Practical Preparation of 2-Halomethyl-Allyl Carboxylates

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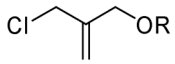
An improved, efficient preparation of 2-(halomethyl)allyl carboxylates starting from diethyl bis(hydroxymethyl)malonate and hydrobromic acid is reported. The allylic halogen of 2-(chloromethyl)acrylate and 2-(bromomethyl)acrylate are readily exchanged during esterification.

Keywords: Acrylate; 2-(Halomethyl)allyl; 1,3-Bifunctional.

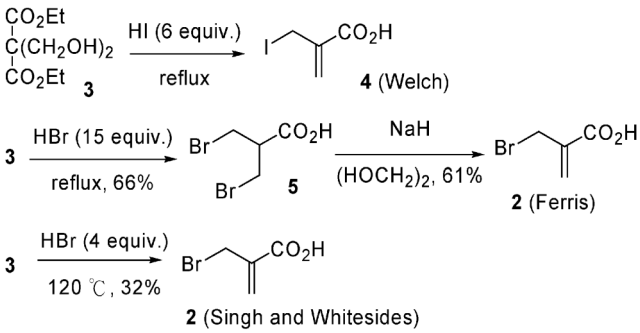
INTRODUCTION

Bifunctional, allylic compounds, such as 2-(chloromethyl)allyl acetate and benzoate (**1a,b**) are useful synthetic blocks. They have been applied in natural product synthesis such as Roseophilin,[1a] Mycalamide A,[1b] Astrogorgin[1c] and in preparing novel materials.[2] In our recent report of palladium catalyzed formate reduction to form heterocycles with an *exo*-olefin, compound **1** was the key component to assemble dienes for ring-closing metathesis (RCM) and the following allylic reduction.[3] Previously reported methods to prepare **1**, include bromination of 2-methylenepropane-1,3-diol,[4a] alkylation of acetic acid with 2-(chloromethyl)allyl chloride,[4b-c] and elimination of 3-bromo-2-bromomethylpropyl acetate with tetrabutylammonium fluoride.[4d] After several repetitions of these existing procedures, we felt that these methods either use expensive starting materials/reagents or lack efficiency. On the other hand, we noticed that 2-(bromomethyl)acrylic acid (**2**) prepared from diethyl bis(hydroxymethyl)malonate (**3**) and hydrobromic acid as reported by Singh and Whitesides is an efficient entrance to compound **1** (Scheme I).[5] This reaction evolved from preparation of labile 2-(iodomethyl)-acrylic acid (**4**), as reported by Welch,[6] and synthesis of β,β′-dibromoisobutyric acid (**5**) and 2-(bromomethyl)-acrylic acid (**2**) by Ferris.[7] Whitesides' group later utilized compound **2** to prepare 2-carboxy-1,3-propanedithiol.[5] In contrast to popular 2-(hydroxymethyl)acrylate as the entrance to the 1,3-bifunctional, allylic compound,[8] this synthetic route circumvents the problematic Baylis-Hillman reaction of formaldehyde and alkyl acrylate, which is time consuming, difficult in purification and varies with each batch.[9] Therefore, we adopted the strategy developed by Ferris et al. for our synthesis, modified it and report our results here. During our preparation, we also found that allylic halide exchange of **2** and its esters (*vide infra*) is prevalent under acidic conditions.



1a, R = Ac
1b, R = Bz

Scheme I Evolution of 2-(halomethyl)acrylic acid synthesis



RESULTS AND DISCUSSION

Diethyl bis(hydroxymethyl)malonate, prepared from condensation of diethyl malonate **5** and paraformaldehyde,[10] refluxed with concentrated hydrobromic acid (4 equiv.) for 14-16 h gives 2-(bromomethyl)acrylic acid. The progress of this reaction was directly monitored by ^{1}H NMR. Additional hydrobromic acid (1 equiv.) was added to drive the reaction to completion, if the starting malonate was detected. This pre-workup analysis avoided the multi-

