Clean and efficient synthesis of *O*-silylcarbamates and ureas in supercritical carbon dioxide†

Matthew J. Fuchter,[a] Catherine J. Smith,[b] Melanie W. S. Tsang,[bc] Alistair Boyer,[b] Simon Saubern,[a] John H. Ryan[a] and Andrew B. Holmes*[c]

Received (in Cambridge, UK) 28th January 2008, Accepted 28th February 2008
First published as an Advance Article on the web 2nd April 2008
DOI: 10.1039/b801537f

The synthesis of a family of *O*-silylcarbamates from the corresponding silylamines has been achieved simply by heating the silylamine in supercritical carbon dioxide ($scCO_2$), and these *O*-silylcarbamates have been shown to be effective precursors for the synthesis of a range of symmetrical and unsymmetrical ureas.

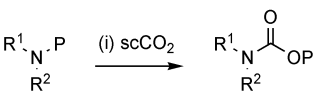
In spite of its considerable synthetic potential, the *O*-silylcarbamate species has received little attention from chemists. A number of methods for the preparation of *O*-silylcarbamates have been reported[1–5] but their application in further synthetic transformations has only recently been considered. During our studies into palladium mediated carbon–nitrogen bond formation in supercritical carbon dioxide ($scCO_2$)[6,7] we observed the unexpected insertion of CO_2 into the silicon–nitrogen bond of *N*-trimethylsilyl dimethylamine to form the *O*-silylcarbamate. Previously, this reaction was reported to require high temperatures and transition metal catalysis.[8]

Here we report a study into the generality of this adventitious CO_2 insertion reaction for the production of both mono- and bis-*O*-silylcarbamates, and we further describe the application of these products to the synthesis of both symmetrical and unsymmetrical ureas. Ureas are extremely useful synthetic building blocks and have found applications as dyes, gasoline antioxidants, corrosion inhibitors, agrochemicals, plant growth regulators, anti-convulsant agents and HIV-1 protease inhibitors.[9] Classically, the synthesis of urea derivatives employs highly toxic reagents such as phosgene, phosgene equivalents or isocyanates.[10] More recently, numerous alternative methods have been developed, based on activated carbonyl derivatives;[9] however, the use of these reagents is somewhat wasteful from an atom economy point of view. Clearly, the use of a one-carbon unit such as CO_2 or CO is vastly preferential. Whilst significant improvements have been reported for transition metal-catalysed carbonylation for the formation of ureas, these methods employ the use of toxic CO under pressurised conditions, and in some cases, the required CO–O_2 mixtures are in the explosion range of CO in O_2.[11] CO_2 is a naturally abundant, environmentally benign one-carbon alternative to CO, although until now harsh conditions (150–200 °C at >100 atm CO_2),[12] or the presence of stoichiometric dehydrating agents, such as dicyclohexylcarbodiimide, PCl_5 or $POCl_3$, are usually required for the formation of ureas from amines.[9] Our methodology avoids the use of such harsh conditions or toxic dehydrating agents, and exploits the reactivity of carbon dioxide as a reagent, whilst simultaneously employing its solvating power in the supercritical state.

An array of silylamines was synthesised by trapping of the lithium salt of the amine with the respective chlorosilane (see ESI†). The silylamines were placed neat into a high pressure stainless steel reaction vessel and stirred at the specified temperature under a pressure of 125 bar (to solubilise the substrates) in $scCO_2$ for 18 h.‡ The results are shown in Table 1. In all cases excellent conversion to the *O*-silylcarbamates **6–10** was achieved by simple selection of the appropriate reaction temperature. The larger the silicon group on the silylamine, the higher the temperature required for complete conversion (Table 1, entries 1–4). *N*-Hexyltrimethylsilylamine **5** (the silyl derivative of a primary amine) also readily underwent CO_2 insertion, yielding the primary *O*-silylcarbamate **10** in excellent yield (Table 1, entry 5).

