Pergamon

Tetrahedron Letters 43 (2002) 9585–9589

TETRAHEDRON
LETTERS

Synthesis of chiral lithium carbamates from (*S*)-2-(*N*,*N*-dialkyl-aminomethyl)pyrrolidines and (*S*)-methoxymethylpyrrolidine

Uwe Köhn and Ernst Anders*

Institut für Organische Chemie und Makromolekulare Chemie der Friedrich-Schiller-Universität, Lessingstrasse 8, D-07743 Jena, Germany

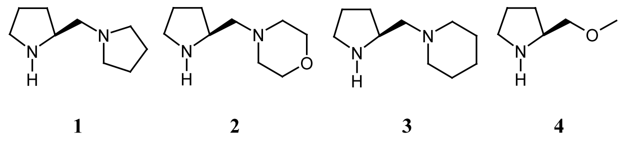
Received 9 October 2002; accepted 24 October 2002

Abstract—A convenient synthesis of chiral lithium *N*-alkyl carbamates **1a**–**4a** from chiral pyrrolidines **1**–**4**, LiH and CO_2 is described. The yields are good to excellent. A combined experimental (^{1}H, ^{6}Li-HOESY, cryoscopy) and theoretical study (B3LYP/6-311++G(d,p)) succeeded in assigning the predominant solution state structure of **1a**. © 2002 Elsevier Science Ltd. All rights reserved.

The preparation and characterization of new chiral carbamates appear to be important in the context of biotin-mediated reactions[1] and for applications in organic synthesis with carbon dioxide.[2] Biological activation of carbon dioxide and its fixation via C–C bonding are realized by biotin-depending enzymes (e.g. acetyl CoA carboxylase). For example, they are able to insert CO_2 into C–H bonds. However, the mechanism of the CO_2 activation reaction has not been completely investigated.[3] Further, lithiated carbamoyl groups play a dominant role in the course of some directed *ortho* metalations (DOM),[4] e.g. for regiospecific introduction of electrophiles into *ortho* position of naphthylamines and tetrahydro-isoquinoline amines.[5] To the best of our knowledge, no attempts to isolate chiral carbamates have been published.

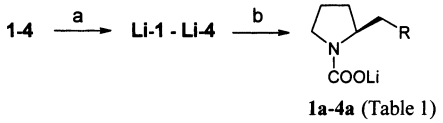
In this article, we summarize our efforts regarding chiral carbamates via the application of a very convenient method starting from (*S*)-2-(1-pyrrolidinyl-, morpholinyl-, piperidinylmethyl)pyrrolidine and (*S*)-2-methoxymethylpyrrolidine (Scheme 1).

We selected the amine **1** to be our model precursor as the corresponding lithiated chiral amide has successfully been applied in a variety of synthetic purposes, e.g. asymmetric deprotonation of epoxides to yield chiral allylic alcohols,[6] and as a chiral catalyst in some asymmetric aldol reactions.[7] (*S*)-2-Methoxymethylpyrrolidine **4** is the precursor in the synthesis of SAMP/RAMP,[8] and has been also used as a chiral auxiliary in the alkylation and silylation of 1,3-diphenylallylamine–alkalimetal compounds.[9] The preparation of the required chiral diamines **1**–**4** has already been described in literature.[10]



Scheme 1. Chiral diamines.

Scheme 2 depicts our approach of a one-pot carbamination. The experimental procedure for the synthesis of lithium carbamate from (*S*)-2-(1-pyrrolidinylmethyl)-pyrrolidine **1** is described as follows.



Scheme 2. *Reagents and conditions*: (a) LiH, THF, 50°C, 1 day; (b) CO_2, 25°C, 1 h.

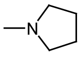
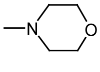
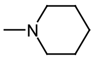
Keywords: carbamates; chiral diamines; lithium; 2D-NMR; cryoscopy; PM3/DFT.

