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Rapid and Efficient Synthesis of 1,2,4-Oxadiazoles Utilizing Polymer-Supported Reagents under Microwave Heating

Ying Wang,* Reagan L. Miller,† Daryl R. Sauer, and Stevan W. Djuric

High-Throughput Organic Synthesis Group, Global Pharmaceutical Research and
Development, Abbott Laboratories, 100 Abbott Park Road,
Abbott Park, Illinois 60064-6113

wang.ying@abbott.com

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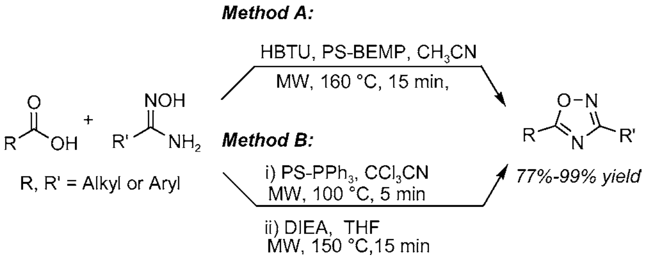
ABSTRACT



1,2,4-Oxadiazoles can be rapidly and efficiently synthesized from a variety of readily available carboxylic acids and amidoximes using either method A or method B. The use of commercially available polymer-supported reagents combined with microwave heating resulted in high yields and purities of the product 1,2,4-oxadiazoles in an expeditious manner.

Polymer-assisted solution-phase (PASP) synthesis, which uses either polymeric reagents or scavenger resins, has become a prevalent method for the rapid generation and purification of solution-phase chemical libraries in the pharmaceutical industry in recent years.[1] In PASP synthesis, excess polymer-supported reagents can be used to drive a reaction to completion and can then be easily removed by filtration after completion of the reaction. This ultimately results in shorter synthesis times and higher purities of the compounds produced. Unlike solid-phase synthesis, all of the advantages associated with solution-phase chemistry can be exploited, such as monitoring the reaction in real time by conventional methods, easy reaction optimization, and no residual functionality from bead attachment in the final product.[2] All of these features are important factors to consider in a high-throughput organic synthesis environment for the rapid generation of compounds.

As part of our ongoing program to develop efficient and robust methods for the preparation of libraries of biologically interesting compounds from readily available building blocks, we turned our attention to 1,2,4-oxadiazoles. 1,2,4-Oxadiazoles have often been described as bioisosteres for amides

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† Department of Chemistry, University of Wisconsin-Madison.

(1) For recent reviews, see: (a) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 650−679. (b) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815−4195. (c) Parlow, J. J.; Devraj, R. V.; South, M. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 320−336. (d) Drewry, D. H.; Coe, D. M.; Poon, S. *Med. Res. Rev.* **1999**, *19*, 97−148.

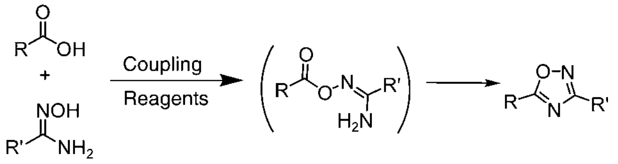
(2) For some of the recent examples, see: (a) Storer, P. I.; Takemoto, T.; Jackson, P. S.; Brown, D. S.; Baxendale, I. R.; Ley, S. V. *Chem. Eur. J.* **2004**, *10*, 2529−2547. (b) Storer, R. I.; Takemoto, T.; Jackson, P. S.; Ley, S. V. *Angew. Chem., Int. Ed.* **2003**, *42*, 2521−2525. (c) Nicolaou, K. C.; Pfefferkorn, J. A.; Barluenga, S.; Mitchell, H. J.; Roecker, A. J.; Cao, G. Q. *J. Am. Chem. Soc.* **2000**, *122*, 9968−9976. (d) Jaunzems, J.; Hofer, E.; Jesberger, M.; Sourkouni-Argirusi, G.; Kirschning, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1166−1170. (e) Rademann, J.; Smerdka, J.; Jung, G.; Grosche, P.; Schmid, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 381−385. (f) Sauer, D. R.; Kalvin, D.; Phelan, K. M. *Org. Lett.* **2003**, *5*, 4721−4724. (g) Wang, Y.; Sauer, D. R. *Org. Lett.* **2004**, *6*, 2793−2796.

