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IMPROVED SYNTHESES OF ETHYL α-(BROMOMETHYL)ACRYLATE AND 2-METHYLENE-1,3-PROPANEDIOL VIA ETHYL α-(HYDROXYMETHYL)ACRYLATE

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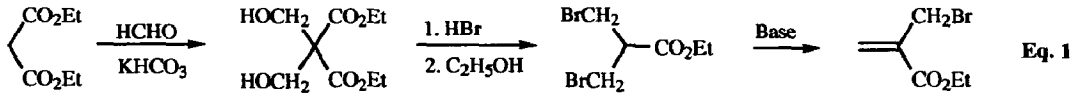
Abstract: Ethyl α-(bromomethyl)acrylate (**1**) and 2-methylene-1,3-propanediol (**2**) have been prepared via formaldehyde addition to ethyl acrylate in the presence of DABCO, giving α,β-unsaturated ester **3**. Reduction of hydroxy ester **3** with one equivalent of alane, then borohydride reduction of the resulting aldehyde **4** gives **2**.

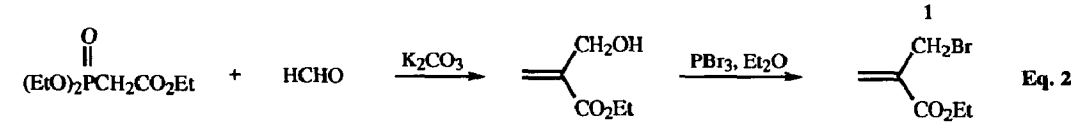
Ethyl α-(bromomethyl)acrylate (**1**), prepared by the reaction of PBr_3 and ethyl α-(hydroxymethyl)-acrylate (**3**),[1] is a useful compound for the synthesis of α-methylene-γ-lactones from ketones and aldehydes,[2] α-methylene-γ-lactams from imines,[3] and glutarimide nucleosides.[4] Ethyl α-(bromomethyl)acrylate also undergoes a variety of substitution reactions with carbon,[5] benzenesulfinate,[6] and oxygen[7] nucleophiles. Addition of bromine to **1** followed by dehydrobromination is a facile route to ethyl α-(bromomethyl)-β-bromoacrylate.[8]

Despite the widespread synthetic utility of ethyl α-(bromomethyl)acrylate (**1**), a convenient large-scale synthesis has not been reported yet. Two known routes to this synthon are illustrated in Eqs. 1 and 2. In one method,[9] diethyl malonate is subjected to bisformylation, then the formylated product is treated with hydrobromic acid followed by decarboxylation; dehydrobromination in the presence of base affords ethyl α-(bromomethyl)acrylate in 28% overall yield starting from diethyl bis(hydroxymethyl)malonate[9c] (Eq. 1). An improved preparation[1] was based on the Wittig-Horner reaction of triethyl phosphonoacetate with formaldehyde followed by treatment of the ethyl α-(hydroxymethyl)acrylate with phosphorus tribromide, as shown in Eq. 2.



Eq. 1

1

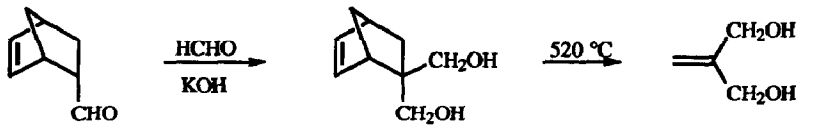


Eq. 2

1

The coupling reaction of an acrylic ester with aldehydes catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO)[2i, 10] is a good method for the preparation of an α-(hydroxyalkyl) acrylic ester, but formaldehyde has not yet been used in this type of coupling reaction. This communication shows for the first time that formaldehyde reacts with ethyl acrylate in the presence of DABCO to give **3**, which is readily converted into the useful synthons ethyl α-(bromomethyl)acrylate (**1**) or 2-methylene-1,3-propanediol (**2**).

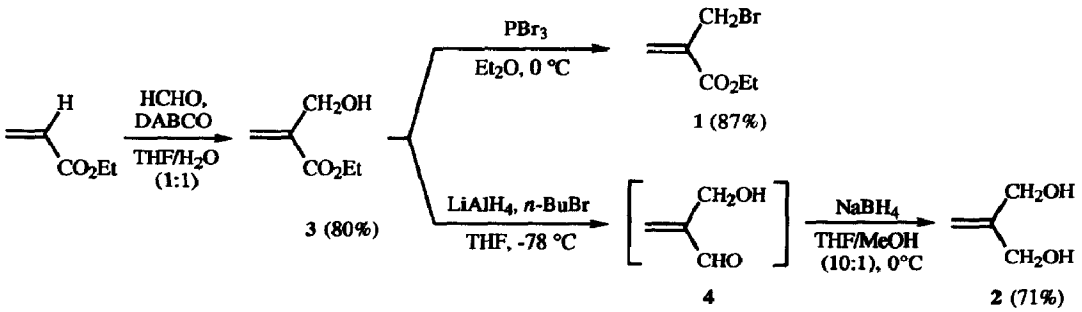
2-Methylene-1,3-propanediol (**2**) has been used to protect carbonyl groups, and deprotection of the resulting 5-methylene-1,3-dioxane was achieved by different methods. The only current method for preparing **2** is inconvenient, because very high temperature is needed for the retro Diels-Alder reaction of 2,2-bis(hydroxymethyl)-5-norbornene, which was prepared by the Cannizzaro reaction of 5-norbornene-2-carboxaldehyde with formaldehyde (Eq. 3).[11]



