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Diastereoselective cyclopropanation of cyclic enones with methyl dichloroacetate anion

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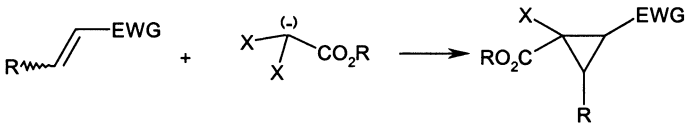
Abstract—The reaction of α,β-unsaturated cyclic ketones with methyl dichloroacetate anion in the presence of DBU leads to the corresponding bicyclic chlorocyclopropanes in a highly diastereoselective fashion. In the cases of 2-cyclopentenone and 2-cyclohexenone the reaction affords exclusively the *endo*-Cl isomer.

Cyclopropanes occur among several classes of natural products, they have a number of commercial applications, and they serve as useful synthetic intermediates leading to other classes of cyclic and acyclic compounds.[1] A great variety of substrates bearing the cyclopropane subunit have attracted much attention due to their interesting biological effects. Introduction of the cyclopropane moiety into biologically active substances has been recognized as an important chemical modification owing to its conformational rigidity and potential chemical reactivity.[2]

Methods for the synthesis of cyclopropanes have been the subject of several earlier reviews.[3] Among these methods the 1,3-coupling of difunctional compounds has been widely studied, especially those in which the required C3 building block for nucleophilic displacement is generated by in situ conjugate addition of a nucleophile to an electron-deficient alkene,[4] known as Michael initiated ring closure (MIRC) reaction.[5] In some cases the attacking nucleophile bearing an anion-stabilizing group also contains the leaving group necessary for the final cyclization (Scheme 1).

The formation of polysubstituted cyclopropanes from acyclic α,β-unsaturated systems with electron-withdrawing substituents (e.g CO_2R, COR, CN, NO_2, SO_2R) and α-haloester carbanions in the presence of base has been described.[6] So, the reaction of alkyl dichloroacetates with α,β-unsaturated acyclic esters in the presence of sodium hydride or potassium carbonate leads to the corresponding substituted chlorocyclopropanes.[6e,7] Also, addition of different monohalocarbanions, stabilized with electron withdrawing groups different from ester such as cyano,[8] nitro[9] or sulfonic acid derivative,[10] to acyclic α,β-unsaturated systems have been reported. However this type of cyclopropanation leading to bicyclic derivatives from a cyclic enone has been confined to a few examples only.[11] Generally, mixtures of racemic diastereomeric cyclopropanes are obtained, the ratio of the diastereomers depends on the solvent polarity, the base used for the generation of the anion and the steric interactions.[12]

In this paper, we report the diastereoselective cyclopropanation of cyclic α,β-unsaturated enones by conjugate addition of methyl dichloroacetate anion and subsequent ring closure, leading to bicyclic cyclopropane derivatives endowed with functional diversity.



Scheme 1.

Keywords: cyclopropanation; cyclic enones; diastereoselectivity; Michael initiated ring closure.
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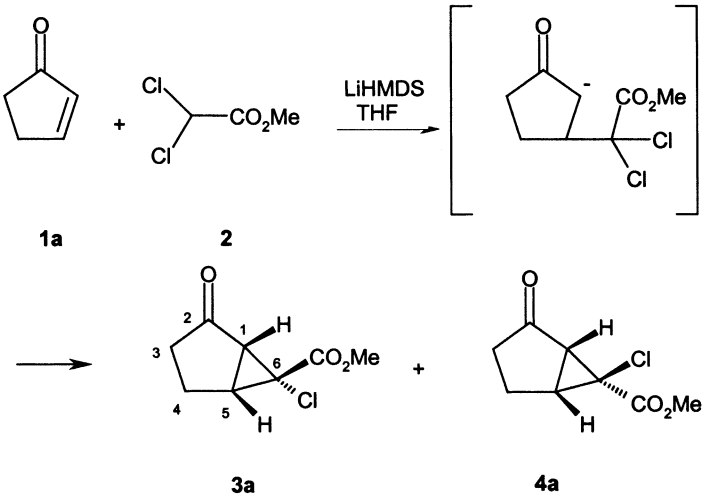


Scheme 2.