* Corresponding author. Fax: +49(0)3641/948212; e-mail: c5eran@rz.uni-jena.de

PII: S0040-4039(02)02388-2

The addition of chiral diamine **1** to 1 equiv. of LiH in THF solution at 50°C resulted in the deprotonation of the diamine and the formation of lithium (*S*)-2-(1-pyrrolidinyl-methyl)pyrrolidine, **Li-1**. Subsequent reaction with gaseous CO_2 at 25°C yielded a white precipitate in high purity (**1a**, 79%). All compounds are hygroscopic and decompose in acidic conditions. Results are summarized in Table 1.[11]

Table 1. Results of carbamate synthesis

Products	R	Yield [%]$^{a, b}$	$[\alpha]_D^{25}$
1a		79	-15
2a		95	-18
3a		85	-17
4a	—OMe	89	-10

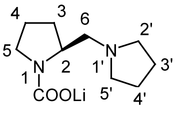
Reactions and conditions: a) LiH/THF/50°C/1d; b) CO_2/THF/25°C/1h. All reactions were carried out under argon atmosphere.

The structures of **1a**–**4a** were determined by 1D-NMR (^1H, ^{13}C, DEPT 135) and 2D-NMR experiments (COSY, HMBC, HMQC, NOESY). The NMR experiments were carried out in deuterated THF at a temperature of 25°C.

At a δ value of 158 ppm, a broad ^{13}C NMR resonance signal from the -N-C=O carbon (pyrrolidine ring) was observed (see Table 2). The HMBC experiment provided additional evidence for the clarification of the structure of the carbamates **1a**–**4a**. The apparent correlation between the -N-C=O carbon atom and the two protons (H2 and H5) indicated the anticipated structure. In addition, a shift to lower field was observed in the ^1H-spectrum for the H2 and H5 protons (see Table 2).

Examination of the aggregation behavior of the carbamates **1a**–**4a** in THF solution by cryoscopy was expected to provide further information on the structures prevalent in solutions. Investigations on this subject have been carried out successfully on a number of organolithium compounds,[12] however, not on any lithium carbamates.

Table 2. Selected ^1H (400 MHz) and ^{13}C (100 MHz) signals of the carbamates **1a**–**4a** in deuterated THF at 25°C



	δ ^{13}C (ppm) NCO	δ ^1H (ppm)	
		H2	H5
1a	158.25	3.19 (**1**)–3.88	2.89 (**1**)–3.30
2a	157.55	3.23 (**2**)–4.11	2.88 (**2**)–3.50
3a	157.96	3.24 (**3**)–4.00	2.89 (**3**)–3.55
4a	157.72	3.26 (**4**)–4.13	2.81 (**4**)–3.43

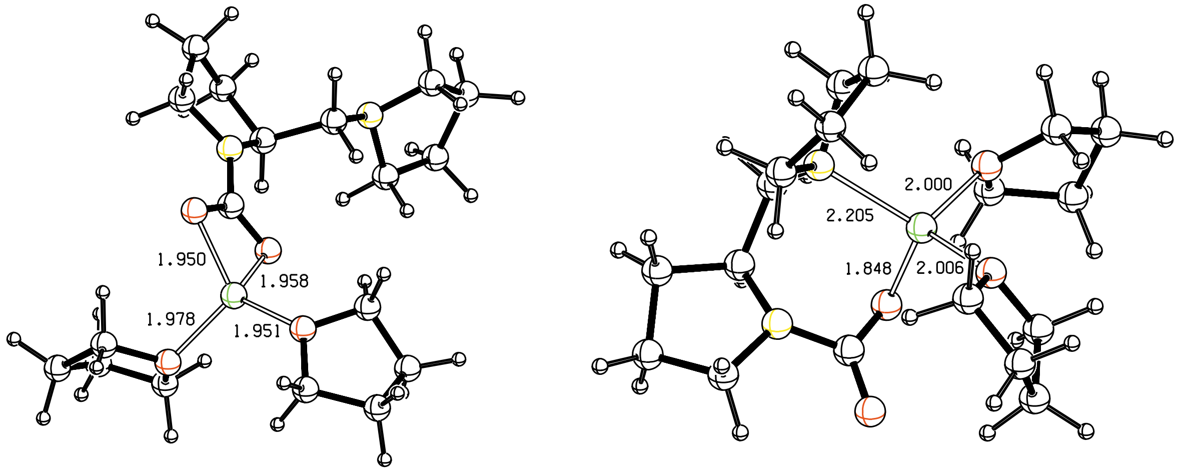
To check the accuracy of our measurement procedure, the degree of aggregation *n* of MeLi was determined. The required cryoscopic constant E_k of THF is described in literature.[12] For MeLi, values of *n* between 3.8–4.3 were found. These results are in good agreement with those reported in literature.[12] Thus, the validity of our experimental procedure was proven, and supported the application of the same procedure to the lithium carbamates. The carbamates **1a**–**4a** were found to exist as monomers in THF. The results are summarized in Table 3.

