

COPPER(I)-INDUCED RADICAL CYCLIZATION OF DIETHYL
o-(ALLYLOXY)PHENYLMALONATES TO CHROMAN DERIVATIVES

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The reaction of o-(allyloxy)bromobenzenes with copper(I) diethyl malonate afforded diethyl o-(allyloxy)phenylmalonates which under the reaction conditions cyclized to give 4,4-bis(ethoxycarbonyl)-3-methylchromans, 4,4-bis(ethoxycarbonyl)-3-methylenchromans, and 3-(3-butenyl)-4,4-bis(ethoxycarbonyl)chromans.

Radical cyclization is currently offering a new method for the construction of five- and six-membered rings.¹⁻⁴⁾ The usefulness of this reaction depends on the means of generating a radical center within a molecule which possesses a multiple bond in an appropriate position relative to the radical center. Organic radicals were generated under mild conditions by the reductive dehalogenation of organic halides with tributylstannane in the presence of a catalytic amount of azobisisobutyronitrile,¹⁾ and with cobaloxime in the presence of sodium borohydride.²⁾ Tributylstannane was also employed to generate aryl radicals from arene diazonium salts,³⁾ and copper(I) catalysis was reported in the reaction of allyl trichloroacetate.⁴⁾ In this report is described the radical cyclization of diethyl o-(allyloxy)phenylmalonates to chromans which is induced by homolysis of a Cu(I)-C bond.

A mixture of o-(allyloxy)bromobenzene (1a) (5 mmol) and copper(I) diethyl malonate⁵⁾ (12 mmol) was stirred for 5 h under reflux in dioxane under nitrogen. After ordinary work-up, fractional distillation, and column chromatography on silica gel with benzene, 4,4-bis(ethoxycarbonyl)-3-methylchroman⁶⁾ (3a) and 3-(3-butenyl)-4,4-bis(ethoxycarbonyl)chroman (5a) were obtained in 37% and 11% GLC yield, respectively, on the basis of the converted starting material 1a (44% conv.) using biphenyl as an internal standard. When o-bromo(2-methylallyloxy)benzene (1b) and o-bromo(3-butenyloxy)benzene (1d) were allowed to react with copper(I) diethyl

malonate under the same reaction conditions as 1a, simple coupling products, diethyl o-(2-methylallyloxy)phenylmalonate (2b) and diethyl o-(3-butenyloxy)phenylmalonate (2d), were obtained in 81% (51% conv.) and 88% (50% conv.) yield, respectively. We showed that copper(I) diethyl malonate was easily obtainable by metathesis of sodium diethyl malonate and copper(I) bromide, thermally stable up to 100 °C under an inert atmosphere, and useful in the nucleophilic substitution reaction toward aromatic halides which are not substituted with electron-withdrawing groups.⁵⁾ Failure for 2b and 2d to cyclize under the reaction conditions is ascribable to a sterically unfavorable overlap of the active methine carbon and the intramolecular carbon-carbon double bond. A similar steric effect was noted in the free radical cyclization of ω-alkenylmalonic acid derivatives.⁷⁾ The reaction of o-(2-butenyloxy)bromobenzene (1c) afforded 4,4-bis(ethoxycarbonyl)-3-ethylchroman (3c) as shown

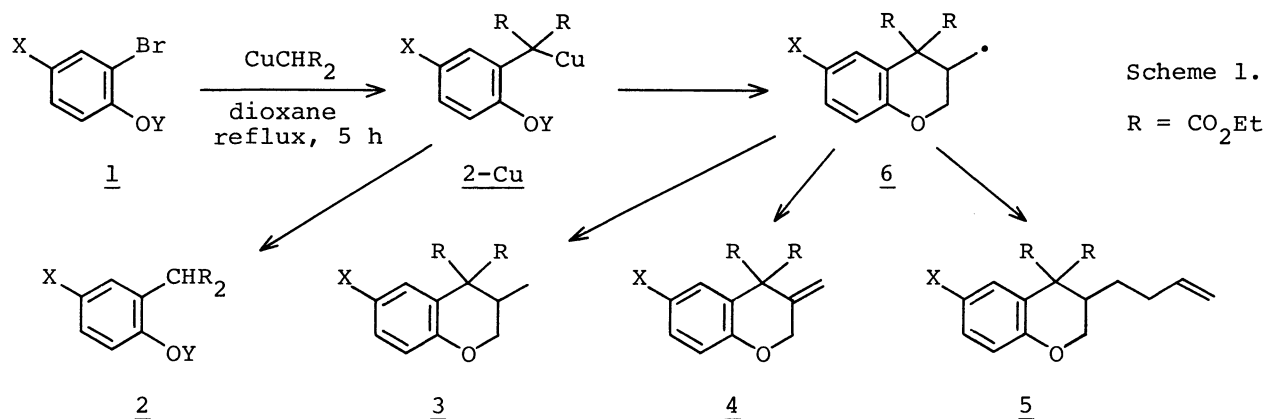


Table 1. Products yields of the reaction of o-(allyloxy)bromobenzenes with copper(I) diethyl malonate ^{a)}

