Controlled Ring Opening of *N*-Sulfinyl- and *N*-Silyl-*N*-carboxyanhydrides (NCA): One-Pot Synthesis of Dipeptides and Unsymmetrical Peptidyl Ureas from Unprotected NCA

Julia Mateos-Caro,[a] Yves Robin,[b] Vincent Levacher,*[a] Francis Marsais[a]

[a] Laboratoire de Chimie Organique Fine et Hétérocyclique, UMR 6014, IRCOF, CNRS, Université et INSA de Rouen, B.P. 08, 76131 Mont-Saint-Aignan Cédex, France
Fax +33(2)35522475; E-mail: Vincent.levacher@insa-rouen.fr

[b] ISOCHEM, Centre de Recherches du Bouchet, 91710 Vert-le-Petit, France

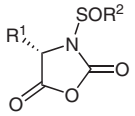
Received 24 September 2008

Abstract: We report herein new labile protecting groups of *N*-carboxyanhydrides (NCA) useful to prevent polymerization during coupling reactions with nitrogen nucleophiles. Thus, *N*-sulfinyl-NCA **1** and *N*-silyl-NCA **2** were prepared in situ and involved, without being isolated, in coupling reactions with various α-amino esters to furnish dipeptides **3** and unsymmetrical peptidyl ureas **4**, respectively, in good yields.

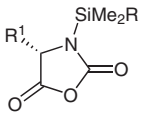
Key words: N-protected carboxyanhydrides (NCA), peptidyl ureas, dipeptides

So far, *N*-carboxyanhydrides (NCA), also known as Leuchs' anhydrides, have found application mainly as monomers for the preparation of polypeptides.[1] In principle, these amino acid derivatives are also appealing synthons for stepwise peptide synthesis considering that both the activation of the carbonyl group and the N-protection of the amino group are combined within the NCA ring. Although this coupling process is highly attractive in terms of atom economy since carbon dioxide is the sole byproduct of the reaction, this approach has not attracted much interest in the past. The poor storage stability of NCA, together with oligomerization reactions accompanying the coupling reaction, seriously limit their development in stepwise peptide synthesis.[2] To overcome these problems, various N-protected NCA have been developed, allowing peptide coupling reactions to take place in good yields. One can mention urethane-protected NCA (UNCA),[3] *N*-trityl-NCA[4] and *N*-nitrophenylsulfenyl-NCA[5] as the most representative examples. While N-protected NCA generally gave rise to significant improvement in terms of yields, many of them still suffered from poor stability making them difficult to handle and/or from noticeable loss of the enantiomeric purity during the coupling step. In this context, there still remains important research to be done in the development of straightforward and robust procedures, which inhibit polymerization side reactions, while guaranteeing high yields and enantiomeric integrity of the coupling product. We turned our interest to the synthetic potential of *N*-sulfinyl- and *N*-silyl NCA **1** and **2** as new synthons in stepwise peptide synthesis (Figure 1).

By means of labile protecting groups, our intent was to accomplish a N-protection–coupling–N-deprotection sequence from unprotected NCA in a one-pot procedure.



1a: R^1 = *i*-Pr; R^2 = Ph
1b: R^1 = *i*-Pr; R^2 = *t*-Bu
1c: R^1 = *i*-Bu; R^2 = *t*-Bu



2a: R^1 = *i*-Pr; R = Me
2b: R^1 = *i*-Pr; R = *t*-Bu
2c: R^1 = *i*-Bu; R = Me

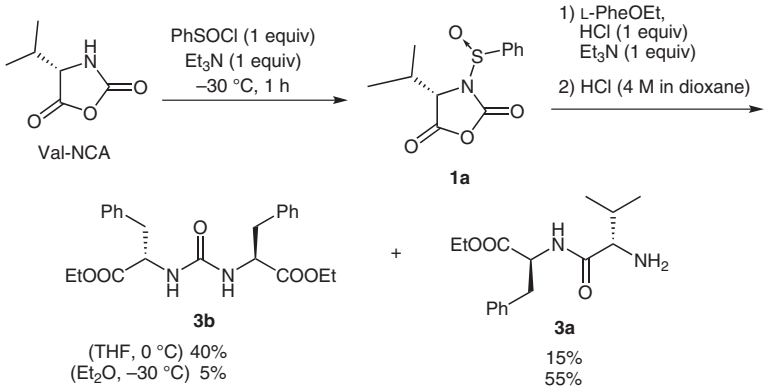
Figure 1 New labile protecting groups of NCA: *N*-sulfinyl-NCA **1** and *N*-silyl-NCA **2**

