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Halogenation of electron-deficient vicinal substituted alkenes: regio- and stereoselectivity

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Abstract: The halogenation of electron-deficient vicinal substituted alkenes leads mainly to the mixture of regio- and stereoisomers of monohalogenated derivatives. Their ratio depends on the stability of the intermediate anionic complex and is determined by properties of both electron-withdrawing groups.

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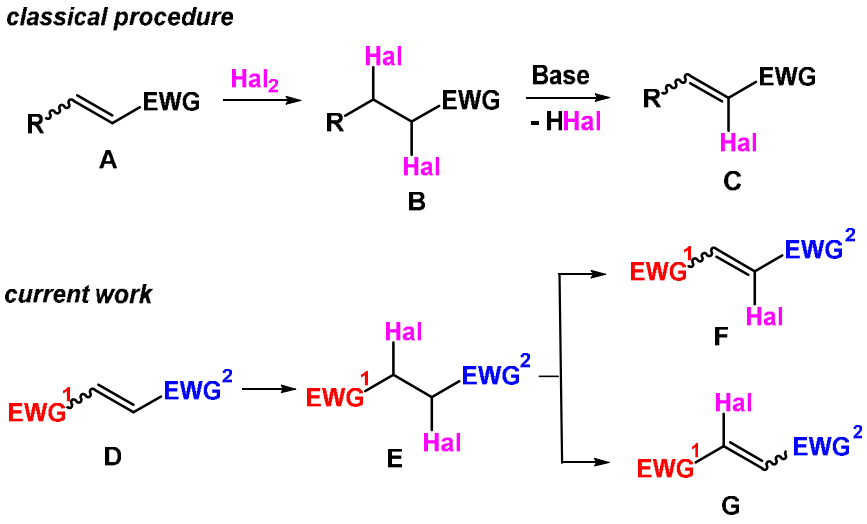
Keywords: electron-deficient alkenes • halogenation • selectivity

Introduction

Conjugated α- or β-halogenated α,β-unsaturated carbonyl compounds (enals, enones, and enoates) represent an important class of small building blocks which are widely used in organic synthesis.[1-3] Their molecules contain two electrophilic centres: olefinic and carbonyl carbons. It is not surprise that these compounds have received significant attention from synthetic and pharmaceutical chemists as highly functionalized scaffolds for design of biologically active molecules (namely, α- or β-amino acid derivatives) as well as for assembly of diverse carbo- and heterocycles.[4] Polyfunctionality of halogenated enals, enones and enoates allows them to be involved in the domino reactions which offer access to a variety of complex molecules in a one-pot fashion.

The simplest route to these derivatives is based on the halogenation – dehydrohalogenation sequence of the parent unsaturated carbonyl-bearing compounds **A** and **D** (Scheme 1).[5]



Scheme 1. Halogenation of electron-deficient alkenes.

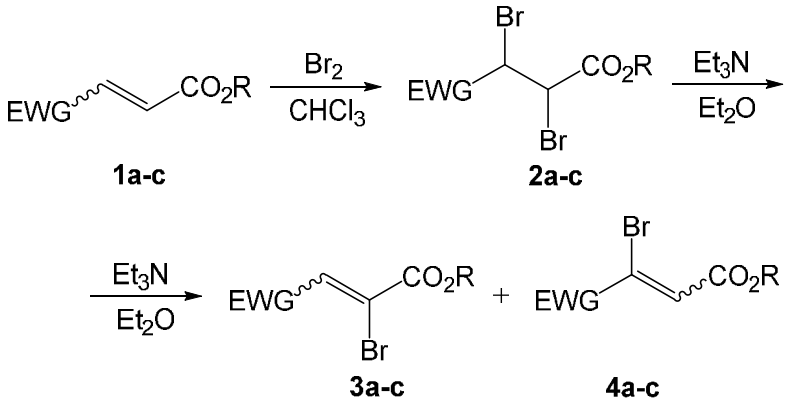
Obviously, when dihaloderivative **B** is treated with any base, the only α-proton is removed. As a result, the target compound **C** is formed as the sole reaction product. However, if the second electron-withdrawing group is introduced in the vicinal position of initial electron-deficient alkene, the problem of regioselectivity of the hydrogen halide elimination from intermediate **E** arises: in this case the formation of two regioisomers **F** and **G** should be expected. The structural elucidation of preferable formation of one or another isomer in these cases is crucial for the control the synthesis selectivity. In continuation of our on-going research into the application of halogenated α,β-unsaturated carbonyl compounds in organic synthesis, we now focus on the chemistry of haloalkenes bearing more than one electron-withdrawing group. We report here the application of NMR spectroscopy and quantum chemical calculations to determine the selectivity in the bromination of alkenes bearing two electron-withdrawing groups in vicinal position (so-called pull-pull alkenes).[6]

