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Carbolithiation of *S*-Alkenyl-*N*-aryl Thiocarbamates: Carbanion Arylation in a Connective Route to Tertiary Thiols

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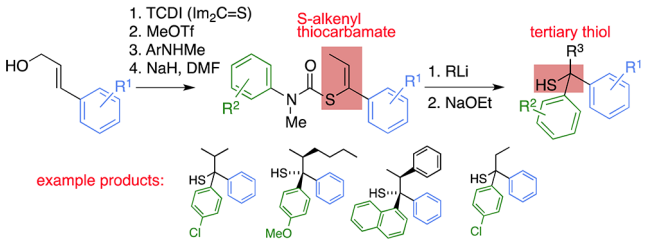
ABSTRACT



***S*-Alkenyl-*N*-arylthiocarbamates are formed from allylic alcohols by sigmatropic rearrangement and isomerization or C=C bond cleavage. They undergo carbolithiation with a range of organolithium reagents, generating benzyllithium intermediates in a stereospecific manner which may undergo N to C aryl migration to yield thiocarbamates with tertiary substituents. A simple base-promoted alcoholysis reveals a series of hindered tertiary thiols with branched carbon skeletons.**

Sulfur plays an essential role in many classes of functional molecules,[1] and 7 of the top 10 best selling drugs in 2011 contain sulfur.[2] Despite this, methods for the synthesis of sulfur-containing compounds are much less well developed than those leading to their O or N counterparts. Sulfur functions are often considered more as useful tools for the synthesis of nonsulfur containing targets than for the synthesis of targets that retain the sulfur atom.[3] Functional groups containing S(II) in particular are generally introduced late in a synthetic sequence, using substitution chemistry, and even quite simple classes of compounds (chiral tertiary thiols for example) remain relatively unexplored as synthetic targets.[4]

Here we show that the thiocarbamate group, by virtue of its Li-coordinating abilities,[5] provides a useful tool for the connective synthesis of thiols by promoting the carbolithiation of *S*-alkenyl groups. Coupling the carbolithiation with intramolecular delivery of an aryl group from N to C allows the synthesis of tertiary thiols with, in many cases, diastereoselective control.

We previously showed that the deprotonation of *S*-benzyl-*N*-aryl thiocarbamates leads to configurationally stable organolithiums that undergo aryl migration reactions typical of related functional groups to form,

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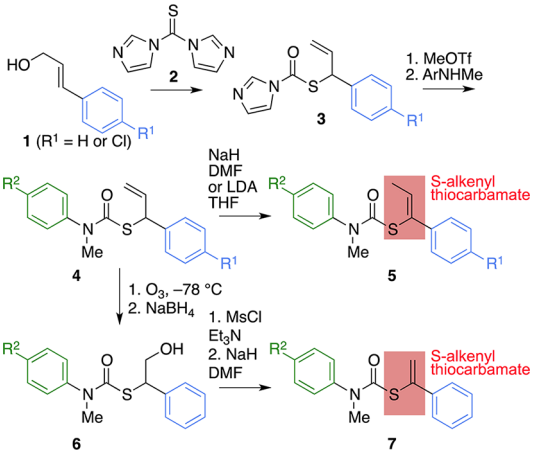
stereospecifically, a new quaternary center adjacent to the sulfur atom.[6] Carbolithiation provides a connective alternative to deprotonation for the formation of organolithiums,[7] and with the aim of investigating the hitherto unexplored carbolithiation of unsaturated thiocarbamates,[8] two series of alkenes were made by the methods illustrated in Scheme 1. Adapting approaches to *N*-alkenylureas[9] or *O*-alkenylcarbamates[10] requiring a C=X-containing precursor was not an option, given the offensiveness of thioketones,[11] so an alternative route was developed. Cinnamyl alcohols **1** were treated with thiocarbonyldiimidazole (TCDI, **2**) to form an adduct which underwent immediate [3,3]-sigmatropic rearrangement to **3**. Methylation of the remaining imidazole and substitution by an *N*-methylaniline gave the thiocarbamates **4**.[12] These were converted into the two classes of *S*-alkenyl thiocarbamates either by base-promoted isomerization to the trisubstituted alkenes **5**[13] or by oxidative cleavage and reduction to give **6** followed by elimination to the disubstituted alkenes **7**.[14] The trisubstituted alkenes **5** were formed as an inseparable mixture of *E*/*Z* isomers, in which the *Z* isomer predominated (as shown by NOE).

