), 3.68s (2 H), 2.48t (2 H), 1.68m (2 H), 1.04t (3 H)	This work
3-*n*-Propyl-1H-2-benzopyran[a]	50	82.77 (82.67)	8.05 (8.20)			90 (3 mm)		7.18m (4 H), 5.6s (1 H), 5.05 (2 H), 2.2t (2 H), 1.55m (2 H), 0.97t (3 H)	This work
o-Phenylethynyl-*trans*-cinnamic acid[a]	60	82.24 (82.56)	4.84 (5.12)			160 (pet. ether)			Ref 1a
o-Cyanophenyl-*n*-propylacetylene[a]	45			8.29 (8.31)			1590, 2212	7.56m (4 H), 2.48t (2 H), 1.61m (2 H), 1.12m (3 H)	Ref 1a
Ethyl β-*o*-iodophenylpropiolate[a]	20	39.7 (39.82)	1.84 (1.98)			146 ($CHCl_3$)			Ref 1a proc
Methyl *p*-phenylethynylbenzenesulfonate[a]	76	66.20 (66.17)	4.44 (4.43)		11.75 (11.65)	155 (EtOAc)			Ref 1a proc
Chroman	*b*	80.55 (80.46)	7.52 (7.54)					6.9m (4 H), 4.1t (2 H), 2.7t (2 H), 1.9m (2 H)	This work
β-*o*-Chlorophenylethanol[a]	*b*	61.04 (60.66)	5.79 (5.66); for Cl	22.14 (22.15)		*c*		7.2m (4 H), 3.7t (2 H), 2.95t (2 H), 2.72s (1 H)	This work
β-*o*-Chlorophenyl-1-propanol[a]	*b*	63.09 (62.81)	6.65 (6.57)			*c*		7.25m (4 H), 3.65t (2 H), 2.85m (3 H), 1.86m (24)	This work
2-Phenylpyrrolo[3,2-*b*]pyridine	26	80.40 (79.96)	5.19 (5.34)	13.90 (14.05)		192 (Sublimed)			Ref 4

[a] Not previously described. [b] See Table IV. [c] Pure sample trapped from vpc.

Anal. Calcd: C, 86.51; H, 5.81. Found: C, 86.24; H, 5.70. This material was identical in all respects with a sample prepared from the lithium aluminum hydride reduction of 3-benzylidenephthalide.

Dihydrobenzofuran. For this reaction the usual[1a] apparatus was employed except that the condensor was fitted with a series of two cold traps preceding the mercury trap. A gentle sweep of nitrogen was passed through the reaction at all times. A mixture of β-(*o*-iodophenyl)ethynyl alcohol (4.12 g, 0.0166 mol), cuprous *n*-propylacetylide (2.21 g, 0.0169 mol) in pyridine (125 ml) at 125° for 19 hr afforded upon work-up 1.58 g (79%) of pure dihydrobenzofuran, bp 96° (38 mm): nmr 6.9 (4 H) multiplet, and triplets at 4.5 (2 H) and 3.1 (2 H); (C=O) at 1224 cm^{-1}.

The cold trap contents were distilled to yield 0.55 g (49%) of 1-pentyne, bp 40°. The nmr and ir spectra were identical with authentic acetylene. A quantitative analysis of this and related reactions was accomplished by gas chromatography using a column of Carbowax 20M coated with 5% silver nitrate. The results are presented in Table III.

β-Phenylethanoyl-*n*-propylacetylene. A mixture of hydrocinnamoyl chloride (1.74 g, 0.0104 mol) and cuprous phenylacetylide (0.88 g, 0.0053 mol) was allowed to stand at room temperature for 24 hr under nitrogen. Ether was added, the insoluble copper salts were filtered, and the solution was concentrated and distilled *in vacuo* to yield 0.66 g of unreacted hydrocinnamoyl chloride. The residue was chromatographed on 30 g of silicic acid. The product was eluted with 1:1 benzene–petroleum ether. A pure substance was obtained by thin layer chromatography. The solvent was removed finally at 0.05 mm to yield 0.55 g, 81% of acetylene.

