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Non-phosgene route to unsymmetrical ureas from *N*-Cbz-α-amino acid amides

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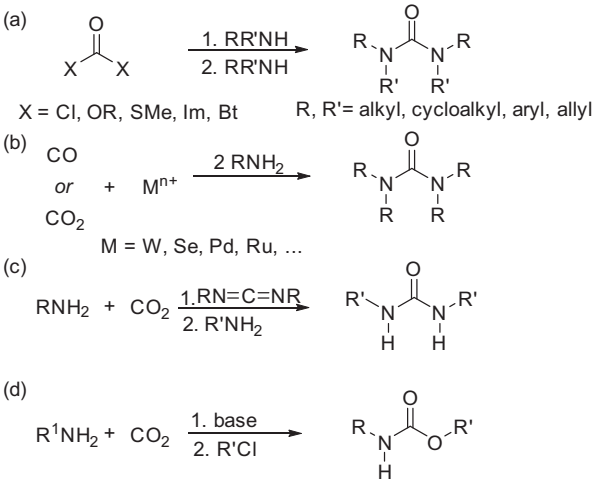
ABSTRACT

A convenient method toward the synthesis of α-amino acid-derived unsymmetrical ureas **2** is described herein. This route involves an interesting rearrangement of amides of *N*-Cbz-α-amino acids **1**, which presumably entails the intermediacy of hydantoins that is followed by hydrolysis to afford unsymmetrical ureas **2** in quantitative yields and high purity.

Introduction

Ureas are widely used as antioxidants,[1] intermediates in dyes,[2] and corrosion inhibitors[3] as well as in many biologically active compounds,[4] agrochemicals,[5] and polymers.[6] The classical literature methods devised for the preparation of urea-containing compounds employ hazardous reagents such as phosgene gas or isocyanates[7] whose production and storage impose serious toxicological and environmental issues. Thus, continuous efforts are made to design 'safer' methods for the preparation of urea derivatives.[8] Toward that goal, new protocols involving reagents such as *S,S*-dimethylthiocarbonate,[9] *N,N′*-carbonyldiimidazole,[10] 1,1′-carbonylbisbenzotriazole,[11] and carbamoyl azides[12] are implemented, yet often demand longer reaction times, tedious preparations of phosgene-based reagents, and the isolation of the reactive intermediates (Scheme 1).

Milder catalytic processes that exploit simple and cheap raw materials such as CO and CO_2 have surfaced recently.[13] These involve carbonylation of primary amines using organometallic complexes, which are often present in stoichiometric ratio and hence lead to the generation of large amounts of inorganic wastes (Scheme 1).[14] The formation of ureas through the intermediacy of carbamic acids usually demands high pressures of CO_2 (10 MPa) at elevated temperatures (~200 °C) to generate the reactive isocyanate intermediates.[15] The use of carbodiimides facilitates the conversion of carbamic acids into intermediates that are susceptible to condensation with other amines in order to afford the desired urea derivatives (Scheme 1).[16] This route is of little practical interest since it requires multistep preparation and the use of stoichiometric amounts of relatively expensive and moisture-sensitive reagents. More conveniently, carbamate esters, which can be prepared from amines or amino acids and CO_2 using



Scheme 1. Various routes to substituted ureas and carbamates.

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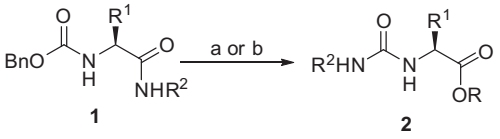


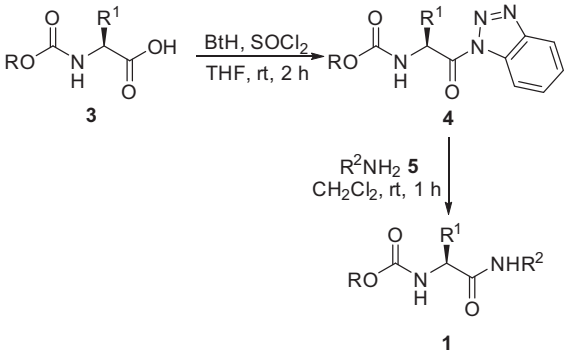
Scheme 2. Basic rearrangement of *N*-Cbz-α-amino acid amides **1** into ureas **2**. Reagents and conditions: (a) $NaOH_{aq}$, 15 °C, 5 min; (b) MeOK, anhydrous MeOH, 15 °C, 5 min.