One potential application of *O*-silylcarbamates lies in their use as masked isocyanates. In 1983, Knausz and co-workers reported that the attempted distillation of a primary trimethylsilyl carbamate **11** at temperatures of between 100 and 120 °C

Table 1 Formation of *O*-silylcarbamates from *N*-silylamines in $scCO_2$[a]



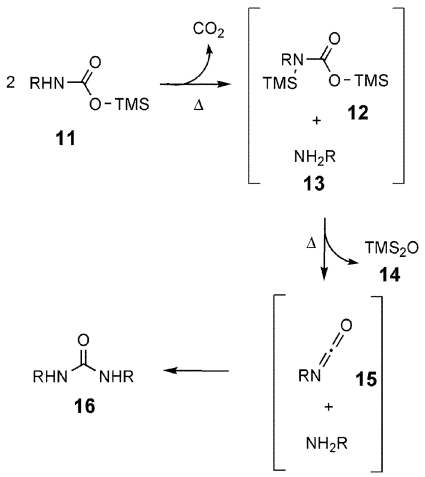
6: $R^1 = R^2$ = Et, P = TMS
7: $R^1 = R^2$ = Et, P = TBS
8: $R^1 = R^2$ = Et, P = TBDPS
9: R^1 = Bn, R^2 = Me, P = TIPS
10: R^1 = *n*-C_6H_{13}, R^2 = H, P = TMS

Entry	Silylamine	R^1	R^2	P	Conversion (%) at T/°C[bc] 40 °C	60 °C	80 °C	100 °C
1	**1**	Et	Et	TMS	100 (81)	—	—	—
2	**2**	Et	Et	TBS	61	98 (83)	—	—
3	**3**	Et	Et	TBDPS	—	20	68	98 (95)
4	**4**	Bn	Me	TIPS	—	—	—	100 (95)
5	**5**	*n*-C_6H_{13}	H	TMS	92 (82)	—	—	—

[a] *Reagents and conditions*: (i) $scCO_2$, 125 bar, T °C, 18 h. [b] Conversion determined by ^{1}H-NMR analysis. [c] Isolated yield reported in parentheses.

[a] *CSIRO Molecular and Health Technologies, Bag 10, Clayton South, Vic. 3169, Australia*
[b] *Melville Laboratory, Department of Chemistry, Lensfield Road, Cambridge, UK CB2 1EW*
[c] *School of Chemistry, Bio21 Institute, University of Melbourne, 30 Flemington Road, Parkville, Vic. 3010, Australia*

† Electronic supplementary information (ESI) available: Experimental procedures, full characterisation data, and copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/b801537f

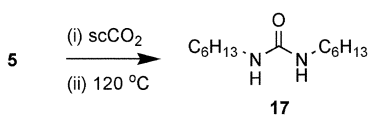


Scheme 1

led to the unintentional formation of urea **16** (Scheme 1).[3] It was proposed that under such conditions autosilylation occurred to generate an *N*,*O*-bis-silylated species **12** along with one equivalent of amine **13** and carbon dioxide. At high temperatures the *N*,*O*-bis-silylated species **12** is unstable and is converted into an aliphatic isocyanate **15** with loss of hexamethyldisiloxane **14**. The newly formed isocyanate **15** subsequently reacts with the free amine **13** to generate a 1,3-dialkylurea **16**.

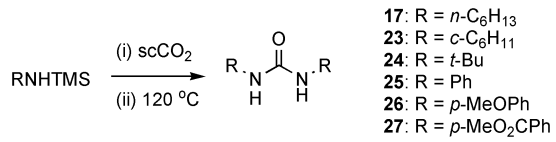
With an efficient route to primary *O*-silylcarbamates in hand we investigated the possibility of exploiting this reaction in the synthesis of a variety of functionalised ureas. Primary *O*-silylcarbamate **10** was synthesised *in situ* in $scCO_2$. The reaction vessel was subsequently vented, and the crude reaction mixture was heated to 120 °C for 18 h. The reaction vessel was allowed to cool to ambient temperature to leave a white crystalline solid. The solid was washed with $scCO_2$ (three cycles, 125 bar, 40 °C) to furnish 1,3-dihexylurea **17** in excellent yield (72% from *N*-hexyltrimethylsilylamine **5**) without the need for further purification (Scheme 2).

