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An Efficient Synthesis of Symmetric and Unsymmetric Bis-(β-aminoamides) via Ugi Multicomponent Reaction

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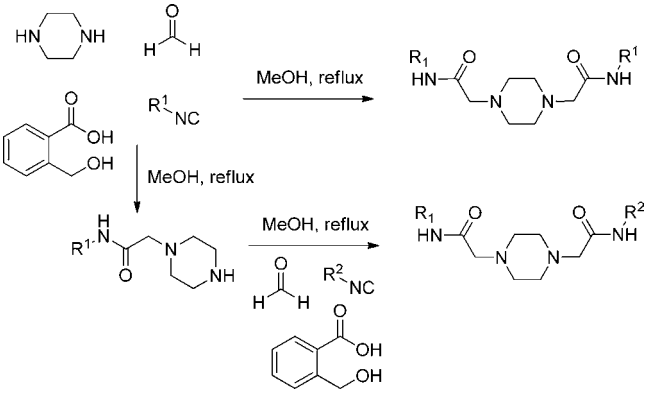
ABSTRACT



A library of symmetrical and unsymmetrical bis-(β-aminoamides) has been prepared starting from symmetrical secondary diamines by using a double Ugi four-component reaction. A sacrifical Mumm rearrangement, thanks to the use of 2-hydroxymethyl benzoic acid, is necessary to suppress the competing split-Ugi reaction, increasing the yield and simplifying the purification step. The scope, the reaction conditions, and the role of water in trapping the nitrilium intermediate are also discussed.

Symmetrical compounds have played an important role in several branches of chemistry including medicinal chemistry.[1] For example the symmetry of the binding site of HIV protease has brought a plethora of *C*-2 symmetrical protease inhibitors with low nanomolar activity, which paved the way for the nonsymmetrical protease inhibitors currently on the market.[2] For this reason the ability to synthesize symmetrical compounds in a simple manner and in a one-pot operation is a surplus value for the medicinal chemists involved in drug discovery and it is worth being continually investigated. For one of our medicinal chemistry programs we needed to synthesize a library of symmetrical and unsymmetrical bis-(β-aminoamides) (**1**) as shown in Figure 1.

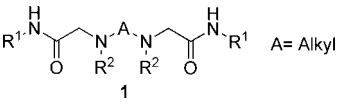


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Figure 1. Bis-(β-aminoamide) scaffold.

A four-component bis-Ugi-like reaction,[3] using water as an acid component, was recognized as a valuable, faster alternative strategy for the synthesis of these compounds compared to the reported methods.[4]

(1) Conreas, J. M.; Sippl, W. Homo and heterodimer ligands: the twin drug approach. In *The practice of medicinal chemistry*, 3rd ed.; Wermuth, C. G., Ed.; Elsevier Ltd.: The Netherlands, 2008; pp 380−414.

(2) Greer, J.; Erickson, J. W.; Baldwin, J. J.; Varney, M. D. *J. Med. Chem.* **1994**, *37*, 1035–1054.

(3) (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (b) Marcaccini, S.; Torroba, T. *Nat. Protoc.* **2007**, *2*, 632–639. (c) Symmetrical compounds using a double Ugi reaction have been prepared; see for example: Michalik, D.; Schaks, A.; Wessjohann, L. A. *Eur. J. Org. Chem.* **2007**, 149–157. Westermann, B.; Michalik, D.; Schaks, A.; Kreye, O.; Wagner, C.; Merzweiler, K.; Wessjohann, L. A. *Heterocycles* **2007**, *73*, 863–872.

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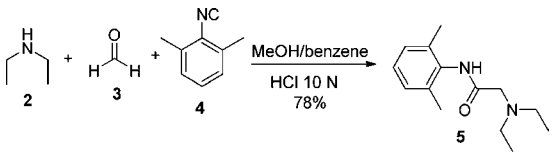
Also, a survey in the literature showed us the lack of a general and valid one-pot procedure using water as an acid component in the Ugi reaction. A main reason can explain the lack of such a reaction: the poor nucleophilicity of water in attacking the nitrilium ion.

