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Efficient Synthesis of Imidazoles from Aldehydes and 1,2-Diketones under Superheating Conditions by Using a Continuous Flow Microreactor System under Pressure

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Abstract:

A simple and efficient method for the synthesis of 2,4,5-trisubstituted imidazoles has been developed by using a continuous flow microreactor system under pressure; aryl-, alkyl-, and heteroaryl-substituted imidazoles were obtained in high yields within 2 min under superheating conditions.

Introduction

Imidazoles and their derivatives, based on their diverse biological activities, play important roles in the synthesis of pharmaceuticals and versatile building blocks for natural products.[1] 2,4,5-Trisubstituted imidazoles, especially, occur in a number of biologically active structures, such as modulators of P-glycoprotein and inhibitors of P38 MAP kinase, etc.[2] This structural motif is also found in diverse therapeutic agents, for example, antibacterial and anti-inflammatory agents.[3] Therefore, the organic synthesis of these imidazole derivatives has a significant impact on medicinal chemistry. Many routes to synthesize 2,4,5-trisubstituted imidazoles have been developed.[4] The classic synthesis by a one-pot reaction of aldehydes, benzil, and ammonium acetate, refluxing in acetic acid for many hours,[5] proceeds with low yields. Recent modifications on the synthesis route have focused on the usage of catalysts[6] and microwave irradiation.[7] However, preparations of some catalysts require relatively expensive reagents, harsh reaction conditions, and sometimes tedious workup using toxic reagents or solvents.[6] A microwave reaction system can provide an environment in which the reaction mixture can be rapidly dielectrically heated in sealed vessels at temperatures far above the boiling point of the solvent under pressure. However, it is difficult to scale up due to the limited penetration depth of microwave irradiation into absorbing media.[8] Consequently, exploring a simpler, greener, and easy to scale-up method for the efficient synthesis of 2,4,5-trisubstituted imidazoles is highly desirable.

Recently, more and more attention has been paid to performing organic synthesis in continuous flow microreactor systems.[9] Microreactors, compared with the conventional batch reactors, hold a higher surface area-to-volume ratio,[9] which leads to faster heat and mass transfer. In addition, the continuous flow microreactor system can be easily scaled up due to its numbering-up property.[10] As a result, through performing reactions in continuous microflow systems under pressure, we can achieve a rapid and evenly superheated (above the boiling point of solvents) environment similar to that provided by a microwave reactor, while avoiding the scale-up problem of the latter.[11] These advantages have been reflected in improvement of the multicomponent thermal reactions,[12,13] for which the heat and mass transfer are the key factors. Earlier, we successfully

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(1) (a) Almirant, L.; Polo, L.; Mugnaini, A.; Provinci, E.; Rugarli, P.; Biancott, A.; Gamba, A.; Murmann, W. *J. Med. Chem.* **1965**, *8*, 305–312. (b) Jin, Z. *Nat. Prod. Rep.* **2009**, *26*, 382–445. (c) Biagi, G.; Costantini, A.; Costantino, L.; Giorgi, I.; Livi, O.; Pecorari, P.; Rinaldi, M.; Scartoni, V. *J. Med. Chem.* **1996**, *39*, 2529–2535.

(2) (a) Sarshar, S.; Zhang, C. Z.; Moran, E. J.; Krane, S.; Rodarte, J. C.; Benbatoul, K. D.; Dixon, R.; Mjalli, A. M. M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2599–2601. (b) Kim, K. H. *Bioorg. Med. Chem.* **2001**, *9*, 1517–1523. (c) Boehm, J. C.; Smietana, J. M.; Sorenson, M. E.; Garigipati, R. S.; Gallagher, T. F.; Sheldrake, P. L.; Bradbeer, J.; Badger, A. M.; Laydon, J. T.; Lee, J. C.; Hillegass, L. M.; Griswold, D. E.; Breton, J. J.; ChabotFletcher, M. C.; Adams, J. L. *J. Med. Chem.* **1996**, *39*, 3929–3937.

(3) (a) Khan, M. S.; Siddiqui, S. A.; Siddiqui, M.; Goswami, U.; Srinivasan, K. V.; Khan, M. I. *Chem. Biol. Drug Des.* **2008**, *72*, 197–204. (b) Barta, T. E.; Stealey, M. A.; Collins, P. W.; Weier, R. M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3443–3448. (c) Puratchikody, A.; Doble, M. *Bioorg. Med. Chem.* **2007**, *15*, 1083–1090. (d) Lombardi, Jg; Wiseman, E. H. *J. Med. Chem.* **1974**, *17*, 1182–1188.