Results and Discussion

Three electron-deficient alkenes bearing simultaneously two different electron-withdrawing groups were chosen: (*E*)-4,4,4-trifluoro-2-butenoate (**1a**), ethyl (*Z*)-2-cyanoacrylate (**1b**) and methyl (*E*)-4-oxo-2-pentenoate (**1c**). We attempted to prepare monobromoesters **3a-c** by traditional two-steps approach involving the reaction of **1a-c** with bromine in anhydrous $CHCl_3$, and subsequent dehydrobromination of the intermediates **2a-c** by Et_3N in dry ether. We found, that in contrast to classical alkenes, these derivatives were less active in electrophilic reactions such as bromination due to the high electron deficiency of the double bond which was caused by the strong electron-withdrawing property of trifluoromethyl, cyano-, and carbonyl (alkoxycarbonyl) groups. Thus, if the reaction of methyl (*E*)-4-oxo-2-pentenoate (**1c**) with bromine was completed for less than an hour at 0^{o}C the bromination of ethyl (*E*)-4,4,4-trifluoro-2-butenoate (**1a**) proceeded in several days at room temperature. In all cases dibromoesters **2a-c** were formed as a mixture of two diastereomers (Table S1, see Supporting information). Thus, in the ^{1}H NMR spectrum of the intermediate **2b** there were two sets of methine proton signals at 4.50-4.90 ppm in the ratio 2:1. The same ratio of signals was observed in the ^{13}C NMR spectrum of **2b**: two adjacent bromine bearing carbons resonate at 26.1, 26.7 and 41.7, 42.0 ppm (see Supporting Information). These intermediates **2a-c** were used in the next step without additional purification. All of the reactions gave the target derivatives **3** and/or **4** in moderate to good yield. The moderate yields of bromoenoate **3a** probably can be explained by the side reactions (such as polymerization) due to the instability of these derivatives.

In the case of enoate **1** the choice between two alternative structures **3a** and **4a** can be easy made thanks to the presence of trifluoromethyl moiety. In fact, the ^{1}H NMR spectrum of the compound **3a** contains a quartet of olefinic proton CH= at 7.38 ppm with constant $^3J_{HF}$ = 7.1 Hz. In the ^{13}C NMR spectrum the signal of olefinic carbon appears as a quartet at 130.3 ppm with coupling constant $^3J_{CF}$ = 36.9 Hz. It strongly indicates that the carbon CH= is attached to the CF_3 group.

Table 1. Bromination of enoates **1a-c**.



EWG = CF_3, R = Et (**a**), EWG = CN, R = Et (**b**), EWG = Ac, R = Me (**c**)

Entry	Enoate	Product				
		Overal yield, %	Ratio, %			
			(*Z*)-**3**	(*E*)-**3**	(*Z*)-**4**	(*E*)-**4**
1	**1a**	49	100	0	0	0
2	**1b**	62	25	0	0	75
3	**1c**	83	10	70	10	10

The structural elucidation of regio- and stereoisomers of monobromoesters **3b,c** and **4b,c** is not a trivial task and requires a careful analysis of 2D NMR spectra, employing NOESY and HMBC experiments as well as the proton-coupled ^{13}C NMR spectroscopy. For example, the structures of enoate **3c** is reliably confirmed by the presence in its proton-coupled ^{13}C NMR spectrum a doublet of olefinic carbon CH= ($^{1}J_{HC}$ = 162.1 Hz), the both components of which are quartets having coupling constant $^{3}J_{HC}$ = 1.6 Hz. In contrast, for its isomer **4c** there is no long-range couplings of olefinic carbon CH= at 128.2 ppm ($^{1}J_{HC}$ = 165.0 Hz). These spin-spin interactions were confimed by the carefull analysis of 2D NMR (HMBC) spectra (Fig. 1).

