A FACILE AND EFFICIENT SYNTHESIS OF HIGHLY FUNCTIONALIZED TERMINAL OLEFINES FROM α-ALKOXY-β-HALIDES USING ZINC DUST∗

SAKKARAPALAYAM M. MAHALINGAM†, HEMA KRISHNAN† AND HARI N. PATI‡, *

†Department of Chemistry, Indian Institute of Technology Madras, Chennai 600 036, India
‡Department of Chemistry, Sambalpur University, Jyoti Vihar 768 019, India

Dedicated to Prof. V. S. Parmar, University of Delhi on his 60th birthday.
(Received 8 July 2008 - Accepted 30 September 2008)

ABSTRACT

A simple and efficient method of zinc dust/ammonium chloride system for the terminal olefination of α-alkoxy-β-halides has been described. The reaction is carried out under mild conditions and yields of the corresponding terminal olefinic products are good. The significant feature of this method is the isolation of the pure product by simple work up in a short time.

Keywords: Terminal olefines / zinc dust / olefination / dehydrohalogenation.

INTRODUCTION

The terminal olefination or dehydrohalogenation of α-alkoxy-β-halides is a useful chemical transformation in the synthesis of numerous organic compounds and also desired during the synthesis of compounds which are key intermediates in the synthesis of many pharmacologically important substances. These terminal olefinic compounds are very important key precursors to synthesis the natural products via the ring closing metathesis1 and radical cyclization.2

Earlier reports reveal that the terminal olefination or dehydrohalogenation of α-alkoxy-β-halides has been achieved with systems like Cp₂TiBH₄ and [Cp₂Ti·nBu²]·MgCl+.3 However, these systems require reaction times as long as 5–10 hours at reflux, expensive catalysts and also offer very low yields. Therefore, there is need of an efficient and inexpensive non toxic reagent system for the terminal olefination of α-alkoxy-β-halides.

In order to develop new organic transformation, we report herein that zinc dust/NH₄Cl reagent system, might be a useful and inexpensive reagent for the reduction of α-alkoxy-β-halides. Although, zinc has also been extensively used in the preparation of organometallic compounds4 and as a reducing agent5 in organic synthesis. The utility of zinc for the synthesis of β, α-unsaturated ketones by a reaction of an acid chloride with allyl bromide6 and homoallylic alcohols7 has been demonstrated. Furthermore, the zinc mediated amide formation,8 Friedel–Crafts acylation9 and carbamate formation10 has also been reported. In this context, the use of zinc as non-toxic ‘green’ reagent in organic synthetic processes has gained considerable importance due to its ability to promote and catalyze organic transformations of commercial importance under ambient conditions, without the need for any added catalyst or ligand.

RESULTS AND DISCUSSION

We began our study with the α-alkoxy-β-halide 1a.11 Compound containing a neighbouring alkoxy group (OBn) and a halo (iodo) group at β position and reaction with zinc dust in ammonium chloride could conceivably give rise to either the acylic β-elimination product 2a or the simple reduced compound 3.

In this letter, we report a rapid and efficient reductive elimination of α-alkoxy-β-halides to the corresponding terminal olefinic products using low cost zinc dust and ammonium chloride at 60 °C in methanol as depicted in Scheme 1.

We found that the reductive elimination of 1a with zinc dust and ammonium chloride furnished only the β-elimination product 2a and not the simple reduced compound 3. The reaction was very clean with satisfactory yield and there was no side products observed.

The possible mechanism is depicted in figure 1. Probably, the α-alkoxy-β-halides react with zinc leads to the formation of either the intermediate A or B. These reactions are obviously substitution reactions, but they cannot be classified as nucleophilic substitutions. The facile elimination of the POZnX from the intermediate A or B furnished the terminal olefin 2. From these observations the α-alkoxy-β-halides are considered to be masked olefins (Figure 1).

The reaction on substrate 1a afforded compound 2a, which was conformed by 1H NMR and 13C NMR spectrum. The one proton from the methine (CH) unit of the olefinic residue appeared as multiplets from δ 5.77 to δ 5.88 ppm and the remaining two terminal olefinic protons (CH₂) appeared as multiplets from
Reductive elimination of α-alkoxy-β-halides using zinc and ammonium chloride was completed within three to four hours (Table 1). The course of reaction was monitored by TLC. The work-up and isolation of the products were as usual. Thus, the α-alkoxy-β-halides reduced by this system were obtained in good yields and no undesired side product was observed. Some of the results shown in table 1 clearly indicate the scope and generality of the reaction with respect to various α-alkoxy-β-halides. All products were characterized by different spectroscopic techniques.

Compound 1b and 1c underwent reductive elimination, to give vinyl compounds 2b with good yields. We have also examined the four carbon α-benzylxy-β-halide 1d under the similar reaction conditions and as expected, we isolated the olefinic product 2e with 78% yield (Figure 2).

