COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Dearomatising rearrangements of lithiated thiophenecarboxamides†

Jonathan Clayden,*[a] Rachel Turnbull,[a] Madeleine Helliwell[a] and Ivan Pinto[b]

[a] *Department of Chemistry, University of Manchester, Oxford Road, Manchester, UK M13 9PL. E-mail: j.p.clayden@man.ac.uk*

[b] *GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts, UK SG1 2NY*

Received (in Cambridge, UK) 17th June 2004, Accepted 13th August 2004
First published as an Advance Article on the web 22nd September 2004

Thiophene-3-carboxamides bearing allyl or benzyl substituents at nitrogen undergo dearomatising cyclisation on treatment with LDA. Rearrangements transform the dearomatised products into pyrrolinones, azepinones or partially saturated azepinothiophenes.

The dearomatisation of aromatic and heteroaromatic compounds is a valuable synthetic tool, because it allows the control over regioselectivity possible in aromatic systems (using either classical electrophilic substitution or directed metallation techniques) to be coupled with the introduction of stereochemistry at newly created tetrahedral centres in the dearomatised products.[1–4] Particularly valuable are methods for partial dearomatisation, which allow the reactivity of the remaining unsaturation to be exploited. Methods for dearomatisation such as partial reduction under Birch conditions,[1,5,6] nucleophilic addition to arene-chromium complexes,[3] and dearomatising cyclisation[7,8] have been applied to both benzenoid and heteroaromatic systems, but thiophenes have remained relatively unexplored, partly because of their instability towards ring-opening on reduction.[6,9]

We recently reported that the dearomatising cyclisation of lithiated amides,[8] which was initially reported for *N*-benzylbenzamides,[10,11] is a successful method for the stereocontrolled synthesis of a variety of unusual azaheterocycles from pyrrolecarboxamides.[12] We now report that lithiated thiophenecarboxamides also undergo dearomatising cyclisation, sometimes followed by further rearrangement of the products, to yield pyrrolinones, azepinones or partially saturated azepinothiophenes.

The starting thiophenecarboxamides **3**, **4**, **7** and **8** were made by standard methods from thiophene-3-carboxylic acid or its 5-bromo derivative. Suzuki coupling between **4** and methyl- or phenylboronic acid gave the 5-substituted amides **5** and **6**.

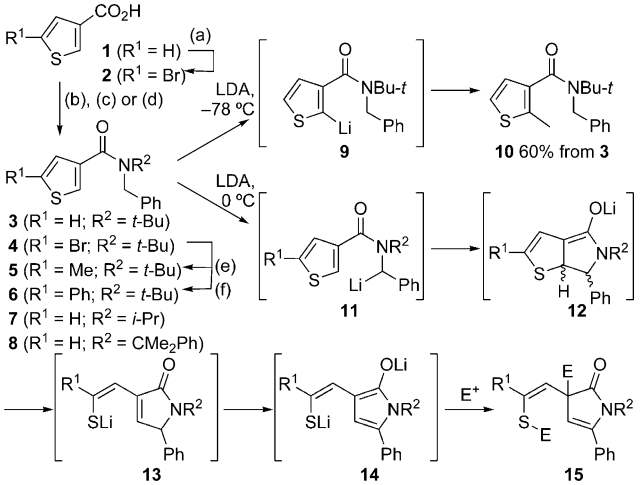
Treatment of **3** with LDA at −78 °C and methylation returned the 2-methylated amide **10** in 60% yield, presumably *via* the ortholithiated intermediate **9**.[13] We assume therefore that **9** is the kinetically favoured lithiation product from **3**. However, treatment of **3** or **5–8** with an excess of LDA at 0 °C gave, after electrophilic quench, good yields of the rearranged products **15** as shown in Table 1. We propose the mechanism outlined in Scheme 1 for the formation of **15**: some concentration of the benzylic organolithium **11** is presumably formed from **9** by "anion translocation",[14,15] and **11** undergoes dearomatising cyclisation[8] into the 2-position of the thiophene, possibly by an electrocyclic mechanism.[16] The 5,5-fused bicyclic enolate **12** is evidently rather strained, and the C–S bond breaks to yield the pyrrolinone **13**. Excess LDA forms the dianion **14**, and alkylation yields products **15** with the yields shown in Table 1. Protonation of **14** gave only a complex mixture of products, presumably arising from decomposition of the resulting thioaldehyde.

The regiochemistry of the final quench is in accord with previous alkylations of related extended enolates,[10] and the *cis* stereochemistry of the vinyl sulfide, preserved from the thiophene, is evident from the ^{1}H NMR spectrum of **15** (where R^1 = H). It was however possible to form an alternative regioisomeric set of pyrrolinones by cyclising **16** (Scheme 2). Remarkably, but in accordance with previous related results,[17] this cyclisation is fully stereospecific (the products **18** all have enantiomeric excesses > 99%) and must therefore proceed *via* an intermediate organolithium which has configurational stability on the timecale of its cyclisation.[18]

Overall, the cyclisation–rearrangements are a method for pyrrolinone formation by conjugate substitution of the thiophene's sulfur atom.[19] However, our original intention had been to retain

Table 1 Dearomatising cyclisation of *N*-benzyl thiophenecarboxamides

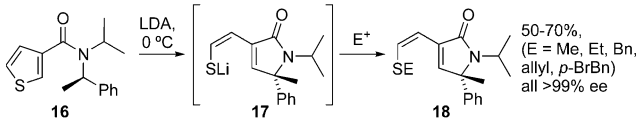
Entry	S. M.	R^1 =	R^2 =	E =	Product	Yield (%)
1	**3**	H	*t*-Bu	Me	**15a**	60
2				Et	**15b**	65
3				Allyl	**15c**	60
4				Bn	**15d**	55
5				*p*-BrBn	**15e**	50
6				*p*-PhBn	**15f**	65
7	**5**	Me	*t*-Bu	Me	**15g**	66
8				Allyl	**15h**	75
9				Bn	**15i**	56
10	**6**	Ph	*t*-Bu	Me	**15j**	60
11				Et	**15k**	61
12				Allyl	**15l**	71
13				Bn	**15m**	50
14				4-BrBn	**15n**	60
15	**7**	H	*i*-Pr	Me	**15o**	65
16				Et	**15p**	62
17				Allyl	**15q**	60
18				Bn	**15r**	67
19				4-BrBn	**15s**	58
20	**8**	H	CMe_2Ph	Me	**15t**	62
21				Et	**15u**	75
22				Allyl	**15v**	66
23				Bn	**15w**	62



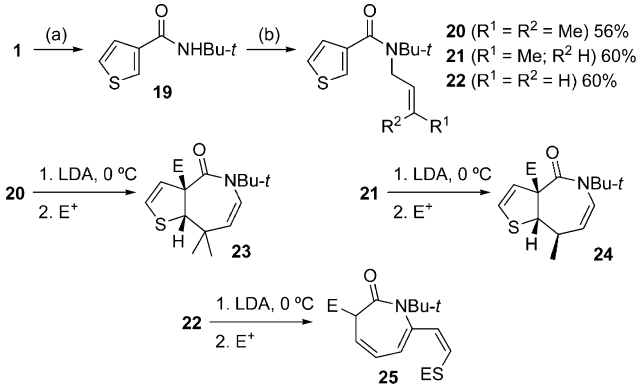
Scheme 1 Dearomatising cyclisation–rearrangement of thiophenecarboxamides. (a) Br_2, AcOH (75%); (b) $SOCl_2$; (c) R^2NHBn; (d) 1. $PhMe_2CNH_2$; 2. NaH, BnBr; (e) $MeB(OH)_2$, $PdCl_2(dppf)$, $NaHCO_3$, MeCN; (f) $PhB(OH)_2$, $PdCl_2(dppf)$, $NaHCO_3$, MeCN.