We first investigated *N*-sulfinyl-NCA **1a–c** as potential candidates to develop the three-step sequence. With the exception of *N*-sulfenyl derivatives,[5] to the best of our knowledge, sulfur-based protecting group for NCA has not been reported. The required *N*-phenylsulfinyl-Val-NCA **1a** was prepared by reaction of the corresponding Val-NCA[6] with phenylsulfinyl choride[7] in dry THF at 0 °C in the presence of triethylamine. The reaction was monitored by in situ infrared spectroscopy indicating that the reaction was completed within one hour. At this stage, *N*-phenylsulfinyl-Val-NCA **1a** could be isolated and identified by ^{1}H NMR revealing the presence of two diastereomers in a 6:4 ratio.[8]

Addition of phenylalanine ethyl ester hydrochloride afforded the dipeptide **3a** in 15% yield along with the symmetrical urea **3b** in 40% yield, the former resulting from a double addition of phenylalanine ethyl ester at the C-2 position of **1a**. This side reaction could be reduced, but not eliminated, by conducting the whole reaction sequence in Et_2O at –30 °C. As expected from literature,[9] the *N* -sulfinyl group was easily cleaved under acidic conditions, affording the desired dipeptide H-Val-Phe-OEt (**3a**) in 55% from **1a** (Scheme 1).

Encouraged by these preliminary results, controlled ring opening of *N*-sulfinyl-NCA was then further investigated. Interestingly, the delicate balance of the ambident reactivity between C-2 and C-5 positions of *N*-sulfinyl-NCA could be finely tuned at C-5 by increasing the steric hin-

SYNLETT 2009, No. 2, pp 0279–0283
Advanced online publication: 15.01.2009
DOI: 10.1055/s-0028-1087510; Art ID: G31308ST

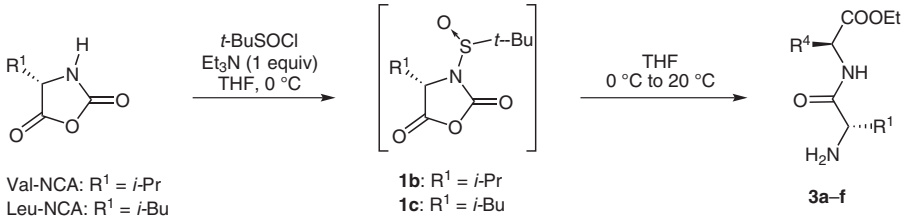


Scheme 1 Ambident reactivity of *N*-phenylsulfinyl-Val-NCA **1a** with phenylalanine ester

drance of the sulfinyl moiety (Table 1). Thus, with the more sterically hindered *N*-*tert*-butylsulfinyl-Val-NCA **1b**, phenylalanine ethyl ester reacted exclusively at C-5, affording H-Val-Phe-OEt (**3a**) in 80% overall yield (entry 1). In practice, the formation of *N*-*tert*-butylsulfinyl-Val-NCA **1b** from Val-NCA and *tert*-butylsulfinyl chloride[10] was monitored by in situ infrared spectroscopy and then engaged in the next step without being isolated. Following this one-pot procedure[11] from Leu-NCA, H-Leu-Phe-OEt (**3b**) was obtained in 76% overall yield (entry 2). The usefulness of the procedure was then illustrated with various amino esters affording the corresponding dipeptides **3c**–**f** in 40% to 91% yields (entries 3–6). We were pleased to notice that neither byproducts resulting from the ring opening at C-2 nor polymerization products were detected in the crude mixture. Although the conversion proved to be excellent in all cases, entries 5 and 6 exhibit rather modest yields owing to the difficulty in isolating dipeptides **3e** and **3f** .

We then focused on the preparation of N-silylated NCA **2a**–**c**. Both Val- and Leu-NCA were reacted with chlorotrialkylsilanes at –30 °C in THF in the presence of triethylamine. The corresponding N-silylated-NCA **2a**–**c** were stable enough to be isolated in 92–99% yields and fully characterized.[12] The ^{1}H NMR, ^{13}C NMR, and infrared spectra of the isolated products showed that, in both $CDCl_3$ and solid state, *N*-carboxyanhydrides **2b**,**c** co-exist with isocyanates **2′b**,**c**, while only *N*-carboxyanhydride **2a** could be dectected.[12] These data strongly suggest that, under the reaction conditions (THF, –30 °C), an equilibrium may occur between *N*-carboxyanhydrides **2** and isocyanates **2′**, leading, respectively, by addition of an nitrogen nucleophile, to either the formation of a dipeptide or an urea. In attempting to anticipate the outcome of the reaction sequence, the course of the silylation was monitored by means of in situ infrared spectroscopy. Initial precooled solutions of NCA in THF (–30 °C) showed two characteristic absorption bands in the region of 1790 cm^{-1} and 1830 cm^{-1}. Although no significant absorbance

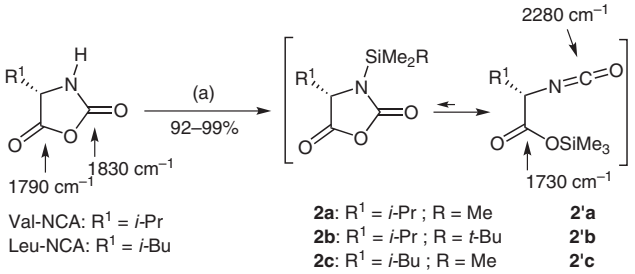
Table 1 One-Pot Synthesis of Dipeptides **3a**–**f**[11] from Val-NCA and Leu-NCA