Anal. Calcd for $C_{17}H_{14}O$: C, 87.14; H, 6.02. Found: C, 86.72; H, 6.20. The ir spectrum showed a strong C=O at 1660 cm^{-1} and a strong C≡C at 2200 cm^{-1}. The nmr spectrum contained a multiplet at 7.38 (10 H) and a singlet at 2.98 (4 H).

Butenylphenylacetylenes. A mixture of either *cis*- or *trans*-crotyl chloride (2.2 g, 0.023 mol) and cuprous phenylacetylide (1.2 g, 0.0072 mol) under nitrogen was warmed at 75° for 16 hr in a glass-stoppered test tube. Unreacted crotyl chloride was distilled from the mixture (1.0 g). The cooled product mixture was triturated with ether, filtered, and concentrated to provide 1.91 g, 85%, of crude olefinic acetylene. Pure substances were fractionated by gas chromatography upon a 20% Carbowax column that contained 5% wt of silver nitrate. The retention times of 3-phenylethynylbutene-1 and *trans*-crotylphenylacetylene were 4 and 8 minutes, respectively. The substances were characterized by ir and nmr analysis. The *trans* isomer showed *trans* olefin bands at 1600 and 760 cm^{-1}, C≡C at 2210 cm^{-1} and phenyl at 690 and 755 cm^{-1}. The nmr of the substance exhibited multiplets at 7.38 (5 H), 5.6 (2 H), and 1.7 (3 H). The terminal olefin absorbed in the ir at 920 (5) and 990 (5), and the C≡C was at 2220 cm^{-1}; nmr 7.38 (5 H) multiplet, 5.15 and 5.45 (2 H) singlets, 3.32 (1 H) multiplet, 1.35 (3 H) doublet. No evidence for the *cis* isomer was detected in the ir spectrum. This substance could coemerge with the *trans* isomer and a small amount of it would not be detected. The same results but with very low conversions were obtained when the reaction was conducted in DMF at 126°.

Reaction of the 3-Bromo-2-butanols with Cuprous Chloride. A mixture of 2-bromo-3-butanol (either *threo* or *erythro*) (2.6 g, 0.0175 mol) and cuprous chloride (1.7 g, 0.017 mol) in 5 ml of acetonitrile was warmed at 80° for 19 hr. The mixture was distilled at atmospheric pressure. The distillate (4.43 g) contained 20% 2-butanone (71%). The pure material was trapped by gas chromatography on a 5% $AgNO_3$–Carbowax column. It had an ir and nmr spectrum identical with authentic ketone. Reaction of either isomer without solvent gave the same results. The butenoxides were recovered unchanged from a similar acetonitrile reaction solution, and no butanone could be detected.

Kinetics. The reaction of *o*-iodoaniline with cuprous phenylacetylide was followed by flame ionization gas chromatography using diphenylmethane as a calibrated marker for *o*-iodoaniline and a 6 ft 5% SE Gum 30 column at 115°. The emergence of the aniline and diphenylmethane were 8 min and 15 min, respectively. Initial concentrations in pyridine were varied from 2×10^{-2} *M* to 0.5×10^{-2} *M* acetylide and 2×10^{-2} *M* to 0.5×10^{-2} *M* for iodoaniline. Initial slopes and general second-order plots showed the reaction to second order over-all and first order in each reactant. Typically, from a 25-ml reaction solution thermostated at 100° under nitrogen and protected with a serum cap, a 0.50-ml sample was withdrawn and quenched in 1 ml of a stock ethyl acetate solution of diphenylmethane. The precipitated acetylide was centrifuged and the supernatant solution was analyzed by averaging the

