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Ethyl-2-(2-chloroethyl)acrylate: a new very versatile α-cyclopropylester cation synthon. Efficient synthesis of cyclopropane ester derivatives by Michael addition-induced cyclization reaction

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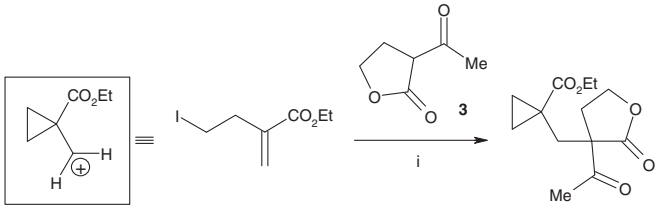
ABSTRACT

We report here the use of the readily accessible ethyl-2-(2-chloroethyl)acrylate as a new very versatile α-cyclopropylester cation synthon, which reacts efficiently and selectively with carbon-, nitrogen-, sulfur- or phosphorus-centered nucleophiles through Michael addition followed by intramolecular capture of the incipient ester enolate to afford funtionalized cyclopropane esters in high yields.

Cyclopropanes occur widely in biologically active natural products as well as in pharmaceutical and agrochemical products.[1] Therefore, a variety of methods to access these valuable target molecules have been developed.[2] Among these synthetic methods, the Michael addition-initiated ring-closure reactions (MIRCs) are usually performed on electron-deficient olefins carrying an electron withdrawing substituent at C1 and a leaving group at the C3 allylic position. [2e–j] MIRC reactions of olefins having a homo allylic leaving group at C1 have received less attention and only very specific examples have been reported.[3,4] It is noteworthy that the synthesis of optically pure cyclopropanes involving vinylsulfones derived from carbohydrates has been investigated.[5] However, a systematic study on a general Michael acceptor is still missing.

Recently, we have reported the synthesis of spirocyclopropyl cyclohexane-1,3-diones using the α-cyclopropylester cation synthon **1**, derived from olefin **2** having both an ester and a homo allylic leaving group attached at C1 (Scheme 1).[6]

This first example of the use of **2** as a α-cyclopropylester cation synthon demonstrated its ability to undergo Michael addition with a stabilized enolate. The subsequent intramolecular substitution leads to the three-membered ring derivative **4**, without any severely competing reactions such as direct S_N2 displacement of the iodine and/or its β-elimination due to its homoallylic structure. We report here the use of **2** and its improved chloro analog **11** as α-cyclopropylester cation synthons, which react with a broad



1 2 4

Scheme 1. Reagents and conditions: (i) 2-acetyl-γ-butyrolactone **3** (1.0 equiv), NaH (1.1 equiv), DMF, 0 °C to rt, 20 h.

variety of nucleophiles, leading to the corresponding cyclopropane derivatives in very good yields.

Initially, we investigated the use of **2** with other nucleophiles **6** (Scheme 2 and Table 1). The derivative **2** is readily obtained in very good yield from ethyl-2-(bromomethyl)acrylate **5**, according to the procedure described by Knochel.[7] Although satisfactory results were obtained with monosubstituted and unsubstituted ethyl acetoacetates (Table 1, entries a and b), it became obvious that, with harder nucleophiles, S_N2 and β-elimination processes are competing with the desired Michael-induced ring closure pathway. With phthalimide as a nucleophile, the only product isolated was **8**, resulting from competitive S_N2 reaction (Table 1, entry c).

We therefore turned our attention to the chloro analog **11** as a α-cyclopropylester cation synthon. Replacement of the iodine in **2** by chlorine in **11** should decrease the rates of the intermolecular

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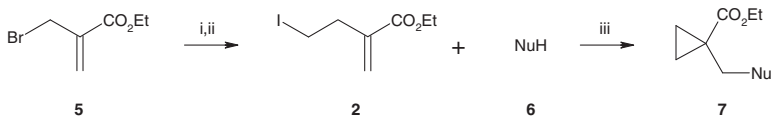
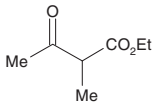
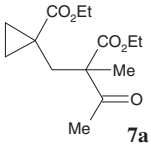
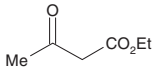
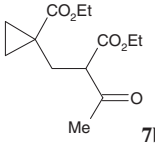
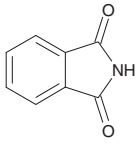
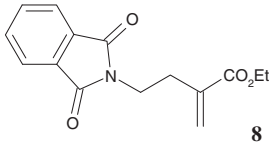