Entry	NCA	Amino ester[a]	Product[c]	Yield (%)[b]
1	Val-NCA	L-Phe-OEt	H-Val-Phe-OEt (**3a**)	80
2	Leu-NCA	L-Phe-OEt	H-Leu-Phe-OEt (**3b**)	76
3	Val-NCA	L-Thr-OEt	H-Val-Thr-OEt (**3c**)	91
4	Val-NCA	L-Pro-OEt	H-Val-Pro-OEt (**3d**)	70
5	Val-NCA	L-Met-OMe	H-Val-Met-OEt (**3e**)	50
6	Val-NCA	L-Ala-OEt	H-Val-Ala-OEt (**3f**)	40

[a] Amino ester used as their hydrochloride salt.
[b] Overall yield from Val-NCA and Leu-NCA.
[c] Dipeptides **3a**–**f** were determined to be diastereomerically pure by ^{1}H NMR spectroscopy.

changes were detected after addition of triethylamine, the appearance of two new absorption bands at 2280 cm^{-1} and 1730 cm^{-1} upon addition of the silylating agent was associated with the formation of the isocyanates **2′a–c**. In addition, a quantitative ^{13}C NMR study performed in THF-d_8 at –30 °C confirmed the presence of the isocyanates **2′a–c** as the major product (Scheme 2).

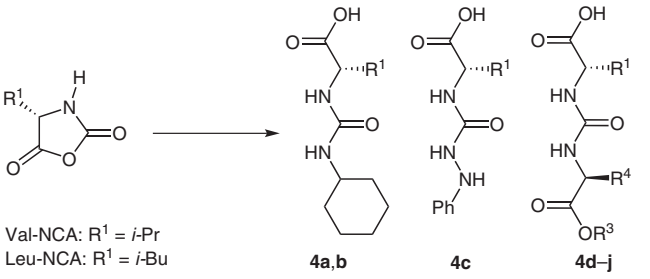


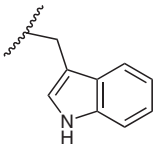
Scheme 2 Silylation of Val-NCA and Leu-NCA. Equilibrium between *N*-silyl-NCA **2a–c** and isocyanates **2′a–c**. *Reagents and conditions*: (a) RMe_2SiCl (1.5 equiv), Et_3N (1 equiv), THF, –30 °C, 5 h.

As a result of the presence of the isocyanate form, addition of amino esters is therefore expected, in contrast to *N*-sulfinyl NCA, to give rise to unsymmetrical peptidyl ureas resulting from a formal addition at C-2 of the NCA ring.[13] Unsymmetrical peptidyl ureas have recently gained interest in the design of peptidomimetics.[14] Although a survey of the literature makes it apparent that there are numerous ways of preparing unsymmetrical peptidyl ureas,[15] it also reveals that existing methods generally require several steps, long reaction times, and excessive use of reagents.[15e–15k] In addition to these disadvantages, symmetrical ureas are formed as byproducts in many cases.[15a–15d] We thus explored the reactivity of silylated NCA with various amino esters with intent to develop an efficient one-pot access to unsymmetrical peptidyl ureas from unprotected NCA.

After silyl protection of NCA by means of TMSCl in THF at –30 °C, the resulting silylated NCA were subsequently subjected to reaction with different amines at 0 °C. As one would have predicted, all amines reacted regioselectively at the C-2 position, providing the corresponding unsymmetrical ureas in 55–90% overall yields (Table 2). In addition to various amino esters (entries 4–10) and cyclohexyl amine (entries 1 and 2), phenylhydrazine could smoothly react with silylated Val-NCA to give **4c** in 55% yield (entry 3). As previously mentioned, although NMR analyses revealed that N-silylated Val-NCA **2a** is the major form present in chloroform, attempts to switch the regioselectivity of the ring opening of silylated NCA at C-5 by performing the reaction in that solvent failed, affording urea **4h** as the sole product (entry 8). This one-pot procedure provides a straightforward access to unsymmetrical peptidyl ureas from unprotected NCA, with the additional advantage over existing methods of leading to the carboxylic acid at one end of the ureas.