hindered guanidine bases, may represent simple intermediates for the synthesis of ureas (Scheme 1).[17] However, the condensation of amines with carbamates of α-amino acids has not been well explored. In fact, most reported amino acid-based ureas are prepared following the classical methods which make use of phosgene gas, isocyanates, or phosgene substitutes.[18] This necessitates the use of α-amino acid esters that prevent the formation of the corresponding *N*-carboxyanhydrides that are obtained from the cyclization of the intermediate isocyanates. This results in an additional step in order to hydrolyze the ester moiety and may lead to lower overall yields.

In order to limit the use of phosgene gas or its substitutes for the preparation of α-amino acid derived ureas, we now introduce a convenient synthesis of unsymmetrical ureas **2** by rearrangement of *N*-Cbz-α-amino acid amides **1a**–**g** (Scheme 2). Compounds **1a**–**g** were prepared from commercially available *N*-Cbz-α-amino acids **3** via their Bt derivatives **4** by reaction with arylamines **5** (Scheme 3).

Results and discussion

In an effort to design new protein-binding molecules as potential inhibitors of β-amyloid deposition that is associated with neurodegenerative disease,[19] we became interested in the preparation of novel amino acid conjugates of ethyl 2-(4-amino-1*H*-pyrazol-1-yl)acetate **1a**, **1c**–**f** (Scheme 3, Table 1). Compound **1** were prepared on a basis similar to that of 3-aminopyrazoles that can slow or block Aβ aggregation by binding through the corresponding donor–acceptor–donor H-bonding pattern to sites at the surface of peptide dimers, which can effectively block further aggregation. Interestingly, one study shows that the arylacetic acid NSAIDs, ibuprofen, indomethacin, and sulindac sulfide, may preferentially inhibit β-amyloid deposition; this prompted us to prepare the corresponding carboxylic acids of **1**.[20] Therefore, **1a** was treated with aq NaOH then quenched with dilute HCl (2 N). ^{1}H NMR spectrum of the pure product showed, in addition to the absence of the peaks corresponding to the ethyl group, an unexpected loss of the benzyl component of the carbobenzyloxy (Cbz) group. A cross-peak in the gHMBC spectrum between the NH proton at position



Scheme 3. Synthesis of amides **1** starting from α-amino acids **3**.

Table 1
Preparation of *N*-Cbz-α-amino acid amides **1a** and the corresponding urea derivatives **2** starting from *N*-Cbz-α-amino acids **3**

Entry	1	R	R^1	R^2	% Yield	2	% Yield
1	**a**	Cbz	Bn	4-APA[a]	89	**a**	99
2	**b**	Cbz	CH_2-2-indole	*p*PD[b]	87	**b**	99
3	**c**	Cbz	$CH(CH_3)_2$	4-APA[a]	90	**c**	99
4	**d**	Cbz	Bn-4-(OBn)	4-APA[a]	89	**d**	99
5	**e**	Cbz	$CH_2CH_2SCH_3$	4-APA[a]	89	**e**	—
6	**f**	Cbz	H	4-APA[a]	82	**f**	0
7	**g**	Cbz	Bn	*p*AT[c]	95	**g**	99

[a] 4-APA is abbr. for 2-(4-amino-1*H*-pyrazol-1-yl)acetic acid.
[b] *p*PD is abbr. for *p*-phenylenediamine.
[c] *p*AT is abbr. for *p*-toluidine.

4 of the pyrazole and the carbonyl on the other NH demonstrated that the hydrolysis product of **1** is structure **2a** (Fig. 1). This was further supported by the HRMS spectrum which indicated a peak of $[M+H]^-$ 333.1185.