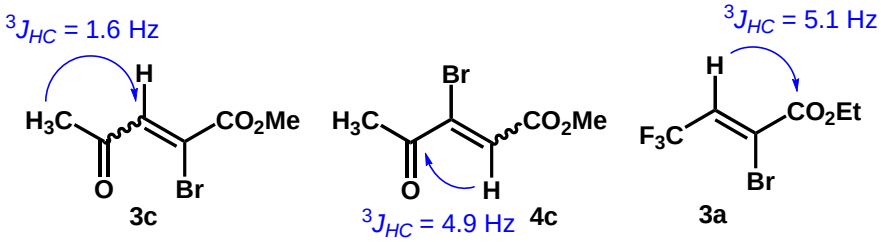


Figure 1. Main HMBC correlations for bromoenoates **3c**, **4c** and **3a**.

The geometry of bromoenoates **3** and **4** was established by the concerted application of ^{1}H – ^{1}H 2D homonuclear experiment NOESY and especially ^{1}H – ^{13}C 2D heteronuclear

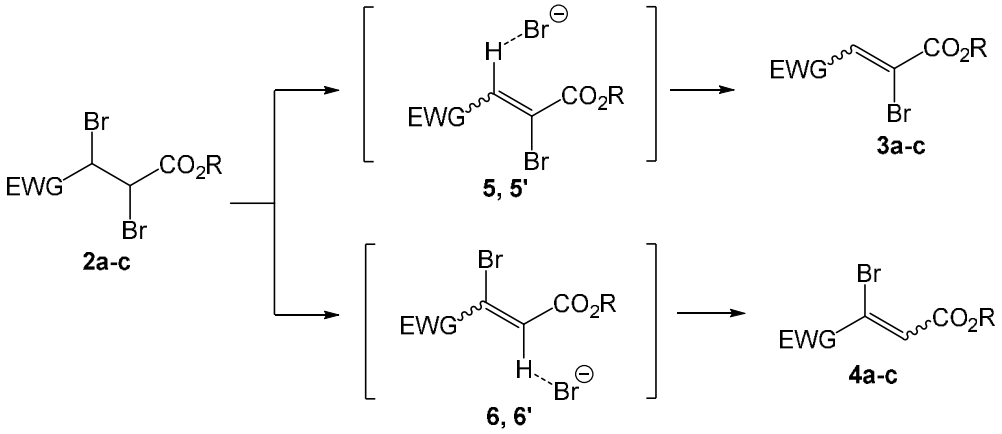
experiment HMBC. It is well known that the vicinal C-H couplings are very useful tool to determine the geometry of tri-substituted alkenes. Previously, this approach allowed us to determine the correct arrangement of substituents around the double bond C=C in trifluoromethylated bromoenones.[7,8] For example, the value of the vicinal coupling constant $^{3}J_{CH}$ between the carbonyl carbon of ethoxycarbonyl group and the olefinic proton CH= in the enoate **3a** was found to be 5.1 Hz (Figure 1). The same constant for one of the isomer of bromoenoate **4c** is 4.9 Hz. It was reported that this constant ranged from 0 to 6 Hz for *s-cis*-isomer and 9-14 Hz for *s-trans*-one.[9,10]

In an effort to explain the preferential formation of α- or β-bromoenoates **3** or **4**, we have determined the thermodynamic characteristics of both isomers. It was found that the calculated values of thermodynamic parameters for bromoenoates **3** and **4** are very close and, consequently, do not effect on the ratio of regioisomers (Table S2, see Supporting Information).

Next, we put forward a hypothesis that the reaction direction depends on the electron-withdrawing ability of both functional groups. It is well known that the inductive and resonance electronic effects of the substituents can be quantified by Hammett constants.[11] According to this scale, the cyano- (σ_I = 0.51) and trifluoromethyl (σ_I = 0.38) groups are the better acceptors than alkoxycarbonyl one. In contrast, the moieties CO_2R and C(O)Me have approximately the same electron attractive ability (σ_I = 0.34 and 0.33, correspondingly). At first sight, this feature of the substituents is in a good accordance with the experimental data. Thus, the proton of the CH(Br)CN moiety of dibromoderivatives **2b** should be more acidic than $CH(Br)CO_2Et$ one. Therefore, the elimination of the former under the action of the base should be more preferable. In fact, the ratio of regioisomers in this case was found to be 3:1. At the same time, it is difficult to explain why the only *α*-bromoester **3a** is isolated for substrate bearing the trifluoromethyl group which is slightly more attractive than ester function. It was previously reported that the bromination of 3-nitroacrylate gives exclusively *β*-bromoester.[12] This result led us to the conclusion that the regioselectivity of the dehydrobromination of the corresponding dibromoderivative **2a** depends strongly on the reaction mechanism.

