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Copper(II) Halide Catalyzed Cyclopropanation of Olefins Involving Dehydrobromination of Bromomalonic Ester by Amine

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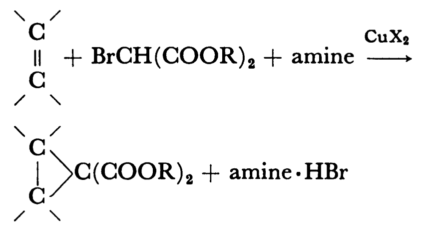
Synopsis. The reaction of olefins with bromomalonic ester and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) proceeded in the presence of a catalytic amount of copper(II) halide to give 1,1-bis(alkoxycarbonyl)cyclopropane derivatives. DBU was converted into DBU-hydrobromide during the reaction. The reaction was electrophilic and proceeded nonstereospecifically.

Cyclopropane derivatives activated by two electron-withdrawing substituents at geminal position are called electrophilic cyclopropanes, and have recently been recognized as useful intermediates in organic synthesis.[1] Their inter- and intramolecular ring opening reactions by various nucleophiles have been investigated intensively, and applied to the synthesis of several natural products.[1] Recently we have reported a new cyclopropanation reaction of olefins with *gem*-dibromides such as dibromomalonic ester using a stoichiometric amount of copper[2] or copper(I) salt.[3] In this paper we wish to describe that electrophilic cyclopropanes were obtained by use of only a catalytic amount of copper(II) salt in the reaction of olefins with bromomalonic ester and amine (Eq. 1).



$$\mathrm{>C{=}C<} + \mathrm{BrCH(COOR)_2} + \text{amine} \xrightarrow{\mathrm{CuX_2}} \mathrm{>C\!-\!C<\,(cyclo\text{-}C(COOR)_2)} + \text{amine}\cdot\mathrm{HBr} \qquad (1)$$

When bromomalonic ester was allowed to react with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and olefins in the presence of a catalytic amount of copper(II) bromide, 1,1-bis(alkoxycarbonyl)cyclopropane derivatives were obtained. For example, the reaction with styrene proceeded smoothly at room temperature in benzene to give 1,1-bis(ethoxycarbonyl)-2-phenylcyclopropane in 87% yield. During the course of the reaction, a solid material precipitated which was identified as DBU-hydrobromide by comparison of its IR spectrum with that of an authentic sample.

The effect of a variety of amines on the yield of the cyclopropane derivative was examined in the reaction with styrene (Table 1). DBU ($\mathrm{p}K_a$ 11.5) was the most effective amine among the examined. Triethylamine ($\mathrm{p}K_a$ 10.7), diethylamine ($\mathrm{p}K_a$ 10.9), and butylamine ($\mathrm{p}K_a$ 10.6) were less effective. 1,4-Diazabicyclo[2.2.2]octane (DABCO) ($\mathrm{p}K_{a1}$ 3.0; $\mathrm{p}K_{a2}$ 8.6), pyridine ($\mathrm{p}K_a$ 5.2), and aniline ($\mathrm{p}K_a$ 4.6) were scarcely effective. In the absence of amine, the cyclopropane derivative was not formed. These results seemed to indicate that basicity of the added amine was of major importance. It should be noted, however, that sodium hydride was inactive in spite of its higher basicity than that of DBU. Presumably the amine played some important role, *e.g.*, coordination to the copper ion and accelerating the reaction, in addition to functioning as a simple base.

TABLE 1. EFFECT OF AMINE ON THE COPPER(II) BROMIDE CATALYZED CYCLOPROPANATION OF STYRENE INVOLVING DEHYDROBROMONATION OF DIETHYL BROMOMALONATE BY THE AMINE[a)]

Amine	Yield of cyclopropane/%[b)]	
DBU	87	
Triethylamine	Trace[c)]	(26)
Diethylamine	47	(59)
Butylamine	16	(25)
DABCO	Trace[c)]	(Trace[c)])
Pyridine	0	(0)
Aniline	0	(Trace[c)])
Sodium hydride	Trace[c)]	(Trace[c)])

a) Reactions were carried out with styrene (2.0 mmol), diethyl bromomalonate (3.0 mmol), amine or sodium hydride (3.6 mmol), copper(II) bromide (0.10 mmol), and benzene (2.0 ml) at room temperature for 1 h. b) Determined by GLC, based on the olefin. Yields after 24 h are given in parentheses. c) GLC analysis of the reaction mixture showed a very small peak having the identical retention time with that of the cyclopropane derivative, but the product was not fully identified.

TABLE 2. SYNTHESIS OF 1,1-BIS(ALKOXYCARBONYL)-CYCLOPROPANES FROM VARIOUS OLEFINS[a)]

Olefin	Yield of cyclopropane/%[b)]	
Styrene	87	(Trace[c)])
p-Methylstyrene	76	(Trace[c)])
m-Trifluoromethylstyrene	27	(Trace[c)])
p-Chlorostyrene	53	(Trace[c)])
Acrylonitrile	62	(63)
Methyl vinyl ketone	56	(56)
Ethyl acrylate	18	(20)

a) Reactions were carried out with an olefin (2.0 mmol), diethyl bromomalonate (3.0 mmol), DBU (3.6 mmol), and benzene (2.0 ml) in the absence or presence of copper(II) bromide (0.10 mmol). b) Determined by GLC, based on the olefin. Yields obtained in the absence of copper(II) bromide are given in parentheses. c) See footnote (c) in Table 1.