Indeed, even if the attack of water to the nitrilium ion is considered possible and it is reported in both books and papers,[5] there is a paucity of such examples in the literature and the reaction did not appear of general use. For a deeper insight, this reaction always requires the presence of a Lewis or Brønsted acid pointing out a different mechanism of action. The most puzzling situation is in the first example of an Ugi reaction in which a carboxylic acid has been replaced with water, reported by Ugi himself, in order to obtain the local anesthetic xylocaine (**5**) in an one-pot process. To accomplish this reaction a strong excess of hydrochloric acid was used[6] (Scheme 1).

Scheme 1. Ugi's Synthesis of Xylocaine

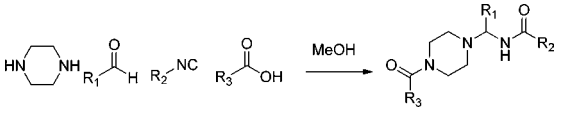


The mechanism of the reaction can be rationalized by the fact that the more nucleophilic chloride ion attacks the nitrilium ion instead of water.[7] At this point the unstable chloroimidate is then converted into the desired amide by reaction with water.[8] Note the presence of a secondary amine which directly gives an iminium ion, ruling out the use of the acid to activate the imine.[9,10]

Other works in which water was the fourth component of the Ugi reaction have been and are continuously reported, but in all cases a Lewis or Brønsted acid is always used.[11] Very recently Sugimone et al., in order to bypass the problem of the lack of reactivity of water in the Ugi reaction, reported the use of an aminoborane to give the desired α-aminoamides using secondary amines.[12]

Another way to overcome this problem was the use of an acid such as trifluoroacetic acid. The corresponding amide can then be easily hydrolyzed under basic conditions.[13] Also, when symmetrical secondary diamines react with a carbonyl compound, an isocyanide, and a carboxylic acid, a novel competing reaction, named split-Ugi, occurs[14] (Scheme 2). In this case, the second secondary amine intercepts the imino-anhydride intermediate. Even in the presence of 2 equiv of acid, a carbonyl group and isocyanide, and 1 equiv of the diamine, the intramolecular split-Ugi reaction still *competes* and *prevails* over the classical Ugi reaction being the major component of the mixture.

Scheme 2. Split-Ugi Reaction



Because of the limitations cited above, in this paper we wish to present a novel strategy to synthesize, in an easy and straightforward manner, symmetrical and unsymmetrical bis-(β-aminoamides) suppressing the competing split-Ugi reaction, and without using an excess of mineral or Lewis acids and aminoboranes. In order to demonstrate, once more, the poor nucleophilicity of water, at the beginning, we carried out a reaction between a symmetrical secondary diamine (**6**), paraformaldehyde (**3**), water (**7**), and pentyl isocyanide (**8**) in methanol both at room temperature and at reflux. In both cases we were able to recover only the aminal (**9**) (Scheme 1). The use of the diamine as dichloridrate[6a] did not change the result of the reaction as well as the use of phenylphosphonic acid (**10**) as the catalyst.[11b] These results confirm once again the poor nucleophilicity of water and its low propensity to attack the nitrilium ion, opening up other reaction pathways. The presence of a carboxylic acid is therefore necessary both to hydrolyze the aminal and to give the iminoanhydride intermediate. In this particular situation the imidate should be attacked by the nucleophilic solvent of the reaction (methanol) to release the desired compound. Unfortunately, when 2 equiv of acetic acid (**11**), pentyl isocyanide, and praraformaldeyde were used, the product of the split-Ugi reaction (**12**) was always the major component compared to the symmetrical bis-(β-aminoamide) **13** (Scheme 3).

(4) See for example: (a) Katritzky, A.; Qi, M.; Feng, D. *J. Org. Chem.* **1998**, *63*, 6712–6714. (b) Tsukube, H.; Adachi, H.; Morosawa, S. *J. Org. Chem.* **1991**, *25*, 7102–7108.

(5) (a) *Isonitrile Chemistry*; Ugi, I., Ed.; Academic Press: New York, 1971. (b) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 53–66.

