Sodium Perborate – A Convenient Baeyer–Villiger Oxidation Reagent in the Synthesis of the Corey Aldehyde

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Abstract: Sodium perborate tetrahydrate is a cheap, safe and readily available alternative to the commonly used peracetic acid for the Baeyer–Villiger oxidation step of the Corey aldehyde synthesis. Chloroketo acid **1** is smoothly converted by sodium perborate tetrahydrate in formic acid to the chloroketolactone **2** in 66% isolated yield. In contrast to previously reported reactions using other oxidants, the formation of the lactone is completely regioselective in favour of the "bridgehead-migrated" isomer **2**.

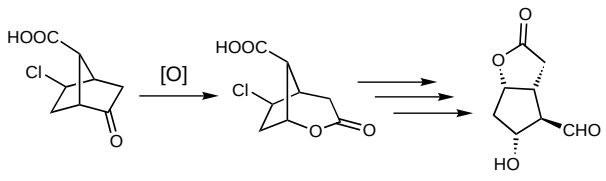
Keywords: Baeyer–Villiger oxidation; Corey aldehyde; prostaglandins; regioselectivity; sodium perborate

Introduction

In the development of the scalable process for the synthesis of the Corey aldehyde, 5-hydroxy-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-4-carbaldehyde (**3**), a safe and cost effective method for the oxidation of bicyclic 2-chloro-5-oxobicyclo[2.2.1]heptane-7-carboxylic acid **1** to 6-chloro-3-oxo-2-oxabicyclo[3.2.1]octane-8-carboxylic acid **2** was required.

Many published syntheses[1,2] employ peracetic acid in various concentrations. The preparation and use of peracetic acid is extremely hazardous, and concentrated solutions have been reported to detonate spontaneously in the presence of metal catalysts, heat, shock or even with organic materials such as grease.[3,4] More stable peracids such as perbenzoic acid demonstrated reduced regioselectivity in the oxidation of the bicyclic system.[5]

In order to overcome these difficulties we have investigated the utility of sodium perborate tetrahydrate in acidic solutions for the Baeyer–Villiger oxidation. Sodium perborate has been used successfully in the Baeyer–Villiger oxidation of aryl and diaryl ketones.[6] More recently the sodium perborate/formic acid system has found a wider application in the formation of simple monocyclic lactones.[7] Here we report the implementation of sodium perborate tetrahydrate in the Corey aldehyde synthetic pathway as a cheap, non-toxic, safe, easily handled, crystalline and readily available oxidant.[6]



1 2 3

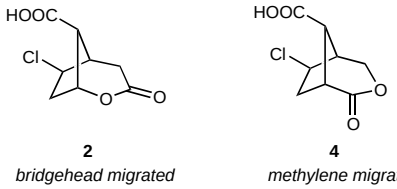
Scheme 1. Synthetic pathway for Corey aldehyde **3**.

Results and Discussion

Initial experiments, following the literature procedure[1] using freshly prepared 40% peracetic acid as the oxidant failed to give clean conversion of chloroketo acid **1**. NMR analysis of a recrystallised product mixture indicated the presence of approximately 12% of the undesired "methylene-migrated" isomer **4**, identified by a low field shift of the 4-H methylene group. Several recrystallisations were necessary to remove **4** from the mixture, with the consequence of lower yield.

Formation of "methylene-migrated" products in similar systems has been rationalised[8] as the consequence of conformational effects in the transition state. *Endo* attack of the oxidant favours a low-energy chair conformation during methylene migration, whereas bridgehead migration must proceed through the less-favoured boat conformation.

The nature of the oxidant and solvent influences the regioselectivity in the Baeyer–Villiger oxidation of



2 *bridgehead migrated* 4 *methylene migrated*

Figure 1. Isomeric products from Baeyer–Villiger oxidation of compound **1**.

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bicyclic ketones.[5] A higher proportion of "methylene-migrated" products is observed with peracids derived from aromatic acids, while peracids derived from weaker acids tend to favour bridgehead migration. We therefore turned our attention to the sodium perborate tetrahydrate/acetic acid system. To our delight, the ^{1}H NMR spectrum of the crude product showed the presence of only one isomer. Although the regioselectivity was now optimised, the yield was unsatisfactory. Since the reaction was slow, the lactone product may have been partially hydrolysed under the reaction conditions. In order to increase the reaction rate, a more acidic solvent was required. Oxidation of **1** employing formic acid as solvent was complete within 8 hours, and consequently an improved yield was achieved (see Table 1).

Sodium perborate tetrahydrate in acetic acid has previously been used in the oxidation of organic sulphides, where it was shown[9] that hydrogen peroxide is the active oxidising species. Although in our case the nature of the oxidising species remains unknown, we speculate that a weak acid like boric acid or water could act as the leaving group in the oxidation step. Either possibility should favour the desired bridgehead migration product.

Figure 2 shows the temperature profile of the reaction in formic acid on a 0.36 molar scale. Initially, dimeric sodium perborate (which has the 1,4-diboratetraoxane structure[10]) is endothermically cleaved to give the active oxidising monomer. Since the oxidation reaction is strongly exothermic, a sharp temperature rise is observed after the induction period. While this presents no problems on a small scale, larger scale reactions require external cooling.

