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Enantioselective Synthesis of α-Aryl Thioglycolic Acid Derivatives

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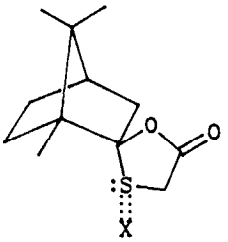
Summary: An enantioselective synthesis of α-aryl substituted thioglycolic acid from thioglycolic acid via a Pummerer reaction employing (1R)-(+)-camphor as chiral auxiliary is described.

Optically active α-aryl thioglycolic acids had been prepared from the corresponding optically active α-arylglycolic acids with inversion of configuration at C_2.[1] Recently, we have reported an enantioselective alkylation of α-mercaptoacetic acid via the enolate of 1,3-oxathiolan-5-one 1[2]. Herein we wish to report substitution reaction at C_4 of 1,3-oxathiolan-5-one 1 with reverse polarity.

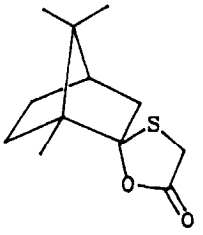
Sulfoxides bearing at least one α-hydrogen atom, when treated with an electrophilic reagent, will undergo a facile rearrangement and give the corresponding α-functionalized sulfides[3]. It is known that the formation of a sulfenium ion intermediate is responsible for such transformation[4]. Therefore formation of sulfenium ion intermediate in the presence of aromatic compound would lead to an α-aryl substituted sulfides[5].

When 1 was treated with *m*-chloroperoxybenzoic acid, a single S-oxide 1,3-oxathiolan-5-one was obtained.[6] Based on our previous experience[2] the stereochemistry of this S-oxide 1,3-oxathiolan-5-one was temporally assigned as **2**. Pummerer rearrangement of **2** using 2 eq of Ac_2O in CH_2Cl_2 and in the presence of excess aromatic compound gave a 79% yield of **3a** and **3b** (ratio 20:1) with no sign of expected aryl substituted product. However, treatment of **2** using 2.2 eq of trifluoroacetic anhydride in an 1:1 mixture of CH_2Cl_2 and aromatic compound afforded the corresponding 4-substituted 1,3-oxathiolan-5-one **4** in good yield. The major product presumably arised from an attack of aromatic compound from the less hindered face of the sulfenium ion intermediate. Yields and diastereoselectivities were summarized in the following table. Bromobenzene and chlorobenzene were unreactive under this reaction condition due to their low reactivity toward electrophilic substitution.[7] An attempt using TMSOTf to improve this reaction was fruitless. McIntosch and coworker reported that C_4-aryl substitution on S-oxide-2,2-dialkyl-1,3-oxathiolan-5-ones **5** through a Pummerer rearrangement was unsuccessful.[5b] They reasoned this may be ascribed to the steric hinderance imparted by the C_2 gem substitution and (or) the instability of the lactone function to the strongly acidic conditions of the Pummerer rearrangement. However, C_4-aryl substitution on 1,3-oxathiolan-5-one **1** through a Pummerer rearrangement could be achieved easily except for deactivated aromatic compounds.

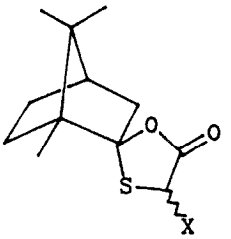


1 X = lone pair electron

2 X = O



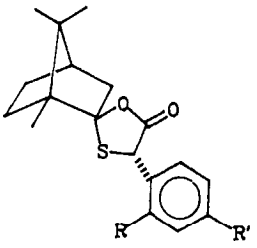
1'



3a X = α -O-C(=O)-CH_3

3b X = β -O-C(=O)-CH_3

3c X = O-C(=O)-CF_3



4a R = R' = H

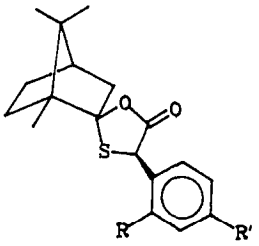
o-4b R = OCH_3 , R' = H

p-4b R = H , R' = OCH_3

o-4c R = CH_3 , R' = H

p-4c R = H , R' = CH_3

4d R = R' = OCH_3



4a' R = R' = H

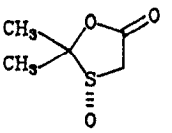
o-4b' R = OCH_3 , R' = H

p-4b' R = H , R' = OCH_3

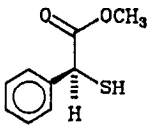
o-4c' R = CH_3 , R' = H

p-4c' R = H , R' = CH_3

4d' R = R' = OCH_3



5



6

Table: Asymmetric Pummerer Reaction of 1,3-oxathiolan-5-one 2

entry	aromatic solvent	product (ratio)	yield
1	benzene	4a (89.4%) + 4a' (10.6%)	75%
2	anisole	o-4b (36.6%) + p-4b (58.7%) o-4b' (2.9%) + p-4b' (1.8%)	79%
3	toluene	o-4c (15.7%) + p-4c (78.3%) o-4c' (6.0%)	75%
4	1,3-dimethoxy benzene	4d	63%

The facial differentiated substitution was controlled by the two different alkyl groups at C_2 of the 1,3-oxathiolan-5-one 1.

