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Efficient Synthesis of Imidazoles from Aldehydes and 1,2-Diketones Using Microwave Irradiation

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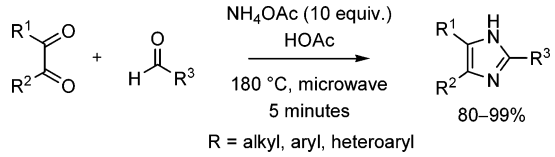
ABSTRACT



A simple, high-yielding synthesis of 2,4,5-trisubstituted imidazoles from 1,2-diketones and aldehydes in the presence of NH_4OAc is described. Under microwave irradiation, alkyl-, aryl-, and heteroaryl-substituted imidazoles are formed in yields ranging from 80 to 99%. Short syntheses of lepidiline B and trifenagrel illustrate the utility of this approach.

Since the introduction of controlled, precise microwave reactors, microwave-assisted organic synthesis (MAOS) has had a significant impact on synthetic chemistry. Reductions in reaction time, increases in yield, and suppression of side product formation have all been described for microwave conditions relative to conventional thermal heating.[1] Although the basis of these practical benefits remains speculative,[2] the preparative advantages are obvious and have motivated a large and continuing survey of nearly all classes of thermal reactions for improvement upon microwave heating. This exploration has extended to cross-coupling reactions, cycloadditions, condensations, and heterocycle-forming reactions.[1,3,4]

As part of an ongoing development of efficient protocols for the preparation of substituted heterocycles from common intermediates, we recently discovered technically simple, high-yielding microwave conditions for the synthesis of triazines,[3] quinoxalines, and pyrazinones[4] from 1,2-diketones (Figure 1). These conditions (microwave, 5 min, 80−95%)

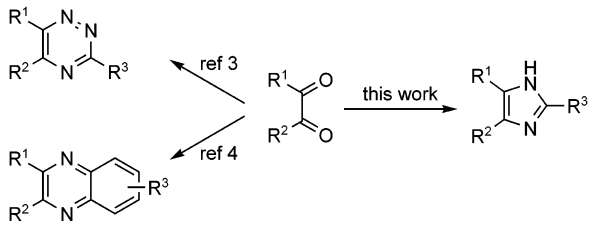


Figure 1. Microwave-assisted reactions of 1,2-diketones which furnish diverse substituted heterocycles.

represent a dramatic improvement over conventional thermal heating (8−24 h, 30−65%)[5] and enable the use of 1,2-diketones as diversification points in routes to biologically active heterocycles. Importantly, when employed in an

(1) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.
(2) Garbacia, S.; Desai, B.; Lavastre, O.; Kappe, O. *J. Org. Chem.* **2003**, *68*, 9136. Kuhnert, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 1863. Strauss, C. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3589.
(3) Zhao, Z.; Leister, W. H.; Strauss, K.; Wisnoski, D. D.; Lindsley, C. W. *Tetrahedron Lett.* **2003**, *44*, 1123.
(4) Zhao, Z.; Wisnoski, D. D.; Wolkenberg, S. E.; Leister, W. H.; Wang, Y.; Lindsley, C. W. Manuscript in preparation.

(5) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. Benson, S. C.; Li, J.-H.; Snyder, J. K. *J. Org. Chem.* **1992**, *57*, 5285.

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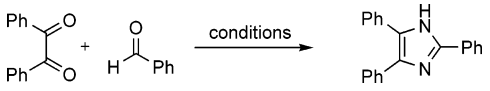
iterative analogue library approach this strategy permits access to libraries containing diverse skeletons, thus distinguishing itself from the more limited approach in which a central scaffold is "decorated" with various substituents. Herein, we report the extension of this methodology to the synthesis of trisubstituted imidazoles and demonstrate its utility in expedient preparations of the imidazolium alkaloid lepidiline B[6] and the platelet aggregation inhibitor trifenagrel.[7]

The original synthesis of imidazole utilized glyoxal, formaldehyde, and ammonia and established that the formation of four N−C bonds was a viable route.[8,9] Although classical methods were derived from this early success, the reaction suffered low yields, mixtures of products (including reversed aldol condensations and oxazole formation), and lack of generality. Synthetic methodology alternatives are many and varied[10] and have resorted to harsh conditions (e.g., the formamide synthesis, which requires excess reagents, H_2SO_4 as a condensing agent, 150−200 °C, 4−6 h, 40−90%).[9,11] Additionally, reagents for these procedures are not readily or commercially available, a key deficiency when developing conditions for library synthesis.

In light of the improvements MAOS has bestowed upon similar thermal reactions, reinvestigation of the classical conditions seemed warranted. Initial efforts focused on optimizing microwave conditions for the formation of 2,4,5-triphenylimidazole using NH_4OAc in acetic acid, based on prior investigations of conventional thermal conditions (Table 1).[7] In 5 min reactions, yields increased with higher reaction

Table 1. Optimization of Imidazole Formation under Microwave Irradiation



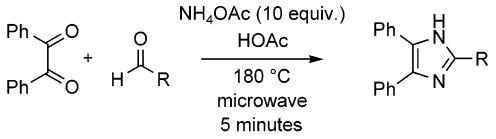
entry	*T* (°C)	time (min)	conversion[a] (%)
1	60	5	24
2	80	5	51
3	100	5	61
4	120	5	68
5	140	5	87
6	160	5	98
7	160	0.5	71
8	160	1	82
9	160	3	95