1. Results and discussion

The reaction of cyclopentenone **1a** with the methyl dichloroacetate anion generated with LiHMDS in THF at −78°C gives rise diastereoselectively to the chlorocyclopropane derivative **3a** (Scheme 2). The diastereomeric cyclopropane **4a** was not observed in the reaction mixture.

The stereochemical assignment of cyclopropane **3a** was very troublesome since a quaternary carbon has been created and no vicinal coupling constants are observed.

Determination of the relative stereochemistry of the quaternary center (C_6) with respect to the bridgehead carbon centers (C_1 and C_5) was achieved initially through NMR studies. Conventional methods, using proton–proton interactions (scalar or dipolar couplings) were precluded by the quaternary nature of C_6. Instead a method was developed to measure the 3-bond H–C couplings between H-1 and H-5 and the carbonyl of the C-6 methyl ester substituent.

The size of a $^3J_{1H-13C}$ coupling is dependent on the dihedral angle between the groups (ω) according to the Karplus relationship, $^3J_{1H-13C}=4.26-(1.00\cos\omega)+(3.56\cos 2\omega)$.[13] Computer models were used to estimate ω between the methyl ester C═O and the bridge head protons in **3a** and **3b**. When the (C═O)OMe is *cis* to the bridge head protons (**3a**) $\omega=5°$, whilst for the *trans*-(**3b**) $\omega=130°$. Using these figures and the Karplus relationship the expected $^3J_{1H-13C}$ values can be calculated (6.80 Hz for **3a** and 4.30 Hz for **3b**).

The complexity of the proton coupled ^{13}C spectra prevented direct measurement of the required coupling constants. Hence, a simple pulse sequence was developed which, using shaped pulses, selectively decoupled protons from one or more sites, leaving only the required coupling networks. Using this experiment, to selectively decouple the CH_3 of the methyl ester, resulted in the observation of a triplet for the C═O resonance with a measured $^3J_{1H-13C}$ value of 7.2 Hz, consistent with the carbonyl group being *cis* to the bridge head protons, for this compound (**3a**). These findings were also confirmed by X-ray diffraction experiments[14] (Fig. 1).

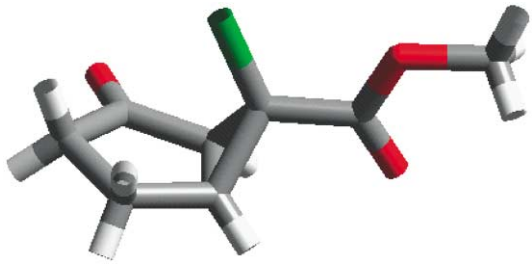


Figure 1.

The high diastereoselectivity observed can be explained considering that the most favored conformation of the methyl dichloroacetate group in the intermediate enolate, would be that in where the methyl ester is *exo* from the ring, as it is sterically larger than the chlorine atom.

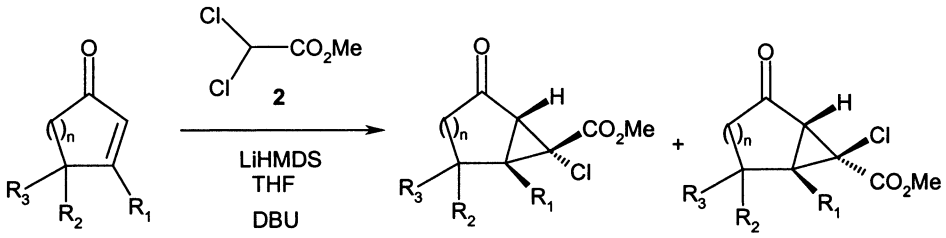
In order to study the scope of this diastereoselective cyclopropanation, the reaction was carried out with different cyclic enones (Table 1).

Although the reaction of cyclopentenone with methyl dichloroacetate anion gives rise directly to the corresponding cyclopropane, the other enones examined afforded the 1,4 addition products that required the presence of DBU for subsequent cyclization. Therefore, the cyclopropanation can be considered as the result of a 'tandem process'.

As shown in Table 1, excellent diastereoselectivity is also achieved in the cyclopropanation of cyclohexenone **1b**, with the *endo*-Cl adduct **3b**, being the only diastereomer observed.

