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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 8353–8355

2-Alkylidene oxetanes by stereospecific elimination of mesylates

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Received 4 July 2007; revised 7 September 2007; accepted 18 September 2007
Available online 21 September 2007

Abstract—α-Mesyloxyoxetanes undergo stereospecific elimination to 2-alkylidene oxetanes upon treatment with potassium *t*-butoxide.

We have been interested in the synthesis and exploitation of oxetanes with α-unsaturation. In particular, we reported that 2-methyleneoxetanes are prepared by treatment of β-lactones with dimethyltitanocene (the Petasis reagent[1])[2] and that they showed useful reactivity in their conversion to, among other things, homopropargyl alcohols,[3] functionalized ketones,[4–6] oxaspirohexanes,[7] and 1,5-dioxaspiro[3.2]hexanes.[8] The utility of these transformations would be greatly extended if substituents were efficiently incorporated on the exocyclic alkene. In this Letter we demonstrate that 2-alkylidene oxetanes can be stereoselectively prepared by the elimination of α-mesyloxyoxetanes.

There are few examples in the literature of the preparation of 2-alkylidene oxetanes. The first, reported by Arnold and Glick,[9] involved Paterno-Buchi reaction of ketones/aldehydes with allenes. This strategy has also been examined by other groups,[10–12] including our own.[13] Unfortunately, this approach is plagued with unfavorable stoichiometries, low regio- and stereoselectivities, the formation of side products, and low yields of desired products. Other strategies used to prepare 2-alkylidene oxetanes include ketene–olefin cycloaddition,[14,15] photochemically-initiated free radical cyclization,[16] photochemical degradation,[17] and O-alkylation.[18] However, the utility of these approaches is limited by low yields, the formation of side products, and/or applicability to a narrow range of starting materials.[19]

Since none of the previously reported strategies for the synthesis of 2-alkylidene oxetanes appeared to be broadly applicable, we decided to examine other approaches. A literature search revealed that α-alkylidenated tetrahydrofurans and tetrahydropyrans have been prepared from γ- and δ-lactones using a variety of alkylidenation strategies.[20–28] However, in our hands, attempts to employ these strategies for the conversion of β-lactones to 2-alkylidene oxetanes were unsuccessful. α-Alkylidenated tetrahydrofurans and tetrahydropyrans have also been prepared by 1,2-elimination of selenoxides,[29,30] halides,[31–36] or activated alcohols[37–40] (Fig. 1). A number of these reactions proceeded stereoselectively to give solely the *E*- or *Z*-alkylidenated products,[33,37,39,41] depending on the relative stereochemistry of the atoms/groups undergoing elimination. Because of ring strain oxetanes do not necessarily behave like furans or pyrans; so, we decided to investigate the potential of an elimination strategy for preparing 2-alkylidene oxetanes using α-mesyloxyoxetanes **1**.

The preparation of **1** began with the reaction between dihydrocinnamaldehyde **2** and vinylmagnesium bromide (Scheme 1). An initial attempt to prepare benzyloxyepoxide **3** by benzyl protection of the resultant alcohol, followed by epoxidation, was unsuccessful. However, reversing the reaction order by starting with epoxidation of the allyl alcohol, followed by benzyl protection, gave

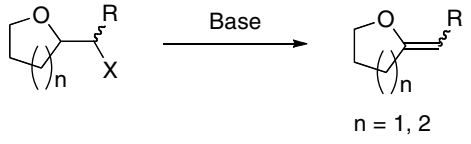

Figure 1. Elimination route to alkylidenated tetrahydropyrans and furans.

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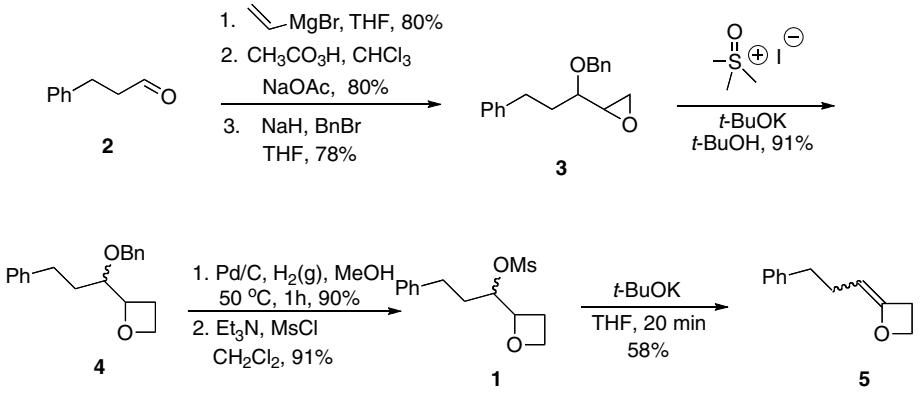
doi:10.1016/j.tetlet.2007.09.109



Scheme 1.

