Organic LETTERS

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Tertiary Thiols from Allylic Thiocarbamates by Tandem Enantioselective [3,3]-Sigmatropic Rearrangement and Stereospecific Arylation

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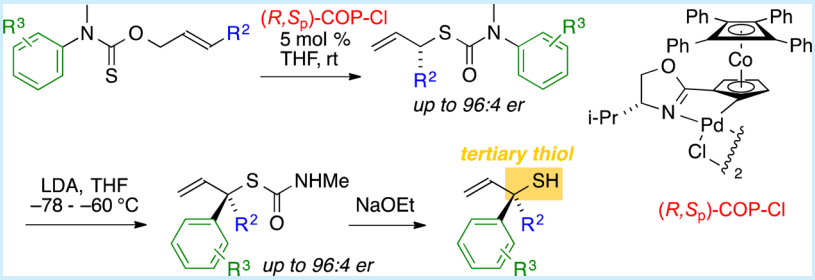
Supporting Information



ABSTRACT: The synthesis of tertiary thiols in enantiomerically enriched form is accomplished by lithiation of enantiomerically enriched *N*-aryl allylic thiocarbamates. Formation of an allyllithium derivative promotes intramolecular N to C aryl migration to the position α to sulfur, generally with good stereospecificity. The substrates may themselves be obtained by Pd-catalyzed enantioselective [3,3]-sigmatropic rearrangement of *N*-aryl *O*-allyl thiocarbamates. Solvolysis of the product thiocarbamates yields tertiary thiols, which may be converted to sulfide derivatives.

Of simple functional groups based on commonly occurring elements, thiols must be among the most neglected. Thiols have little associated synthetic chemistry beyond trivial substitution, addition, and redox reactions, and the synthesis of thiols is invariably accomplished by late-stage introduction of sulfur.[1] Because of the impracticality of using thiocarbonyl compounds as precursors,[2] the asymmetric synthesis of thiols and their simple derivatives is, with a handful of exceptions, achieved by stereospecific substitution of chiral electrophilic precursors.[1] For substitution patterns compatible with S_N2 reactions, this strategy has general application, but it means that the general asymmetric synthesis of simple *tertiary* thiols remains, remarkably, essentially an incompletely solved problem.[3]

Thiols are nonetheless widespread in nature (Figure 1). Though a rare residue in proteins, Cys is present in the key metabolic antioxidant glutathione **1**. Tertiary thiol functionality is present in (*S*)-3-thio-3-methylhexan-1-ol **2**, a component of the smell of sweat, while (*R*)-thioterpineol **3** and 4-thio-4-methylpentan-2-one **4** give the characteristic odors to grapefruit and passion fruit.[4]

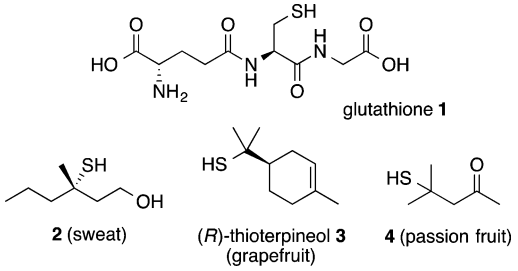


Figure 1. Naturally occurring thiols.

In this paper, we show that the rich chemistry of allylic thiocarbamates[5] provides a solution to the challenge of synthesizing a range of tertiary thiols in enantiomerically pure form. We show that enantiomerically pure allylic *N*-aryl thiocarbamates may be synthesized by enantioselective [3,3]-sigmatropic rearrangement and that lithiation of these compounds promotes aryl migration from N to C, leading to enantiospecific construction of quaternary stereogenic centers bearing sulfur. From these products a range of tertiary thiols and their derivatives may be made by simple thiocarbamate hydrolysis.

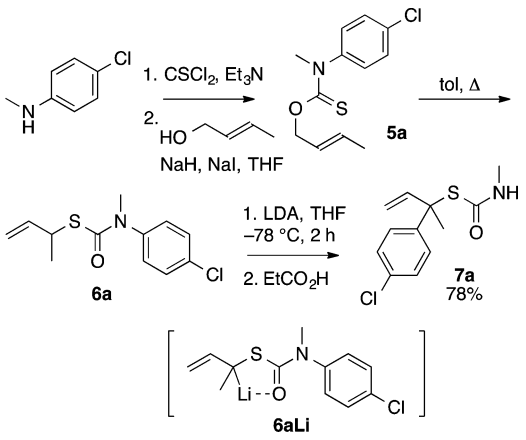
In the past few years, it has become clear that deprotonation of *N*-aryl derivatives of the class of functional groups ArNRCOX (X = NR'_2: ureas;[6] OR′: carbamates;[7] SR′: thiocarbamates[8]) typically leads to migration of the aryl substituent from N to C, generally[9] stereospecifically. Such reactions create a new quaternary stereogenic carbon atom,[10] and therefore with X = SR provide a plausible strategy for the synthesis of tertiary thiols.[3]

