

Note

SYNTHESIS OF 3-BENZYL-GLYCERIC ACID: A KEY INTERMEDIATE OF A
NOVEL CYCLIC ESTER MONOMER*Jian Yu^a, Mei Li^a, Ji-yuan Yang^{a,b}, Zhong-wei Gu^b, Wei-xiao Cao^a and Xin-de Feng^{a**}^a Department of Polymer Science and Engineering, Peking University, Beijing 100871, China^b National Research Institute for Family Planning, Beijing 100081, China

Abstract A route was proposed to synthesize 3-benzyl-glyceric acid (3-BGA) as an important intermediate for the synthesis of a novel six-membered cyclic ester monomer — 3-benzoyloxymethyl-1,4-dioxane-2,5-dione (3-BMG). According to this route, 3-BGA was obtained from ring-opening reaction of benzyl alcohol with methyl glycidate, which was prepared from the epoxidation of methyl acrylate using sodium hypochlorite as the oxidant.

Keywords 3-Benzyl-glyceric acid, Epoxidation, Benzyl alcohol, Ring-opening reaction

INTRODUCTION

Much attention has been paid to the synthetic biodegradable polyesters, such as polylactide (PLA) and its related copolymers, for applications as absorbable sutures and drug delivery systems. Recently, the development of water-soluble peptides and protein drugs has posed some requirements for such polyesters. In order to meet the requirements for use as pharmaceutical carriers, the properties for polyesters, such as hydrophilicity, adequate biodegradation rate, cell adhesion, drug affinity, etc., should be carefully tailored^[1–3].

One general strategy to improve the hydrophilicity of polyesters is by introduction of the water-soluble segments, such as a moiety of poly(vinyl alcohol) (PVA) or poly(ethylene glycol) (PEG), through branching or blocking into the polymer chain^[4, 5]. Another approach is to introduce functional pendant groups along the backbone of the polymers by block copolymerization with functionalized comonomers^[6, 7]. Recently, we synthesized a new cyclic diester monomer, 3-benzoyloxymethyl-1,4-dioxane-2,5-dione (3-BMG), which can be polymerized by the ring-opening method and further deprotected to form water-soluble polyester in bulk using stannous 2-ethylhexanoate (Sn(Oct)₂) as the catalyst^[8]. Subsequently, copolymerization of 3-BMG with *dl*-lactide has been conducted successfully^[9].

3-Benzyl-glyceric acid (3-BGA) is the key intermediate for the preparation of 3-BMG. In our previous paper^[8], 3-BGA was prepared through the reaction of sodium benzyl alcohol with β -chlorolactic acid which was obtained by the oxidation of 3-chloro-propanediol for one to two weeks. The overall yield of 3-BGA was 24.9%. In this paper, we report another route to obtain 3-BGA from methyl acrylate via two steps (Scheme 1). The first step is the epoxidation of methyl acrylate with NaOCl, and the second step is the ring-opening reaction of epoxy compound obtained. This method is timesaving and the yield is the same as that of the former method.

EXPERIMENTAL

Materials

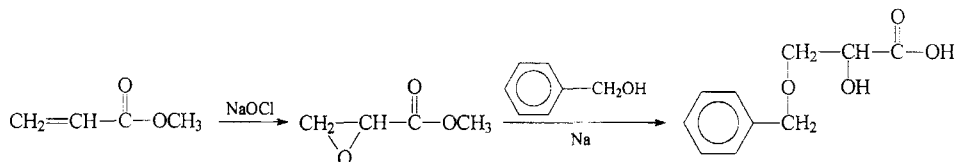
NaOCl (5% chlorine) was purchased from Acros. Methyl acrylate was washed three times with 10% NaOH

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solution then washed with water to neutral, dried with anhydrous Na_2SO_4 and distilled. Benzyl alcohol was dried over calcium hydride and distilled. All other chemicals and solvents were reagent grade and were used without further purification.



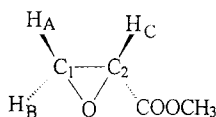
Scheme 1 The synthesis of 3-BGA from methyl acrylate via epoxidation and ring-opening reaction

Characterisation

The ^1H - and ^{13}C -NMR spectra were recorded on a Bruker ARX-400 spectrometer with tetramethylsilane as an internal standard. Mass spectra were obtained on a VG ZAB-MS mass spectrometer (EI). FTIR spectra were recorded on a Nicolet Magna-IR 750 spectrometer.

Epoxidation of Methyl Acrylate

The procedure described by Hansen^[10] was adopted with some modifications. To a solution of 5% NaOCl (330 mL) at 0°C , 30 g of methyl acrylate (0.35 mol) was added with vigorously stirring. After standing for 0.5 h at 0°C , the reaction mixture was placed in a water-bath (ca. 20°C) and stirred for additional 3 h. The mixture was then extracted with CH_2Cl_2 (5×100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 . Most of the solvent was evaporated in vacuo at a temperature not exceeding 30°C . The residual liquid was then distilled under reduced pressure ($76\text{--}77^\circ\text{C}$, 51 torr) to yield 12.1 g of methyl glycidate (34.0% yield). Elementary analysis (%): Calcd. (for $\text{C}_4\text{H}_6\text{O}_3$): C 47.06, H 5.92. Found: C 47.03, H 5.94; MS (E/I, m/z): 101 [$(\text{M}-1)^+$]; ^1H -NMR (CDCl_3 , δ): 3.79 (CH_3 , 3H), 3.45 (CH, 1H) and 2.98 (CH_2 , 2H); FTIR (cm^{-1}): 3003, 2959, 2859, 1754, 1442 and 1262.



