JOC Article

Novel and Expeditious Microwave-Assisted Three-Component Reactions for the Synthesis of Spiroimidazolin-4-ones†

Ping Ye, Katie Sargent, Ethan Stewart, Ji-Feng Liu,* Daniel Yohannes, and Libing Yu

ArQule, Incorporated, Division of Chemical Technologies, 19 Presidential Way, Woburn, Massachusetts 01801

jifeng.liu@yahoo.com; jliu@arqule.com

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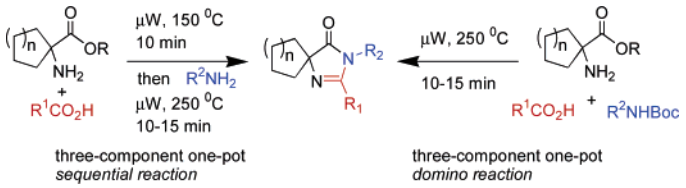

Highly efficient methods for the syntheses of spiroimidazolinones via microwave-assisted three-component one-pot sequential reactions or one-pot domino reactions are described. The efficiency and utility of the methods have been demonstrated by quickly accessing the antihypertensive drug irbesartan (**2**).

Introduction

Microwave-assisted organic synthesis has impacted synthetic chemistry significantly since the introduction of precision-controlled microwave reactors.[1] Numerous reactions including heterocycle-forming, metal catalyzed cross-coupling, condensation, and cycloaddition reactions have been explored under microwave conditions.[2] In addition, microwave-heating technology has been applied in the total syntheses of natural products.[3]

Imidazolin-4-ones (**1**) constitute an important class of pharmacologically active compounds (Figure 1). The spiroimidazolinone irbesartan (**2**), in particular, has been a marketed drug for the treatment of hypertension.[4] Moreover, the compounds containing core **1** also show the potential for the treatment of cancer[5] and obesity-related disorders.[6] Arsenal herbicide also embodies this core scaffold.[7] For these reasons, much attention has been paid to the synthesis and biological evaluation of this class of compounds.[8]

As part of our ongoing efforts to develop efficient methodologies and processes for the high-throughput synthesis of pharmacologically interesting libraries for drug discovery, we recently developed highly efficient protocols using microwave technology.[9] This new methodology was used for the synthesis of quinazolinone compounds including both natural products[3j−l] and natural product-templated libraries.[10] As an extension of this highly efficient methodology and in conjunction with our interests in the synthesis of other drug-like heterocycles, we started the investigation of a spiroimidazolinone heterocyclic system. We envisioned that the development of *efficient and concise* methods for the synthesis of this heterocyclic system,

† This paper is dedicated to Professor Akira Mori for his retirement from Kyushu University, Japan, in March 2006.

(1) For a recent review of microwave-assisted organic synthesis, see: (a) Kappe, C. O.; Dallinger, D. *Nat. Rev. Drug Discovery* **2006**, *5*, 55. (b) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. (c) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (d) Perreux, L.; Loupy, A. *Tetrahedron*, **2001**, *57*, 9199 and references therein.

(2) (a) Shipe, W. D.; Wolkenberg, S. E.; Lindsley, C. W. *Drug Discovery Today* **2005**, *2*, 155. (b) Leadbeater, N. E. *Chem. Commun.* **2005**, 2881 and references therein.

