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# Solid phase synthesis of mandelic acid-derived thioethers by α-keto carbocation trapping

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**Abstract**—Resin-bound α-keto mesylates were cleaved under acidic conditions (TFA/$CH_2Cl_2$) in the presence of a variety of aryl or alkyl thiols to give the corresponding thioethers. Access to the target compounds via standard nucleophilic displacement proved to be much less efficient. The stereochemical outcome of the reaction suggested formation of a highly reactive α-keto carbocation trapped in situ by the thiol acting as a scavenger.


The development of novel synthetic methods for access to thioethers is an important task in medicinal chemistry.[1] We report here the synthesis of mandelic acid-derived thioethers **1** (Scheme 1) using a novel solid phase approach. The polymer-supported synthesis of thioethers **1** could be envisaged as starting from an alcohol **2** (Scheme 1) by exploiting the reactivity of the hydroxyl group. In an initial approach, thioether formation was envisaged by activation of the hydroxyl function via the corresponding mesylate[2] followed by nucleophilic displacement with a thiol, RSH. Isolation of the target sulfides **1** required long reaction times and an additional cleavage step. Alternatively, we describe here that the supported mesylate **3** could be readily converted to a thioether **1** in one step using a strong acid medium in the presence of an excess of thiol RSH (Scheme 1).

Supported intermediate **2** was obtained as described in Scheme 1. Initial Fmoc removal from the Rink-amide resin with piperidine was followed by acylation with Fmoc-β-Ala-OH using a standard HBTU/HOBT/DIEA[3] activation procedure. The attachment of unprotected D,L-mandelic acid required optimization. An excess of D,L-mandelic acid was found to be necessary and among the various activating reagents tested, PyBop/DIEA gave the best results as visualized by the negative 2,4,6-trinitrobenzene-sulfonic acid test.[3] Partial polycondensation of mandelic acid was reversed by aminolysis with an excess of 1,3-diaminopropane. Alcohol **4** was isolated in 86% yield following TFA cleavage (RP-HPLC purity 98%; C18 Nucleosil column, 50 °C, flow rate 1 mL $min^{-1}$, 0–80% aqueous $CH_3CN$ gradient).

Conversion of resin **2** into the mesylate **3** was performed with an excess of MsCl in the presence of $Et_3N$ and was complete after 12 h, as determined by magic angle spinning NMR spectroscopy. Nucleophilic displacement of the mesylate **3** with PhSH in the presence of $Et_3N$ proved to be slow, as shown by RP-HPLC analysis of the crude material obtained after TFA cleavage.[4] The conversion reached only 56% after 24 h of reaction at room temperature. Interestingly, reaction of resin **3** with PhSH/$Et_3N$ for 16 h followed by cleavage using a TFA/$CH_2Cl_2$ (1/1) mixture in the presence of 5% $Me_2S$ yielded the expected thioether **1a** along with sulfonium trifluoroacetate **5**. Formation of **5** during the cleavage step by reaction of unreacted mesylate **3** with $Me_2S$ in TFA suggested that thioethers **1** could be obtained analogously in one step from **3** by treating the resin with RSH/TFA.

To test this hypothesis, the polymer-bound mesylate **3** was treated for 30 min with TFA/$CH_2Cl_2$ (1/1) containing 5% of thiophenol. The RP-HPLC of the crude product revealed a clean transformation leading to **1a** in 49% yield after purification.[5] The scope of this reaction was evaluated by reacting **3** with a series of aromatic or