Copper(II) bromide was the catalyst of choice for the reaction of styrene with diethyl bromomalonate and DBU in benzene, and the yield of the cyclopropane derivative was 87%. Copper(II) chloride (50% yield), copper(I) chloride (76%), and copper(I) iodide (51%) were somewhat less effective. Use of copper(II) acetate and copper(II) acetylacetonate resulted in very low yields. In the absence of catalyst, the cyclopropane derivative was not obtained. The yield was also greatly influenced by the nature of the solvent. In methanol and hexane, the cyclopropane derivative was not obtained in an appreciable amount. Polar aprotic solvents such as dimethyl sulfoxide (82%), *N,N*-dimethylformamide (54%), and acetonitrile (52%) were effective, but benzene was the most suitable solvent among the examined.

Other examples of the reaction (Eq. 1) are summarized in Table 2. The reaction with substituted styrenes gave the corresponding cyclopropane derivatives in moderate to high yields. Electron-deficient olefins such as acrylonitrile and methyl vinyl ketone also reacted smoothly to give the cyclopropane derivatibes in good yields. Electron-rich olefins such as isobutyl vinyl ether were inactive under the conditions. The reaction with alkyl-substituted olefins such as 1-octene and cyclooctene gave the cyclopropane derivatives only in very low yields.

The cyclopropanation reactions of (*E*)- and (*Z*)-*β*-methylstyrene were studied to determine the stereospecificity of the reaction. From both olefins were obtained the (*E*)- and (*Z*)-cyclopropane derivatives in essentially the same ratio ($E/Z=95/5$), indicating that the reaction proceeded in a non-stereospecific way. Isomerization of (*E*)- and (*Z*)-*β*-methylstyrene and that of (*E*)- and (*Z*)-cyclopropane derivatives were not observed under the conditions.

The relative reactivity of substituted styrenes was also investigated. The logarithm of relative reactivity was plotted against Hammett σ value to obtain a straight line with good correlation. A slope of -0.8 indicates that the reaction is electrophilic.

It should be noted that the reaction with electron-deficient olefins such as acrylonitrile proceeded even in the absence of the catalyst, whereas the reaction with styrene derivatives essentially required the copper salt as catalyst. Therefore it seems reasonable to consider that the reaction with electron-deficient olefins proceeded through a different reaction pathway from that with styrene derivatives. A mechanism involving Michael type addition of the carbanion of bromomalonic ester may be plausible for the reaction with electron-deficient olefins.[4] For the copper(II) bromide catalyzed reaction with styrene derivatives, a mechanism involving a free radical intermediate or an organocopper intermediate seems to be plausible. Relatively low reactivity of unconjugated olefins such as isobutyl vinyl ether or 1-octene may accommodate the free radical mechanism. Further mechanistic studies will hopefully delineate the detailed mechanism.

Experimental

Infrared spectra were measured with a Hitachi Model 215 grating spectrophotometer. ^{1}H NMR spectra were obtained with a Varian Model T-60A spectrometer in CCl_4 using Me_4Si as the internal standard. GLC analysis and preparative purification were performed by a Shimadzu GC-4C gas chromatograph equipped with a 1 m × 3 mm column (Silicone DC-550 5% on Celite 545, 60—80 mesh) and a thermal conductivity detector. Diethyl bromomalonate was prepared by light-induced bromination of diethyl malonate[5] and purified by fractional distillation under reduced pressure. *p*-Methylstyrene,[6] *p*-chlorostyrene,[6] *m*-trifluoromethylstyrene,[6] (*E*)-*β*-methylstyrene,[6] and (*Z*)-*β*-methylstyrene[7] were prepared according to the literature procedures with minor modifications. Other olefins were commercially available and were distilled before use. An authentic sample of DBU-hydrobromide was prepared by treatment of DBU with dry hydrogen bromide in benzene. All solvents were dried in a usual manner and distilled before use. Other chemicals including copper salts and amines were used as obtained commercially.

General Reaction Procedure for Synthesis of 1,1-Bis(alkoxycarbonyl)cyclopropanes from Olefins. A mixture of an olefin (2.0 mmol), DBU (548 mg, 3.6 mmol), and anhydrous copper(II) bromide (22 mg, 0.10 mmol) in benzene (2.0 ml) was placed in a 20-ml one-necked flask fitted with a magnetic stir bar and a stopcock. Diethyl bromomalonate (717 mg, 3.0 mmol) was added dropwise with stirring under cooling in a water bath (15—25 °C). An exothermic reaction took place and DBU-hydrobromide gradually precipitated. After the addition was completed, the mixture was stirred for 1 h. An appropriate hydrocarbon internal standard was added and the mixture was analyzed by GLC. The products were isolated by preparative GLC and identified by comparison of their IR and ^{1}H NMR spectra with those of authentic samples.[2] DBU-hydrobromide was separated from the reaction mixture by filtration, washed with ether, dried under vacuum, and identified by comparison of its IR spectrum with that of an authentic sample (88% yield based on diethyl bromomalonate).

The reaction with other amines, sodium hydride, or other copper salts, and the reaction in other solvents were carried out in a similar fashion.

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