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The reactions of thiols and diphenyldisulfide with terminally substituted methylenecyclopropanes

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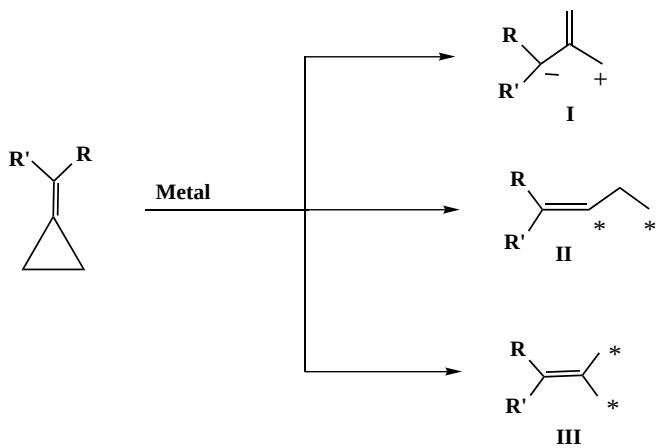
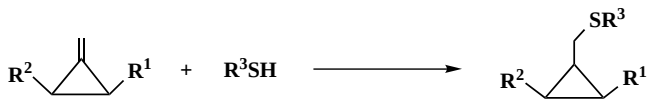
Abstract—In the reactions of thiols with terminally substituted methylenecyclopropanes, we found that the Markovnikov adducts were produced exclusively along with cyclopropyl ring-opened products via a radical reaction mechanism. The substituent effects and the reaction with diphenyldisulfide were also examined.

Methylenecyclopropanes (MCPs) are highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis.[1] Recently, much attention has been paid to transition-metal catalyzed reactions of MCPs with various reactants. The reaction patterns of MCPs were both interesting and troublesome. Three kinds of reaction patterns of MCPs have been disclosed based on the concept of synthons (Scheme 1). MCPs can react with polar reactants such as ROH,[2] R_2NH,[3] malonate derivatives,[4] carbon dioxide,[5] aldehydes,[6] and imines[7] in the presence of a Pd metal catalyst to give type I products. MCPs can also react with nonpolar reactants such as R_3SiH,[8] R_3SnH,[9] $R_2B–BR_2$,[10] $R_3Si–BR_2$,[11] $R_3Si–CN$[12] and olefins[13] in the presence of Pd or Rh metal catalysts to afford type II and/or type III products depending on the reaction conditions (Scheme 1). However, these reactions usually need severe reaction conditions such as very high temperature (120°C) and prolonged reaction time (3 days). Little attention has been paid to the free radical reactions of MCPs.[14]

It is well known that many reactions involving thiols and disulfides proceed via a free radical mechanism. Moreover, metal-catalyzed reactions of thiols[15] and disulfides[16] have also been explored in recent years although their scope and limitations are not very clear. Gilchrist[17] in 1968 and Kozhushkov[18] in 1998 reported that in the reactions of thiols with terminal unsubstituted methylenecyclopropanes, the anti-Markovnikov adducts were formed exclusively with retention of the cyclopropyl ring (Scheme 2). However, during our own examination of the reactions of thiophenol with terminally substituted MCPs, we found that the reaction products are different from those reported before and that these reactions are completed within 24 h at room temperature in the absence of metal catalysts and radi-



Scheme 1.



Scheme 2.

Keywords: thiol; methylenecyclopropane; radical reaction; Markovnikov adduct; terminally substituted; diphenyldisulfide.