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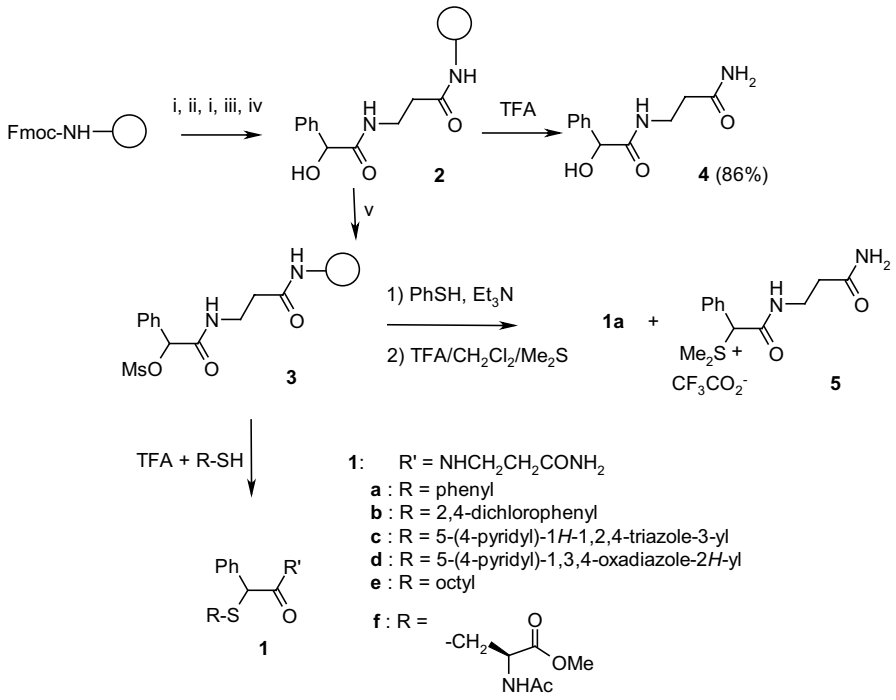
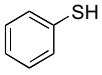
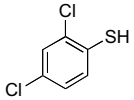
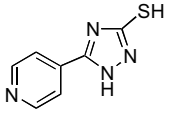
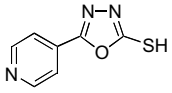
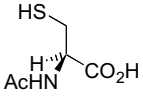
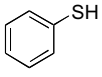


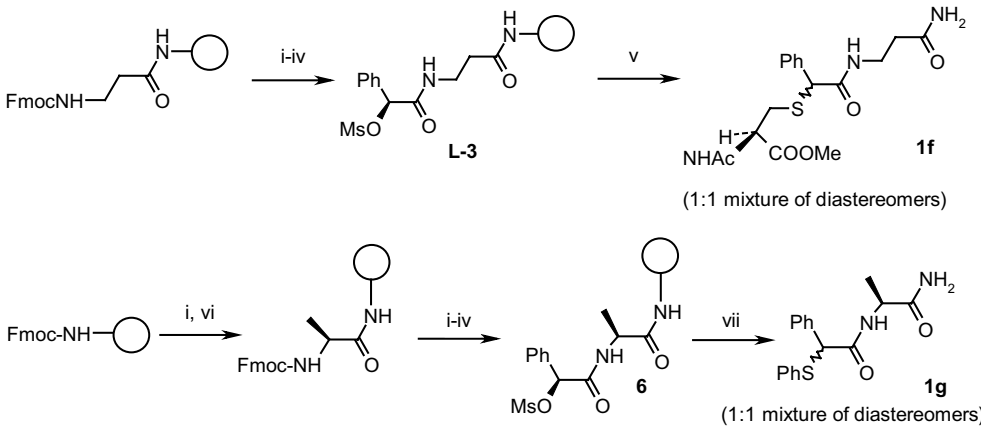

**Scheme 1.** Reagents and conditions: (i) 20% piperidine, DMF; (ii) Fmoc-β-Ala (4 equiv), HOBT (4 equiv), HBTU (4 equiv), DIEA (4 equiv), DMF; (iii) PyBop (8 equiv), D,L-mandelic acid (8 equiv), DIEA, DMF; (iv) 1,3-diaminopropane, DMF; (v) MsCl (8 equiv), $Et_3N$ (12 equiv), THF.

**Table 1.** Thioethers **1a–g** produced from resin-bound α-keto mesylates

| Entry | Resin | Reagent (RSH) | Product[a] | Overall yield (%)[b] |
|---|---|---|---|---|
| 1 | **3** |  | **1a** | 48[c] |
| 2 | **3** |  | **1b** | 30[c] |
| 3 | **3** |  | **1c** | 39[d] |
| 4 | **3** |  | **1d** | 43[d] |
| 5 | **3** | $CH_3$–$(CH_2)_7$–SH | **1e** | 39[d] |
| 6 | L-**3** |  | **1f** | 11[d] |
| 7 | **6** |  | **1g** | 63[c] |

[a] All compounds gave satisfactory analytical and spectroscopic data.
[b] Overall yield of purified compounds calculated from initial resin loading.
[c] Silica gel flash chromatography ($CH_2Cl_2$/ethyl acetate/MeOH, 90/5/5 by volume).
[d] Semi-preparative RP-HPLC.