(3) For recent applications of microwave technology in syntheses of natural products, see: (a) Baxendale, I. R.; Ley, S. V.; Piutti, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2194. (b) Kang, Y.; Mei, Y.; Du, Y.; Jin, Z. *Org. Lett.* **2003**, *5*, 4481. (c) Grainger, R. S.; Patel, A. *Chem. Commun.* **2003**, 1072. (d) Raheem, I. T.; Goodman, S. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706. (e) Baran, P. S.; O'Malley, D. P.; Zografos, A. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 2674. (f) Hughes, R. A.; Thompson, S. P.; Alcaraz, L.; Moody, C. J. *Chem. Commun.* **2004**, 946. (g) Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. H.; Wang, Y.; Zhao, Z.; Lindsley, C. W. *Org. Lett.* **2004**, *6*, 1453. (h) Lépine, R.; Zhu, J. *Org. Lett.* **2005**, *7*, 2981. (i) Geske, G. D.; Wezeman, R. J.; Siegel, A. P.; Blackwell, H. E. *J. Am. Chem. Soc.* **2005**, *127*, 12762. (j) Liu, J.-F.; Ye, P.; Zhang, B.-L.; Bi, G.; Sargent, K.; Yu, L.; Yohannes, D.; Baldino, C. M. *J. Org. Chem.* **2005**, *70*, 6339. (k) Liu, J.-F.; Ye, P.; Sprague, K.; Sargent, K.; Yohannes, D.; Baldino, C. M.; Wilson, C. J.; Ng, S.-C. *Org. Lett.* **2005**, *7*, 3363. (l) Liu, J.-F.; Kaselj, M.; Isome, Y.; Chapnick, J.; Zhang, B.; Bi, G.; Yohannes, D.; Yu, L.; Baldino, C. M. *J. Org. Chem.* **2005**, *70*, 10488.

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(5) (a) Qian, X.; Bergnes, G.; Morgans, D. WO 2004103282, 2004. (b) Lyssikatos, J. P. WO 9749700, 1997. (c) Yang, B. V.; Lyssikatos, J. P. US 6194438, 2001.

(6) Chen, Y.; O'Connor, S. J.; Guan, D.; Newcom, J.; Chen, J.; Yi, L.; Zhang, H.; Hunyadi, L. M.; Natero, R. WO 2004058727, 2004.

(7) Los, M. EP 41623, 1981; GB 2174395, 1986.

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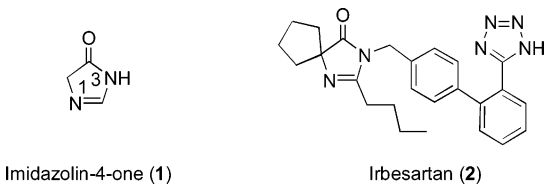


FIGURE 1. The structures of the imidazolin-4-one (**1**) and irbesartan (**2**).

which overcomes the drawbacks of the existing methods in terms of simplicity and versatility, would provide a practical way for both target-oriented and diversity-oriented syntheses of this class of compounds.[11] Herein, we report our methodologies for the synthesis of spiroimidazolinones and demonstrate their utilities by the highly efficient synthesis of irbesartan (**2**) in two steps from the readily available starting materials.

A number of methods have been reported for the synthesis of spiroimidazolinones. One way was the dehydration−cyclization of a diamide to generate (*3H*)-imidazolinones, followed by the installation of R^2 via a nucleophilic substitution.[4] An alternative way was to construct the spiroimidazolinone scaffold by a condensation of an amino acid ester with a pre-made imidate ester or an imidoyl chloride.[8c] However, the existing methods are not practical for the high-throughput synthesis because of low yield, instability of the intermediates, and the use of hazardous reagents.

Results and Discussion

Our retrosynthetic design of **3** envisions the reactions taking place as a three-component one-pot sequential process from commercially available starting materials as illustrated in Figure 2. Spiroimidazolinone **3** could be formed via a cyclization reaction of **4**, which could be generated in situ by the amidation of the ester **6** with an amine **5**. Intermediate **6**, in turn, could be formed in situ via a coupling reaction of an amino acid ester **8** with a carboxylic acid **7**. All of these transformations would be carried out under microwave conditions.

An empirical validation of our design (method A) started from the synthesis of **3a** by employing our standard microwave conditions.[9] Initial efforts focused on optimizing microwave conditions (Table 1). The reaction of methyl-1-amino-1-cyclopentanecarboxylate hydrochloride (**8a**, 1.0 equiv) with valeric acid (**7a**, 1.0 equiv) in the presence of $P(OPh)_3$ (1.2 equiv) in pyridine under microwave irradiation at 150 °C for 10 min generated intermediate **6a** as the only product detected by LC-MS. Without isolating **6a**, benzylamine (**5a**, 1.0 equiv) was added to the reaction mixture. The conditions for forming the final product **3a** via a dehydration−cyclization reaction were examined (Table 1). While the reactions at lower temperatures (200−240 °C) for 10 min only gave a mixture of intermediates (**6a** and **9a**) and product **3a**, microwave irradiation of the reaction mixture at 250 °C for 10 min triggered the effective dehydration−cyclization reaction, which resulted in a one-pot assembling of the desired product **3a** in 75% isolated yield.