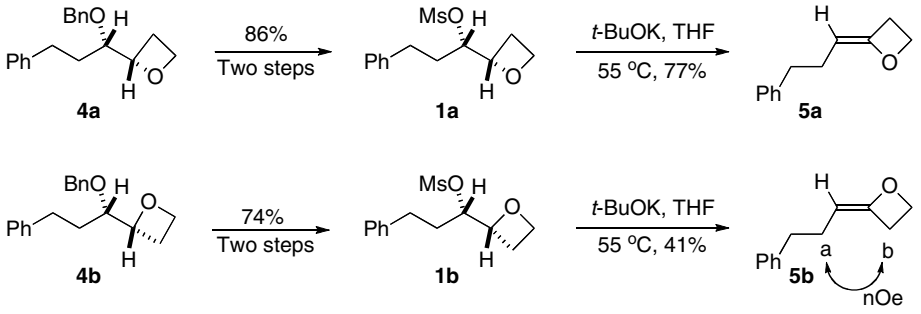


Figure 2. Stereoselective elimination of mesyloxyoxetanes.

3 as an inseparable mixture of diastereomers. Epoxide **3** was subjected to a regioselective ring expansion reaction using the procedure reported by Fitton et al.[42] to give benzyloxyoxetanes **4** in 91% yield. Oxetane mixture **4** was converted to **1**, and treatment of **1** with *t*-BuOK in THF at 50 °C gave 2-alkylidene oxetanes **5** as an inseparable mixture of diastereomers in 58% yield.

Our assumption was that elimination proceeded by an E-2 mechanism, and, if this were the case, elimination of each mesylate diastereomer would yield a single 2-alkylidene oxetane. In order to test this, access to each diastereomer of **1** was needed. We found that benzyloxyoxetanes **4** could be separated into diastereomers **4a** and **4b** by careful column chromatography. The relative stereochemistries of **4a** and **4b** were inferred from the elimination product of the corresponding mesylates (vide infra).

Diastereomer **4a** was converted to mesyloxyoxetane **1a** by the approach shown in Scheme 1 (Fig. 2). As expected, treatment of **1a** with *t*-BuOK in THF for 1 h, led to the formation of only one stereoisomer, *Z*-2-alkylidene oxetane **5a** in 77% yield. The relative stereochemistry of oxetane **5a** could not be conclusively deduced from NOESY experiments. However, it was inferred from successful NOESY experiments assigning **5b** as the *E*-isomer (NOE observed between protons a and b—see Fig. 2 and Supplementary data). Likewise, diastereomer **4b** was converted to mesyloxyoxetane **1b** in 74% yield.[43] Treatment of **1b** with *t*-BuOK in THF

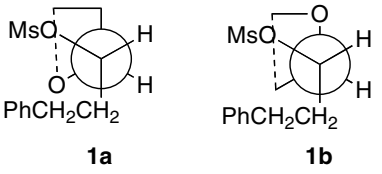


Figure 3. Elimination alignments for mesyloxyoxetanes **1a** and **1b**.

at 50 °C led to *E*-2-alkylidene oxetane **5b** in 41% yield. The elimination of **1b** was slower and less efficient than that observed for **1a**. However, no *Z*-product was observed. The decreased yield and reaction rate are presumably due to unfavorable steric interactions in the transition state required for the elimination (Fig. 3).

In conclusion, 2-alkylidene oxetanes have been prepared by 1,2-elimination of mesylates. The elimination proceeded in a stereospecific fashion to yield either the *E*- or the *Z*-2-alkylidene oxetane. Having established that α-mesyloxyoxetanes can be converted stereospecifically and with reasonable yields to 2-alkylidene oxetanes, we are currently investigating more efficient approaches to α-mesyloxyoxetanes.

Acknowledgments

We thank Dr. Martha Morton for assistance with NMR experiments. Mary Khalili is acknowledged for her

contributions to the separation of **4**. This Letter is based upon work partially supported by the National Science Foundation (NSF) under Grant No. CHE-0111522.

Supplementary data

Full experimental procedures and characterization data are provided as supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.109.

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43. *(Z)-2-(3-Phenylpropylidene)oxetane* (**5a**). *t*-BuOK (78 mg, 0.49 mmol) was added to a stirred solution of (1*R**)-1-[(2*R**)-oxetan-2-yl]-3-phenylpropylmethanesulfonate (**1a**) (44 mg, 0.16 mmol) in THF (20 mL) and stirred at 55 °C for 1 h. The reaction mixture was diluted with H_2O (20 mL) and petroleum ether (40 mL). The layers were separated, and the aqueous layer was further extracted with petroleum ether (3×30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/Et_3N 99.6:0.4) gave *Z*-diastereomer **5a** (22 mg, 77%) as a yellowish oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.19 (m, 3H), 4.61 (m, 2H), 4.10 (m, 1H), 3.18 (m, 2H), 2.65 (m, 2H), 2.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 142.5, 128.7, 128.4, 125.9, 95.5, 68.3, 36.5, 28.9, 24.8; IR (CH_2Cl_2) 3084, 3025, 2924, 2853, 1716; MS (EI) *m/z* 174 (M^+), 91, 83 (100), 77, 65, 55; HRMS (FAB) calcd for $C_{12}H_{15}O$ (M^++H), 175.1123; found, 175.1135.