aliphatic thiols (Table 1). In most cases, analytically pure compounds were obtained after purification by silica gel flash chromatography or RP-HPLC in ca. 40% overall yield.[6] Only compound **1f** was isolated in a poor 11% yield, the major product of the reaction being the alcohol **4** in this case. In comparison, nucleophilic sub-




**Scheme 2.** Reagents and conditions: (i) 20% piperidine, DMF; (ii) PyBop (8 equiv), L-mandelic acid (8 equiv), DIEA, DMF; (iii) 1,3-diaminopropane, DMF; (iv) MsCl (8 equiv), $Et_3N$ (12 equiv), THF; (v) Ac-L-Cys-OH (10 equiv), TFA, $CH_2Cl_2$; (vi) Fmoc-L-Ala-OH (4 equiv), HOBT (4 equiv), HBTU (4 equiv), DIEA (4 equiv), DMF; (vii) PhSH, TFA, $CH_2Cl_2$.

stitution of the mesylate **3** with Ac-Cyc-OH/$Et_3N$ failed to give the target thioether **1f**.

In the last series of experiments, optically active substrates were used in order to give some insight into the reaction mechanism. In the first experiment, resin L-**3** was prepared from L-mandelic acid and reacted with Ac-L-Cys-OH in TFA. In the second experiment the solid support **6**, obtained by coupling L-mandelic acid to H-L-Ala-NH-PS resin, was reacted with PhSH using the conditions stated above (Scheme 2). In each case epimerization of the benzylic chiral centre was observed yielding a 1/1 mixture of both possible diastereoisomers.[7] These results together with previous studies on the solvolysis of α-keto mesylates[8,9] suggest that formation of thioethers **1** could proceed through a highly reactive carbocation-like intermediate. Indeed, mesylates derived from mandelic acid were found to give the corresponding α-keto aryl carbocations in the presence of TFA. However, to our knowledge, the trapping of these reactive intermediates by thiols has not been exploited for the synthesis of mandelic acid-derived thioethers.

In conclusion, the present study provides an interesting way of generating α-keto thioethers derived from mandelic acid. The experimental conditions used for the substitution of the α-keto mesylate (TFA, thiol in excess) also permitted the cleavage of the target compound from the solid support, thus simplifying the overall synthetic scheme. Both aromatic and alkyl thiols were found to be useful and the presumed generation of highly reactive carbocation intermediates permitted access to some mandelic acid-derived thioethers, whose synthesis was found to be more difficult via a standard $S_N2$ reaction.[10]

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## References and notes

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3. Chan, W. C.; White, P. D. *Fmoc Solid-Phase Peptide Synthesis, A Practical Approach*; Oxford University Press: Oxford, 2000.
4. HPLC monitoring: resin aliquots were transferred into a 5 mL polypropylene syringe equipped with a 20 μM polyethylene filter, washed with MeOH and $CH_2Cl_2$ and treated with TFA/$CH_2Cl_2$/anisole/water (45/45/5/5 by volume) to liberate **1a** and generate **4** from the residual mesylate. RP-HPLC analysis was performed after evaporation of the crude mixture. Conversion was deduced from relative integration of the corresponding peaks.
5. Formation of thioethers **1** by reaction of the thiol with alcohol **2** that could be formed in situ by hydrolysis of mesylate **3** in TFA was ruled out since treatment of resin **2** with TFA/$CH_2Cl_2$/RSH gave alcohol **4** as the only reaction product.
6. Typical experimental procedure: mesylate resin **3** or **6** (222 mg, 0.45 mmol/g) was weighed under argon and was treated with a solution of freshly distilled $CH_2Cl_2$ (1 mL), TFA (1 mL) and RSH (100 μL or 10 equiv). After 30 min of stirring, the resin was filtered and washed twice with TFA (1 mL). The combined filtrates were co-evaporated twice with heptane (15 mL). The crude residue was purified by preparative RP-HPLC or flash chromatography on silica gel (see Table 1).
7. Epimerization of thioethers **1** through enolization did not occur in the acidic reaction medium used for the cleavage and substitution since no proton/deuterium exchange of the benzylic-H ($\delta = 5.2$ ppm) was observed for compound **1b** after 30 min in $CD_2Cl_2$/$CF_3COOD$.
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9. Creary, X.; McDonald, S. R.; Eggers, M. D. *Tetrahedron Lett.* **1985**, *26*, 811.
10. Attempts to obtain thioethers **1** from resin-bound alcohol **2** via a standard Mitsunobu procedure ($PPh_3$, DEAD) failed.