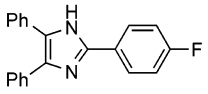
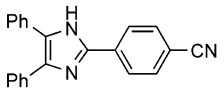
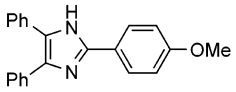
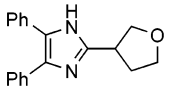
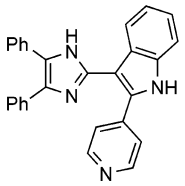
[a] Reactions run in HOAc with 0.2 mmol each of benzil and benzaldehyde and 10 equiv of NH_4OAc. Conversion determined by LCMS; isolated yield for entry 6, 88%.

temperatures up to 160 °C with complete conversions observed in all cases at 180 °C (Table 1, entries 1−6). Likewise, in 160 °C trials, only reactions times >3 min provided optimal yields (entries 7−9). Impressively, and akin to observations made previously,[2] conversions for short reaction times are quite high (entries 7 and 8). Isolation of the product from this and subsequent reactions required neutralization of the reaction mixture (typically performed with concentrated NH_4OH) and filtration to provide solid substituted imidazoles of analytical purity.

These conditions proved to be general for the reacting aldehyde, as shown in Table 2. Aldehydes bearing either

Table 2. Representative 2,4,5-Trisubstituted Imidazoles



entry	product	yield (%)[a]
1		97
2		88
3		87
4		93
5		90

[a] Isolated yields for analytically pure compounds obtained after neutralization of the reaction mixture followed by filtration. For details, see the Supporting Information.

electron-withdrawing (Table 2, entry 2) or electron-donating groups (entry 3) perform equally well in the reaction. Additionally, aliphatic (see entry 4 and Scheme 1 below) and heterocyclic aldehydes (entry 5) deliver the corresponding imidazoles in high yield.

Importantly for the ultimate goal of applying this reaction in a diversity-generating strategy, this broad generality extends to the 1,2-diketone substrate as well (Table 3). Heteroaromatic, aryl, and aliphatic 1,2-diketones uniformly provide excellent yields of the corresponding imidazoles. This includes both electron-deficient (entry 2) and electron-

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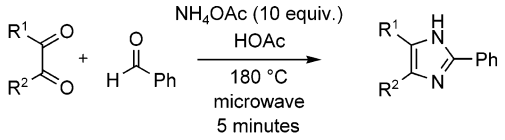
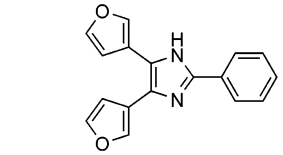
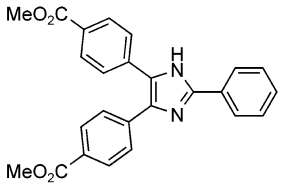
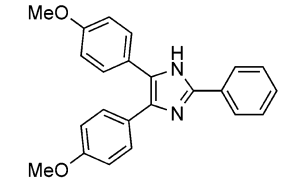
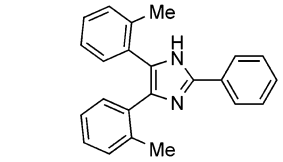
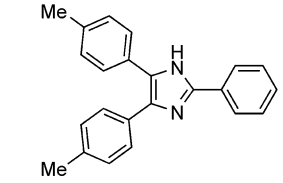
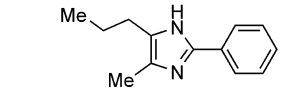
Table 3. Representative 2,4,5-Trisubstituted Imidazoles



entry	product	yield (%)[a]
1		89
2		95
3		99
4		94
5		94
6		93

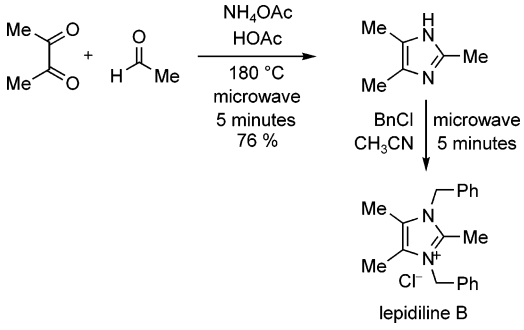
[a] Isolated yields for analytically pure compounds obtained after neutralization of the reaction mixture followed by filtration. For details, see the Supporting Information.

rich (entry 3) 1,2-diketones, as well as sterically hindered systems (entry 4).

Part of the motivation for pursuing libraries of imidazoles is their prevalence among naturally occurring and synthetic biologically active compounds. The well-known microtubule stabilizing agents eleutherobin and sarcodictyin,[12] among numerous other marine- and plant-derived natural products,[13] contain imidazole. Furthermore, a recent report indicates that synthetic imidazoles can exhibit potent inhibition of protein−protein interactions.[14] As an exercise aimed at determining the utility of the conditions described here, an example from each of these two classes was prepared.

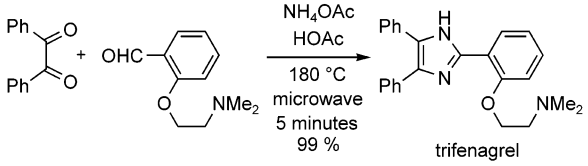
Lepidilines A and B were recently isolated from the root extract of *Lepidium meyenii* ("Peruvian ginseng") collected from the Andes Mountains of Peru during a search for bioactive natural products.[6] Characterized by their symmetrical imidazolium structures (Scheme 1), these simple alkaloids exhibit micromolar cytotoxicity against several human cancer cell lines. Lepidiline B was prepared in an expedient two-step procedure from 2,3-butanedione and acetaldehyde (Scheme 1). Since both steps are microwave-assisted, evaluation of the route and, in fact, completion of the synthesis was possible in <2 h. