Tetrahedron Letters, Vol.32, No.27, pp 3155-3158, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

A Practical Synthesis of D-Malate Esters from L-Tartrate Esters

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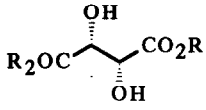
Abstract: D-malate esters were synthesized in one-pot from L-tartrate esters in 70-80% overall yields via the corresponding tartrate cyclic sulfites.

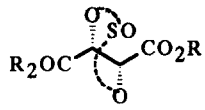
Enantiomerically pure malic acid and its derivatives are valuable chiral starting materials in organic synthesis.[1] While the natural L-malic acid, also known as apple acid, is readily available, the unnatural D-isomer is more difficult to obtain. Due to their usefulness as chiral synthons, extensive efforts have been directed to the development of methods for the preparation of enantiomerically pure malic acid and its derivatives, especially the D-isomers.[2] Several methods based on the relatively inexpensive L-tartaric acid have been developed for the production of D-malic acid.[3] However, these methods involve either multistep transformations or expensive and hazardous reagents. We report here a practical one-pot synthesis of D-malate esters from L-tartrate esters via the corresponding tartrate cyclic sulfites. The results are summarized in the Table.

L-Tartrate esters **1a-c** were transformed quantitatively to the corresponding cyclic sulfites **2a-c** by reaction with a slight excess of thionyl chloride.[4] This reaction was best performed without base and solvent. The resulting cyclic sulfites could either be used without further purification or purified by simple vacuum distillation. Except being used as starting materials for the preparation of tartrate cyclic sulfates, these tartrate cyclic sulfites have seldom been used in organic synthesis.[3c] Although cyclic sulfites are less reactive than the cyclic sulfate counterparts, we have found that they can react with some good nucleophiles such as LiBr, LiCl, NaN_3, NH_4SCN, NaOAc in polar aprotic solvents to give the β-substituted malates.[5] In the D-malate synthesis, cyclic sulfites **2a-c** reacted with 1.5-2.0 equiv of LiBr or LiCl (use of NaI resulted in some elimination products) in a polar aprotic solvent (e.g. acetone, DME, THF, or DMF) to give intermediates **3a-c**. Without isolation, **3a-c** were reduced with pre-washed zinc powder (2.5-3 equiv) in an aqueous-organic solvent mixture to give the malates **4a-c** after a simple workup (Table).[6] Alternatively, the reduction could be performed by catalytic hydrogenation. For example, **3b** or **3c** was reduced to **4b** or **4c** at 15-50psi of H_2 in the presence of Pd/C and a base, MgO, at room temperature (entry 5 or 3). Besides Pd/C, Raney-Ni could also be used (entry 6). The whole process could be performed in one-pot from L-tartrates without isolation of any intermediates (entries 1-3, see typical procedures 1-2). The overall yield of D-malates was usually in the range of 70-80%. No loss of optical purity was observed in the products as shown by the ^1H NMR analysis of the corresponding Mosher's esters of the D-malates.

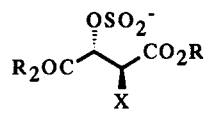
Table. Synthesis of D-Malate Esters **4a-c** from L-Tartrate Esters **1a-c**.



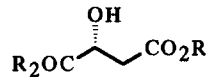
1a, R = Me
1b, R = Et
1c, R = i-Pr



2a-c



3a-c, X = Br, or Cl



4a-c

Entry	Starting compds	Opening condition	Reduction condition	Overall yield (%)[a]
1	**1a**	LiBr (2 eq.), 80 °C, 5 h.	DME, Zn (2.5 eq.), 80 °C, 5 h	38[b]
2	**1b**	LiBr (2 eq.), acetone, 50 °C, 7 h.	Zn (2.5 eq.), 50 °C, H_2O (cat.), 2 h.	70
3	**1c**	LiBr (1.5 eq.), acetone, 50 °C, 12 h.	Pd/C, MgO (3.5 eq.), H_2O H_2 (15 psi), 25 °C, 5.5 h.	80
4	**2b**	LiBr (1.5 eq.), DME, 80 °C, 2 h.	Zn (3.0 eq.), H_2O, 80 °C, 1 h.	82
5	**2b**	LiBr (1.5 eq.), acetone, 50 °C, 6 h.	Pd/C, MgO (3 eq.), H_2O, H_2 (15-40 psi), 25 °C, 2 h.	74
6	**2b**	LiBr (1.5 eq.), DME, 70 °C, 12 h.	Raney-Ni (10 g, 50%aq), MeOH, H_2 (50 psi), 25 °C, 5 h.	70
7	**2c**	LiBr (1.5 eq.), DME, 65 °C, 2 h.	Zn (3 eq.), H_2O, 65 °C, 2 h.	82
8	**2c**	LiBr (1.5 eq.), THF, 60 °C, 16 h.	Zn (2 eq.), H_2O, 60 °C, 2 h.	82
9	**2c**	LiCl (2 eq.), DMF, 70 °C, 3 h.	Zn (3 eq.), H_2O, 70 °C, 3 h.	67

a. Yields were isolated yields. b. low yield was due to the high water solubility of D-dimethyl malate.

