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Michael addition reactions of Grignard reagents to 2-halogenoacrylates: a convenient method for the synthesis of polysubstituted cyclopropane compounds

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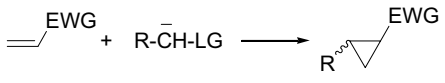
Abstract—Grignard reagents undergo Michael addition reactions to methyl 2-halogenoacrylate compounds to afford polysubstituted cyclopropane in high yields.

Cyclopropane rings are found as basic structural elements in a wide range of compounds, and their unique features provide important opportunities in the field of drug design.[1] Moreover, cyclopropane containing compounds have also been used as versatile intermediates in the synthesis of both more highly functionalized cyclic compounds and acyclic compounds.[2] Therefore, large methods for the synthesis of cyclopropane rings have been reported and the stereocontrolled synthesis of cyclopropane derivatives continues to attract considerable interest in recent years.[3] These methods include Michael initiated ring closure (MIRC) reactions that have been widely studied (Scheme 1),[4] and great progress has been made in this area of research. Efficient asymmetric cyclopropanation reactions have been achieved using this strategy with a variety of nucleophiles, such as α-halo carbanions,[5,6] and sulfur,[7] phosphorus,[8] arsenium[9] and telluronium[10] containing ylide compounds.

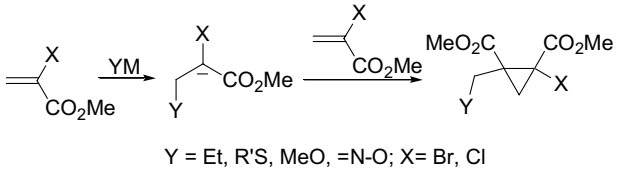
The common mechanism of all of these reactions is the addition of a carbanion with a leaving group (LG) to an electron-deficient alkene, followed by subsequent expulsion of the leaving group. This conceptually simple synthetic methodology does present some drawbacks, such as a strong base (NaH, KH, NaOH, *t*-BuOK, etc.) used to generate the nucleophiles, and a lack of high stereoselectivity in formation of products, although efficient stereocontrolled cyclopropanation reactions have been achieved using a variety of chiral auxiliaries attached to both the Michael acceptors and the nucleophiles.[3a]

It has been reported that the conjugated addition of methoxide, thiolates,[11] oxime anions, hydrazones[12] and EtZnCl[13] to methyl α-bromoacrylate generates an ester enolate that undergoes conjugated addition to another molecule of the bromoacrylate, which is followed by displacement of bromide to stereospecifically form tetrasubstituted cyclopropane rings (Scheme 2).

As an extension of our studies on the formation of cyclic compounds, this communication discloses our finding that 2 equiv of 2-halogenoacrylates react with Grignard



Scheme 1.



Scheme 2.

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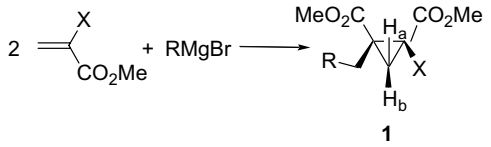


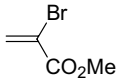
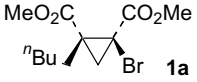
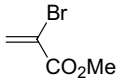
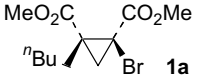
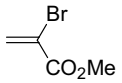
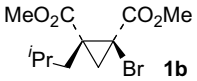
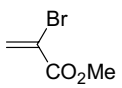
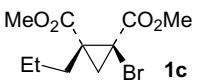
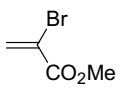
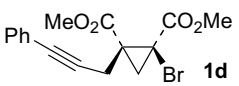
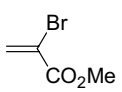
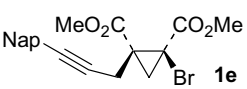
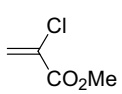
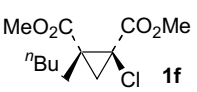
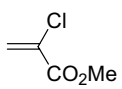
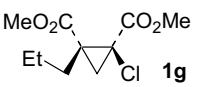
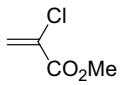
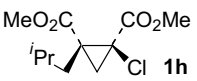
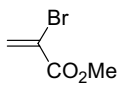
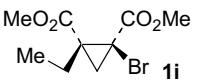
Scheme 3.

reagents[14] to form cyclopropanedicarboxylates **1** in excellent yields (Scheme 3).