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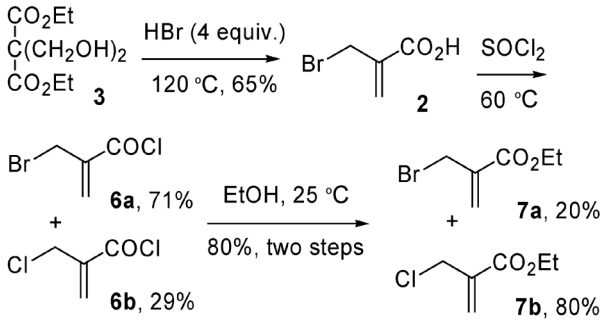
ple crystallization steps to harvest 2-(bromomethyl)acrylic acid as reported in the literature.[5] We then intended to convert the crude acrylic acid **2** to acryloyl chloride **6** with thionyl chloride, and then generated the desired ethyl 2-(bromomethyl)acrylates (**7a**) with ethanol in two steps. However, we observed that acrylate **7a** was contaminated with 2-(chloromethyl)acrylates **7b** in a ratio of 1:4. To gain further insight in to the process of bromide-chloride exchange, we analyzed the intermediate **6** by ^{1}H NMR and found that it contains a mixture of **6a** (71%) and **6b** (29%). This result is consistent with Cusk's report that the reaction of **2** with oxalyl chloride also produced the same mixture with a slightly different ratio (60:40; **6a**:**6b**).[11,12] However, the different ratios between acryloyl chlorides (**6a**:**6b** = 7:3) and acrylates (**7a**:**7b** = 1:4) indicated that the chloride replacement also occurred during esterification. This speculation was later confirmed by the fact that when the mixture of **7a** and **7b** was heated with additional hydrochloric or hydrobromic acids, one component became dominant (>90%, Table 1). Thus, the allylic halide of acrylate **7** is replaceable under the reaction conditions.[13]

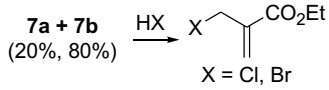
Scheme II Preparation of 2-(halomethyl)acrylate



Acrylate **7b** was reduced to 2-(chloromethyl)-2-propen-1-ol (**8**) by DIBAL-H at -78 °C. Due to the high volatility of alcohol **8**, the crude product might be esterified to form **1b** without further purification. Thus, acetylation and benzoylation of **8** with corresponding acyl chlorides provided the desired compounds **1a** and **1b** (Scheme III). The chlorine atom of **1b** was readily replaced with more reactive iodine for further substitution reactions.

In conclusion, we report here an improved, practical route to prepare the bifunctional, allylic compound 2-(chloromethyl)-2-propen-1-ol **8** and its esters **1a-b** and **9**. The merits of this synthesis include inexpensive starting materials and simple operations, which provide a reliable access

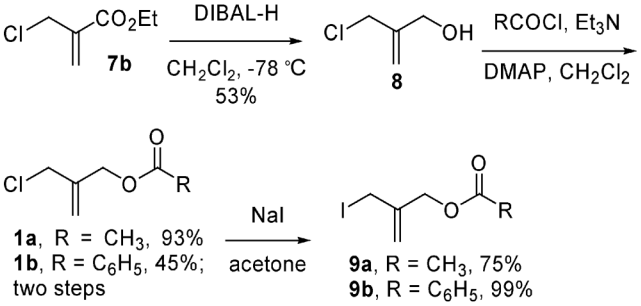
Table 1. Halide exchange of 2-(halomethyl)acrylate



Entry	Reaction Condition	Product Ratio (Cl:Br)[a]	Yield (%)[b]
1	HCl (4 equiv.), 80 °C, 3 h	93:7	81
2	HBr (4 equiv.), 80 °C, 3 h	21:79	62
3	HBr (5 equiv.), 80 °C, 3 h	8:92	47

[a] Ratio determined by ^{1}H NMR ($CDCl_3$).
[b] Isolated yields.

Scheme III



to these useful compounds. We also found that the halogens of **7** are exchangeable during esterification.