A priori, the elimination of hydrogen halide from dibromoderivatives **2a-c** and formation of monobromoenoates **3** and/or **4** could be rationalized by one of the mechanisms – E1, E2 or E1cB. The later mechanistic pathway usually occurs when compound bearing an acidic hydrogen and electron withdrawing group attached to this carbon center is treated with a suitable base. Thus, the formation of *α*-bromocyclohexenone proceeds through the bromine addition to starting cyclic enone followed by dehydrobromination reaction according to E1cB mechanism.[13] The presence of two acidic hydrogens in the molecule of dibromoesters **2** favors the same mechanistic pathway.[14] It could be predicted that if the reaction is carried out through the anionic complex that is formed after proton elimination, the overall selectivity of reaction is determined by the relative stability of this intermediate. Therefore, enoates **4** bearing bromine in the *β*-position with respect to the group most efficiently stabilizing the negative charge at the adjacent carbon atom should be formed as the major reaction product. To confirm this hypothesis we carried out the quantum chemical calculations at M06-2X/6-311G(d,p) and B3LYP/6-311++G(d,p) levels of theory with full geometry optimization which provide good energy characteristics for heteroatom molecules and their anions.[15,16] The results are collected in Table 2.

Table 2. M06-2X/6-311G(d,p) (normal) and B3LYP/6-311++G(d,p) (*italic*), relative energies with ZPE correction (ΔE^0), relative free energies (ΔG^{298}) and formation enthalpies (ΔH^{298}), kcal/mol for anions **5,5'a-c** and **6,6'a-c**. Dihedral angles CCCC at the **5** and **6** orientation are 160 – 170° and at the **5'** and **6'** 50 – 60°.



Entry	Anion	ΔE^o, kcal/mol	ΔG^{298}, kcal/mol	ΔH^{298}, kcal/mol	Ratio, %
1	**5a**	0	0	318.17	100
		0	*0*	*311.89*	
2	**5′a**	10.61	10.34	326.04	0
		4.48	*3.66*	*314.40*	
3	**6a**	2.56	2.24	320.80	0
		2.47	*2.28*	*314.32*	
4	**6′a**	4.24	4.20	319.71	0
		3.90	*3.87*	*313.78*	
5	**5b**	0	0	309.78	25
		0	*0*	*304.10*	
6	**5′b**	9.02	7.47	319.18	0
		6.00	*4.68*	*311.62*	
7	**6b**	7.77	7.19	317.65	0
		6.10	*5.07*	*310.34*	
8	**6′b**	5.96	5.64	316.46	75
		5.38	*5.28*	*310.97*	
9	**5c**	0.36	0.09	322.60	10
		1.65	*1.27*	*314.36*	
10	**5′c**	0	0	321.67	70
		0	*0*	*311.82*	
11	**6c**	1.12	1.06	323.23	10
		3.64	*4.07*	*316.29*	
12	**6′c**	2.03	2.22	323.67	10
		3.87	*4.30*	*316.03*	

The similar results were obtained for enoate **2b** bearing cyano moiety in *β*-position. The proton H_α of dibromoderivative **2b** is the most acidic; therefore, the anion **5b** is the most stable. According to the calculations, the order for anionic complex stability is as followed: **5b** > **6′b** > **6b** > **5′b**. It should be noted that the acidity of all protons of the intermediate **2b** is higher than

that for trifluoromethylated enoate **2a**. In fact, NMR monitoring of both reactions has shown that the transformation of dibromoderivative **2b** into the corresponding bromoenoates **3b** and **4b** proceeds much faster that the similar reaction for **2a**. This result could lead to simultaneous formation of anion **6′b** as a kinetically formed product. The kinetic stability of this anion can also be explained by the presence of more electron-attractive group C≡N in **2b** as compared with CF_3-moiety in **2a**. We assumed that the dehydrobromination of **2b** follows two pathways: formation of enoate (*E*)-**4b** is kinetically controlled, while the formation of its isomer (*Z*)-**3b** occurs through thermodynamically more stable anion **5b** (Table 1, entry 2).

Finally, there is no a large difference in acidity of all methine protons of dibromoester **2c** (Table 2, entries 9-12). Therefore, all these protons can be successively lost to give all four isomeric anions. At the same time, the free energy of formation of anions **5c**, **5′c**, **6c** and **6′c** differ by only ~1 kcal/mol. However, the slightly higher acidity of H_α in **2c** as well as the slightly higher stability of anion **5′c** corresponds well to the preferable formation of enoate (*E*)-**3c** in the dehydrobromination reaction under the action of triethylamine (Table 1, entry 3). Remarkably, the acidity of the H_α in **5′c** is higher than that in **5′a** for 4.37 kcal/mol. This feature of this anion favors the formation of enoate (*E*)-**3c**.