Structure formula of methyl glycidate

Ring-opening Reaction of Methyl Glycidate

A 250 mL round-bottomed flask equipped with a magnetic stirring bar was charged with 50 mL benzyl alcohol and 1.4 g (0.060 mol) fresh metal sodium under N_2 atmosphere at 10°C until the sodium was fully dissolved. 5.0 g methyl glycidate (0.049 mol) in 50 mL benzyl alcohol was added over a 2 h period, then the solution was warmed to room temperature (ca. 25°C) and stirring continued for 10 h. 150 mL of water was added and stirred for 2 h. After the aqueous layer was extracted with diethyl ether to remove the dissolved benzyl alcohol, the remainder was acidified with 6 mol/L HCl and extracted with diethyl ether. The extraction product was dried over anhydrous MgSO_4 and the solvent was evaporated under vacuum to yield crude product which was recrystallized from ethyl acetate to yield 6.01 g of white crystalline solid 3-BGA (62.5% yield). Elemental analysis (%): Calcd. (for $\text{C}_{10}\text{H}_{12}\text{O}_4$): C 61.22, H 6.12. Found: C 60.81, H 6.05; MS (E/I, m/z): 196 (M^+); ^1H -NMR (CDCl_3 , δ): 3.80 (BzOCH_2 , 2H), 4.38 ($\text{OCH}(\text{CH}_2\text{OBz})\text{COO}$, 1H), 4.57 (phCH_2 , 2H) and 7.255–7.339 (ph, 5H); ^{13}C -NMR (CDCl_3 , δ): 70.3 (BzOCH_2), 70.9 (phCH_2), 76.7 ($\text{CH}(\text{OH})\text{COOH}$), 127.8–137.1 (ph) and 176.3 (COOH); FTIR (cm^{-1}): 3440, 3399, 3060, 3033, 1743, 1497, 1200, 1137, 735 and 697.

RESULTS AND DISCUSSION

The epoxidation of α,β -unsaturated esters having electron deficient $\text{C}=\text{C}$ double bonds is rather difficult because of the electrophilic mechanism of the reaction. H_2O_2 ^[11, 12] and NaOCl ^[10, 13, 14] were widely used as the oxidant and

the oxidation reactions were usually carried out under low temperatures. In our study, NaOCl solution was adopted as epoxidation reagent at room temperature. An outline of the synthetic pathway for preparing 3-BGA is shown in Scheme 1. The overall yield was 21.3%.

Because the epoxy ring is readily attacked by the hydroxyl group in an alkaline solution of NaOCl, a high pH value (> 10) of the reaction medium would reduce the yield of epoxide. On the other hand, raising the reaction temperature would accelerate the decomposition of ClO^- but decelerate the epoxidation. Therefore, the epoxidation conditions of methyl acrylate must be carefully controlled to get a satisfactory yield of methyl glycidate.

Methyl glycidate was characterized by ^1H -NMR, MS and FTIR spectroscopies. Because C_2 (see structure formula) is a chiral carbon, the two protons (H_A , H_B) connected to C_1 have different chemical shifts in ^1H -NMR spectrum as shown in Fig. 1 (bottom). The resonance of proton H_C (linked to C_2) was split into 4 peaks, while those of protons H_A and H_B were split into 8 peaks. In order to obtain an understanding of the spectrum, resonances of the three protons of the epoxide-ring were treated as an ABX system and the corresponding spin-spin coupling constants were estimated to be $J_{\text{AB}} = 6.5 \text{ Hz}$, $J_{\text{AC}} = 2.6 \text{ Hz}$ and $J_{\text{BC}} = 4.0 \text{ Hz}$ (Fig. 1, top). The mass spectrum exhibits m/z peaks at 101, 71, 59, 43 and 31, where peak 43 is the strongest. In the FTIR spectrum, there is no absorption band at $1620\text{--}1640 \text{ cm}^{-1}$ which is the stretching vibration of $\text{C}=\text{C}$ double bond. The absorption bands at 1754 and 1262 cm^{-1} are the stretching vibration of the ester $\text{C}=\text{O}$ and the deformation vibration of the epoxy ring, respectively.

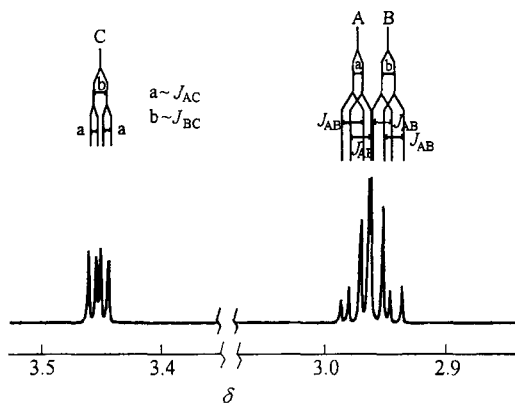


Fig. 1 The ^1H -NMR spectrum of methyl glycidate (bottom) and the spin-spin coupling constants of three protons of the epoxide-ring of methyl glycidate treated as an ABX system (top)

Methyl glycidate was then ring-opened by benzyl alcohol. The favorable product of α - or β -substituted in the ring-opening reaction of epoxide will depend on the electric charge distribution and the steric effect of the reactants as well as the reaction conditions such as temperature and pH value of the medium. In the present work, 3-BGA was obtained through the reaction of methyl glycidate with benzyl alcohol in alkaline medium. Its structure has been carefully characterized and confirmed by ^1H -, ^{13}C -NMR, MS and FTIR spectroscopies.

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