Functionalization of Epoxy Esters with Alcohols as Stoichiometric Reagents

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Dedicated to the memory of Prof. Dr. Jurij V. Brenčič.

Abstract

Glycidyl esters, frequently employed as reactive groups on polymeric supports, were functionalized with alcohols as stoichiometric reagents, yielding β-alkoxyalcohols. Among the solvents studied, best results were obtained in ethers in the presence of a strong proton acid as a catalyst. Alcohols include simple alkanols, diols, protected polyols, 3-butyn-1-ol, 3-hydroxypropanenitrile and cholesterol. This protocol represents a convenient way for introduction of various functionalities onto epoxy-functionalized polymers. Under the reaction conditions, some side reactions take place, mostly due to the reactive ester group and water present in the reaction mixture.

Keywords: Epoxides, alcohols, homogeneous catalysis, glycidyl esters, β-alkoxyalcohols

1. Introduction

Epoxides or oxiranes are among the most important groups of compounds in the field of organic synthesis. They are easy to prepare by a variety of synthetic methods, in most cases directly or indirectly from alkenes. Ring strain, polarity of C–O bond and basicity of oxygen atom make them substantially reactive and thus suitable intermediates for transformation to other classes of compounds.1–4 The most extensively employed reaction of epoxides is a nucleophilic attack to one of ring carbons, accompanied by ring opening. C, N, P, O, S and halogen nucleophiles comprise the most important reagents for achieving such transformations.5,6 In most such reactions, an acid catalysis, induced by Brønsted or Lewis acid is crucial. Attachment of an acid to the oxygen atom increases the polarization on the C–O bond, thus facilitating the attack of the nucleophile and increasing leaving group ability of the oxygen atom.

Addition of oxygen nucleophiles to epoxides is limited to water and alcohols and, to a lesser extent, phenols and carboxylic acids. Hydroxy group of these compounds is a weak nucleophile and acid catalysis is generally required. A plentitude of papers, presenting the employment of various catalysts for alcoholysis of epoxides can be found in literature including strong proton acids, such as sulfuric and organic sulfonic acids as well as boron trifluoride. Regioselectivity of the addition can be influenced somewhat by the use of metal salts (Li, Mg, Zn) as catalysts.7 In more recent times a number of Lewis acid catalysts, based on mostly transition metals was introduced, including copper(II) tetrafluoroborate,8 iron(III) perchlorate,9 titanium compounds,10 aluminum triflate11 and others.

Alcoholysis of epoxides is usually performed in the reactive alcohol as a solvent; this is the case in most of the procedures mentioned above. In pure alcohol, the alcohol is present in high concentration and reactions proceed smoothly and cleanly. However, alcohols with more complex structure and solid compounds cannot be used in this manner and must be applied in the form of more or less diluted solutions in an appropriate solvent.

Crosslinked poly(glycidyl methacrylate) is widely applied as a material for chromatographic supports in biochemical applications and other areas. Reactive epoxy groups attached to a polymer backbone offer numerous possibilities for post-polymerization modification of polymer surface by nucleophilic ring opening of epoxide.12 Our background interest was functionalization of epoxy groups on solid polymer surface of crosslinked poly(glycidyl methacrylate) with alcohols, with the emphasis on long chain diols and (protected) polyols. As the
reactions on solid materials are difficult to follow and measure, we had to test first the reaction conditions in solution with an appropriate monomeric epoxide. Also, we wished to avoid as much as possible the application of transition metal catalysts, since on insoluble polymers, functionalized with polar groups, a strong chelation of metal ions might occur and complete removal of the metal after the reaction can be difficult if not impossible. Therefore the acid catalysts we have applied were limited mainly to proton or Lewis acids containing main group elements. In this paper, the results of reactions of a series of alcohols with a model epoxide, glycidyl 4-chlorobenzoate (1) in various solvents using different catalysts is presented.

2. Results and Discussion

Our first choice of a model epoxide was glycidyl methacrylate, since its reactivity was expected to resemble glycidyl methacrylate polymer most closely. Preliminary experiments showed that the catalyst is essential and the best catalysts are anhydrous strong acids, e.g. sulfuric, methanesulfonic or HBF₄ in diethyl ether. In these initial experiments, it was established that besides the addition to epoxy group some side reactions also occur, one of them being the addition of alcohol to C=C group of methacrylate. Consequently, glycidyl methacrylate was replaced by glycidyl 4-chlorobenzoate, because of the simplicity of its preparation, easier tracking of the reaction by TLC and simpler chromatographic separation of the products.

