This article was downloaded by: [Umeå University Library] On: 23 September 2013, At: 04:20 Publisher: Taylor & Francis Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: <u>http://www.tandfonline.com/loi/lsyc20</u>

Znl₂/NaCNBH₃ as an Efficient Reagent for Regioselective Ring Opening of the Benzylic Epoxide Moiety

L. M. Finkielsztein^a, J. M. Aguirre^b, B. Lantaño^a, E. N. Alesso^a & G. Y. Moltrasio Iglesias^a

^a Departamento de Quínica Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956, (1113), Buenos Aires, Argentina

^b Departamento de Ciencias Básicas, Universidad Nacional de Luján, Luján, Argentina Published online: 20 Aug 2006.

To cite this article: L. M. Finkielsztein , J. M. Aguirre , B. Lantaño , E. N. Alesso & G. Y. Moltrasio Iglesias (2004) Znl₂/NaCNBH₃ as an Efficient Reagent for Regioselective Ring Opening of the Benzylic Epoxide Moiety, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:5, 895-901, DOI: <u>10.1081/SCC-120028362</u>

To link to this article: http://dx.doi.org/10.1081/SCC-120028362

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

SYNTHETIC COMMUNICATIONS[®] Vol. 34, No. 5, pp. 895–901, 2004

ZnI₂/NaCNBH₃ as an Efficient Reagent for Regioselective Ring Opening of the Benzylic Epoxide Moiety

L. M. Finkielsztein,¹ J. M. Aguirre,² B. Lantaño,¹ E. N. Alesso,¹ and G. Y. Moltrasio Iglesias^{1,*}

¹Departamento de Quínica Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Buenos Aires, Argentina
²Departamento de Ciencias Básicas, Universidad Nacional de Luján, Luján, Argentina

ABSTRACT

In the presence of zinc iodide, sodium cyanoborohydride was found to produce regioselective ring opening of benzylic epoxides in mild reaction conditions.

Key Words: Sodium cyanoborohydride; Zinc iodide; Benzylic epoxide; α -Chloroketone; β -Chlorohydrin.

895

DOI: 10.1081/SCC-120028362 Copyright © 2004 by Marcel Dekker, Inc. 0039-7911 (Print); 1532-2432 (Online) www.dekker.com

^{*}Correspondence: G. Y. Moltrasio Iglesias, Departamento de Quínica Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956, (1113), Buenos Aires, Argentina; E-mail: gmoltra@ffyb.uba.ar.



Figure 1. Synthetic pathway of alcyopterosins.

In an attempt to find a synthetic route to the natural occurring sesquiterpenes named alcyopterosins,^[1] we needed to reduce α -chloroketone **1** to the indanic compound **2** (Fig. 1). To this end, we chose sodium cyanoborohydride in the presence of zinc iodide. This system afford reductive deoxygenation of aryl aldehydes and ketones^[2] and benzylic alcohols^[3] to the corresponding hydrocarbons.

When the reaction was carried out with zinc iodide/sodium cyanoborohydride at room temperature, compound **1** cleanly furnished the corresponding halohydrin **3** in good yield, but when the reaction was performed under reflux conditions, the main product isolated was alcohol **4**. To generalize this reaction, several examples were performed, and results are given in Table 1.

The obtention of alcohols **4**, **9**, and **13** prompted us to consider the possibility of *in situ* epoxide formation, whereby the epoxide would be opened by attack of the hydride moiety to afford the primary alcohol.

To test this hypothesis, we synthesized several epoxides, which were then treated with $ZnI_2/NaCNBH_3$ in the same conditions used for reductive deoxygenation reaction. It was found that this mixture of reagents is able to perform ring opening of the epoxide moiety to render, in all examples, the less substituted alcohol in an efficient manner (see Table 2), better than when the starting material was the α -chloroketone or β -chlorohydrin. The presence of a Lewis acid is required to activate the epoxide toward nucleophilic attack, since this moiety is essentially inert to sodium cyanoborohydride. Hydride is trapped at the site best able to accommodate a carbonium ion, and thus the less substituted alcohol is preferentially obtained.