The synthesis of ureas through the hydrolysis of substituted hydantoins has been achieved using metal hydroxides.[18,21] In addition, unsubstituted hydantoins can be converted into *N*-carbamoylamino acids using D-hydantoinase at pH 10.5.[22] Therefore, we suggest that following the hydrolysis of the ester group, the amidic nitrogen is deprotonated, resulting in a resonance-stabilized anion that displaces the benzyloxy group leading to the formation of a hydantoin intermediate, which undergoes base-catalyzed hydrolysis to afford **2** (Scheme 4).

Insight into the mechanism and therefore the versatility of this transformation were obtained by the reaction of N^1,N^4-bis-(Z-Trp)benzene-1,4-diamine **1b** with potassium methoxide in anhydrous methanol. Remarkably, ^{1}H and ^{13}C NMR spectra indicated that both amide groups rearranged into the corresponding urea through hydrolysis of the hydantoin ring intermediate with methoxide ion. This led to the formation of methyl ester derivative **2b**. This suggests that anhydrous alcoholic solvents can be used to afford the corresponding esters when intended. In addition, more controlled conditions (use of hindered base) can afford various conjugates of α-amino acid-derived ureas by adding the desired nucleophile into the reaction mixture.

In order to investigate the scope of this transformation, **1b** and **1d**,**e** (Table 1, entries 2, 4, and 5) were treated with aq NaOH. While

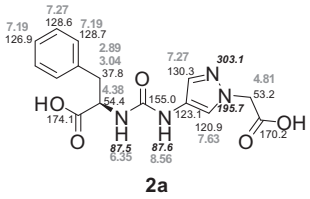
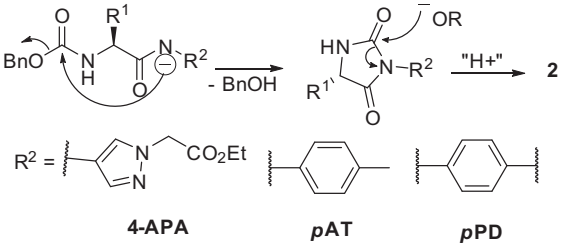


Figure 1. Chemical shifts of **2a** deduced from ^{1}H ^{13}C and ^{1}H ^{15}N gHMBC experiments.



Scheme 4. Postulated reaction mechanism for the formation of **2**.

the valine **1d** and tyrosine **1e** derivatives rearranged quantitatively to give the urea derivatives **2d** and **2e**, respectively, the glycine derivative **1f** gave only the hydrolysis product. This result is in agreement with the Thorpe–Ingold effect[20] where the amino acid side chains facilitate the cyclization step through decreasing the spatial distance between the amidic amine and the carbamate carbon.

We also examined the ability of *N*-Cbz-protected dipeptides to rearrange into unsymmetrically substituted ureas under the same reaction conditions. Regrettably, no rearrangement was observed when Z-Met-Ala-OH was treated under the same conditions, presumably because of the poor acidity of amidic nitrogen. We reasoned that the electron withdrawing nature of the pyrazole ring may have facilitated the deprotonation step under these conditions. Indeed, the electronics argument held true when *N*-Cbz-Phe-*p*-toluidide **1f** was treated with aq NaOH to give the corresponding urea **2f** in quantitative yield.

Conclusions

In summary, we have described a reliable approach toward the preparation of unsymmetrical ureas from commercially available *N*-Cbz-α-amino acids. Unlike traditional synthetic routes that are based on the use of phosgene and isocyanates, this method may lead to the minimization of waste production, avoidance of hazardous reagents or unstable intermediates, short reaction times, simple workup and high yields, and purity with the concomitant benefit of using carbamates that are prepared from CO_2 in an eco-friendly process.

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Supplementary data

Supplementary data (copies of ^{1}H, ^{13}C NMR spectra for compounds **1a**–**g**, and **2a**–**d** and **2g,** ^{1}H ^{13}C and ^{1}H ^{15}N gHMBC spectra for compounds for **2a** and **2c**,**d**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.141.