Addition of alcohols to simple epoxides, e.g. cyclohexene oxide is usually a clean reaction, yielding nearly exclusively the β-alkoxyalcohol (Table 1, entry 6). A corresponding reaction of glycidyl esters is less straightforward, since the substrate contains an ester group, which is also prone to react under the conditions of the ring opening addition. Transesterification, acyl group migration and ester hydrolysis are usual byproducts.

A reaction of 1 with methanol in dioxane or excess methanol in the presence of an acid catalyst (methanesulfonic acid or HBF₄/Et₂O) led to the formation of the adduct 2, accompanied with several minor compounds. The structure of products was determined by a combination of separation and analytical methods (GC/MS, HPLC/ESI-TOF-MS, ¹H NMR) as well as independently prepared – standards and the presence of the following compounds was established (Scheme 1).

Diol 4 is formed by hydrolysis of the epoxide by water present in the reaction mixture; its proportion increases with the concentration of water in the system (Table 1, entry 5). The use of dry solvents and anhydrous catalysts is therefore essential. Compounds 5 and 6 are rearranged 2 and 4, respectively. Compounds 3 and 5–7 were not isolated because they are formed in small amounts and are difficult to separate and purify. The structures were assigned tentatively on the basis of their MS and NMR spectra. Migration of the acyl group in acylglycerols in the presence of acid catalyst is a known and frequently observed process, and the amount of rearranged products increases with longer reaction times (Table 1, entries 2, 3). Besides the principal products from Table 1, minute amounts of dimeric products of the type 7 was found to be formed. HPLC/ESI-TOF-MS analysis showed several peaks with molecular mass 457 and 443, which corresponds to the re-

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gio- and stereoisomeric products of the addition of methoxyalcohols 2 or 3 and diols 4 and 6 to 1. Their amounts increase with the dilution of alcohol, e.g. in reaction mixtures where a solution of alcohol was used.

The influence of solvent on the reaction course was studied with methanol as a substrate and HBF_4/Et_2O as a catalyst. The choice of this catalyst was based on the facts that it is a strong and non-nucleophilic acid, it is anhydrous and soluble in organic solvents. The reaction mixture, composed of 1 mmol of 1, 2 mmol of methanol, 0.10 mmol of HBF_4/Et_2O and 1 mL of solvent was stirred at room temperature until the glycidyl ester completely reacted (TLC), or it was established that the reaction doesn’t take place at all (Table 2). The reaction mixture was then analyzed by ^1^H NMR, GC or GC-MS. Generally, an opening of the epoxide ring occurred, leading selectively to 3-methoxy-2-hydroxypropyl 4-chlorobenzoate (2, Scheme 1), accompanied with up to 30% of compounds 4–6.

In any case, the best solvent is the reactive alcohol by itself. However this is not always possible and among the solvents tested, reactions are cleanest in ethers (except THF) and dichloromethane with reasonable yield of desired product. In THF, a ring opening oligomerization occurred and substantial amount of products with oligomeric chain of THF, attached to the glycidyl moiety, was formed (Figure 1). In 1,4-dioxane, the amount of analogous compounds is negligible, though not completely zero. In acetonitrile, some polymer was formed; in NMR spectra of reaction mixtures, several broad absorptions beneath »normal« peaks are notable. In basic solvents, such as N,N-dimethylformamide the reaction doesn’t take place at all.

Catalysts were tested in two solvents of different type, dioxane and dichloromethane (Table 3). Among several Brønsted and Lewis acids, the best activity exhibit anhydrous strong acids, such as trifluoromethanesulfonic and HBF_4 in diethyl ether. Similar results are obtained also with BF_3/Et_2O. Despite the highest yields of the desired adduct, this catalyst was not applied in preparative runs because the reaction mixtures contained several byproducts, which were difficult to separate. Sulfuric acid yields complex reaction mixtures. Somewhat weaker sul-

Table 2. The effect of solvent on the reaction of 1 with methanol\(^{a,b}\)

| Solvent      | 2  | time/h |
|--------------|----|--------|
| MeOH         | 74 | 1      |
| 1,4-dioxane  | 67 | 1      |
| CH\(_2\)Cl\(_2\)| 49 | 1      |
| Et\(_2\)O    | 67 | 1      |
| THF          | 75\(^d\) | 1     |
| MeCN         | 45 | 22     |
| DMF          | 0  | >48    |

\(^a\) 1 mmol of 1, 2 mmol MeOH, 1 mL solvent, 0.1 mmol HBF\(_4\). \(^b\) Yields in %, determined by \(^1^H\) NMR and GC. \(^c\) In methanol as a solvent. \(^d\) Together with oligomers, see text.

Fig. 1. MS (ESI-TOF+) measurement of the products of the reaction of 1 and methanol in THF.

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fonic acids, functioning well in pure methanol, are less efficient in dioxane or dichlorometane. Among metal salts tested, only copper tetrafluoroborate exhibits considerable efficiency, however as it contains water of crystallization, substantial amounts of diols are formed as byproducts thus diminishing its applicability.