Table 2 One-Pot Synthesis of Unsymmetrical Peptidyl Ureas **4a–j**[16] from Val-NCA and Leu-NCA[a]



Entry	NCA	R^3	R^4	Yield (%)[b]
1	Val-NCA	–	–	**4a** 90
2	Leu-NCA	–	–	**4b** 75
3	Val-NCA	–	–	**4c** 55
4	Val-NCA	Bn	*i*-Bu	**4d** 67
5	Val-NCA	Me	CH_2CH_2COOMe	**4e** 47
6	Val-NCA	Me	s-Bu	**4f** 72
7	Val-NCA	Et	CH_2CH_2SMe	**4g** 70
8	Val-NCA	Et	Bn	**4h** 90 **4h** 52[c]
9	Val-NCA	Et		**4i** 65
10	Leu-NCA	Et	Bn	**4j** 80

[a] TMSCl, Et_3N, –30 °C, THF, 4.5 h, then cyclohexylamine or phenyl hydrazine or amino esters were added at 0 °C.
[b] Overall yield from Val- and Leu NCA; ureas **4a–j** were determined to be diastereomerically pure by ^1H NMR.
[c] Reaction carried out in $CHCl_3$.

In summary, *N*-sulfinyl and *N*-silyl protecting groups of NCA have been successfully used to prevent polymerization during coupling reactions with amino esters. One-pot procedures have been developed from unprotected NCA, avoiding the necessity of isolating N-protected NCA intermediates and making them more useful as building blocks for the synthesis of dipeptides and unsymmetrical peptidyl ureas. Whereas *N*-*tert*-butylsulfinyl-NCA reacted regioselectively at C-2 to give dipeptides **3a–f** in 40–91% overall yields, the reactivity of NCA could be completely inverted at C-5 by means of *N*-silyl-NCA furnishing unsymmetrical peptidyl ureas **4a–j** in 47–90% overall yields.

References and Notes

(1) For an excellent review on the main applications of NCA, see: Kricheldorf, H. R. *Angew. Chem. Int. Ed.* **2006**, *45*, 5752.