The reactivity of *S*-alkenyl thiocarbamates was explored initially with thiocarbamates **7**. A series of compounds **7a**–**d** was first treated at −78 °C in THF with a range of organolithiums (Scheme 2). The results are reported in Table 1. Treatment of thiocarbamate **7a**–**c** with *n*-BuLi, *s*-BuLi, PhLi, and MeLi led to the formation of the corresponding rearranged products **9** (entries 1, 3, 4, 6, 8–12). The reaction in these cases presumably proceeds by initial attack of the alkyllithium on the *β*-position of the

Scheme 1. Synthesis of *S*-Alkenyl-*N*-aryl Thiocarbamates



vinylthiocarbamate, resulting in the formation of an intermediate organolithium **8Li** by carbolithiation. The known[6] N to C aryl migration ensues, giving the rearranged thiocarbamate anion **9Li** and hence, after low temperature protonation,[15] the tertiary thiocarbamate **9**.

Rearrangement was not seen with **7a** using *i*-PrLi or with *t*-BuLi as nucleophiles. In the first case the carbolithiation took place to give **8b** in low yield and was accompanied by amide byproducts arising from attack of *i*-PrLi on the carbonyl group of the thiocarbamate. With *t*-BuLi, the carbolithiation was high yielding, and on quenching the unrearranged addition product **8e** was obtained, presumably because steric hindrance at the C α to S is too great to allow intramolecular attack on the aromatic ring[16] (though rearrangement does take place with **7b**). Yields from **7c** were low, probably because of the poor reactivity of the electron-rich tolyl ring toward attack by the benzyllithium. With the 2,6-dimethylated ring of **7d**, unsurprisingly, carbolithiation (giving **8l**) but not rearrangement was observed, even with *n*-BuLi (entry 13).[17]

Rearrangements of the carbolithiation products of **5** were slower than those from **7** (Scheme 3). In an initial study (Table 2, entry 1), **5a** was treated with *n*-BuLi at −78 °C for 2 h. The carbolithiation product **10a** was formed in high yield, but no traces of rearranged **11a** were detected (entry 1). Although the starting material **5a** was a mixture of 7:1 *Z*/*E* isomers, the product **10a** was formed as a 4:1 mixture of diastereoisomers **10a** and ***epi*-10a** suggesting that the intermediate organolithium **10Li** may undergo

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(7) (a) Klein, S.; Marek, I.; Poisson, J.-F.; Normant, J.-F. *J. Am. Chem. Soc.* **1995**, *117*, 8853. (b) Norsikian, S.; Marek, I.; Poisson, J.-F.; Normant, J.-F. *J. Org. Chem.* **1997**, *62*, 4898. (c) Wei, X.; Taylor, R. J. K. *Tetrahedron: Asymmetry* **1997**, *8*, 665. (d) Norsikian, S.; Marek, I.; Normant, J. F. *Tetrahedron Lett.* **1997**, *38*, 7523. (e) Norsikian, S.; Marek, I.; Klein, S.; Poisson, J.-F.; Normant, J.-F. *Chem.—Eur. J.* **1999**, *5*, 2055. (f) Norsikian, S.; Baudry, M.; Normant, J.-F. *Tetrahedron Lett.* **2000**, *41*, 6575. (g) Hogan, A.-M. L.; O'Shea, D. F. *J. Org. Chem.* **2008**, *73*, 2503.

