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Development of a Practical and Efficient Synthesis of Chloromethyl 2-Ethoxy-2-methylpropanoate

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Abstract:

An efficient synthesis of chloromethyl 2-ethoxy-2-methylpropanoate from 2-bromoisobutyric acid is reported. Four developments were key to this route: (i) a mild, base-mediated ethanolysis of a tertiary alkyl bromide, (ii) a sodium bisulfite purge of 2-methylacrylic acid, (iii) preparation of a thiomethyl ester via a formal Pummerer process with DMSO, and (iv) improved conversion of a thiomethyl ester to a chloromethyl ester through suppression of a competing chlorination pathway.

1. Introduction

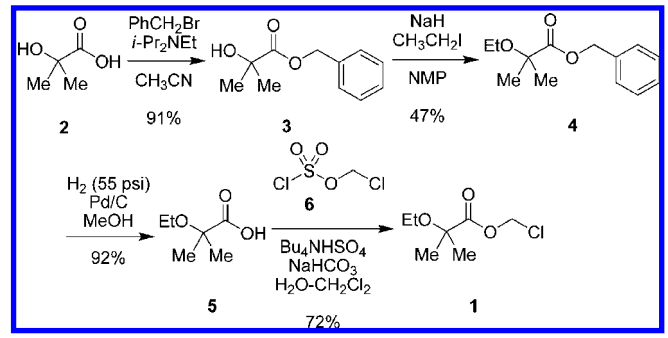
We recently required multikilogram quantities of chloromethyl 2-ethoxy-2-methylpropanoate (**1**) for use in the preparation of a drug candidate. Several challenges were associated with this target, including the reactivity/instability of chloromethyl esters and the fact that this material is a volatile oil.

The original preparation of **1** (Scheme 1) was conceptually and operationally straightforward but suffered from a relatively lengthy linear sequence of reactions.[1] Three of these reactions were required for the conversion of 2-hydroxyisobutyric acid (**2**) to 2-ethoxyisobutyric acid (**5**). Additionally, this route made use of the expensive and toxic reagent chloromethyl chlorosulfate (**6**), which is difficult and hazardous to handle.[2] The route shown in Scheme 1 provided access to 100 g quantities of **1**, but with modest purity (~65%), confirming that further scale-up would require a more efficient synthesis.

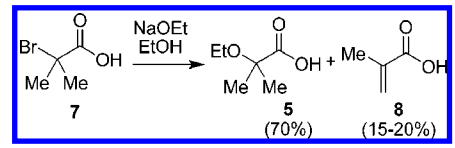
2. Discussion

2.1. A More Efficient Synthesis of 2-Ethoxyisobutyric Acid (5). We initially focused our efforts on identifying a more efficient synthesis of 2-ethoxyisobutyric acid (**5**). A review of the literature showed numerous citations for acid **5**.[1,3−7] We did pursue an intriguing report of the one-step conversion of acetone

Scheme 1. **Original synthesis of chloromethyl 2-ethoxy-2-methylpropanoate (1)**



Scheme 2. **Ethanolysis of 2-bromoisobutyric acid (7)**



chloroform (1,1,1-trichloro-2-methylpropan-2-ol) to **5** using potassium hydroxide in ethanol.[4] This reaction displayed an uncontrolled exotherm on small scale, consistent with the original report.[8] It appeared to us that developing a safe, dose-controlled, and scaleable version of this transformation would be challenging.

A key finding was identified in House's report of the preparation of 2-methoxyisobutyric acid from 2-bromoisobutyric acid and sodium methoxide.[9] This reaction is not the primary focus of the original paper and receives no discussion beyond the detailed experimental describing its execution. Mechanistically, the reaction is intriguing and is discussed further in section 2.2. We found that the conditions reported by House worked equally well with sodium ethoxide in ethanol to provide our target product (**5**). After 48 h at room temperature, ethoxy acid **5** was observed as the major product (70%) along with 15−20% of the acrylate elimination product **8** (Scheme 2). Shorter reaction times could be realized by heating the reaction, but increased elimination product was observed.[10]

Fractional distillation did partially remove the acrylate impurity, with the purest fractions containing 2−3% of **8**. A simpler and more efficient method for purification was realized