Methanolysis of 4a (78% optical purity) in refluxing methanol and the presence of anhydrous hydrochloric acid for 10 hours afforded methyl *α*-phenylthioglycolate 6 in 98% yield and recovered camphor. The optical rotation $[\alpha]_D^{23}$ for compound 6 is 85° (c=2, 95% EtOH). The reported $[\alpha]_D^{25}$ for a sample of (S)-methyl *α*-phenylthioglycolate is 126° (c=2, 95% EtOH)[1]. Therefore the configuration of the chiral center in 6 is an S configuration. The stereochemical assignments for compounds 4 were confirmed by this chemical correlation.

In a typical experiment, a solution of 1 (2.26g, 10 mmol) in dichloromethane (15 ml) was dropwise added *m*-CPBA solution (10 mmol in 10 ml of dichloromethane) during a period of 30 min at -78°C. The mixture was stirred at -78°C for an additional hour, then solid sodium bisulfite (0.21g) was added. The resulting mixture was stirred for 20 min then was diluted with dichloromethane (30 ml) and washed with saturated aqueous sodium bicarbonate solution until the aqueous washing was slightly basic. The organic layer was dried and concentrated *in vacuo*. Chromatographic purification (silica gel; ethyl acetate-hexanes 1:4) of the residue afforded S-oxide 2 (2.19g, 91%). To a stirred solution containing S-oxide 2 (0.5 mmol), dichloromethane (2 ml) and aromatic compound (2 ml) was dropwise added trifluoroacetic anhydride (0.15 ml, 1.1 mmol) at ice-bath temperature. The mixture was stirred at room temperature for 8 to 12 hr, then was diluted with ethyl acetate (15 ml) and neutralized with saturated aqueous sodium bicarbonate solution. After washed with water and brine, the organic layer was dried and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel; ethyl acetate-hexanes 1:10) provided compounds 4.[8] The ratio of the diastereoisomers in each run was determined by HPLC analysis and/or their 400 MHz ^{1}H NMR spectrum.

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References and Notes

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6. This S-oxide could also be obtained from the oxidation of a mixture of 1 and its diastereomer 1' by *m*-CPBA in CH_2Cl_2 at -78°C followed by flash column chromatography.

2 IR (KBr) ν 1780, 1232, 1187, 1067 cm^{-1}. ^1H NMR δ 0.89 (s, 3H), 0.91 (s, 3H), 1.06 (s, 3H), 1.21~1.25 (m, 1H), 1.65~1.79 (m, 3H), 1.98 (t, J=4.2Hz, 1H), 2.03~2.08 (m, 1H), 2.58 (d, J=14.7Hz, 1H), 3.54 (d, J=16.9Hz, 1H), 3.85 (d, J=16.9Hz, 1H). $[\alpha]_D^{27}$ +27° (C=2.55, $CHCl_3$).

7. In these two reactions only Pummerer product **3c** was obtained. Compound **3c** tends to decompose on standing at room temperature or during purification. **3c** MS (EI, m/z, rel. intensity) 338 (M , 5); ^1H NMR(90 MHz) δ 0.88 (s, 3H), 0.91(s, 3H), 1.02(s, 3H), 1.13~1.45 (m, 1H), 1.50~2.20 (m, 5H), 2.54~2.83 (m, 1H), 6.39 (s, 1H, minor isomer, 36%). 6.47 (s, 1H, major isomer 64%).