10.1021/ol050007r CCC: $30.25

or esters as a result of the increased hydrolytic and metabolic stability of the ring. They have been incoporated into muscarinic agonists, benzodiazepine receptor agonists, serotoninergic (5-HT_3) antagonists, and antirhinovirals.[3] In addition, they have also been used as dipeptide mimics.[4] These applications make this heterocycle an important structural motif in drug discovery programs.

Several methods have been reported for the synthesis of 1,2,4-oxadiazoles.[5] Among those, the condensation of amidoximes with carboxylic acids in the presence of a coupling reagent was considered to be particularly attractive (Scheme 1). A wide variety of structurally diverse carboxylic acids are readily available, which is beneficial for the development of SAR in medicinal chemistry studies. Amidoximes are often either commercially available or easily accessible by reaction of nitriles with hydroxylamines. Our aim was to quickly develop a convenient, robust, and high-yielding reaction protocol for the synthesis of 1,2,4-oxadiazoles, which would also be highly amenable for automation.

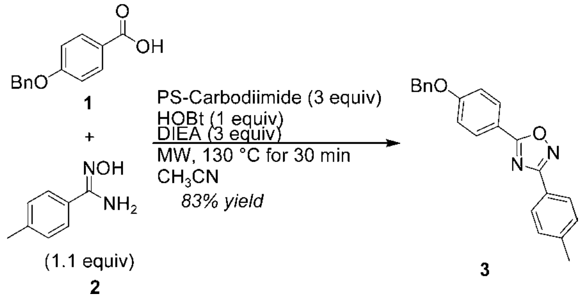
Scheme 1. Synthesis of 1,2,4-Oxadiazoles from Carboxylic Acids and Amidoximes



High-speed microwave synthesis has attracted a substantial amount of attention in recent years.[6] It has been demonstrated that the use of microwave heating can dramatically shorten reaction times, increase product purities and yields, and allow precise control of reaction parameters.

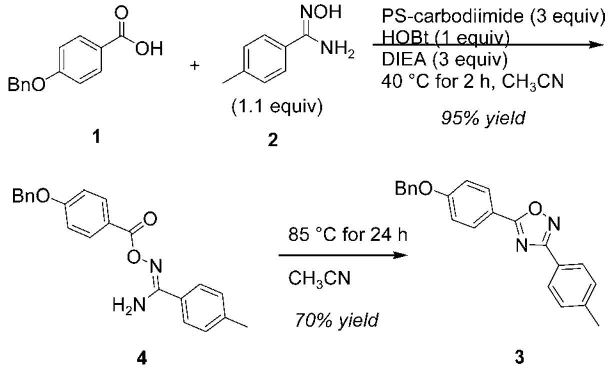
Initially, our studies commenced by heating carboxylic acid **1** and amidoxime **2** under microwave conditions[7] at different temperatures using various solvents and coupling reagents including polymer-supported coupling reagents. The reactions were conveniently monitored by LC/MS analysis in all cases, and it was observed that the use of microwave heating greatly reduced the reaction screening and optimization time. Among the conditions studied, we found that using PS-Carbodiimide[8]/HOBt for the coupling reagents gave good conversion to 1,2,4-oxadiazole **3** under microwave heating. The optimal reaction conditions are shown in Scheme 2, whereby 1,2,4-oxadiazole **3** was isolated in 83% yield.

Scheme 2. Synthesis of 1,2,4-Oxadiazole **3** with PS-Carbodiimide/HOBt under Microwave Heating



Interestingly, under conventional heating conditions, *O*-acylamidoxime **4** was formed exclusively within 2 h at 40 °C with PS-Carbodiimide/HOBt and could be isolated in high yield (Scheme 3). Further heating of the reaction mixture at 85 °C for another 24 h afforded the cyclized 1,2,4-oxadiazole **3** in 70% yield. Thus, under microwave heating conditions, a higher conversion of 1,2,4-oxadiazole **3** was obtained in a much shorter reaction time.