Conclusion

In summary, we have studied the regio- and stereoselectivity of the bromination of electron poor alkenes bearing two vicinal electron-withdrawing groups. The selectivity of HBr elimination step can be explained by acidity of the proton in intermediate dibromoderivative and the Gibbs energy of the corresponding anion formation and can be successfully predicted by DFT calculation methods. The theoretical study showed a good agreement with experiments. Obtained bromoenoates could be useful starting materials in the selective assembly of complex molecules especially carbo- and heterocycles.

Experimental Part

General remarks.

^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer at 400.16, 100.61, and 376.5 MHz, respectively, for solution in $CDCl_3$ or CD_3CN. Chemical shift (δ) in ppm are reported using residual chloroform (7.24 for ^1H and 77.20 for ^{13}C) or acetonitrile (1.94 for ^1H and 1.40, 118.60 for ^{13}C) as internal reference. The coupling constants (*J*) are given in Hertz. The concerted application of ^1H-^1H 2D homonuclear experiments NOESY [17] as well as ^1H-^{13}C 2D heteronuclear experiment HMBC [18] were used for the distinction of the carbon and proton resonances in all cases. The IR spectra were recorded with a Bruker Vertex 70 FT-IR spectrometer and with a portable Varian 3100 diamond ATR/FT-IR spectrometer. The GC/MS analyses were performed with a Shimadzu GCMS-QP5050A instrument (EI, 70 eV). The silica gel used for column chromatography was 230-400 Mesh. All reagents were of reagent grade and were used as such or distilled prior to use. All the solvents were dried according to standard procedures and freshly distilled prior to use.

Computational details.

Calculations were performed by the M06-2X/6-311G(d,p) and B3LYP/6-311++G(d,p) methods with full geometry optimization as implemented in the Gaussian09 program package.[19]

Belonging of stationary points on the potential energy surface to minima was proved by positive eigenvalues of the corresponding Hessian matrices. The proton affinity of acid centers was calculated as the enthalpy difference ($D_{acid}H^0$) between corresponding neutral and charged molecules.[20, 21]

Bromination of alkenes (1a-c). General Procedure.

Bromine (1 equiv.) in $CHCl_3$ (5 mL for 1 mmol) was added dropwise into a stirred solution of the alkene (1 equiv.) in $CHCl_3$ (2 mL for 1 mmol). During the addition the temperature was kept at +10°C. The mixture was then stirred at room temperature until the orange color did not fade away. The solvent was evaporated and crude products – dibromoderivatives **2a-c** – were found suitable for further transformation without any purification.

Triethylamine (1.1 equiv.) in anhydrous ether (10 mL for 1 mmol) was added dropwise into a stirred solution of the dibromo derivative **2** in Et_2O (30 mL for 1 mmol) at +10°C. The mixture was kept at rt overnight and filtered. After the solvent was evaporated, the target bromoenoates **3a-c** were obtained by column chromatography (Silica gel, Pentane/Et_2O 7:1 (for **3a**), Hexane/Et_2O 2:1 (for **3b,c**)). The reactions were generally performed for 5 and 10 mmol of initial enoates **1a-c**.

Ethyl (*Z*)-2-bromo-4,4,4-trifluorobuten-2-oate (*Z*)-3a.[22] IR (KBr, ν, cm^{-1}): 1647 (C=C), 1738 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.34 (t, J = 7.1, 3H), 4.32 (q, J = 7.1, 2H), 7.38 (q, J = 7.1, 1H). ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 64.0 (CH_2), 121.6 (q, J = 271.6, CF_3), 124.7 (q, J = 5.6, =C-Br), 130.3 (q, J = 36.9, CH=), 161.0 (C=O). MS (EI) *m/z* (relative intensity): 248 (M^++1, <1), 246 (M^+-1, <1), 203 (44), 201 (47), 179 (74), 177 (66), 69 (100). $C_6H_6BrF_3O_2$ (247.01): calcd. C 29.18, H 2.45; found C 29.22, H 2.68.