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(1) Brighty, K. E.; Marfat, A.; McLeod, D. G.; O'Donnell, J. P. (Pfizer Products Inc., U.S.A.). Application: WO 2008, 29 pp, 2008. CAN 148:100428.
(2) Efforts to source this material from commercial vendors indicated that it would not be possible to ship multikilogram quantities of this reagent (**6**) via any practical means.
(3) Blaise, E. E.; Picard, L. *Bull. Soc. Chim. Fr.* **1912**, *11*, 587–90.
(4) Weizmann, C.; Sulzbacher, M.; Bergmann, E. *J. Am. Chem. Soc.* **1948**, *70*, 1153–8.
(5) Wada, T.; Oda, J.; Inouye, Y. *Agric. Biol. Chem.* **1972**, *36*, 799–807.
(6) Mori, Y.; Fujiwara, S.; Miyachi, T.; Kitanishi, H.; Oya, M.; Yamamoto, K.; Suzuki, M. *Chem. Pharm. Bull.* **1983**, *31*, 1505–17.
(7) Ishihara, S.; Kogen, H.; Koga, T.; Kitazawa, E.; Serizawa, N.; (Sankyo Co., Ltd., Japan). Application: EP, 1994, p 173; CAN 122:213765.
(8) "The violent reaction... was checked by energetic cooling." (quote from Experimental Section of ref 4).
(9) House, H. O.; Prabhu, A. V.; Wilkins, J. M.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 3067–76.
(10) The level of acrylate formation was based on integration of the well-resolved vinyl proton signals in the ^{1}H NMR. No correction for relaxation times was applied, so this is an approximation.

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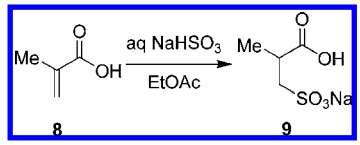
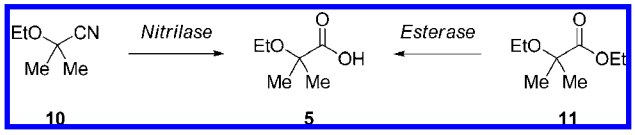
Scheme 3. **Removal of acrylate 8 via bisulfite adduct formation**



Scheme 4. **Biocatalytic approaches to acid 5**



by treatment with aqueous sodium bisulfite, which resulted in formation of the bisulfite conjugate addition derivative **9** (Scheme 3).[11] The substantial water solubility of this derivative allowed for easy removal by aqueous extraction. Control of pH was found to be important for minimizing loss of acid **5** during the aqueous wash. After the 16 h bisulfite treatment, the aqueous phase was adjusted from pH ~4 to ~1 using 1 N HCl, which minimized the loss of acid **5** to the aqueous phase (the increased polarity of **9** as the free carboxylic acid relative to acid **5** allowed for effective removal of **9** in the aqueous phase at pH 1).[12] Distillation of the crude product provided acid **5** in >97% chemical purity by GC and elemental analysis.

A significant improvement was realized when sodium ethoxide was replaced with Hünig's base (*i*-Pr_2NEt). With 2.1 equiv of this base in refluxing ethanol, starting material was consumed in 2 h, and at 40 °C the reaction was complete in 12 h. These reaction times are comparable to those realized with the significantly stronger base, sodium ethoxide. Importantly, under these conditions the formation of the acrylate impurity was significantly reduced (<5%).

Biocatalytic approaches to **5** were also studied (Scheme 4). Two substrates were evaluated: 2-ethoxy isobutyronitrile (**10**) and ethyl 2-ethoxy-2-methylpropanoate (**11**). The former was obtained by treatment of acetone cyanohydrin with $ZnCl_2$ in EtOH (the analogous reaction in methanol has been reported),[13] and the latter was prepared by diethylation of 2-hydroxy isobutyric acid. Several nitrilases were examined for the hydrolysis of nitrile **10**, and >95% conversion was observed with nitrilase NIT 106 (Codexis). For the hydrolysis of ethyl ester **11**, five esterases were identified from screening (95 different hydrolases including lipases, proteases and esterases from various sources) that provided >95% conversion, including *Candida antarctica* lipase B, pig liver esterase, and esterase N (Dow Pharma). It should be noted that chemical saponification of this ester is extremely slow, due to steric hindrance, and suffers from competitive elimination to the acrylate.

