Hydroamination

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Diversity-Oriented Synthesis of Hydrazine-Derived Compounds from Amino Isocyanates Generated In Situ**

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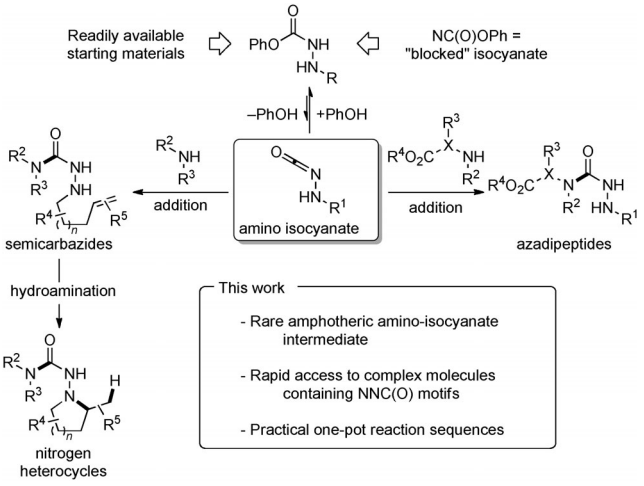
The ability to rapidly assemble complex molecules from simple starting materials is essential to improve current chemical processes and discovery efforts. Development of novel pharmaceuticals relies on practical synthetic strategies offering step-economy and chemoselectivity. This consequently restricts the use of certain reagents bearing unique and interesting functionalities. For example hydrazine derivatives have inherent chemoselectivity issues because of the possibility that both nitrogen atoms could react and form different products.[1] Nevertheless, the importance of these motifs led to many recent reports, but inclusion of hydrazines in molecular scaffolds can be problematic. Difficult control over reaction outcomes has made their use in cascade sequences challenging and therefore scarce, especially for the assembly of peptidomimetics.[2] For this reason, development of nitrogen-substituted isocyanate equivalents as synthetic reagents is particularly attractive. Indeed, amino isocyanates combine the highly electrophilic nature of isocyanates while retaining differentiation and nucleophilicity of only one nitrogen atom. Such amphoteric intermediates are rare and have not been used in cascade reactions.[3] Herein we describe the use of amino isocyanate equivalents for the synthesis of complex semicarbazide derivatives including azadipeptide motifs, and formation of diverse heterocyclic structures by a substitution/hydroamination reaction sequence (Scheme 1).

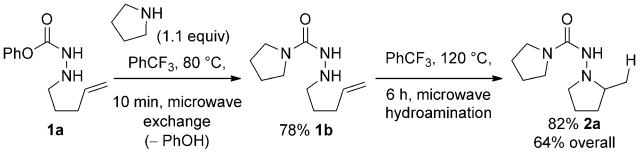


Scheme 1. Novel reactivity using amino isocyanates.

Recently, our group has reported the use of nitrogen-substituted isocyanates to access β-amincarbonyl motifs from alkenes.[4] We were surprised to find only a few reports of nitrogen-substituted isocyanates in the literature, especially considering the synthetic and industrial relevance of isocyanates.[5,6a,b] In further studies, we noted that amino isocyanates can be conveniently generated in situ from simple precursors and reacted to generate hydrazine derivatives.[6] As part of our ongoing work on Cope-type hydroaminations, we often faced the issue that intramolecular alkene hydroaminations are generally not amenable to rapid generation of molecular complexity.[7,8]

Indeed, synthesis of the precursors typically requires several steps, and cyclization can only form one product. To address this fundamental limitation and to explore the use of nitrogen-substituted isocyanates in reaction sequences, we targeted using amino isocyanate intermediates to form diverse hydroamination precursors in situ, precursors which then cyclize to afford various heterocyclic derivatives through a substitution/hydroamination sequence.

We first validated this approach using a stepwise process (Scheme 2). After optimization, we observed that the OPh leaving group present in the carbazate **1a** was rapidly exchanged for a pyrrolidinyl substituent in the presence of a slight excess of the amine nucleophile at 80 °C. The resulting semicarbazide **1b** was isolated and then submitted to our Cope-type hydroamination conditions (120 °C) to provide the cyclization product **2a** in good yield. In contrast to our previous report on the amination reactivity of simpler semi-



Scheme 2. Stepwise substitution/hydroamination sequence.