In preparative runs, carried out in dioxane and HBF₄/Et₂O as a catalyst, conversion of the starting epoxide was in all cases complete and the yields of the target adduct were, according to NMR, in most cases 50–90%. Isolated yields are lower due to difficulties in purification. Generally, the expected adducts were formed, the exception is the reaction with protected D-glucose, 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose, which reacted very slowly and after a prolonged reaction time, a transesterified and rearranged product (15) was isolated. The glycidyl moiety is replaced by glucose, which is bound to an acyl fragment not by O3 (free OH in the reactant) but by O5 instead. The structure of this unexpected product was determined by NMR techniques and X-ray diffraction analysis (Figure 2).

Table 3. The effect of catalyst on the reaction of 1 with methanol in dichloromethane and dioxane

| Catalyst     | CH₂Cl₂ time/h | Dioxane time/h |
|--------------|---------------|----------------|
| none         | 0             | 0              |
| MeSO₃H       | 22            | 3              |
| CF₃SO₃H      | 59            | 56             |
| HBF₄/Et₂O    | 51            | 65             |
| H₂SO₄        | 50            | 7              |
| BF3/Et₂O     | 53            | 72             |
| LiClO₄       | 0             | 48             |
| Mg(ClO₄)₂    | 2             | 48             |
| Cu(BF₄)₂×H₂O | 26            | 36             |

| Catalyst     | CH₂Cl₂ time/h | Dioxane time/h |
|--------------|---------------|----------------|
| HBF₄/Et₂O    | 51            | 1              |
| H₂SO₄        | 50            | 3              |
| BF3/Et₂O     | 53            | 2              |
| LiClO₄       | 0             | 48             |
| Mg(ClO₄)₂    | 2             | 48             |
| Cu(BF₄)₂×H₂O | 26            | 36             |

* 1 mmol of 1, 2 mmol MeOH, 1 mL solvent, 0.1 mmol catalyst
* Yields in %, determined by ¹H NMR and GC.

Table 4. Syntheses of alkoxy derivatives of 1

| ROH           | Product                          | t/h | Yield % |
|---------------|----------------------------------|-----|---------|
| MeOH          | ArCOOCH₂CH(OH)CH₃               | 1   | 39      |
| BuOH          | ArCOOCH₂C₄H₉O                  | 2   | 44      |
| Octan-1-ol    | ArCOOCH₂C₄H₁₇O                  | 4   | 29      |
| H(OC₂H₄)₃OH  | ArCOOCH₂CH(OH)OH                 | 1   | 40      |
| PEG 400       | ArCOOCH₂CH(OH)OH                 | 1   | 42      |
| But-3-yn-1-ol | ArCOOCH₂                    | 2   | 37      |
| 3-Hydroxypropane-nitrile | ArCOOCH₂OH           | 12  | 4       |
| 1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose | ArCOOCH₂OH | 14  | 14      |
| Cholesterol   | ArCOOCH₂                     | 5   | 24      |

* 1 mmol of 1, 2 mmol alcohol, 1 mL dioxane, 0.1 mmol HBF₄/Et₂O, room temperature.
* Isolated yields.
Interestingly, polyethylene glycol (PEG 400) depolymerized under the reaction conditions. In the $^1$H NMR spectrum of the product, the integral of mid-chain ethylene protons is less than expected. Mass measurement exhibits several peaks corresponding to 5–7 ethyleneoxy units. To the contrary, in the mass spectrum of the starting PEG 400, masses of compounds correspond to 8–10 ethyleneoxy units (see Experimental).

It should be pointed out, that alcohols containing electron-withdrawing groups, such as 3-hydroxypropanenitrile (similarly propyn-1-ol), give the corresponding adducts in low yields; the principal product being a diol. These alcohols are 1–2 pK$_a$ units more acidic than unsubstituted ones and thus less nucleophilic.\(^\text{15}\) Despite the reactants and solvents were dried, in these cases traces of water present in the reaction mixture successfully competed with alcohol in the addition.

### 3. Experimental

**General.** Solvents and alcohols were purchased as δry or dried over molecular sieves 4A. NMR spectra were measured on Bruker Avance 300 or 500 instruments, IR (ATR) spectra on Bruker Alpha-Platinum spectrometer, HRMS measurements in combination with HPLC on Agilent Technologies 6224 TOF instrument. GC and GC/MS analyses were performed on Hewlett-Packard 6890 chromatographs. X-ray diffraction was measured on Agilent SuperNova diffractometer.

