ORIGINAL ARTICLE

A C G publications

*Org. Commun.*1:3 (2008) 48-53

organic communications

Improved preparation of halopropyl bridged carboxylic ortho esters*

Richard J. Petroski

USDA, Agricultural Research Service, National Center for Agricultural Utilization Research, Crop Bioprotection Research Unit, 1815 N. University Street, Peoria, Illinois 61604

(Received September 14, 2008; Revised October 6, 2008; Accepted October 15,2008)

Abstract: Bridged ortho esters of 3-halopropyl carboxylic acids were prepared by esterification of 3-methyl-3-hydroxymethyloxetane with 3-bromopropionyl chloride and pyridine in dry THF, followed by rearrangement with boron trifluoroetherate, to afford 1-(2-bromoethyl)-4-methyl-2,6,7-trioxabicyclo[2,2,2]-octane. The 1-(2-iodoethyl)-4-methyl-2,6,7-trioxabicyclo[2,2,2]-octane analogue could not be prepared directly by halogen exchange of 1-(2-bromoethyl)-4-methyl-2,6,7-trioxabicyclo[2,2,2]-octane but could be prepared by halogen exchange of the (3-methyloxetan-3-yl)methyl 3-bromopropanoate with a mixture of sodium iodide and anhydrous sodium sulfate in acetone, followed by rearrangement with boron trifluoroetherate.

Keywords: bridged carboxylic ortho esters, 1-(2-bromoethyl)-4-methyl-2,6,7-trioxabicyclo[2,2,2]-octane, 1-(2-iodoethyl)-4-methyl-2,6,7-trioxabicyclo[2,2,2]-octane, protected 3-halopropionic acid

1. Introduction

3-Bromopropyl bridged ortho-esters of carboxylic acids or 3-iodopropyl bridged ortho-esters of carboxylic acids[1,2] can behave like alkyl halides because the protons, alpha to the halide function, are less acidic when not also alpha to a carbonyl group. These derivatives of 3-halocarboxylic acids are much more stable than 3-halocarboxylic acids, under strongly basic conditions, because unwanted elimination of HBr or HI is less likely. The advantages of these three-carbon molecular building blocks were utilized in synthetic organic chemistry, to prepare phosphonium salts for use in Wittig reactions[3-5], to prepare lithiated carboxylic acid alkyl-anion equivalents for the synthesis of lactones[6] and for direct use of the "alkyl halide" in a Williamson ether synthesis[7]. Deprotection, of the carboxylic acid function, is easily accomplished under mildly acidic conditions[1,2].

3-Halopropyl bridged carboxylic ortho esters are representative derivatives of haloalkyl carboxylic acids; however, these compounds were chosen for preparation because three-carbon

* The mention of trade names or commercial products in this article is solely for the purpose of providing specific information and does not imply recommendation or endorsement by the U.S. Department of Agriculture.
E mail: Richard.Petroski@ars.usda.gov

The article was published by Academy of Chemistry of Globe Publications
www.acgpubs.org/OC/index.htm © Published 10/24/2008 EISSN:1307-6175

molecular building blocks are especially useful.[1] Also, halogen at the 3-position makes these compounds especially difficult and demanding synthetic targets.

3-Halopropyl bridged carboxylic ortho esters can be prepared in two steps from 3-bromopropionic acids[2,3], but attempted direct preparation of the 3-iodopropyl bridged carboxylic ortho ester from halogen exchange[3,4] of the bromo compound, as suggested by the literature, was unsuccessful. In this paper, an improved preparation of both bromopropyl- and iodopropyl- bridged carboxylic ortho esters is presented (Figure 1), which introduces a new synthetic pathway to the 3-iodopropyl bridged carboxylic ortho ester. Helpful suggestions are also given related to product storage and use.

2. Results and Discussion

The route to 3-halopropyl bridged carboxylic ortho esters involves esterification of 3-methyl-3-hydroxymethyloxetane with 3-bromopropionyl chloride and pyridine in dry tetrahydrofuran, followed by rearrangement with boron trifluoroetherate.[2,3] The initial esterification reaction proceeded in 85% yield, consistent with previous results.

Halogen exchange of compound **1**, afforded compound **2** in excellent yield (94% conversion of starting material to product). The halogen exchange reaction[8] works well at ambient temperature with NaI in acetone in the presence of anhydrous Na_2SO_4. The addition of the neutral drying agent (not previously reported) improved the yield from about 85% to 94%.