† Electronic supplementary information (ESI) available: typical procedure: synthesis of **25e**. See http://www.rsc.org/suppdata/cc/b4/b409150g/

DOI: 10.1039/b409150g



Scheme 2 Stereospecific cyclisation of chiral thiophenecarboxamides.



Scheme 3 Preparation and cyclisation of thiophenecarboxamides with allylic *N*-substituents. (a) *t*-BuNH$_2$; (b) NaH, R^{1}R^{2}C=CHCH$_2$Br.

Table 2 Cyclisation of **20–22**: products and yields (%)

S. M. =	**20**	**21**	**22**
E =			
H	**23a**, 71	**24a**, 65	—
Me	**23b**, 51	**24b**, 52	**25a**, 61
Et	**23c**, 60	**24c**, 55	**25b**, 70
Allyl	**23d**, 55	**24d**, 65	**25c**, 65
Bn	**23e**, 50	**24e**, 50	**25d**, 45
p-BrBn	**23f**, 65	—	**25e**, 50

the thiophene ring and form bicyclic products containing both sulfur and nitrogen. We therefore alkylated the amide **19** to form a series of substituted *N*-allyl thiophenecarboxamides, which may undergo cyclisation to yield less strained seven-membered rings.[20] As hoped, exposure of the *N*-prenyl or *N*-crotyl amide **20** or **21** to the usual cyclisation conditions (3 equiv. LDA, 0 °C, 3 h) gave the 5,7-fused heterocycles **23** and **24** (Scheme 3 and Table 2). Allylic deprotonation to yield **26** is followed by dearomatising cyclisation to the enolate **27**. The mechanism then diverges from the one leading to **15** because the dearomatised 7,5-fused bicyclic enolate **27** is sufficiently free of strain to be stable. Quenching with electrophiles yields **23** and **24** without further rearrangement.

However, cyclisation of the *N*-allyl amide **22** under the same conditions gave a product in which the thiophene ring was no longer intact (Scheme 3). The X-ray crystal structure‡ of **25e** (Fig. 1) proved that **25** was not merely the result of thiophene ring opening but was instead a [3*H*]-azepinone which had been formed by a remarkable 1,5-shift of the thiovinyl group from C3 to C7.[21] Scheme 4 shows a suggested mechanism for this rearrangement, in which a proton shift (presumably mediated by LDA, and less favourable or impossible in derivatives of **20** and **21**) sets up the π array required to allow [1,5]-sigmatropic rearrangement. Further

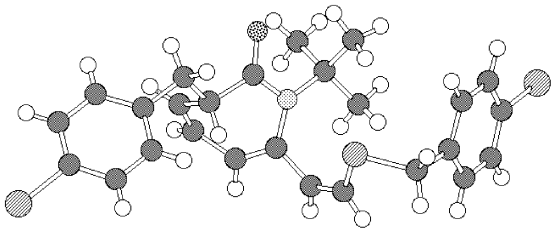
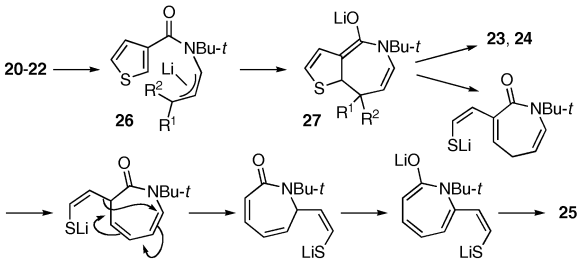


Fig. 1 X-ray crystal structure of **25e**.



Scheme 4 Proposed mechanism of the rearrangement.

deprotonation of the product yields an anionic azepine which is alkylated to give **25**.[22]

We are grateful to the EPSRC for support of this work.

Notes and references

‡ CCDC 242986. See http://www.rsc.org/suppdata/cc/b4/b409150g/ for crystallographic data in .cif or other electronic format.