Table 3. Cryoscopic investigation of lithium carbamates in THF[13]

Substrate	C_{nom} (mM)	$n = C_{nom}/C_{exp}$
MeLi	60.56–94.53	3.64–4.18
1a	62.44–107.28	1.06–1.39
2a	132.35–165.85	1.11–1.40
3a	63.14–139.44	0.92–1.13
4a	107.82–259.62	1.20–1.30

As the free lithium coordination sites have to be occupied by THF molecules, the cryoscopic measurements allow us to determine reasonable structures for compounds **1**–**4** in THF solution using high-level quantum chemical calculations. We chose the carbamate **1a** and its corresponding THF microsolvated structures to be our model system (vide infra). The pre-optimizations were performed with the PM3 method.[14] It has been reported that this semiempirical method is well suited to predicting the geometries of organolithium compounds deducted from experimental data, or from high-level ab initio and as well from density functional theory methods.[15] Full geometry optimizations (i.e. without symmetry constrains) were carried out with the GAUSSIAN98 program package 98.[16] The final structures and relative energies were calculated using the hybrid Hartree–Fock–DFT approach (B3LYP/6-311++G(d,p)).[17] The DFT calculated geometries were characterized as minima on the potential surface (PES) by calculating the vibrational frequencies. Some computational studies on solvation in lithium organic chemistry at the semiempirical level can be found in literature,[18] but only sparsely at higher levels.[19]

Starting with unsolvated **1a**, we found several structures[20] that are quite similar in their energies. They are derived from two parent structures (**A** and **B**) and differ in the number of coordinating THF ligands: The **A** type structures, in which the lithium is placed between the two carboxylate oxygen atoms and which are slightly more stable than the **B** type structures, in which the lithium is coordinated by one oxygen of the



A•(THF)$_2$ **B•(THF)$_2$**

Figure 1. Solvated structures of **A·(THF)$_2$** and **B·(THF)$_2$** including selected bond distances (B3LYP/6-311++G(d,p) optimizations).

carboxylate and the nitrogen of the cyclic dialkylaminomethyl substituent.

