

A GENERAL AND EFFICIENT SYNTHESIS OF OPTICALLY PURE *S*-ARYLMERCAPTURATES

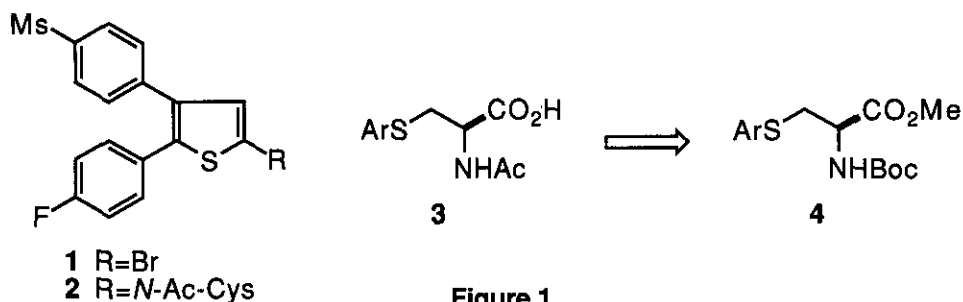
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Abstract - Optically pure *S*-arylmecapturate derivatives (**4_{a-d}**) were efficiently synthesized *via* the reaction of Boc-L-Ser-OMe (**6**) with a variety of disulfides (**5_{a-d}**) in the presence of tri-*n*-butylphosphine. The procedure was successfully applied to the synthesis of the enantiomerically pure *S*-thienylmercapturic acid (**2**), a metabolite of antiinflammatory drug DUP697 (**1**).

Mercapturic acid (**3**), aromatic *S*-substituted derivative of *N*-acetyl-L-cysteine, is one of the important metabolites in glutathione conjugation,¹ which has been considered as a major detoxication pathway in drug metabolism.² During the course of our study concerning the metabolic pathway of antiinflammatory drug DUP697 (**1**),³ we intended to synthesize the *S*-thienylmercapturic acid (**2**),⁴ one of the metabolites of **1**, not only as an authentic standard but also as a cytotoxic candidate.⁵ To date, the efficient methods for synthesizing optically pure *S*-arylmecapturic acids^{6a-c} including *S*-thienyl derivatives^{6d} are few. In this communication, we wish to report a general and efficient access to *S*-arylmecapturate derivative (**4**), an intermediate of **3**, and a concise synthesis of **2** in enantiomerically pure forms. (Figure 1)



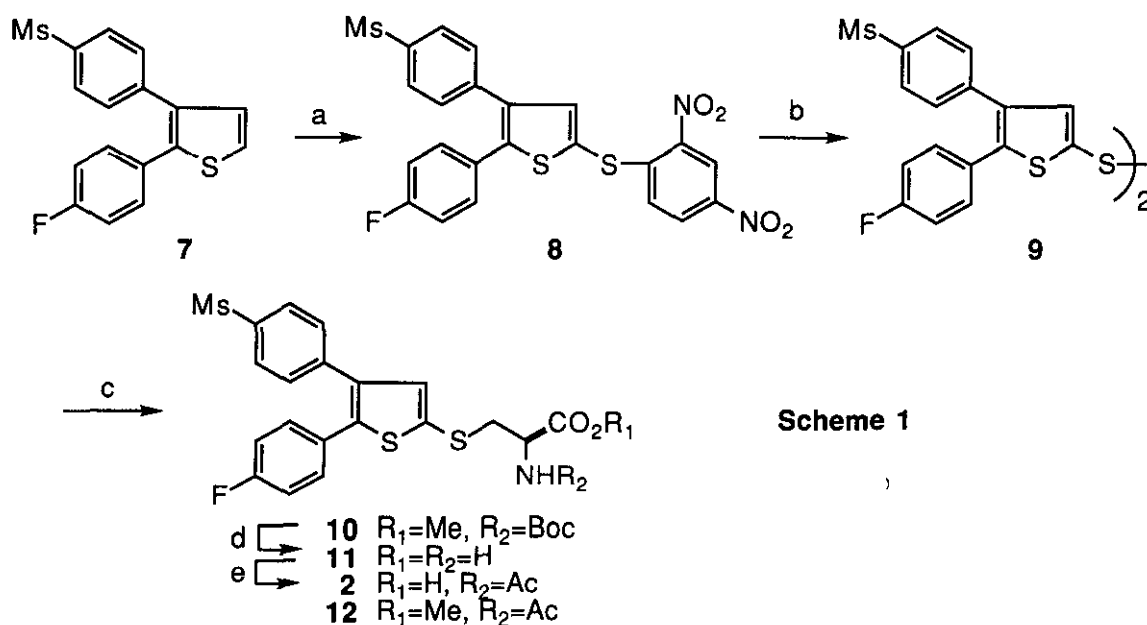
Initial efforts to explore an efficient procedure for obtaining **4**, which would readily be converted into the corresponding mercapturic acid (**3**), was focused upon the coupling of *Boc-L-Ser-OMe* (**6**)⁷ with an arylthio component. The reaction was carried out under Mitsunobu conditions⁸ using thiophenol, triphenylphosphine, diethyl azodicarboxylate and *Boc-L-Ser-OMe* (**6**) in THF to give the desired *S*-phenylmercapturate (**4_a**) (99 %ee) only in 17 % yield. The lower yield was not improved even by changing the reaction conditions. However, large enhancement of coupling yields was obtained for all four mercapturate derivatives (**4_{a-d}**) by using the procedure developed by Hata.⁹ On exposure of **6** to 2 eq. of disulfides (**5_{a-d}**) in the presence of tri-*n*-butylphosphine, coupling reaction smoothly occurred to provide the corresponding mercapturate derivatives (**4_{a-d}**) with high ee in good yields. When the reaction was carried out in a mixture of THF-pyridine (1:1), the best yield and ee were achieved. It should be noted that a loss of the optical purity in **6** was not observed during the conversion. (Table 1)