(6) (a) Ugi, I.; Steinbrückner, C. U.S. Patent 3247200, 1966. (b) Ugi, I; Werner, B. The four-component reaction and other multicomponent reactions of the isocyanides. In *Methods and reagents for green chemistry*; Tundo, P., Perosa, A., Zecchini, F., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, 2007; pp 3−22.

(7) Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 16–24.

(8) The formation of a chloroimidate intermediate has been reported. See for example: (a) Yue, T.; Wang, M. X.; Wang, D. X.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 9454–9457. (b) Giustiniano, M.; Pirali, T.; Massarotti, A.; Biletta, B.; Novellino, E.; Campiglia, P.; Sorba, G.; Tron, G. C. *Synthesis* **2010**, *23*, 4107–4118.

(9) Paraformaldeyde reacts with diethylamine without the need of an acid as catalyst; see: Bhat, A. R.; Bhat, A. I.; Athar, F.; Azam, A. *Helv. Chim. Acta* **2009**, *92*, 1644–1656.

(10) The acid could also be important to hydrolize back the aminal.

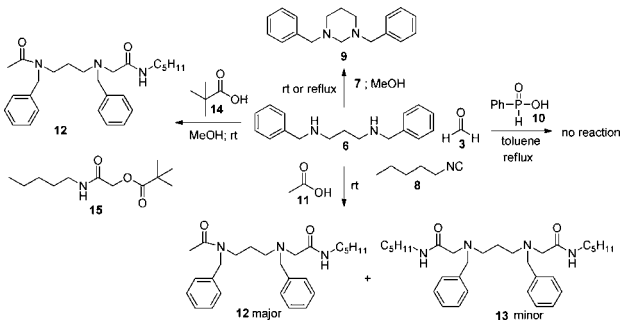
(11) (a) McFarland, J. *J. Org. Chem.* **1963**, *28*, 2179–2181. For more recent exemples, see: (b) Pan, C. S.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 3622–3625. (c) Ramazani, A.; Rezai, A.; Mahyari, A.; Rouhani, M.; Khoobi, M.; Yaaghubi, E.; Shabrendi, H.; Vessally, E.; Azizkhani, V.; Amini, I.; Lashgari, H.; Noohi, G.; Shaghaghi, Z.; Sadri, F. *Synth. Commun.* **2001**, *41*, 1444–1454. (d) Shaabani, A.; Keshipour, S.; Shaabani, S.; Mahyari, M. *Tetrahedron Lett.* **2012**, *53*, 1641–1644. (e) Dömling, A. Amino Group Chemistry. In *From Synthesis to the Life Science*; Ricci, A., Ed.; Wiley-VCH: 2008; pp 149−182.

(12) (a) Tanaka, Y.; Hasui, T.; Sugimone, M. *Org. Lett.* **2007**, *9*, 4407–4410. (b) Tanaka, Y.; Hidaka, K.; Hasui, T.; Suginome, M. *Eur. J. Org. Chem.* **2009**, 1148–1151.

(13) Carniato, D.; Jaillardon, K.; Busnel, K.; Gutmann, M.; Briand, J. F.; Deprez, B.; Thomas, D.; Bougeret, C. WO 2009150248.

(14) Giovenzana, G. B.; Tron, G. C.; Di Paola, S.; Menegotto, I.; Pirali, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1099–1102.

Scheme 3. Failed Attempts To Prepare the Symmetrical Bis-(β-aminoamides)



Even with the sterically hindered pivalic acid (**14**) we could only recover the split-Ugi adduct along with the Passerini reaction product (**15**). At this point, given the importance of the presence of a carboxylic acid to attack the nitrilium intermediate, we thought to use a functionalized carboxylic acid with a nucleophilic arm. This moiety should be able to compete with the other amine component for reaction with the imino-anhydride intermediate to give a *sacrifical* Mumm rearrangement. To accomplish our task, we thought that 2-hydroxymethyl benzoic acid (**16**) could be the right partner (Figure 2).

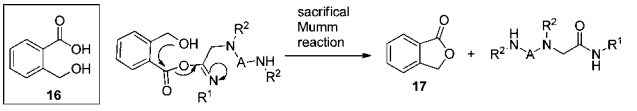
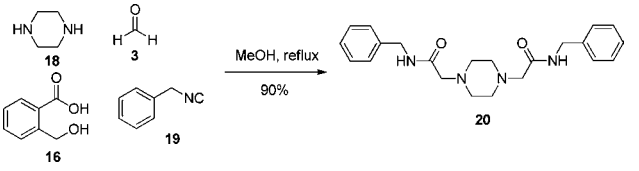


Figure 2. Sacrifical Mumm rearrangement.