Scheme 2. Reagents and conditions: (i) Zn (1.0 equiv), 1,2-dibromoethane (0.04 equiv), trimethylchlorosilane (0.03 equiv), diiodomethane (1.0 equiv), THF, rt, 5 h; (ii) ethyl-2-(bromomethyl)acrylate **5** (1.0 equiv), LiI (2.3 equiv), CuI (1.2 equiv), THF, rt, 16 h, 80% (over two steps); (iii) NaH (1.1 equiv), NuH **6** (1.0 equiv), DMF, 0 °C, 1 h, then **2** (1.0 equiv), 0 °C to rt, 16 h.

Table 1
Reactivity of **2** with various nucleophiles **6**

Entry	NuH 6	Yield[a] (%)	Product
a		48	 **7a**
b		50	 **7b**
c		29	 **8**

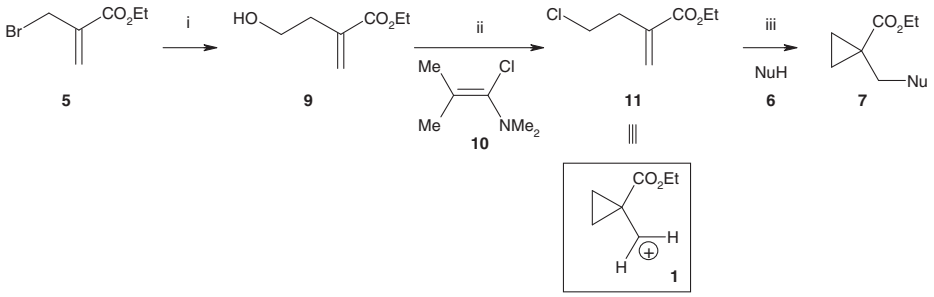
[a] Yields refer to isolated compounds after purification by chromatography on silicagel.

substitution reaction (S_N2), as well as the elimination reaction of the homoallylic halogen (E_2). However, changing iodine into chlorine should not affect the Michael addition reaction. Furthermore, the capture of the incipient ester enolate through intramolecular S_N2 reaction should proceed readily, even in the case of chloride as the leaving group, due to the entropically favored three-membered ring cyclization reaction (Scheme 3). Indeed, we have obtained high yields of cyclopropane derivatives by reaction of various stabilized enolates with **11** (Scheme 3, Table 2).

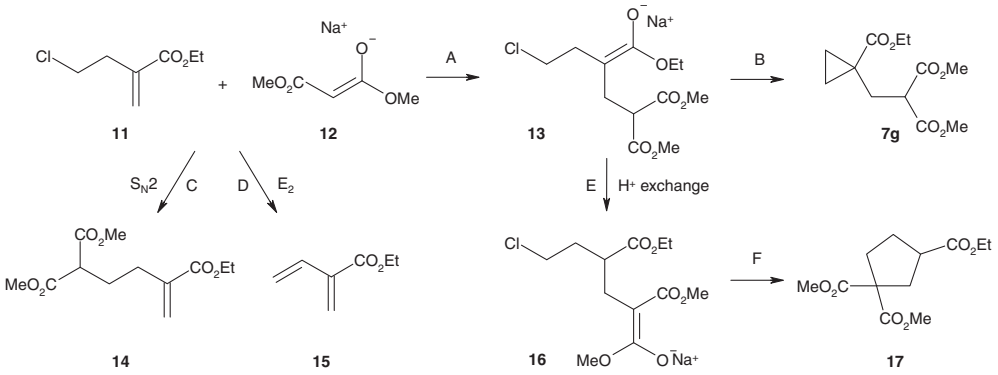
The ethyl-2-(2-chloroethyl)acrylate **11** is conveniently prepared on multigram scale by reaction of the bromide **5** with indium and formaldehyde.[8] The alcohol **9** is then transformed into the corresponding chloride **11** by treatment with the chloroenamine **10** (Ghosez's reagent).[9]

Esters, amides, aryls, sulfones and ketones are suitable activating groups for carbon-centered nucleophiles to react with **11**, giving the desired cyclopropane derivatives in high yields (Table 2). An additional alkyl substituent on the methylene moiety does not alter the course of the cyclopropanation reaction, as previously observed with the iodo analog **2** (Table 2, entry a and Table 1, entry a, respectively). The α-fluoro ethyl acetoacetate delivers the expected cyclopropane **7c** in good yield (Table 2, entry c). In contrast, a mixture of compounds is obtained from the corresponding α-chloro ethyl acetoacetate.[10]