In order to take complete advantage of the use of CO_2 as both solvent and reagent the urea synthesis could be simplified to a one-step procedure by increasing the temperature and pressure of the reaction mixture, maintaining a homogeneous $scCO_2$ phase throughout. Thus, a variety of aliphatic and aromatic silylamines (see ESI†) were smoothly converted into their symmetrical urea counterparts by heating to 120 °C in $scCO_2$ (140 bar) for 17 h (Table 2). Both electron-deficient and electron-rich *N*-silylanilines gave the corresponding ureas in moderate to good yield (Table 2, entries 4–6). Indeed, the insertion of CO_2 into *N*-trimethylsilylaniline **20** was efficient despite the low nucleophilicity of the nitrogen atom as reported by Zoeckler and Lain.[8] Steric hindrance was observed to influence the reaction markedly with urea **24** being isolated



Scheme 2 *Reagents and conditions*: (i) $scCO_2$, 125 bar, 40 °C, 18 h; (ii) 120 °C, neat, 72% (2 steps).

Table 2 Formation of symmetrical ureas from *N*-silylamines in $scCO_2$ in one step



17: R = *n*-C_6H_{13}
23: R = *c*-C_6H_{11}
24: R = *t*-Bu
25: R = Ph
26: R = *p*-MeOPh
27: R = *p*-MeO_2CPh

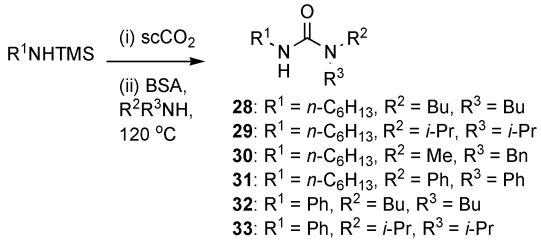
Entry	R	Substrate	Yield (%)
1	*n*-C_6H_{13}	**10**	68
2	*c*-C_6H_{11}	**18**	52
3	*t*-Bu	**19**	13
4	Ph	**20**	85
5	4-MeO-C_6H_4	**21**	69
6	4-MeO_2C-C_6H_4	**22**	40

Reagents and conditions: (i) $scCO_2$, 140 bar, 120 °C, 17 h.

in low yield (Table 2, entry 3). It is noted that *N*-silyl derivatives of secondary amines such as **1** were found not to undergo the fragmentation reaction, even under forcing conditions; this observation supports the proposal of involvement of a transient isocyanate intermediate.

To extend this methodology to the synthesis of unsymmetrical ureas, we reasoned that *N*-silylation of a primary *O*-silylcarbamate **11** would yield an *N*,*O*-bis-silylcarbamate **12**, which, after fragmentation to the isocyanate **15**, could be ensnared by an alternative ancillary amine. This would allow access to unsymmetrical ureas. While silylation of the primary *O*-silylcarbamate **10** was readily achieved using TMSOTf and Et_3N at low temperature, this procedure was not applicable to an operationally simple, one-pot approach. After surveying numerous *in situ* silylating agents, we found *N*,*O*-bis-trimethylsilylacetamide (BSA) to be a suitable reagent for silylation without interfering with the subsequent fragmentation–capture reaction. Following some optimisation, an efficient two-step, one-pot method was developed for the synthesis of unsymmetrical ureas. Firstly, the silylamine was smoothly converted into the corresponding *O*-silylcarbamate using the above method. The vessel was then vented and the crude *O*-silylcarbamate was treated with BSA and a secondary amine, and the mixture was heated to 120 °C for 18 h (Table 3). For *n*-hexylsilylamine **5**, good yields of the unsymmetrical ureas were achieved even with bulky ancillary amines (Table 3, entries 1–3), the reaction consisting of four discrete steps: CO_2 insertion, silylation, fragmentation and capture. Disappointingly, the use of the more electronically deactivated diphenylamine resulted in poor conversion (Table 3, entry 4). *N*-Trimethylsilylaniline **20** gave a moderate yield of dibutyl urea **32** (Table 3, entry 5), but this decreased for the bulkier di-isopropylamine (Table 3, entry 6). While the higher temperature required to form the *O*-silylcarbamate from *N*-trimethylsilylaniline **20** could have resulted in lower yields owing to partial self fragmentation (see Table 2), another explanation could be the variability of BSA in mediating silylation of this less reactive *O*-silylcarbamate. In fact, we found that the subtle reactivity differences in silylating reagents had a strong effect on the reaction. For example, *N*,*O*-bis-trimethylsilyl trifluoroacetamide (BSTFA) afforded only traces of product **28** and numerous side-products.

