Highly diastereoselective formation and reactions of a non-mesomerically stabilized, lithiated α-thiocarbanion†

Ravindra P. Sonawane, Roland Fröhlich‡ and Dieter Hoppe*

Received (in Cambridge, UK) 20th March 2006, Accepted 23rd May 2006
First published as an Advance Article on the web 14th June 2006
DOI: 10.1039/b604029b

A new class of non-mesomerically stabilized, unbranched, configurationally stable lithiated α-thiocarbanion has been synthesized and its stereospecific reactions with several electrophiles were investigated.

Asymmetric induction on a prochiral methylene group through deprotonation followed by electrophilic substitution is one of the basic asymmetric C–C bond forming reactions.[1] Synthetic utility of this process has been limited to the α-heteroatom substituted organolithium compounds wherein excellent enantio- and diastereoselectivities have been achieved.[1] Especially, α-oxy[1b] and α-amino[1d] organolithium compounds have proved to be highly valuable in synthetic organic chemistry. In contrast, α-thio substituted carbanions are known for their high configurational instability and rapid epimerization even at low temperatures.[1c,2] Configurational stability could be achieved in very few examples[3] in which the carbanionic center bears branching which enhances the barrier of epimerization as proposed by Hoffmann and coworkers.[4] Lack of such a branching at the carbanionic center results in configurational instability of the lithiated carbanion. In such cases, one has to rely on post deprotonation enantioenrichment for obtaining useful selectivity.[5] In order to find an unbranched, configurationally stable α-thiocarbanion and establishing its stereochemical behaviour, we became interested in the thiocarbamates derived from α-amino acids.

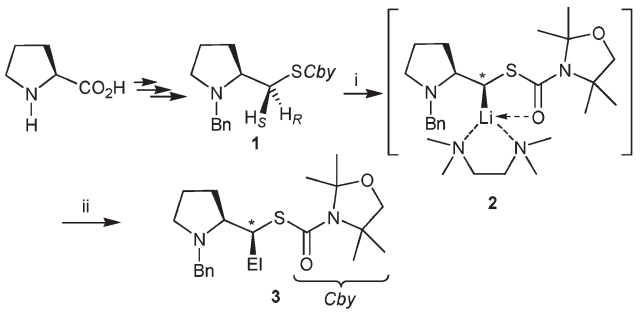
Herein, we present the initial results obtained from our investigations on the deprotonation and stereochemical behaviour of thiocarbamate **1** derived from (*S*)-prolinol (Scheme 1).

When thiocarbamate **1** was deprotonated with 1.2 eq. of *sec*-BuLi in the presence of achiral additive *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), one of the two diastereotopic protons is abstracted to form the lithiated species **2**. Trapping this lithiated species with various electrophiles afforded the corresponding substitution products **3** in high yields and excellent diastereoselectivities (Table 1).§

The results outlined in Table 1 show that the deprotonation–substitution process takes place in a highly selective manner. In all cases, no trace of the second diastereomer could be detected by TLC, NMR, or GC.

In order to gain information regarding the configurational stability of the intermediate lithium species **2** and to find out whether the selectivity is achieved in the deprotonation step or in the post-deprotonation reactions, an *in situ* deprotonation was carried out wherein the substrate **1** was deprotonated in the presence of the electrophile *tert*-butyldimethylsilyl triflate (TBDMSOTf) (Scheme 2).

This experiment resulted in the formation of the same diastereomer (*dr* > 97 : 3) as is obtained by the normal deprotonation–substitution sequence. This observation is indicative of the fact that the lithium species **2** is formed by selective deprotonation and is configurationally stable at −78 °C.[6] If **2** would be formed non-selectively, a mixture of two diastereomers should be obtained.