### 3.1. Typical Procedures

**Reactions with methanol in different solvents in the presence of HBF$_4$/Et$_2$O (typical procedure).** A mixture of glycidyl 4-chlorobenzoate (214 mg, 1.01 mmol), methanol (79 μL, 1.94 mmol), HBF$_4$/Et$_2$O (14 μL, 0.10 mmol) and 1 mL solvent (1,4-dioxane, dichloromethane, diethyl ether, tetrahydrofuran, acetonitrile, N,N-dimethylformamide) was stirred at room temperature. When the reaction was completed, the mixture was diluted with diethyl ether, washed with aqueous sodium hydrogen carbonate, dried with anhydrous sulfate and the solvent was evaporated under the reduced pressure. Products were then analyzed with $^1$H NMR and GC.

**Reactions with different catalysts in dichloromethane or dioxane (typical procedure).** A mixture of glycidyl 4-chlorobenzoate (214 mg, 1.00 mmol), methanol (79 μL, 1.94 mmol), 0.10 ± 0.01 mmol catalyst (HBF$_4$/Et$_2$O, MeSO$_3$H, BF$_3$/Et$_2$O, LiClO$_4$, Mg(ClO$_4$)$_2$, Cu(BF$_4$)$_2$ × nH$_2$O, H$_2$SO$_4$, CF$_3$SO$_3$H) and solvent (1 mL) was stirred at room temperature. When the reaction was completed or if it wasn’t completed in 48 hours, the mixture was diluted with diethyl ether, washed with aqueous sodium hydrogen carbonate, dried with anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Products were then analyzed with $^1$H NMR and GC.

### 3.2. Synthetic procedures

**Glycidyl 4-chlorobenzoate (1)** A mixture of 4-chlorobenzoyl chloride (17.51 g, 100 mmol) and glycidol (8.94 g, 121 mmol) was diluted with 70 mL of diethyl ether, cooled in an ice bath and triethylamine (10.63 g, 105 mmol) in diethyl ether (70 mL) was slowly added under stirring. The reaction mixture was stirred for 18 hours and allowed to warm to room temperature. The mixture was diluted with diethyl ether, washed with water, aqueous citric acid and aqueous sodium hydrogen carbonate, dried with anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The resulting oil was crystallized at low temperature from dichloromethane/hexane and 11.96 g (56%) of white crystalline 1 was obtained, mp. 42–44 °C.

$^1$H NMR (CDCl$_3$) δ/ ppm 2.72 (dd, $J = 4.9$, 2.6 Hz, 1H, CH$_2$), 2.90 (dd, $J = 4.8$, 4.2 Hz, 1H, CH$_2$), 3.34 (m, 1H, CH), 4.16 (dd, $J = 12.3$, 6.3 Hz, 1H, CH$_2$), 4.66 (dd, $J = 12.3$, 3.0 Hz, 1H, CH$_2$), 7.43 (d, $J = 8.7$ Hz, 2H, Ar-H), 8.00 (d, $J = 8.8$ Hz, 2H, Ar-H). $^{13}$C NMR (CDCl$_3$) δ/ ppm 44.7 (CH$_2$), 49.4 (CH), 65.7 (CH$_2$), 128.2 (C), 131.2 (CH), 139.7 (C), 165.4 (CO). MS, EI, m/z (%) 212 (M$^+$, 2), 214 (M$^+$+2, 1), 141 (33), 139 (100), 113 (11), 111 (35), 75 (32). Anal. Calcd for C$_{10}$H$_7$ClO$_3$: C, 56.48; H, 4.27 Found: C, 56.56; H, 4.53. IR (ATR) ν/cm$^{-1}$ 1717 (C=O), 1265 (C=O), 1089 (C=O), 907 and 848 (epoxide).