Starting with the (non-solvated) carbamates **A** and **B** of **1a**, we increased the number of coordinating THF molecules. This procedure finally led to **A·(THF)$_2$** (0.0 kcal mol^{-1}) and **B·(THF)$_2$** (+9.0 kcal mol^{-1}, ZPE corrected). At present, these structures appear to be the most stable microsolvated complexes (cf. Fig. 1). Though **B·(THF)$_2$** is less stable, we detected this complex in solution by means of Heteronuclear Overhauser Enhancement Spectroscopy (^{6}Li-^{1}H-HOESY). This technique allows identification of short Li–H distances (<3.5 Å).[21] The presence of cross-peaks in the HOESY-spectrum[22] obtained at room temperature between Li and the protons at C2, C5, C2′/5′ and C3′/4′ provides information only about the structure **B·(THF)$_2$**, while **A·(THF)$_2$** will not show any such peaks. Interestingly, in case of the carbamate **1a** both structures are coexisting with the less stable **B·(THF)$_2$** being the predominant isomer. Mechanistic investigations on the pathways from **Li-1** to **A·(THF)$_2$** or **B·(THF)$_2$**, respectively, which should explain these observations are presently underway. Additional support for the presence of the **B** structure in solution is provided by calculation of the isotropic shielding constants (GIAO-DFT calculations[23]). The latter agree surprisingly well with the experimental results for **B·(THF)$_2$**. The shifts were referenced to TMS which was optimized at the B3LYP/6-311++G(d,p), its isotropic chemical shift was calculated at the same level of theory. The calculated NMR shifts of **B·(THF)$_2$** are summarized in Table 4.

Table 4. Comparison of theoretical (B3LYP/GIAO) and experimental ^{13}C NMR shifts of **B·(THF)$_2$** in ppm (deuterated THF, 25°C, $\delta_{TMS}=0.00$ ppm)

Carbon atom	Calcd (uncorrected)	Exp.
2	61.9	55.92
3	41.9	28.78
4	29.6	23.03
5	52.8	46.29
6	64.4	58.21
2′	57.4	53.98
3′	28.4	23.26
4′	26.0	23.26
5′	61.4	53.98
CO	169.6	158.25

The isotropic chemical shift for carbon dioxide in this solution is relative to the experimental value downfield with ca. 5 ppm. After correction of the computed values, the deviations between experimental and calculated ^{13}C shifts are in the range 1–8 ppm.

In conclusion, we have developed a convenient and efficient synthesis of chiral carbamates starting from α-substituted methylpyrrolidine derivates, and using lithium hydride and CO$_2$. This reaction is applicable to a broad range of amines (e.g. indole or imidazole), and provides a general method for preparing chiral carbamates under mild conditions and in high yields. We succeeded in assigning one of the predominant solution state structures by a combined experimental and theoretical (DFT) study. Experimental investigations of novel CO$_2$ transfer reactions from the Li-carbamates **1a**–**4a** to prochiral carbon atoms are the topic of further research.

Acknowledgements

Financial support by the Deutsche Forschungsgemeinschaft (SFB 436) is gratefully acknowledged for of this work. We would also like to thank Dr. W. Günther for the stimulating NMR discussions. In addition we thank the Hewlett–Packard Company for support.