Previous explorations in the area[8] had employed only benzylic thiocarbamates. Generalization of the reaction to a fuller range of tertiary thiol targets is made possible by

Received: January 23, 2014
Published: February 6, 2014

   dx.doi.org/10.1021/ol5002522 | *Org. Lett.* 2014, 16, 1252–1255

Scheme 1. *N* to *C* Aryl Migration in an *N*-Aryl Allylic Thiocarbamate



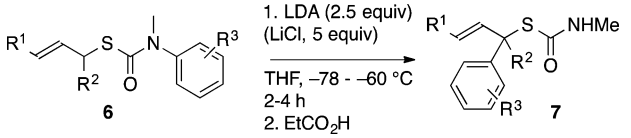
exploiting the chemistry of allylic thiocarbamates.[11] Thiocarbamate **6a** was made straightforwardly from crotyl alcohol via [3,3]-sigmatropic rearrangement of **5a**[12] and treated with LDA in THF for 2 h at −78 °C (Scheme 1). After acidic quench, the rearranged tertiary thiocarbamate **7a** was recovered in 78% yield. Presumably, α-deprotonation of **6a** generates an allyllithium intermediate **6aLi** whose nucleophilic α-carbon attacks the *N*-aryl ring in an intramolecular aromatic substitution reaction[13] to yield the anion of **7a**, which is protonated on workup.

The successful arylation of **6a** led us to explore a range of allyl thiocarbamate structures and a range of migrating aromatic rings. The results of these rearrangements are shown in Table 1. Rearrangements took place between −78 and −45 °C, and in some cases lithium chloride was added[14] to improve yields. Migration was successful with a range of electron-deficient and electron-rich rings substituted in the *o*, *m*, or *p* positions, despite the nucleophilic aromatic substitution step of the rearrangement. Rearrangement was invariably regiospecific, with the substitution pattern of the starting material conserved in the product. Warming the reaction mixture above −40 °C prior to acidification led to partial or complete collapse of the product thiocarbamate to the free thiol (see, for example, the reaction of **6l**).

Enantiomerically enriched *S*-allyl thiocarbamates may be readily generated by enantioselective palladium-catalyzed sigmatropic rearrangement of *O*-allyl thiocarbamates **5** in the presence of either the $[(R,S_p)$-(−)-COP-Cl$]_2$ complex ((*R*)-COP-Cl) **8**[15] or with the bisphosphine [(*R*,*R*)-DACH-phenyl] **9**[16] as a chiral ligand. These two catalytic methods were compared in the rearrangement of **5b** to **6b**, as shown in Scheme 2 and Table 2, with method A employing catalyst **8** promoting the generation of (*R*)-**6b** in 92% yield and 91:9 er.[17] Method B gave lower enantioselectivity (ca. 80:20 er) and was not explored further.

Using method A of Scheme 2, with **8** as a catalyst, we prepared a series of enantioenriched *S*-allyl thiocarbamates **6** in excellent yields, with enantiomeric ratios from 80:20 to 95:5. Resubjection of rearranged *S*-allyl thiocarbamate **6g** (3-F) (with 82:18 er) to the standard reaction conditions for a period of 15−40 h led to no racemization, indicating that the rearrangement is irreversible. Reaction at a lower temperature (0 °C) gave a better er of 94:6, but the reaction reached only half-completion.

Table 1. Aryl Migration in Racemic *S*-Allylic Thiocarbamates



starting material	R^1	R^2	R^3	product	yield (%)
6b	H	Me	H	**7b**	68
6c	H	Me	4-Me	**7c**	56[a]
6d	H	Me	4-F	**7d**	97
6e	H	Me	3-OMe	**7e**	86[a]
6f	H	Me	3-Cl	**7f**	73
6g	H	Me	3-F	**7g**	68[a]
6h	H	Me	2,3-benzo[b]	**7h**	68
6i	H	Me	2-pyridyl	**7i**	54[a]
6j	H	*n*-Pr	4-Cl	**7j**	62[a]
6k	H	*n*-Pr	4-F	**7k**	42[a]
6l	H	*n*-Pr	3-Cl	**10l**	56[a,c]
6l	H	*n*-Pr	3-Cl	**7l**	33[a]
6m	H	*n*-Pr	4-Me	**7m**	44[a]
6n	Me	Me	4-Me	**7n**	78[a]
6o	Me	Me	4-F	**7o**	78[a]

[a]LiCl (5 equiv) was added. [b]1-Naphthyl. [c]Reaction warmed to −45 to −40 °C: the isolated product is the free thiol.