It is noteworthy that in all examples in Table 2, the desired pathway preferentially leading to the cyclopropane derivatives is followed by the stabilized nucleophiles (Scheme 4, equations A

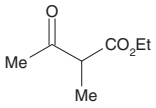
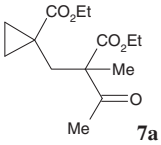
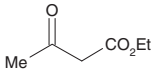
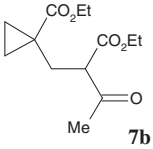
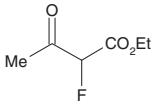
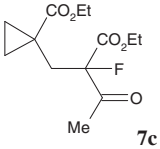
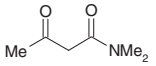
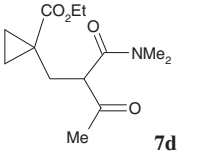
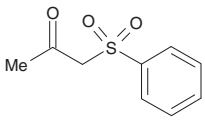
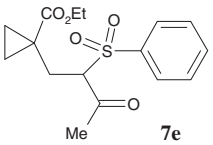
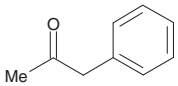
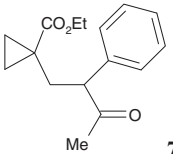
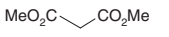
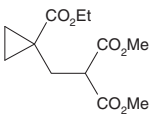
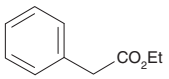
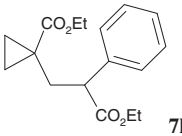
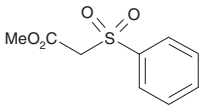
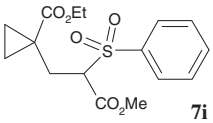
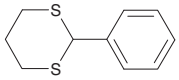
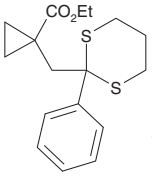


Scheme 3. Reagents and conditions: (i) ethyl-2-(bromomethyl)acrylate **5** (1.0 equiv), indium (1.1 equiv), formaldehyde (1.8 equiv), EtOH/H_2O (1:1), rt, 22 h, 79%; (ii) **9** (1.0 equiv), chloroeneamine **10** (1.0 equiv), CH_2Cl_2, rt, 1 h, 80%; (iii) NaH (1.1 equiv), NuH **6** (1.0 equiv), DMF, 0 °C, 1 h, then **11** (1.0 equiv), 0 °C to rt, 12 h.



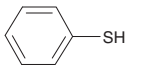
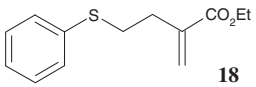
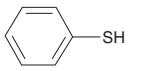
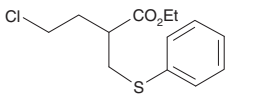
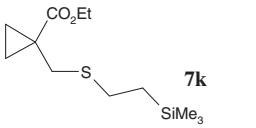
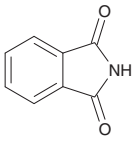
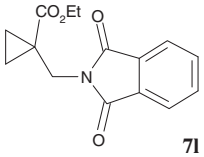
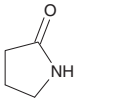
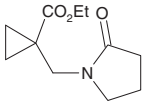
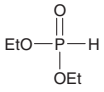
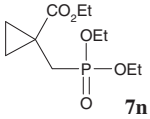
Scheme 4. Possible reaction pathways for the reaction of **11** and **12**.

Table 2
Reactivity of **11** with various carbon-centered nucleophiles **6**

Entry	NuH 6	Yield[a] (%)	Product
a		77	 **7a**
b		62	 **7b**
c		70	 **7c**
d		77	 **7d**
e		77	 **7e**
f		83	 **7f**
g		94	 **7g**
h		71	 **7h**
i		96	 **7i**
j		63	 **7j**

[a] Yields refer to isolated compounds after purification by chromatography on silicagel.