(8) Related unsaturated ureas and carbamates undergo carbolithiation: *N*-vinyl carbamates: (a) Gericke, R.; Harting, J.; Lues, I.; Schittenhelm, C. *J. Med. Chem.* **1991**, *34*, 3074. (b) Lepifre, F.; Cottineau, B.; Mousset, D.; Bouyssou, P.; Coudert, G. *Tetrahedron Lett.* **2004**, *45*, 483. (c) Cottineau, B.; Gillaizeau, I.; Farard, J.; Auclair, M. L.; Coudert, G. *Synlett* **2007**, 1925. *O*-Vinyl carbamates: (d) Peters, J. G.; Seppi, M.; Fröhlich, R.; Wibbeling, B.; Hoppe, D. *Synthesis* **2002**, *3*, 381. (e) Superchi, S.; Sotomayor, N.; Miao, G.; Joseph, B.; Campbell, M. G.; Snieckus, V. *Tetrahedron Lett.* **1996**, *37*, 6061. (f) Fournier, A. M.; Clayden, J. *Org. Lett.* **2012**, *14*, 142. *N*-Vinyl ureas: (g) Clayden, J.; Donnard, M.; Lefranc, J.; Minassi, A.; Tetlow, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 6624. (h) Tait, M.; Donnard, M.; Minassi, A.; Lefranc, J.; Bechi, B.; Carbone, G.; O'Brien, P.; Clayden, J. *Org. Lett.* **2013**, *15*, 34. (i) Lefranc, J.; Minassi, A.; Clayden, J. *Beilstein J. Org. Chem.* **2013**, *6*, 628.

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(11) Voss, J. *J. Sulfur Chem.* **2009**, *30*, 167.

(12) For a more general method developed recently, see: Mingat, G.; Clayden, J. *Synthesis* **2012**, 2723.

(13) An attempted isomerization using a ruthenium hydride catalyst (see ref 9) failed.

(14) We have since developed a more efficient route to thiocarbamates **7**: Castagnolo, D.; Luisi, R.; Clayden, J. *Manuscript in preparation.*

(15) Propionic acid remains liquid even at low temperature, avoiding lack of reproducibility associated with the warming caused by freezing of for example acetic acid. Warming the reaction mixture before this acidifation leads to hydrolysis of the thiocarbamate: see later.

(16) The related vinylurea behaves similarly with *t*-BuLi: see ref 8a

(17) 2,6-Dimethylphenyl rings do however rearrange in lithiated ureas: Clayden, J.; Dufour, J.; Grainger, D.; Helliwell, M. *J. Am. Chem. Soc.* **2007**, *129*, 7488.

(18) Although we could not unequivocally assign the relative configuration of **10** or **11**, we assume, in line with precedent (ref 6, 8g) that the carbolithiation proceeds with *syn* stereospecificity, that the resulting organolithiums are (in general) configurationally stable on the time scale of the reactions, and that both protonation and aryl migration are retentive.