On the basis of these results we feel that an enzymatic approach to acid **5** is viable. However, due to project timeline constraints and the concurrent identification of the chemistry described in Schemes 2−3, the biocatalytic approaches were not pursued further.

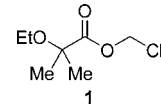


Figure 1. **Structure of chloromethyl 2-ethoxy-2-methylpropanoate (1).**

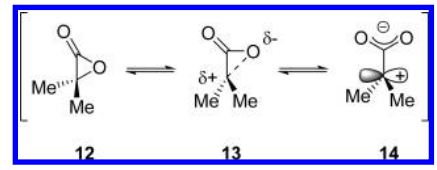


Figure 2. **Possible reactive intermediates in the ethanolysis of 7.**

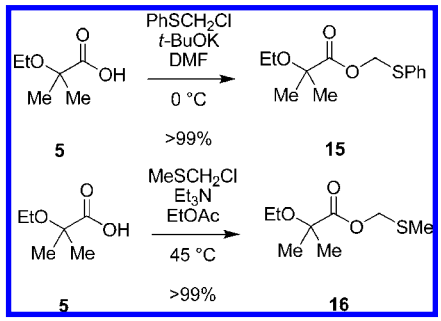
2.2. Mechanistic Considerations. The comparable rates observed with NaOEt and *i*-Pr_2NEt in the conversion of **7** to **5** are consistent with an S_N1 mechanism wherein the bromide departs in a rate-limiting step to generate a carbocation (and suggest that ethoxide is not involved in the rate-determining step). The adjacent carboxylate can stabilize the carbocation via anchimeric assistance,[14−17] with the extreme form of this assistance resulting in the formation of an α-lactone (Figure 2).[18] A report by Edwards supports this mechanism.[19] Edwards' work determined retention of configuration for chiral α-bromo acids upon displacement with lithium azide (LiN_3), a result consistent with the intermediacy of α-lactone **12** or tight ion pair **13**, but not zwitterion **14**. In contrast, clean inversion of configuration was observed for α-bromo ketones, esters, and lactones. Taken together, this data suggests that a free carboxylate provides anchimeric assistance in these systems.

The decreased formation of the acrylate side product **8** with Hünig's base suggests that the elimination pathway is dependent upon the strength of the base, which is consistent with an E2 mechanism. Fortunately for our application, the fact that base was involved in the rate-determining step for formation of the impurity, but not for formation of product, allowed us to modify the base and achieve desirable results.

2.3. Conversion of Acid 5 to Chloromethyl Ester 1. The cost, toxicity, and limited availability of chloromethyl chlorosulfate (**6**) led us to consider alternative approaches to **1**. There are numerous literature examples of converting carboxylic acids directly into chloromethyl esters. These include direct reaction with bis-alkylating reagents (e.g., XCH_2X') such as chloromethyl chlorosulfate,[20,21] bromochloromethane,[22] and chloroiodoethane.[23−25] Handling and toxicity issues are relevant for all of these reagents; additionally, the use of bromochloromethane is limited due to its ozone-depleting properties.[26] Competitive

(11) Hejchman, E.; Haugwitz, R. D.; Cushman, M. *J. Med. Chem.* **1995**, *38*, 3407–10.
(12) With this pH adjustment, predistillation recoveries of 80−85% were realized; absent the adjustment, the yield was reduced to 65−70%.
(13) Ramalingam, K. *Org. Prep. Proced. Int.* **1989**, *21*, 511–14.
(14) Cowdrey, W. A.; Hughes, E. D.; Ingold, C. K. *J. Chem. Soc.* **1937**, 1208–36.
(15) Winstein, S.; Lucas, H. J. *J. Am. Chem. Soc.* **1939**, *61*, 1576–81.
(16) Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* **1948**, *70*, 841–6.
(17) Bordwell, F. G.; Knipe, A. C. *J. Org. Chem.* **1970**, *35*, 2956–9.
(18) Chapman, O. L.; Wojtkowski, P. W.; Adam, W.; Rodriguez, O.; Rucktaeschel, R. *J. Am. Chem. Soc.* **1972**, *94*, 1365–7.
(19) Edwards, O. E.; Grieco, C. *Can. J. Chem.* **1974**, *52*, 3561–2.
(20) Baltzer, B.; Binderup, E.; Von Daehne, W.; Godtfredsen, W. O.; Hansen, K.; Nielsen, B.; Soerensen, H.; Vangedal, S. *J. Antibiot.* **1980**, *33*, 1183–92.
(21) Pop, E.; Wu, W. M.; Bodor, N. *J. Med. Chem.* **1989**, *32*, 1789–95.
(22) Gomes, P.; Santos, M. I.; Trigo, M. J.; Castanheiro, R.; Moreira, R. *Synth. Commun.* **2003**, *33*, 1683–1693.
(23) Chen, A.-j.; Han, Z.-s.; Huang, X.-y. *Zhongguo Yaowu Huaxue Zazhi* **2003**, *13*, 299–300.

