Selective Side-chain Halogenoalkoxylation of Unsaturated (Meth)acrylic Esters

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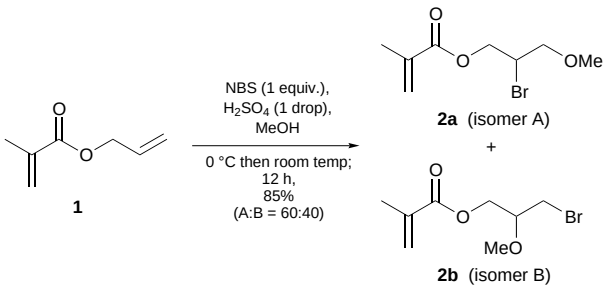
A convenient preparation of new halogenoalkoxylated methacrylates is described by selective side-chain halogenoalkoxylation of unsaturated methacrylic esters.

As part of our ongoing interest in industrial (meth)acrylic esters,[3–6] we needed an easy and economical route to bifunctional monomers which possibly could be useful intermediates in the synthesis of many polyfunctional derivatives. In this context, halogenoalkoxylation of unsaturated (meth)acrylates appeared attractive. This reaction has been successfully used in the synthesis of methoxybromide adducts from olefins[7–11] but has never been described with polyolefinic compounds such as side-chain unsaturated (meth)acrylates. Here we report the selective preparation of some halogenoalkoxylated methacrylic esters.

The halogenoalkoxylation was firstly investigated with the industrially available prop-2-enyl 2-methylprop-2-enoate (**1**), commonly called allyl methacrylate, which is probably the best model in order to study selective electrophilic functionalisation.[3] In exploratory experiments under classical conditions using bromine and methanol, treatment of **1** failed to give the bromomethoxylated adducts, giving rise to degradation of the starting material. We then changed to favourable conditions[7–9] for the liberation of bromonium ions such as acidic conditions.[10] Upon treatment with *N*-bromosuccinimide and a catalytic amount of sulfuric acid in methanol at room temperature, **1** was selectively converted to a mixture of the expected methoxy bromide derivatives **2a** and **2b** in 85% isolated yield (Scheme 1).

As far as the regioselectivity of the reaction is concerned, Markovnikoff's rule predicts the major formation of the isomer **2b**. However this rule fails when electronic and steric effects intervene.[14] In particular with allyl methacrylate (**1**), the formation of isomer **2a** must be allowed both by the steric hindrance of the methacrylic part and still more by the $-I$ effect of the ester group. The **2a**:**2b** ratio was determined as

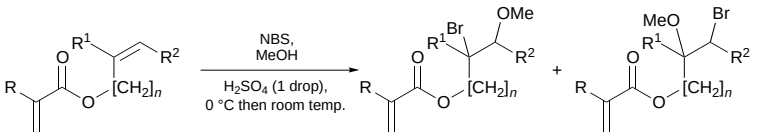


Scheme 1

60:40 on the basis of the 400 MHz ^{1}H NMR spectra obtained from the isolated mixture. It may thus be concluded that the major isomer **2a** results from an anti-Markovnikoff addition favoured by the inductive and steric effects of the ester group. It must be noted that the absence of rearranged products in addition to **1** allows the direct neighbouring group participation observed in other electrophilic additions to allylic esters[15,16] to be ruled out.

To investigate further the participation of the ester in the product ratio obtained, we carried out several reactions with allylic acrylate and homologues or with methylated analogues of **1**. The results are shown in Table 1. It first appeared that addition to allyl acrylate (entry 2) proceeds with the same regiochemistry as that obtained with **1**. This observation allowed us to conclude that the steric effect of the (meth)acrylic moiety is weak. On the other hand, entries 3 and 4 showed that an extra methyl substituent on the unsaturated side-chain has a large effect on the regioselectivity of the reaction. The addition to 2-methylprop-2-enyl methacry-

Table 1 Selective bromomethoxylation of unsaturated (meth)acrylates[a]



	Substrate						
Entry	R	*n*	R^1	R^2	*t*/h	Yield (%)[b]	A:B[c]
1	Me	1	H	H	12	85	60:40
2	H	1	H	H	15	78	57:43
3	Me	1	Me	H	15	76	5:95
4	Me	1	H	Me	15	63	88:12
5	Me	2	H	H	15	80	55:45
6	Me	8	H	H	15	77	33:67
7	H	8	H	H	24	70	30:70

[a]Reactions performed on a 10 mmol scale. Satisfactory spectroscopic data (^{1}H and ^{13}C NMR, IR, MS) were obtained. [b]Isolated yields by flash chromatography (purity up to 98% determined by ^{1}H NMR and GC analyses.) [c]Determined by 400 MHz ^{1}H NMR spectroscopy and confirmed by derivatization.