(4) (a) Eisch, J. J.; Chan, T. Y.; Gitua, J. N. *Eur. J. Org. Chem.* **2008**, 392–397. (b) Das, B.; Srinivas, Y.; Holla, H.; Krishnaiah, M.; Narender, R. *Chem. Lett.* **2007**, *36*, 1270–1271. (c) Shaabani, A.; Rahmati, A.; Farhangi, E.; Badri, Z. *Catal. Commun.* **2007**, *8*, 1149–1152. (d) Habersaat, N.; Frohlich, R.; Wurthwein, E. U. *Eur. J. Org. Chem.* **2004**, 2567–2581. (e) Chou, C. H.; Chu, L. T.; Chiu, S. J.; Lee, C. F.; She, Y. T. *Tetrahedron* **2004**, *60*, 6581–6584.

(5) Sarshar, S.; Siev, D.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 835–838.

(6) (a) DasSharma, S.; Hazarika, P.; Konwar, D. *Tetrahedron Lett.* **2008**, *49*, 2216–2220. (b) Khodaei, M. M.; Bahrami, K.; Kavianinia, I. *J. Chin. Chem. Soc.* **2007**, *54*, 829–833. (c) Khosropour, A. R. *Ultrason. Sonochem.* **2008**, *15*, 659–664. (d) Kidwai, M.; Mothsra, P.; Bansal, V.; Somvanshi, R. K.; Ethayathulla, A. S.; Dey, S.; Singh, T. P. *J. Mol. Catal. A: Chem.* **2007**, *265*, 177–182. (e) Sharma, G. V. M.; Jyothi, Y.; Lakshmi, P. S. *Synth. Commun.* **2006**, *36*, 2991–3000.

(7) (a) Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. H.; Wang, Y.; Zhao, Z. J.; Lindsley, C. W. *Org. Lett.* **2004**, *6*, 1453–1456. (b) Xia, M.; Lu, Y. D. *J. Mol. Catal. A: Chem.* **2007**, *265*, 205–208.

(8) Moseley, J. D.; Lenden, P.; Lockwood, M.; Ruda, K.; Sherlock, J. P.; Thomson, A. D.; Gilday, J. P. *Org. Process Res. Dev.* **2008**, *12*, 30–40.

(9) (a) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300–2318. (b) Watts, P.; Haswell, S. *J. Chem. Soc. Rev.* **2005**, *34*, 235–246. (c) Jahnisch, K.; Hessel, V.; Lowe, H.; Baerns, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 406–446. (d) Geyer, K.; Codee, J. D. C.; Seeberger, P. H. *Chem.—Eur. J.* **2006**, *12*, 8434–8442. (e) Fletcher, P. D. I.; Haswell, S. J.; Pombo-Villar, E.; Warrington, B. H.; Watts, P.; Wong, S. Y. F.; Zhang, X. L. *Tetrahedron* **2002**, *58*, 4735–4757.

(10) Fukuyama, T.; Rahman, T.; Sato, M.; Ryu, I. *Synlett* **2008**, 151–163.

(11) Razzaq, T.; Glasnov, T. N.; Kappe, C. O. *Eur. J. Org. Chem.* **2009**, 1321–1325.

(12) (a) Gustafsson, T.; Gilmour, R.; Seeberger, P. H. *Chem. Commun.* **2008**, 3022–3024. (b) Odedra, A.; Geyer, K.; Gustafsson, T.; Gilmour, R.; Seeberger, P. H. *Chem. Commun.* **2008**, 3025–3027.

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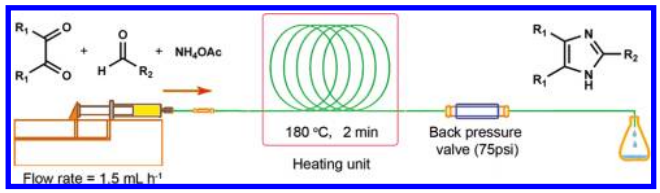


Figure 1. **Continuous synthesis of 2,4,5-trisubstituted imidazoles using a microreactor system under pressure.**

performed Claisen rearrangement reaction in a continuous flow microreactor at high temperature.[14] On this basis, we report the development of a more efficient method for the synthesis of 2,4,5-trisubstituted imidazoles by using an optimized system under pressure.