The rearrangement of the oxetane esters **1** or **2** to bridged ortho esters **3** or **4** was easily accomplished with boron trifluoroetherate and the yields of about 60% were in accord with published results[2,3]; however, some purification by column chromatography was required for removal of byproducts. Previously, the use of hexane as a column chromatography solvent for compounds **3** and **4** was reported[3], but compounds **3** and **4** are nearly insoluble in hexane. The Corey group used silica gel eluted with CH_2Cl_2 as the solvent[2] for similar compounds. The silica gel was neutralized[2], prior to chromatography because bridged carboxylic ortho esters are labile to the mildly acidic conditions encountered in typical silica gel column chromatography.

Attempts to directly convert **3** to **4** by a published method[3] failed. A complex mixture of products was observed, possibly because of the need to heat the reaction mixture to 100^{o} C for two hours. The published yield[3] for this conversion was 49%. The tricky conversion of **3** to **4** is best avoided by using an improved reaction sequence, in which the halogen exchange reaction is done at the oxetane ester stage (compound **1** to compound **2**, previously unreported) and this halogen exchange reaction occurs under very mild conditions (NaI in acetone at ambient temperature[8]). The conversion of **1** to **2** proceeded in 94% yield; therefore, the overall yield in the new synthesis of compound **4** was nearly doubled with the same number of synthetic steps. Also, commercially available 3-bromopropionyl chloride can be used as the starting material for the preparation of both compounds **3** and **4**.

Compounds **3** and **4** are very hygroscopic (not mentioned previously in the cited references), so care must be taken during the handling and storage of the compounds. Water can be removed by evaporation under high vacuum in the presence of NaOH pellets as a drying agent. Storage should be in an argon atmosphere within a tightly capped container in a freezer.

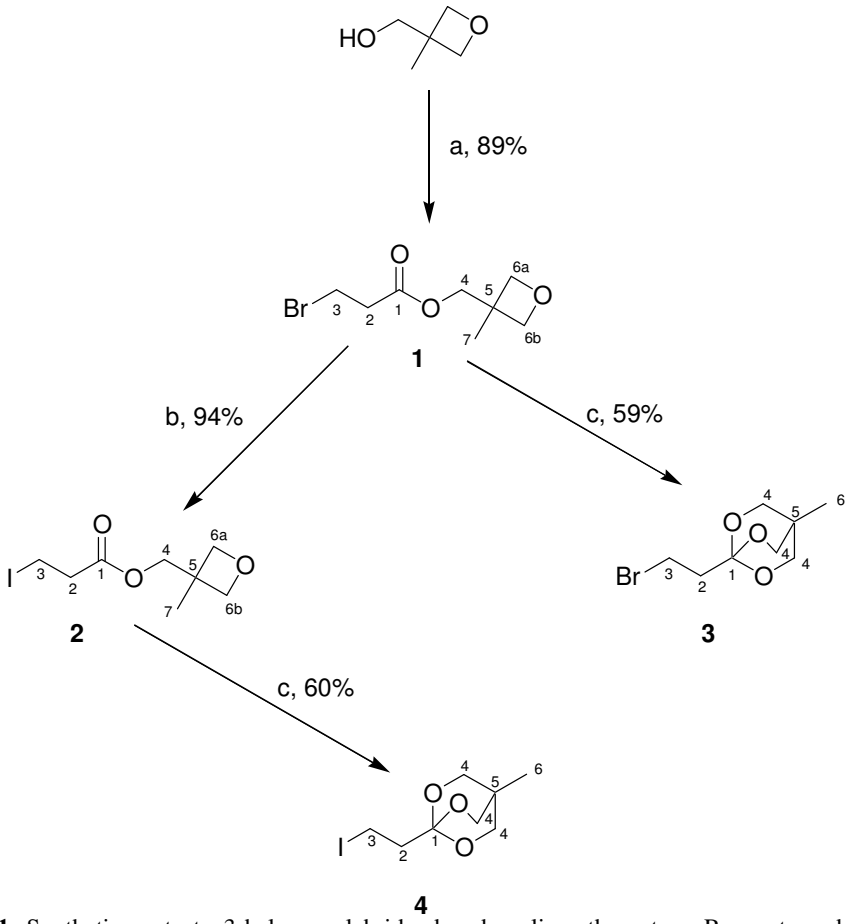

Figure 1. Synthetic route to 3-halopropyl bridged carboxylic ortho esters. Reagents and Conditions: (a) dry THF, pyridine, 3-bromopropionyl chloride, 0 ^{o}C, 1 h. 89% yield (b) Compound **1**, acetone, NaI, anhydrous Na_2SO_4, 25 ^{o}C, 5 h. 94% yield (c) Compound **1** or **2**, CH_2Cl_2, $BF_3.Et_2O$, 0 ^{o}C, 4 h, then quench reaction with triethylamine. The yield for **3** was 59% and the yield for **4** was 60%.