Scheme 3. Synthesis of 1,2,4-Oxadiazole under Conventional Thermal Heating Condition



However, when the electron-deficient amidoxime **5** was used (Table 1), the PS-Carbodiimide/HOBt method failed to give the desired product **6** despite prolonged heating in the microwave. It has been reported that 1,2,4-oxadiazoles can be obtained by heating carboxylic acids and amidoximes

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(3) (a) Orlek, B. S.; Blaney, F. E.; Brown, F.; Clark, M. S. G.; Hadley, M. S.; Hatcher, J.; Riley, G. J.; Rosenberg, H. E.; Wadsorth, H. J.; Wyman, P. J. *J. Med. Chem.* **1991**, *34*, 2726−2735. (b) Watjen, F.; Baker, R.; Engelstoff, M.; Herbert, R.; Macleod, A.; Knight, A.; Merchant, K.; Moseley, J.; Saunder, J.; Swain, C. J.; Wong, E.; Springer, J. P. *J. Med. Chem.* **1989**, *32*, 2282−2291. (c) Swain, C. J.; Baker, R.; Kneen, C.; Moseley, J.; Saunders, J.; Seward, E. M.; Stevenson, G.; Beer, M.; Stanton, J.; Watling, K. J. *J. Med. Chem.* **1991**, *34*, 140−151. (d) Diana, G. D.; Volkots, D. L.; Hitz, T. J.; Bailey, T. R.; Long, M. A.; Vescio, N.; Aldous, S.; Pevear, D. C.; Dutko, F. J. *J. Med. Chem.* **1994**, *37*, 2421−2436.

(4) Borg, S.; Vollinga, R. C.; Labarre, M.; Payza, K.; Terenius, L.; Luthman, K. *J. Med. Chem.* **1999**, *42*, 4331−4342.

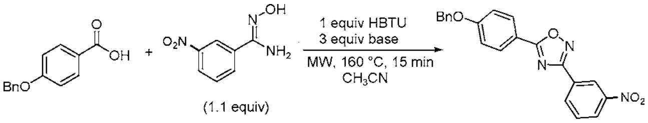
(5) For some examples, see: (a) Deegan, T. L.; Nitz, T. J.; Cebzanov, D.; Pufko, D. E.; Porco, J. A., Jr. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 209−212. (b) Evans, M. D.; Ring, J.; Schoen, A.; Bell, A.; Edwards, P.; Berthelot, D.; Micewonger, R.; Baldino, C. R. *Tetrahedron Lett.* **2003**, *44*, 9337−9341. (c) Poulain, R. F.; Tartar, A. L.; Deprez, B. P. *Tetrahedron Lett.* **2001**, *42*, 1495−1498. (d) Liang, G.; Feng, D. D. *Tetrahedron Lett.* **1996**, *37*, 6627−6630. (e) Romdhane, A.; Gharbi, R.; Mighri, Z. *Heterocycl. Commun.* **2004**, *10*, 151−156. (5f) Barrett, A. G. M.; Cramp, S. M.; Roberts, R. S.; Zecri, F. J. *Comb. Chem. High Throughput Screening* **2000**, *3* (2), 131−138.

(6) For some recent reviews, see: (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250−6284. (b) Kappe, C. O. *Curr. Opin. Chem. Biol.* **2002**, *6*, 314−320. (c) Santagada, V.; Perissutti, E.; Caliendo, G. *Curr. Med. Chem.* **2002**, *9*, 1251−1283. (d) Dzierba, C. D.; Combs, A. P. *Annu. Rep. Med. Chem.* **2002**, *37*, 247−256.

(7) All microwave reactions were performed on an Emrys Optimizer (Personal Chemistry, http://www.personalchemistry).

(8) Argonaut Technologies, http://www.argotech.com

Table 1. Synthesis of 1,2,4-Oxadiazole with HBTU Using Different Bases



1 **5** **6**

entry	base	conversion (%)[a]
1	DIEA	40
2	K_2CO_3	<10
3	MP-Carbonate	70
4	PS-BEMP	95

[a] Conversion was determined by LC/MS and crude ^{1}H NMR.

