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LETTERS

HOLE-TRANSFER CATALYZED REACTION: ONE-ELECTRON OXIDATION AS A STRATEGY FOR THE SELECTIVE CYCLOPROPANATION OF π BONDS

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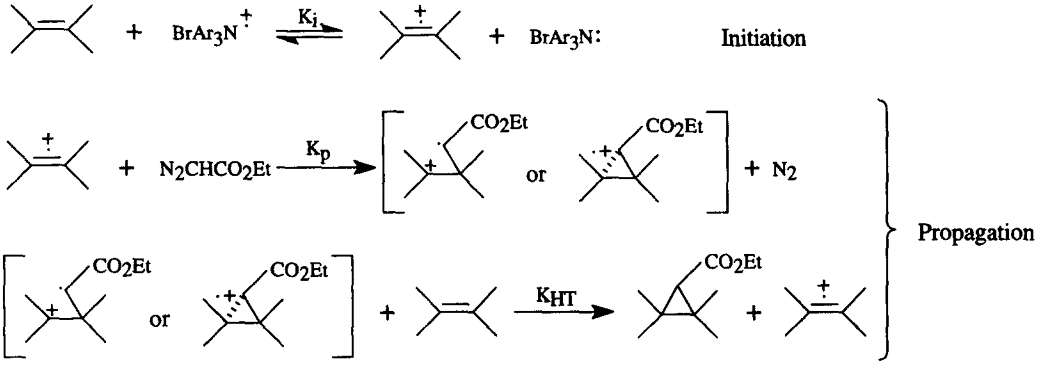
ABSTRACT: The cyclopropanation of alkenes, dienes and trienes with ethyl diazoacetate catalyzed by *tris*(4-bromophenyl)aminium hexachloroantimonate have been studied. The efficiency and selectivity of cyclopropanation is based solely upon, and is highly sensitive to, the ease of ionization of π bonds in the substrate. Simple double bonds such as norbornene and 1-octene are not amenable to cyclopropanation *via* this method. © 1998 Elsevier Science Ltd. All rights reserved.

One-electron oxidation (hole formation) is increasingly being exploited as a fundamental option for activating molecules toward synthetically useful chemistry mediated by cation radicals.[1,2]

One catalytic reaction that has been studied is cation-radical cyclopropanation. This type of catalytic reaction requires aminium salt (a hole-catalyst), ethyl diazoacetate, a moderately electron rich olefin, and very mild experimental conditions (≤ 0°C, 1-20 min).[3]

The proposed mechanism of aminium salt (hole-catalyzed) cyclopropanation of π bonds with ethyl diazoacetate is shown below:



Due to the importance of the cyclopropyl ring system in many naturally occurring compounds, much attention has been focused on new methods for preparation and selective cyclopropanation.[3,4]

We herein report our results on the regio- and site- selectivity experiments for cation-radical cyclopropanation reactions on diene and triene substrates. Simple ionizable olefins such as *trans*-anethole, and *trans*-stilbene have been shown to produce a high yield of cyclopropanation products.[3] Similarly, we find that the cyclopropanation of 1,1'-*bis*(*p*-methylphenyl)ethylene, and 4,4'-dimethyl-*trans*-stilbene produces high yields of cyclopropanated products (78%, and 82% respectively). Upon addition of catalyst, decolorization of the aminium salt occurs rapidly and is accompanied by vigorous nitrogen evolution. Completion of the reaction is assumed when no further nitrogen bubbles are observed.

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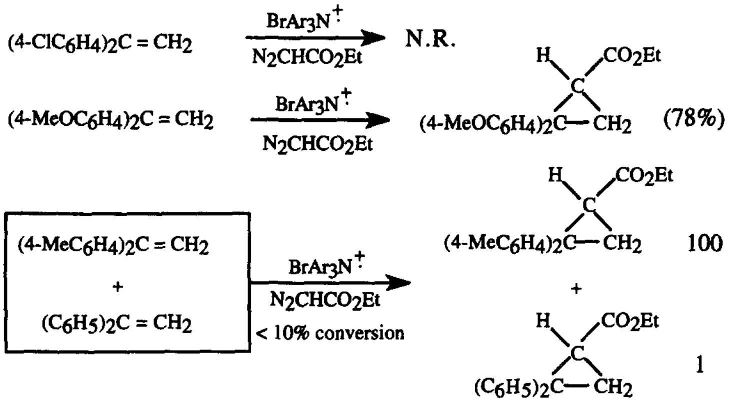
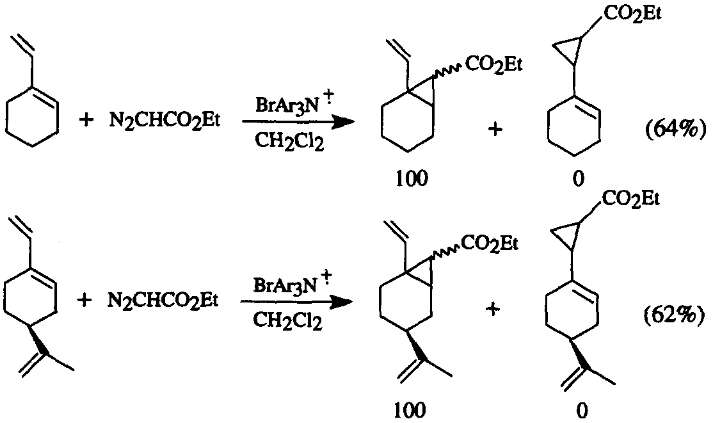
The possibility of a Bronsted acid catalyzed mechanism is ruled out by the observation that excess 2,6-di-*tert*-butylpyridine fails to suppress the reaction.[5] Moreover, the cyclopropanation of 2,4-dimethyl-1,3-pentadiene yields, as a byproduct, 5-10% of the cyclodimer resulting from hole-transfer catalyzed Diels-Alder cycloaddition but none of the acid-catalyzed cyclodimerization product.[1]