References and notes

1. Šimunović, M.; Perković, I.; Zorc, B.; Ester, K.; Kralj, M.; Hadjipavlou-Litinac, D.; Pontiki, E. *Bioorg. Med. Chem.* **2009**, *17*, 5605.
2. (a) Wang, Q.; Yao, X.; Tang, S.; Lu, X.; Zhang, X.; Zhang, S. *Green Chem.* **2012**, *14*, 2559; (b) Kazakova, L.; Shabarchinaa, L.; Sukhorukov, G. *Chem. Chem. Phys.* **2011**, *13*, 11110.
3. (a) Mistry, B.; Patel, N.; Patel, M.; Jauhari, S. *Res. Chem. Intermed.* **2012**, *37*, 659; (b) Kap, I.; Starostin, M.; Shter, G.; Grader, G. *Mater. Corros.* **2012**, *63*, 571.
4. (a) Mehta, N.; Diuguid, C.; Soroko, F. *Med. Chem.* **1981**, *24*, 465; (b) Chrusciel, R.; Strohbach, J. *Curr. Top. Med. Chem.* **2004**, *4*, 1097; (c) Gallou, I. *Org. Prep. Proced. Int.* **2007**, *39*, 355.
5. (a) Xin, Z.; Zhao, H.; Serby, M.; Liu, B.; Szczepankiewicz, B.; Nelson, L.; Smith, H.; Suhar, T.; Janis, R.; Cao, N.; Camp, H.; Collins, C.; Sham, H.; Surowy, T.; Liu, G. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4298; (b) Abraham, J.; Rajasekharan Pillai, V. *J. Appl. Polym. Sci.* **1996**, *60*, 2347.
6. (a) Roy, I.; Gupta, M. *Protein Eng.* **2003**, *16*, 1153; (b) Kumar, A.; Meijer, E. *Chem. Commun.* **1998**, 1629; (c) Pinto, G.; Maaroufi, A. *Polym. Compos.* **2012**, *33*, 2188.
7. (a) Majer, P.; Randad, R. *J. Org. Chem.* **1994**, *59*, 1937; (b) Narendra, N.; Chennakrishnareddy, G.; Sureshbabu, V. *Org. Biomol. Chem.* **2009**, *7*, 3520.
8. Bigi, F.; Maggi, R.; Sartori, G. *Green Chem.* **2000**, *2*, 140.
9. Leung, M.-K.; Lai, J.-L.; Lau, K.-H.; Yu, H.-h.; Hsiao, H.-J. *J. Org. Chem.* **1996**, *61*, 4175.
10. Batey, R.; Santhakumar, V.; Yoshina-Ishii, C.; Taylor, S. *Tetrahedron Lett.* **1998**, *39*, 6267.
11. Katritzky, A.; Pleynet, D.; Yang, B. *J. Org. Chem.* **1997**, *62*, 4155.
12. Verardo, G.; Bombardella, E.; Venneri, C.; Strazzolini, P. *Eur. J. Org. Chem.* **2009**, *35*, 6239.
13. (a) Gerack, C.; McElwee-White, L. *Chem. Commun.* **2012**, 11310; (b) Hylton, K.; Main, A.; McElwee-White, L. *J. Org. Chem.* **2003**, *68*, 1615; (c) Shelton, P.; Zhang, Y.; Nguyen, T.; McElwee-White, L. *Chem. Commun.* **2009**, 947; (d) Shi, F.; Deng, Y.; SiMa, T.; Peng, J.; Gu, Y.; Qiao, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 3257; (e) Della Ca', N.; Bottarelli, P.; Dibenedetto, A.; Aresta, M.; Gabriele, B.; Salerno, G.; Costa, M. *J. Catal.* **2011**, *282*, 120.
14. (a) McCusker, J.; Abboud, K.; McElwee-White, L. *Organometallics* **1997**, *16*, 3863; (b) Nudelman, N.; Lewkowicz, E.; Pérez, D. *Synthesis* **1990**, 917; (c) Gao, J.; Li, H.; Zhanga, Y.; Zhang, Y. *Green Chem.* **2007**, *9*, 572; (d) Barzagli, F.; Mani, F.; Peruzzinib, M. *Green Chem.* **2011**, *13*, 1267.