In summary, the present method offers a simple and practical synthesis of D-malate esters from L-tartrates. By the same method, L-malates can be obtained from D-tartrates. Since malate esters can be readily hydrolyzed to the corresponding malic acid, the present procedure also provides a practical synthesis of either D- or L-malic acid from L- or D-tartrates.

The followings are two typical procedures.

(1) By zinc reduction: Thionyl chloride (8.1 mL, 110 mmol) was added dropwise to L-(+)-diethyl tartrate (20.6 g, 100 mmol) , followed by 10 drops of dry DMF. The solution was slowly heated to ca. 50 °C and stirred while the HCl evolved was swept away by a stream of nitrogen. After one hour, the solution was cooled with ice water and diluted with acetone (100 mL). LiBr (17.4 g, 200 mmol) was added slowly in portions with stirring. The resulting mixture was then heated at 45-50 °C for 7 h. Zinc powder (16.4 g, 250 mmol), washed with 10% HCl aq. and dried, was added, followed by 0.5 mL of water (if purified cyclic sulfite was employed as the starting material, the same amount of water as to that of organic solvent was added). The mixture was stirred at 45-50 °C for 2 h. After cooling, the mixture was filtered through Celite®. The residue was washed with water (2x10 mL) and EtOAc (2x10 mL). The combined filtrates were then acidified with dilute HCl and concentrated under vacuum to remove acetone, and the residual aqueous solution was extracted with EtOAc (3x150 mL). The organic extracts were then washed with brine and dried over $MgSO_4$. After removal of solvent, the crude product was distilled to give D-diethyl malate **4b** (13.3 g, 70%). $[\alpha]^{25}_D$ +10.5 (c 2.05, EtOH).

(2) By catalytic hydrogenation: Thionyl chloride (8.1 mL, 110 mmol) was added dropwise to L-(+)-diisopropyl tartrate (23.4 g, 100 mmol) , followed by 10 drops of dry DMF. The solution was slowly heated to ca. 50 °C and stirred while the HCl evolved was swept away by a stream of nitrogen. After one hour, the solution was cooled with ice water and diluted with acetone (200 mL). LiBr (13.0 g, 150 mmol) was added slowly in portions with stirring. The resulting mixture was then heated at 50 °C for 12 h. The mixture was cooled and transferred to a hydrogenation flask containing 10% Pd/C (3.5 g) and MgO (14.0 g, 350 mmol) in 150 mL of water. The mixture was hydrogenated at ambient temperature under 15 psi of H_2 for 5.5 h. The mixture was then filtered and the filtrates were acidified with dilute HCl and concentrated under vacuum to remove acetone. After workup as above, the crude product was distilled at 76-80 °C/0.4 mmHg to give D-diisopropyl malate **4c** (17.4 g, 80 %). $[\alpha]^{25}_D$ +11.6 (c 2.56, EtOH).

Acknowledgement: We thank Dr. Robert L. Bratzler and Professor K. Barry Sharpless for encouragement.

REFERENCES AND NOTES:

1. For recent examples, see: (a) Keck, G. E.; Andrus, M. B.; Romer, D. R. *J. Org. Chem.* **1991**, *56*, 417. (b) Bellamy, F. D.; Bondoux, M.; Dodey, P. *Tetrahedron Lett.* **1990**, *31*, 7323. (c) Ohta, T.; Shiokawa, S.; Sakamoto, R.; Nozoe, S. *Tetrahedron Lett.* **1990**, *31*, 7329.
2. (a) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166. (b) Chibata, I. *Pure Appl. Chem.* **1978**, *50*, 667. (c) Yamamoto, K.; Tosa, T.; Yamashita, K.; Chibata, I. *Eur. J. Appl. Microbiol. Biotechnol.* **1976**, *3*, 169. (d) Henrot, S.; Larchevêque, M.; Petit, Y. *Synth. Commun.* **1986**, *16*, 183.
3. (a) Hungerbühler, E.; Seebach, D.; Wasmuth, D. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 958. (b) Alpegiani, M.; Hanessian, S. *J. Org. Chem.* **1987**, *52*, 278. (c) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538. (d) Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, *30*, 2945.
4. Schiller, E. *Chem. Ber.* **1909**, *42*, 2017.
5. (a) Gao, Y. unpublished results. (b) also see: Lohray, B. B.; Ahuja, J. R. *J. Chem. Soc., Chem.Commun.* **1991**, 95.
6. For a review on reduction of organic halides, see: Pinde , A. R. *Synthesis* **1980**, 425.

(Received in USA 19 March 1991)