However, diastereoselectivity decreases when larger size cyclic enones were used as starting materials, so in the case of cycloheptenone a 3:1 mixture of diastereomers was obtained (entry c).

Table 1. Cyclopropanation reaction with cyclic enones



1 3 4

Entry	*n*	R_1	R_2	R_3	Ratio **3**:**4**	Yield (%)
a	1	H	H	H	100:0	62
b	2	H	H	H	100:0	66
c	3	H	H	H	75:25	48
d	1	H	CH_3	CH_3	88:12	53
e	1	CH_3	H	H	80:20	20

The cyclopropanation process for substituted cyclic enones was also studied (entries d, e). As can be seen from the data, the *endo*/*exo* ratio of the resulting chlorocyclopropanes decreases with substitution on the ring, although diastereoselectivity is still high. These results are in agreement with the high steric control of this cyclopropanation reaction.

In an attempt to widen the scope of the cyclopropanation, the reaction of some acyclic enones was tried. In the case of methyl vinyl ketone the only product obtained was the 1,4-addition adduct and no further cyclization to the cyclopropane took place. In the case of the iso-propylvinyl methyl ketone the starting material was recovered, probably due to steric effects.

We also studied the dependence of diastereoselectivity of the reaction on solvent polarity and the base used to generate the anion. We carried out these experiments using cyclohexenone as starting material.

In all cases described in Table 2, only diastereomer **3b** was obtained, independently on the solvent or base. Entries a–c show that no *exo* isomer was produced either in more polar solvents as DMF or in the less polar 1:1 mixture of hexane/toluene. On the other hand, we have also proved that there was not any counter ion effect in the stereochemical course of the reaction (entries a, d, e) while variable yields were observed.

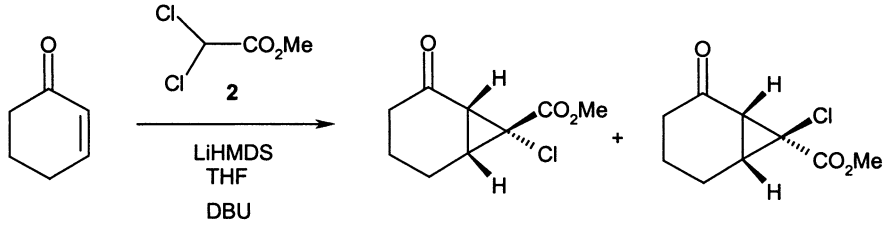
In summary, we have shown that the reaction of cyclic enones with the methyl dichloroacetate anion by 1,4-addition of the anion to the Michael acceptor and subsequent cyclization takes place with high diastereoselectivity and steric control, with different solvents and bases.

2. Experimental

2.1. General

All manipulation of moisture sensitive materials was conducted under nitrogen atmosphere. Most of the reagents were purchased and used without previous purification. Solvents were distilled over sodium or calcium hydride under nitrogen before use. All the temperatures are uncorrected. IR spectra were taken on a Mattson 3000 FT

Table 2. Solvent and base effect on diastereoselectivity



1b 3b 4b

Entry	Base	Solvent	**3b**:**4b** ratio[a]	Yield (%)
a	LiHMDS	THF	100:0	66
b	LiHMDS	Hex/tol 1:1	100:0	60
c	LiHMDS	DMF	100:0	30
d	^{t}BuOK	THF	100:0	55
e	NaH	THF	100:0	40

[a] HPLC analysis was carried out on a Kromasil Si60 (5 μm, 4.6×250 mm ID) column with hexane/acetone 9:1 as mobile phase and at a flow rate of 1.0 ml min^{-1}. Compound **3b** was detected (UV–Vis detector at 205 nm) at a retention time of 8.8 min.

spectrometer. NMR spectra were measured on Bruker AC-200, Bruker AC-300 and Bruker AMX-400 spectrometers, using TMS and $CDCl_3$ as internal standards for ^1H and ^{13}C NMR respectively. MS were measured on a Hewlett–Packard 5880 A spectrometer and the HRMS were obtained on a Finnigan_Mat 95 spectrometer. Single crystal X-ray diffaction measurements of **3a** were accomplished by a Bruker SMART.