To our satisfaction, when piperazine (**18**) was mixed with 2 equiv of acid (**16**), benzyl isocyanide (**19**), and paraformaldehyde (**3**) in methanol at reflux, we obtained the desired product (**20**) in 90% yield (Scheme 4). It is important to highlight that the 2-hydroxymethyl benzoic acid behaves like a pseudo water molecule by first trapping the nitrilium ion as in a normal Ugi reaction. This acid then undergoes an intramolecular cyclization to deliver only one oxygen atom to the product, as water would, producing the aromatic lactone phthalide (**17**). This latter can be easily recovered by column chromatography due to its lipophilic nature and can be used again to prepare **16** (see Supporting Information).

Scheme 4. Formation of the Symmetrical Bis-(β-aminoamide) **20**



The scope of this reaction was next examined, and different isocyanides and bis-amines were used in order to demonstrate the generality of the reaction.

The symmetrical bis-(βaminoamides) synthesized (**21**–**30**) are listed in Figure 3 showing the generality of this novel procedure.

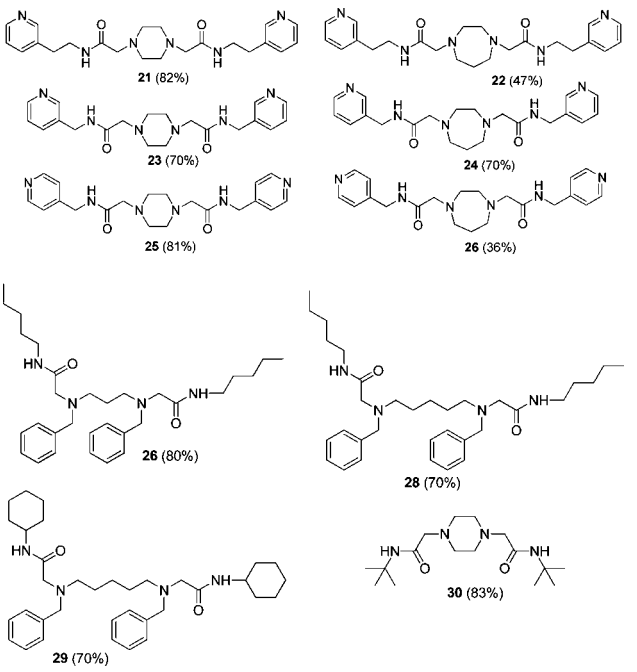
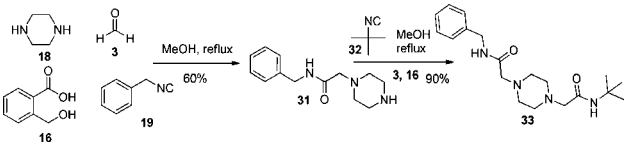


Figure 3. Symmetrical bis-(βaminoamides) synthesized.

Then, we wondered, using only 1 equiv of acid **16**, aldehyde, and isocyanide, if the sacrifical Mumm rearrangement could still prevail over the competing split-Ugi reaction. Satisfactorily, reaction among piperazine, paraformaldehyde, benzylisocyanide, and **16** gave the desired Ugi product (**31**) in 60% yield along with the symmetrical bis-(β-aminoamide) in 10% yield. After chromatographic purification, the compound can undergo a similar reaction using a different isocyanide (**32**) to give in 90% yield the desired unsymmetrical bis-(β-aminoamide) (**33**) (Scheme 5).

Scheme 5. Formation of the Unsymmetrical Bis-(β-aminoamide) **33**



Even in this case a library of unsymmetrical bis-(β-aminoamides) has been prepared (Figure 4).

Finally, we applied our methodology for the formal synthesis of the antianginal agent ranolazine (**46**) (Figure 5).