3. Conclusion

In summary, an improved synthetic pathway to either bridged ortho-esters of 3-bromopropyl carboxylic acid or 3-iodopropyl carboxylic acid has been presented. These compounds have a broad spectrum of potential use in synthetic organic chemistry. In particular, some insect pheromones[3], prostaglandin metabolites[4] and irreversible HIV protease inhibitors[5] have been constructed by the use of these compounds.

4. Experimental

Chemicals and General Methods. Dry THF was prepared by distillation from sodium benzophenone ketyl. Commercially available organic reagents were obtained from Aldrich and were used without further purification. Reactions were generally performed under an atmosphere of dry argon in oven-dried glassware. Removal of solvent during workups was accomplished by rotary evaporation under a vacuum, established with a water aspirator.

Analysis of Reaction Products. Progress of synthetic reactions was monitored by gas chromatography (GC) or GC mass spectrometry (GC/MS). All structures were additionally verified by NMR.

The Hewlett-Packard (HP) 5890 Series II gas chromatograph was equipped with flame ionization detector and split/splitless inlet and was interfaced to an HP ChemStation data system. The column was a DB-5 capillary (30 m x 0.25 mm, 0.25-μm film thickness, J&W Scientific, Folsom, CA). Carrier gas was He. The oven temperature was programmed from 50 to 280°C at 10°C/min, and the detector temperature was 280°C. The inlet temperature was 220° C, and 1.0 μL sample injections were made in splitless mode.

Electron impact mass spectra (70 eV) were obtained with an HP 5973 MSD instrument, interfaced to an HP 6890 GC, equipped with a splitless inlet. Several columns were used, but gave comparable results to that used for GC. The oven temperature was programmed from 50 to 250°C at 10°C/min; the inlet temperature was 220°C, and the transfer line temperature was 250°C.

^{1}H-NMR, ^{13}C-NMR and 2D NMR spectra were acquired on a Bruker (Bellerica, MA) Avance 500 spectrometer using a 5 mm inverse broadband probe. Samples were dissolved in $CDCl_3$ and all spectra were acquired at 300°K. ^{1}H and 2-D homonuclear one-bond *J* coupling correlation spectroscopy (COSY) spectra were acquired at 500 MHz whereas ^{13}C and distortionless enhancement by polarization transfer (DEPT) spectra were acquired at 125 MHz. Heteronuclear Single Quantum Coherence (HSQC) and Heteronuclear Multiple Bond Correlation (HMBC) experiments were conducted to aid in the assignment of chemical shifts. ^{1}H- and ^{13}C-Predictive software[9] and reference or analogy to known compounds[3] also aided shift assignment. Chemical shifts are reported as parts per million relative to tetramethylsilane.

4.1 Preparation of Oxetane Esters.

3-methyl-3-oxetanylmethyl 3-bromopropanoate (**1**). Pyridine (1.66 g, 21 mmol) was added to dry THF (35 mL) and the mixture was cooled to 0 °C (ice bath) and stirred under an argon atmosphere before 3-methyl-3-hydroxymethyloxetane (1.79 g, 17.5 mmol) was added. 3-Bromopropionyl chloride (3.33 g, 19.5 mmole, slight excess) was added dropwise and the reaction mixture was allowed to stir at 0 °C for an additional 1 h. The reaction mixture was poured into ice-water (150 mL) then extracted with CH_2Cl_2 (5 x 100 mL). The organic phase was saved. The aqueous phase was concentrated by rotary evaporation to remove remaining THF and CH_2Cl_2, then extracted with CH_2Cl_2 (2 x 100 mL). The combined organic phases were dried (anhydrous Na_2SO_4), filtered, and removal of solvent afforded 4.14 g of **1**. Purity by GC was 89%, and yield corrected for purity was 89%. The synthesis of **1** was repeated as needed to supply the starting material for subsequent work. MS (EI) *m/z* (%) 237, 235 (M^+, 1), 155 (4), 153 (4), 137 (15), 135 (14), 109 (20), 97 (22), 72 (100), 55 (25). ^{1}H NMR δ 0.98 (3H, s, H-7), 2.24 (2H, t, $J_{2\text{-}3}$ = 6.6, H-2), 3.18 (2H, t, $J_{2\text{-}3}$ = 6.6, H-3), 3.96 (2H, s, H-4), 4.16 and 4.37 (4H, d, *J* = 6.0, H-6a and H-6b). ^{13}C NMR δ 20.5 (C-7), 26.0 (C-3), 37.2 (C-2), 38.6 (C-5), 68.6 (C-4), 78.7 (C-6a and C-6b), 169.7 (C-1).