When the reaction was carried out starting from either α -chloroketone or β -chlorohydrin at reflux conditions, an iododerivative was also obtained in all cases. In an early publication, Lau et al.^[2] proposed the formation of a spiro cyclopropyl intermediate when 4-methoxyphenethyl alcohol was treated with ZnI₂/NaCNBH₃. Such an intermediate, favored by the electron donor effect of the methoxyl group, is then attacked by an iodide anion to produce 4-methoxyphenethyl iodide. Our results would seem to indicate that the production of the iododerivative is not entirely due to the formation of this intermediate. As the epoxide is formed, starting from the β -chlorohydrin or

Marcel Dekker, Inc

270 Madison Avenue, New York, New York 10016



ZnI₂/NaCNBH₃ as Efficient Reagent

^aReaction carried out in dichloromethane at room temperature. ^bReaction carried out in dichloroethane under reflux conditions. ^cYields refer to chromatographically pure products. ^dAll the products exhibited spectral data consistent with their structures. 897



| ORDER | | REPRINTS |
|-------|--|----------|
|-------|--|----------|

Finkielsztein et al.

Table 2. Ring opening of benzylic epoxides with $ZnI_2/NaCNBH_3$.

| Epoxide | Product ^a | Yield (%) ^b |
|----------------------|-----------------------------------|------------------------|
| 0 18 | С ОН 19 | 76 [°] |
| 0 20 | ССС ^{ОН} 21 | 81 ^c |
| 22 | ССС-ОН 23 | 85 ^c |
| 24 | С — ОН 25 | 79 ^c |
| 26 | 27 | 82 ^c |
| H ₃ CO 28 | н ₃ со Он 29 | 80 ^d |

^aReaction time: 16 h.

898

^bYields refer to isolate and chromatographically pure products. All the products exhibited spectral data consistent with their structures carried out.

^cReaction carried out in dichloroethane under reflux conditions.

^dReaction carried out in dichloroethane at room temperature.

 α -chloroketone, the former is rapidly cleaved to render the corresponding alcohol. When epoxide formation is more difficult, as in the case of compound **12** and **16**, required reaction times are greater. In such conditions, the substitution of the alcohol by the iodide occurs, thus leading to the iodo-derivative. In support, when phenethyl alcohol was treated in the same conditions used for compound **16**, the corresponding iododerivative was obtained (yield: 91%). Throughout, the progress of the reaction was monitored by tlc.

In conclusion, the combination of ZnI_2 and $NaCNBH_3$ is capable of achieving the formation and cleavage of epoxides starting from α -chloro-





ZnI₂/NaCNBH₃ as Efficient Reagent

ketones and β -chlorohydrins. The mixture of reagents proves also a convenient and efficient method for ring opening of benzylic epoxides. The reaction is invariably regioselective and proceeds in mild conditions. Due to, the ease in handling and inertness toward other functional groups, this method is recommended when chemoselectivity is crucial. Full investigation of ring opening of diverse classes of epoxides, with this reagent, are under way.

EXPERIMENTAL

The epoxides used were prepared from the corresponding alkenes and *m*chloroperbenzoic acid in CHCl₃.^[4] ¹H and ¹³C NMR spectra were recorded with a Bruker AC-300 spectrometer with CDCl₃ as solvent, employing Me₄Si as internal standard (δ : 0.00), *J* values are given in Hz. Mass spectra were obtained by direct injection of the sample as chloroform solution by using Shimadzu GCQP 1000 mass spectrometer operating at an ionizing electron energy of 70 eV. Elemental analysis was carried out in our laboratories with a Colleman Analyser. Melting point (uncorrected) was obtained with a Thomas Hoover apparatus. Preparative thin layer chromatography (*p*-tlc) was performed on a 20 × 20 cm glass coated with silica gel 60 F₂₅₄ (0.50 mm).

General Procedure for Reaction of $ZnI_2/NaCNBH_3$ with α -Chloroketones, β -Chlorohydrins and Epoxides

To a solution of α -chloroketone, β -chlorohydrin or epoxide (2 mmol) in ethylene dichloride (10 mL) at room temperature were added zinc iodide (3 mmol) and sodium cyanoborohydride (15 mmol). The reaction mixture was stirred at room temperature or refluxed and, after completion of the reaction (monitored by tlc), the mixture was then cooled and poured onto a solution of 6N HCl (40 mL). Lastly, the mixture was extracted with dichloromethane (20 mL) and the organic extract was washed with water (15 mL), dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The residue obtained was chromatographed using hexane–ethyl acetate (4:1) as eluent.