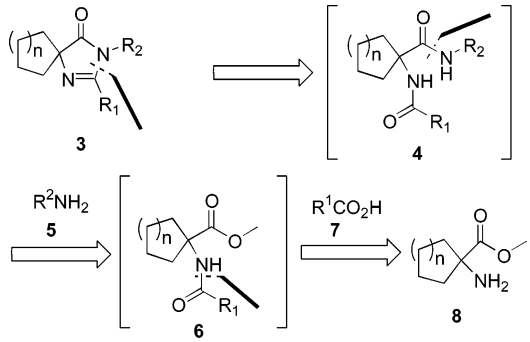
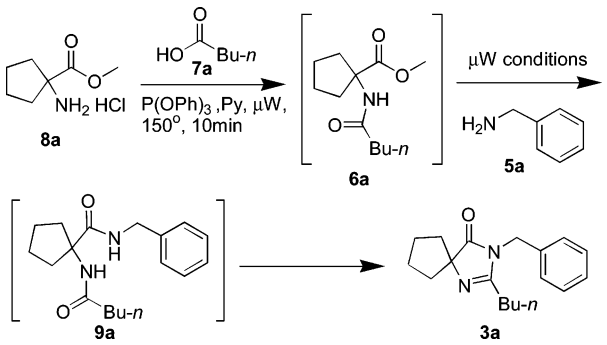


FIGURE 2. Retrosynthetic strategy of **3** (three-component one-pot *sequential* process, method A).

TABLE 1. Optimization of Microwave-Assisted Three-Component One-Pot (Method A) Imidazolinone Formation[a]



temp (°C)	reaction time (min)	**6a**[b] (%)	**9a**[b] (%)	**3a**[b] (%)
200	10	30	30	30
220	10	28		62
240	10	2		98
250	10			100 (75)[c]

[a] Reactions were conducted on a 0.2-mmol scale. [b] The reactions were monitored by HPLC (ELSD) from LC-MS results of the reaction mixture. [c] Isolated yield.

The successful synthesis of **3a** via a three-component one-pot sequential process (method A) encouraged us to further simplify this *sequential process* to a *domino process* (method B), which carries out a series of transformations as a single operation in one pot.[12,13] The modified retrosynthetic strategy is depicted in Figure 3. We postulated that by heating the reaction mixture of the three reactants **7**, **8**, and **10**, the reaction

(8) (a) Murugesan, N.; Gu, Z.; Fadnis, L.; Tellew, J. E.; Baska, R. A. F.; Yang, Y.; Beyer, S. M.; Monshizadegan, H.; Dickinson, K. E.; Valentine, M. T.; Humphreys, W. G.; Lan, S.-J.; Ewing, W. R.; Carlson, K. E.; Kowala, M. C.; Zahler, R.; Macor, J. E. *J. Med. Chem.* **2005**, *48*, 171. (b) Kumar, Y.; Prasad, M.; Nath, A.; Arora, S. K. WO 2005 051943, 2005. (c) Nisnevich, G.; Rukhman, I.; Pertsikov, B.; Kaftanov, J.; Dolitzky, B.-Z. WO 2004 072064, 2004. (d) Nisnevich, G.; Rukhman, I.; Pertsikov, B.; Kaftanov, J. WO 2004 065383, 2004.

(9) Liu, J.-F.; Lee, J.; Dalton, A. M.; Bi, G.; Yu, L.; Baldino, C. M.; McElory, E.; Brown, M. *Tetrahedron Lett.* **2005**, *46*, 1241.

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(12) For multicomponent reactions, see: (a) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (c) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51. (d) Orru, R. V. A.; De Greef, M. *Synthesis* **2003**, 1471. (e) Murakami, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 718. (f) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133.

(13) For domino reactions, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Tietze, L. F.; Haunert, F. In *Stimulating Concepts in Chemistry*; Shibasaki, M., Stoddart, J. F., Vögtle, F., Eds.; Wiley-VCH: Weinheim, Germany, 2000.