Scheme 5. **Preparation of thiomethyl esters via alkylation**

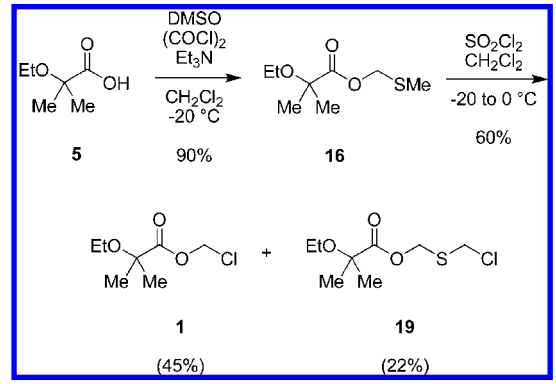


formation of the bis-condensation product (e.g., $(RCO_2)_2CH_2$) is also problematic with many of these methods. A method involving condensation of a carboxylic acid with formaldehyde in the presence of $ZnCl_2$ has also been reported.[27,28] While we successfully utilized this method for the synthesis of simpler chloromethyl esters, it was ineffective for the preparation of **1**.

We next turned to an indirect approach from an aryl- or alkylthiomethyl ester (Scheme 5). There is good precedent for the conversion of thioaryl esters (**15**)[29] and thiomethyl esters (**16**)[30] into the corresponding chloromethyl esters by treatment with electrophilic chlorinating reagents such as chlorine gas or sulfuryl chloride (SO_2Cl_2). The chlorination of methylthiomethyl esters (e.g., **16**) is typically less efficient due to competitive chlorination of the methyl group (e.g., **19** in Scheme 6).[30] Our initial approach was based on alkylation with chloromethyl phenyl sulfide or chloromethyl methyl sulfide to generate **15** and **16**, respectively. While these alkylations were efficient, the chloromethylsulfide reagents were expensive, corrosive, and foul-smelling.

An approach based on Swern oxidation conditions (DMSO, oxalyl chloride, triethylamine), as reported by Jadhav and Ghosh,[31] was then considered, as it offered cost and safety advantages over the alkylation strategy (Scheme 6). This formal Pummerer rearrangement is occasionally evidenced in standard Swern oxidations by the formation of methyl thiomethyl ether byproducts. While this approach provided practical access to **16** (from DMSO), **15** was not as readily accessible.[32] Extensive experimentation indicated that the reaction to form **16** proceeds within a wide temperature range (−78−0 °C) with an optimal temperature of −20 °C. The reaction was found to work in either dichloromethane or ethyl acetate. The former provided a

Scheme 6. **Pummerer reaction to form 16 and conversion to 1 with sulfuryl chloride**



cleaner reaction, but ethyl acetate allowed for better removal of the triethylamine hydrochloride during aqueous workup.

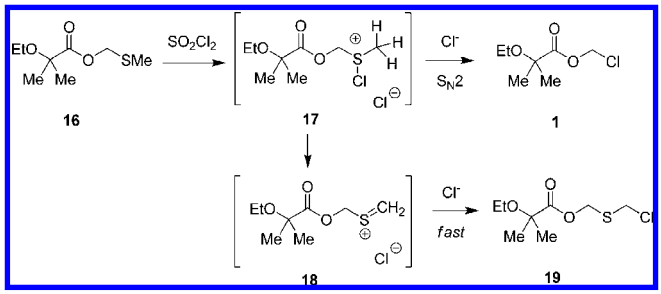
While the Pummerer strategy provided an effective alternative to the alkylation strategy for the synthesis of **16**, the subsequent chlorination was problematic, as predicted by literature precedent.[30] The conversion of **16** to **1** was effected by sulfuryl chloride in dichloromethane at −20 °C. Ascorbic acid was added during the aqueous workup in order to scavenge the methylsulfenyl chloride (ClSMe) generated during the reaction. This resulted in the isolation of a 67% yield of a 2:1 mixture of the desired chloromethyl ester **1** and chlorinated side product **19**. The latter impurity was efficiently removed by distillation, but this side reaction reduced the yield of the desired product.