2.2. General procedure for cyclopropanation of cyclic enones with methyl dichloroacetate

To a 0.5 M solution of methyl dichloroacetate (1 equiv.) in THF under nitrogen atmosphere at −78°C was added a 1 M solution of lithium bis(trimethylsilyl)amide in THF (1.2 equiv.). After 10 min, the corresponding enone (1 equiv.) was added. The reaction mixture was stirred at −78°C for 4 h. Then DBU (20 equiv.) was added and the reaction mixture was allowed to reach room temperature overnight. The reaction was quenched with a saturated solution of ammonium chloride and extracted with ethyl acetate. The organic phase was washed with 0.5N HCl, then dried over Na_2SO_4, filtered and concentrated in vacuo. The final product was purified by flash chromatography (EtOAc/hexane 1:3)

2.2.1. (1*RS*,5*RS*,6*RS*) Methyl 6-chloro-2-oxobicyclo-[3.1.0]hexano-6-carboxylate (3a). Mp 38–40°C; IR (KBr) 2955, 1738, 1437, 1259, 1188 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.1–2.8 (m, 6H), 3.8 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 209.5 (C), 167.8 (C), 53.8 (CH_3), 48.1 (C), 41.6 (CH), 36.5 (CH_2), 35.9 (CH), 20.3 (CH_2); HRMS Calcd for $C_8H_9ClO_3$: 188.0240. Found: 188.0235.

2.2.2. (1*RS*,6*RS*,7*RS*) Methyl 7-chloro-2-oxobicyclo-[4.1.0]heptano-7-carboxylate (3b). IR (neat) 2954, 2871, 1728, 1704, 1437, 1267, 1156 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.8 (s, 3H), 2.6–2.5 (m, 2H), 2.4–2.2 (m, 3H), 2.1–1.8 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 202.7 (C), 168.7 (C), 53.4 (CH_3), 48.6 (C), 38.8 (CH_2), 34.0 (CH), 30.1 (CH), 23.6 (CH_2), 17.5 (CH_2); MS (EI) 204 (5), 202 (16), 174 (58), 170 (100). HRMS Calcd for $C_9H_{11}ClO_3$: 202.0397. Found: 202.0397.

2.2.3. (1*RS*,7*RS*,8*RS*) Methyl 8-chloro-2-oxobicyclo-[5.1.0]octano-8-carboxylate (3c). IR (neat) 2959, 2863, 1745, 1710, 1437, 1272, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.7 (s, 3H), 2.6–1.3 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 203.0 (C), 169.6 (C), 53.4 (CH_3), 47.6 (C), 43.8 (CH_2), 38.4 (CH), 28.0 (CH), 24.7 (CH_2), 23.3 (CH_2); MS (EI) 218 (5), 216 (16), 188 (72), 121 (100). HRMS Calcd for $C_{10}H_{13}ClO_3$: 216.0553. Found: 216.0571.

2.2.4. (1*RS*,5*RS*,6*RS*) Methyl 6-chloro-4,4-dimethyl-2-oxobicyclo[3.1.0]heptano-6-carboxylate (3d). IR (neat) 2958, 1744, 1436, 1370, 1260, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.7 (s, 3H), 2.6 (d, J=6.5 Hz, 1H), 2.45 (d, J=19.3 Hz, 1H), 2.4 (d, J=6.5 Hz, 1H), 2.0 (d, J=19.3 Hz, 1H), 1.3 (s, 3H), 1.2 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 208.1 (C), 168.0 (C), 53.8 (CH_3), 49.7 (CH_2), 49.6 (C); 45.9 (CH), 42.1 (CH), 36.7 (C), 32.1 (CH_3), 23.2 (CH_3); MS (EI) 218 (1), 216 (1), 184 (31), 149 (50), 147 (100). HRMS Calcd for $C_{10}H_{13}ClO_3$: 216.0553. Found: 216.0558.

2.2.5. (1*RS*,5*RS*,6*RS*) Methyl 6-chloro-5-methyl-2-oxobicyclo[4.1.0] hexano-6-carboxylate (3e). ^1H NMR ($CDCl_3$) δ 3.8 (s, 3H), 2.8 (s, 1H), 2.5–2.0 (m, 4H), 1.4 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 210.0 (C), 166.6 (C), 53.5 (CH_3), 52.1 (C), 44.8 (CH), 41.7 (C), 37.4 (CH_2), 28.9 (CH_2), 16.6 (CH_3).

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