(2) (a) Barlett, P. D.; Jones, R. H. *J. Am. Chem. Soc.* **1957**, *79*, 37. (b) Grant, N. H.; Alburn, H. E. *J. Am. Chem. Soc.* **1964**, *86*, 3870. (c) Brenner, M.; Hofer, W. *Helv. Chim. Acta* **1961**, *44*, 1798.
(3) Fuller, W. D.; Cohen, M. P.; Shabankareh, M.; Blair, R. K. *J. Am. Chem. Soc.* **1990**, *112*, 7414.
(4) Sim, T. B.; Papoport, H. *J. Org. Chem.* **1999**, *64*, 2532.
(5) Katakai, R. *J. Org. Chem.* **1975**, *40*, 2697.
(6) Val-NCA and Leu-NCA were generously gifted by ISOCHEM company.
(7) Youn, J.; Herrmann, R. *Tetrahedron Lett.* **1986**, *27*, 1493.
(8) After elimination of the triethylamine hydrochloride salt by filtration and evaporation of THF, the major diastereomer could be isolated by precipitation in Et_2O. Selected data of the major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (m, 5 H), 3.77 (d, 1 H, *J* = 3.4 Hz), 2.45 (m, 1 H), 1.02 (d, 3 H, *J* = 6.8 Hz), 0.95 (d, 3 H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.0, 17.9, 31.7, 65.8, 125.3, 130.5, 133.6, 139.7, 150.8, 165.2. IR (KBr): 1853, 1787 cm^{-1}.
(9) Tang, T. P.; Volkman, S. K.; Ellman, J. A. *J. Org. Chem.* **2001**, *66*, 8772.
(10) Evans, J. W.; Fierman, M. B.; Miller, S. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 8134.
(11) **General Procedure for the One-Pot Synthesis of Dipeptides 3a–f**
To a solution of Val-NCA or Leu-NCA (7 mmol) in dry THF (20 mL) at 0 °C was added dropwise Et_3N (1 mL, 7 mmol) followed by *tert*-butylsulfinyl chloride (0.98g, 7 mmol). The resultant solution was stirred at this temperature for 5 h before adding the amino ester hydrochloride (7 mmol) and Et_3N (7 mmol). After stirring for 5 h at r.t., the solvent was evaporated under reduced pressure. Ethanol (20 mL) and dry HCl (4 M) in dioxane (3.5 mL) were added at 0 °C. The solution was stirred for 2 h at 0 °C and then concentrated under vacuum. Dipeptides **3a–f** were obtained as white solids after precipitation from EtOH with Et_2O.
H-Val-Phe-OEt (**3a**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23 (d, 1 H, *J* = 7.1 Hz), 7.92 (s, 2 H), 6.92 (m, 5 H), 4.38 (m, 1 H), 3.78 (q, 2 H, *J* = 7.1 Hz), 3.43 (d, 1 H, *J* = 5.3 Hz), 2.73 (m, 2 H), 1.85 (m, 1 H), 0.86 (t, 3 H, *J* = 7.1 Hz), 0.66 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 17.7, 18.6, 30.4, 37.5, 54.1, 58.2, 61.3, 126.9, 128.6, 129.5, 136.8, 168.7, 171.2. IR (KBr) 1721, 1692 cm^{-1}. HRMS: *m/z* calcd for $C_{16}H_{25}N_2O_3$ [MH$^+$]: 293.1865; found: 293.1864. $[\alpha]_D^{20}$ +21.1 (*c* 0.75, EtOH).
H-Leu-Phe-OEt (**3b**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.38 (d, 1 H, *J* = 7.5 Hz), 7.89 (s, 2 H), 6.77 (m, 5 H), 4.17 (m, 1 H), 3.61 (q, 2 H, *J* = 7.0 Hz), 3.40 (m, 1 H), 2.60 (m, 3.5 H), 1.19 (m, 3 H), 0.89 (t, 1.5 H, *J* = 7.4 Hz), 0.70 (t, 3 H, *J* = 7.0 Hz), 0.45 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.7, 14.1, 22.2, 22.8, 24.0, 37.3, 45.9, 51.6, 54.2, 61.1, 126.8, 128.4, 129.4, 136.8, 169.4, 171.0. IR (KBr): 1732, 1667 cm^{-1}.
H-Val-Thr-OEt (**3c**): ^{1}H NMR (300 MHz, DMSO): δ = 11.12 (s, 1 H), 9.12 (d, 1 H, *J* = 6.6 Hz), 8.33 (s, 3 H), 7.61 (d, 1 H, *J* = 7.7 Hz), 7.47 (d, 1 H, *J* = 7.9 Hz), 7.19 (s, 1 H), 7.13 (m, 2 H), 4.65 (dd, 1 H, *J* = 6.6, 7.7 Hz), 4.51 (s, 1 H), 4.12 (q,
2 H, *J* = 7.2 Hz), 3.81 (s, 1 H), 3.27–3.15 (m, 2 H), 2.26 (m, 1 H), 1.18–1.06 (m, 6 H). ^{13}C NMR (75 MHz, DMSO): δ = 14.2, 17.9, 18.6, 27.2, 30.2, 39.0, 40.4, 53.8, 56.4, 57.3, 61.0, 109.2, 111.8, 118.2, 121.3, 124.5, 127.3, 136.4, 168.5, 171.6. IR (KBr): 1728, 1672 cm^{-1}. Anal. Calcd for $C_{18}H_{26}ClN_3O_3$: H, 7.48; N, 10.75. Found: H, 7.46; N, 10.72. Mp 152 °C. $[\alpha]_D^{20}$ –125.1 (*c* 0.51, EtOH).
H-Val-Pro-OEt (**3d**): ^{1}H NMR (300 MHz, DMSO): δ = 8.34 (s, 1 H), 4.35 (m, 1 H), 4.08 (q, 2 H, *J* = 7.0 Hz), 3.99 (d, 1 H, *J* = 5.5 Hz), 3.79 (m, 1 H), 3.50 (m, 1 H), 2.23–2.11 (m, 2 H), 1.89 (m, 3 H), 1.17 (t, 3 H, *J* = 7.0 Hz), 0.99 (dd, 6 H, *J* = 6.8, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, DMSO): δ = 14.3, 17.6, 18.5, 25.1, 29.0, 29.8, 47.6, 55.8, 59.2, 61.0, 167.4, 171.6. IR (KBr): 1739, 1652 cm^{-1}. HRMS: *m/z* calcd for $C_{12}H_{22}N_2O_3$ [MH$^+$]: 243.1705; found: 243.1708. $[\alpha]_D^{20}$ –47.7 (*c* 1.01, EtOH).
H-Val-Met-OEt (**3e**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, 1 H, *J* = 7.7 Hz), 4.68 (m, 1 H), 4.20 (q, 2 H, *J* = 7.2 Hz), 3.28 (d, 1 H, *J* = 4.0 Hz), 2.49 (m, 2 H), 2.30–1.95 (m, 6 H), 1.28 (t, 3 H, *J* = 7.2 Hz), 0.99 (d, 3 H, *J* = 7.0 Hz), 0.84 (d, 3 H, *J* = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.6, 15.9, 16.6, 20.0, 30.4, 31.2, 32.4, 51.6, 60.5, 61.9, 172.4, 174.6. IR (KBr): 1720, 1650 cm^{-1}. HRMS: *m/z* calcd for $C_{12}H_{24}N_2O_3S$ [MH$^+$]: 277.1508; found: 277.1510.
H-Val-Ala-OEt (**3f**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, 1 H, *J* = 6.0 Hz), 4.55 (m, 1 H), 4.15 (q, 2 H, *J* = 7.2 Hz), 3.23 (d, 1 H, *J* = 4.0 Hz), 2.25 (m, 1 H), 1.39 (d, 3 H, *J* = 7.2 Hz), 1.26 (t, 3 H, *J* = 7.0 Hz), 0.97 (d, 3 H, *J* = 7.0 Hz), 0.81 (d, 3 H, *J* = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 16.4, 18.5, 20.0, 31.3, 48.1, 60.4, 61.7, 173.5, 174.5. IR (KBr): 1745, 1636 cm^{-1}. HRMS: *m/z* calcd for $C_{10}H_{20}N_2O_3$ [MH$^+$]: 217.1556; found: 217.1552.
(12) **General Procedure for the Preparation of N-Silylated-NCA 2a–c**
To a solution of Val-NCA or Leu-NCA (7 mmol) in dry THF (20 mL) at –30 °C, were added dropwise Et_3N (7 mmol) and then Me_3SiCl or TBSCl (10.5 mmol). The resulting solution was stirred at this temperature for 5 h. The reaction mixture was filtered under a nitrogen atmosphere and evaporated in vacuo at r.t. to give *N*-trialkylsilyl-NCA **2a–c** in 95–99% yields as white solids without further purification.
Selected Data for *N*-TMS-Val-NCA 2a
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.07 (d, 1 H, *J* = 3.4 Hz), 2.08 (m, 1 H), 1.19 (d, 3 H, *J* = 7.1 Hz), 0.94 (d, 3 H, *J* = 7.1 Hz), 0.39 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.0, 16.5, 18.2, 32.4, 66.1, 154.2, 169.7. IR (KBr): 1840, 1785 cm^{-1}.
Selected Data for *N*-TBS-Val-NCA 2b
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.87 (d, 1 H, *J* = 3.4 Hz), 2.19 (m, 1 H), 0.99 (d, 3 H, *J* = 6.8 Hz), 0.90 (s, 9 H), 0.84 (d, 3 H, *J* = 6.8 Hz), 0.27 (s, 3 H), 0.26 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 3.4, 3.5, 17.9, 18.2, 19.2, 21.5, 26.9, 27.2, 32.4, 33.2, 64.7, 65.8, 128.9, 154.3, 171.3, 172.7. IR (KBr): 2258, 1857, 1786, 1733 cm^{-1}.
Selected Data for *N*-TMS-Leu-NCA 2c
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.19 (dd, 0.5 H, *J* = 3.8, 9.8 Hz), 3.96 (dd, 0.5 H, *J* = 6.8, 7.9 Hz), 1.99 (m, 0.5 H), 1.85–1.61 (m, 3.5 H), 0.96 (m, 6 H), 0.39 (s, 4.5 H), 0.32 (s, 0.5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.01, 0.39, 21.5, 21.8, 23.3, 24.2, 25.5, 42.4, 42.9, 57.4, 59.4, 68.4, 127.0, 154.8, 171.5, 172.5. IR (KBr): 2255, 1845, 1780, 1720 cm^{-1}.
(13) The formation of ureas from the reaction of unprotected NCA with silylated amines has been reported previously and was explained by the formation of an isocyanate as intermediate: Kricheldorf, H. R.; Greber, G. *Chem. Ber.* **1971**, *104*, 3168.
(14) (a) Myers, A. C.; Kowalski, J. A.; Lipton, M. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5219. (b) Dales, N. A.; Bohacek, R. S.; Satyshur, K. A.; Rich, D. H. *Org. Lett.* **2001**, *3*, 2313. (c) Moriuchi, T.; Tamura, T.; Hirao, T. *J. Am. Chem. Soc.* **2002**, *124*, 9357. (d) He, J. X.; Cody, W. L.; Doherty, A. M. *J. Org. Chem.* **1995**, *60*, 8262. (e) Zhang, X.; Rodrigues, J.; Evans, L.; Hinkle, B.; Ballantyne, L.; Pena, M. *J. Org. Chem.* **1997**, *62*, 6420. (f) Konda, Y.; Takahashi, Y.; Arima, S.; Sato, N.; Takeda, K.; Dobashi, K.; Baba, M.; Harigaya, Y. *Tetrahedron* **2001**, *57*, 4211.