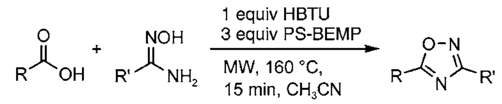
in the presence of HBTU and *N*,*N*-diisopropylethylamine (DIEA).[5b] Indeed, under microwave heating conditions, 1,2,4-oxadiazole **6** was formed as judged by LC/MS analysis, although the conversion was low (Table 1, entry 1). Attempts to improve the conversion by exploring higher temperatures, prolonged heating, and other solvents in the microwave uniformly failed. We then investigated the use of several bases including polymer-supported bases. These results are summarized in Table 1. To our delight, we quickly discovered that both MP-carbonate[8] and PS-BEMP[9] afforded a much better conversion than DIEA. Near quantitative conversion of carboxylic acid **1** to 1,2,4-oxadiazole **6** was obtained with 1 equiv of HBTU and 3 equiv of PS-BEMP in acetonitrile at 160 °C for 15 min under microwave heating (Table 1, entry 4). The reaction worked much better in acetonitrile than in DMF and other solvents. For solubility reasons, up to 20% DMF could be added to the reaction system as a cosolvent without compromising the yield. This is particularly desirable in an automation format where most of the reagents are added through liquid delivery lines. The PS-BEMP resin could be easily filtered off upon completion of the reaction.

The HBTU/PS-BEMP protocol worked well with a range of amidoximes, affording good to excellent yield of the corresponding 1,2,4-oxadiazoles (Table 2, entries 1−7, method A). In only two cases that we have studied, less than satisfactory yields were obtained (Table 2, entries 8 and 9), where the starting materials and the intermediate *O*-acyl-amidoximes were both observed in the LC/MS analysis after the reaction.

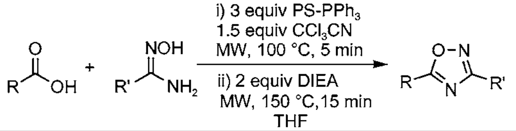
It is known that 1,2,4-oxadiazoles can generally be synthesized from amidoximes and carboxylic acid chlorides.[10] However, this method is not very attractive at first glance. Acid chlorides are relatively reactive and thus hard

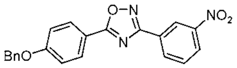
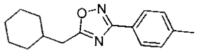
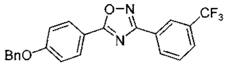
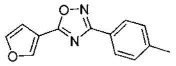
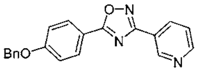
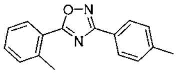
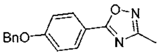
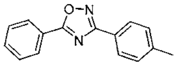
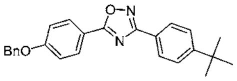
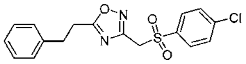
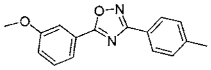
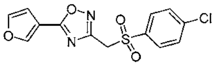
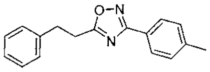
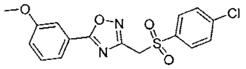
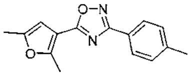
Table 2. Synthesis of 1,2,4-Oxadiazoles from Carboxylic Acids and Amidoximes with Method A or Method B

Method A:



Method B:

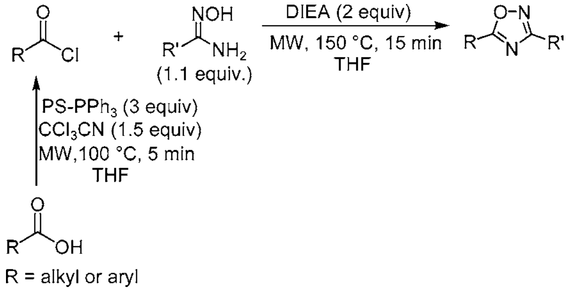


entry	product	method A yield[a] (conversion)[b]	method B yield[a] (conversion)[b]	entry	product	method A yield[a] (conversion)[b]	method B yield[a] (conversior
1		89% (95%)	90% (100%)	9		45% (55%)	97% (99%)
2		81% (100%)	80% (100%)	10		--[c]	96%
3		82% (93%)	94% (100%)	11		--[c]	98%
4		76% (95%)	80% (98%)	12		--[c]	95%
5		93% (98%)	93% (99%)	13		--[c]	83%
6		79% (80%)	98% (100%)	14		--[c]	77%
7		87% (95%)	93% (100%)	15		--[c]	89%
8		40% (57%)	90% (94%)				