We suspected that impurity **19** was being generated *via* a chloro-Pummerer rearrangement (Scheme 7).[33] We hypothesized that the chloro-Pummerer reaction might proceed *via* a rate-determining elimination of HCl, followed by rapid addition of chloride to quench the reactive sulfocarbenium ion **18**. In contrast, we expected the desired reaction to proceed *via* an S_N2 displacement of methylsulfenyl chloride (ClSMe) with chloride ion. If this mechanistic hypothesis was correct, then chloride ion would be involved in the rate-determining step for the desired pathway, but not for the undesired pathway. For this reason, we added an external chloride source (2.0 equiv of tetrabutylammonium chloride) to the reaction and found that this completely suppressed the formation of **19**. The use of triethylamine hydrochloride provided the same benefit at a lower cost. Having shown that triethylamine hydrochloride was beneficial for the chlorination reaction, the removal of this byproduct during the workup of **16** was no longer necessary or desirable. Because dichloromethane provided a cleaner formation of **16**, whereas the main benefit of ethyl acetate had been that it allowed for the removal of triethylamine hydrochloride, this observation allowed us to use a single solvent (dichloromethane) for both steps (**5** to **16** and **16** to **1**).

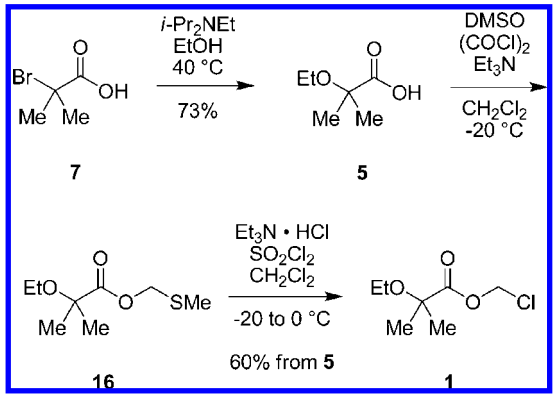
The optimized synthesis of **1** from 2-bromoisobutyric acid (**7**) is shown in Scheme 8. The Experimental Section describes a laboratory-scale preparation starting with 75 g of 2-bromoisobutyric acid. The overall yield for this three-step sequence was 44%. Scale-up to multikilogram scale was successfully realized at an outside vendor with comparable yields and purity. Purity was controlled by distillation of acid **5** and final product

(24) Andrianjara, C.; Chantel-Barvian, N.; Gaudilliere, B.; Jacobelli, H.; Ortwine, D. F.; Patt, W. C.; Pham, L.; Kostlan, C. R.; Wilson, M. W. (Warner-Lambert Company, U.S.A.). Application: WO 2002, 264 pp. CAN 137:185501.
(25) Chen, A. Q.; Willis, C. L. *Chin. Chem. Lett.* **2001**, *12*, 397–398.
(26) http://www.epa.gov/EPA-AIR/2003/July/Day-18/a18154.htm.
(27) Baudy, R. B.; Butera, J. A.; Abou-Gharbia, M. A.; Chen, H.; Harrison, B.; Jain, U.; Magolda, R.; Sze, J. Y.; Brandt, M. R.; Cummons, T. A.; Kowal, D.; Pangalos, M. N.; Zupan, B.; Hoffmann, M.; May, M.; Mugford, C.; Kennedy, J.; Childers, W. E., Jr. *J. Med. Chem.* **2009**, *52*, 771–778.
(28) Brunin, T.; Legentil, L.; Henichart, J.-P.; Rigo, B. *Tetrahedron* **2006**, *62*, 3959–3968.
(29) Hageman, D. L.; Crawford, T. C. (Pfizer Inc., U.S.A.). Application: EP, 1982, 27 pp, CAN 97:182105.
(30) Benneche, T.; Strande, P.; Wiggen, U. *Acta Chem. Scand.* **1989**, *43*, 74–7.
(31) Jadhav, S. B.; Ghosh, U. *Tetrahedron Lett.* **2007**, *48*, 2485–2487.
(32) While DMSO was chosen to provide the methylthiomethyl ester **15**, use of methyl phenyl sulfoxide would provide access to phenylthiomethyl ester **14**. However, the cost of this sulfoxide discouraged us from pursuing this strategy.
(33) Bordwell, F. G.; Pitt, B. M. *J. Am. Chem. Soc.* **1955**, *77*, 572–7.

