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Asymmetric syntheses of α-mercapto carboxylic acid derivatives by dynamic resolution of *N*-methyl pseudoephedrine α-bromo esters

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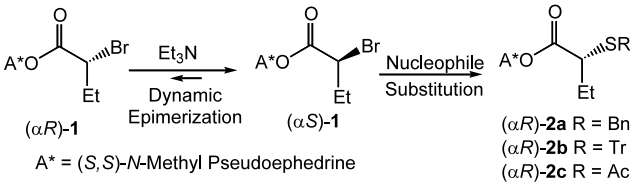
Abstract—Dynamic resolution of *N*-methyl pseudoephedrine α-bromo esters in nucleophilic substitution reaction with trityl thiol has been successfully used for the asymmetric preparation of α-mercapto carboxylic acid derivatives up to 97:3 dr. The best results are obtained when α-bromo esters are allowed to equilibrate to the thermodynamic ratios before the addition of sulfur nucleophile. We have shown that the chiral auxiliary can be removed by both reductive cleavage and acidic alcoholysis to provide β-tritylthio alcohol **15** and α-tritylthiolated ester **16**, respectively, without detectable racemization.

Optically active α-mercapto carboxylic acids are ubiquitous structural subunits in numerous biologically active natural and unnatural peptides.[1] Accordingly, there is growing interest in the preparation of enantioenriched α-mercapto carboxylic acids and several efficient methods have been developed.[2] Most of straightforward methods are based on the stereospecific substitution reaction of enantioenriched α-halo or α-hydroxy carboxylic acid derivatives with sulfur nucleophiles. However, very few methods for high asymmetric nucleophilic substitution of readily accessible racemic precursors were reported so far. Here we wish to report an efficient method for asymmetric syntheses of α-mercapto carboxylic acid derivatives via nucleophilic substitution reactions of racemic α-bromo esters with sulfur nucleophile.

The methodology reported here makes use of the dynamic resolution of (*S*,*S*)-*N*-methyl pseudoephedrine α-bromo esters.[3] Initial studies on the dynamic resolution of α-alkyl-α-bromo esters were carried out with α-ethyl-α-bromo ester **1** and benzyl thiol as a nucleophile. The reaction of *N*-methyl pseudoephedrine α-ethyl-α-bromo ester (α*RS*)-**1** (58:42 dr) with benzyl thiol (BnSH, 1.2 equiv.) and Et_3N (1.0 equiv.) in CH_3CN at room temperature was completed within 0.5 h (>99% conversion) and produced α-benzylthio substituted ester **2a** in 70% yield with 76:24 diastereomeric ratio (dr), as shown in Table 1 (entry 1). For an efficient dynamic resolution, there must be a fast epimerization of the diastereomers with respect to their

Table 1.



Entry	Epimerization[a] (time, dr of **1**)	Nucleophile	Yield of **2** (%)[b]	dr of **2**[c] (α*R*:α*S*)
1	0 h, 58:42 dr	BnSH	70 (**2a**)	76:24
2	0 h, 58:42 dr	TrSH	52 (**2b**)	91:9
3	0 h, 58:42 dr	AcS^-K^+	80 (**2c**)	65:35
4	24 h, 89:11 dr	BnSH	50 (**2a**)	92:8
5	24 h, 89:11 dr	TrSH	65 (**2b**)	96:4

[a] Time for epimerization with Et_3N and dr (α*S*:α*R*) before the addition of nucleophile are shown.

[b] All reactions were carried out at rt in CH_3CN and yields are not optimized.

[c] Drs of **2a**, **2b** and **2c** were determined by ^1H NMR of reaction mixture and drs of **2b** were confirmed by CSP-HPLC analyses of the corresponding β-tritylthio alcohol **15**.

Keywords: asymmetric synthesis; α-mercapto carboxylic acids; chiral auxiliaries; dynamic resolution.

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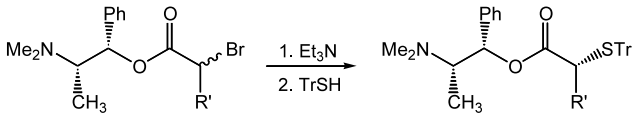
rate of substitution with sulfur nucleophile. The high reactivity of benzyl thiol nucleophile resulted in a rapid nucleophilic displacement reaction with respect to the epimerization process of (α*RS*)-**1** and this may explain the lack of high stereoselectivity. When the nucleophile was changed to the more sterically demanding nucleophile, trityl thiol (Ph_3CSH),[2c,d] the sulfur nucleophile showed sufficient reactivity for the nucleophilic substitution of the secondary bromide (α*RS*)-**1**. The reaction was completed within 5 h (>95% conversion) to provide the α-tritylthiolated carboxylic acid derivatives (α*R*)-**2b** in 52% yield with a dr of 91:9 (entry 2).[4] The size of trityl thiol nucleophile could decrease the rate of substitution and give the ester (α*RS*)-**1** more time for epimerization before the substitution to increase the stereoselectivity. In agreement with the reactivity–selectivity relationship shown in entries 1 and 2, the reaction of (α*RS*)-**1** with a metalated nucleophile, potassium thioacetate (AcS^-K^+) was completed within 10 min (>99% conversion) and produced α-acetylthio substituted ester **2c** in 80% yield with 65:35 dr (entry 3).

