DOI: 10.1002/ejoc.201001385

# Study of the Reaction between Carbamoyl Azides of α-*N*-Protected Amino Acids and Hydrazine Monohydrate

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**Keywords:** Azides / Amino acids / Semicarbazides

Two simple and efficient synthetic methods for the preparation of semicarbazide amino acid derivatives are reported. The procedures involve reaction between the carbamoyl azides of α-*N*-protected amino acids and hydrazine monohydrate: 4-[(alkoxycarbonylamino)(alkyl)methyl]semicarbazides **1** are obtained when hydrazine is added to the separated tetrahydrofuran (THF) solution containing the carbamoyl azide at 0 °C, whereas 1-[(alkoxycarbonylamino)(alkyl)methylcarbamoyl]-4-[(alkoxycarbonylamino)(alkyl)methyl]semicarbazides **4** are produced by adding hydrazine directly into the final THF/aqueous buffer ($KH_2PO_4$) biphasic mixture containing the prepared carbamoyl azide at 50 °C, respectively. NMR experimental data obtained from samples dissolved in [$D_6$]dimethyl sulfoxide suggest a dimeric association for semicarbazides **4** with intermolecular hydrogen bonds. Moreover, the ESI–MS–MS spectra reveal some interesting common features.

## Introduction

Semicarbazides are useful intermediates in the synthesis of biologically active compounds containing a heterocyclic moiety. Representative examples involving these intermediates include pyrazole,[1] pyrazoline,[2] oxazole,[3] 1,2,4-triazole,[4] 1,3,4-oxadiazole,[5] and 3,4-dihydrophthalazine[6] moieties. It has been reported that some of these nitrogen-containing heterocyclic molecules possess antibacterial,[1e,2a–2e,3b,5b–5d,5f,6a,6b,7] antimycotic,[1e,2e,5b] or antiviral[1a,4c] activities, as well as exhibiting antiinflammatory,[1b,1d] anticonvulsant,[5a] bronchodilator,[4a] PPAR alpha agonist,[4b,4f] and antitumor[4b] properties. Moreover, a number of studies have reported that some semicarbazones[8] as well as their Schiff base transition metal complexes[9] also exhibit similar biologically active behavior.

A literature survey revealed a number of different procedures for the synthesis of semicarbazides using hydrazines[8i,10] or acid hydrazides[3a,5b,5e,7,11] combined with isocyanates. Alternative methods involving carbamates and hydrazine[1b,5b,8h,8i,12] or ethyl carbazate,[13] isocyanates and ethyl carbazate,[14] thiosemicarbazides and $HIO_4$[15] or $KIO_3$,[16] 1*H*-imidazole-1-carbohydrazide and amines,[17] and ureas and hydrazine,[8f,8g,8j] are also known. Interestingly, the synthesis of semicarbazides of type –NH–*CRH–NHCONHNH$_2$, bearing the chiral moiety of an α-amino acid, is not described in the literature.

Recently, we have reported a simple and fast one-pot synthesis of the carbamoyl azides of α-*N*-protected amino acids,[18] as well as their use as suitable building blocks in the preparation of unsymmetrical ureas[19] and ureidopeptides.[20] Taking into account the potential biological interest of semicarbazides and their heterocycle derivatives, we attempted the synthesis of α-amino acid-containing target compounds starting from the corresponding α-*N*-protected carbamoyl azides, which were used as a NCO equivalent.

## Results and Discussion

On the basis of our previous experience, two different protocols were considered for the synthesis of semicarbazides **1**, using α-*N*-(ethoxycarbonyl)-L-phenylalanine (**2db**) as the model substrate. One approach was carried out in a two-step reaction sequence (Method A):[19] the first step of the process consisted of the preparation of the carbamoyl azide of α-*N*-(ethoxycarbonyl)phenylalanine (**3db**), which was readily available through a previously described procedure.[20] In the second step, hydrazine monohydrate (6 equiv. with respect to **3db**) was slowly added to the cold (0 °C) separated tetrahydrofuran (THF) solution containing the carbamoyl azide **3db**. The reaction mixture was then stirred at room temperature for 2 h and, after removal of THF under reduced pressure, the residue was washed with water to afford pure 4-[1-(ethoxycarbonylamino)-2-phenyl-

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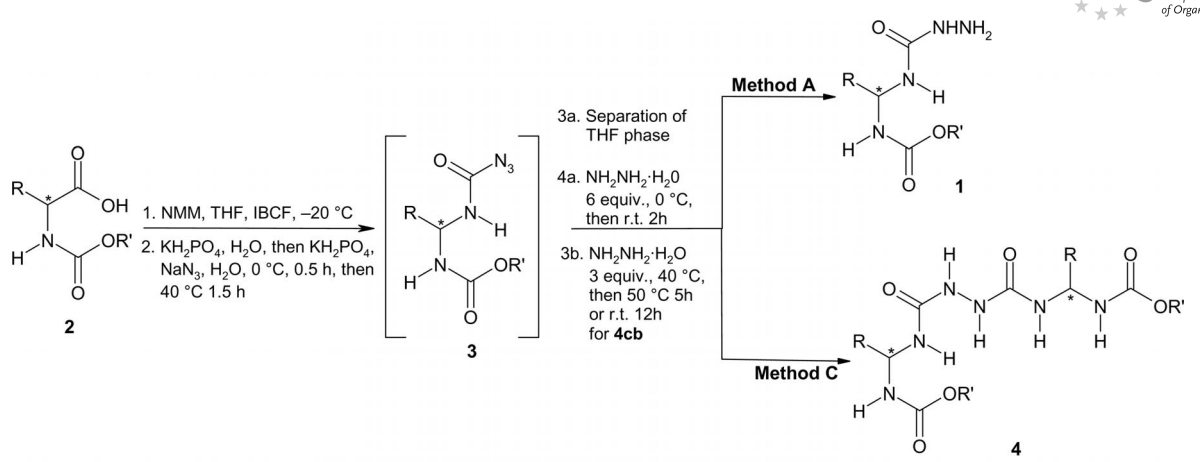
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201001385.




| 1-3 | 4 | R | R' |
|---|---|---|---|
| **ab** | | $(CH_3)_2CH$ | Et |
| **ad** | **ad** | $(CH_3)_2CH$ | Bn |
| **bb** | | $(CH_3)_2CH_2CH$ | Et |
| **bd** | **bd** | $(CH_3)_2CH_2CH$ | Bn |
| **cb** | **cb** | Ph | Et |
| **cd** | **cd** | Ph | Bn |
| **db** | **db** | $PhCH_2$ | Et |
| **dc** | **dc** | $PhCH_2$ | *t*Bu |
| **dd** | | $PhCH_2$ | Bn |
| **ea** | **ea** | 1*H*-indole-3-$CH_2$ | Me |
| **fb** | **fb** | $Mes(CH_2)_2$ | Et |

Scheme 1. Synthesis of semicarbazides **1** and **4**. NMM = *N*-methylmorpholine; IBCF = isobutyl chloroformate.

ethyl]semicarbazide (**1db**) in 82% overall yield. Alternatively, we tried to perform the reaction in one-pot (Method B)[20] by simply adding hydrazine monohydrate (6 equiv. with respect to **3db**) directly into the final THF/aqueous buffer ($KH_2PO_4$) biphasic mixture containing the previously prepared carbamoyl azide **3db**. The ESI-MS analysis of this crude reaction mixture showed, after 2 h, the presence of some unreacted **3db**, **1db**, and 1-[1-(ethoxycarbonylamino)-2-phenylethyl-carbamoyl]-4-[1-(ethoxycarbonylamino)-2-phenylethyl]semicarbazide (**4db**) in an approximate 20:40:40 ratio. After 12 h, the carbamoyl azide **3db** was fully converted into the corresponding semicarbazides **1db** and **4db** in an approximate 35:65 ratio. Under the described experimental conditions, the presence of water in the reaction mixture greatly reduced the amount of hydrazine dissolved in THF, where **3db** is soluble and very rapidly reacted with hydrazine, yielding the semicarbazide **1db**. As the reaction proceeds, the amount of **1db** in the THF increases and, although less reactive, begins to compete effectively with hydrazine for the carbamoyl azide **3db**, producing the semicarbazide **4db**. On the basis of these experimental findings, Method A was extended to other α-*N*-protected amino acids **2** (Scheme 1, Method A), affording **1** in 73–92% overall yield (Table 1).