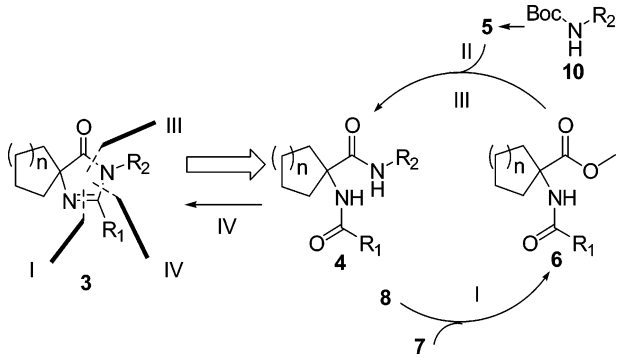
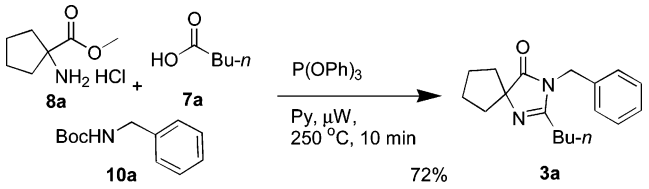


FIGURE 3. Retrosynthetic strategy of **3** (one-pot *domino* process, method B).

SCHEME 1



sequence would be (I) to form **6**, (II) to generate amine **5**, (III) to form **4**, and (IV) to yield products **3**. To realize this designed domino sequence, the key would be the in situ de-Boc of the masked amines **10** to amine **5** at the right step in the process of a series of transformations under the reaction conditions. This new design allows access to the products **3** in one operation step (despite using masked amines **10**), which would be an attractive complementary method of a three-component one-pot *sequential* process. For a faster exploration of the structure−activity relationships (SAR) in drug discovery, this one-pot domino process would be, in particular, simple and efficient in the synthesis of a focused library that crosses only a few numbers of masked amines, **10**, but large numbers of amino acid esters, **8**, and carboxylic acids, **7**.

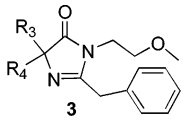
Toward this end, we first evaluated the following modified reaction process (Scheme 1). Gratifyingly, simply by mixing **8a** (1.0 equiv), **7a** (1.0 equiv), *N*-Boc-benzylamine (**10a**, 1.0 equiv), and $P(OPh)_3$ (1.2 equiv) in pyridine and heating in microwave at 250 °C for 10 min, the desired product **3a** was obtained with a yield of 72%, which was essentially as good as method A.

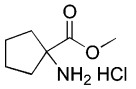
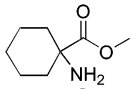
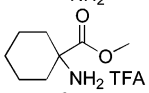
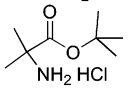
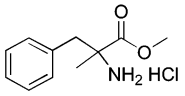
The preliminary success with two sets of reactions on both method A and method B prompted us to commence with the evaluation of the reaction scope by applying an array of carboxylic acids **7**, amino acid esters **8**, and amines **5** (or *N*-Boc amines **10**), aiming at achieving the ultimate goal of applying these two methods for both the target-oriented and the diversity-oriented synthesis.

Different amino acid esters **8** were evaluated with method A, as shown in Table 2. In general, all the reactions gave excellent conversion (82−100%) with good isolated yields (65−75%).[14] The HCl or TFA salt forms of **8** (entries 1 and 3−5) worked, essentially, equally as well as the free base form (entry 2). In addition, *tert*-butyl ester (entry 4) also worked as

(14) We isolated ~10% of the products of the oxidized benzylic position of the benzyl group, which were not observed in the reaction mixture. This may contribute to the discrepancy between the conversion yield and the isolated yield. For example, the product of entry 1 in Table 2 was oxidized after sitting in a NMR tube for days.

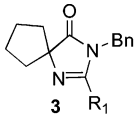
TABLE 2. Representative Imidazolinones 3 with Different Amino Acid Esters 8

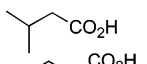
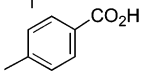
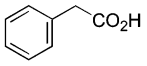
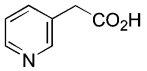


entry	amino esters (**8**)	yield of **3** (%)[a]
1		**3b**, 100 (75)
2[b]		**3c**, 82 (66)
3[b]		**3c**, 95 (72)
4		**3d**, 85 (65)
5		**3e**, 95 (75)

[a] The yields are determined by HPLC (ELSD) from LC-MS results of the reaction mixture. In parentheses are the isolated yields by preparative TLC. [b] This reaction needs 250 °C for 15 min.