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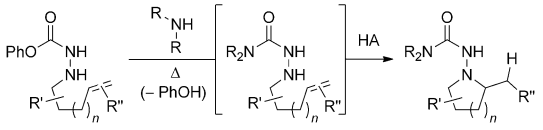
carbazides,[4a] we were delighted to note the absence of a competing aminocarbonylation pathway.

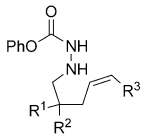
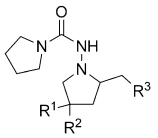
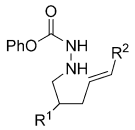
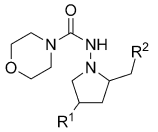
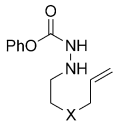
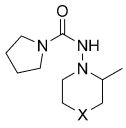
We then attempted to combine both steps in a substitution/hydroamination sequence. Using the same reagents, the reaction mixture was directly heated at 120 °C since we expected rapid substitution under the hydroamination conditions. Gratifyingly, the desired sequence was achieved in excellent yield (Table 1, entry 1). We thus embarked on a study to determine if this cascade reaction could provide access to various heterocyclic hydrazides: the results obtained are shown in Table 1. As expected, the gem-dimethylated substrate **1c** cyclized under milder reaction conditions (80 °C) because of a favorable Thorpe–Ingold effect (Table 1, entry 2). Substitution was also tolerated on the distal position of the alkene but slightly higher temperatures were required to achieve the parent sequence on both *cis* and *trans* alkenes (entries 3–4). The sequence also proved versatile to form six-membered-ring systems and led to the formation of piperidine and piperazine motifs (entries 6–8).

Since the scope of the sequence had only been explored using pyrrolidine and morpholine in Table 1, we then surveyed various amine nucleophiles under our substitution/hydroamination sequence conditions. As shown in Table 2, ten different hydroamination products were formed using the same precursor, **1a**. Both cyclic (**3a**–**h**) and acyclic (**3i**) secondary amines proved to be competent nucleophiles. For cyclic amines, four- (**3a**), five- (**3b**), and six-membered (**3c**–**h**) amines led to the desired hydroamination product. (*S*)-Prolinol also proved a competent nucleophile (**3b**), but only showed modest diastereoselectivity under the reaction conditions (1.2:1 d.r.). Piperidine derivatives, including the medicinally relevant 2-oxopiperazine motif, exchanged and cyclized efficiently (**3c**,**d**,**h**). Other nitrogen heterocycles such as morpholine and piperazines underwent the reaction sequence to provide the hydroamination products **3e**–**g** in good to excellent yields. We then compared the reactivity of cyclic versus acyclic secondary amines. *N*,*N*-Dibenzylamine provided the hydroamination product **3i** in good yield but proved less reactive than the cyclic derivatives. In contrast, primary amines such as benzylamine only gave a moderate yield of the hydroamination product **3j**. We explain this difference in hydroamination reactivity between the adducts of the primary and secondary amines by the increased population of the *Z* conformer present in the hydroamination substrate. This *Z* conformer is in the appropriate conformation to react via the proposed concerted, Cope-type hydroamination (hydrohydrazidation) transition-state structure (Scheme 3).[4a,9,10]

Having demonstrated the versatility of sequential reactions involving amino isocyanates in the context of hydroamination, we then focused on the synthesis of other important and medicinally relevant hydrazine subunits. We thus sought to demonstrate that this substitution reactivity could provide access to various azadipeptide subunits.[2] Indeed, azapeptides and peptoids are part of the rapidly expanding repertoire of amino acid mimics which are used in peptidomimetics.[11] The increased metabolic stability of the resulting unnatural oligomers is well-established. However,

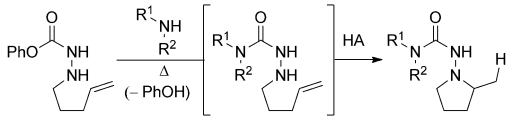
Table 1: Substitution/hydroamination sequence using carbazates.[a]

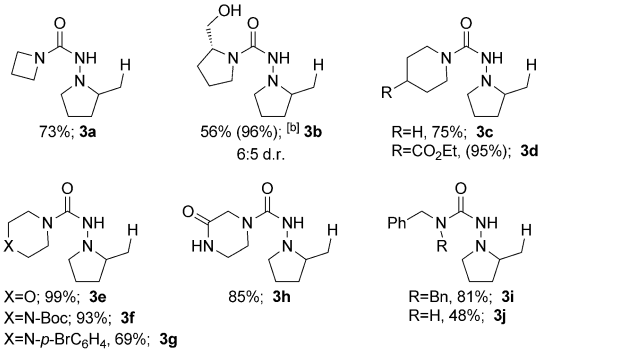


Entry	Alkenyl hydrazide	*T* [°C]	*t* [h]	Product	Yield [%][b]
					