3-methyl-3-oxetanylmethyl 3-iodopropanoate (**2**). A mixture of acetone (90 mL), anhydrous Na_2SO_4 (9 g, 63 mmol), NaI (9 g, 60 mmol, fivefold excess) and **1** (3.3 g of previous product, 12.4 mmol) was stirred at 25 °C for 5 h under an atmosphere of argon. The mixture was filtered and the solvent was removed by rotary evaporation at reduced pressure. The oily residue was taken up in CH_2Cl_2 (100 mL) then filtered again. After removal of solvent, dark orange-red oil remained (3.94 g). Purity by GC was 84%, and the conversion of **1** to **2** was 94%. The material contained about 4% compound **1**. MS (EI) *m/z* (%) 284 (M^+, 12), 254 (66), 183 (25), 155 (54), 127 (2), 72 (100), 55 (38). ^{1}H NMR δ 1.00 (3H, s, H-7), 2.53 (2H, t, $J_{2,3}$ = 6.8, H-2), 2.93 (2H, t, $J_{2,3}$ = 6.8, H-3), 3.97 (2H, s, H-4), 4.17 and 4.38 (4H, d, *J* = 5.9, H-6a and H-6b). ^{13}C NMR δ -3.7 (C-3), 20.5 (C-7), 38.1 (C-2), 38.7 (C-5), 68.7 (C-4), 78.8 (C-6a and C-6b), 170.3 (C-1).

4.2 Preparation of Bridged Ortho Esters.

1-(2-bromoethyl)-4-methyl-2,6,7-trioxabicyclo[2,2,2]octane (**3**). A solution of **1** (4.14 g of above product, 15.5 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C and boron trifluoride etherate ($BF_3.Et_2O$, 0.65 mL, 5.3 mmol) was added dropwise under an atmosphere of argon. After stirring the reaction mixture at 0 °C for 4 h, the reaction was quenched by the addition of triethylamine (2.8 mL, 20 mmol). Ether (15 mL) was added, and the mixture was stirred an additional five min at 0 °C. The mixture was filtered and the filtrate was stored at -20 °C overnight. The formation of additional precipitate was observed. The mixture was filtered again and the crude material was purified further by chromatography on a silica gel column. A slurry of silica gel (20 g), was prepared in hexane containing 5% triethylamine, applied to a column, and the silica gel was washed with additional hexane containing 5% triethylamine (100 mL) then with CH_2Cl_2 (50 mL) to remove excess triethylamine. Crude **3** was applied to the column and eluted with CH_2Cl_2 (100 mL). After removal of the solvent, oil remained. Hexane (50 mL) was added to the oil and the solvent was again removed, along with some water picked up from the air during the workup. A very pale tan powdery material remained (2.5 g), which was nearly pure by NMR. The purity by GC was 87%, and yield from **1**, corrected for purity was 59%. The sample contained 4-Methyl-1-vinyl-2,6,7-trioxa-bicyclo[2.2.2]octane (4%, possibly formed by elimination of HBr at the GC inlet) and a small amount of triethylamine. The compound is hygroscopic. MS (EI) *m/z* (%) 237 (M^+, 17), 235 (M^+, 21), 208 (17), 206 (17), 137 (16), 135 (18), 109 (20), 107 (20), 72 (100), 55 (27). 1H NMR δ 0.08 (3H, s, H-6), 2.63 (2H, m, second order, H-2), 3.53 (6H, s, H-4), 3.67 (2H, m, second order, H-3). 13C NMR δ 13.5 (C-6), 25.9 (C-3), 29.6, (C-5), 41.1 (C-2), 72.2 (C-4), 108.1 (C-1).