TABLE 3. Representative Spiroimidazolinones 3 with Different Carboxylic Acids 7



entry	R^1CO_2H (**7**)	yield of **3** (%)[a]
1		**3f**, 91 (74)
2		**3g**, 90 (67)
3		**3h**, 93 (65)
4		**3i**, 77 (59)

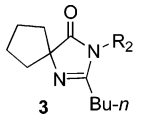
[a] Microwave irradiation at 250 °C for 10 min. The yields were determined by HPLC (ELSD) from LC-MS results of the reaction mixture. In parentheses are the isolated yields by preparative TLC.

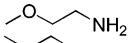
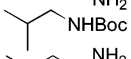
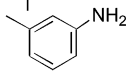
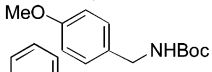
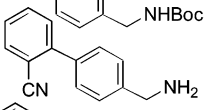
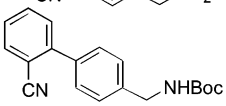
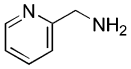
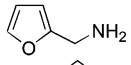
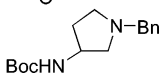
effectively as methyl ester. These features allow for the easy selection of the amino acid esters from whichever readily available forms. To further expand the diversity, nonspiro imidazolinones **3** were synthesized in good yields from the corresponding **8** (entries 4 and 5).

In addition, these microwave reaction conditions also proved to be general for carboxylic acids **7**, as shown in Table 3 (evaluated with method A). Aliphatic (entry 1), aromatic (entry 2), and benzyl carboxylic acids (entries 3 and 4) all worked smoothly, providing overall yields ranging from 59 to 74% with conversion >90%, except pyridin-3-yl-acetic acid (entry 4, 77%).[14]

Next, the amines **5** and masked amine **10** were examined with both methods (Table 4). Aliphatic amines (entries 1 and

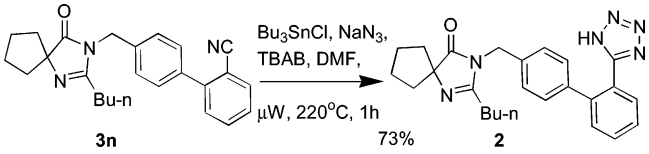
TABLE 4. Representative Spiroimidazolinones 3 with Different Amines, 5 or 10



entry	amines (**5** or **10**)	yield of **3** (%)
1[a]		**3j**, 95 (54)[c]
2[b]		**3k**, 90 (50)[c]
3[a]		**3l**, 96 (69)[c]
4[b]		**3m**, 95 (48)[c]
5[a]		**3n**, 97 (75)[d]
6[b]		**3n**, 98 (71)[d]
7[a]		**3o**, 94 (43)[c]
8[a]		**3p**, 90 (36)[c]
9[b]		**3q**, 97 (78)[c]

[a] Method A. [b] Method B. [c] The yields are determined by HPLC (ELSD) from LC-MS results of the reaction mixture. In parentheses are the isolated yields by preparative HPLC. [d] In parentheses are the isolated yields by preparative TLC.

SCHEME 2



2), anilines (entry 3), benzylamines (entries 4−7), as well as heterocyclic amines (entries 8 and 9), generally provided excellent conversion (90−98%). To evaluate the purification conditions for the library synthesis, products were purified using standard in-house high-throughput HPLC methods, which provided moderate to good recoveries (36−78%). In addition, method B proved to work as well as method A (entries 2, 4, 6, and 9). It is noteworthy that the benzyl-protecting group stayed intact under the microwave-reaction conditions (entry 9).