Microreactor Fabrication. The continuous flow microreactor system (MR) we used for our studies mainly consists of five parts: microsyringe pumps (flow rate 0.005−36 mL min^{-1}), microchannels (250 μm in I.D.), a heating bath, a back pressure unit (75 psi), and collection devices. The microchannel is a 120-cm long stainless steel pipe with the heating length of 102 cm. It is acid/base resistant and high-temperature endurable and is commonly used in high-performance liquid chromatography (HPLC). The back pressure unit is placed between the heating bath and the collection devices. The solution of reactants mixture is injected through the pipe, heated in the oil bath, and finally the effluent liquid is collected. When the microreactor system is running, the internal pressure of the microchannels is maintained at 75 psi by the back pressure valve to give a superheating environment.

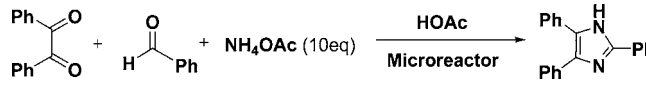
Results and Discussion

Initial efforts focused on optimizing the microreaction conditions for the synthesis of 2,4,5-triphenyl-1*H*-imidazole using acetic acid as the solvent with NH_4OAC in the microreactor system, based upon previous investigations of conventional thermal conditions[15] (see Figure 1).

Ten equivalents is a classic reactant ratio for ammonium acetate in the synthesis of 2,4,5-trisubstituted imidazoles using 1,2-diketone (1 equiv) and aldehyde (1 equiv) under conventional conditions. The yield will decrease when the reactant ratio of ammonium acetate is reduced. Hence, we chose 10 equiv of ammonium acetate directly in our initial exploration of the synthesis of 2,4,5-trisubstituted imidazoles in the microreactor system.

The conversion increased from 91% to 98% as the reaction temperature rose from 120 to 180 °C when the residence time is 10 min, and then we reduced the amount of ammonium acetate to 8 equiv in the microreaction, but the conversion of the imidazole showed an obvious decrease (92%). As a result we gave up further exploration on the amount of ammonium acetate. In addition, we gradually reduced the residence time from 10 to 1 min at 180 °C to further optimize the reaction conditions. It was observed that only when the residence time is ≥2 min can the conversion be maintained at 98% (isolated yield: 93%), and further residence time reduction lead to lower conversion (Table 1).

Table 1. **Optimization of temperature and residence time for the synthesis of 2,4,5-triphenyl-1*H*-imidazole**



entry	*T* (°C)	residence time (min)	conversion (%)[a]
1	120	10	91
2	140	10	93
3	160	10	97
4	180	10	98
5	180	5	98
6	180	3	98
7	180	2	98 (93[b])
8	180	1	96

[a] Back pressure of the MR is 75 psi. Conversion determined by LC/MS. [b] isolated yield.

We believe that the high reaction efficiency primarily benefits from the excellent heat exchange in the microchannels under superheating conditions. The reactants can absorb heat more rapidly under the temperature higher than the boiling point of the solvent to reach the reaction activation energy. As a result, the reaction rate increases remarkably compared with the reaction performed under conventional conditions.

In addition, this procedure is continuous. Thus, this method has potential to avoid the scale-up problem which occurs in the microwave reactors. The numbering-up property of the microreactor is another potential advancement to solve the scale-up problem.[10]

Using the optimized conditions (180 °C, 2 min), reactions with various substrates were examined. Reactions of the *o*-, *m*-, *p*-substituted aromatic aldehydes with either electron-withdrawing groups or electron-donating groups were effective to give corresponding imidazole derivatives (Table 2, entries 2−7). Aromatic heterocyclic aldehydes were also found to be equally reactive substrates for the system (Table 2, entry 8). In addition, aliphatic aldehydes with short carbon chains and small carbocyclic rings could also be employed in this microreactor process (Table 2, entries 9−10).

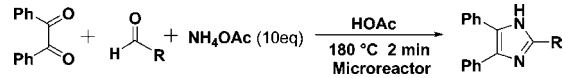
We next expanded our study to various 1,2-diketones. Benzils were proven to be effective as the candidates in the preparation of 2,4,5-trisubstituted imidazoles in good to excellent yields. These substrates include both benzils with electron-donating groups and those with electron-withdrawing groups (Table 3, entries 1−3). In addition to benzil-derived substrates, heteroaromatic (entries 4−5) and aliphatic 1,2-diketones (entry 6) gave corresponding imidazoles with satisfactory yields (Table 3, entries 4−6). The results illustrate the high ability of this method for the synthesis of 2, 4, 5-trisubstituted imidazoles.

