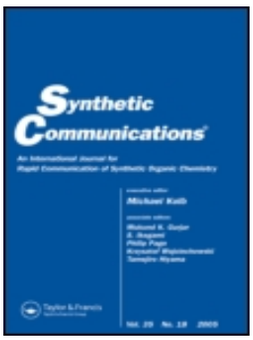

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A Method for Preparation of Unnatural (*R*)-Malic Acid Derivatives with Phenylsilanes

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ABSTRACT

Enantiomerically pure unnatural (*R*)-malic acid derivatives were prepared from (*R*,*R*)-tartrates via their cyclic thionocarbonate derivatives using phenylsilanes in high isolated yields.

Key Words: Radical; Reduction; Malic acid; Phenylsilanes; Cyclic thionocarbonate.

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Enantiomerically pure malic acid and its derivatives have been frequently used as chiral building blocks in natural product synthesis.[1] Although several methods have been reported for the preparation of enantiopure unnatural malic acid derivatives that are less readily available than naturally occurring ones, they usually used either multistep synthesis or expensive and toxic chemicals.[2] We wish to report here an efficient and convenient method for the preparation of enantiomerically pure unnatural malic acid derivatives from (*R*,*R*)-tartrates via their cyclic thionocarbonate derivatives using environmental friendly phenylsilanes. It has been shown that phenylsilanes are cost-effective, ecologically compatible radical hydrogen donors in radical reactions.[3]

When the cyclic thionocarbonate of dibutyl (*R*,*R*)-tartrate (**1a**) prepared from dibutyl (*R*,*R*)-tartrate by reacting with thiocarbonyldiimidazole in 85% yield[4] was treated with 2.0 equiv of diphenylsilane in benzene at 80°C in the presence of azobisisobutyronitrile (AIBN) for 1 h, dibutyl (*R*)-malate (**1b**) was obtained in 93% isolated yield. (Table 1, Entry 1). Higher reaction temperature was required to accomplish the reaction efficiently with 1.5 equiv of diphenylsilane (Entries 2 and 3). We examined various radical initiators to find out suitable initiators for the reaction. It turned out that AIBN is the most suitable initiator among them (Entries 1 and 4–6). Interestingly, when ABCVA (4,4′-azo*bis*-(4-cyanovaleric acid)) was used as an initiator, the compound **1c** that the C=S bond was reduced was obtained (Entry 6). Thionocarbonate derivatives of diethyl and dimethyl (*R*,*R*)-tartrates (**2a** and **3a**) were also transformed into the corresponding (*R*)-malates (**2b** and **3b**) in high isolated yields under the conditions.

Phenylsilane was also very efficient for the radical reduction of thionocarbonates of (*R*,*R*)-tartrates. The results are summarized in Table 2. From the practical point of view, its low boiling point makes it easy to work up the reaction and isolate the desired products.

In conclusion, an efficient and ecologically compatible process for the synthesis of enantiopure (*R*)-malates from their thionocarbonate derivatives of (*R*,*R*)-tartrates has been developed. The advantages of the reaction include using cost-effective reagents and affording easy work-up process capable of carrying out on large scale.

EXPERIMENTAL

Typical procedure for reaction of cyclic thionocarbonates of (*R*,*R*)-tartrates with Ph_2SiH_2: (*R*)-Dibutyl malate (1b): A solution of the cyclic thionocarbonate of dibutyl (*R*,*R*)-tartrate **1a** (80 mg, 0.26 mmol),

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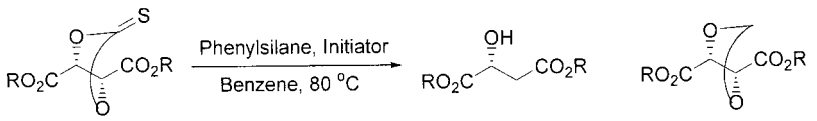

1a: R = Bu
2a: R = Et
3a: R = Me

1b: R = Bu
2b: R = Et
3b: R = Me

1c: R = Bu

Table 1. Reaction of cyclic thionocarbonates of (*R*,*R*)-tartrates with Ph_2SiH_2 in boiling benzene.

Entry	Substrate	Ph_2SiH_2 (equiv)	Initiator[a] (equiv)	Time (min)	Product	Yield (%)[b]
1	**1a**	2.0	AIBN (0.5)	60	**1b**	93
2	**1a**	1.5	AIBN (0.75)	90	**1b**	64 (30)[c]
3	**1a**	1.5	AIBN (0.5)[d]	60	**1b**	96
4	**1a**	2.0	BBPO (0.5)	60	**1b**	65 (32)[c]
5	**1a**	2.0	ABCN (0.5)	60	**1b**	85 (10)[c]
6	**1a**	2.0	ABCVA (0.5)	60	**1c**	47 (52)[c]
7	**2a**	2.0	AIBN (0.75)	90	**2b**	90
8	**3a**	2.0	AIBN (1.0)	110	**3b**	92

[a]ABCN = 1,1′-azo*bis*(cyclohexanecarbonitrile); BBPO = ^{t}butyl benzoylperoxide; ABCVA = 4,4′-azo*bis*(4-cyanovaleric acid).
[b]Isolated yield.
[c]Recovered starting material.
[d]In toluene.