Scheme 2. Carbolithiation–Rearrangement of Thiocarbamates **7**

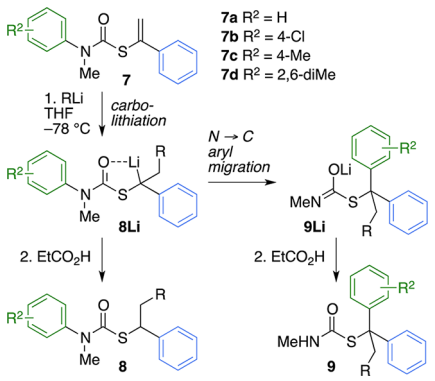


Table 1. Carbolithiation–Rearrangement of **7**

entry	R^2	thiocarbamate	R	product	yield/%
1	H	**7a**	*n*-Bu	**9a**	60
2	H	**7a**	*i*-Pr	**8b**	10
3	H	**7a**	Ph	**9c**	84
4	H	**7a**	*s*-Bu	**9d**	54
5	H	**7a**	*t*-Bu	**8e**	46
6	4-Cl	**7b**	*n*-Bu	**9f**	66
8	4-Cl	**7b**	Ph	**9g**	60
9	4-Cl	**7b**	*t*-Bu	**9h**	38
10	4-Cl	**7b**	Me	**9i**	44
11	4-Me	**7c**	*n*-Bu	**9j**	31
12	4-Me	**7c**	Ph	**9k**	24
13	2,6-diMe	**7d**	*n*-Bu	**8l**	80

partial epimerization (as indicated in Scheme 3) to ***epi*-10Li** on the time scale of the reaction.[18]

Next, thiocarbamate **5a** was treated with *n*-BuLi for 1 h at −78 °C and the reaction mixture was then allowed to warm slowly to room temperature over 1 h (entry 2). Rearrangement was complete under these conditions: no traces of carbolithiation product **10a** were detected, and instead the rearranged thiol **12a** was isolated in 52% yield. Rearrangement to thiocarbamate **11Li**, followed by elimination of lithium thiolate **12Li** from the lithiothiocarbamate, probably occurs at > −40 °C.

Reaction of **5a** with *i*-PrLi at −78 °C also led to the formation of the carbolithiated thiocarbamate **10b** as the only reaction product in good yield (entry 3). In an attempt to accelerate the reaction without promoting epimerization or elimination, DMPU was added to this reaction, resulting in a 1:2 mixture of **10b** and **11b** (entry 4).[19] Carbolithiation of **5a** with PhLi and *t*-BuLi led however to the formation of the carbolithiated adducts **10c** and **10d** as the only products even in the presence of DMPU (entries 5, 6).

Since the electronic properties of the migrating ring may influence the rate of the rearrangement, the carbolithiation of thiocarbamates **5b**–**e** bearing a range of *N*-aryl substituents was explored. Thiocarbamates **5b** and **5c** with a *p*-chlorophenyl and 1-naphthyl migrating ring respectively were treated with MeLi, *n*-BuLi, *i*-PrLi, PhLi, or *t*-BuLi (entries 7–13). Even in the absence of DMPU, all reactions gave generally moderate to good yields of carbolithiation–rearrangement products **11c**–**i**. However, as had been noted with **7a**, the *t*-BuLi adduct of **5b** was reluctant to rearrange and the major product obtained was the addition product **10f** (entry 10). The increased rate of the rearrangement relative to any epimerization of the reaction intermediate is evident in the stereospecificity of these reactions. The diastereoisomeric ratios of the rearrangement products **11** were uniformly 6.5:1 from **5b** and 30:1 from **5c**, both the same as the ratios of geometrical isomers of the starting thiocarbamates. Presumably, in these cases, rearrangement is faster than epimerization of the organolithium intermediate **10Li**.

Two thiocarbamates **5d** and **5e** bearing an electron-donating group on the *N*-phenyl ring (*p*-Me and *p*-OMe respectively) were carbolithiated with *n*-BuLi in the presence of DMPU (entries 14, 15). Carbolithiation of **5d** did not initiate rearrangement, and **10j** was isolated as the only product. Interestingly, the methoxy-substituted thiocarbamate **5e** underwent stereospecific rearrangement to give a 8:1 mixture of the diastereoisomers of **11k**.

Finally, carbolithiation of thiocarbamates substituted on the ring α to the S atom were explored. Treatment of **5f** with *n*-BuLi at −78 °C led to the carbolithiation product **10l** in high yield (entry 16), indicating that the *p*-chlorophenyl ring is compatible with the carbolithiation step. However no traces of rearranged **11l** were observed. Increasing the temperature to −60 °C promoted some rearrangement, with a small amount of **11l** formed after 16 h (entry 17). A further increase of the temperature to −40 °C afforded **11l** in 28% yield together with a considerable amount of **10l** (entry 18). However, when the carbolithiation was carried out at −60 °C for 16 h in the presence of LiCl,[20] rearranged product **11l** was obtained almost exclusively in good yield, but as a 4:1 mixture of diastereoisomers (entry 19), probably due to epimerization during the prolonged reaction time.

