This article was downloaded by: [Temple University Libraries] On: 20 November 2014, At: 14:26 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

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

Synthesis of Unnatural (R)-Malates from L-Tartrates

Ho-Sik Rho^a

^a Pharmaceutical & Health Science Research Institute, Pacific Corporation, Yongin-Si, Kyounggi-do, 449-900, Korea Published online: 20 Aug 2006.

To cite this article: Ho-Sik Rho (1998) Synthesis of Unnatural (R)-Malates from L-Tartrates, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 28:5, 843-847, DOI: 10.1080/00032719808006482

To link to this article: http://dx.doi.org/10.1080/00032719808006482

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

SYNTHESIS OF UNNATURAL (R)-MALATES FROM L-TARTRATES

Ho-Sik Rho

Pharmaceutical & Health Science Research Institute, Pacific Corporation, Yongin-Si, Kyounggi-do 449-900, Korea.

Abstract: The cyclic thionocarbonates of L-tartrates were cleanly converted to (R)-malates by treating with magnesium iodide or magnesium and iodine.

Optically pure malic acid and its derivatives are useful chiral synthons in the synthesis of natural products.¹ While the natural L-malic acid is readily available, the unnatural (R)-isomer is more difficult to obtain. Several synthetic methods for their preparation have been developed which include reduction of cyclic sulfates,² ring opening of cyclic sulfites³ or cyclic carbonates⁴ and subsequent reduction of the resulting iodohydrins, free radical deoxygenation of cyclic thionocarbonates.⁵ In the literature, the cyclic thionocarbonates are easily converted to thiolcarbonates by treating with tetrabutylammonium bromide.⁶ Here we wish to report a convenient one-step procedure for the synthesis of (R)-malates based on the ring opening of the cyclic thionocarbonates of L-tartrates by using magnesium iodide or magnesium and iodine (Scheme 1).



Table 1. Ring opening of the cyclic thionocarbonates of L-tartrates by using MgI₂ or Mg/I₂ in acetonitrile.

Entry	Substrate	Condition	^a Time (min)	Product ^b	Yield(%) ^c
1	1a	Α	30	2a	60
2	1b	Α	20	2b	85
3	1b	В	35	2b	78
4	1c	Α	30	2c	89
5	1c	В	40	2c	80

^a A : MgI₂ (2 equiv.), CH₃CN, reflux ; B: Mg (2 equiv.), I₂ (2 equiv.), CH₃CN, reflux ^bThe specific rotations $[\alpha]_D^{25}$ values ; **2a:** +8.9 (*c*, 0.12, EtOH), lit.⁵ +9.5 (*c*, 2.20, EtOH); **2b:** +9.4 (*c*, 0.14, EtOH), lit.⁴ +9.7 (*c*, 1.25, EtOH); **2c:** +11.2 (*c*, 0.18, EtOH), lit.³ +11.6 (*c*, 2.56, EtOH). ^cThe yields are isolated ones.

The results are summarized in Table I. L-Tartrates were transformed to the corresponding cyclic thionocarbonates by reaction with thiophosgene. The cyclic thionocarbonate **1a** was reacted with magnesium iodide (2 equiv.) in refluxing acetonitrile for 30 min to afford an unnatural dimethyl (*R*)-malate (**2a**)⁵, $[\alpha]_{D}^{2^{5}}$

+8.9 (*c*, 0.12, EtOH) in 60% yield (Method A, entry 1, in Table 1). None of iodo malate or thiolcarbonate was detected in the crude product. It is presumed that the initial ring opening product is iodo malate, which is subsequently converted to enolate by nucleophilic displacement of iodide ion. When the cyclic thionocarbonate **1b** was reacted in the same condition, diethyl (*R*)-malate (**2b**)^{2, 3, 4}, $[\alpha]_D^{25}$ +9.4 (*c*, 0.14, EtOH) was obtained as the sole product (entry 2). The cyclic thionocarbonate **1b** was also converted to diethyl (*R*)-malate (**2b**) with magnesium (2 equiv.) and iodine (2 equiv.) in refluxing acetonitrile (Method B, entry 3). Treatment of the cyclic thionocarbonate **1c** with magnesium iodide provided diisopropyl (*R*)-malate (**2c**)³, $[\alpha]_D^{25}$ +11.2 (*c*, 0.18, EtOH) in 89% yield (entry 4). Also, diisopropyl (*R*)-malate (**2c**) was synthesized from the cyclic thionocarbonate **1c** with magnesium and iodine condition (entry 5). However, the reaction of the cyclic thionocarbonate **1b** with magnesium bromide did not give diethyl (*R*)-malate (**2b**). Only small amount of bromo malate was obtained.