1	$R^1=R^2=R^3=H$; **1a**	120	6	**2a**	88
2	$R^1=R^2=CH_3$, $R^3=H$; **1c**	80	6	**2b**	99
3	$R^1=R^2=H$, $R^3=CH_3$; **1d**	175	6	**2c**	86
					
4	$R^1=H$, $R^2=CH_2OMOM$; **1e**	175	6	**2d**	74
5	$R^1=CH_3$, $R^2=H$; **1f**	120	6	**2e**	94[c]
					
6	X = CH_2; **1g**	175	16	**2f**	79
7	X = NTs; **1h**	175	6	**2g**	86
8	X = $C(CH_3)_2$; **1i**	150	12	**2h**	82

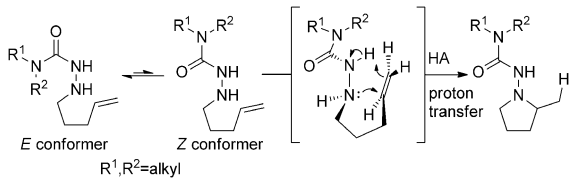
[a] Reaction conditions: carbazate (1 equiv), amine (1.1 equiv) in $PhCF_3$ (0.3 M) heated in a sealed vial (microwave reactor). [b] Yield of the isolated product. [c] 1:1 d.r. MOM = methoxymethyl, Ts = 4-toluenesulfonyl.

Table 2: Substitution/hydroamination cascade: Amine scope.[a]





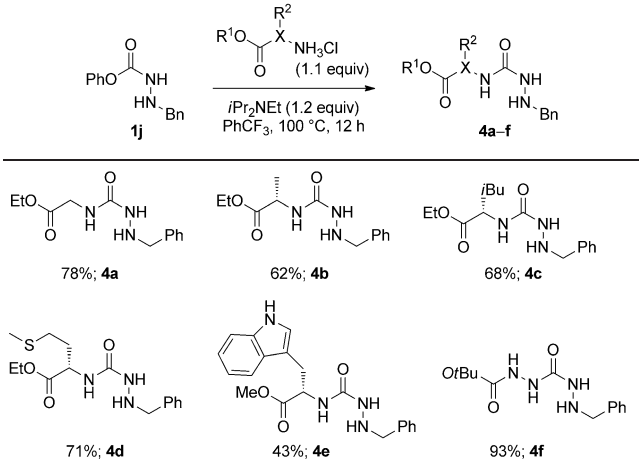
[a] Reaction conditions: carbazate (1 equiv), amine (1.1 equiv) in $PhCF_3$ (0.3 M) heated in a sealed vial (microwave reactor, 120 °C, 6 h). Yields shown are those of the isolated product. [b] Yield determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.



Scheme 3. Cope-type hydroamination transition state. HA = hydroamination.

a notable advantage of azapeptides is that their subunits lack stereochemical information in contrast to α, β, and γ-amino acids derivatives, which require the use of enantiopure unnatural amino acids. Consequently, we felt that simple substitution reactivity would provide a useful tool in peptidomimetics, and decided to perform exploratory studies with the N-benzyl azapeptoid building block **1j** (Table 3). Encouragingly, the use of the commercially available α-aminoester ethyl glycinate (HCl salt) provided the azadipeptide subunit **4a** in 78% yield. A similar result was obtained with L-alanine ethyl ester to form **4b**, and we ensured that racemization did not occur under the reaction conditions (see the Supporting Information). Several encouraging results were also obtained with enantiopure α-aminoesters (**4c**–**4e**). Seeking to form the parent nitrogen analogue (an azatide subunit), *tert*-butylbenzylcarbazate was able to undergo an efficient substitution with **1j** despite a much slower reaction (**4f**, 93% yield). We explain this observation by the reduced nucleophilicity of *tert*-butylbenzylcarbazate relative to primary and secondary amines.