Table 3 Formation of unsymmetrical ureas from *N*-silylamines in $scCO_2$



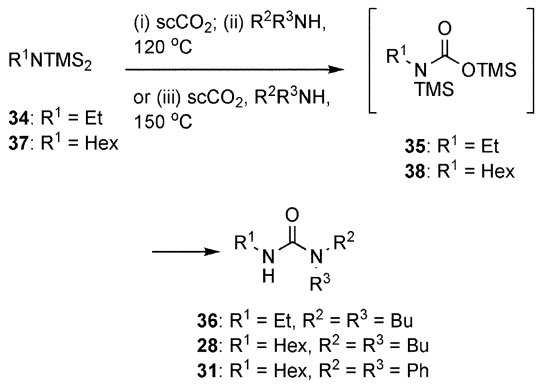
Entry	R^1	R^2	R^3	Substrate	Yield (%)
1[a]	*n*-C_6H_{13}	*n*-C_4H_9	*n*-C_4H_9	**10**	73
2[a]	*n*-C_6H_{13}	*i*-Pr	*i*-Pr	**10**	70
3[a]	*n*-C_6H_{13}	Me	Bn	**10**	57[c]
4[a]	*n*-C_6H_{13}	Ph	Ph	**10**	6
5[b]	Ph	*n*-C_4H_9	*n*-C_4H_9	**20**	42
6[b]	Ph	*i*-Pr	*i*-Pr	**20**	9

[a] *Reagents and conditions*: (i) $scCO_2$, 125 bar, 40 °C, 17 h; (ii) BSA, R^2R^3NH (1.5 equiv.), 120 °C, 18 h. [b] *Reagents and conditions*: (i) $scCO_2$, 140 bar, 100 °C, 17 h; (ii) BSA, R^2R^3NH (1.5 equiv.), 120 °C, 18 h. [c] Purity 90% by ^1H NMR and GCMS.

In all cases, the major side-product was the symmetrical urea resulting from competing capture of the isocyanate by any released primary amine. Indeed, authentic neat *N*-hexyl-*N*,*O*-bis-silylcarbamate (see **10**; R^2 = P = TMS) was shown to undergo fragmentation and symmetrical urea formation in the absence of any additional reagents. The exact mechanistic details including the active silylating reagent are poorly understood and the mechanism of this step is currently under further investigation.

As an alternative clean method for preparing unsymmetrical ureas, we proposed that mono-insertion of CO_2 into a bulky bis-*N*-silylamine would also yield the desired *N*,*O*-bis-silylcarbamate **12**, which could undergo fragmentation–capture (Scheme 3). *N*-Ethylhexamethyldisilazane **34** was synthesised from NaHMDS and iodoethane according to literature methods.[13] Despite the use of forcing conditions (120 °C, 200 bar $scCO_2$, 52 h) complete conversion into ethylamine *N*,*O*-bis-silylcarbamate **35** could not be achieved. However, heating the crude reaction mixture at 120 °C in the presence of 1.5 equiv. of dibutylamine did result in the formation of the unsymmetrical urea **36** in moderate yield (34% from **34**, Scheme 3). Increasing the reaction temperature to 150 °C allowed the overall reaction time to be lowered to 18 h, and a simple one-step procedure to be carried out. Thus, unsymmetrical ureas **28** and **31** were prepared in 26% and 40% yield, respectively (Scheme 3). The reason for the improved yield of urea **31** compared with the *in situ* silylation method (see Table 3) lies in the beneficial effect of solvating $scCO_2$. In this case any released hexylamine is captured as the unreactive carbamic acid salt, whereas diphenylamine, which is far less prone to forming such adducts, is free to react with the transient isocyanate **15**. This therefore favours the formation of the unsymmetrical urea **31** over the competing side reaction, *viz*. formation of the symmetrical adduct **17**.