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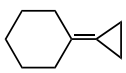
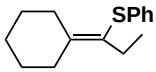
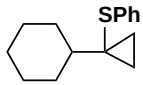
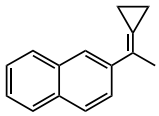
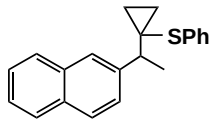
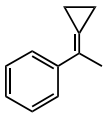
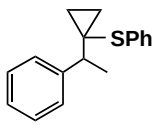
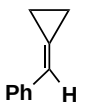
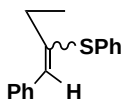
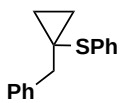
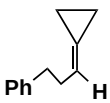
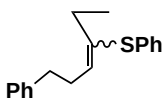
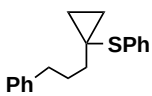
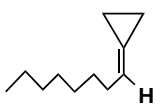
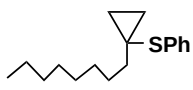
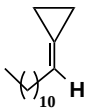
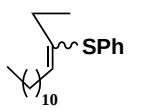
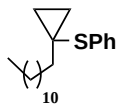
cal initiators (Table 1). As can be seen from Table 1, Markovnikov adducts were produced along with the cyclopropyl ring-opened products. The substituents can affect the selectivity of the products. Aryl and alkyl disubstituted MCPs gave exclusively Markovnikov adducts **3** in very high yields (Table 1, entries 2 and 3). Dialkyl substituted MCPs and MCPs with only one aryl substituent produced Markovnikov adducts **3** along with cyclopropyl ring opened products **2** as the major products (Table 1, entries 1, 4–7).

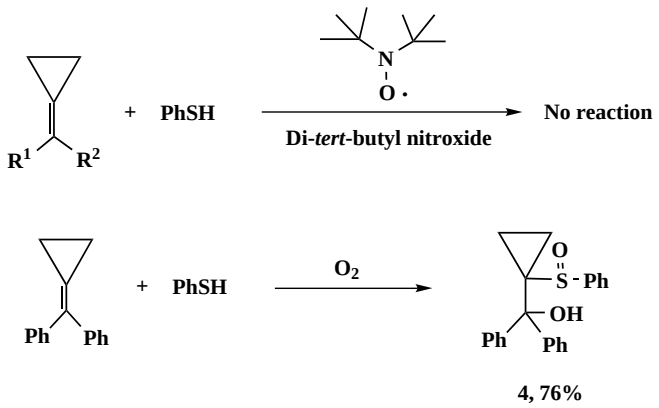
In order to gain more mechanistic insights into this thiol addition reaction, we carried out the same reaction in the presence of an excess of di-*tert*-butyl nitroxide (1.2 equiv.) (a free radical scavenger) (Scheme 3), but we found that no reaction occurred at all. The

Table 1. The free radical reactions of thiophenol with methylenecyclopropanes[a]

Entry	Substrate	Time/h	Product Yield/%[b]	
1	 1a	24	 2a, 32%	 3a, 41%
2	 1b	24	 3b, 95%	
3	 1c	24	 3c, 90%	
4	 1d	2	 2d (*E*/*Z*= 2.4/1), 21%	 3d, 53%
5	 1e	3	 2e (*E*/*Z*= 1.3/1), 58%	 3e, 4%
6	 1f	24	 2f (*E*/*Z* mixture), 40%	 3f, 45%
7	 1g	24	 2g (*E*/*Z*= 1/3.3), 61%	 3g, 31%

[a] All reactions were carried out with 0.5 mmol MCPs (1a-1g) and 1.0 mmol thiophenol in toluene at r.t.

[b] All yields were isolated yields.



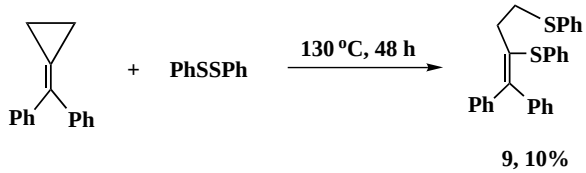
Scheme 3.

reactions were probably initiated by adventitious oxygen because a trace of PhSSPh was also detected in all cases.[15] Furthermore, if the reaction was carried out under air, product **4**, derived from a radical 'TOCO reaction', was obtained in 76% yield (Scheme 3).[19] Based on the results obtained and the distribution of products, a stepwise radical mechanism is proposed in Scheme 4. In contrast to the addition to terminal unsubstituted methylenecyclopropanes, the thiophenol radical attacks C1 of the double bond to generate the cyclopropyl radical **5**, which undergoes the well-established rapid ring opening rearrangement to give the corresponding homoallylic radical **6**. The radicals **5** and **6** abstract hydrogen to give **2** and **3**, respectively.