**2-Hydroxy-3-methoxypropyl 4-chlorobenzoate (2).** A mixture of glycidyl 4-chlorobenzoate (213 mg, 1.00 mmol) and methanol (79 μL, 1.94 mmol), HBF$_4$/Et$_2$O (14 μL, 0.10 mmol) and 1 mL solvent (1,4-dioxane, dichloromethane, diethyl ether, tetrahydrofuran, acetonitrile, N,N-dimethylformamide) was stirred at room temperature. When the reaction was completed, the mixture was diluted with diethyl ether, washed with aqueous sodium hydrogen carbonate, dried with anhydrous sodium sulfate and the solvent was evaporated under the reduced pressure. Products were then analyzed with $^1$H NMR and GC.
2,3-Dihydroxypropyl 4-chlorobenzoate (4) A mixture of glycidyl 4-chlorobenzoate (113 mg, 0.53 mmol) and 5% CF₃COOH (aq) (1.50 mL, 0.98 mmol) was stirred at room temperature for 24 hours. CF₃COOH was evaporated under reduced pressure. The resulting oil was purified by column chromatography (silica, ethyl acetate : petroleum ether = 2 : 1) and 99 mg (29%) of 4 was obtained as colorless oil. 1H NMR (CDCl₃) δ/ppm 2.85 (t, 3H, CH₃), 3.14 (m, 1H, CH), 4.07 (m, 2H, CH₂), 7.41 (d, J = 8.5 Hz, 2H, Ar-H). 2-Hydroxy-3-[2-[2-(2-hydroxyethoxy)ethoxy]ethoxy]propyl 4-chlorobenzoate (10) A mixture of glycidyl 4-chlorobenzoate (218 mg, 1.03 mmol), triethylene glycol (0.50 mL, 3.74 mmol), HBF₄/Et₂O (17 mg, 0.11 mmol) and dioxane (0.5 mL) was stirred at room temperature for 1 hour. The reaction mixture was filtered through neutral aluminum oxide column and the solvent was evaporated under reduced pressure. The resulting oil was purified by column chromatography (silica, ethyl acetate : petroleum ether = 1 : 3) and 99 mg (29%) of 10 was obtained as colorless oil. 1H NMR (CDCl₃) δ/ppm 1.80 (s, 3H, OH), 3.61–3.73 (m, 14H, CH₂), 4.14 (m, 1H, CH), 4.37 (m, 2H, CH₂), 7.41 (d, J = 8.8 Hz, 2H, Ar-H), 8.01 (d, J = 8.8 Hz, 2H, Ar-H). 13C NMR (CDCl₃) δ/ppm 61.57 (CH₃), 65.84 (CH₂), 68.76 (CH), 69.13 (CH₂), 70.43 (CH₂), 70.62 (CH₂), 72.93 (CH₃), 73.11 (CH₂), 128.44 (C), 128.71 (CH), 131.16 (CH), 139.49 (C), 165.69 (CO). HRMS(ESI-TOF) Calcd for C₁₆H₂₃ClO₄ + H⁺: 343.1673, found: 343.1671, 362–370. Reaction of glycidyl 4-chlorobenzoate with polyethylene glycol 400. A mixture of glycidyl 4-chlorobenzoate
(225 mg, 1.06 mmol), PEG 400 (0.80 mL, 2.26 mmol), HBF$_4$/Et$_2$O (18 mg, 0.11 mmol) and dioxane (0.5 mL) was stirred at room temperature for 1 hour. The reaction mixture was filtered through short neutral aluminum oxide column and the solvent was evaporated under reduced pressure. The resulting oil was diluted with water and washed three times with CH$_2$Cl$_2$. The organic phase was dried with anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The product (11) was obtained as colorless oil (274 mg, 42%). $^1$H NMR (CDCl$_3$) δ/ppm 3.55–3.84 (m, 24H, CH$_2$), 4.13 (m, 1H, CH), 4.38 (d, J = 5.4 Hz, 2H, CH$_2$), 7.41 (d, J = 8.5 Hz, 2H, Ar-H). IR (ATR) ν/cm$^{-1}$ 3429 (OH), 2870 (C-H), 1718 (C=O). HRMS(ESI-TOF) Calcd for C$_{14}$H$_{15}$ClO$_4$: C, 59.48; H, 5.54.

HRMS (ESI-TOF):

| Formula | Calcd m/z | Found m/z |
|---------|-----------|-----------|
| C$_{14}$H$_{15}$O$_4$Cl + NH$_4$ + (n = 4) | 424.1733 | 424.1735 |
| C$_{20}$H$_{21}$O$_9$Cl + NH$_4$ + (n = 4) | 468.1995 | 468.1997 |
| C$_{23}$H$_{26}$O$_{10}$Cl + NH$_4$ + (n = 6) | 512.2257 | 512.2259 |
| C$_{24}$H$_{28}$O$_{11}$Cl + NH$_4$ + (n = 7) | 556.2519 | 556.2521 |
| C$_{25}$H$_{31}$O$_{12}$Cl + NH$_4$ + (n = 8) | 600.2779 | 600.2781 |

3-(But-3-yn-1-yloxy)-2-hydroxypropyl 4-chlorobenzoate (12). A mixture of glycidyl 4-chlorobenzoate (213 mg, 1.00 mmol), 3-butyn-1-ol (0.3 mL, 3.96 mmol), HBF$_4$/Et$_2$O (18 mg, 0.12 mmol) and dioxane (0.5 mL) was stirred at room temperature for 1 hour. The reaction mixture was diluted with diethyl ether, washed with aqueous sodium hydrogen carbonate and water, dried with anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The product (12) was obtained as colorless oil (274 mg, 42%). $^1$H NMR (CDCl$_3$) δ/ppm 3.54–3.65 (m, 3H, CH$_2$), 4.06 (m, 1H, CH$_2$), 4.16 (m, 1H, CH), 4.40 (d, J = 5.6, 11.6 Hz, 1H, CH$_2$), 2.80 (d, J = 5.0; 11.6 Hz, 2H, Ar-H); 7.42 (d, J = 8.6 Hz, 2H, Ar-H). IR (ATR) ν/cm$^{-1}$ 3495 (OH), 2253 (CN), 1717 (C=O).