Table 3: Synthesis of dipeptide analogues using a substitution reaction.[a]



[a] Reaction conditions: carbazate (1 equiv), amine (1.1 equiv), iPr_2NEt (1.2 equiv) in $PhCF_3$ (0.3 M) heated in a sealed vial (100 °C, 12 h). Yields shown are those of the isolated product. [b] Reaction conditions: similar, except: hydrazide (10 equiv), heating in oil bath.

In summary OPh-substituted carbazates allow the convenient in situ generation of amino isocyanate intermediates. These reagents react readily with primary and secondary amines, and enable the rapid assembly of various hydrazine-derived compounds. This reactivity was used in sequential reactions, including a substitution/hydroamination cascade allowing the synthesis of diverse nitrogen-containing heterocycles from a single, common hydroamination precursor. Simple substitution of the O-phenyl leaving group with primary amino esters also provides a convenient synthesis of azadipeptide-like structures. Overall, these results demonstrate the usefulness of amino isocyanates to rapidly generate molecular complexity and assemble complex hydrazide derivatives. Efforts to develop other reaction sequences and access different hydrazine-based heterocycles are in progress and will be reported in due course.

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[1] For reviews on hydrazines and hydrazides: a) E. F. Rothgery, *Kirk-Othmer Encyclopedia Chemical Technology*, *Vol. 13*, 5th ed., Wiley, New York, **2004**, pp. 562–607; b) U. Ragnarsson, *Chem. Soc. Rev.* **2001**, *30*, 205; c) E. Licandro, D. Perdicchia, *Eur. J. Org. Chem.* **2004**, 665.

[2] Azapeptides: a) C. B. Bourguet, C. Proulx, S. Klocek, D. Sabatino, W. D. Lubell, *J. Pept. Sci.* **2010**, *16*, 284; b) C. Gibson, S. L. Goodman, D. Hahn, G. Holzemann, H. Kessler, *J. Org. Chem.* **1999**, *64*, 7388; c) E. Wieczerzak, E. Jankowska, S. Rodziewicz-Motowidlo, A. Gieldon, J. Lagiewka, Z. Grzonka, M. Abrahamson, A. Grubb, D. Bromme, *J. Pept. Res.* **2006**, *66*, 1; d) E. Wieczerzak, S. Rodziewicz-Motowidlo, E. Jankowska, A. Gieldon, J. Ciarkowski, *J. Pept. Sci.* **2007**, *13*, 536; e) H.-J. Lee, J.-W. Song, Y.-S. Choi, H.-M. Park, K.-B. Lee, *J. Am. Chem. Soc.* **2002**, *124*, 11881; f) N. S. Freeman, Y. Tal-Gan, S. Klein, A. Levitzki, C. Gilon, *J. Org. Chem.* **2011**, *76*, 3078; azatides: g) H. Han, K. D. Janda, *J. Am. Chem. Soc.* **1996**, *118*, 2539; h) Y. Han, J. Yoon, K. D. Janda, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 117; (Hydrazino azapeptoids: i) A. Aubin, B. Martin, J.-G. Delcros, Y. Arlot-Bonnemains, M. Baudy-Floc'h, *J. Med. Chem.* **2005**, *48*, 330; For selected reviews, see: j) C. Proulx, D. Sabatino, R. Hopewell, J. Spiegel, Y. Garcia Ramos, W. D. Lubell, *Future Med. Chem.* **2011**, *3*, 1139; k) J. Gante, *Angew. Chem. Angew Chem.* **1994**, *106*, 1780; *Angew. Chem.* **1994**, *106*, 1780; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1699; l) A. Giannis, T. Kolter, *Angew. Chem.* **1993**, *105*, 1303; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244.

[3] For examples of nitrogen-containing amphoteric reagents, see: a) R. Hili, A. K. Yudin, *J. Am. Chem. Soc.* **2006**, *128*, 14772; b) Z. He, A. Zajdlik, J. D. St. Denis, N. Assem, A. K. Yudin, *J. Am. Chem. Soc.* **2012**, *134*, 9926; c) N. Assem, R. Hili, Z. He, T. Kasahara, B. L. Inman, S. Decker, A. K. Yudin, *J. Org. Chem.* **2012**, *77*, 5613; d) R. Hili, S. Baktharaman, A. K. Yudin, *Eur. J. Org. Chem.* **2008**, 5201.