References

1. Moss, J.; Lane, M. D. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1971**, *35*, 321.
2. For a comprehensive review of organic carbamates as synthetic intermediates, see: Adam, P.; Baron, F. A. *Chem. Rev.* **1965**, *65*, 527.
3. (a) Walther, D.; Ritter, U.; Kempe, R.; Sieler, J.; Undeutsch, B. *Chem. Ber.* **1992**, *125*, 1529; (b) Ruben, M.; Walther, D.; Knake, R.; Görls, H.; Beckert, R. *Eur. J. Inorg. Chem.* **2000**, 1055; (c) Martini, H.; Retey, J. *Angew. Chem.* **1993**, *105*, 287; (d) Taylor, S. D.; Kluger, R. *J. Am. Chem. Soc.* **1993**, *115*, 867; (e) Kuo, D. J.; Rose, I. A. *J. Am. Chem. Soc.* **1993**, *115*, 387.
4. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
5. Opitz, A.; Koch, R.; Katritzky, R. A.; Anders, E. *J. Org. Chem.* **1995**, *60*, 3743.
6. (a) Cox, J. P.; Simpkins, S. N. *Tetrahedron: Asymmetry* **1991**, *2*, 1; (b) Nilsson-Lill, O. S.; Arvidsson, I. P.; Ahlberg, P. *Tetrahedron: Asymmetry* **1999**, *10*, 265; (c) Asami, M.; Ogawa, M.; Inoue, S. *Tetrahedron Lett.* **1999**, *40*, 1563; (d) Asami, M.; Suga, S.; Honda, K.; Inoue, S. *Tetrahedron Lett.* **1997**, *38*, 6425.
7. Kandasamy, S.; Notz, W.; Bui, T.; Barbas, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260.
8. (a) Ahlbrecht, H.; Boche, G.; Harms, K.; Marsch, M.; Sommer, H. *Chem. Ber.* **1990**, *123*, 829; (b) Ahlbrecht, H.; Schmidt, R.; Bayer, U. *Eur. J. Org. Chem.* **1998**, 1371.
9. Ahlbrecht, H.; Sommer, H. *Chem. Ber.* **1990**, *123*, 829.
10. (a) Asami, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 721; (b) Khan, A. Z. Q.; Arvidsson, P. I.; Ahlberg, P. *Tetrahedron: Asymmetry* **1996**, *7*, 399; (c) Seebach, D.; Kalinowski, H. O.; Bastani, B.; et al. *Helv. Chim. Acta* **1977**, *60*, 301; (d) Ahlbrecht, H.; Enders, D.; Santowski, L.; Zimmermann, G. *Chem. Ber.* **1989**, *122*, 1995.
11. Representative experimental procedure: Under an argon atmosphere, LiH (51.3 mg, 6.46 mmol) was added to a stirred solution of (*S*)-2-(1-pyrrolidinylmethyl)pyrrolidine **1** (1 g, 6.46 mmol) in anhydrous THF (30 mL) at 50°C. After 1 day, CO_2 gas (or $^{13}CO_2$ [99% enriched] in case of all NMR experiments) was bubbled through the reaction mixture for 1 h at ambient temperature. The carbon dioxide flow was stopped, and the mixture was stirred for another hour. The solvent was evaporated in vacuo, and the residue was washed with anhydrous pentane. The synthesis gave a yield of 79% **1a** as a white solid.

    1a: ^{1}H NMR (400 MHz, THF): δ 3.88 (s, 1H), 3.30 (t, 2H), 2.60–2.53 (m, 6H), 1.98–1.74 (m, 8H). ^{13}C NMR (100 MHz, THF): δ 158.25 (C=O), 58.21 (C6), 55.92 (C2), 53.98 (C2′/5′), 46.29 (C5), 28.78 (C3), 23.26 (C3′/4′), 23.03 (C4). $[\alpha]_D^{25}$ −15 (*c* 0.02 g/mL, THF).

    1b: ^{1}H NMR (400 MHz, pyridine): δ 4.11 (s, CH), 3.63 (m, 4H), 3.50 (m, 2H), 2.65 (m, 1H), 2.56–2.35 (m, 4H), 2.23 (dd, 1H), 1.90–1.55 (m, 4H). ^{13}C NMR (100 MHz, pyridine): δ 157.55 (CO), 67.27 (C3′/5′), 62.22 (C6), 55.40 (C2), 54.82 (C2′/6′), 47.22 (C5), 29.88 (C3), 23.79 (C4). $[\alpha]_D^{25}$ −18 (*c* 0.03 g/mL, THF).

    1c: ^{1}H NMR (400 MHz, pyridine): δ 4.00 (s, CH), 3.65 (m, 1H), 3.46 (s, 1H), 2.56 (dd, 1H), 2.44 (m, 4H), 2.27 (dd, 1H), 1.82 (m, 1H), 1.71 (m, 2H), 1.64 (m, 1H), 1.49 (m, 4H), 1.29 (m, 2H). ^{13}C NMR (100 MHz, pyridine): δ 157.96 (CO), 63.18 (C6), 55.42 (C2), 54.94 (C2′/6′), 47.61 (C5), 30.18 (C3), 25.81 (C3′/5′), 24.23 (C4′), 23.70 (C4). $[\alpha]_D^{25}$ −17 (*c* 0.03 g/mL, THF).