3-[2,2-Dimethyl-1,3-dioxolan-4-ylmethoxy]-2-hydroxypropyl 4-chlorobenzoate (14). A mixture of glycidyl 4-chlorobenzoate (217 mg, 1.02 mmol), D,L-α,β-isopropylidenedi-2,2-dimethylhexahydrofuro[2,3-d]furo[2,3-d]dioxol-6-yl 4-chlorobenzoate (15).

**3-(2-Cianoethoxy)-2-hydroxypropyl 4-chlorobenzoate (13).** A mixture of glycidyl 4-chlorobenzoate (638 mg, 3.00 mmol), 3-hydroxypropanenitrile (430 mg, 6.0 mmol), HBF$_4$/Et$_2$O (32 mg, 0.22 mmol) and 3 mL dioxane was stirred at room temperature for 12 hours. The mixture was diluted with diethyl ether, washed with aqueous sodium hydrogen carbonate and water, dried with anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The resulting oil was purified by column chromatography (silica, ethyl acetate = 1 : 3) and 35 mg (4%) of 13 was obtained as colorless oil. $^1$H NMR (CDCl$_3$) δ/ppm 2.64 (t, J = 6.2 Hz, 2H, CH$_2$), 2.80 (d, J = 5.1 Hz 1H, OH), 3.62 (dd, J = 6.0, 9.7 Hz, 1H, CH$_3$), 3.68 (dd, J = 4.3; 9.7 Hz, 1H, CH$_3$), 3.75 (t, J = 6.2 Hz, 2H, CH$_3$), 4.17 (m, 1H, CH), 4.40 (dd, J = 5.9; 11.7 Hz, 1H, CH$_3$), 4.43 (dd, J = 4.4; 11.7 Hz, 1H, CH$_3$), 7.42 (d, J = 8.5 Hz, 2H, Ar-H), 7.94 (d, J = 8.5 Hz, 2H, Ar-H). $^{13}$C NMR (CDCl$_3$) δ/ppm 18.90 (CH$_3$), 66.04 (CH$_3$), 66.07 (CH$_2$), 68.85 (CH), 72.21 (CH), 117.72 (CN), 128.15 (C), 128.83 (CH), 131.12 (CH), 139.75 (C), 165.84 (CO). HRMS(ESI-TOF) Calcd for C$_{14}$H$_{15}$ClO$_4$ + H$: 284.0684, found: 284.0685. Anal. Calcd for C$_{14}$H$_{15}$ClO$_4$: C, 55.04; H, 4.97; N 4.94 Found: C, 55.36; H, 5.02; N 4.62. IR (ATR) ν/cm$^{-1}$ 3495 (OH), 2253 (CN), 1717 (C=O).

3,5-Di(2-Cianoethoxy)-2-hydroxypropyl 4-chlorobenzoate (15). A mixture of glycidyl 4-chlorobenzoate (222 mg, 1.04 mmol), 1,2:5,6-di-O-isopropylidene-α-D-glucopyranose (525 mg, 2.02 mmol), HBF$_4$/Et$_2$O (20 mg, 0.12 mmol) and dioxane (2 mL) was stirred at room temperature for 97 hours. The

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mixture was diluted with diethyl ether, washed with aqueous sodium hydrogen carbonate and water. The ether phase was diluted with petroleum ether, washed with water, dried with anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The resulting oil was purified by column chromatography (silica, ethyl acetate : petroleum ether = 1 : 5) and 76 mg (21%) of 15 was obtained as colorless oil, which crystallized in refrigerator, mp 64–69 °C. 1H NMR (CDCl3) δ/ppm 1.34 (s, 3H, CH3), 1.50 (s, 3H, CH3), 3.88 (t, J = 8.3 Hz, 1H, CH3), 4.17 (dd, J = 8.7, 7.0 Hz, 1H, CH3), 4.59 (d, J = 3.7 Hz, 1H, CH3), 4.65 (d, J = 3.6 Hz, 1H, CH3), 5.07 (t, J = 4.0 Hz, 1H, CH3), 5.32 (m, 1H, CH), 5.96 (d, J = 3.6 Hz, 1H, CH), 7.42 (d, J = 8.5 Hz, 2H, Ar-H), 8.00 (d, J = 8.5 Hz, 2H, Ar-H). 13C NMR (CDCl3) δ/ppm 27.08 (CH3), 27.71 (CH3), 69.37 (CH3), 74.25 (CH), 81.39 (CH), 85.11 (CH), 85.62 (CH), 107.50 (CH), 113.17 (C), 128.07 (C), 129.11 (CH), 131.61 (CH), 140.20 (C), 165.43 (CO). HRMS(ESI-TOF) Calcd for C16H17ClO6: C, 56.40; H, 5.03 Found: C, 56.70; H, 5.34.