The treatment of (α*RS*)-**1** with Et_3N in CH_3CN for 24 h for an epimerization without substitution provided the equilibrated mixture of **1** with a thermodynamic ratio of 89:11.[3e,5] When the benzylthiol was added to the equilibrated mixture, a significant and practical improvement in the stereoselectivity was obtained to give **2a** in 50% yield with 92:8 dr (entry 4). This stepwise epimerization–substitution protocol also improved the stereoselectivity of the reaction with trityl thiol to give (α*R*)-**2b** in 65% yield with an increased dr of 96:4 (entry 5). In the epimerization process induced by Et_3N, the thermodynamically less stable (α*R*)-**1** epimer is converted into more stable (α*S*)-**1** epimer, which reacts faster with TrSH to give (α*R*)-**2b** with inversion of configuration in the subsequent substitution. Limited results shown in Table 1 clearly indicate that the product ratio is dependent on both the size of nucleophile and the dr of α-bromo ester (α*S*)-**1**, which suggest the asymmetric induction by a dynamic kinetic and thermodynamic resolution.[3e]

The scope of this epimerization–substitution methodology was investigated with six different α-bromo esters **3**–**8**, as shown in Table 2. Treatment of **3** with Et_3N in CH_3CN for 24 h for an epimerization provided the equilibrated mixture **3** with a thermodynamic ratio of 85:15. The substitution with trityl thiol for 18 h provided **9** in 60% yield with 95:5 dr (entry 1). We were pleased to observe that the epimerization–substitution protocol is also efficient for a variety of α-alkyl-α-bromo esters **4**–**6**, affording α-tritylthio substituted esters **10**–**12** in 61–80% isolated yields with high stereoselectivities, as shown in entries 2–4. On the other hand, the epimerization–substitution protocol could not be used for the α-phenyl-α-bromo ester **7** and the α-benzyl-α-bromo ester **8** due to their instability under the epimerization condition to give complex reaction mixture. Upon treatment of **7** (50:50 dr) with trityl thiol and Et_3N for 2 h, the substitution provided **13** in 57% yield with 97:3 dr (entry 5). It is noteworthy that highly stereoselective nucleophilic substitution was accomplished in the reaction of α-aryl-α-bromo ester without the epimerization–substitution sequences. However, this methodology is not practical for the preparation of α-benzyl α-mercapto carboxylic acid or analogues due to the domination of elimination reaction (entry 6).

Table 2.



3-8 **9-14**

Entry	R′	Epimerization[a]	Yield (%)[b]	dr[c]
1	*n*-Butyl (**3**)	24 h, 85:15	60 (**9**)	95:5
2	$PhCH_2CH_2$ (**4**)	7 h, 80:20	71 (**10**)	95:5
3	CH_3 (**5**)	2 h, 97:3	80 (**11**)	97:3
4	*iso*-Butyl (**6**)	24 h, 80:20	61 (**12**)	91:9
5	Ph (**7**)	0 h, 50:50	57 (**13**)	97:3
6	$PhCH_2$ (**8**)	0 h, 51:49	12 (**14**)[d]	92:8

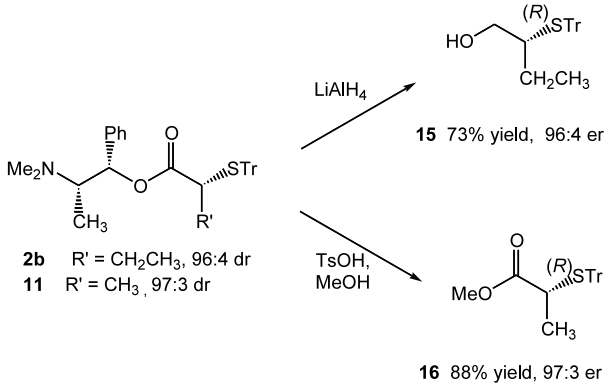
[a] Time for epimerization with Et_3N and dr before the addition of nucleophile are shown.

[b] All reactions were carried out at rt in CH_3CN and yields are not optimized.

[c] Drs of **9**–**14** were determined by ^1H NMR of reaction mixture and drs of **11** and **13** were confirmed by CSP-HPLC analyses of the corresponding methyl α-tritylthio esters.

[d] Elimination product was obtained in 42% isolated yield.