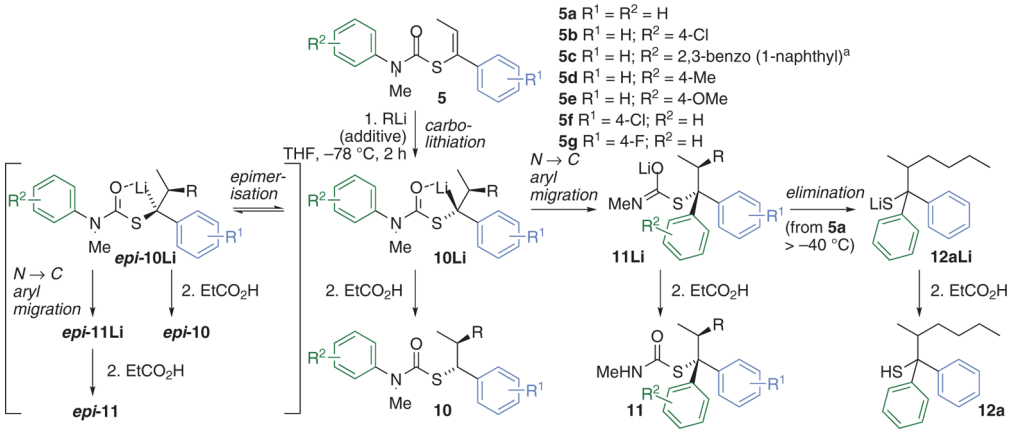
Similarly, carbolithiation of **5f** with PhLi under the same reaction conditions led to rearranged **11m** as a 2:1 mixture of diastereoisomers (entry 20). The *p*-fluoro group of **5g** appears to be too anion stabilizing to permit rearrangement, and the carbolithiated product **10n** was isolated in good yield (entry 21).

Rearranged products **9** and **11** were isolated as thiocarbamates by quenching with acid[15] at temperatures < −40 °C. Nevertheless, the carbolithiation–rearrangement sequence provides an effective method to make functionalized thiols stereospecifically, since 'deprotection' of *N*-methyl thiocarabamates is straightforward. Treatment of **9** or **11** with NaOEt in EtOH reveals thiols **13** (from **9**) and **12** (from **11**) in good yield (Scheme 4).

(19) DMPU, like other lithium coordinating cosolvents, typically accelerates aryl migrations in organolithiums. See ref 17.

(20) LiCl, like DMPU, accelerates the rate of related rearrangements, but without causing rapid epimerization at the lithium-bearing centre: see Fournier, A. M.; Brown, R. A.; Farnaby, W.; Miyatake-Ondozabal, H.; Clayden, J. *Org. Lett.* **2010**, *12*, 2222.

Scheme 3. Stereospecificity in the Carbolithiation–Rearrangement of Thiocarbamates **5**



[a] **5c** has an *N*-ethyl rather than an *N*-methyl substituent.