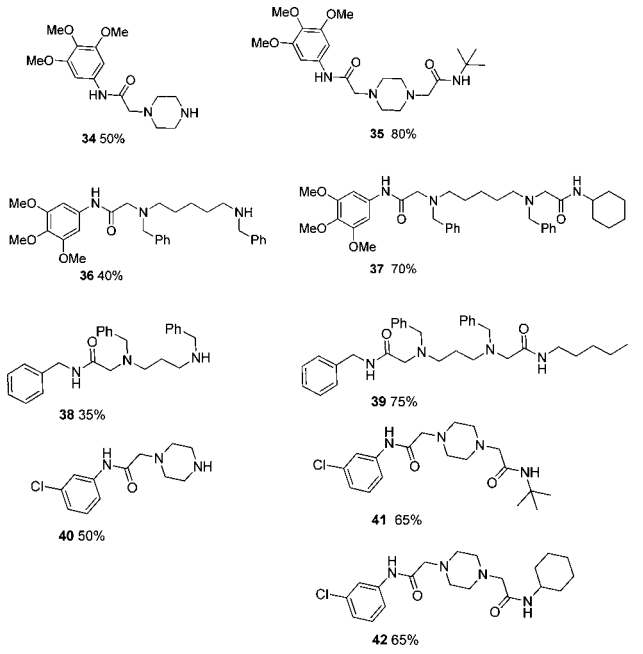


Figure 4. Unsymmetrical bis-(βaminoamides) synthesized.

Indeed, the advanced intermediate **44** can be prepared with our chemistry in 70% yield under optimized conditions and can then be coupled with the epoxy derivative (**45**) as already shown.[15]

(15) Aalla, S.; Gilla, G.; Anumula, R. R.; Kurella, S.; Padi, P. P.; Vummenthla, P. R. *Org. Process Res. Dev.* **2012**, *16*, 748–754.

(16) Huang, Y.; Khoury, K.; Dömling, A. *Top. Heterocycl. Chem.* **2010**, *23*, 85–127.

(17) Yang, Z. Q.; Barrow, J. C.; Shipe, W. D.; Schlegel, K. A.; Shu, Y.; Yang, F. V.; Lindsley, C. W.; Rittle, K. E.; Bock, M. G.; Hartman, G. D.; Uebele, V. N.; Nuss, C. E.; Fox, S. V.; Kraus, R. L.; Doran, S. M.; Connolly, T. M.; Tang, C.; Ballard, J. E.; Kuo, Y.; Adarayan, E. D.; Prueksaritanont, T.; Zrada, M. M.; Marino, M. J.; Graufelds, V. K.; DiLella, A. G.; Reynolds, I. J.; Vargas, H. M.; Bunting, P. B.; Woltmann, R. F.; Magee, M. M.; Koblan, K. S.; Renger, J. J. *J. Med. Chem.* **2008**, *51*, 6471–6477.

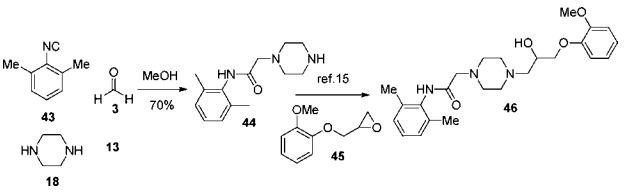


Figure 5. Formal synthesis of ranolazine.

In conclusion we developed a novel methodology for the preparation of symmetrical and unsymmetrical bis-(β-aminoamides) using available starting materials and avoiding the use of protective groups. The use of **16** is mandatory to suppress the competing split-Ugi reaction and circumvent the poor reactivity of water on the nitrilium ion. As the piperazine ring is considered a privileged structure in medicinal chemistry with at least 73 drug entries of piperazine-related drugs deposited in the Drug Bank,[16] this novel strategy may be an added value for medicinal chemists. Use of these compounds as potential calcium channel inhibitors[17] and application of this reaction to the synthesis of symmetrical polyamines[18] will be reported in due course.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) Pirali, T.; Callipari, G.; Ercolano, E.; Genazzani, A. A.; Giovenzana, G. B.; Tron, G. C. *Org. Lett.* **2008**, *10*, 4199–4202.

The authors declare no competing financial interest.