Taking into account that semicarbazides **4** are interesting compounds that possess potential biological activity and have not been previously described in the literature, we revised Method B by making the appropriate changes in order to minimize any side reaction, using α-*N*-(ethoxycarbonyl)-L-phenylalanine (**2db**) as the model substrate. Accordingly, the amount of hydrazine monohydrate was reduced to 3 equiv. with respect to **3db** and the resulting mixture was stirred at 50 °C for 5 h. After conventional work-up, these experimental conditions (Method C) allowed the pure semicarbazide **4db** to be obtained in 82% overall yield. With the exception of α-*N*-(ethoxycarbonyl)phenylglycine (**2cb**), the extension of this method to other α-*N*-protected amino acids **2** (Scheme 1, Method C) gave **4** in 72–93% overall yield (Table 1). Interestingly, when the reaction was

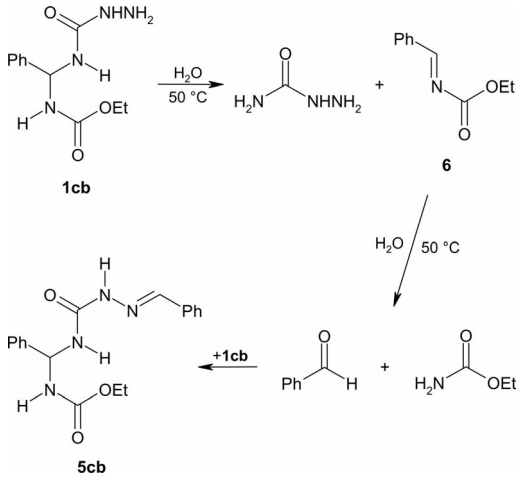
Table 1. Yields and some properties of semicarbazides **1** and **4**.

| Product[a] | Yield [%][b] | M.p. [°C] | $[\alpha]_D^{20}$ (*c*, solvent) |
|---|---|---|---|
| **1ab** | 73 | 175–177 | –32.6 (0.5, DMSO) |
| **1ad** | 87 | 161–163 | +18.0 (0.5, DMSO) |
| **1bb** | 76 | 107–109 | +17.4 (0.5, DMSO) |
| **1bd** | 78 | 150–152 | –15.0 (0.2, DMSO) |
| **1cb** | 83 | 140–141 | –22.3 (0.5, DMSO) |
| **1cd** | 92 | 141–143 | –18.5 (0.5, DMSO) |
| **1db** | 82 | 170–172 | +16.3 (0.5, DMSO) |
| **1dc** | 74 | 171–172 | –15.6 (0.2, DMSO) |
| **1dd** | 80 | 185–187 | –36.4 (0.5, DMSO) |
| **1ea** | 77 | 175–177 | –30.2 (0.3, DMSO) |
| **1fb** | 74 | 149–151 | –14.0 (0.5, DMSO) |
| **4ad** | 72 | 214–216 | +10.6 (0.3, DMSO) |
| **4bd** | 93 | 217–219 | +20.3 (0.3, DMSO) |
| **4cb** | 57,[c] 83[d] | 204–206 | –57.2 (0.2, DMSO) |
| **4cd** | 93 | 210–212 | +34.4 (1.0, DMSO) |
| **4db** | 81 | 193–195 | +7.5 (0.5, DMSO) |
| **4dc** | 86 | 197–198 | –7.8 (0.3, DMSO) |
| **4ea** | 72 | 203–205 | +10.0 (0.3, DMSO) |
| **4fb** | 89 | 199–201 | –26.7 (0.3, DMSO) |

[a] Semicarbazides **1** were synthesized according to Method A; semicarbazides **4** according to Method C. [b] Isolated yield. [c] Yield obtained at 50 °C. [d] Yield obtained at room temperature.

carried out with **2cb** at 50 °C, ESI-MS analysis of the crude mixture showed, in addition to the semicarbazide **4cb**, the the presence of 1-benzylidene-4-[(ethoxycarbonylamino)-(phenyl)methyl]semicarbazide (**5cb**)[21] in an approximate ratio of 70:30. This by-product arises from the reaction of 4-[(ethoxycarbonylamino)(phenyl)methyl]semicarbazide (**1cb**) with benzaldehyde produced by the hydrolysis of ethyl benzylidenecarbamate (**6**) at 50 °C. As described in Scheme 2, the presence of water introduced with the buffer mixture and the reaction temperature also proved to be responsible for the decomposition of **1cb** into **6** and semicarbazide.




Scheme 2.

To verify the mechanism outlined in Scheme 2, a THF/water mixture of **1cb** was heated at 50 °C for 5 h: initially, the ESI-MS analysis of the reaction mixture showed the appearance of an ion at *m*/*z* 178 due to the protonated adduct of **6**.[22] Then, as the reaction proceeds, MS signals corresponding to this ion and to the sodium cationized molecule [**1cb** + Na]$^+$ at *m*/*z* 275 decreased, whereas the sodium adduct of **5cb** at *m*/*z* 363 increased. Surprisingly, the semicarbazide **1cb** proved to be stable in hot THF (50 °C) and in a THF/water mixture at room temperature for a long time (24 h), and therefore the synthesis of semicarbazide **4cb** was better performed at room temperature (12 h). On the other hand, when the reaction was accomplished with α-*N*-(benzyloxycarbonyl)phenylglycine (**2cd**) at 50 °C, ESI-MS analysis of the reaction mixture did not indicate the formation of any of the corresponding benzylidene-substituted semicarbazone **5cd** (sodium adduct at *m*/*z* 425) nor of the benzyl benzylidenecarbamate (protonated adduct at *m*/*z* 240), most likely because the steric hindrance of the α-*N*-benzyloxycarbonyl group prevented the incursion of water.

As previously reported,[19,20] we did not observe any racemization under our experimental conditions: $^1$H and $^{13}$C NMR spectra of 1-[(ethoxycarbonylamino)(phenyl)methylcarbamoyl]-4-[(ethoxycarbonylamino)(phenyl)methyl]semicarbazide (**4cb**), prepared by reacting *N*-(ethoxycarbonyl)-L-phenylglycine (**2cb**) with hydrazine monohydrate, were compared with those obtained by employing racemic *N*-(ethoxycarbonyl)-D,L-phenylglycine (*rac*-**2cb**). The spectra of the diastereoisomeric mixture of semicarbazide diast-**4cb** obtained from *rac*-**2cb** revealed two sets of peaks for each proton and carbon signal, whereas the corresponding spectra of **4cb** did not show a similar complexity. The obtained results, as well as some properties of semicarbazides **1** and **4**, are reported in Table 1.

All the $^1$H NMR spectra of semicarbazides **1**, which were recorded in [D$_6$]dimethyl sulfoxide (DMSO), exhibit a broad singlet in the $\delta$ = 3.7–4.5 ppm range due to the semicarbazide NH$_2$ nuclei, and contain two further common features: (1) a broad doublet ($J$ = 7.3–9.4 Hz) ranging from $\delta$ = 6.5 to 7.0 ppm, which were assigned from $^1$H–$^1$H decoupling experiments to the proton of the semicarbazide nitrogen linked to the α-carbon of the starting amino acid, and (2) a sharp singlet at $\delta$ = 7.0–7.3 ppm, which was attributed to the other semicarbazide NH signal. These assignments were confirmed by analysis of the 2D TOCSY spectra (see the Supporting Information), which exhibited a cross-peak between the vicinal hydrogens of semicarbazide (i.e., the NH$_2$ at $\delta$ = 3.7–4.5 ppm and the NH at $\delta$ = 7.0–7.3 ppm), which was not connected with the remaining $J$-coupling network of the molecule. The NH$_2$–NH connectivity demonstrates that the observed singlet multiplicity for the two resonances is only apparent because an unresolved vicinal coupling must exist. Comparison of the corresponding signals obtained from the $^1$H NMR spectra of semicarbazides **4** shows that the semicarbazide doublet NH resonance within the *gem*-diamino moiety occurs at the same position ($\delta$ = 6.3–6.9 ppm) and exhibits a similar coupling constant ($J$ = 8.5–9.1 Hz) to those of semicarbazides **1**, although with a sharper linewidth, whereas the singlet NH signal (a true singlet because of chemical equivalence) shifts downfield by about 0.7 ppm ($\delta$ = 7.7–8.0 ppm). Moreover, the carbamate NH spin, which is sometimes obscured by overlapping aromatic signals, resonates at $\delta$ = 7.2–8.0 ppm as a broad doublet ($J$ = 7.9–8.2 Hz) in semicarbazides **1**, and in a similar region ($\delta$ = 7.2–7.9 ppm) as a barely resolved doublet in **4**.