Table 2. Reaction of cyclic thionocarbonates of (*R*,*R*)-tartrates with $PhSiH_3$ in boiling benzene.

Entry	Substrate	$PhSiH_3$ (equiv)	Initiator (equiv)	Time (min)	Product	Yield (%)[a]
1	**1a**	2.0	AIBN (0.4)	50	**1b**	95
2	**2a**	2.0	AIBN (0.6)	70	**2b**	90
3	**3a**	2.0	AIBN (0.75)	90	**3b**	92

[a]Isolated yield.

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Ph_2SiH_2 (97 mg, 0.53 mmol) in benzene (1 mL) under argon was heated to reflux for 5 min, and then AIBN (22 mg, 0.13 mmol in 0.5 mL of benzene) was added through the syringe pump to the reaction mixture for 1 h. The reaction mixture was diluted with CH_2Cl_2 and washed with water. 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, 9:1) to afford 60 mg (93%) of **1b**. oil; $[\alpha]_D^{25}$ +10.5° ($c = 1.1$, EtOH) (lit.[5] +8.0° ($c = 1$, CH_2Cl_2)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, $J = 7$ Hz, 6H), 1.20–1.73 (m, 8H), 2.78–2.84 (m, 2H), 3.24 (d, $J = 5.4$ Hz, 1H), 4.05–4.28 (m, 4H), 4.41–4.56 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 19.1, 30.6, 38.9, 65.0, 65.9, 67.4, 173.6, 173.6. MS m/z (relative intensity) 246 (M^+, 1), 192 (1), 173 (8), 155 (1), 145 (32), 117 (15), 89 (100), 71 (21), 57 (32).

(*R*,*R*)-Dibutyl 1,3-dioxolane-4,5-dicarboxylate (1c): Oil; $[\alpha]_D^{25}$ −0.02° ($c = 1.0$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, $J = 6.9$ Hz, 6H), 1.37–1.41 (m, 4H), 1.62–1.68 (m, 4H), 4.21 (t, $J = 6.5$ Hz, 4H), 4.78 (s, 2H), 4.96 (d, $J = 1.2$ Hz, 1H), 5.21 (d, $J = 1.2$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 19.2, 30.6, 65.8, 77.6, 92.9, 168.4. MS m/z (relative intensity) 274 (M^+, 2), 244 (3), 174 (36), 157 (26), 144 (14), 117 (91), 101 (18), 88 (100), 71 (15), 57 (52).

(*R*)-Diethyl malate (2b): Silica gel column chromatography (eluent: hexanes/EtOAc, 6.5:3.5): oil; $[\alpha]_D^{25}$ +11.2° ($c = 0.95$°, EtOH) (lit.[4b] +9.7° ($c = 1.25$, EtOH)); ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.20–1.42 (m, 6H), 2.79–2.85 (m, 2H), 3.28 (d, $J = 5.3$ Hz, 1H), 4.07–4.56 (m, 5H). MS m/z (relative intensity) 190 (M^+, 1), 161 (1), 145 (11), 127 (4), 117 (99), 99 (6), 89 (41), 71 (100), 55 (3).

(*R*)-Dimethyl malate (3b): Silica gel column chromatography (eluent: hexanes/EtOAc, 5.5:4.5): oil; $[\alpha]_D^{25}$ +9.6° ($c = 2.3$, EtOH) (lit.[4e] +9.5° ($c = 2.20$, EtOH)); ^{1}H NMR ($CDCl_3$) δ 2.81–2.87 (m, 2H), 3.40 (d, $J = 5.1$ Hz, 1H), 3.72 (s, 3H), 3.82 (s, 3H), 4.45–4.60 (m, 1H). MS m/z (relative intensity) 162 (M^+, 1), 131 (6), 113 (5), 103 (100), 85 (2), 71 (89), 61 (39), 55 (3).

Typical procedure for reaction of cyclic thionocarbonates of (*R*,*R*)-tartrates with $PhSiH_3$: (*R*)-Dibutyl malate (1b): A solution of the cyclic thionocarbonate of dibutyl (*R*,*R*)-tartrate **1a** (100 mg, 0.33 mmol), $PhSiH_3$ (81 μL, 0.66 mmol) in benzene (1 mL) under argon was heated to reflux, and then AIBN (21 mg, 0.13 mmol in 0.5 mL of benzene) was added through the syringe pump to the reaction mixture for 50 min. The reaction mixture was diluted with CH_2Cl_2, washed with water, and dried over anhydrous $MgSO_4$. After filtration and evaporation, the residue was separated by silica gel column chromatography (eluent: hexane/EtOAc, 9:1) to afford 77 mg (95%) of **1b**.

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