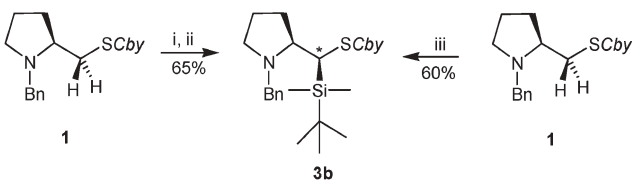


Scheme 1 *Reagents and conditions*: i) 1.2 eq. *sec*-BuLi, 1.2 eq. TMEDA, toluene, −78 °C, 3 h; ii) 3.0 eq. electrophile (ElX).

Table 1 Results of the substitution of **2** by various electrophiles

Entry	ElX (product)	Yield	*dr*	$[\alpha]_D$/deg cm^2 g^{-1}
1	TMSCl (**3a**)	83%	>97 : 3	−81.5 (*c* = 1.15, $CHCl_3$)
2	TBDMSOTf (**3b**)	65%	>97 : 3	−88.0 (*c* = 0.96, CH_2Cl_2)
3	MeI (**3c**)	83%	>97 : 3	−47.7 (*c* = 1.23, $CHCl_3$)
4	EtI (**3d**)	84%	>97 : 3	−76.3 (*c* = 1.17, $CHCl_3$)
5	BnBr (**3e**)	98%	>97 : 3	−4.7 (*c* = 1.09, $CHCl_3$)

[a] ElX = electrophile; *dr* = diastereomeric ratio.



Scheme 2 *Reagents and conditions*: i) 1.2 eq. *sec*-BuLi, 1.2 eq. TMEDA, toluene, −78 °C; ii) 3.0 eq. TBDMSOTf; iii) 1.2 eq. *sec*-BuLi, 1.2 eq. TMEDA, toluene, −78 °C, 3.0 eq. TBDMSOTf, *in situ*.

Organisch-Chemisches Institut der Universität, Westfälische Wilhelms-Universität Münster, Corrensstrasse 40, 48149, Münster, Germany. E-mail: dhoppe@uni-muenster.de

† Electronic supplementary information (ESI) available: Experimental details for the preparation of starting material **1**, analytical data for compounds **3a–3e** and **5**. See DOI: 10.1039/b604029b

‡ Responsible for X-ray crystal structure analysis.

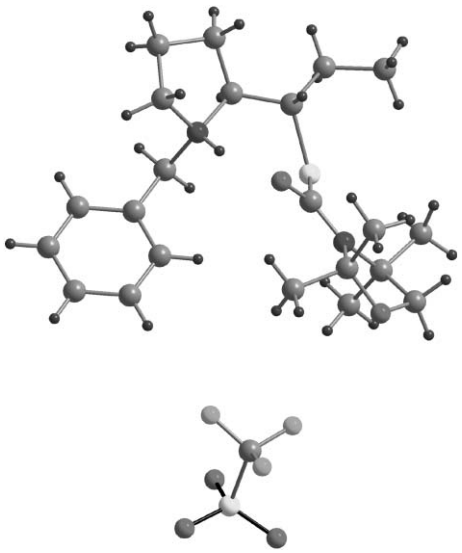
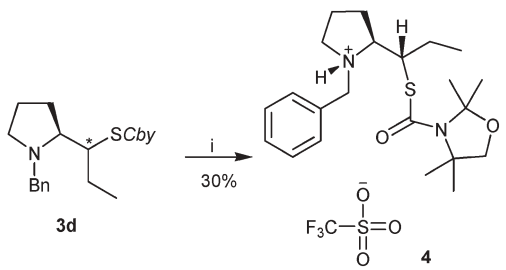


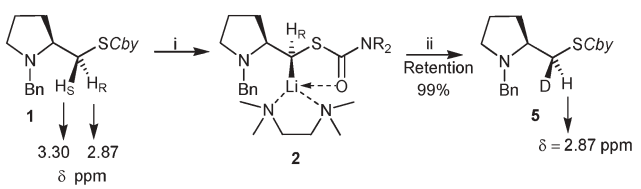
Fig. 1 X-Ray crystal structure of triflate salt **4**.