Figure 2.

This similar kind of observation was noted by Hersant et. al. when using excess of Cp₂TiCl as a reducing agent for α-acetoxy-β-halides under photo irradiation conditions. But they observed a mixture of products like β-eliminated product with higher yields (Table 1). The reduction of α-alkoxy-β-halides in the presence of zinc dust and ammonium chloride shows more reactivity, less reaction times and exclusive β-elimination product with higher yields (Table 1).

Table 1: Reductive elimination of α-alkoxy-β-halides using zinc and NH₄Cl in methanol.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Reaction conditions &amp; Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>60 °C, 3 h</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>2b</td>
<td>60 °C, 3 h</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>2b</td>
<td>60 °C, 4 h</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>2e</td>
<td>60 °C, 3.5 h</td>
<td>76</td>
</tr>
</tbody>
</table>

*Yields refer to pure isolated products and were characterized by spectral data.*

The starting substrate 1-deoxy-1-ido-2,3-dio-O-benzyl-4,5-O-isopropylidene-D-arabinitol (1a) was prepared from the corresponding standard literature method starting from D(-)-arabinose. The substrates 2-O-benzyl-1-bromo-3,4,5,6-di-O-isopropylidene-D-glucitol (1b) and 2-O-methyl-1-bromo-3,4,5,6-di-O-isopropylidene-D-glucitol (1c) were conveniently prepared starting from D-glucolactone (Scheme 2). The procedure starts from peaks at δ 119.7 ppm. Firm evidence for the terminal olefination was obtained from peaks at δ 119.7 (methylene; CH₂) and δ 135.3 ppm. Firm evidence for the terminal olefination was obtained from the DEPT spectrum, one olefinic methylene carbon [at δ 135.3 ppm] and one olefinic methane carbon [at δ 135.3 ppm] were visible and it was clearly indicating the terminal olefinic product formation.

The reduction of α-alkoxy-β-halides using this system was obtained in good yields and no undesired side product was observed. Some of the results shown in table 1 clearly indicate the scope and generality of the reaction with respect to various α-alkoxy-β-halides. All products were characterized by different spectroscopic techniques.

In conclusion, we have demonstrated a very simple, efficient and practical method for the terminal olefination using zinc dust with ammonium chloride. The important features of this method include: (a) operational simplicity, (b) no need for any other additive to promote the reaction, (c) shorter reaction time, (d) the use of cheap, commercially available, non toxic reagents, and (e) good to moderate yields of desired products. Moreover, 14 new compounds have been synthesized and their data cited in this report for the first time.

CONCLUSIONS
EXPERIMENTAL SECTION

General information

1H NMR spectra were recorded on 400MHz Bruker AVANCE 400 spectrometer and 13C NMR spectra were recorded on 100MHz Bruker AVANCE 400 spectrometer, respectively, using CDCl3 as solvent and TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FT/IR 100 spectrometer. Mass spectra were recorded on Agilent-1100 mass spectrometer. Optical rotations were measured using a Rudolph Autopol V polarimeter. All the reactions were monitored by thin layer chromatography (TLC). TLC was performed on F254 plates (Merck). Plates were eluted with appropriate solvent systems, and then stained with either alcoholic KMnO4 or Ceric ammonium molybdate solutions prepared in the laboratory. The developed plates were first analysed under UV 254nm then stained with appropriate reagent. Column chromatography was performed using silica gel with particle size 100-200 mesh.

General procedure for O-alkylation using NaH.

A solution of the hydroxy compound (1 mmol) in dry DMF (6 ml) was added to oil-free sodium hydride (11 mmol) and the mixture was stirred at 90 °C for 12 hours. On completion of the reaction as monitored by thin layer chromatography, the reaction mixture was allowed to cool and the product was extracted with diethyl ether (2 x 30 ml). The crude product was subjected to silica gel column chromatography (ethyl acetate: hexane, 2: 8) to give a pure compound.

Morpholino (3,4,5,6-di-O-isopropylidene)-D-glucamid (5):

To a solution of the triacetonate 4 (5 g, 5.8 mmol) in toluene (16 ml), morpholine (5.5 mL, 63.3 mmol) was added and the reaction mixture was stirred at 90 °C for 18 hours. On completion of the reaction as monitored by thin layer chromatography, the reaction mixture was allowed to stir at room temperature for 30 minutes. On completion of the reaction as monitored by thin layer chromatography, the product was extracted using ethyl acetate (20 ml) and the DMF was removed by washing with brine solution (2 x 50 ml). The organic layer was separated and evaporated under reduced pressure to yield the O-alkylated product. The crude product was subjected to silica gel column chromatography (ethyl acetate: hexane, 2: 8) to give a pure compound.