[a] Isolated yields after purification. [b] Conversion is determined by crude LC/MS or ^{1}H NMR. [c] Not determined.

to store and handle. In addition, compared to the diverse array of carboxylic acids, very few carboxylic acid chlorides are readily available, which makes it difficult to perform thorough SAR studies in a medicinal chemistry setting. One way to solve this problem is to convert the carboxylic acids to the corresponding carboxylic acid chlorides, preferably in situ. Among the many reported procedures, the use of PS-PPh$_3$/CCl$_3$CN is particularly attractive (Scheme 4).[11] The reaction is easy to perform under mild reaction conditions and can be easily adapted to automation. In addition, PS-PPh$_3$ can be easily filtered off after the reaction. We have found that under microwave heating conditions, usually at 100 °C for 5 min, a variety of carboxylic acid chlorides can be easily obtained in situ from diverse carboxylic acids with nearly quantitative yields.[12]

Scheme 4. Synthesis of 1,2,4-Oxadiazoles by in Situ Fromation of Carboxylic Acid Chlorides[13]



In the process of developing the HBTU/PS-BEMP method, we were also delighted to find that carboxylic acid chlorides generated in situ with PS-PPh$_3$/CCl$_3$CN reacted in a facile manner with a variety of amidoximes to generate the corresponding 1,2,4-oxadiazoles (Scheme 4). THF was found to be the best solvent for both steps. The PS-PPh$_3$ resin from the first step did not interfere with the second step in our hands. Thus, the reaction can be performed in one pot in THF without the need for filtration. After the carboxylic acid chloride was generated in situ, amidoxime and DIEA were added and the reaction mixture was heated in the microwave at 150 °C for 15 min to afford the desired 1,2,4-oxadiazole in high yield (Table 2, method B). In many cases, the conversion was quantitative and only the desired product and a small amount of excess amidoxime were observed in the crude LC/MS and ^{1}H NMR analysis. This one-pot two-step reaction was found to be quite general and worked on a variety of alkyl and aryl carboxylic acids and amidoximes. In most cases, the isolated yield was more than 85%. In most expamples, either the HBTU/PS-BEMP or the PS-PPh$_3$/CCl$_3$CN method gave good yields of the desired products (Table 2, entries 1−7). Of particular note, however, are two examples (Table 2, entries 8 and 9), where method B afforded the desired products with much higher conversion and isolated yields.

In summary, we have developed two microwave-enhanced, rapid, and efficient methods for the synthesis of 1,2,4-oxadiazoles. Both methods use readily available solid-phase reagents that not only result in higher yields but also greatly simplify the purification process. Additionly, the use of microwave technology allowed us to quickly identify optimal reaction conditions with reaction times reduced from hours to minutes. Both methods are suitable for the preparation of either individual analogues or the production of libraries using automated protocols.

Supporting Information Available: General experiment details and characterizations of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) 2-*tert*-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine, polymer-bound; http://www.sigmaaldrich.com

(10) (a) Korbonits, D.; Horvath, K. *Heterocycles* **1994**, *37*, 2051−2068. (b) Mathvink, R. J.; Barritta, A. M.; Candelore, M. R.; Cascieri, M. A.; Deng, L.; Tota, L.; Strader, C. D.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1869−1874.

(11) (a) Jang, D. O.; Park, D. J.; Kim, J. *Tetrahedron Lett.* **1999**, *40*, 5323−5326. (b) Buchstaller, H.; Ebert, H. M.; Anlauf, U. *Synth. Commun.* **2001**, *31*, 1001−1005.

(12) Unpublished results.

(13) Partial conversion to 1,2,4-oxadiazoles was observed with 3 equiv of PS-DIEA or PS-Carbonate. Comparable yields of 1,2,4-oxadiazoles were obtained when 3 equiv of PS-BEMP was used in place of DIEA.