The $^{13}$C NMR spectra of **1** contained a signal corresponding to the semicarbazide C=O carbon in the $\delta$ = 159.7–160.3 ppm range; in **4**, this peak shifted upfield by about 2 ppm ($\delta$ = 157.7–158.3 ppm). This upfield shift of the semicarbazide carbonyl and the simultaneous sharpening of the semicarbazide NH resonance within the *gem*-diamino moiety in compounds **4** are consistent with a reduced conformational mobility of the molecules. Indeed, whereas the chemical shift thermal coefficient for the latter NH type resonance in both semicarbazide **4** and **1** models (**1db** and **4db**) proved to be significantly smaller than the corresponding parameter measured for the carbamate NH (–2.9 vs. –5.0 and –2.3 vs. –5.1 ppb/°C, respectively), the result obtained for the other semicarbazide NH resonance of model semicarbazides **4** and **1** (the genuine and apparent singlet, respectively) were significantly different (i.e., 2.2 and 39.3 ppb/°C, respectively). This suggests that a remarkable degree of exchange occurs in semicarbazide **1**, which is in contrast to a possible hydrogen bonded network in semicarbazide **4**. This seems to be consistent with the upfield

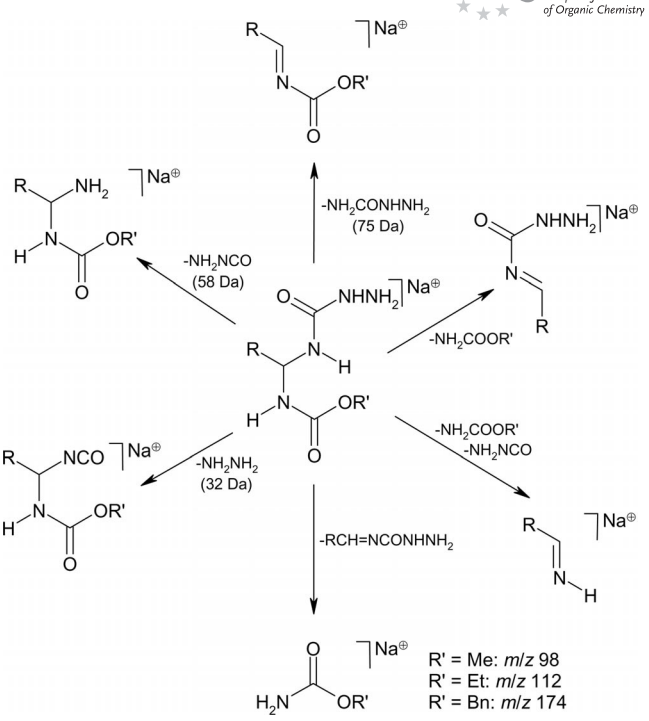
  

shift of the semicarbazide carbonyl observed for compounds **4**, which was interpreted as a reflection of the extent of hydrogen bonding (as donor) of the NH groups covalently linked to this C=O moiety (in contrast to the direct carbonyl involvement as acceptor).[23] Further evidence in favor of this interpretation came from the ROESY and DOSY experiments (see the Supporting Information). The 2D ROESY maps showed much stronger cross peaks between either semicarbazide NH groups and the carbamate NH group in model compound **4** than the corresponding amplitudes observed with model compound **1**. The DOSY maps enabled a diffusion coefficient of $(2.7 \pm 0.1) \times 10^{-10}$ m$^2$/s for semicarbazide **1db** and $(1.8 \pm 0.1) \times 10^{-10}$ m$^2$/s for semicarbazide **4db** at 30 °C in [D$_6$]DMSO to be estimated. Because, in general, for two closely related molecules (*a* and *b*) under the same conditions, a relationship between the diffusion coefficient (*D*) and the molecular weight (*M*) can be established according to Equation (1);[24] our data indicate an effective molecular weight ratio of $3.2 \pm 0.6$ for semicarbazides **4db** and **1db**, against the expectation of a ratio of 2 from the chemical structures.

$$\frac{D_a}{D_b} = \sqrt[3]{\frac{M_b}{M_a}} \quad (1)$$

The occurrence of a dimerization equilibrium of semicarbazide **4db** with a reduction in the carbamate moiety, the flexibility and the overall molecular shape anisotropy, rather than fast association/dissociation kinetics, could be hypothesized to accommodate both intra- and intermolecular hydrogen bonds and could account for the small thermal coefficients of the two semicarbazide NH chemical shifts, as well as for the slower than expected experimental diffusion coefficient. This interpretation appears more plausible than resorting to the assumption of a monomeric rigid conformation for compound **4db** with a flat geometry, which may account for a reduction in the rate of diffusion, but would require tightly bound solvent molecules to establish the hydrogen bonds required to account for the experimental data measured for all the semicarbazide NH groups.

Taking into account the importance of ESI-MS-MS techniques for the elucidation of structures of non-volatile, thermally labile molecules, we considered it useful to report some common features that were found in the ESI-MS spectra of α-*N*-protected semicarbazides **1** and **4**. In detail, with the exception of *N*-Boc-derivatives **1dc** and **4dc**, the MS$^2$ spectra of sodium-cationized molecule [M + Na]$^+$ for **1** are characterized by the presence of two intense ions due to the loss of semicarbazide (75 Da; 50–100% relative intensity) and carbamate (NH$_2$COOR′; 60–100% relative intensity) molecules (Scheme 3). Moreover, four additional peaks (10–70% relative intensity) corresponding to the imine of the α-amino acid side chain, to the carbamate, and to the loss of hydrazine (32 Da), and aminoisocyanate (58 Da) molecules were also observed (Scheme 3).




Scheme 3.

In the case of semicarbazides **4**, the fragmentation (MS$^2$) of [**4** + Na]$^+$ produces, in addition to the most intense (100% relative intensity) daughter ion corresponding to [**1** + Na]$^+$, four more peaks (30–80% relative intensity) due to the loss of carbamate (NH$_2$COOR′), alkylidenecarbamate (RCH=NCOOR′), α-aminoalkylcarbamate [RCH(NH$_2$)NHCOOR′], and 1-(aminocarbonyl)-4-[1-(alkoxycarbonylamino)alkyl]semicarbazide [RCH(NHCOOR′)-NHCONHNHCONH$_2$] molecules, respectively (Scheme 4). As expected, MS$^3$ experiments on the [**1** + Na]$^+$ daughter ions produced fragmentation patterns that were essentially identical to those observed in the MS$^2$ spectra of the sodium-cationized molecule [M + Na]$^+$ of **1**.