Scheme 7. **Competing S_N2 and sulfocarbenium pathways for formation of 1 and 19**



Scheme 8. **Optimized synthesis of chloromethyl 2-ethoxy-2-methylpropanoate (1)**



1. The final potency was 95% based on GC analysis, which compares favorably with typical potencies realized using the route shown in Scheme 1 (~65%). As noted in the introduction, chloro methyl esters are reactive alkylating agents, and thus we have avoided prolonged storage of the title compound, whose purity is further limited by its lack of crystallinity. However, we have observed that higher-purity samples (e.g. >90%, per Scheme 8) are more stable than their less pure counterparts (e.g. ~65%, per Scheme 1). In general we recommend that these reagents be prepared near the time that they are needed for their use in downstream operations.

In conclusion, we have developed a three step synthesis of chloromethyl ester **1** from 2-bromoisobutyric acid. Key developments include (i) a mild, base-mediated ethanolysis of a tertiary alkyl bromide (**7** to **5**), (ii) a sodium bisulfite purge of the byproduct acrylic acid (**8**), (iii) preparation of thiomethyl ester **16** via a formal Pummerer process with DMSO, and (iv) conversion of thiomethyl ester **16** to chloromethyl ester **1** and suppression of a competing chlorination pathway by addition of an external chloride source.

3. Experimental Section

Reactions were monitored primarily by ^{1}H NMR. HPLC was not utilized due to the absence of UV-active chromophores. GC/MS analysis was also used to monitor the ethanolysis reaction to generate acid **5** (Hewlett-Packard 5890, HP-1 column, 12 m × 0.2 mm × 0.33 μm, 1.5 mL/min, injector temp 280 °C, oven temp 60−300 at 20 °C/min; bromoisobutyric acid R_T = 5.47 min, ethoxyisobutyric acid R_T = 5.07 min).

3.1. Preparation of 2-Ethoxyisobutyric Acid (5). A solution of 2-bromoisobutyric acid (75.0 g, 0.449 mol, 1.00 equiv) and anhydrous ethanol (600 mL) was cooled to −5−0 °C and diisopropylethylamine (164 mL, 0.943 mol, 2.10 equiv) was added at 0 ± 2 °C over 30 min. Upon complete addition the clear reaction mixture was allowed to warm to room temperature over 15 min. The reaction was then warmed to 40 °C for 12 h. After cooling to room temperature, the reaction mixture was concentrated on a rotary evaporator to remove the majority of ethanol (20−35 mbar, 30−35 °C), leaving ~200 mL of a thick, white slurry. Methyl *tert*-butyl ether (MTBE, 300 mL) and water (100 mL) were added, the mixture was cooled to 0 °C, and then acidified with 10% aqueous HCl (130−140 mL, final pH 1.0 ± 0.5). The contents of the flask were diluted with MTBE (450 mL) and brine (100 mL), the aqueous phase was removed, and the organic phase was washed with a second portion of brine (250 mL). The organic phase was stirred vigorously with 10% aqueous $NaHSO_3$ (75 mL) for 6 h. The biphasic mixture was acidified with 10% aqueous HCl (ca. 30 mL) to a final pH of 1.0 ± 0.5. The solution was extracted with brine (2 × 100 mL), dried over sodium sulfate, filtered, and concentrated to provide 52 g of product as a clear, colorless oil (15 mbar, 30 °C). A majority portion of this material (50.3 g) was purified by vacuum distillation (17 mbar). A small fore-run (1.7 g) was collected, with the major fraction collected at 103−106 °C, providing 43.3 g of **5** as a colorless oil (73% yield).