In summary, we have demonstrated that insertion of CO_2 into the N–Si bond of *N*-silylamines occurs by simple heating



Scheme 3

of the amine in $scCO_2$. The resulting *O*-silylcarbamates are synthetically useful intermediates, which can be transformed into both symmetrical and unsymmetrical ureas in good yield.

We thank the EPSRC, Girton College, the Cambridge MIT Institute (CMI), the Australian Research Council, the Victorian Endowment for Science Knowledge Innovation (VESKI) and CSIRO (Australia) for financial support. The EPSRC National Mass Spectrometry Centre, University of Swansea provided high resolution mass spectrometric data.

Notes and references

‡ *General procedure for the synthesis of silylcarbamates in scCO*$_2$.[14] A 10 mL high pressure stainless steel cell was sealed and evacuated and refilled with nitrogen (three cycles). The silylamine was injected through the inlet port and the cell was connected to the CO_2 line and charged with CO_2 (99.9995%—further purified over an Oxisorb® catalyst) to approximately 50 bar (volume *ca*. 1 mL liquid carbon dioxide). The cell was heated to the specified temperature, and the pressure was adjusted to *ca*. 125 bar by the addition of further CO_2. The reagents were maintained at this temperature and pressure for 17 h before the cell was allowed to cool to room temperature. The contents of the cell were vented into dry diethyl ether (50 mL); when atmospheric pressure had been reached, the cell was opened and washed with dry diethyl ether (3 × 10 mL). The combined organic fractions were concentrated *in vacuo* to furnish the crude material which was analysed by ^1H NMR spectroscopy.

1 H. Breederveld, *Recl. Trav. Chim. Pays-Bas*, 1962, **81**, 276.
2 L. Birkofer and K. Krebs, *Tetrahedron Lett*., 1968, 885.
3 D. Knausz, A. Meszticzky, L. Szakacs, B. Csakvari and K. Ujszaszy, *J. Organomet. Chem*., 1983, **256**, 11.
4 M. Sakaitani and Y. Ohfune, *J. Org. Chem*., 1990, **55**, 870.
5 B. H. Lipshutz, P. Papa and J. M. Keith, *J. Org. Chem*., 1999, **64**, 3792.
6 C. J. Smith, T. R. Early, A. B. Holmes and R. E. Shute, *Chem. Commun*., 2004, 1976.
7 C. J. Smith, M. W. S. Tsang, A. B. Holmes, R. L. Danheiser and J. W. Tester, *Org. Biomol. Chem*., 2005, **3**, 3767.
8 M. T. Zoeckler and R. M. Lain, *J. Org. Chem*., 1983, **43**, 2539.
9 F. Bigi, R. Maggi and G. Sartori, *Green Chem*., 2000, **2**, 140 and references therein.
10 A. F. Hegarty and L. J. Drennan, in *Comprehensive Organic Functional Group Transformations*, ed. A. R. Katritzky, O. Meth-Cohn and C. W. Rees, Pergamon, Oxford, 1995, vol. 6, p. 499.
11 B. Gabriele, G. Salerno, R. Mancuso and M. Costa, *J. Org. Chem*., 2004, **69**, 4741 and references therein.
12 B. M. Bhanage, S.-I. Fujita, Y. Ikushima and M. Arai, *Green Chem*., 2003, **5**, 340.
13 H. J. Bestmann and G. Wölfel, *Chem. Ber*., 1984, **117**, 1250.
14 W. P. Hems, T. M. Yong, J. L. M. van Nunen, A. I. Cooper, A. B. Holmes and D. A. Griffin, *J. Mater. Chem*., 1999, **9**, 1403.