The MS$^2$ spectrum of *N*-Boc derivatives **1dc** and **4dc** revealed two additional fragment ions corresponding to the loss of isobutene and $CO_2$.[19]

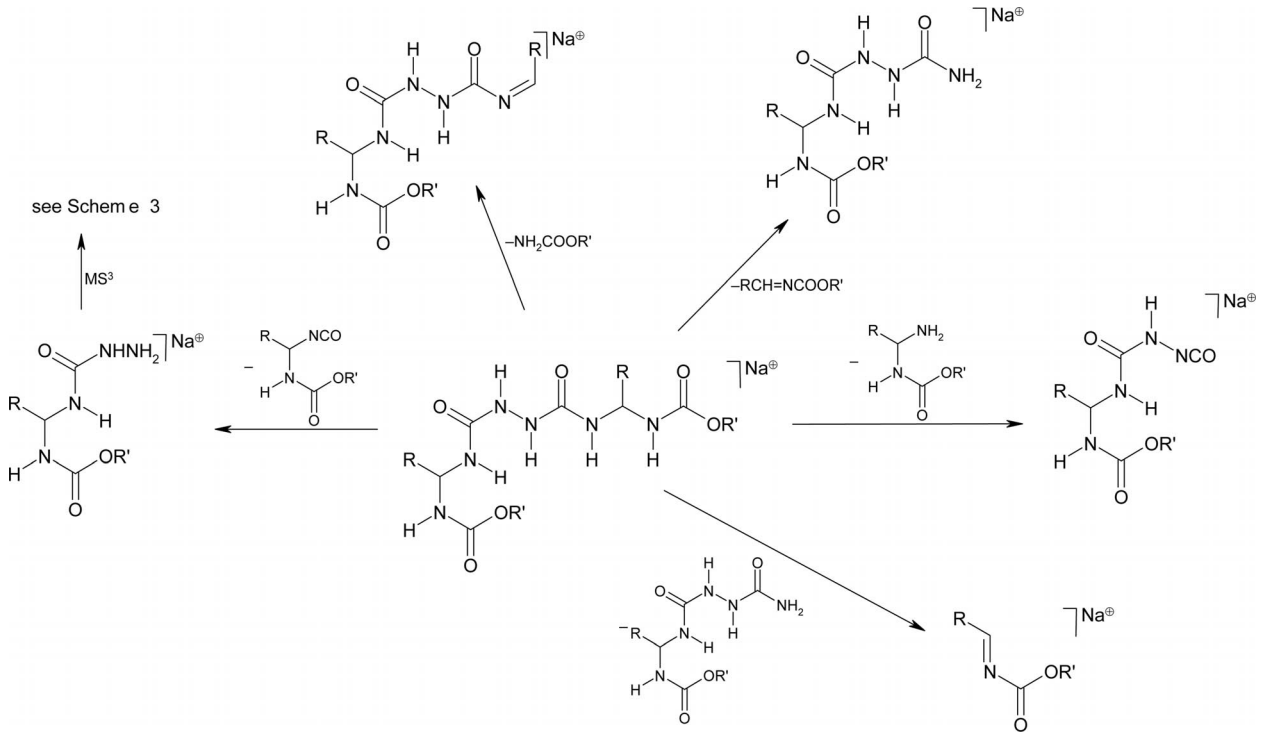
## Conclusions

We have developed two simple and efficient synthetic methods, starting from carbamoyl azides of α-*N*-protected amino acids, for the preparation of semicarbazides **1** and **4** containing one and two amino acid residues, respectively. The NMR spectroscopic data suggest that the condensed semicarbazides **4** tend to associate, even in DMSO, into dimers, thereby forming intermolecular hydrogen bonds and reducing the diffusion rate.

Moreover, the ESI-MS-MS spectra revealed some common fragmentation pathways involving the protecting group of the amino acid and the semicarbazide moiety.

These compounds may be useful building blocks in the synthesis of biologically active heterocyclic compounds




Scheme 4.

containing an amino acid moiety. We are currently investigating these semicarbazides to assess whether their capacity to form intermolecular hydrogen bonds might be exploited in cross-reactions with amiloidogenic proteins, thus preventing aggregation and fibrillogenesis.

## Experimental Section

**General:** *N*-Protected amino acids **2** were prepared by reported procedures.[25] Solvents and reagents were purchased from Aldrich Chemical Company and used without further purification. Column chromatography was carried out using silica gel 60 (Merck, 230–400 mesh) and thin-layer chromatography (TLC) was performed on Merck 60 $F_{254}$ 0.25 μm silica gel coated aluminum plates. Direct-inlet mass spectra (DI-MS) were obtained with a Thermo Scientific Polaris Q ion trap mass spectrometer, working in the positive ion 70 eV electron impact mode. Spectra were recorded in the range 35–450 u, and temperatures between 100 and 250 °C were found to be suitable to vaporize all the compounds into the ion source. The reactions were monitored by ESI-MS in the positive ion mode with a Finnigan LXQ (linear trap) by simply diluting the reaction mixture with MeCN and directly infusing the obtained solution into the ion source with the aid of a syringe pump. IR spectra were obtained with a Bruker Vector 22 spectrophotometer using the KBr disc technique for solids; spectra were recorded in the range 4000–400 $cm^{-1}$. $^1H$ and $^{13}C$ NMR spectra were recorded with a Bruker AC-F 200 spectrometer operating at 200 and 50 MHz, respectively, using [$D_6$]DMSO at 40 °C as the solvent. NMR shifts are reported as $\delta$ values relative to TMS. Some $^1H$ multiplets are characterized by the term app. (apparent): this refers only to their appearance and may be an oversimplification. To assign the $^{\alpha}$CHN*H*CONH proton resonance, $^1H$–$^1H$ decoupling experiments were performed by irradiating the $^{\alpha}$CH proton at the center of its signal. 2D $^1H$ NMR experiments and chemical shift thermal coefficient determinations were performed at 500 MHz, with a Bruker Avance system equipped with triple-axis pulsed field gradients, at 30 °C and over the interval 22–30 °C, using a sample concentration of approximately 30 mg/mL for both semicarbazides **1** and **4**. For 2D TOCSY,[26] a mixing time of 100 ms with a MLEV17[27] train was employed, with $\gamma B_2/2\pi$ = 8.3 kHz, 500 μs trim pulses and recycling delay of 1 s. 2D ROESY experiments[28] were obtained using a continuous-pulse mixing time of 150 ms, at $\gamma B_2/2\pi$ = 2.5 kHz with recycling delay of 1 s. A sweep width of 5 kHz was always selected for matrices of 2K × 256 and 8 (TOCSY) or 16 (ROESY) transients/$t_1$ point were collected; 32 dummy scans were performed only upon starting acquisition. Quadrature detection in the indirect dimension was always achieved by time proportional phase incrementation.[29] Diffusion ordered spectroscopy (DOSY) experiments were conducted with a sequence including bipolar gradients in a double stimulated echo module and longitudinal eddy current delay for convection artefact and eddy current suppression.[30] The *z*-axis gradient was incremented linearly through 79 increments within the range 2–95% over a maximum of 65 G/cm. The other relevant parameters of DOSY were: $\delta$ = (2.5 × 2) ms, Δ ranging from 100 to 400 ms, recycling delay 1 s, 32 transients/gradient increment, and 32 dummy scans. All data were processed using the Bruker routine software (TOPSPIN) with a squared sine shifted by 90°. Optical rotations were determined with suitable solutions (g/100 mL) at 20 °C with an AP-300 automatic polarimeter purchased from AT-AGO (Japan). Elemental analyses were performed with a Carlo–Erba Mod. 1106 elemental analyzer. Melting points were determined with an automatic Mettler (Mod. FP61) melting point apparatus.

**General Procedure for the Synthesis of Semicarbazides 1 (Method A):** *N*-Methylmorpholine (NMM; 0.30 mL, 2.73 mmol) was slowly added to a stirred solution of α-*N*-protected amino acid **2** (2.50 mmol) in THF (15 mL). After 5 min, isobutyl chloroformate

(IBCF; 0.36 mL, 2.73 mmol) was slowly added to the previously cooled (–20 °C) reaction mixture and stirring was continued for 20 min at the same temperature. The reaction mixture was warmed to 0 °C and a solution of $KH_2PO_4$ (0.17 g, 1.25 mmol) in $H_2O$ (1 mL) was added in one portion, followed, after 5 min, by a solution of $KH_2PO_4$ (1.70 g, 12.50 mmol) and $NaN_3$ (0.41 g, 6.25 mmol) in $H_2O$ (9 mL). After 30 min at 0 °C, the mixture was warmed to 40 °C, stirred for 1.5 h, cooled to room temperature, and the organic phase was separated. The obtained THF solution containing the carbamoyl azide **3** was cooled to 0 °C and hydrazine monohydrate (0.73 mL, 15.00 mmol) was slowly added. The mixture was warmed to room temperature whilst stirring and, after an additional 2 h, THF was removed under reduced pressure. The obtained crude residue was washed with water to afford, after drying in vacuo, semicarbazide **1** in a 73–92% overall yield (Table 1).