Scheme 2. Palladium-Catalyzed [3,3]-Sigmatropic Rearrangements for the Enantioselective Synthesis of 6

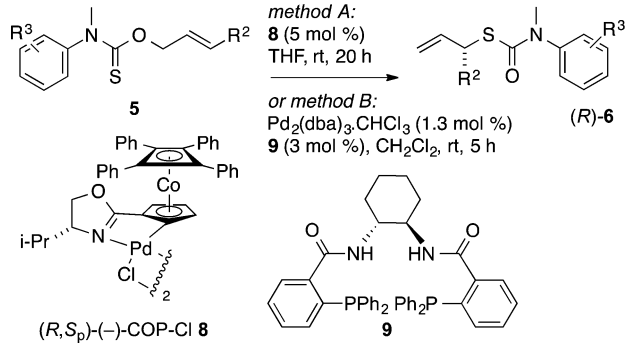


Table 2. Enantioselective Synthesis of Thiocarbamates 6 by Pd-Catalyzed Asymmetric Sigmatropic Rearrangement (Scheme 2, Method A)

starting material	R^2	R^3	product	yield (%)	er
5a	Me	4-Cl	(*R*)-**6a**	95	89:11
5b	Me	H	(*R*)-**6b**	92	91:9
5c	Me	4-Me	(*R*)-**6c**	99	89:11
5d	Me	4-F	(*R*)-**6d**	94	90:10
5e	Me	3-OMe	(*R*)-**6e**	95	83:17
5f	Me	3-Cl	(*R*)-**6f**	98	80:20
5g	Me	3-F	(*R*)-**6g**	97	82:18
5g	Me	3-F	(*R*)-**6g**	<50[a]	94:6[a]
5h	Me	2,3-benzo[b]	(*R*)-**6h**	95	84:16
5j	*n*-Pr	4-Cl	(*R*)-**6j**	91[c]	94:6
5k	*n*-Pr	4-F	(*R*)-**6k**	92[d]	91:9
5l	*n*-Pr	3-Cl	(*R*)-**6l**	93[d]	95:5

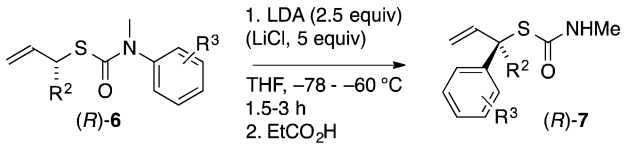
[a]Reaction run at 0 °C, 48 h. 50% conversion was determined by ^{1}H NMR . [b]1-Naphthyl. [c]Rearranged at 14 °C for 48 h. [d]Rearranged at 21 °C for 4−5 days.

dx.doi.org/10.1021/ol5002522 | *Org. Lett.* 2014, 16, 1252−1255

In general, *para*-substituted *N*-aryl rings gave the best er values (89:11 to 94:6), while *ortho*- or *meta*-substituted rings showed decreased enantioselectivity. Notably, the propyl-bearing allylic thiocarbamates all rearranged with excellent enantioselectivities, whatever the substitution pattern of the aromatic ring.

The enantiomerically enriched thiocarbamates (*R*)-**6** were lithiated with LDA in THF and gave thiocarbamates (*R*)-**7** in enantiomerically enriched form (Table 3). The *R* configuration

Table 3. Stereospecificity in the *N* to *C* Aryl Migration



starting material	R^2	R^3	product	yield (%)	er of **6**	er of **7**
(*R*)-**6a**	Me	4-Cl	(*R*)-**7a**	98	91:9	91:9
(*R*)-**6b**	Me	H	(*R*)-**7b**	63	91:9	85:15
(*R*)-**6c**	Me	4-Me	**7c**	11[a]	89:11	57:43
(*R*)-**6d**	Me	4-F	(*R*)-**7d**	40[a]	89:11	70:30
(*R*)-**6e**	Me	3-OMe	(*R*)-**7e**	89[a]	83:17	82:18
(*R*)-**6f**	Me	3-Cl	(*R*)-**7f**	94	80:20	80:20
(*R*)-**6g**	Me	3-F	(*R*)-**7g**	100[a]	82:18	82:18
(*R*)-**6h**	Me	2,3-benzo[b]	(*R*)-**7h**	100	84:16	80:20
(*R*)-**6j**	*n*-Pr	4-Cl	(*R*)-**7j**	81[a]	96:4	96:4
(*R*)-**6k**	*n*-Pr	4-F	(*R*)-**7k**	52[a]	91:9	72:28
(*R*)-**6l**	*n*-Pr	3-Cl	(*R*)-**7l**	48[a,c]	95:5	94:6

[a]LiCl (5 equiv) was added. [b]1-Naphthyl. [c]Reaction warmed to −50 °C.