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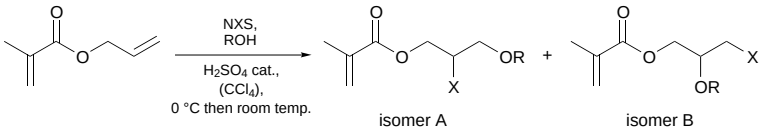
Table 2 Bromoalkoxylation of allyl methacrylate (**1**)[a]



Entry	X	ROH (equiv.[b])	*t*/h	Yield (%)[c]	A:B[d]
1	Cl	MeOH (solvent)	50[e]	60	52:48
2	I	MeOH (solvent)	2.5	80	58:42
3	Br	EtOH (solvent)	12	80	57:43
4	Br	Bu^{n}OH (solvent)	24	75	56:44
5	Br	*n*-$C_{10}H_{23}OH$ (10)	72	75	58:42
6	Br	Pr^{i}OH (solvent)	72	74	65:35
7	Br	*c*-$C_6H_{11}OH$ (10)	62	44	65:35
8	Br	norborneol (10)	48	59	66:34
9	Br	Bu^{t}OH (solvent)	144	19[f]	n.d.[h]
10	Br	$Cl[CH_2]_2OH$ (10)	48	50	59:41
11	Br	$Cl[CH_2]_3OH$ (10)	48	62	56:44
12	Br	$Me[(OCH_2)_2]_2OH$ (10)	24	83	58:42
13	Br	$H[(O(CH_2)_2]_2OH$ (10)	24	62[g]	57:43
14	Br	glycerol (10)	5	48[g]	61:39

[a]Reactions performed on a 10 mmol scale. Satisfactory spectroscopic data (^1H and ^{13}C NMR, IR, MS) were obtained. [b]CCl_4 (20 mL) was used as solvent when 10 equiv. of alcohol were used. [c]Isolated yields by flash chromatography (purity up to 98% determined by ^1H NMR and GC analyses). [d]Determined by 400 MHz ^1H NMR spectroscopy. [e]Reaction performed at 60 °C. [f]48% Conversion. [g]Yields in mono-adducts. [h]n.d. = not determined.

late (entry 3) provided almost exclusively the methoxybromide derivative expected on the basis of carbonium ion stability while the addition to crotyl methacrylate led to an increase in the anti-Markovnikoff selectivity (entry 4). In the case of the homoallylic methacrylate (entry 5), only a weakly diminished effect of the ester moiety was observed leading to a 55:45 isomer ratio. Surprisingly, when the methacrylic or acrylic group is further removed from the double bond (entries 6 and 7) the anti-Markovnikoff adduct was obtained in a larger proportion although there are no longer any inductive effects. This led us to postulate that an ω-assistance between the carbonyl group and the intermediate bromonium or carbonium ion exists. These results show the influence of the (meth)acrylic moiety on the functionalisation of the ester side-chain. Such an influence is not unique to bromomethoxylation but can be compared to other nucleophilic substitutions of a halogen atom on the esterifying chain.[4–6]

We next examined routes to other halogenoalkoxylated methacrylates, the results of which are shown in Table 2. These results clearly indicated that: (i) iodo- and chloromethoxylated derivatives of **1** can easily be obtained (entries 1 and 2). The reaction of *N*-chlorosuccinimide required 60 °C to work. In entry 1, the selectivity is weakly affected showing the effect of the steric hindrance on the attack of the nucleophile; (ii) primary and secondary alcohols (entries 3–8) were effective in the addition while tertiary alcohols (entry 9) were probably too sterically hindered to attack the intermediate bromonium ion. This hypothesis is in accordance with the results obtained with secondary alcohols where the regiochemical outcome was more oriented towards the anti-Markovnikoff addition product (entries 6–8); (iii) some functional alcohols may be introduced (entries 10–14). Particularly interesting were the reactions of 2-chloroethanol and 3-chloropropanol leading to dihalogenated derivatives (entries 10 and 11).

In conclusion, we have shown that halogenoalkoxylated (meth)acrylic monomers can easily be obtained by selective electrophilic functionalisation of side-chain unsaturated methacrylates. The regioselectivity of the addition was influenced by steric and above all by electronic effects due to the (meth)acrylic part of the monomer. These results are the second example we have found of these particular interactions governing the functionalisation of (meth)acrylic monomers.

Techniques used: ^1H and ^{13}C NMR, IR, CI-MS, elemental analysis
References: 18

Schemes: 3 Figures: 2

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