**Semicarbazide 1ab:** White solid (398 mg, 73%). IR (KBr): $\tilde{\nu}$ = 3306 (br), 2980, 2959, 1693, 1635, 1573, 1525, 1308, 1257, 1047 $cm^{-1}$. $^1H$ NMR: $\delta$ = 0.87 [d, $J$ = 6.8 Hz, 6 H, $(CH_3)_2CH$], 1.19 (t, $J$ = 7.0 Hz, 3 H, $CH_3CH_2$), 1.86 (app. sextet, $J$ = 7.0 Hz, 1 H, CH), 4.01 (q, $J$ = 7.0 Hz, 2 H, $OCH_2$), 4.50 (br. s, 2 H, $NH_2$), 4.93 (app. q, $J$ = 8.5 Hz, 1 H, *CH), 6.51 (br. d, $J$ = 9.4 Hz, 1 H, N*H*CONHNH$_2$), 7.00 (s, 1 H, N*H*NH$_2$), 7.18 (br. d, $J$ = 7.9 Hz, 1 H, NHCOO) ppm. $^{13}C$ NMR: $\delta$ = 15.4, 19.0, 19.2, 33.7, 60.3, 63.5, 156.1, 159.8 ppm. DI-MS (EI): *m*/*z* (%) = 175 (24) $[M - 43]^+$, 144 (72), 132 (26), 116 (100), 98 (54), 86 (61), 72 (89), 55 (80). MS ($ESI^+$): *m*/*z* = 241 $[M + Na]^+ \rightarrow (MS^2)$ 209, 183, 166, 152, 112, 94. $C_8H_{18}N_4O_3$ (218.26): calcd. C 44.03, H 8.31, N 25.67; found C 44.00, H 8.29, N 25.69.

**Semicarbazide 1ad:** White solid (610 mg, 87%). IR (KBr): $\tilde{\nu}$ = 3318 (br), 2960, 1695, 1509, 1309, 1251, 1028, 731, 696 $cm^{-1}$. $^1H$ NMR: $\delta$ = 0.89 [d, $J$ = 6.8 Hz, 6 H, $(CH_3)_2CH$], 1.89 (app. sextet, $J$ = 7.0 Hz, 1 H, CH), 4.50 (br. s, 2 H, $NH_2$), 5.01 (app. q, $J$ = 8.5 Hz, 1 H, *CH), 5.06 (app. s, 2 H, $CH_2$), 6.54 (br. d, $J$ = 9.4 Hz, 1 H, N*H*CONHNH$_2$), 7.02 (s, 1 H, N*H*NH$_2$), 7.22–7.35 (m, 6 H, 5× ArH + NHCOO) ppm. $^{13}C$ NMR: $\delta$ = 18.9, 19.2, 33.6, 63.6, 65.9, 128.4, 128.5, 129.1, 138.0, 155.9, 159.8 ppm. DI-MS (EI): *m*/*z* (%) = 237 (7) $[M - 43]^+$, 193 (6), 162 (19), 108 (15), 107 (11), 91 (100), 86 (11), 79 (23), 77 (12), 72 (16). MS ($ESI^+$): *m*/*z* = 303 $[M + Na]^+ \rightarrow (MS^2)$ 271, 245, 228, 174, 152, 94. $C_{13}H_{20}N_4O_3$ (280.33): calcd. C 55.70, H 7.19, N 19.99; found C 55.65, H 7.21, N 19.90.

**Semicarbazide 1bb:** White solid (441 mg, 76%). IR (KBr): $\tilde{\nu}$ = 3346 (br), 2958, 1686, 1544, 1508, 1256, 1148, 1058 $cm^{-1}$. $^1H$ NMR: $\delta$ = 0.93 [d, $J$ = 5.9 Hz, 6 H, $(CH_3)_2CH$], 1.22 (t, $J$ = 7.0 Hz, 3 H, $CH_3CH_2$), 1.55–1.80 (m, 3 H, $CHCH_2$), 4.12 (br. s, 2 H, $NH_2$), 4.09 (q, $J$ = 7.3 Hz, 2 H, $OCH_2$), 5.22 (app. quintet, $J$ = 7.6 Hz, 1 H, *CH), 6.54 (br. d, $J$ = 8.5 Hz, 1 H, N*H*CONHNH$_2$), 7.13 (s, 1 H, N*H*NH$_2$), 7.35 (br. d, $J$ = 7.9 Hz, 1 H, NHCOO) ppm. $^{13}C$ NMR: $\delta$ = 14.8, 22.7, 25.1, 44.2, 57.8, 61.1, 156.4, 160.3 ppm. DI-MS (EI): *m*/*z* (%) = 175 (19) $[M - 57]^+$, 158 (64), 143 (21), 132 (15), 117 (19), 102 (70), 86 (100). MS ($ESI^+$): *m*/*z* = 255 $[M + Na]^+ \rightarrow (MS^2)$ 223, 197, 180, 166, 112, 108. $C_{13}H_{20}N_4O_3$ (232.28): calcd. C 46.54, H 8.68, N 24.12; found C 46.50, H 8.74, N 24.08.

**Semicarbazide 1bd:** White solid (574 mg, 78%). IR (KBr): $\tilde{\nu}$ = 3345 (br), 3281 (br), 2958, 1690, 1545, 1507, 1255, 1225, 1160, 1028, 730 $cm^{-1}$. $^1H$ NMR: $\delta$ = 0.85 [d, $J$ = 5.9 Hz, 6 H, $(CH_3)_2CH$], 1.37–1.62 (m, 3 H, $CHCH_2$), 4.12 (br. s, 2 H, $NH_2$), 5.00 (app. s, 2 H, $OCH_2$), 5.21 (app. quintet, $J$ = 7.3 Hz, 1 H, *CH), 6.54 (br. d, $J$ = 8.5 Hz, 1 H, N*H*CONHNH$_2$), 7.08 (s, 1 H, N*H*NH$_2$), 7.22–7.43 (m, 5 H, ArH), 7.49 (br. d, $J$ = 7.9 Hz, 1 H, NHCOO) ppm. $^{13}C$ NMR: $\delta$ = 23.3, 25.4, 45.6, 57.4, 66.2, 128.8, 129.3, 129.4, 138.1, 156.0, 159.8 ppm. DI-MS (EI): *m*/*z* (%) = 237 (6) $[M - 57]^+$, 193 (4), 176 (22), 143 (6), 108 (14), 91 (100), 86 (29), 79 (15). MS ($ESI^+$): *m*/*z* = 317 $[M + Na]^+ \rightarrow (MS^2)$ 285, 259, 242, 174, 166, 108. $C_{14}H_{22}N_4O_3$ (294.35): calcd. C 57.13, H 7.53, N 19.03; found C 57.17, H 7.50, N 19.00.

**Semicarbazide 1cb:** White solid (523 mg, 83%). IR (KBr): $\tilde{\nu}$ = 3349 (br), 3287 (br), 1686, 1643, 1536, 1496, 1264, 1053, 750, 698 $cm^{-1}$. $^1H$ NMR: $\delta$ = 1.19 (t, $J$ = 7.0 Hz, 3 H, $CH_3$), 4.03 (q, $J$ = 7.0 Hz, 2 H, $CH_2$), 4.26 (br. s, 2 H, $NH_2$), 6.31 (app. t, $J$ = 9.1 Hz, 1 H, *CH), 7.04 (br. d, $J$ = 7.6 Hz, 1 H, N*H*CONHNH$_2$), 7.30 (s, 1 H, N*H*NH$_2$), 7.31–7.46 (m, 5 H, ArH), 7.93 (br. d, $J$ = 8.2 Hz, 1 H, NHCOO) ppm. $^{13}C$ NMR: $\delta$ = 15.6, 60.4, 60.9, 126.8, 128.4, 129.3, 142.9, 156.2, 159.7 ppm. DI-MS (EI): *m*/*z* (%) = 193 (5) $[M - 59]^+$, 178 (100), 163 (19), 150 (9), 132 (58), 106 (94), 105 (25), 104 (36), 79 (51), 77 (36). MS ($ESI^+$): *m*/*z* = 275 $[M + Na]^+ \rightarrow (MS^2)$ 243, 217, 200, 186, 128, 112. $C_{11}H_{16}N_4O_3$ (252.27): calcd. C 52.37, H 6.39, N 22.21; found C 52.40, H 6.34, N 22.17.