15. Wu, C.; Cheng, H.; Liu, R.; Wang, Q.; Hao, Y.; Yua, Y.; Zhao, F. *Green Chem.* **1811**, *2010*, 12.
16. (a) Goyal, N. *Synlett* **2010**, 335; (b) Sureshbabu, V.; Lalithamba, H.; Narendra, N.; Hemantha, H. *Org. Biomol. Chem.* **2010**, *8*, 835.
17. (a) Yoshida, M.; Okuyama, N. *Chem. Commun.* **2000**, 151; (b) Aresta, M. *Chem. Ind. (Milan)* **1998**, *80*, 1051; (c) Shang, J.; Liu, S.; Ma, X.; Lua, L.; Deng, Y. *Green Chem.* **2012**, *14*, 2899; (d) Gallou, I.; Eriksson, M.; Zeng, X.; Senanayake, C.; Farina, V. *J. Org. Chem.* **2005**, *70*, 6960.
18. (a) Lunn, J.; Shantz, D. *Chem. Mater.* **2009**, *21*, 3638; (b) Sedlák, M.; Keder, R.; Hanusek, J.; Růžička, A. *J. Heterocycl. Chem.* **2005**, *42*, 899; (c) Le Gal, J.; Gonera, M.; Lelait, M.-A.; Servent, D.; Dugave, C. *J. Inorg. Biochem.* **2011**, *105*, 880; (d) Chong, P.; Petillo, P. *Tetrahedron Lett.* **1999**, *40*, 4501; (e) Plummer, M.; Holland, D.; Shahripour, A.; Lunney, E.; Fergus, J.; Marks, J.; McConnell, P.; Mueller, W.; Sawyer, T. *J. Med. Chem.* **1997**, *40*, 3719.
19. (a) Gong, Y.; Chang, L.; Viola, K.; Lacor, P.; Lambert, M.; Finch, C.; Krafft, G.; Klein, W. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *100*, 10417; (b) Karran, E.; Mercken, M.; De Strooper, B. *Nat. Rev. Drug Disc.* **2011**, *10*, 698; (c) Maccioni, R.; Muñoz, J.; Barbeito, L. *Arch. Med. Res.* **2001**, *3*, 2355; (d) Rzepecki, P.; Schrader, T. *J. Am. Chem. Soc.* **2005**, *127*, 3016; (e) Rzepecki, P.; Nagel-Steger, L.; Feuerstein, S.; Linne, U.; Molt, O.; Zadmard, R.; Aschermann, K.; Wehner, M.; Schrader, T.; Riesner, D. *J. Biol. Chem.* **2004**, *46*, 47497; (f) Saweczko, P.; Enright, G.; Kraatz, H.-B. *Inorg. Chem.* **2001**, *40*, 4409; (g) Kisten, C.; Schrader, T. *J. Am. Chem. Soc.* **1997**, *119*, 12061; (h) Fricke, H.; Gerlach, A.; Unterberg, C.; Wehner, M.; Schrader, T.; Gerhards, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 900; (i) Wang, W.; Weisz, K. *Chem. Eur. J.* **2007**, *13*, 854.
20. Weggen, S.; Eriksen, J. L.; Das, P.; Sagi, S.; Wang, R.; Pietrzik, C.; Findlay, K.; Smith, T.; Murphy, M.; Bulter, T.; Kang, D.; Marquez-Sterlingk, N.; Golde, T.; Koo, E. *Nature* **2001**, *414*, 212.
21. (a) Bogolubsky, A.; Ryabukhin, S.; Pakhomov, G.; Ostapchuk, E.; Shivanyuk, A.; Tolmachev, A. *Synlett* **2008**, 2279; (b) Mann, S.; Carillon, S.; Breyne, O.; Marquet, A. *Chem. Eur. J.* **2002**, *8*, 439.
22. Borthwick, A.; Davies, D.; Exall, A.; Livermore, D.; Sollis, S.; Nerozzi, F.; Allen, M.; Perren, M.; Shabbir, S.; Woollard, P.; Wyatt, P. *J. Med. Chem.* **2005**, *48*, 6956.