<u>1</u>	X	Y	Conv./%	Product (Yield/%)			
				<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>
<u>1a</u>	H	CH ₂ CH=CH ₂	44	-	37 (<u>3a</u>)	-	11 (<u>5a</u>)
<u>1b</u>	H	CH ₂ C(CH ₃)=CH ₂	51	81 (<u>2b</u>)	-	-	-
<u>1c</u>	H	CH ₂ CH=CHCH ₃	46	-	41 (<u>3c</u>) ^{b)}	-	-
<u>1d</u>	H	CH ₂ CH ₂ CH=CH ₂	50	88 (<u>2d</u>)	-	-	-
<u>1e</u>	NO ₂	CH ₂ CH=CH ₂	64	30 (<u>2e</u>)	35 (<u>3e</u>)	-	5 (<u>5e</u>)
<u>1f</u>	CO ₂ Et	CH ₂ CH=CH ₂	70	-	38 (<u>3f</u>)	-	11 (<u>5f</u>)
<u>1g</u>	Cl	CH ₂ CH=CH ₂	80	-	26 (<u>3g</u>)	30 (<u>4g</u>)	16 (<u>5g</u>)
<u>1h</u>	F	CH ₂ CH=CH ₂	85	-	23 (<u>3h</u>)	24 (<u>4h</u>)	17 (<u>5h</u>)

a) The reaction conditions are the same as described for 1a. GLC yields are based on the converted starting material and uncorrected for stoichiometry.

b) 3c is 4,4-bis(ethoxycarbonyl)-3-ethylchroman.

in Table 1. The absence of a butenyl-transfer product 5 in this case also points to the steric obstacle of a methyl substituent in the reaction of 1-(3-chroman-1-yl)-ethyl radical intermediate with 2-butenyloxy moiety of 1c.⁸⁾

The acidic active methine proton of diethyl phenylmalonate, the product of the aromatic substitution reaction, would be replaced by copper(I) in the presence of copper(I) diethyl malonate in excess. Therefore, diethyl[o-(allyloxy)phenylmalonyl]-copper(I) (2-Cu) would be formed under the reaction conditions of 1, and the cyclization is considered to be initiated by homolysis of the Cu(I)-C bond, which is consistent with the observed deposition of metallic copper.⁹⁾ Thus generated radical species would cyclize to produce a 3-chroman-1-ylmethyl radical (6) which subsequently abstracts a hydrogen or an allyl radical from the o-allyloxy moiety of 1 as shown in Scheme 1.¹⁰⁾

Table 1 shows that an electron-withdrawing substituent on the aromatic ring accelerates the initial aromatic substitution reaction and therefore better isolation yields of chromans are obtained. The rate of radical cyclization is much faster than that of formation of diethyl o-(allyloxy)phenylmalonate except for the reaction of 1-allyloxy-2-bromo-4-nitrobenzene (1e) which gave a mixture of uncyclized (2e) and cyclized (3e, 5e) products. A strongly electron-withdrawing effect of the nitro group would stabilize the corresponding organocopper intermediate 2e-Cu against Cu(I)-C bond homolysis. Whereas 3-chroman-1-ylmethyl radicals, 6a, 6e, and 6f, abstract a hydrogen atom presumably from the starting materials,¹⁰⁾ disproportionation pathway becomes predominant in the reactions of 1-allyloxy-2-bromo-4-halobenzenes (1g, 1h), resulting in the formation of 4,4-bis(ethoxycarbonyl)-6-halo-3-methylchromans (3g, 3h) and 4,4-bis(ethoxycarbonyl)-6-halo-3-methylenechromans (4g, 4h) in approximately equal amounts. The reason of this change in the reaction behavior of 3-chroman-1-ylmethyl radical 6 may be the inductive effect of the halogens which through σ -bonds labilize the C-H bond at the 3-position of the chroman structure.

In conclusion, this work showed that diethyl o-(allyloxy)phenylmalonate underwent radical cyclization to give chroman derivatives in the presence of copper(I) diethyl malonate and the products distribution was greatly influenced by the substituent at the o-allyloxy group and at the aromatic ring.

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- 10) The effect of some additives (diisopropyl ether, diallyl ether, allyl phenyl ether, and allyl 2,6-xylyl ether) on the products distribution was investigated in the reaction of 1a. While the yield of 3a was not affected (between 39% and 30%), the yield of 5a increased to 37% in the case of allyl 2,6-xylyl ether as an additive.

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