Scheme 3 *Reagents and conditions*: i) 2 eq. $Cu(OTf)_2$, CH_2Cl_2, rt, 24 h.

The absolute configuration of one of the substitution products, derived from ethyl iodide (Entry 4, Table 1), was elucidated by X-ray crystal structure analysis (under anomalous dispersion)¶ of its triflate salt **4** (Fig. 1). The triflate salt was obtained by reaction of **3d** with copper(II) triflate in dichloromethane (Scheme 3). The newly generated stereocenter is conclusively proved to be *S*-configured.

Strong evidence was found that the lithium compound **2** has [2*S*,2(1*S*)]-configuration and the substitution with the reported electrophiles proceeds with retention of configuration: Deuteration of **2** with CH_3OD afforded **5** as a single diastereomer (Scheme 4). Since the diastereotopic protons H_R and H_S in **1** have very distinct ^1H NMR shifts (supported by quantum-chemical calculations[7]), **5** could be assigned to the [2*S*,2(1*S*)] configuration as deuteration of chiral lithium carbanions proceeds with retention in all known examples. The reasons why the deprotonation of **1** takes the opposite stereochemical course to that observed for the *O*-carbamate case (**1**, O for S)[8] are presently unknown.



Scheme 4 *Reagents and conditions*: i) 1.2 eq. *sec*-BuLi, 1.2 eq. TMEDA, toluene, −78 °C, 3 h; ii) 10.0 eq. CH_3OD.

Thus, we have found a new class of unbranched, non-mesomerically stabilized, configurationally stable α-thiocarbanion[9] which undergoes electrophilic substitution with various electrophiles to furnish the products in good to excellent yields and excellent diastereoselectivities. This method provides an easy access to chiral secondary β-amino thiols. The origin of the selectivity, mode of electrophilic substitution, and further extension of this protocol to other substrates is currently under investigation.

This work was supported by Sonderforschungsereich 424. R. P. S. gratefully acknowledges International NRW Graduate School of Chemistry, Münster, Germany, for doctoral scholarship. Excellent experimental assistance from Ms Mareike Renger is also acknowledged.

Notes and references

§ Typical experimental procedure: In a flame dried 10 mL round bottom flask was dissolved **1** (100 mg, 0.27 mmol, 1.0 eq.) in 5 mL of absolute toluene under argon atmosphere. To this was added 37 mg (0.32 mmol, 1.2 eq.) of TMEDA and the reaction flask was cooled to −78 °C. *sec*-BuLi (1.36 M, 0.23 mL, 0.32 mmol, 1.2 eq.) was added in a dropwise manner and the reaction mixture was stirred at −78 °C for 3 hours. Afterwards, appropriate electrophile (0.81 mmol, 3.0 eq.) was injected and the reaction mixture was stirred till no starting material could be detected by TLC. The reaction was then quenched with 2 mL of water, the phases were separated and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The collective organic layer was dried over anhydrous $MgSO_4$, filtered through glass wool, concentrated and subjected to flash column chromatography (diethyl ether–pentane) to obtain analytically pure product.

¶ $C_{23}H_{35}F_3N_2O_5S_2$, *M* 540.65, orthorhombic, space group $P2_12_12_1$, *a* 8.353(1), *b* 13.073(1), *c* 24.181(1) Å, *U* 2640.5(4) $Å^3$, *Z* 4, *T* 198(2) K, μ(Mo-Kα) 0.259 mm^{-1}, 6278 reflections measured, final *R*1 and *wR*2 0.0536 and 0.0995. CCDC 602731. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b604029b

1 Reviews: (*a*) D. Hoppe and T. Hense, *Angew. Chem., Int. Ed.*, 1997, **36**, 2282; *Angew. Chem.*, 1997, **109**, 2376; (*b*) D. Hoppe, F. Marr and M. Brüggemann, *Top. Organomet. Chem.*, 2003, **5**, 61–137; (*c*) T. Toru and S. Nakamura, *Top. Organomet. Chem.*, 2003, **5**, 177–216; (*d*) P. Beak, T. Johnson, D. Kim and S. Kim, *Top. Organomet. Chem.*, 2003, **5**, 139–176; (*e*) D. Hoppe and G. Christoph, in *The Chemistry of Organolithium Compounds*, ed. Z. Rappoport and I. Marek, Wiley, Chichester, 2004, pp. 1055–1164.