2-O-Benzyl-3,4,5,6-di-O-isopropylidene-D-glucitol (7a):

This compound was obtained as colourless syrup. [α]D: +23.40° (c 1, CHCl3), IR (neat) \(\nu_{\text{cm}^{-1}}\): 3481, 1217, 1071, 772, 698, 669. 1H NMR: δ 1.35, 1.39, 1.42 (3 x 3, 12H, 4 x CH3); 3.60-4.20 (multiplets, 8H), 4.68 (d, \(J = 11.7\) Hz, 1H, PhCH2); 4.78 (d, \(J = 11.7\) Hz, 1H, PhCH2); 7.25-7.39 (m, 5H, Ar-H); 13C NMR: δ 25.2, 26.4, 26.7, 27.2 (4 x CH3) 62.2 (CH3OH); 67.9 (O-CH3); 72.5 (O-C-CH2 CH); 77.4, 77.9 (2 x CH3); 81.9 (PhCH2); 81.9 (CH2OH); 109.77, 109.8 (2 x CH2E); 127.7, 127.8, 129.1, 138.3 (aromatic); HRMS (TOF MS ES+): m/z [M+Na]+ calcld. for C26H38O8, 375.1784, found 375.1789.

2-O-Methyl-3,4,5,6-di-O-isopropylidene-D-glucitol (7b):

This compound was obtained as colourless syrup. [α]D: +23.40° (c 1, CHCl3), IR (neat) \(\nu_{\text{cm}^{-1}}\): 1210, 1075, 772, 698, 669. 1H NMR: δ 1.36, 1.38, 1.42, (4 x s, 12H, 4 x CH3); 3.38-3.42 (m, 1H), 3.51 (s, 3H, H-OCH3); 3.75-3.80 (m, 1H), 3.87-3.92 (m, 1H), 3.95-4.02 (m, 2H), 4.03-4.12 (m, 2H), 4.16-4.20 (m, 1H). 13C NMR: δ 25.2, 26.4, 26.7, 27.1 (4 x CH3); 52.1, 58.4 (OCH3); 61.5 (C2H5OH); 65.8, 68.0, 80.1, 81.9, 107.9, 109.7 (2 x CH2E).

General procedure for bromination using N-bromosuccinimide.

To a solution of the hydroxy compound (1 mmol) in dry DMF (10 ml) was added triphenylphosphine (2 mmol) and N-bromosuccinimide (2 mmol). The reaction mixture was then heated at 60 °C for 12 hours. On completion of the reaction, water (20 ml) was added and the mixture was extracted with diethyl ether (3 x 10 ml). The combined organic layer was dried over anhydrous sodium sulphate, and evaporated under reduced pressure to afford the crude residue. The residue was purified by silica-gel column chromatography (8:2, hexane-ethyl acetate) to produce the pure bromo compound.

2-Benzyl-1-bromo-3,4,5,6-di-O-isopropylidene-D-glucitol (1b):

This compound was obtained as colourless syrup. IR (neat) \(\nu_{\text{cm}^{-1}}\): 1215, 1071, 772, 690. 1H NMR: δ 1.27, 1.30, 1.31, 1.33 (4 x s, 12H, 4 x CH3); 3.47-3.51 (m, 2H), 3.70-3.76 (m, 1H), 3.78-3.84 (m, 1H), 3.87-3.93 (m, 1H), 3.96-4.03 (m, 1H), 4.04-4.10 (m, 1H), 4.15-4.20 (m, 1H), 4.55 (d, \(J = 11.7\) Hz, 1H, PhCH2); 4.72 (d, \(J = 11.7\) Hz, 1H, PhCH2); 7.21-7.30 (m, 5H, Ar-H); 13C NMR: δ 25.2, 26.6, 26.7, 27.2 (4 x CH3); 30.17 (CH2Br); 67.9 (O-C-CH2); 73.5 (O-C-CH3); 77.1, 77.3 (2 x CH); 78.4 (PhCH3); 80.1 (CH2CHBr); 109.7, 109.8 (2 x CH2E); 127.8, 127.9, 128.2, 137.9 (Aromatic).

2-Methyl-1-bromo-3,4,5,6-di-O-isopropylidene-D-glucitol (1c):

This compound was obtained as colourless syrup. IR (neat) \(\nu_{\text{cm}^{-1}}\): 1215, 1071, 772, 690. 1H NMR: δ 1.28, 1.29, 1.32, 1.35 (4 x s, 12H, 4 x CH3); 3.45-3.50 (m, 6H), 3.82-3.90 (m, 2H), 3.95-4.03 (m, 1H), 4.07-4.17 (m, 1H); 13C NMR: δ 21.65, 25.63, 26.05 (4 x CH3); 29.88 (CH2Br), 58.38 (OCH3), 66.95 (O-C-CH3); 76.16, 78.81 (2 x CH2), 79.09 (CH2CHBr), 105.8, 108.69 (2 x CH2E).