EXPERIMENTAL

2-(Bromomethyl)acrylic acid (2)

Diethyl bis(hydroxymethyl)malonate (50 g, 0.23 mol) and hydrobromic acid (48%, 104 mL, 0.91 mol) was heated to reflux in a 120 °C oil bath for 14 h. Some drops of this reaction mixture were taken out and analyzed by ^{1}H NMR ($CDCl_3$). If the starting malonate remained, additional hydrobromic acid (26 mL, 0.23 mol) was added and the reaction was heated for another 3-4 h. After all the starting material was consumed, the excess hydrobromic acid was removed under reduced pressure to give a light-orange solid. The crude product was redissolved in CH_2Cl_2 (50 mL), washed with water (10 mL × 2), dried over $Na_2SO_{4(s)}$, filtered, and concentrated to give compound **2** (24.5 g, 0.15 mol, 65%) as a light orange solid; mp 74.0-75.0 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.48 (s, 1H), 6.08 (s, 1H), 4.16 (d, J = 0.7 Hz, 2H).[5]

Ethyl 2-(chloromethyl)acrylates (7b)

Caution: ethyl 2-(chloromethyl)acrylate and 2-(bromomethyl)acrylate are vesicants!

Thionyl chloride (4.5 mL, 0.06 mol) was added to

acrylic acid **2** (4 g, 24.4 mmol) in a round bottom flask. The reaction mixture was heated to 60 °C and stirred for 1.5 h. The golden solution was concentrated to give a mixture of acryloyl chlorides **6a** and **6b**. ^{1}H NMR ($CDCl_3$, 200 MHz) of **6a**: δ 6.71 (s, 1H), 6.40 (s, 1H), 4.15 (d, J = 0.64 Hz, 2H); ^{1}H NMR ($CDCl_3$, 200 MHz) of **6b**: δ 6.76 (s, 1H), 6.43 (s, 1H), 4.27 (d, J = 0.94 Hz, 2H). The mixture of **6a** and **6b** was cooled in an ice-water bath, and ethanol (5.7 mL, 0.1 mol) was added. The reaction mixture was stirred at room temperature for another 2 h. Excess ethanol and hydrogen chloride was removed under reduced pressure. The reaction mixture was neutralized by sat. $NaHCO_{3(aq)}$, extracted with ether (3 mL × 5), and the combined organic solution was dried over $Na_2SO_{4(s)}$, filtered, and concentrated to give a mixture of **7b** and **7a** (4:1, 3.14 g, 19.5 mmol, 80%) as a light yellow oil. The crude product may be further purified by column chromatography (SiO_2, ethyl acetate/hexanes 1:9, R_f 0.53). ^{1}H NMR ($CDCl_3$, 200 MHz) of **7a**: δ 6.30 (s, 1H), 5.92 (s, 1H), 4.25 (q, J = 7.1 Hz, 2H), 4.16 (s, 1H), 4.16 (s, 1H), 1.31 (t, J = 7.1 Hz, 3H);[8c] ^{1}H NMR ($CDCl_3$, 200 MHz) of **7b**: δ 6.36 (s, 1H), 5.92 (s, 1H), 4.22 (s, 1H), 4.22 (s, 1H), 4.20 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H).[8c]

2-(Chloromethyl)-2-propen-1-ol (8)

Diisobutylaluminum hydride (DIBAL-H, 1.0 M in cyclohexane, 120 mL, 0.12 mol) was added to the solution of acrylate **7b** (7.2 g, 60 mmol) and CH_2Cl_2 (57 mL) at -78 °C. The reaction mixture was stirred at -78 °C for another 2 h, warmed to 0 °C, and sat. sodium tartrate$_{(aq)}$ was added until the solution turned to a gel (~ 20 mL). To the gel-like solution was added ether (40 mL), which was than homogenized by stirring, filtered, and concentrated to give alcohol **8** (3.4 g, 32 mmol, 53%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (s, 2H), 4.20 (s, 2H), 4.10 (s, 2H).[14]

2-(Chloromethyl)allyl acetate (1a)

Triethylamine (14 mL, 100 mmol), 4-dimethylaminopyridine (195 mg, 1.6 mmol) and alcohol 8 (3.4 g, 32 mmol) in CH_2Cl_2 (50 mL) was cooled in an ice-water bath for 10 min. Acetyl chloride (3.5 mL, 49.3 mmol) was added to the solution dropwise at 0 °C and stirred at room temperature for 14 h. The reaction mixture was washed with $HCl_{(aq)}$ (1N, 20 mL × 2), sat. $NaHCO_{3(aq)}$ (20 mL × 2) and sat. $NaCl_{(aq)}$ (20 mL). The organic layer was dried over $Na_2SO_{4(s)}$, filtered and concentrated to give acetate **1a** (4.4 g, 29.6 mmol, 93%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40 (s, 1H), 5.31 (s, 1H), 4.65 (s, 2H), 4.07 (s, 2H), 2.09 (s, 3H).[14]