1-(2-iodoethyl)-4-methyl-2,6,7-trioxabicyclo[2,2,2]octane (**4**). A solution of **2** (3.36 g of above product, 9.9 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 °C and boron trifluoride etherate (BF_3Et_2O, 0.45 mL, 3.7 mmol) was added dropwise under an atmosphere of argon. After stirring the reaction mixture at 0 °C for 4 h, the reaction was quenched by the addition of triethylamine (2.0 mL, 14.3 mmol) then ether (20 mL) was added and the mixture was stirred an additional five min at 0 °C. The mixture was filtered and the filtrate was stored at -20 °C overnight. The formation of additional precipitate was observed. After another filtration and removal of solvent, the crude material was purified further by chromatography on a silica gel column. A slurry of silica gel (15 g), was prepared in hexane containing 5% triethylamine, applied to a column, and the silica gel was washed with additional hexane containing 5% triethylamine (80 mL) then with CH_2Cl_2 (40 mL). Crude **4** was applied to the column and eluted with CH_2Cl_2 (100 mL). After removal of the solvent, hexane (50 mL) was added and the solvent was removed, along with some water picked up from the air during the workup. A very pale tan powdery material remained (2.4 g), which was nearly pure by NMR. The purity by GC was 70%, and yield from **2**, corrected for purity was 60%. The material contained about 4% compound **3**, from compound **1** carried through the synthesis and small amount of triethylamine. The sample also contained 4-methyl-1-vinyl-2,6,7-trioxa-bicyclo[2.2.2]octane (4%, possibly formed by elimination of HI at the GC inlet). There was evidence for other impurities, but none of these exceeded 2% by GC. The compound is hygroscopic. MS (EI) *m/z* (%) 284 (M^+, 22), 254 (66), 183 (24), 155 (54), 127 (5), 72 (100), 55 (59). ^{1}H NMR δ 0.08 (3H, s, H-6), 2.65 (2H, m, second order, H-2), 3.40 (2H, m, second order, H-3), 3.53 (6H, s, H-4). ^{13}C NMR δ -3.8 (C-3), 13.5 (C-6), 29.6 (C-5), 42.4 (C-2), 72.2 (C-4), 108.7 (C-1).

Acknowledgment

I thank Karl Vermillion of NCAUR for the acquisition of NMR data.

References

[1] Stowell, J. Three-carbon homologating agents. *Chem. Rev*. **1984**, *84*, 409-435.
[2] Corey, E. J.; Raju, N. A new general synthetic route to bridged carboxylic ortho esters. *Tetrahedron Lett*. **1983**, *24 (50)*, 5571-5574.
[3] Keinan, E.; Sinha, S. C.; Singh, S. P. Thermostable enzymes in organic synthesis, Part 5. Total synthesis of S-(+)-Z-dodec-3-en-11-olide (ferrulactone II) using a TBADH-generated bifunctional chiron. *Tetrahedron* **1991**, *47*, 4630-4638.
[4] Corey, E. J.; Shimoji, K. Total synthesis of the major human urinary metabolite of prostaglandin D_2, a key diagnostic indicator. *J. Am. Chem. Soc.* **1983**, *105*, 1662-1664.
[5] Lee, C.S.; Choy, N.; Son, Y.C.; Park, C.; Choi, H.; Moon, K.T.; Jung, W.H.; Kim, S.C., Yoon, H. A key intermediate for irreversible HIV protease Inhibitors: Synthesis of optically pure N-Cbz-5S-amino-6-phenyl-hex-3Z-enoic acid. *Bull. Korean Chem. Soc.***1996**, *17*, 294-295.
[6] Pastor, I. M.; Yus, M. Masked β-, γ- and δ-lithium ester enolates: useful reagents in organic synthesis. *Tetrahedron Lett*. **2001**, *42*, 1029-1032.
[7] Kraft, P.; Cadalbert, R. 4-Substituted 1,7-dioxacycloalkan-8-ones: Preparation and olfactory properties. *Synthesis* **1998**, 1662-1669.
[8] Xu, Z.; Byun, H-S.; Bittman, R. Synthesis of photopolymerizable long-chain conjugated diacetylenic acids and alcohols from butadiyne synthons. *J. Org. Chem*. **1991**, *56*, 7183-7186.
[9] ACD ^{1}H- and ^{13}C-Predictive software, version 6.0 is available from Advanced Chemistry Development, Toronto, Ontario, Canada.