We examined the removal of the chiral auxiliary from α-tritylthio substituted esters, as shown in Scheme 1. Reductive cleavage of α-ethyl-α-tritylthio ester **2b** (96:4 dr) using $LiAlH_4$ (1.5 equiv.) in THF furnished the enantioenriched β-tritylthio alcohol **15** in 73% yield with a small amount of trityl group deprotected β-mercapto alcohol (11% yield), nicely regenerating the unchanged chiral auxiliary in 76% yield.[6] The enantiomeric ratio (er) of **15** was shown to be 96:4 er implying no detectable racemization. Also, the *N*-methyl pseudoephedrine auxiliary can be removed by refluxing the esters in methanol with catalytic amounts of *p*-toluenesulfonic acid. The acidic methanolysis of α-methyl-α-tritylthio ester **11** (97:3 dr) furnished methyl α-tritylthiolated ester **16** in 88% yield with 97:3 er without any detectable racemization and the unchanged chiral auxiliary in 80% yield.[6]



Scheme 1.

We have developed a convenient synthetic method for asymmetric syntheses of α-mercapto carboxylic acid derivatives through dynamic resolution of *N*-methyl pseudoephedrine α-bromo esters. The simple protocol with mild conditions and the easy removal of chiral auxiliary without detectable racemization suggests further development of this methodology. Current work is aimed at understanding mechanistic details of these processes and expanding the utility of this methodology.

Acknowledgements

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4. The absolute configurations at α-positions of **2b** and **11** were assigned as *R*-configuration by the conversion to corresponding α-mercapto carboxylic acids and comparison of their optical rotations with those of authentic compounds in the following literature.[6] Noe, C. R. *Chem. Ber*. **1982**, *115*, 1607. The absolute configurations of **2a** and **2c** were assigned by analogy to the formation of (α*R*)-**2b**. We have found that the α-position of **2b** is configurationally stable under the reaction condition (1.0 equiv. of Et_3N in CH_3CN).
5. (α*S*)-**1** epimer was assigned as a major isomer by comparison to the ^1H NMR of authentic epimer obtained from the coupling of (*S*,*S*)-*N*-methyl pseudoephedrine and (*S*)-2-bromobutanoic acid obtained from commercially available (*S*)-2-aminobutyric acid.
6. **General procedure for the asymmetric preparation of (*R*)-2-tritylthiobutanol (15) and methyl (*R*)-2-tritylthiopropanoic ester (16)**: To a solution of (α*RS*)-**1** (or (α*RS*)-**5**) in CH_3CN (ca. 0.1 M) at room temp. was added Et_3N (1.0 equiv.). The resulting reaction mixture was stirred at room temperature for 24 h (or 2 h), and then trityl thiol (1.2 equiv.) was added. After 5 h, the solvent was evaporated and the crude material was purified by column chromatography to give **2b** and **11** in 65 and 80% yield, respectively. (a) After the addition of $LiAlH_4$ (1.5 equiv.) to **2b** in THF, the mixture was stirred at rt for 18 h and then quenched with EtOAc and water. Extractive workup and column chromatography gave (*R*)-**15** in 73% yield. ^1H NMR ($CDCl_3$, 400 MHz) 7.54–7.19 (m, 15H), 3.14 (br, 1H), 2.91 (dd, $J=5.3$ and 5.3 Hz, 1H), 2.33 (m, 1H), 1.56 (m, 3H), 0.84 (t, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 145.5, 130.0, 128.3, 127.1, 67.7, 63.4, 49.7, 25.5, 11.7. The enantiomeric ratio of **15** was determined to be 96:4 in favor of the *R* enantiomer by CSP-HPLC using racemic material as a standard. (Chiralcel OD column; 5% 2-propanol in hexane; 0.5 mL/min; the *R*-enantiomer (major) had a retention time of 15.7 min, and the *S*-enantiomer (minor) had a retention time of 16.8 min). (b) The mixture of **11** and *p*-toluenesulfonic acid (0.1 equiv.) in methanol were refluxed for 24 h. The solvent was evaporated and the crude material was purified by column chromatography to give (*R*)-**16** in 88% yield. ^1H NMR ($CDCl_3$, 400 MHz) 7.45–7.19 (m, 15H), 3.46 (s, 3H), 2.98 (q, $J=7.4$ Hz, 1H), 1.19 (d, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 174.4, 144.8, 130.1, 128.3, 127.2, 68.6, 52.5, 42.8, 19.2. The enantiomeric ratio of **16** was determined to be 97:3 in favor of the *R* enantiomer by CSP-HPLC using racemic material as a standard. (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min; the *R*-enantiomer (major) had a retention time of 9.7 min, and the *S*-enantiomer (minor) had a retention time of 10.3 min). For the conversion of **16** to 2-mercapto propanoic acid, **16** was treated with 1:1 mixture of 0.5 M NaOH and dioxane for 5 h at room temperature. After acidic workup, the organic phase was concentrated. The residue was dissolved in 1:1 mixture of methylene chloride and trifluoroacetic acid and Et_3SiH (1.0 equiv.) was added. After stirring for 1 h at room temperature, the reaction mixture was concentrated and chromatographed on SiO_2 to give the trityl deprotected 2-mercapto propanoic acid in 93% yield. $[\alpha]_D^{24}=+24.0°$ ($c=0.13$, $CHCl_3$).