[4] a) J.-G. Roveda, C. Clavette, A. D. Hunt, C. J. Whipp, S. I. Gorelsky, A. M. Beauchemin, *J. Am. Chem. Soc.* **2009**, *131*, 8740; b) C. Clavette, W. Gan, A. Bongers, T. Markiewicz, A. B. Toderian, S. I. Gorelsky, A. M. Beauchemin, *J. Am. Chem. Soc.* **2012**, *134*, 16111; c) W. Gan, P. J. Moon, C. Clavette, N. Das Neves, T. Markiewicz, A. B. Toderian, A. M. Beauchemin, *Org. Lett.* **2013**, *15*, 1890.

[5] For reports on the reactivity of nitrogen-substituted isocyanates, see: Amino isocyanates: a) W. S. Wadsworth, W. D. Emmons, *J. Org. Chem.* **1967**, *32*, 1279; b) W. J. S. Lockley, W. Lwowski, *Tetrahedron Lett.* **1974**, *15*, 4263; c) M. Kurz, W. Reichen, *Tetrahedron Lett.* **1978**, *19*, 1433; Imino isocyanates: d) D. W.

Jones, *J. Chem. Soc. Chem. Commun.* **1982**, 766; e) See Ref. [1i]. For reviews, see: f) W. Reichen, *Chem. Rev.* **1978**, *78*, 569; g) C. Wentrup, J. J. Finnerty, R. Koch, *Curr. Org. Chem.* **2011**, *15*, 1745.

[6] Carbamate precursors generating isocyanates in situ are commonly used in industry. For reviews, see: a) D. A. Wicks, Z. W. Wicks, Jr., *Prog. Org. Coat.* **1999**, *36*, 148; b) D. A. Wicks, Z. W. Wicks, Jr., *Prog. Org. Coat.* **2001**, *41*, 1. For ureas as masked isocyanates, see: c) M. Hutchby, C. E. Houlden, J. G. Ford, S. N. G. Tyler, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem.* **2009**, *121*, 8877; *Angew. Chem. Int. Ed.* **2009**, *48*, 8721.

[7] a) J. Bourgeois, I. Dion, P. H. Cebrowski, F. Loiseau, A.-C. Bédard, A. M. Beauchemin, *J. Am. Chem. Soc.* **2009**, *131*, 874; b) F. Loiseau, C. Clavette, M. Raymond, J.-G. Roveda, A. Burrell, A. M. Beauchemin, *Chem. Commun.* **2011**, *47*, 562. See also Ref. [4a]. For a review on intramolecular Cope-type hydroaminations, see: c) N. J. Cooper, D. W. Knight, *Tetrahedron* **2004**, *60*, 243.

[8] a) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795, and reviews cited therein; b) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675.

[9] The *E* conformation of hydrazides is thermodynamically favored (Ref. [1c]). However, DFT calculations on related derivatives supports a transition state in which the *Z* conformers reacts (see Ref. [4a]).

[10] For other hydrohydrazidation reactivity, see: a) J. Waser, B. Gaspar, H. Nambu, E. M. Carreira, *J. Am. Chem. Soc.* **2006**, *128*, 11693; b) K. Alex, A. Tillack, N. Schwarz, M. Beller, *Angew. Chem.* **2008**, *120*, 2337; *Angew. Chem. Int. Ed.* **2008**, *47*, 2304, and references therein; c) Y. Li, Y. Shi, A. L. Odom, *J. Am. Chem. Soc.* **2004**, *126*, 1794; d) C. Cao, Y. Shi, A. L. Odom, *Org. Lett.* **2002**, *4*, 2853; e) J. M. Hoover, A. DiPasquale, J. M. Mayer, F. E. Michael, *J. Am. Chem. Soc.* **2010**, *132*, 5043; f) S. L. Dabb, B. A. Messerle, *Dalton Trans.* **2008**, 6368; g) A. M. Johns, Z. Liu, J. F. Hartwig, *Angew. Chem.* **2007**, *119*, 7397; *Angew. Chem. Int. Ed.* **2007**, *46*, 7259; h) S. Banerjee, E. Barnea, A. L. Odom, *Organometallics* **2008**, *27*, 1005; i) K. Alex, A. Tillack, N. Schwarz, M. Beller, *Org. Lett.* **2008**, *10*, 2377.

[11] a) D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes, J. S. Moore, *Chem. Rev.* **2001**, *101*, 3893; b) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173; c) P. Vlieghe, V. Lisowski, J. Martinez, M. Khrestchatisky, *Drug Discovery Today* **2010**, *15*, 40.