Data: IR (thin film): 3250−2950 (br), 2982, 2938, 1711, 1471, 1395, 1164, 1107, 1066, 974, 773 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.49 (q, 2H, J = 7.0 Hz), 1.44 (s, 6H), 1.21 (t, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ 179.6, 77.2, 60.0, 24.1, 15.7; HRMS Calcd for $C_6H_{11}O_3$ (M − H): 131.07137. Found: 131.07138; Anal. Calcd for $C_{10}H_9Cl_3N_4$: C, 54.53; H, 9.15. Found: C, 54.20; H, 8.82.

3.2. Preparation of Thiomethyl 2-ethoxy-2-methylpropanoate (16). A solution of DMSO (30.1 mL, 0.424 mol, 2.24 equiv) and dichloromethane (100 mL) was cooled to an internal temperature of −20 °C, and oxalyl chloride (26.0 mL, 0.300 mol, 1.58 equiv) was added over 20 min, during which the internal temperature remained <0 °C. The reaction mixture was then stirred for an additional hour at −10 ± 5 °C. 2-Ethoxyisobutyric acid (**5**) (25.0 g, 0.189 mol, 1.00 equiv) was added over 10 min, rinsing with dichloromethane (25 mL). The reaction mixture was cooled to −20 °C, and triethylamine (103 mL, 0.739 mol, 3.91 equiv) was added at −15 ± 5 °C. The reaction was then stirred for an additional hour at 0 ± 5 °C. The reaction was quenched with water (175 mL), the phases were separated, and the organic phase was concentrated (15 mbar, 40 °C) to provide the crude product as a clear, yellow oil (37.0 g). Purity was estimated at 85% by ^{1}H NMR, with the primary impurity being triethylamine hydrochloride. This material was used directly in the next reaction. On larger scale, the final concentration from dichloromethane was omitted, and the solution was carried directly into the next reaction.

Data: IR (thin film): 2159, 1738 (C═O), 1469, 1439, 1381, 1262, 1188, 1125, 1103, 1071, 977, 942, 918, 895 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.23 (s, 1H), 3.42 (q, 2H, J = 7 Hz), 2.29 (s, 3H), 1.44 (s, 6H), 1.18 (t, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$): δ 174.3, 77.0, 68.5, 60.1, 24.4, 15.6, 15.2; MS (EI): (M + Na)$^+$ 215; GC purity (FID): 89%.

3.3. Preparation of Chloromethyl 2-ethoxy-2-methylpropanoate (1). The methylthiomethyl ester (**16**) prepared in the preceding procedure (37.0 g, 0.16 mol based on ^{1}H NMR assessment of 85% potency) was dissolved in dichloromethane (148 mL). Triethylamine hydrochloride (27.5 g, 0.200 mol, 1.25 equiv) was added, and the mixture was cooled to −30 °C. Sulfuryl chloride (16.2 mL, 0.200 mol, 1.25 equiv) was added over 10 min at −20 to −30 °C. The solution was stirred at −20 °C for 1 h, then warmed to 0 °C and stirred for 2 h. The cooling bath was removed, and L-ascorbic acid (33.8 g, 0.192 mol, 1.2 equiv) was added, followed by water (185 mL). The two-phase system was stirred for 30 min and the phases were separated. The organic phase was washed with 10% aq $NaHCO_3$ (400 mL) and water (185 mL), then concentrated on a rotary evaporator (15 mbar, 20 °C) to provide 30 g of a clear, yellow oil. This material was purified by fractional distillation (15 mbar), collecting the main fraction at bp 66−68 °C (20.5 g, 0.114 mol, 60% overall yield from acid **5**). The product was a clear, colorless oil.

Data: IR (thin film): 2160, 1759, 1395, 1383, 1363, 1260, 1190, 1154, 1106, 1092, 1070, 1018, 974 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.77 (s, 2H), 3.42 (q, 2H, J = 7 Hz), 1.44 (s, 6H), 1.22 (t, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$): δ 178.5, 77.4, 68.9, 60.5. 24.4, 15.7; GC purity (FID): 95%; (Combustion analysis failed to meet purity specifications, consistent with the GC purity assessment of just 95%): Anal. Calcd for $C_7H_{13}ClO$ C: 46.55, H: 7.25, Cl: 19.63 Found: C, 45.83, H: 6.34, Cl: 18.53.

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