(15) (a) Goldschmidt, S.; Wick, M. *Z. Naturforsch. B: Chem. Biochem. Biophys. Biol.* **1950**, *5*, 170. (b) Goldschmidt, S.; Wick, M. *Justus Liebigs Ann. Chem.* **1952**, *575*, 217. (c) Nowick, J. S.; Holmes, D. L.; Noronha, G.; Smith, E. M.; Ngugen, T. M.; Huang, S. *J. Org. Chem.* **1996**, *61*, 3929. (d) Weiberth, F. J. *Tetrahedron Lett.* **1999**, *40*, 2895. (e) Kruijtzer, J. A. W.; Lefeber, D. J.; Liskamp, R. M. J. *Tetrahedron Lett.* **1997**, *38*, 5335. (f) Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1995**, *36*, 2583. (g) Anbazhagan, M.; Deshmukh, A. R. A. S.; Rajappa, S. *Tetrahedron Lett.* **1998**, *39*, 3609. (h) Azad, S.; Kumamoto, K.; Uegaki, K.; Ichikawa, Y.; Kotsuki, H. *Tetrahedron Lett.* **2006**, *47*, 587. (i) Matsumura, Y.; Satoh, Y.; Onomura, O.; Maki, T. *J. Org. Chem.* **2000**, *65*, 1549. (j) Leung, M.; Lai, J.; Lau, K.; Yu, H.; Hsiao, H. *J. Org. Chem.* **1996**, *61*, 4175. (k) Gallou, I.; Eriksson, M.; Zeng, X.; Senanayake, C.; Farina, V. *J. Org. Chem.* **2005**, *70*, 6960. (l) Patil, B. S.; Vasanthakumar, G.; Babu, V. V. S. *J. Org. Chem.* **2003**, *121*, 1597.