**Semicarbazide 1cd:** White solid (723 mg, 92%). IR (KBr): $\tilde{\nu}$ = 3310 (br), 1693, 1653, 1539, 1498, 1324, 1261, 1048, 754, 696 $cm^{-1}$. $^1H$ NMR: $\delta$ = 4.25 (br. s, 2 H, $NH_2$), 5.09 (app. s, 2 H, $CH_2$), 6.38 (app. t, $J$ = 8.8 Hz, 1 H, *CH), 7.03 (br. d, $J$ = 7.8 Hz, 1 H, N*H*CONHNH$_2$), 7.24 (s, 1 H, N*H*NH$_2$), 7.28–7.48 (m, 5 H, ArH), 8.02 (br. d, $J$ = 8.0 Hz, 1 H, NHCOO) ppm. $^{13}C$ NMR: $\delta$ = 60.5, 66.3, 126.7, 128.2, 128.5, 128.6, 129.0, 129.1, 137.8, 142.7, 155.8, 159.7 ppm. DI-MS (EI): *m*/*z* (%) = 239 (5) $[M - 75]^+$, 238 (29), 196 (13), 194 (26), 132 (70), 108 (51), 107 (37), 91 (100), 79 (74), 77 (62). MS ($ESI^+$): *m*/*z* = 337 $[M + Na]^+ \rightarrow (MS^2)$ 305, 279, 262, 186, 174, 128. $C_{16}H_{18}N_4O_3$ (314.34): calcd. C 61.14, H 5.77, N 17.82; found C 61.10, H 5.81, N 17.78.

**Semicarbazide 1db:** White solid (546 mg, 82%). IR (KBr): $\tilde{\nu}$ = 3299 (br), 1696, 1650, 1570, 1525, 1305, 1256, 1052, 703 $cm^{-1}$. $^1H$ NMR: $\delta$ = 1.13 (t, $J$ = 7.0 Hz, 3 H, $CH_3$), 2.92 (app. d, $J$ = 7.0 Hz, 2 H, $PhCH_2$), 3.95 (q, $J$ = 7.0 Hz, 2 H, $OCH_2$), 4.16 (br. s, 2 H, $NH_2$), 5.29 (app. quintet, $J$ = 8.2 Hz, 1 H, *CH), 6.73 (br. d, $J$ = 9.7 Hz, 1 H, N*H*CONHNH$_2$), 7.14 (s, 1 H, N*H*NH$_2$), 7.16–7.38 (m, 5 H, ArH), 7.46 (br. d, $J$ = 7.9 Hz, 1 H, NHCOO) ppm. $^{13}C$ NMR: $\delta$ = 15.6, 42.3, 60.2, 60.7, 127.3, 129.2, 130.3, 138.8, 156.0, 159.8 ppm. DI-MS (EI): *m*/*z* (%) = 192 (87) $[M - 74]^+$, 191 (37), 178 (25), 175 (35), 148 (17), 132 (22), 120 (100), 91 (27). MS ($ESI^+$): *m*/*z* = 289 $[M + Na]^+ \rightarrow (MS^2)$ 257, 231, 214, 200, 142, 112. $C_{12}H_{18}N_4O_3$ (266.30): calcd. C 54.12, H 6.81, N 21.04; found C 54.17, H 6.84, N 21.00.

**Semicarbazide 1dc:** White solid (545 mg, 74%). IR (KBr): $\tilde{\nu}$ = 3390, 3353, 3314, 1682, 1542, 1499, 1391, 1251, 1169, 1015, 753 $cm^{-1}$. $^1H$ NMR: $\delta$ = 1.35 [s, 9 H, $(CH_3)_3C$], 2.90 (app. d, $J$ = 7.0 Hz, 2 H, $CH_2$), 4.15 (br. s, 2 H, $NH_2$), 5.25 (app. quintet, $J$ = 8.2 Hz, 1 H, *CH), 6.68 (br. d, $J$ = 8.5 Hz, 1 H, N*H*CONHNH$_2$), 7.12 (s, 1 H, N*H*NH$_2$), 7.15–7.38 (m, 6 H, 5× ArH + NHCOO) ppm. $^{13}C$ NMR: $\delta$ = 29.2, 42.5, 59.8, 78.9, 127.1, 129.1, 130.2, 138.8, 155.8, 159.7 ppm. DI-MS (EI): *m*/*z* (%) = 203 (5) $[M - 91]^+$, 178 (13), 177 (25), 164 (22), 163 (17), 147 (33), 128 (15), 120 (100), 119 (27), 118 (30), 91 (44). MS ($ESI^+$): *m*/*z* = 317 $[M + Na]^+ \rightarrow (MS^2)$ 285, 261, 259, 242, 217, 200, 142. $C_{14}H_{22}N_4O_3$ (294.35): calcd. C 57.13, H 7.53, N 19.03; found C 57.08, H 7.55, N 19.06.

**Semicarbazide 1dd:** White solid (657 mg, 80%). IR (KBr): $\tilde{\nu}$ = 3355, 3275, 1691, 1655, 1542, 1504, 1326, 1247, 1049, 756, 733, 702 $cm^{-1}$. $^1H$ NMR: $\delta$ = 2.95 (app. d, $J$ = 6.8 Hz, 2 H, *CHC$H_2$), 4.18 (br. s, 2 H, $NH_2$), 5.01 (app. s, 2 H, $OCH_2$), 5.34 (app. quintet, $J$ = 7.3 Hz, 1 H, *CH), 6.75 (br. d, $J$ = 8.5 Hz, 1 H, N*H*CONHNH$_2$), 7.17 (s, 1 H, N*H*NH$_2$), 7.18–7.47 (m, 10 H, ArH), 7.66 (br. d, $J$ = 7.9 Hz, 1 H, NHCOO) ppm. $^{13}C$ NMR: $\delta$ = 42.2, 60.3, 66.1, 127.3, 128.6, 128.8, 129.2, 129.3, 130.2, 138.1, 138.7, 155.9, 159.7 ppm. DI-MS (EI): *m*/*z* (%) = 254 (4) $[M - 74]^+$, 253 (7), 237 (25), 210 (22), 193 (19), 177 (13), 120 (27), 108 (14), 91 (100). MS ($ESI^+$): *m*/*z* = 351 $[M + Na]^+ \rightarrow (MS^2)$ 319, 293, 276, 200, 174, 142.

$C_{17}H_{20}N_4O_3$ (328.37): calcd. C 62.18, H 6.14, N 17.06; found C 62.13, H 6.18, N 17.10.

**Semicarbazide 1ea:** White solid (561 mg, 77%). IR (KBr): $\tilde{\nu}$ = 3337 (br), 1694, 1666, 1601, 1559, 1531, 1498, 1454, 1443, 1347, 1308, 1251, 1100, 733 $cm^{-1}$. $^1H$ NMR: $\delta$ = 3.03 (app. d; $J$ = 6.5 Hz, 2 H, $CH_2$), 3.49 (s, 3 H, $CH_3$), 4.07 (br. s, 2 H, $NH_2$), 5.37 (app. quintet, $J$ = 7.9 Hz, 1 H, *CH), 6.65 (br. d, $J$ = 8.2 Hz, 1 H, N*H*CONHNH$_2$), 6.92–7.15 (m, 4 H, 3× ArH + N*H*NH$_2$), 7.24–7.42 (m, 2 H, ArH + NHCOO), 7.58 (app. d, $J$ = 7.3 Hz, 1 H, ArH), 10.74 (s, 1 H, ArNH) ppm. $^{13}C$ NMR: $\delta$ = 32.3, 51.9, 59.6, 111.1, 112.1, 119.1, 119.2, 121.7, 124.1, 128.4, 136.9, 156.0, 159.7 ppm. DI-MS (EI): $m/z$ (%) = 217 (19) $[M - 74]^+$, 216 (93), 185 (27), 184 (43), 157 (23), 156 (33), 155 (18), 130 (100). MS ($ESI^+$): $m/z$ = 314 $[M + Na]^+ \rightarrow (MS^2)$ 282, 256, 239, 181, 98. $C_{13}H_{17}N_5O_3$ (291.31): calcd. C 53.60, H 5.88, N 24.04; found C 53.64, H 5.82, N 24.09.