2-Hydroxy-3-cholesterylpropyl 4-chlorobenzoate (16). A mixture of glycidyl 4-chlorobenzoate (220 mg, 1.03 mmol), cholesterol (776 mg, 2.01 mmol), HBF4/Et2O (16 mmol), cholesterol (776 mg, 2.01 mmol), HBF4/Et2O (16 mmol) and dioxane (5 mL) was stirred at room temperature for 5 hours. The mixture was diluted with diethyl ether and petroleum ether, washed with aqueous sodium hydrogen carbonate and water, dried with anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The resulting oil was purified by column chromatography (silica, ethyl acetate : petroleum ether = 1 : 3) and 141 mg (24%) of 16 was obtained as colorless oil, which crystallized in refrigerator, mp 116–123 °C. 1H NMR (CDCl3) δ/ppm 0.86 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H), 1.00 (s, 3H), 1.02–2.05 (m, 26H), 2.20 (m, 1H), 2.36 (m, 1H), 2.70 (s, 1H), 3.20 (m, 1H), 3.55 (m, 1H), 3.64 (m, 1H), 4.11 (m, 1H), 4.40 (m, 2H), 5.34 (m, 1H), 7.42 (d, J = 8.5 Hz, 2H), 7.99 (d, J = 8.6 Hz, 2H). 13C NMR (CDCl3) δ/ppm 11.87 (CH3), 18.73 (CH3), 19.40 (CH3), 21.08 (CH3), 22.59 (CH3), 22.85 (CH3), 23.84 (CH3), 24.30 (CH3), 28.03(CH3), 28.25, 31.88 (CH2), 31.95 (CH2), 35.80 (CH), 36.20 (CH), 36.85 (C), 37.11 (CH3), 38.97 (CH), 39.04 (CH), 39.53 (CH3), 39.77, 42.32 (C), 50.14 (CH), 56.16 (CH), 56.76 (CH), 66.33 (CH3), 68.71 (CH3), 69.03 (CH), 79.85 (CH), 121.93 (CH), 128.36 (C), 128.80 (CH), 131.14 (CH), 139.62 (C), 140.53 (C), 165.81 (CO). HRMS(ESI-TOF) Calcd for C16H17ClO6: C, 56.40; H, 5.03 Found: C, 56.70; H, 5.34.

Determination of the X-ray structure of compound 15. Data for 15 were collected on an Agilent SuperNova diffractometer using monochromated Mo-Kα radiation, l = 0.71073 Å. The coordinates of some or all of the non-hydrogen atoms were found via direct methods using the structure solution SHELXS-97 program.17 Positions of the remaining non-hydrogen atoms were located by using a combination of least-squares refinement and difference Fourier maps in the SHELXL-97 program.17 Except hydrogen atoms, all atoms were refined anisotropically.

4. Conclusion

Glycidyl esters can be derivatized with alcohols as stoichiometric reagents to the corresponding alkoxy adducts, however some points have to be taken into account. Since the alcohol is in this case not present in high concentration, side reactions are more pronounced. Besides the principal 3-alkoxy-2-hydroxy derivatives, certain amount of regioisomers and rearranged products are obtained as a result of parallel and subsequent reactions. The dryness of the reactants and solvents is of prime importance, since a considerable amount of diols are formed with the water present in the reaction medium. Alcohols, bearing electron-attracting groups, give poor yields. The yields of the products are generally lower than with simple epoxides (e.g. cyclohexene oxide) since beside epoxide a relatively reactive ester group is also present. Isolated yields, as presented in table 4 are rather low, due to difficult separation of isomeric products. Nevertheless a reasonable yields of the desired adducts can be obtained by conducting the reaction carefully.

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6. References

1. M. B. Smith, J. March, March’s Advanced Organic Chemistry, 5th ed. Wiley-Interscience: New York, 2001. p. 462–578 and references cited therein.

2. G. Dake, Oxiarines and Oxirenes: Monocyclic, in A. R. Katritzky, C. A. Ramsden; E. F. V. Scriven, R. J. K. Taylor eds., Comprehensive Heterocyclic Chemistry III, Vol. 1. Vol. ed. A. Padwa, Elsevier: Oxford, 2008.