General Procedure for the Preparation of α -Chloroketones

To a magnetically stirred cold solution of corresponding aromatic compound (2 mmol) and chloroacetyl chloride (2.5 mmol) in carbon disulfide (10 mL) was added AlCl₃ (15 mmol) in small portions. The reaction mixture was then refluxed for 30 min, cooled to room temperature, and carefully poured onto ice. The product was extracted into dichloromethane (25 mL) and

899

| | NTS |
|--|-----|
|--|-----|

Finkielsztein et al.

then washed with water (15 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude product was purified by p-tlc using hexane-ethyl acetate (4:1) as eluent.

2-Chloro-1-(2,2,6-trimethylindan-5-yl)ethan-1-one 1

White solid, m.p. $61-63^{\circ}$ C. ¹H NMR δ 1.14 (s, 6H), 2.49 (s, 3H), 2.72 (s, 4H), 4.64 (s, 2H), 7.09 (s, 1H), 7.43 (s, 1H). ¹³C NMR δ 22.3, 29.3, 41.1, 47.7, 48.4, 48.6, 125.8, 129.9, 133.2, 138.6, 141.9, 149.8, 194.5. MS (*m*/*z*): 236 (9, M⁺), 237 (2, M⁺ + 1), 238 (3, M⁺ + 2), 187 (100, M⁺ – CH₂Cl). Calcd. for C₁₄H₁₇ClO: C, 71.03; H, 7.24; Cl, 14.98. Found: C, 71.24; H, 7.18; Cl, 15.09.

2-Chloro-1-(2,2,6-trimethyl-5-yl)ethan-1-ol 3

Oil. ¹H NMR δ 1.11 (s, 3H), 1.15 (s, 3H), 2.30 (s, 3H), 2.60–2.69 (m, 4H), 3.59 (dd, *J*: 9.2, *J*: 11.4, 1H), 3.68 (dd, *J*: 3.0, *J*: 11.4, 1H), 5.07 (dd, *J*: 3.0, *J*: 9.2, 1H), 6.96 (s, 1H), 7.31 (s, 1H). ¹³C NMR δ 19.7, 29.5, 40.9, 48.1, 50.8, 71.8, 122.3, 127.5, 133.1, 136.3, 142.5, 144.4. MS (*m*/*z*): 238 (11, M⁺), 239 (2, M⁺ + 1), 240 (4, M⁺ + 2), 189 (100, M⁺ – CH₂Cl). Calcd. for C₁₄H₁₉ClO: C, 70.43; H, 8.02; Cl, 14.85. Found: C, 70.39; H, 7.88; Cl, 15.02.

2-(2,2,6-Trimethylindan-5-yl)ethan-1-ol 4

Oil. ¹H NMR δ 1.15 (s, 6H), 2.30 (s, 3H), 2.68 (s, 4H), 2.86 (t, *J*: 6.8, 2H), 3.82 (t, *J*: 6.8, 2H), 6.92 (s, 2H). ¹³C NMR δ 20.1, 29.5, 29.6, 37.1, 40.8, 48.1, 63.4, 126.6, 127.3, 134.6, 142.0, 142.6. MS (*m*/*z*): 204 (19, M⁺), 205 (3, M⁺ + 1), 173 (100, M⁺ - CH₂OH). Calcd. for C₁₄H₂₀O: C, 82.30; H, 9.87. Found: C,82.46; H, 9.73.

5-(2-Iodoethyl)-2,2,6-trimethylindane 5

Oil. ¹H NMR δ 1.13 (s, 6H), 2.27 (s, 3H), 2.64 (s, 2H), 2.67 (s, 2H), 3.11– 3.19 (m, 2H), 3.23–3.29 (m, 2H), 6.95 (s, 1H), 6.98 (s, 1H). ¹³C NMR δ 5.1, 19.8, 29.5, 39.1, 40.9, 48.1, 48.2, 126.0, 127.5, 134.0, 137.6, 142.3, 143.2. MS (*m*/*z*): 314 (10, M⁺), 315 (2, M⁺ + 1), 187 (100, M⁺ – I). Calcd. for C₁₄H₁₉I: C, 53.52; H, 6.10; I, 40.39. Found: C, 53.45; H, 6.22; I, 40.65.