2 Eq. 3

Here we report a convenient synthesis of ethyl α-(bromomethyl)acrylate (**1**) on a 1-mol scale by the reaction of ethyl acrylate with formaldehyde catalyzed by DABCO followed by the treatment of ethyl α-(hydroxymethyl)acrylate with PBr_3. We found that the coupling reaction of ethyl acrylate with formaldehyde in THF or methanol in the presence of DABCO was accompanied by byproduct, and the reaction required more than a week to run to completion; however, in aqueous THF the reaction was completed within 36 h with no byproduct.

Scheme 1 also shows the synthesis of 2-methylene-1,3-propanediol (**2**) by the reduction of ethyl α-(hydroxymethyl)acrylate with one equiv. of AlH_3 (generated in situ by the reaction of $LiAlH_4$ with *n*-butyl bromide),[12] followed by the addition of sodium borohydride in THF/methanol (10:1). Reduction of **3** with two equiv. of AlH_3 or diisobutylaluminum hydride provided a low yield of propanediol **2**. Reduction of aliphatic and alicyclic α,β-unsaturated esters with various reducing reagents generally gives low yields of allylic alcohols because of competing 1,2- and 1,4-addition reactions.[13] We suggest that preliminary reaction of **3** with AlH_3 may give an alkoxyalane (AlH_2OR), which reacts with the ester group to produce aldehyde **4**. The aldehyde **4** was subsequently reduced by $NaBH_4$ to give **2** in 71% overall yield.



The preparation of ethyl α-(hydroxymethyl)acrylate (**3**) reported here offers three important advantages compared with the procedure based on the Wittig-Horner approach:[1] (1) it is much more economical, since triethyl phosphonoacetate is more expensive than ethyl acrylate; (2) no byproduct is formed in our procedure, whereas in the phosphonate-based procedure[1] several byproducts co-distill with the product **3** when commercial

formaldehyde solution was used; (3) scale up of our procedure to a 1-mol scale is readily achieved in a 500-mL flask at room temperature, whereas the *Org. Synth.* procedure[1a] requires a 1000-mL four-necked flask with a mechanical stirrer for a 0.4-mol scale, and also requires that the base be added very slowly to form the phosphonate-stabilized anion. In the procedure presented here, the reagents are simply mixed together and stirred at room temperature after formaldehyde has been generated.

In a typical procedure, ethyl α-(hydroxymethyl)acrylate (**3**) was prepared from ethyl acrylate and aqueous paraformaldehyde as follows. Paraformaldehyde (33 g, 1.1 mol), 1 N phosphoric acid (4 mL), and water (100 mL) were heated at 90 °C for 1.5 h to form a clear aqueous formaldehyde solution. After the solution was cooled to room temperature, THF (100 mL), ethyl acrylate (109 mL, 1.0 mol), and DABCO (11.3 g, 0.1 mol) were added, and the reaction mixture was stirred for 36 h. (Formalin may be substituted for paraformaldehyde.) To the reaction mixture sodium chloride (35 g) and ether (100 mL) were added. The organic layers were separated and then the product was extracted from the aqueous layers with ether (three 100-mL portions). The combined organic layers were washed with brine (two 100-mL portions) and dried over magnesium sulfate; the solvents were evaporated under reduced pressure and the residue was distilled under vacuum, giving 104.1 g (80%) of **3**; bp 65-70 °C/1 mm[14] (lit.[1] 65-70 °C). Ethyl α-(bromomethyl)acrylate (**1**) was obtained by reaction of **3** with PBr_3 in ether at 0 °C.[1]

To prepare 2-methylene-1,3-propanediol (**2**), the ester group of **3** was reduced as follows. To a suspension of $LiAlH_4$ (8.36 g, 0.22 mol) in 500 mL of THF was added *n*-butyl bromide (30.2 g, 0.22 mol) at 0 °C; and the mixture was stirred for 3 h. After the reaction mixture was cooled to -78 °C, a solution of ethyl α-(hydroxymethyl)acrylate (26.0 g, 0.20 mol) in 50 mL of THF was added. After 3 h the reaction was quenched by the addition of 10 mL of water. The reaction mixture was allowed to stand at room temperature and filtered through a pad of silica gel, which was washed with chloroform/methanol (9:1). The resultant solution was dried over sodium sulfate and concentrated under reduced pressure to give a residue. The residue was dissolved in 50 mL of THF/methanol (10:1), and sodium borohydride (7.6 g, 0.2 mol) was added at 0 °C. After 3 h the reaction mixture was acidified with concentrated hydrochloric acid and filtered through a pad of silica gel, which was washed with additional chloroform/methanol (9:1). The filtrate was dried over sodium sulfate and concentrated under reduced pressure followed by vacuum distillation to give 12.5 g (71%) of diol **2**; bp 93-95 °C/2 mm[15] (lit.[11] 127-129 °C/32 mm, lit.[16] 93-95 °C/2 mm).

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