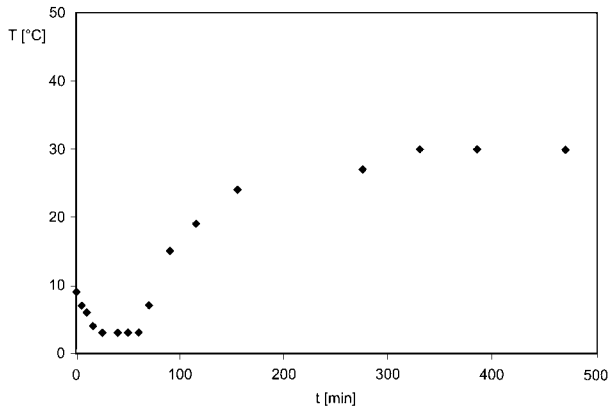

Figure 2. Temperature profile during oxidation of compound **1**.

Conclusion

In summary, an operationally simple method for the synthesis of lactone **2** with sodium perborate tetrahydrate in formic acid is presented, resulting in superior regioselectivity in the Baeyer–Villiger oxidation. The procedure is amenable to scale-up, since the oxidant is cheap, safe and convenient in comparison to organic peracids.

Experimental Section

Baeyer–Villiger Oxidation of Chloroketo Acid 1 with Sodium Perborate Tetrahydrate in Formic Acid

A solution of chloroketo acid **1** (67.90 g, 0.36 mol) in formic acid (815 mL, 98%) was stirred and cooled in an ice bath. Sodium perborate tetrahydrate (91.40 g, 0.53 mol, 90%) was added subsequently in small portions over a period of 6 h. Stirring was continued for another 2 hours. TLC on silica gel (ethyl acetate/hexane/formic acid, 75:25:1; $R_f = 0.5$) indicated the completion of the reaction. The volume of the reaction mixture was reduced in vacuum to 250 mL. The precipitate was filtered off and washed with ethyl acetate (400 mL). The filtrate was diluted with water (1000 mL). Sodium metabisulphite (70 g) was slowly added in order to quench remaining peroxides. The aqueous solution was saturated with sodium chloride (400 g) and separated from the organic layer. The aqueous layer was extracted with ethyl acetate (6 × 250 mL). The combined organic layers were dried over $CaSO_4$ and concentrated in vacuum to dryness. The remaining formic acid was removed by azeotropic distillation with toluene (250 mL) under reduced pressure. The crystalline colourless residue was washed with diethyl ether (2 × 250 mL) and filtered under suction to furnish compound **2**; yield: 48.6 g (66%); mp 172–175 °C (Lit. mp 175–178 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 2.38$ (ddd, $J_{6a,7b} = 3.2$ Hz, $J_{1,7b} = 5$ Hz, $J_{7a,7b} = 16.4$ Hz, 1H, 7b-H), 2.68 (m, 1H, 4a-H), 2.85 (ddd, $J_{1,7a} = 1.7$ Hz, $J_{6a,7a} = 7.9$ Hz, $J_{7a,7b} = 16.4$ Hz, 1H, 7a-H), 2.95-3.02 (m, 2H, 4b-H, 5-H), 3.31 (bs, 1H, 8-H), 4.62 (dd, $J_{6a,7b} = 3.2$ Hz, $J_{6a,7a} = 7.9$ Hz, 1H, 6a-H), 4.98 (dd, $J_{1,7a} = 0.8$ Hz, $J_{1,7b} = 5$ Hz, 1H, 1-H). ^{1}H NMR (acetone-d_6, 400 MHz): $\delta = 2.53$ (ddd, $J_{6a,7b} = 3.1$ Hz, $J_{1,7b} = 4.9$ Hz, $J_{7a,7b} = 16.4$ Hz, 1H, 7b-H), 2.73 (bd, $J_{4a,4b} = 18.5$ Hz, 1H, 4a-H), 2.94 (ddd, $J_{1,7a} = 1.8$ Hz, $J_{6a,7a} = 7.6$ Hz, $J_{7a,7b} = 16.4$ Hz, 1H, 7a-H),

Table 1. Yields and conditions in Baeyer–Villiger oxidation of compound **1**.

Oxidant	Ratio **2**:**4**	Conditions	Combined yield
CH_3COOOH/CH_3COOH	88:12	rt/16 h	75%
$NaBO_3 \cdot 4\ H_2O/CH_3COOH$	100:0	rt/16 h	50%
$NaBO_3 \cdot 4\ H_2O/HCOOH$	100:0	0 °C → 30 °C/8 h	66%

3.05 (dd, $J_{4b,5} = 5.8$ Hz, $J_{4a,4b} = 18.5$ Hz, 1H, 4b-H), 3.14 (bd, $J_{4b,5} = 5.8$ Hz, 1H, 5-H), 3.32 (bs, 1H), 4.60 (dd, $J_{6a,7b} = 3.1$ Hz, $J_{6a,7a} = 7.6$ Hz, 1H, 6a-H), 5.04 (dd, $J_{1,7a} = 1.8$ Hz, $J_{1,7b} = 4.8$ Hz, 1H, 1-H). ^{13}C NMR (acetone-d_6/DMSO-d_6, 50 MHz): $\delta = 38.9$, 44.5, 46.5, 49.8, 60.6, 80.0, 168.1, 171.5.

Acknowledgements

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