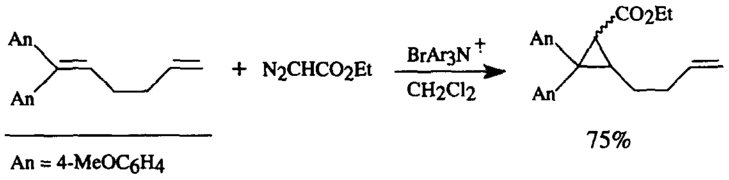
The cation radical cyclopropanation reaction, like other cation radical reactions, is sensitive to polar effects.[1] Thus cyclopropanation fails for substrates which are difficult to ionize, such as terminal olefins like 1-octene and norbornene. We also obtain no reaction when we attempt the cyclopropanation of 4,4'-*bis*(*p*-chlorophenyl)-ethylene. These substrates are outside the oxidation range required ($E_{ox} \leq 1.5$ V vs SCE) for ionization by the hole catalyst. However, we obtain an instantaneous reaction when a more ionizable substrate such as 4,4'-bis(*p*-methoxyphenyl)ethylene is used. A quantitative study of the competitive cyclopropanation of 1,1-diphenyl ethene and its corresponding 4,4'-dimethyl derivative revealed a relative reaction rate of 1:100, supporting the sensitivity of the cation-radical cyclopropanation reaction to polar effects.



The outstanding selectivity of hole-catalyzed cyclopropanation is illustrated by the hole-catalyzed cyclopropanation of 1-vinylcyclohexene, and 4-isopropenyl-1-vinylcyclohexene. In both cases, the diene produces a cation-radical which reacts exclusively at the more substituted endocyclic double bond.

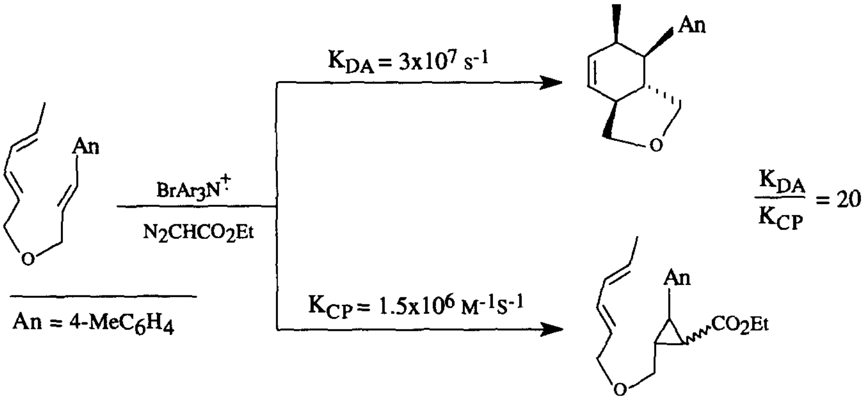


The regiochemistry and site selectivity of the hole-catalyzed cyclopropanation is further exemplified by studies on the substrate 1,1'-*bis*(*p*-methoxyphenyl)hexa-1,5-diene. This reaction produces 75% yield of cyclopropanation at the more ionizable site of the molecule. No cyclopropanation at the terminal double bond is observed.



We believe the cation-radical cyclopropanation reaction is superior over existing methods of cyclopropanations. Both rhodium acetate[6] and metalloporphyrin[7] catalyzed cyclopropanation of double bonds require a long reaction time and show only a modest site selectivity. As a result a mixture of cyclopropanated products is obtained which makes purification extremely difficult. The requirement for the use of a large excess of substrate in these methods, and the need for the preparation of catalysts, makes them less attractive.

We realize that with any chemical reactions there are both advantages and disadvantages, and cation radical cyclopropanation reaction is no exception. The main attractive features of the hole-catalyzed cyclopropanation reaction are that a) the reactions are catalytic, facile, and efficient, b) the reactions are carried out under mild experimental conditions (-78°C - 0°C), c) the reactions are regio- and site- selective, d) an excess of the alkene component is never required, and e) the aminium salt is commercially available.[8] The major limitation of this reaction is the failure in efficient cyclopropanation of substrates that prefer to yield a rapid intramolecular or intermolecular cycloaddition product in the presence of hole catalyst ($k_{CA} > K_{CP}$). For instance cyclopropanation of the triene below produces only a very small amount of cyclopropanation products. The main product of the reaction is an intramolecular Diels-Alder product.[9]



ACKNOWLEDGMENTS

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8. General experimental procedure: The appropriate substrate is dissolved in dichloromethane solution (~0.15 M) and cooled to 0°C. Ethyl diazoacetate (400 mol %) is then added, followed by the aminium salt (20-40 mol %). Both reagents are available from the Aldrich Chemical Company. The reaction mixture is stirred for 1-20 min, depending upon the substrate. The reactions are quenched with excess K_2CO_3/CH_3OH. Products are purified by ether/brine extraction followed by flash silica gel chromatography (hexane followed by 8:2 hexane/ethyl acetate). Structure assignments are based upon GC-MS, and ^{1}H-NMR.
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