2-(Chloromethyl)allyl benzoate (1b)

Diisobutylaluminum hydride (DIBAL-H, 1.0 M in cyclohexane, 57 mL, 57 mmol) was added to the solution of acrylate **7b** (4.0 g, 27 mmol) and CH_2Cl_2 (57 mL) at -78 °C. The reaction mixture was stirred at -78 °C for another 2 h, warmed to 0 °C, and sat. sodium tartrate$_{(aq)}$ was added until the solution turned to a gel. To the gel-like solution was added with ether (30 mL), which was then homogenized by stirring, and filtered. Triethylamine (3.8 mL, 27 mmol) and 4-dimethylaminopyridine (165 mg, 1.35 mmol) were added to the filtrate, and the reaction mixture was cooled in an ice-water bath. Benzoyl chloride (3.7 mL, 32 mmol) was added to the reaction and stirred for 16 h at 25 °C. The reaction mixture was washed with sat. $K_2CO_{3(aq)}$ (20 mL), $HCl_{(aq)}$ (1 N, 20 mL), dried over $Na_2SO_{4(s)}$, filtered and concentrated. The crude product was purified with column chromatography (SiO_2, ethyl acetate/hexanes 1:9, R_f 0.41) to give pure compound **1b** (2.54 g, 12 mmol, 45%, two steps) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.06-7.37 (m, 5H), 5.37 (d, J = 0.7 Hz, 1H), 5.35 (d, J = 0.7 Hz, 1H), 4.92 (s, 2H), 4.16 (s, 1H), 4.15 (s, 1H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.8, 139.8, 133.0, 129.7, 129.5, 128.3, 117.9, 64.4, 44.9; HRMS (FAB) calcd for $[M+H]^+$ ($C_{11}H_{12}O_2Cl$) 211.0526, found 211.0521.

2-Iodomethyl-allyl acetate (9a)

Compound **1a** (160 mg, 1.07 mmol) and sodium iodide (450 mg, 3.21 mmol) in acetone (1 mL) was stirred at 25 °C for 16 h. Acetone was removed under reduced pressure and the residue was diluted with CH_2Cl_2 (5 mL) and water (5 mL). The organic layer was separated and the aqueous solution was further extracted with CH_2Cl_2 (5 mL). The combined organic layer was dried over $MgSO_{4(s)}$, filtered and concentrated to give compound (**9a**) as a light yellow oil (191 mg, 0.79 mmol, 75%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.39 (s, 1H), 5.18 (s, 1H), 4.69 (s, 2H), 3.91 (s, 2H), 2.07 (s, 3H), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4, 141.2,116.7, 64.8, 20.8, 4.9; HRMS (FAB) calcd for $[M+H]^+$ ($C_6H_{10}O_2I$) 240.9726, found 240.9720.

2-Iodomethyl-allyl benzoate (9b)

Compound **1b** (2.54 g, 0.012 mol) and sodium iodide (5.4 g, 0.036 mol) in acetone (10 mL) was refluxed for 16 h. Acetone was removed under reduced pressure and the residue was diluted with CH_2Cl_2 (20 mL) and water (20 mL). The organic layer was separated and the aqueous solution was further extracted with CH_2Cl_2 (20 mL). The combined organic layer was dried over $MgSO_{4(s)}$, filtered and concen-

trated to give compound **9** as a light yellow oil (3.6 g, 0.012 mol, 99%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.06-7.38 (m, 5H), 5.45 (d, J = 0.7 Hz, 1H), 5.29 (d, J = 0.7 Hz, 1H), 4.97 (s, 2H), 3.99 (s, 1H), 3.995 (s, 1H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.8, 141.1, 133.1, 129.6, 129.5, 128.3, 116.7, 65.1, 4.9; HRMS (FAB) calcd for $[M+H]^+$ ($C_{11}H_{12}O_2I$) 302.9882, found 302.9886.

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