Table 3
Reactivity of **11** with various heteroatom-centered nucleophiles **6**. Reaction conditions: see Scheme 3

Entry	NuH 6	Yield[a] (%)	Product
a		90	 **18**
b[b]		64	 **19**
c		70	 **7k**
d		52	 **7l**
e		50	 **7m**
f		60	 **7n**

[a] Yields refer to isolated compounds after purification by chromatography on silicagel.
[b] Et_3N was used as the base instead of NaH.

and B). Side reactions such as S_N2 and E_2 (Scheme 4, equations C and D, respectively) are not competing with the Michael-induced ring closure pathway. For example, the incipient enolate **13** cyclizes readily into the cyclopropane **7g** and neither intra- nor inter-molecular proton exchange occurs as potentially competing pathway (Scheme 4, equation E). Although this reaction proceeds through the more stabilized malonate anion **16**, the resulting cyclopentane product **17** is not observed (Scheme 4, equation F).[11,12]

One of the advantages of the present method is that diactivated methylene derivatives can be successfully used, allowing the subsequent introduction of an additional group by reaction with various electrophiles. Finally, the phenyl dithiane derivative illustrates the broad scope of carbon-centered nucleophiles which can react with **11** to form cyclopropanes (Table 2, entry j).

The present method involving **11** as a α-cyclopropylester cation synthon can be extended to nitrogen-, phosphorous-, and sulfur-centered nucleophiles (Scheme 3 and Table 3). With thiophenol as the nucleophile, we obtained the substitution product **18** under our standard conditions (NaH, DMF) (Table 3, entry a). In contrast, when triethylamine was used as a base, the Michael addition product **19** was isolated (Table 3, entry b). Treatment of the Michael adduct **19** with NaH in DMF converted it in very good yield into **18**. Similar results were obtained with thioacetic acid as the nucleophile. These results suggest that thiophenol and thioacetic acid are undergoing fast and reversible Michael addition to the acrylate **11**. We assume that, in the presence of triethylamine, the incipient intermediate ester enolate does not cyclize into the corresponding cyclopropane but is rather reprotonated in situ to give **19**. However, in the presence of NaH, the enolate of **19** undergoes fast retro-Michael addition of the thiolate which reacts further in S_N2 manner to give **18**. In agreement with this hypothesis, the less labile 2-(trimethylsilyl)-ethanethiol gives the desired cyclopropanation product **7k** (Table 3, entry c).

An example of the improved chemoselectivity of the chloro derivative **11** compared to the iodo analog **2** is observed with

phthalimide as the nucleophile. This reactant furnished the desired cyclopropane **7l** in 52% yield from **11**, compared to the substitution product **8** obtained with the iodo compound **2** (Table 3, entry d and Table 1, entry c, respectively). Other nucleophiles successfully led to the desired three-membered ring products as exemplified in entries e and f with pyrrolidone and diethyl phosphite. However, the reaction with oxygen-centered nucleophiles such as sodium methoxide failed to give the desired product, probably due to competing elimination reactions.

In conclusion, we have reported the use of ethyl-2-(2-chloroethyl)acrylate **11** as an α-cyclopropylester cation synthon, which offers clear improvements in terms of chemoselectivity as well as increased isolated yields compared to the iodo analog **2** that we used initially.[6] The very good accessibility of **11** as well as its ability to react efficiently with a broad variety of carbon-, nitrogen-, sulfur- and phosphorous-centered nucleophiles allowed successful applications of this strategy to the preparation of cyclopropyl ester targets difficult to access by standard methods. We are now generalizing the described method to other Michael acceptors to synthesize a variety of highly substituted small rings.

References and notes

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10. α-Chloro acetates are known to produce cyclopropane derivatives by Michael addition on electron deficient olefins, as reported in the McCoy reaction; McCoy, L. L. *J. Am. Chem. Soc.* **1958**, *80*, 6568. In our case, the reaction of α-chloro acetates with **2** or **11** led to a mixture of products which were not characterized.
11. In the case of methyl cyanoacetate as the nucleophile, the desired cyclopropane derivative is obtained along with side products which might result from proton exchange (Scheme 4, equation E). The intramolecular proton exchange through a six-membered ring between the negatively charged oxygen atom of the ester enolate and the hydrogen atom flanked by both electron withdrawing groups (cyano and ester) could be a competitive pathway depending on the acidity of this proton and the conformation adopted by the ester enolate.
12. For Michael addition reactions followed by 1,3-prototropic rearrangement see for example; (a) Hermann, J. L.; Kieczykowski, G. R.; Romanet, R. F.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, *14*, 4715–4718; (b) Alvarez-Ibarra, C.; Csaky, A. G.; Ortega, E. M.; Jesus de la Morena, M.; Quiroga, M. L. *Tetrahedron Lett.* **1997**, *38*, 4501–4502.