(16) **General Procedure for the One-Pot Preparation of Unsymmetrical Peptidyl Ureas 4a–j**

To a solution of Val-NCA or Leu-NCA (7 mmol) in dry THF (20 mL) maintained at –30 °C were dropwise added Et_3N (1 mL, 7 mmol) and TMSCl (1.33 mL, 10.5 mmol). The resultant solution was stirred at this temperature for 4.5 h before adding the amine nucleophile (7 mmol) and Et_3N (2 mL, 14 mmol). After stirring for 2 h at 0 °C, the solution was acidified to pH 4.0 with HCl (4 M) in dioxane. The precipitate was then filtered and dried to afford peptidyl ureas **4d**,**h**,**i**. Ureas **4a–c**,**e**,**f**,**g**,**j** were isolated as followed. After acidification of the solution to pH 4 with HCl (4 M in dioxane), solvents were evaporated and the resulting residue was dissolved in CH_2Cl_2. The CH_2Cl_2 layer was washed with brine and evaporated in vacuo to provide pure ureas **4a–c**, **e**,**f**,**g**,**j**.

Urea **4a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.58 (s, 1 H), 3.84 (m, 2 H), 2.22–2.05 (m, 3 H), 1.80 (d, 2 H, *J* = 12.8 Hz), 1.62 (d, 3 H), 1.35–1.16 (m, 3 H), 1.01 (d, 3 H, *J* = 6.9 Hz), 0.86 (d, 3 H, *J* = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.0, 19.1, 25.4, 26.1, 26.2, 29.5, 29.8, 30.7, 51.7, 61.9, 158.9, 174.1. IR (KBr): 1641, 1565 cm^{-1}. Anal. Calcd for $C_{18}H_{26}N_2O_5$: C, 59.48; H, 9.15; N, 11.56. Found: C, 59.64; H, 9.32; N, 11.58. Mp 94 °C. $[\alpha]_D^{20}$ –75.9 (*c* 0.7, EtOH).

Urea **4b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.45 (m, 1 H), 3.57 (m, 1 H), 1.92–1.55 (m, 5 H), 1.52–1.30 (m, 3 H), 1.35–1.16 (m, 5 H), 1.01 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.1, 21.9, 22.3, 22.5, 22.9, 28.0, 33.3, 33.4, 39.8, 49.5, 54.3, 157.6, 174.8. IR (KBr): 1638, 1565 cm^{-1}. Anal. Calcd for $C_{13}H_{24}N_2O_3$: C, 60.91; H, 9.44; N, 10.93. Found: C, 60.96; H, 9.48; N, 10.94. $[\alpha]_D^{20}$ –80.0 (*c* 0.7, EtOH).

Urea **4c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (s, 1 H), 7.66 (s, 1 H), 7.15 (t, 2 H, *J* = 7.9 Hz), 6.72 (d, 3 H, *J* = 8.7 Hz), 6.25 (d, 1 H, *J* = 9.0 Hz), 4.07 (dd, 1 H, *J* = 4.9, 9.0 Hz), 2.03 (m, 1 H), 0.84 (d, 3 H, *J* = 6.8 Hz), 0.77 (d, 3 H, *J* = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9, 19.5, 30.8, 57.5, 112.7, 129.1, 158.9, 174.0. IR (KBr): 1703, 1621, 1563 cm^{-1}. Anal. Calcd for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.46; H, 6.90; N, 16.94. $[\alpha]_D^{20}$ +24.0 (*c* 0.58, EtOH).

Urea **4d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28 (m, 5 H), 5.11 (m, 2 H), 4.37 (m, 1 H), 4.25 (m, 1 H), 2.15 (m, 1 H), 1.54 (m, 3 H), 0.85 (m, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4, 17.8, 20.8, 21.6, 23.7, 30.0, 40.5, 51.1, 57.4, 66.5, 127.2, 127.5, 127.6, 134.0, 157.5, 173.7, 175.2. IR (KBr): 1715, 1644, 1566 cm^{-1}. HRMS: *m/z* calcd for $C_{19}H_{28}N_2O_5$ [MH$^+$]: 365.1998; found: 365.2006. $[\alpha]_D^{20}$ –14.5 (*c* 1.0, EtOH).