Treatment of methyl 2-bromoacrylates[15] (330 mg, 2 mmol) with *n*-BuMgBr (1.0 mL, 1 M in Et_2O, 1 mmol) in Et_2O at −78 °C for 0.5 h afforded exclusively the bromocyclopropane derivative **1a** in 58% GC yield (Table 1, entry 1). Characterization of the product by ^1H NMR indicated the presence of two methoxy groups and other data was consistent with the literature.[13] The chemical shifts of protons H_a and H_b (Scheme 3) were observed to be significantly different from one another ($\delta_{Hb} = 1.28$ ppm, doublet, $J = 6.5$ Hz; $\delta_{Ha} = 2.33$ ppm, doublet, $J = 6.5$ Hz). This indicates that the two protons are located in different environments. Presumably, two carbomethoxy groups are located in a *cis*-relationship. It is noteworthy that in the presence of CuCl (0.5 equiv), the yield of **1a** increased to 85% (Table 1, entry 2).[16] When one full equivalent of CuCl was used, the yield of **1a** was not better than 60%. Upon replacement of methyl 2-bromoacrylate with methyl 2-chloroacrylate, the reaction afforded the corresponding chlorocyclopropane **1f** in excellent yield (Table 1, entry 7). Moreover, various substituted Grignard reagents could also be used in this reaction and gave the desired products in high yield. In all cases, the stereochemistry of product is analogous to that of **1a** (Table 1).

To extend this reaction, other reagents were investigated. For example, treatment of phenylethynylmagnesium chloride, generated in situ from phenylacetylene and *i*-PrMgBr, with methyl 2-bromoacrylate in THF at 50 °C for 3 h afforded cyclopropane **1d** in 62% yield. Moreover, treatment of methyl 2-bromoacrylate with MeLi in the presence of CuCl also gave the desired cyclopropane derivative **1i** in 52% yield. However, when *n*-BuLi was used under the same reaction condition, the analogous cyclopropane product was not observed. A possible reason for this is that a halide–metal exchange reaction took place.[17]

Table 1. Cyclopropanation of 2-halogenoacrylates with Grignard reagents

Entry	2-Halogenoacrylate (2 equiv)	Nucleophile (1 equiv)	CuCl (equiv)	Product	Yield (%)[a]
1		*n*-BuMgBr	—	 **1a**	58
2		*n*-BuMgBr	0.5	 **1a**	85 (59)
3		*i*-PrMgCl	0.5	 **1b**	90 (63)
4		EtMgCl	0.5	 **1c**	78 (50)
5			—	 **1d**	62 (44)
6			—	 **1e**	82 (63)
7		*n*-BuMgBr	0.5	 **1f**	94 (80)
8		EtMgBr	0.5	 **1g**	94 (78)
9		*i*-PrMgCl	0.5	 **1h**	95 (76)
10		MeLi	1	 **1i**	52 (35)

[a] GC Yields, isolated yields are given in parentheses.

In summary, we have developed a convenient method for the synthesis of polysubstituted cyclopropane compounds based on Michael addition reactions of various Grignard reagents to methyl 2-halogenoacrylates.

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16. Typical procedure for the preparation of cyclopropane derivatives **1a**: To a solution of methyl α-bromoacrylate (330 mg, 2.0 mmol) in Et_2O (4.0 mL) was added CuCl (49 mg, 0.50 mmol) and the mixture was cooled at −78 °C. After the addition of *n*-BuMgBr (1.0 mmol, 1.0 M in THF), the mixture was stirred for 0.5 h. The slurry was then quenched with 3.0 M HCl and extracted with ether (3×5 mL). The combined organic layer was dried over $CaCl_2$. The solvent was evaporated and the product was purified by column chromatography (silica gel, petroleum ether–ether = 5:1) to afford **1a** as a colorless liquid, 184 mg (59% isolated yield and 85% GC yield). ^1H NMR ($CDCl_3$, $SiMe_4$) δ 0.92 (d, $J = 6.0$ Hz, 3H), 1.28–1.70 (m, 8H), 2.08–2.13 (m, 1H), 2.33 (d, $J = 6.5$ Hz, 1H), 3.68 (s, 3H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, $SiMe_4$) δ 13.96, 22.45, 26.58, 27.54, 31.62, 34.28, 37.52, 38.25, 52.45, 53.41, 168.11, 170.04; HRMS: calcd for $C_{12}H_{19}BrO_4$, 306.0467 (100.0%), 308.0446 (97.3%), found 306.0454, 308.0404.
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