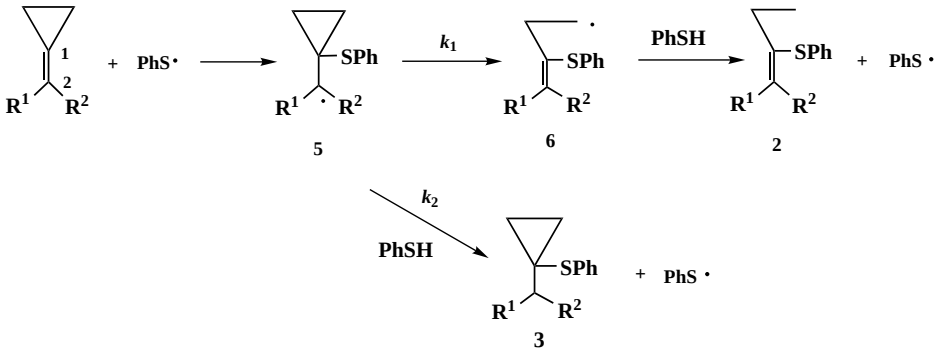
The two processes compete with each other (k_1 and k_2). The stabilities of methylenecyclopropyl radicals have been disclosed before.[20] Groups which can conjugate with the radicals greatly slow down the rearrangement. Thus, in the reaction of **1a** or **1e**–**f** with thiophenol, two products were formed at the same time ($k_2 \sim k_1$). However, in the reaction of **1b** and **1c** with thiophenol, only products **3b** and **3c** were isolated, respectively ($k_2 \gg k_1$).

In addition, the reactions of mercaptoethanol (an aliphatic thiol) with MCPs are, in general, slower than those of thiophenol. Higher reaction temperatures are required to give the analogous products **7** and **8** in moderate yields (Scheme 5).

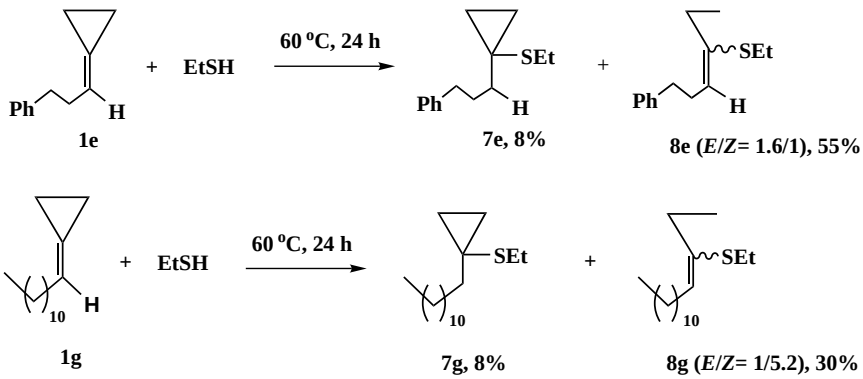
On the other hand, we also examined the reaction of diphenyldisulfide with terminally substituted MCPs. The reaction is very sluggish even at higher temperature giving the cyclopropyl ring-opened product **9** in 10% yield as the sole product (Scheme 6). We believe that the reaction pattern of disulfides with MCPs is very similar to those of thiols.



Scheme 6.



Scheme 4.



Scheme 5.

In conclusion, we disclose a novel reaction pattern of thiols and disulfides with terminally substituted MCPs. The substituents can significantly affect the reaction products. Markovnikov adducts **3** were exclusively formed along with a cyclopropyl ring-opened product via a radical reaction mechanism which is totally different from terminal unsubstituted MCPs. Efforts to elucidate the scope and limitations of this radical reaction system are underway.

Acknowledgements

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