8. **4a** IR (neat) ν 1765 cm^{-1}; ^1H NMR δ 0.92 (s, 3H), 0.97 (s, 3H), 1.08 (s, 3H), 1.13~1.20 (m, 1H), 1.55~1.87 (m, 3H), 1.83 (t, J=4Hz, 1H), 1.98 (d, J=14.3Hz, 1H), 2.62~2.69 (m, 1H), 5.02 (s, 1H), 7.30~7.47 (m, 5H); $[\alpha]_D^{23}$ -11.45° (C=2, $CHCl_3$). **4a'** IR (KBr) ν 1760 cm^{-1}; ^1H NMR δ 0.99 (s, 3H), 1.03 (s, 3H), 1.14 (s, 3H), 1.26 (d, J=12.6Hz, 1H), 1.43 (dd, J=13.8, 2.1Hz, 1H), 1.74~1.78 (m, 3H), 2.23~2.28 (m, 1H), 2.44 (dd, J=14.6, 2.7Hz, 1H), 5.07 (s, 1H), 7.31~7.46 (m, 5H); $[\alpha]_D^{28}$ -14.6° (C=2, $CHCl_3$). *o*-**4b** ^1H NMR δ 0.92 (s, 3H), 0.96 (s, 3H), 1.10 (s, 3H), 1.11~1.15 (m, 1H), 1.53~1.74 (m, 3H), 1.83 (t, J=4.2Hz, 1H), 1.96 (d, J=14.3Hz, 1H), 2.67~2.73 (m, 1H), 3.85 (s, 3H), 5.23 (s, 1H), 6.89~6.92 (m, 2H), 7.19~7.28 (m, 2H). *p*-**4b** ^1H NMR δ 0.92 (s, 3H), 0.96 (s, 3H), 1.07 (s, 3H), 1.11~1.15 (m, 1H), 1.53~1.74 (m, 3H), 1.82 (t, J=4.1Hz, 1H), 1.96 (d, J=14.4Hz, 1H), 2.61~2.66 (m, 1H), 3.79 (s, 3H), 4.98 (s, 1H), 6.87 (d, J=8.6Hz, 2H), 7.36 (d, J=8.6Hz, 2H). *o*-**4b'** ^1H NMR δ 0.93 (s, 3H), 1.08 (s, 3H), 1.10 (s, 3H), 1.20~1.28 (m, 1H), 1.44~1.49 (m, 1H), 1.54~1.58 (m, 1H), 1.74~1.81 (m, 1H), 1.89 (t, J=4.3Hz, 1H), 2.19 (d, J=13.7Hz, 1H), 2.64~2.68 (m, 1H), 3.83 (s, 3H), 5.43 (s, 1H), 6.87~6.96 (m, 2H), 7.27~7.30 (m, 2H). *p*-**4b'** ^1H NMR δ 0.93 (s, 3H), 1.03 (s, 3H), 1.07 (s, 3H), 1.19~1.25 (m, 1H), 1.43~1.48 (m, 1H), 1.59~1.64 (m, 1H), 1.74~1.78 (m, 1H), 1.89 (t, J=4.3Hz, 1H), 2.16 (d, J=13.7Hz, 1H), 2.62~2.65 (m, 1H), 3.78 (s, 3H), 5.02 (s, 1H), 6.87 (d, J=8.6Hz, 2H), 7.29 (d, J=8.6Hz, 2H). *o*-**4c** ^1H NMR, δ 0.92 (s, 3H), 0.98 (s, 3H), 1.11 (s, 3H), 1.14~1.17 (m, 1H), 1.56~1.62(m, 1H), 1.66~1.74 (m, 2H), 1.81 (t, J=4.3Hz, 1H), 1.92 (d, J=14.4Hz, 1H), 2.37 (s, 3H), 2.69~2.76 (m, 1H), 5.19 (s, 1H), 7.17~7.19 (m, 2H), 7.28~7.33 (m, 2H). *p*-**4c** ^1H NMR, δ 0.91 (s, 3H), 0.96 (s, 3H), 1.07 (s, 3H), 1.12~1.15 (m, 1H), 1.56~1.62 (m, 1H), 1.66~1.74 (m, 2H), 1.81 (t, J=4.3Hz, 1H), 1.96 (d, J=14.4Hz, 1H), 2.32 (s, 3H), 2.62~2.69 (m, 1H), 4.99 (s, 1H), 7.16 (d, J=8.0Hz, 2H), 7.32 (d, J=8.0Hz, 2H). *p*-**4c'** ^1H NMR δ 0.91 (s, 3H), 0.96 (s, 3H), 1.10 (s, 3H), 1.33~1.40 (m, 1H), 1.50~1.56 (m, 1H), 1.73~1.81 (m, 2H), 2.07~2.11 (m, 2H), 2.32 (s, 3H), 2.45~2.53 (m, 1H), 4.98 (s, 1H), 7.15 (d, J=7.8Hz, 2H), 7.27 (d, J=7.8Hz, 2H). **4d** IR (neat) ν 1760 cm^{-1}. ^1H NMR, δ 0.91 (s, 3H), 0.95 (s, 3H), 1.10 (s, 3H), 1.06~1.10 (m, 1H), 1.50~1.58 (m, 1H), 1.62~1.69 (m, 2H), 1.81 (t, J=4.1Hz, 1H), 1.94 (d, J=14.4Hz, 1H), 2.68~2.72 (m, 1H), 3.76 (s, 3H), 3.81 (s, 3H), 5.19 (s, 1H), 6.43 (dd, J=8.6Hz, 2.2Hz, 1H), 6.45 (d, J=2.2Hz, 1H), 7.09 (d, J=8.6Hz, 1H); $[\alpha]_D^{28}$ -17.29° (C=2.07, $CHCl_3$).