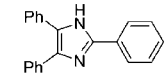
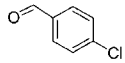
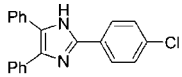
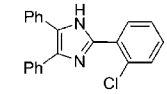
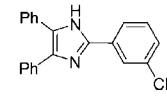
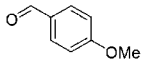
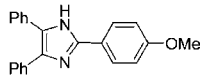
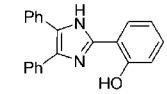
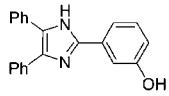
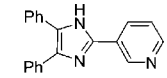
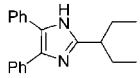
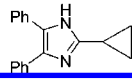
Conclusion

In conclusion, we have developed a new general synthetic method for the synthesis of 2,4,5-trisubstituted imidazoles by using a continuous flow microreactor system under pressure. Aryl-, alkyl-, and heteroaryl-substituted imidazoles were obtained in high yields within 2 min under superheating conditions

(13) (a) Acke, D. R. J.; Orru, R. V. A.; Stevens, C. V. *QSAR Combi. Sci.* **2006**, *25*, 474–483. (b) Richter, T.; Ehrfeld, W.; Hessel, V.; Lowe, H.; Storz, M.; Wolf, A. *Microreaction Technology: Industrial Prospects: IMRET 3: Proceedings of the Third International Conference on Microreaction Technology* 2000; pp 636−644.
(14) Kong, L. J.; Lin, Q.; Lv, X. M.; Yang, Y. T.; Jia, Y.; Zhou, Y. M. *Green Chem.* **2009**, *11* (8), 1108–1111.
(15) Abrahams, S. L.; Hazen, R. J.; Batson, A. G.; Phillips, A. P. *J. Pharmacol. Exp. Ther.* **1989**, *249*, 359–365.

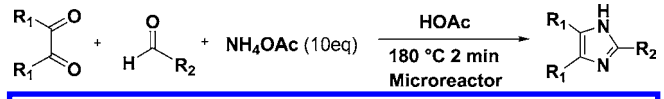
Table 2. **Synthesis of 2,4,5-trisubstituted imidazoles with benzil and various aldehydes**

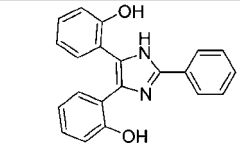
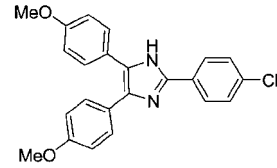
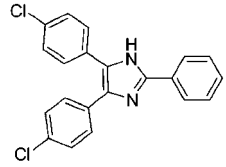
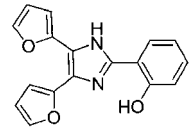
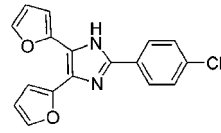
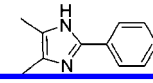


entry	R	product	yield (%)[a]
1			93
2			95
3			90
4			91
5			94
6			92
7			93
8			92
9			88
10			92

[a] Isolated yields.

Table 3. **Synthesis of 2,4,5-trisubstituted imidazoles with various 1,2-dione and aldehydes**



entry	product	yield (%)[a]
1		87
2		80
3		92
4		87
5		88
6		89

[a] Isolated yields.

in this system. In addition to efficiency and simplicity, this platform provides a very fast, green, and easy scale-up procedure for the synthesis of 2,4,5-trisubstituted imidazoles.

Experimental Section

Reagents and solvents were obtained from commercial sources and used as received.

Typical Procedure for the Preparation of 2,4,5-Trisubstituted Imidazoles Using Microreactor under Pressure.

(2,4,5-Triphenylimidazole, Table 2, entry 1): benzil (0.2 M), aldehyde (0.2 M), and ammonium acetate (2 M) were dissolved in HOAc at room temperature. The solution was injected through the microchannel (1.5 mL min^{-1}), heated in an oil bath, and finally collected from the other end of the microchannel. The residence time is 2 min. The internal pressure of the microreactor is provided by the back pressure valve (75 psi). The crude product was added dropwise to a 0 °C concentrated NH_4OH solution. The mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic phases were dried over sodium sulfate and then concentrated. The product was separated and purified by column chromatography on silica gel (300−400 mesh) using ethyl acetate/petroleum ether mixture (1:10, v/v) as eluent to afford pure 2,4,5-triphenylimidazole as a bright, white solid (275 mg, 93%).

For entries 1−2, Table 3, the amount of HOAc is increased to 10 mL when the 1,2-dione is 1.0 mmol.

For entry 3, Table 3, the solvent is changed to the mixture of acetic acid and dimethylbenzene (1:1, v/v), and the mount of the solvent is 20 mL when the 1,2-dione is 1.0 mmol.

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Supporting Information Available

Detailed experimental procedures and compound characterization data, including NMR spectra for all described compounds. This material is available free of charge via the Internet at http://pubs.acs.org/.

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