Copyright @ Marcel Dekker, Inc. All rights reserved

Marcel Dekker, Inc.

270 Madison Avenue, New York, New York 10016

| ORDER | REPRINTS |
|-------|----------|
| | ļ |

ZnI₂/NaCNBH₃ as Efficient Reagent

5-Ethyl-2,2,6-trimethylindane 6

Oil. ¹H NMR ó 1.15 (s, 6H), 1.21 (t, *J*: 7.5, 3H), 2.28 (s, 3H), 2.60 (q, *J*: 7.5, 2H), 2.68 (s, 4H), 6.96 (s, 1H), 6.98 (s, 1H). ¹³C NMR δ 15.3, 19.8, 26.9, 29.7, 40.8, 48.2, 124.9, 127.0, 134.0, 140.7, 141.6, 141.9. MS (*m*/*z*): 188 (53, M⁺), 189 (8, M⁺ + 1), 173 (81, M⁺ - CH₃), 159 (100, M⁺ - CH₂CH₃). Calcd. for C₁₄H₂₀: C, 89.30; H, 10.17. Found: C, 89.17; H, 10.81.

ACKNOWLEDGMENTS

This research was supported by grants from Consejo Nacional de Investigaciones Científicas (CONICET) and Universidad de Buenos Aires.

REFERENCES

- 1. Palermo, J.A.; Rodríguez Brasco, M.F.; Spagnuolo, C.; Seldes, A.M. Illudalane sesquiterpenoids from the soft coral *Alcyonium paessleri*: the first natural nitrate esters. J. Org. Chem. **2000**, *65* (15), 4482–4486.
- Lau, C.K.; Dufresne, C.; Bélanger, P.C.; Piétré, S.; Scheigetz, J. Reductive deoxygenation of aryl aldehydes and ketones and benzylic, allylic, and tertiary alcohols by ZnI₂-NaCNBH₃. J. Org. Chem. **1986**, *51* (15), 3038–3043.
- Alesso, E.N.; Bianchi, D.E.; Finkielsztein, L.M.; Lantaño, B.; Moltrasio, G.Y.; Aguirre, J.M. Reductive deoxygenation of indan-1-ols by ZnI₂/NaCNBH₃. Tetrahedron Lett. **1995**, *36* (19), 3299–3302.
- Fieser, L.; Fieser, M. Reagents for Organic Synthesis; Wiley: New York, 1967; Vol. 1, 135.

Received in the USA October 3, 2003



901

Request Permission or Order Reprints Instantly!

Interested in copying and sharing this article? In most cases, U.S. Copyright Law requires that you get permission from the article's rightsholder before using copyrighted content.

All information and materials found in this article, including but not limited to text, trademarks, patents, logos, graphics and images (the "Materials"), are the copyrighted works and other forms of intellectual property of Marcel Dekker, Inc., or its licensors. All rights not expressly granted are reserved.

Get permission to lawfully reproduce and distribute the Materials or order reprints quickly and painlessly. Simply click on the "Request Permission/ Order Reprints" link below and follow the instructions. Visit the <u>U.S. Copyright Office</u> for information on Fair Use limitations of U.S. copyright law. Please refer to The Association of American Publishers' (AAP) website for guidelines on <u>Fair Use in the Classroom</u>.

The Materials are for your personal use only and cannot be reformatted, reposted, resold or distributed by electronic means or otherwise without permission from Marcel Dekker, Inc. Marcel Dekker, Inc. grants you the limited right to display the Materials only on your personal computer or personal wireless device, and to copy and download single copies of such Materials provided that any copyright, trademark or other notice appearing on such Materials is also retained by, displayed, copied or downloaded as part of the Materials and is not removed or obscured, and provided you do not edit, modify, alter or enhance the Materials. Please refer to our <u>Website</u> User Agreement for more details.

Request Permission/Order Reprints

Reprints of this article can also be ordered at http://www.dekker.com/servlet/product/DOI/101081SCC120028362