was assigned to starting materials **6** on the basis of the known enantioselectivity of sigmatropic rearrangement induced by (R,S_p)-COP-Cl[15] and to products **7** on the basis of circular dichroism studies of the products arising from further transformations of the products **7** and their analogues.[17] In many cases, the aryl migration proceeded with complete enantiospecificity, in other words, without loss of enantiomeric purity. However, there were a few significant exceptions: the greatest loss of er was seen in **7b** (with an unsubstituted Ph ring), **7c** (whose ring has a 4-Me substituent), and **7d** and **7k** (4-F). These all share the feature of lacking a substituent that may activate the *ipso* carbon of the *N*-aryl ring toward nucleophilic attack. Notably, less π donating groups, such as 4-Cl, or π-donating groups located in the 3-position, such as 3-OMe, allow rearrangement with full enantiospecificity. We interpret this as an indication that π donating groups at the 4-position decelerate the rearrangement to the point where racemization of the intermediate allyllithium **6Li** proceeds at a comparable rate.[18]

The product thiocarbamates **7**, which carry an acidic NH proton, were highly susceptible to hydrolysis under mildly basic conditions, and indeed, a low-temperature acidic quench was routinely employed to prevent in situ hydrolysis after rearrangement. Their enantiomerically enriched tertiary thiol derivatives **10** were most cleanly obtained by treatment of the thiocarbamates **7** with NaOEt in EtOH/Et_2O at 0 °C (Scheme 3 and Table 4). Some of the thiols were highly volatile, compromising isolated yields. Alkylation of these hindered thiols was achieved by low-temperature deprotonation with

Scheme 3. Solvolysis and Alkylation

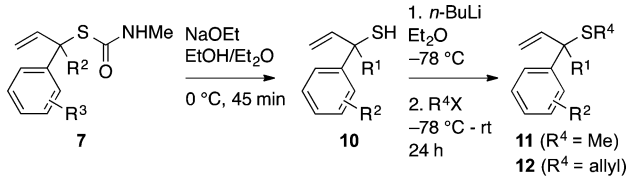


Table 4. Formation of Thiols 10 and Sulfides 11/12

starting material	R^2	R^3	product	yield **10** (%)	R^4	yield **11/12** (%)
(*R*)-**7a**	Me	4-Cl	(*R*)-**10a**	26[a]		
7d	Me	4-F	**10d**	20[a]		
7e	Me	3-OMe	**10e**	90	Me	**11e**, 89
(*R*)-**7f**	Me	3-Cl	(*R*)-**10f**	87		
(*R*)-**7g**	Me	3-F	(*R*)-**10g**	59	allyl	(*R*)-**12g**, 95
(*R*)-**7h**	Me	2,3-benzo[b]	(*R*)-**10h**	92		
7j	*n*-Pr	4-Cl	**10j**	67		
(*R*)-**7l**	*n*-Pr	3-Cl	(*R*)-**10l**	80		

[a]Volatile product. [b]1-Naphthyl.

BuLi and electrophilic quench with methyl iodide or allyl bromide to yield sulfides **11** and **12**.

In summary, we show that the challenge of making enantiomerically enriched tertiary thiols may be met through an enantioselective [3,3]-sigmatropic rearrangement, leading to enantioenriched allylic thiocarbamates. These may be rearranged stereospecifically to give thiocarbamate derivatives of allylic tertiary thiols. The thiols may be revealed by solvolysis and converted by standard chemistry to a range of sulfide derivatives.

■ ASSOCIATED CONTENT

Supporting Information

Experimental data and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the EPSRC for a studentship (to G.M.) and the RSC for the Briggs Scholarship (to P.M.).

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(9) Exceptions are some cyclic (ref 6b) or amino-acid derived (ref 6h) ureas and some carbamates (ref 7b).

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(11) Aryl migration has occurred not only in benzyllitiums but also in allyllithium (refs 6d,e) and enolate (ref 6h,i) derivatives of ureas and in allyllithium (ref 7c,d) derivatives of carbamates.

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(17) The *R* configuration of compounds **6** was assigned initially on the basis of precedent, given the published enantioselectivity (ref 15) of related sigmatropic rearrangements using (R,S_p)-COP-Cl, and the *R* configuration of compounds **7** on the basis that intramolecular arylation of related benzylic thiocarbamates proceeds with retention of configuration (ref 8). Circular dichroism studies of the products arising from further transformations of the products **7** and their analogues (Mingat, G.; McDouall, J. J. W.; Clayden, J. Manuscript in preparation) have since confirmed the assignment of (*R*)-configuration to **7**.

(18) The enantiomeric ratio did not change as the reaction proceeded. Attempts to decelerate the racemization in less coordinating solvents or by using more bulky bases (such as LiTMP; see ref 8a) were unsuccessful.