Table 2. Carbolithiation–Rearrangement of **5**

entry	R^1	R^2	SM	*Z*/*E* ratio	R =	product	yield/%	dr
1	H	H	**5a**	7:1	*n*-Bu	**10a**	78	4:1
2	H	H	**5a**	7:1	*n*-Bu[a]	**12a**	52	–
3	H	H	**5a**	7:1	*i*-Pr	**10b**	63	2:1
4	H	H	**5a**	7:1	*i*-Pr[b]	**10b**	39	3.5:1
						11b	18	
5	H	H	**5a**	7:1	Ph	**10c**	33	–[c]
6	H	H	**5a**	7:1	*t*-Bu	**10d**	36	1.6:1
7	H	4-Cl	**5b**	6.5:1	Me	**11c**	66	–[c]
8	H	4-Cl	**5b**	6.5:1	*n*-Bu	**11d**	81	6.5:1
9	H	4-Cl	**5b**	6.5:1	Ph	**11e**	58	6.5:1
10	H	4-Cl	**5b**	6.5:1	*t*-Bu	**10f**	37	5.6:1
						11f	13	
11	H	2,3-benzo[d]	**5c**[e]	30:1	*n*-Bu	**11g**	65	30:1
12	H	2,3-benzo[d]	**5c**[e]	30:1	*i*-Pr	**11h**	41	30:1
13	H	2,3-benzo[d]	**5c**[e]	30:1	Ph	**11i**	61	30:1
14	H	4-Me	**5d**	6:1	*n*-Bu[b]	**10j**	55	1:1
15	H	4-OMe	**5e**	8:1	*n*-Bu[b]	**11k**	35	8:1
16	4-Cl	H	**5f**	5:1	*n*-Bu	**10l**	81	2.3:1
17	4-Cl	H	**5f**	5:1	*n*-Bu[f]	**10l**	49	1.5:1
						11l	8	>4:1
18	4-Cl	H	**5f**	5:1	*n*-Bu[g]	**10l**	57	1:1
						11l	28	5:1
19	4-Cl	H	**5f**	5:1	*n*-Bu[f,h]	**11l**	55	4:1
20	4-Cl	H	**5f**	5:1	Ph[f,h]	**11m**	65	2:1
21	4-F	H	**5g**	8:1	*n*-Bu	**10n**	76	2.3:1

[a] Allowed to warm to rt. [b] DMPU added (10:1 THF/DMPU by vol. = ca. 6 equiv). [c] Not determined. [d] 1-Naphthyl. [e] **5c** has an *N*-Et rather than an *N*-Me substituent. [f] At –60 °C. [g] At –40 °C. [h] LiCl (4 equiv) added.

In summary, carbolithiation of vinyl thiocarbamates generates benzylic organolithiums that may undergo intramolecular arylation to provide tertiary thiocarbamates, which are themselves precursors to new families of tertiary thiols.

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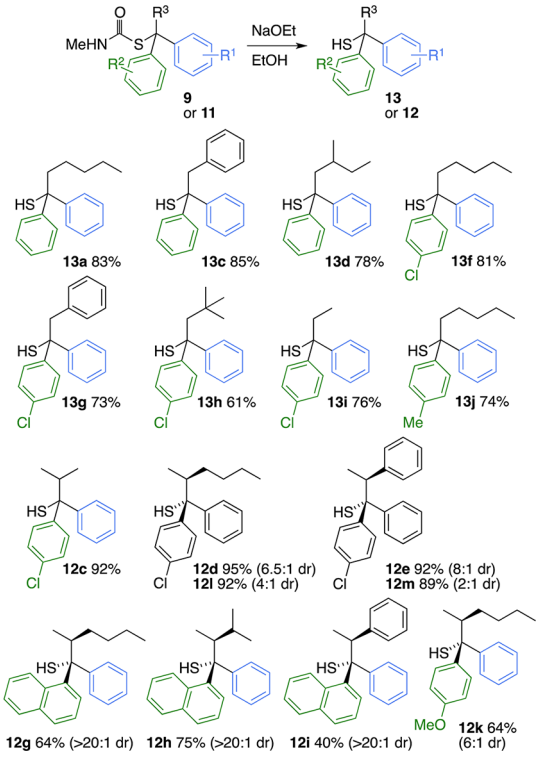
Scheme 4. Tertiary Thiols from Tertiary Thiocarbamates



Supporting Information Available. Characterization and experimental details for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.