In summary, unnatural (*R*)-malates, versatile chiral building blocks for the synthesis of natural product, were synthesized from the natural L-tartrates.

Experimental Section

General procedures

Method A : To a stirred solution of the cyclic thionocarbonate **1a** (200 mg, 0.91 mmol) in acetonitrile (5ml) under nitrogen atmosphere was added MgI₂ (505 mg, 1.82 mmol) and the reaction mixture was heated at reflux for 30 min. The mixture was quenched with saturated Na₂S₂O₃ solution (10ml) and then extracted with CH₂Cl₂ (2X20mL). The organic layer was dried over anhydrous MgSO₄ and evaporated *in vacuo*. The crude product was separated by SiO₂ column chromatography (EtOAc/hexanes 1 : 1, $R_f = 0.52$) to give **2a** (88 mg, 60%).

Method B : To a slurry of magnesium (30 mg, 1.62 mmol) in acetonitrile (4ml) under nitrogen atmosphere was added I₂ (411 mg, 1.62 mmol) and the cyclic thionocarbonate **1b** (200 mg, 0.81 mmol) in acetonitrile (1ml). The reaction mixture was heated at reflux for 35 min. The mixture was quenched with saturated Na₂S₂O₃ solution (10ml) and then extracted with CH₂Cl₂ (2X20mL). The organic layer was dried over anhydrous MgSO₄ and evaporated *in vacuo*. The crude product was separated by SiO₂ column chromatography (EtOAc/hexanes 1 : 1, R_f = 0.56) to give **2b** (120 mg, 78%).

Acknowledgement. The author is grateful to thank Dr. Y. H. Joo, Miss S. M. Ahn, and Professor S. K. Kang, for valuable discussions during the preparation of this manuscript.

References and Notes

- (a) Keck, G. E.; Andrus, M. B.; Romer, D. R. J. Org. Chem. 1991, 56, 417
 -420. (b) Bellamy, F. D.; Bondoux, M.; Dodey, P. Tetrahedron Lett. 1990, 31, 7323-7326. (c) Ohta, T.; Shiokawa, S.; Sakamoto, R. ; Nozoe, S. Tetrahedron Lett. 1990, 31, 7329-7332.
- 2. Gao, Y.; Sharpless, K. B. J. Am. Chem. Soc. 1988, 110, 7538-7539.
- 3. Gao, Y.; Zepp, C. M. Tetrahedron Lett. 1991, 32, 3155-3158.
- Kang, S. K.; Park, D. C.; Rho, H. S.; Yoon, S. H.; Shin, J. S. J. Chem. Soc. Perkin Trans 1 1994, 3513-3514.
- 5. Alpegiani, M.; Hanessian, S. J. Org. Chem. 1987, 52, 278-279.
- 6. (a) Ko, S. Y. J. Org. Chem. 1995, 60, 6250-6251. (b) Jandu, K. S.; Selwood,
 D. L. J. Org. Chem. 1995, 60, 5170-5173.

7. Reduction of α-haloketones with lithium iodide and boron trifluoride is known. see, Townsend, J. M.; Speneer, T. A. *Tetrahedron Lett.* **1971**, 137-140.



When the reaction was performed in the presence of D_2O , α -deutrio malate was obtained.

(Received in the UK 24th July 1997)

Downloaded by [Temple University Libraries] at 14:26 20 November 2014