To demonstrate the feasibilities of these two methods, the synthesis of irbesartan (**2**) was conducted from its precursor **3n** using a modified method (Scheme 2).[8b] Under microwave irradiation at 220 °C, treatment of **3n** with Bu_3SnCl, NaN_3, and a catalytic amount of tetrabutyl ammonium bromide in DMF for 1 h afforded **2** in 73% yield. Thus, the synthesis of irbesartan was achieved in two steps within several hours from commercially available starting materials with a 55% overall yield, which is nearly ideal in terms of step efficiency and operational simplicity.

Summary

In summary, we have developed novel one-pot reactions using microwave technology for the synthesis of spiroimidazolinones via a three-component *sequential process* and *domino process* from readily available starting materials. These new approaches also feature applying only one reagent and one solvent in the entire synthesis. All of these would greatly facilitate both the target-oriented and diversity-oriented syntheses of spiroimidazolinones. The efficiency and utility of the methods have been demonstrated by quickly accessing the antihypertensive drug irbesartan. The further application of this microwave methodology to the synthesis of other heterocycles will be described in due course.

Experimental Section

4′-(2-Butyl-4-oxo-1,3-diaza-spiro[4.4]non-1-en-3-ylmethyl)-biphenyl-2-carbonitrile (3n). Compound **3n** was prepared via a *sequential process* (method A) and a *domino process* (method B).

Method A. To a conical-bottomed Smith Process vial were added 0.4 mL of a 0.5 M solution of methyl 1-amino-1-cyclopentanecarboxylate (0.2 mmol, **8a**) in anhydrous pyridine, 0.4 mL of a 0.5 M solution of valeric acid (0.2 mmol, **7a**) in anhydrous pyridine, and 63 μL (0.24 mmol) of triphenyl phosphate (neat). The reaction vessel was sealed and placed in a monomode microwave reactor. Irradiation was initiated at 300 W to raise the temperature to the set point, and then power was applied at intervals and levels to maintain the desired temperature. Reaction times reported included time for the vial to ramp to the desired temperature. The sealed vial was first irradiated for 10 min at 150 °C. After cooling, to this reaction mixture was added 0.2 mL of a 1.0 M solution of 4′-aminomethyl-biphenyl-2-carbonitrile (0.2 mmol, **5b**) in anhydrous pyridine. The sealed vial was irradiated for 10 min at 250 °C, with the pressure around 10 bar. After cooling, the reaction mixture was concentrated in vacuo and the product was purified by prep-TLC (ethyl acetate/hexane = 1/1), giving the purified product as a yellow solid (58 mg, 75%).

Method B. To a conical-bottomed Smith Process vial were added 0.4 mL of a 0.5 M solution of methyl 1-amino-1-cyclopentanecarboxylate (0.2 mmol, **8a**) in anhydrous pyridine, 0.4 mL of a 0.5 M solution of valeric acid (0.2 mmol, **7a**) in anhydrous pyridine, 0.2 mL of a 1.0 M solution of (2′-cyano-biphenyl-4-ylmethyl)-carbamic acid *tert*-butyl ester (0.2 mmol, **10b**) in anhydrous pyridine, and 63 μL (0.24 mmol) of triphenyl phosphate (neat). The sealed vial was irradiated in the microwave for 10 min at 250 °C with the pressure around 15 bar. After cooling, the reaction mixture was then concentrated in vacuo, and the product was purified by prep-TLC (ethyl acetate/hexane = 1/1), giving the purified product as a yellow solid (55 mg, 71%).

2-Butyl-3-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,3-diaza-spiro[4.4]non-1-en-4-one (Irbesartan, 2). To a conical-bottomed Smith Process vial was added tri-*n*-butyltin chloride (195 mg, 0.6 mmol) along with 0.6 mL of DMF, followed by the addition of sodium azide (39 mg, 0.6 mmol) and tetrabutylammonium bromide (6.4 mg, 0.02 mmol). After vortexing the mixture, compound **3n** (77 mg, 0.2 mmol) in 0.4 mL of DMF was added. The sealed vial was irradiated in the microwave for 1 h at 220 °C with the pressure around 8 bar. The reaction mixture was concentrated in vacuo, and the product was purified by prep-TLC (ethyl acetate/hexane/methanol = 45/45/10), giving the purified product as a light yellow solid (62 mg, 73%).

Supporting Information Available: General information, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for compounds **2** and **3a**−**q**. This material is available free of charge via the Internet at http://pubs.acs.org.

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