    1d: ^{1}H NMR (400 MHz, pyridine): δ 4.13 (s, 1H), 3.43 (m, 2H), 3.65/3.37 (m, 2H), 3.20 (s, 3H), 1.86/1.76 (m, 2H), 1.77/1.57 (m, 2H). ^{13}C NMR (100 MHz, pyridine): δ 157.72 (CO), 73.99 (C6), 58.98 (C7), 57.17 (C2), 47.35 (C5), 28.87 (C3), 24.02 (C4). $[\alpha]_D^{25}$ −10 (*c* 0.02 g/mL, THF).
12. Bauer, W.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 1972.
13. Representative cryoscopy measurement: The cryoscopic measurements were conducted under argon atmosphere in a double-walled Schlenk flask. The temperature was determined with a precision thermolyzer (Kelvimat Type 4322) and a metal-mantled Pt–100 sensor (±0.001 K). The temperature was lowered down to 180 K at 1 K/min^{-1} and further down to the freezing point at 0.05 K/min^{-1} by applying a vacuum to the outer shell of the double-walled flask. The cooling curve was recorded with 'Labview™' and further analyzed with 'Exel™'. The THF was weighed into the flask and cooled with liquid nitrogen.

    For the measurements, **1a** was prepared in the doubled-walled Schlenk flask and dissolved in THF. After dissolution, the freezing point was determined three times and was carefully observed to ensure that **1a** remained completely dissolved prior to its crystallization. Repetition of this procedure with different concentrations of **1a** gave the degree of aggregation *n*. Solid MeLi was obtained by removing the solvent from a commercially available solution in diethyl ether.
14. Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.
15. (a) Anders, E.; Koch, R.; Freundscht, P. *J. Comput. Chem.* **1993**, *14*, 1301; (b) Hilmersson, G.; Arvidsson, P. I.; Davidsson, Ö.; Hakansson, M. *J. Am. Chem. Soc.* **1998**, *120*, 8143; (c) Abotto, A.; Streitwieser, A.; Schleyer, P. von R. *J. Am. Chem. Soc.* **1997**, *119*, 11255.
16. Gaussian 98, Revision A-11: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz. P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A., Gaussian, Inc., Pittsburgh, PA, 1998.
17. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
18. (a) Koch, R.; Wiedel, A.; Anders, E. *J. Org. Chem.* **1996**, *61*, 2523; (b) Nilsson-Lill, S. O.; Arvidsson, P. I.; Ahlberg, P. *Tetrahedron: Asymmetry* **1999**, *10*, 265.
19. (a) Kaufmann, E.; Gose, J.; Schleyer, P. von R. *Organometallics* **1989**, *8*, 2577; (b) Glaser, R.; Streitwieser, A. *J. Org. Chem.* **1991**, *56*, 6612; (c) Braeuer, M.; Weston, J.; Anders, E. *J. Org. Chem.* **2000**, *65*, 1193.
20. The results of the complete theoretical investigations will be published separately.

21. (a) Bauer, W.; Clark, T.; Schleyer, P. von R. *J. Am. Chem. Soc.* **1987**, *109*, 970; (b) Bauer, W.; Müller, R. Pi.; Schleyer, P. von R. *Angew. Chem.* **1986**, *98*, 1130.

22. Deprotonation of **1** with *n*-Bu[^{6}Li] were carried out in deutered THF at room temperature.

23. (a) Wolinski, K.; Hinton, J. F.; Pulay, P. *J. Am. Chem. Soc.* **1990**, *112*, 8251; (b) Ditchfield, R. *Mol. Phys.* **1997**, *27*, 789; (c) Devlin, F. J.; Stephens, P. J.; Cheeseman, J. R.; Frisch, M. J. *J. Phys. Chem.* **1997**, *101*, 9912; (d) Chesnut, D. B.; Foley, C. K. *Chem. Phys. Lett.* **1985**, *118*, 316.