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Facile synthesis of enantiopure (*R*)-malates

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Abstract

(*R*)-Malates were synthesized from cyclic thionocarbonates of (*R*,*R*)-tartrates by reacting with hypophosphorous acid in high isolated yields. © 1999 Elsevier Science Ltd. All rights reserved.

Enantiomerically pure malic acids and its derivatives are useful chiral building blocks in the synthesis of natural products.[1] The unnatural (*R*)-malates have been known to be more difficult to obtain, whereas the naturally occurred (*S*)-malates are readily available. Previous methods for preparing the enantiomerically pure (*R*)-malates include multistep synthesis[2] from chiral starting material and manipulation of (*R*,*R*)-tartrates.[3] Although the methods that convert readily available (*R*,*R*)-tartrates into (*R*)-malates are the most effective, they usually involve either multistep synthesis or expensive and toxic chemicals. We wish to report here a practical and convenient process for the conversion of (*R*,*R*)-tartrates into (*R*)-malates via their cyclic thionocarbonate derivatives using an ecologically compatible hypophosphorous acid.[4]

(*R*,*R*)-Tartrates were transformed into their cyclic thionocarbonates by reacting with thiocarbonyldiimidazole or thiophosgene in 75–85% yields.[3e,5] The cyclic thionocarbonate of dibutyl (*R*,*R)*-tartrate (**1a**) was treated with 5 equiv. of hypophosphorous acid and 5.5 equiv. of triethylamine in 1,4-dioxane at 80°C in the presence of azobisisobutyronitrile (AIBN) for 30 min to afford dibutyl (*R*)-malate (**2a**) in 35% yield along with unpredictable products (Table 1, entry 1).[6] We thought that triethylamine might play a role in decreasing the yield of (*R*)-malate. Several controlled reactions were carried out without triethylamine. Without the base, cyclic thionocarbonate of dibutyl (*R,R)*-tartrate (**1a**) could be converted into dibutyl (*R*)-malate (**2a**) in 91% yield within 1 h (entry 2). The reaction yielded the best result with 3.5 equiv. of hypophosphorous acid in the presence of AIBN at 80°C (entry 3). Diethyl and dimethyl (*R,R*)-tartrates (**1b** and **1c**) were transformed into the corresponding (*R*)-malates (**2b** and **2c**) under the conditions. The optical purity of the products was retained as shown in the ^{1}H NMR analysis with a chemical shift reagent, europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate].[7] It is noteworthy that the high purity of products could be obtained after washing the reaction mixture with aqueous $NaHCO_3$, based on the analysis of the ^{1}H NMR and GC analysis (Scheme 1).

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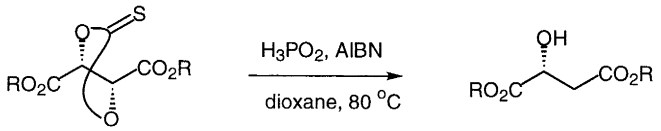
Table 1
Reaction of cyclic thionocarbonates of (*R, R*)-tartarates with H_3PO_2 in 1,4-dioxane at 80°C[a]

Entry	Substrate	H_3PO_2 (equiv.)	Time (h)	Product	Yield (%)[c]
1	**1a**	5.0[b]	0.5	**2a**	35
2	**1a**	5.0	0.5	**2a**	91
3	**1a**	3.5	0.5	**2a**	92
4	**1a**	2.5	1.5	**2a**	84
5	**1a**	1.5	2.0	**2a**	83
6	**1b**	3.5	3.0	**2b**	75
7	**1c**	3.5	1.0	**2c**	70

[a]In the presence of AIBN (0.2 equiv.). [b]In the presence of Et_3N (5.5 equiv.). [c]Isolated yield.



1a: R = ^{n}Bu
1b: R = Et
1c: R = Me

2a: R = ^{n}Bu
2b: R = Et
2c: R = Me

Scheme 1.

In conclusion, the practical process of preparing the enantiomerically pure (*R*)-malates from (*R,R*)-tartrates has been developed. The advantages of the reaction are the usage of inexpensive reagents, easy work-up process capable of carring out on a large scale, and ready availability of enantiomerically pure starting materials.

Typical procedure: A solution of the cyclic thionocarbonate of dibutyl (*R,R*)-tartrate (110 mg, 0.36 mmol), hypophosphorous acid (50% aqueous solution, 0.13 mL, 1.26 mmol), and AIBN (12 mg, 0.072 mmol) in 1,4-dioxane (3 mL) under argon was heated at 80°C for 30 min. The reaction mixture was diluted with CH_2Cl_2 and washed with satd aqueous $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was separated by column chromatography on silica gel (eluent: hexanes/EtOAc, 8:2) to afford 82 mg (92%).

Acknowledgements

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4. Hypophosphorous acid is commercially available from Aldrich. For recent examples using H_3PO_2,see: (a) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1992**, *33*, 5709. (b) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *J. Org. Chem.* **1993**, *58*, 6838. (c) Jang, D. O. *Tetrahedron Lett.* **1996**, *37*, 5367.
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6. Typical reaction conditions for deoxygenation of *S*-methyl xanthates with H_3PO_2, see Ref. 4b.
7. The specific rotation $[\alpha]^{25}_{D}$ values: Compound **2a**: +10.5 (c 1.1, EtOH), **2b**: +11.2 (c 0.95, EtOH) (lit.[3b] +9.7 (c 1.25, EtOH), **2c**: +9.6 (c 2.3, EtOH) (lit.[3e] +9.5 (c 2.20, EtOH).