Table 1. Synthesis of Methyl *S*-Arylmercapturate derivatives (**4_{a-d}**)

Run	Ar	Product	Yield, % ^a	ee, % ^b
1	Ph	4_a	75	99
2	4-MeC ₆ H ₄	4_b	71	98
3	4-MeOC ₆ H ₄	4_c	81	98
4	4-ClC ₆ H ₄	4_d	89	99

^aisolated yields. ^bDetermined by hplc with chiral column.¹³

With an efficient method for the direct preparation of *S*-arylmercapturates in hand, we turned our attention to synthesize the mercapturic acid (**2**). Treatment of (**7**)³ with 2,4-dinitrobenzenesulfonyl chloride in refluxing trifluoroacetic acid¹⁰ afforded the sulfide (**8**), which was then sequentially hydrolyzed and oxidized with iodine to provide the disulfide (**9**) in 50 % overall yield. The disulfide (**9**) thus obtained was exposed to the same conditions as used for **5** to produce the mercapturate (**10**) in 68 % yield.¹¹ Finally, the amino acid (**11**), derived from **10** by acidic hydrolysis, was converted into the requisite mercapturic acid (**2**), whose spectral data supported the structure.¹² The optical purity of **2**, after recrystallization from ethyl acetate - diethyl ether, was determined to be 100 % ee.¹³ (**Scheme 1**)



Reagents and Conditions : a, 2,4-(NO₂)₂C₆H₃SOCl, TFA, reflux, 75%; b, aq. NaOH, MeOH, reflux then I₂, MeOH, 67%; c, Boc-L-Ser-OMe, ⁿBu₃P, THF, room temperature, 68%; d, 4N-HCl, AcOH, 100 °C, 65%; e, Ac₂O, Et₃N, Et₂O, H₂O, 0 °C, 91%.

In summary, we have presented a facile method for the preparation of enantiomerically pure *S*-arylmercapturates. The procedure proved to be applicable to the synthesis of *S*-thienylmercapturic acid (**2**), a metabolite of an antiinflammatory drug DUP697 (**1**).

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11. Attempted coupling of 5-bromo-3-(*p*-methanesulfonylphenyl)-2-(*p*-fluorophenyl)-thiophene with Ac-L-Cys-OMe in the presence of CuI in DMF^{6d} resulted in the formation of **12** with 70 %ee in 35-43 % yield.
12. All new compounds described herein gave satisfactory analytical and spectral data consistent with the assigned structures.
13. Determined by hplc with a CHIRALPAK[®] AD column (0.46 ϕ x 25 cm), DAICEL Chem. Ind., Ltd.

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