Ethyl (*E*)-3-bromo-3-cyanopropen-2-oate (*E*)-4b. IR (KBr, ν, cm^{-1}): 1607 (C=C), 1726 (C=O), 2229 (C≡N). ^{1}H NMR ($CDCl_3$): δ 1.31 (t, J = 7.4, 3H), 4.28 (q, J = 7.4, 2H), 6.93 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 62.6 (CH_2), 102.8 (=CBr), 113.4 (C≡N), 138.5 (CH=), 161.4 (C=O). MS (EI) *m/z* (relative intensity): 205 (M^++1, <1), 203 (M^+-1, <1), 160 (79), 158 (83), 51 (100). $C_6H_6BrNO_2$ (204.02): calcd. C 35.32, H 2.96, N 6.87; found C 35.62, H 3.12, N 6.81.

Ethyl (*Z*)-2-bromo-3-cyanopropen-2-oate (*Z*)-3b (in the (1:1.7) mixture of isomers **(*Z*)-3b** and **(*E*)-4b)**. IR (KBr, ν, cm^{-1}): 1606 (C=C), 1728 (C=O), 2228 (C≡N). ^{1}H NMR ($CDCl_3$): δ 1.33 (t, J = 7.1, 3H), 4.32 (q, J = 7.1, 2H), 7.09 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3), 64.2 (CH_2), 113.3 (CH=), 114.8 (C≡N), 134.5 (=CBr), 160.0 (C=O). ^{15}N NMR ($CDCl_3$): δ -102.7. MS (EI) *m/z* (relative intensity): 205 (M^++1, 17), 203 (M^+-1, 17), 160, 158 (56), 51 (100). $C_6H_6BrNO_2$ (204.02): calcd. C 35.32, H 2.96, N 6.87; found C 35.21, H 2.67, N 6.75.

Methyl (*E*)-3-bromo-4-oxopenten-2-oate (*E*)-4c. ^{1}H NMR ($CDCl_3$): δ 2.41 (s, 3H), 3.70 (s, 3H), 6.30 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 27.3 (CH_3), 52.4 (OCH_3), 123.2 (=CH), 137.7 (=CBr), 163.9 ($\underline{C}O_2Me$), 196.7 (C=O).

Methyl (*Z*)-2-bromo-4-oxopenten-2-oate (*Z*)-3c, **methyl (*Z*)-3-bromo-4-oxopenten-2-oate (*Z*)-4c** and **methyl (*E*)-2-bromo-4-oxopenten-2-oate (*E*)-3c** were isolated as a mixture of isomers in ratio 1:1.2:2.

^{1}H NMR ($CDCl_3$): **(*Z*)-3c**: δ 2.43 (s, 3H), 3.89 (s, 3H), 7.68 (s, 1H); **(*Z*)-4c**: δ 2.55 (s, 3H), 3.84 (s, 3H), 7.28 (s, 1H); **(*E*)-3c**: δ 2.19 (s, 3H), 3.77 (s, 3H), 6.76 (s, 1H). ^{13}C NMR ($CDCl_3$): **(*Z*)-3c**: δ 31.2 (CH_3), 54.2 (OCH_3), 138.0 (=CH), 120.3 (=CBr), 162.7 ($\underline{C}O_2Me$), 197.4 (C=O); **(*Z*)-4c**: δ 27.2 (CH_3), 52.5 (OCH_3), 128.3 (=CH), 133.2 (=CBr), 162.7 ($\underline{C}O_2Me$), 192.6 (C=O); **(*E*)-**

3c: δ 30.0 (CH_3); 53.5 (OCH_3); 123.6 (=CBr); 135.9 (=CH); 164.1 ($\underline{C}O_2Me$); 195.1 (C=O). IR (KBr, ν, cm^{-1}): 1618 (C=C), 1723 (C=O). MS (EI) *m/z* (relative intensity): 208 (M^++1, <1), 206 (M^+-1, <1), 193 (21), 191 (21), 177 (10), 175 (11), 43 (100). $C_6H_7BrO_3$ (207.02): calcd. C 34.81, H 3.41; found C 34.80, H 3.43.

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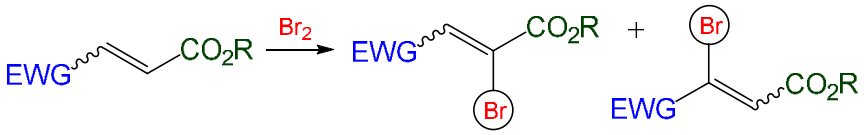

EWG = CF_3, R = Et (**a**), EWG = CN, R = Et (**b**), EWG = Ac, R = Me (**c**)

Treatment with bromine solution converted electron-deficient vicinal substituted alkenes into *α*- or *β*-bromoenoates in different regio- and stereoselectivity. The formation of these polyfunctional isomeric esters is interpreted by DFT calculation methods.

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