2 (*a*) P. G. McDougal, B. Condon, M. Laffose, Jr., A. Lauro and D. Vanderveer, *Tetrahedron Lett.*, 1988, **29**, 2547; (*b*) P. McDougal and B. Condon, *Tetrahedron Lett.*, 1989, **30**, 789; (*c*) A. Krief, G. Evrard, E. Badaoui, V. DeBeys and R. Dieden, *Tetrahedron Lett.*, 1989, **30**, 5635; (*d*) H. J. Reich and M. D. Bowe, *J. Am. Chem. Soc.*, 1990, **112**, 8994.

3 (*a*) D. Hoppe, B. Kaiser, O. Stratmann and R. Fröhlich, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2784, *Angew. Chem.*, 1997, **109**, 2872; (*b*) O. Stratmann, B. Kaiser, R. Fröhlich, O. Meyer and D. Hoppe, *Chem.-Eur. J.*, 2001, **7**, 423; (*c*) F. Marr and D. Hoppe, *Org. Lett.*, 1999, **1**, 2081; (*d*) F. Marr and D. Hoppe, *Org. Lett.*, 2002, **4**, 4217.

4 (*a*) R. W. Hoffmann, T. Ruhl and J. Harbach, *Liebigs Ann. Chem.*, 1992, 725; (*b*) R. W. Hoffmann, M. Julius, F. Chemla, T. Ruhland and G. Frenzen, *Tetrahedron*, 1994, **50**, 6049; (*c*) R. W. Hoffmann, R. K. Dress, T. Ruhland and A. Wenzel, *Chem. Ber.*, 1995, **128**, 861; (*d*) T. Ruhland, R. Dress and R. W. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1467, *Angew. Chem.*, 1993, **105**, 8487.

5 (*a*) R. Otte, R. Fröhlich, B. Wibbeling and D. Hoppe, *Angew. Chem., Int. Ed.*, 2005, **44**, 5492, *Angew. Chem.*, 2005, **117**, 5629; (*b*) S. Nakamura, Y. Ito, L. Wang and T. Toru, *J. Org. Chem.*, 2004, **69**, 1581; (*c*) S. Nakamura, A. Furutani and T. Toru, *Eur. J. Org. Chem.*, 2002, 1690; (*d*) S. Nakamura, R. Nagakawa, Y. Watanabe and T. Toru, *Angew. Chem., Int. Ed.*, 2000, **39**, 353, *Angew. Chem.*, 2000, **112**, 361; (*e*) S. Nakamura, R. Nagakawa, Y. Watanabe and T. Toru, *J. Am. Chem. Soc.*, 2000, **142**, 11342.

6 An unlikely possiblity remains: If the equilibrium between diastereomers **2** is extremely on the side of [2*S*,2(1*S*)]-**2** and the equilibration proceeds extremely rapidly, the same result is expected. All the attempts to synthesize the opposite diastereomer *via* lithio-destannylation failed as α-thio stannanes could not be synthesized. Treatment of **5** with *s*-BuLi/TMEDA resulted only in dedeuteration, showing the high kinetic preference that overrides any possible isotope effect.
7 C. Mück-Lichtenfeld, unpublished results.
8 B. Weber, J. Schwerdfeger, R. Fröhlich, A. Göhrt and D. Hoppe, *Synthesis*, 1999, 1915.
9 The only example where an unbranched α-thioorganolithium compound is believed to be stable has been reported by S. Gibson see: S. Gibson (née Thomas), P. Ham, G. Jefferson and M. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2161.