Table VII. Solubilities of Cuprous Acetylides at 25°

Acetylide, CuC≡C—R	Solvent	Solubility, mol/l.
n-Propyl	Pyridine	10^{-5}
n-Propyl	DMF	0
n-Pyridyl	Pyridine	10^{-5}
β-Ethanolyl	Pyridine	10^{-5}
Phenyl	Pyridine	7.5×10^{-3}

results of three successive shots. This tedious procedure was supplanted with a direct potentiometric determination of iodide. An Orion iodide ion specific working electrode and a double jacketed calomel reference electrode were employed in conjunction with a Beckman Research potentiometer. For kinetic analysis, 1.00 ml of reaction solution was injected into a solution of 8.50 ml of distilled water and 0.50 ml of concentrated ammonium hydroxide. The electrode was calibrated under these conditions. A 10-fold change in concentration amounted to a potential difference of 59.16 mV.

Solubilities of Cuprous Acetylides. The solubilities of some acetylides as determined from atomic absorption analysis for copper are presented in Table VII. Solutions for analysis were prepared by warming at 100°, allowing to cool, and filtering.

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The Total Synthesis of Fulvoplumierin

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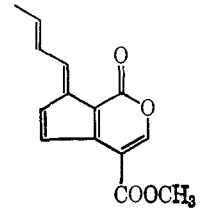
Abstract: Condensation of dimethyl penta-2,3-dienedioate (**3**) with butadiene gave the Diels–Alder adduct **4** which, on oxidation with potassium chlorate–osmium tetroxide, was transformed to the diol **5**. Treatment of the diol with dimethylformamide dimethyl acetal followed by acid hydrolysis yielded the α-pyrone **9**. Cleavage with periodate and aldol condensation of the resulting dialdehyde **10** gave the hydroxyfulvene **12** from which the chloride **15** was prepared with oxalyl chloride. Coupling of this chloride (**15**) with lithium di(*trans*-1-propenyl)cuprate (**16**) gave fulvoplumierin (**1**). The stereochemical outcome of coupling a vinyl cuprate with a vinyl halide is discussed.

Fulvoplumierin, an antibacterial pigment from the bark of *Plumiera acutifolia* and *Plumiera rubra var. alba*, was first isolated in 1952[2] and subsequent structural investigations led to formula **1**.[3,4] The total synthesis of fulvoplumierin described in this paper confirms this structural assignment and represents the first synthesis of a naturally occurring fulvene.[5] Condensation of dimethyl penta-2,3-dienedioate (**3**)[6] prepared from dimethyl β-chloroglutaconate (**2**)[7] and triethylamine in tetrahydrofuran with butadiene gave a mixture of the *cis*- and *trans*-α,β-unsaturated esters **4**. Potassium chlorate in the presence of a catalytic amount of osmium tetroxide[8] in aqueous tetrahydrofuran did differentiate satisfactorily between the two double bonds in **4** and led to a mixture of diastereomeric diols **5** characterized further by transformation to acetonides. Attempts to convert the diol **5** to the α-hydroxymethylene ester **6** with methyl formate and sodium hydride were unpromising and led to methyl 1-oxo-1H-2-benzopyran-4-carboxylate (**7**),[9] the latter probably originating from the desired diol **6**.



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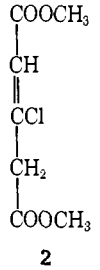

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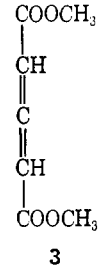

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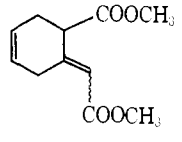

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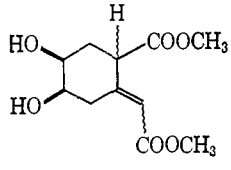

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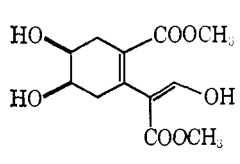

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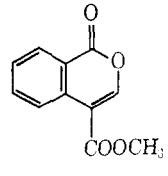

7

We then hoped that the mild conditions used in the condensation of active methylene compounds with dimethylformamide dimethyl acetal[10] would allow the

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