3. I. Erden, Oxiarines and Oxirenes: Monocyclic, in A. R. Katritzky, C. W. Rees, E. F. V. Scriven, eds., Comprehensive Heterocyclic Chemistry II, Vol. 1a. Vol. ed. A. Padwa, Pergamon-Elsevier: Oxford, 1996.

4. A. S. Rao, S. K. Paknikar, J. G. Kirtane, Tetrahedron, 1983, 39, 2323–2367. http://dx.doi.org/10.1016/S0040-4020(01)91961-1

5. S. K. Taylor, Tetrahedron, 2000, 56, 1149–1163. http://dx.doi.org/10.1016/S0040-4020(99)01074-1

6. Some recent examples: S. Bonollo, D. Lanari, L. Vaccaro, Eur. J. Org. Chem. 2011, 14, 2587–2598. C. Schneider, Synthesis, 2006, 3919–3944. L. I. Kas’yan, A. O. Kas’yan, S. I. Okovityi, Russian J. Org. Chem. 2008, 42, 307–337. M. Hosseini-Sarvari Acta Chim. Slov. 2008, 55, 440–447. R. Outouch, M. Rauchdi, B. Boualy, L. El Firdoussi, M. Ait Ali, Acta Chim. Slov. 2014, 61, 67–72.

7. M. Chini, P. Crotti, L. A. Flippin, C. Gardelli, E. Giovani, F. Macchia, M. Pineschi, J. Org. Chem. 1993, 58, 1221–1227. http://dx.doi.org/10.1021/jo00057a040

8. J. Barluenga, H. Vasquez-Villa, A. Ballesteros, J. M. Gonzalez, Org. Letters, 2002, 4, 2817–2819. http://dx.doi.org/10.1021/ol025997k

9. P. Salehi, B. Seddighi, M. Irandoost, F. K. Behbahani, Synthetic Commun., 2000, 30, 2967–2973. http://dx.doi.org/10.1080/00397910008087447

10. N. Iranpoor, B. Zeynizadeh, Synthetic Commun., 1999, 29, 1017–1024. http://dx.doi.org/10.1080/0039791990806066

11. D. B. G. Williams, M. Lawton, Org. Biomol. Chem. 2005, 3, 3269–3272. http://dx.doi.org/10.1039/b508924g

12. For some recent examples see eg. M. Benaglia, A. Alberti, L. Giorgini, F. Magnonia, S. Tozzi, Polym. Chem. 2013, 4, 124–132. R. Barbey, V. Laporte, S. Alnabulsi, H-A. Klok, Macromolecules 2013, 46, 6151–6158. M. R. Buchmeiser, Polymer, 2007, 48, 2187–2198. C. J. Evenhuis, W. Buchberger, E. F. Hilder, K. J. Flook, C. A. Pohl, P. N. Nesterenko, P. R. Haddad, J. Sep. Sci., 2008, 31, 2598–2604.

13. O. E. Lohuizen, P. E. Verkade, Rec. Trav. Chim. Pays Bas 1960, 79, 133–159. H. Hibbert, N. M. Carter, J. Am. Chem. Soc. 1929, 51, 1601–1613. S. Y. Koo, H. Masamune, K. B. Sharpless, J. Org. Chem. 1987, 52, 667–671.

14. See e.g. S. Aoki, T. Otsu, M. Imoto, Kagaku Zasshi 1964, 67, 971–973. W. Z. Antkowiak, Polish J. Chem., 2001, 75, 875–878.

15. Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994–2014 ACD/Labs)

16. L. Farrugia, J. Appl. Crystallogr. 1997, 30, 565. http://dx.doi.org/10.1107/S0021889897003117

17. Sheldrick, G. M. SHELX-97. Programs for Crystal Structure Analysis; University of Göttingen: Göttingen, Germany, 1998.

18. Flack, H. D. Acta Crystallogr. 1983, A39, 876–881. http://dx.doi.org/10.1107/S0108767383001762

Povzetek

Glicidil estre, ki jih pogosto uporabljajo kot reaktivne skupine na polimernih nosilcih, smo funkcionalizirali z alkoholi kot stehiometričnimi reagenti, pri čemer so nastali β-alkoksialkoholi. Reakcija najbolje poteka v etrih v prisotnosti močne protonske kisline kot katalizatorja. Uporabili smo različne alkohole, kot so enostavni alkanoli, dioli, zaščiteni polioli, 3-butin-1-ol, 3-hidroksipropanonitril in holesterol. Na ta način lahko na epoksi-funkcionalizirane polimere uvažamo različne funkcionalne skupine. Pod pogoji reakcije poteka tudi nekaj stranskih reakcij, večinoma v povezavi z estrsko skupino in vlago, prisotno v reakcijski zmesi.

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