Urea **4e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.09 (m, 2 H), 4.47 (m, 1 H), 4.35 (m, 1 H), 3.77 (s, 3 H), 3.70 (s, 3 H), 2.47 (m, 2 H), 2.20 (m, 2 H), 2.06 (m, 1 H), 0.98 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8, 19.1, 27.8, 30.4, 31.4, 52.7, 53.2, 53.3, 58.8, 158.8, 173.9, 175.1, 176.7. IR (KBr): 1720, 1655, 1561 cm^{-1}. HRMS: *m/z* calcd for $C_{13}H_{22}N_2O_7$ [MH$^+$]: 318.1427; found: 318.1430. $[\alpha]_D^{20}$ +4.3 (*c* 0.58, EtOH).

Urea **4f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.33 (m, 2 H), 3.77 (s, 3 H), 2.21 (m, 2 H), 1.87 (m, 1 H), 1.41 (m,1 H), 1.18 (m, 1 H), 0.95 (m, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.8, 15.7, 18.0, 19.2, 25.4, 31.5, 38.5, 52.9, 58.8, 68.3, 158.8, 174.7, 175.6. IR (KBr): 1721, 1640, 1566 cm^{-1}. HRMS: *m/z* calcd for $C_{13}H_{24}N_2O_5$ [MH$^+$]: 289.1762; found: 289.1763. $[\alpha]_D^{20}$ +10.1 (*c* 0.89, EtOH).

Urea **4g**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.98 (m, 2 H), 4.54 (m, 1 H), 4.33 (m, 1 H), 4.19 (q, 2 H, *J* = 7.1 Hz), 2.50 (m, 2 H), 2.16–1.91 (m, 6 H), 1.26 (t, 3 H, *J* = 7.1 Hz), 0.94 (d, 3 H, *J* = 6.8 Hz), 0.88 (d, 3 H, *J* = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 15.7, 18.1, 19.4, 30.3, 31.5, 32.7, 52.8, 58.6, 62.2, 158.5, 174.1, 176.3. IR (KBr): 1740, 1704, 1634 cm^{-1}. Mp 118 °C. Anal. Calcd for $C_{13}H_{24}N_2O_5S$: C, 48.73; H, 7.55; N, 8.74. Found: C, 48.79; H, 7.58; N, 8.65. $[\alpha]_D^{20}$ +7.6 (*c* 0.8, EtOH).

Urea **4h**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13 (m, 3 H), 7.00 (m, 2 H), 5.87 (d, 1 H, *J* = 8.7 Hz), 5.73 (d, 1 H, *J* = 7.9 Hz), 4.70 (m, 1 H), 4.30 (m, 1 H), 3.98 (m, 2 H), 3.02 (m, 2 H), 2.07 (m, 1 H), 1.09 (t, 3 H, *J* = 7.1 Hz), 0.87 (d, 3 H, *J* = 6.8 Hz), 0.79 (d, 3 H, *J* = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 17.9, 19.2, 31.1, 54.6, 58.5, 81.8, 127.1, 128.6, 129.6, 136.2, 158.0, 176.1. IR (KBr): 1733, 1637, 1562 cm^{-1}. Anal. Calcd for $C_{17}H_{24}N_2O_5$: C, 60.7; H, 7.1; N, 8.3. Found: C, 60.31; H, 7.2; N, 8.3. Mp 102.6 °C. $[\alpha]_D^{20}$ +34.5 (*c* 0.70, EtOH).

Urea **4i**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28 (m, 5 H), 5.11 (m, 2 H), 4.37 (m, 1 H), 4.25 (m, 1 H), 2.15 (m, 1 H), 1.54 (m, 3 H), 0.85 (m, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4, 17.8, 20.8, 21.6, 23.7, 30.0, 40.5, 51.1, 57.4, 66.5, 127.2, 127.5, 127.6, 134.0, 157.5, 173.7, 175.2. IR (KBr): 1715, 1644, 1566 cm^{-1}. HRMS: *m/z* calcd for $C_{19}H_{25}N_3O_5$ [MH$^+$]: 375.1794; found: 375.1799. $[\alpha]_D^{20}$ +34.0 (*c* 0.15, EtOH).

Urea **4j**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.11 (m, 3 H), 7.01 (m, 2 H), 5.77 (s, 1 H), 5.66 (d, 1 H, *J* = 7.5 Hz), 4.69 (m, 1 H), 4.31 (m, 1 H), 3.96 (m, 2 H), 2.98 (m, 2 H), 1.57 (m, 2 H), 1.37 (m, 1 H), 1.08 (t, 3 H, *J* = 7.1 Hz), 0.81 (d, 6 H, *J* = 5.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 22.3, 23.3, 25.1, 39.8, 42.1, 52.7, 54.6, 61.8, 127.2, 136.5, 160.5, 173.3. IR (KBr): 1740, 1644, 1557 cm^{-1}. Anal. Calcd for $C_{18}H_{26}N_2O_5$: C, 61.7; H, 7.48; N, 7.99. Found: C, 61.66; H, 7.46; N, 8.04. $[\alpha]_D^{20}$ +1.2 (*c* 0.4, EtOH).