**Semicarbazide 1fb:** White solid (463 mg, 74%). IR (KBr): $\tilde{\nu}$ = 3336 (br), 2980, 2916, 1696, 1636, 1559, 1522, 1447, 1257, 1055 $cm^{-1}$. $^1H$ NMR: $\delta$ = 1.19 (t, $J$ = 7.0 Hz, 3 H, C$H_3$CH$_2$), 1.81–1.97 (m, 2 H, *CHC$H_2$), 2.07 (s, 3 H, $SCH_3$), 2.34–2.50 (m, 2 H, $SCH_2$), 3.68 (br. s, 2 H, $NH_2$), 4.01 (q, $J$ = 7.0 Hz, 2 H, $OCH_2$), 5.20 (app. quintet, $J$ = 8.4 Hz, 1 H, *CH), 6.62 (br. d, $J$ = 8.9 Hz, 1 H, N*H*CONHNH$_2$), 7.01 (s, 1 H, N*H*NH$_2$), 7.29 (br. d, $J$ = 8.0 Hz, 1 H, NHCOO) ppm. $^{13}C$ NMR: $\delta$ = 15.4, 15.6, 30.2, 35.9, 58.2, 60.5, 156.0, 159.8 ppm. DI-MS (EI): $m/z$ (%) = 176 (27) $[M - 74]^+$, 175 (7), 128 (100), 114 (25), 86 (79), 61 (51), 56 (66). MS ($ESI^+$): $m/z$ = 273 $[M + Na]^+ \rightarrow (MS^2)$ 241, 215, 198, 184, 126, 112. $C_8H_{18}N_4O_3S$ (250.32): calcd. C 38.39, H 7.25, N 22.38; found C 38.34, H 7.22, N 22.40.

**General Procedure for the Synthesis of Semicarbazides 4 (Method C):** NMM (0.30 mL, 2.73 mmol) was slowly and dropwise added into a stirred solution of α-*N*-protected amino acid **2** (2.50 mmol) in THF (15 mL). After 5 min, IBCF (0.36 mL, 2.73 mmol) was slowly added into the reaction mixture, which was cooled to –20 °C and stirring was continued for 20 min at the same temperature. The reaction mixture was subsequently warmed to 0 °C and a solution of $KH_2PO_4$ (0.17 g, 1.25 mmol) in $H_2O$ (1 mL) was added in one portion, followed, after 5 min, by a solution of $KH_2PO_4$ (1.70 g, 12.50 mmol) and $NaN_3$ (0.41 g, 6.25 mmol) in $H_2O$ (9 mL). After stirring 30 min at 0 °C, the mixture was warmed to 40 °C for 1.5 h, hydrazine monohydrate (0.73 mL, 7.50 mmol) was slowly added and the resulting mixture was warmed to 50 °C and stirred for 5 h. THF was finally removed under reduced pressure, water was filtered off, and the obtained crude residue was washed with water and EtOAc affording, after drying in vacuo, semicarbazide **4** as a white solid in 57–93% overall yield (Table 1).

To optimize the yield of semicarbazide **4cb** by avoiding the formation of the semicarbazide **5cb**,[21] the addition of hydrazine monohydrate (0.73 mL, 7.50 mmol) into the reaction mixture containing the synthesized carbamoyl azide **3cb** was carried out at room temperature and stirring was continued for 12 h at the same temperature. Under these conditions, after usual work-up, semicarbazide **4cb** was obtained in 83% yield (Table 1).

**Semicarbazide 4ad:** White solid (476 mg, 72%). IR (KBr): $\tilde{\nu}$ = 3320 (br), 1698, 1655, 1570, 1508, 1265, 1244, 1125, 1036, 697 $cm^{-1}$. $^1H$ NMR: $\delta$ = 0.88 [d, $J$ = 6.8 Hz, 12 H, 2× (C$H_3$)$_2$CH], 1.87 (app. sextet, $J$ = 7.0 Hz, 2 H, 2× CH), 4.99 (app. q, $J$ = 8.5 Hz, 2 H, 2× *CH), 5.05 (app. s, 4 H, 2× $CH_2$), 7.28–7.46 [m, 12 H, 2× (5× ArH + NHCOO)], 7.79 (s, 2 H, NHNH) ppm. $^{13}C$ NMR: $\delta$ = 19.0, 19.1, 33.6, 63.9, 6.1, 128.5, 128.6, 129.1, 137.9, 155.9, 158.3 ppm. DI-MS (EI): $m/z$ (%) = 206 (7) $[M - 322]^+$, 162 (25), 140 (9), 108 (19), 107 (21), 91 (100), 86 (20), 79 (35), 77 (15). MS ($ESI^+$): $m/z$ = 551 $[M + Na]^+ \rightarrow (MS^2)$ 400, 346, 329, 303, 228. $C_{26}H_{36}N_6O_6$ (528.61): calcd. C 59.08, H 6.86, N 15.90; found C 59.14, H 6.81, N 15.94.

**Semicarbazide 4bd:** White solid (647 mg, 93%). IR (KBr): $\tilde{\nu}$ = 3330, 3279, 1699, 1655, 1504, 1255, 1156, 1127, 1049, 698 $cm^{-1}$. $^1H$ NMR: $\delta$ = 0.86 [d, $J$ = 6.2 Hz, 12 H, 2× (C$H_3$)$_2$CH], 1.38–1.64 (m, 6 H, 2× CHCH$_2$), 5.01 (app. s, 4 H, 2× $OCH_2$), 5.22 (app. quintet, $J$ = 8.2 Hz, 2 H, 2× *CH), 6.34 (d, $J$ = 8.8 Hz, 2 H, 2× N*H*CONHNH), 7.25–7.43 [m, 12 H, 2× (5× ArH + NHCOO)], 7.70 (s, 2 H, NHNH) ppm. $^{13}C$ NMR: $\delta$ = 23.1, 23.2, 25.0, 45.2, 57.6, 66.1, 128.5, 129.1, 137.9, 155.7, 157.7 ppm. DI-MS (EI): $m/z$ (%) = 220 (3) $[M - 336]^+$, 176 (5), 158 (6), 143 (8), 108 (38), 107 (27), 91 (100), 86 (27), 79 (51), 65 (18). MS ($ESI^+$): $m/z$ = 579 $[M + Na]^+ \rightarrow (MS^2)$ 428, 360, 343, 317, 242. $C_{26}H_{36}N_6O_6$ (556.66): calcd. C 60.42, H 7.24, N 15.10; found C 60.40, H 7.24, N 15.13.

**Semicarbazide 4cb:** White solid (490 mg, 83%). IR (KBr): $\tilde{\nu}$ = 3252 (br), 1696, 1672, 1509, 1254, 1108, 1056, 616 $cm^{-1}$. $^1H$ NMR: $\delta$ = 1.20 (t, $J$ = 7.0 Hz, 6 H, 2× $CH_3$), 4.05 (q, $J$ = 7.0 Hz, 4 H, 2× $CH_2$), 6.32 (app. t, $J$ = 8.5 Hz, 2 H, 2× *CH), 6.94 (d, $J$ = 9.1 Hz, 2 H, 2× N*H*CONHNH), 7.26–7.42 (m, 10 H, 5× ArH), 7.73 (br. s, 2 H, 2× NHCOO), 8.01 (s, 2 H, NHNH) ppm. $^{13}C$ NMR: $\delta$ = 15.4, 60.6, 126.7, 128.2, 129.0, 142.2, 155.9, 158.1 ppm. DI-MS (EI): $m/z$ (%) = 251 (8) $[M - 221]^+$, 178 (49), 163 (18), 132 (100), 120 (18), 106 (38), 105 (57), 104 (93), 91 (23), 77 (56). MS ($ESI^+$): $m/z$ = 495 $[M + Na]^+ \rightarrow (MS^2)$ 406, 318, 301, 275, 200. $C_{22}H_{28}N_6O_6$ (472.50): calcd. C 55.92, H 5.97, N 17.79; found C 55.96, H 5.96, N 17.76.