1 L. N. Mander, *Synlett*, 1991, 134.
2 T. Bach, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 729.
3 A. R. Pape, K. P. Kaliappan and E. P. Kündig, *Chem. Rev.*, 2000, **100**, 2917.
4 T. J. Donohoe, R. Garg and C. A. Stevenson, *Tetrahedron: Asymmetry*, 1996, **7**, 317.
5 A. G. Schultz, *Chem. Commun.*, 1999, 1263.
6 T. J. Donohoe, P. M. Guyo and M. Helliwell, *Tetrahedron Lett.*, 1999, **40**, 435.
7 J. Clayden, *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, 2002.
8 J. Clayden and M. N. Kenworthy, *Synthesis*, 2004, 1721.
9 For attempts to dearomatise thiophenes, see W. G. Blenderman and M. M. Joullié, *Synth. Commun.*, 1981, **11**, 881; K. Nishino, S. Yano, Y. Kohashi, K. Yamamoto and I. Murata, *J. Am. Chem. Soc.*, 1979, **101**, 5059; P. N. Confalone, G. Pizzolato and M. R. Uskokovi'c, *Helv. Chim. Acta*, 1976, **59**, 1005; P. N. Confalone, G. Pizzolato and M. R. Uskokovi'c, *J. Org. Chem.*, 1977, **42**, 135; Z. N. Parnes, I. Yu, M. Lyakhovetskii, M. I. Kalinkin, D. N. Kursanov and L. I. Belen'kii, *Tetrahedron*, 1978, **34**, 1703.
10 A. Ahmed, J. Clayden and S. A. Yasin, *Chem. Commun.*, 1999, 231.
11 J. Clayden, C. J. Menet and D. J. Mansfield, *Org. Lett.*, 2000, **2**, 4229.
12 J. Clayden, R. Turnbull and I. Pinto, *Org. Lett.*, 2004, **6**, 609.
13 M. A. F. Brandao, A. B. de Oliveira and V. Snieckus, *Tetrahedron Lett.*, 1993, **34**, 2437.
14 A. Ahmed, J. Clayden and M. Rowley, *Tetrahedron Lett.*, 1998, **39**, 6103.
15 J. Barluenga, F. J. Fañanás, R. Sanz, C. Marcos and M. Trabada, *Org. Lett.*, 2002, **4**, 1587.
16 J. Clayden, S. Purewal, M. Helliwell and S. J. Mantell, *Angew. Chem., Int. Ed.*, 2002, **41**, 1049 . However, see also A. M. Ramallal, F. López-Ortiz and J. González, *Org. Lett.*, 2004, **6**, 2141.
17 J. Clayden, F. E. Knowles and C. J. Menet, *Synlett*, 2003, 1701 . The stereochemistry of **18**, and hence the sense (retention or inversion) of the reaction is assigned by analogy with this work.
18 Related *N*-substituted tertiary organolithiums have relatively high configurational stability. See N. C. Faibish, Y. S. Park, S. Lee and P. Beak, *J. Am. Chem. Soc.*, 1997, **119**, 11561.
19 Such reactions have been termed "monocyclic rearrangements": see A. J. Boulton, A. R. Katritzky and A. M. Hamid, *J. Chem. Soc. (C)*, 1967, 2005.
20 A. Ahmed, J. Clayden and M. Rowley, *Synlett*, 1999, 1954.
21 [1,5]-Shifts of unsaturated groups are relatively fast. See D. J. Field, D. W. Jones and G. Kneen, *J. Chem. Soc., Chem. Commun.*, 1976, 873; C. D. Anderson, J. T. Sharp and R. S. Strathdee, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2730; C. D. Anderson, J. T. Sharp, E. Stefaniuk and R. S. Strathdee, *Tetrahedron Lett.*, 1976, 305.
22 Protons at the 3-position of azepinones lack the usual acidity associated with positions α to a carbonyl group (L. A. Paquette, *J. Org. Chem.*, 1963, **28**, 3590) and we propose that rearrangement takes place rather than formation of the azepinoxy anion. However, an azepinoxy anion must be formed at some point in the sequence in order to allow α alkylation, and we are unable to rule out the possibility that rearrangement may take place *after* alkylation.