Synthesis of (2R,3R)-dimethyl 2,3-bis(hydroxibenzyl)tartrate (10):

A suspension of (+)-dimethyl tartrate (9) (0.5 g, 2.8 mmol) in dichloromethane (10 ml) was treated with silver oxide (1.43 g, 6.2 mmol), and allowed to stir for 12 hours at room temperature. The reaction mixture was filtered through a celite bed, and washed with additional volumes of dichloromethane. The original filtrate and the dichloromethane washings were combined and evaporated to dryness on the rotary evaporator. The residue was subjected to silica gel column chromatography to yield (0.72 g; 75%) pure 10 as colourless syrup. 1H NMR: δ 3.65 (6H, s, -H(2 CH3)), 4.38-4.44 (4H, m), 4.85-4.88 (2H, m), 7.25-7.36 (10H, m, H-Ph); 13C NMR: δ 52.1 (OCH3), 73.2 (CH3(benzyl)), 78.2 (CH2), 126.9, 127.6, 128.0, 128.3, 136.8 (CH-Ph), 169.5 (C=O).
(2R,3R)-2,3-Bis(benzylox)butane-1,4-diol (11):

This compound was obtained as colourless syrup in 72% yield. H NMR: δ 3.68-3.83 (6H, m), 4.63-4.67 (4H, m), 7.25-7.36 (10H, m). 13C NMR: δ 60.8 (CH$_2$-OH), 72.6 (CH$_2$(benzyllic)), 78.9 (CH), 126.9, 127.9, 128.0, 128.5, 138.0 (C-Phe).

Synthesis of (2R,3R)-2,3-bis(benzyloxy)-4-(tert-butyl)diphenylsiloxylbutan-1-ol (12):

To a solution of the dihydroxy compound 11 (0.5 g, 1.65 mmol) in dry DMF (4 ml) was added imidazole (0.224 g, 3.3 mmol) followed by chloro tert-butyl diphenylsilane (0.5 g, 1.8 mmol) at room temperature. After 6 hours stirring, water (15 ml) was added and the reaction mixture was extracted with ether (3 x 10 ml). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue thus obtained was purified by silica-gel column chromatography (8:2, hexane: ethyl acetate) to produce pure compound 12 as colourless syrup (0.48 g; 74%). H NMR: δ 1.05 (9H, s), 3.63-3.70 (2H, m), 3.70-3.80 (2H, m), 3.82-3.87 (2H, m), 4.47-4.70 (4H, m), 7.25-7.43 (16H, m), 7.66-7.70 (4H, m). 13C NMR: δ 20.33, 27.9, 62.9, 64.0, 66.5, 73.9, 74.1, 80.2, 81.1, 128.1, 128.8, 128.9, 128.9, 129.0, 129.1, 129.5, 129.7, 130.9, 130.9, 134.2, 134.3, 136.7, 136.8, 139.4, 139.4. HRMS (TOF MS+) m/z [M+Na]$^+$ calcd. for C$_{33}$H$_{34}$O$_2$Si 563.2594, found 563.2590.

((2R,3R)-2,3-Bis(benzyloxy)-4-bromobutyl)diphenylsilane(1d):

This compound was obtained as colourless syrup in 72% yield. H NMR: δ 1.04 (6H, s), 1.57 (3H, s), 3.43-3.45 (1H, m), 3.50-3.58 (1H, m), 3.73-3.85 (2H, m), 3.87-4.00 (2H, m), 4.55-4.75 (4H, m), 7.25-7.37 (16H, m), 7.63-7.66 (9H, m). 13C NMR: δ 19.0, 26.8, 30.0, 31.3, 62.6, 73.3, 73.7, 78.9, 127.7, 127.7, 127.7, 128.0, 128.1, 128.3, 128.5, 129.7, 129.8, 135.6. HRMS (TOF MS+) m/z [M+Na]$^+$ calcd. for C$_{35}$H$_{36}$O$_2$Si 625.1750, found 625.1777.

General procedure for the reductive elimination and debromination of α-alkoxy-β-halides:

To a solution of the starting substrates 1a-d (1 mmol) in methanol (10 ml) was added ammonium chloride (0.5 mmol) and zinc dust (2 mmol). The mixture was stirred at 60°C for 3-4 hours. After the completion of the reaction (monitored by TLC), the reaction mixture was filtered through celite. The filtrate was evaporated under vacuum and the residue was taken into chloroform or ether, washed twice with saturated brine solution and finally with water. The organic layer was dried over anhydrous sodium sulphate, and evaporation of the organic layer was followed by purification by column chromatography to yield the desired product.

**REFERENCES**


**ACKNOWLEDGEMENTS**

The authors thank the Department of Chemistry, IIT-Madras and Sambalpur University for support to the research.