**Semicarbazide 4cd:** White solid (694 mg, 93%). IR (KBr): $\tilde{\nu}$ = 3307 (br), 1701, 1655, 1558, 1543, 1508, 1347, 1310, 1236, 1055, 755 $cm^{-1}$. $^1H$ NMR: $\delta$ = 5.09 (app. s, 4 H, 2× $OCH_2$), 6.38 (app. t, $J$ = 8.9 Hz, 2 H, 2× *CH), 6.98 (d, $J$ = 8.9 Hz, 2 H, 2× N*H*CONHNH), 7.24–7.59 (m, 20 H, ArH), 7.90 (br. s, 2 H, 2× NHCOO), 8.01 (s, 2 H, NHNH) ppm. $^{13}C$ NMR: $\delta$ = 60.8, 66.4, 126.8, 128.3, 128.6, 128.7, 129.1, 129.2, 137.7, 142.1, 155.9, 158.1 ppm. DI-MS (EI): $m/z$ (%) = 239 (34) $[M - 357]^+$, 238 (57), 194 (45), 132 (98), 108 (60), 107 (56), 91 (96), 79 (100), 77 (75). MS ($ESI^+$): $m/z$ = 619 $[M + Na]^+ \rightarrow (MS^2)$ 468, 380, 363, 337, 262. $C_{32}H_{32}N_6O_6$ (596.64): calcd. C 64.42, H 5.41, N 14.09; found C 64.36, H 5.46, N 14.03.

**Semicarbazide 4db:** White solid (507 mg, 81%). IR (KBr): $\tilde{\nu}$ = 3307 (br), 1698, 1672, 1547, 1512, 1323, 1298, 1253, 1054, 701 $cm^{-1}$. $^1H$ NMR: $\delta$ = 1.14 (t, $J$ = 7.3 Hz, 6 H, 2× $CH_3$), 2.91 (app. d, $J$ = 7.1 Hz, 4 H, 2× PhCH$_2$), 3.97 (q, $J$ = 7.1 Hz, 4 H, 2× $OCH_2$), 5.30 (app. quintet, $J$ = 8.2 Hz, 2 H, 2× *CH), 6.53 (d, $J$ = 8.5 Hz, 2 H, 2× N*H*CONHNH), 7.16–7.39 [m, 12 H, 2× (5× ArH + NHCOO)], 7.76 (s, 2 H, NHNH) ppm. $^{13}C$ NMR: $\delta$ = 15.3, 41.9, 60.4, 60.5, 127.0, 128.9, 130.0, 138.4, 155.8, 157.7 ppm. DI-MS (EI): $m/z$ (%) = 192 (40) $[M - 308]^+$, 191 (72), 175 (20), 163 (41), 145 (51), 120 (52), 119 (63), 118 (79), 117 (67), 91 (100), 65 (26). MS ($ESI^+$): $m/z$ = 523 $[M + Na]^+ \rightarrow (MS^2)$ 434, 332, 315, 289, 214. $C_{24}H_{32}N_6O_6$ (500.55): calcd. C 57.59, H 6.44, N 16.79; found C 57.55, H 6.46, N 16.84.

**Semicarbazide 4dc:** White solid (598 mg, 86%). IR (KBr): $\tilde{\nu}$ = 3349 (br), 1698, 1656, 1568, 1500, 1367, 1250, 1171, 1120, 1049, 700 $cm^{-1}$. $^1H$ NMR: $\delta$ = 1.13 [s, 18 H, 2× (C$H_3$)$_3$C], 2.88 (app. d, $J$ = 6.8 Hz, 4 H, 2× $CH_2$), 5.22 (app. quintet, $J$ = 8.5 Hz, 2 H, 2× *CH), 6.46 (d, $J$ = 8.5 Hz, 2 H, 2× N*H*CONHNH), 7.12–7.33 [m, 12 H, 2× (5× ArH + NHCOO)], 7.74 (s, 2 H, NHNH) ppm. $^{13}C$ NMR: $\delta$ = 28.9, 42.0, 60.2, 78.8, 126.9, 128.8, 130.0, 138.5, 155.6, 157.7 ppm. DI-MS (EI): $m/z$ (%) = 220 (6) $[M - 336]^+$, 203 (11), 177 (16), 163 (41), 146 (33), 145 (54), 119 (56), 118 (97), 117 (43), 91 (100), 86 (28). MS ($ESI^+$): $m/z$ = 573 $[M + Na]^+ \rightarrow (MS^2)$ 498,

357, 340, 314, 239 $C_{28}H_{40}N_6O_6$ (556.66): calcd. C 60.42, H 7.24, N 15.10; found C 60.45, H 7.20, N 15.15.

**Semicarbazide 4ea:** White solid (496 mg, 72%). IR (KBr): $\tilde{\nu}$ = 3330 (br), 1703, 1667, 1511, 1458, 1343, 1248, 1101, 1052, 743 $cm^{-1}$. $^1H$ NMR: $\delta$ = 3.07 (app. d, $J$ = 6.7 Hz, 4 H, 2× $CH_2$), 3.52 (s, 6 H, 2× $CH_3$), 5.38 (app. quintet, $J$ = 7.4 Hz, 2 H, 2× *CH), 6.55 (d, $J$ = 8.6 Hz, 2 H, 2× N*H*CONHNH), 6.94–7.22 (m, 6 H, ArH), 7.25–7.46 [m, 4 H, 2× (ArH + NHCOO)], 7.62 (app. d, $J$ = 7.0 Hz, 2 H, ArH), 7.77 (s, 2 H, NHNH), 10.78 (s, 2 H, 2× ArNH) ppm. $^{13}C$ NMR: $\delta$ = 36.2, 52.0, 60.0, 110.9, 112.1, 119.0, 119.1, 121.7, 124.3, 128.3, 136.9, 155.9, 158.1 ppm. DI-MS (EI): $m/z$ (%) = 217 (15) $[M - 333]^+$, 216 (98), 184 (100), 157 (26), 156 (48), 155 (21), 130 (70). MS ($ESI^+$): $m/z$ = 579 $[M + Na]^+ \rightarrow (MS^2)$ 523, 479, 462, 360, 343, 317, 242. $C_{26}H_{30}N_8O_6$ (550.57): calcd. C 56.72, H 5.49, N 20.35; found C 56.70, H 5.52, N 20.30.

**Semicarbazide 4fb:** White solid (521 mg, 89%). IR (KBr): $\tilde{\nu}$ = 3315 (br), 1695, 1656, 1561, 1527, 1509, 1263, 1226, 1059, 977 $cm^{-1}$. $^1H$ NMR: $\delta$ = 1.19 (t, $J$ = 7.2 Hz, 6 H, 2× $CH_3CH_2$), 1.80–1.98 (m, 4 H, 2× *CHC$H_2$), 2.07 (s, 6 H, 2× $SCH_3$), 2.35–2.52 (m, 4 H, 2× $SCH_2$), 4.02 (q, $J$ = 7.1 Hz, 4 H, 2× $OCH_2$), 5.20 (app. quintet, $J$ = 8.4 Hz, 2 H, 2× *CH), 6.49 (d, $J$ = 8.8 Hz, 2 H, 2× N*H*CONHNH), 7.24 (br. s, 2 H, 2× NHCOO), 7.74 (s, 2 H, NHNH) ppm. $^{13}C$ NMR: $\delta$ = 15.4, 15.6, 30.1, 35.7, 58.4, 60.6, 155.9, 159.1 ppm. DI-MS (EI): $m/z$ (%) = 176 (18) $[M - 292]^+$, 175 (10), 128 (100), 114 (14), 102 (14), 86 (48), 61 (52), 56 (74). MS ($ESI^+$): $m/z$ = 523 $[M + Na]^+ \rightarrow (MS^2)$ 402, 316, 299, 273, 198. $C_{16}H_{32}N_6O_6S_2$ (468.59): calcd. C 41.01, H 6.88, N 17.93; found C 41.00, H 6.91, N 17.90.

**Supporting Information** (see footnote on the first page of this article): 2D TOCSY, 2D ROESY, and DOSY NMR spectra of **1db** and **4db**.

## Acknowledgments

The authors are grateful to Dr. S. Turco for recording $^1H$ and $^{13}C$ NMR spectra and to Dr. I. Duse for MS measurements.

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Received: October 8, 2010
Published Online: January 18, 2011

  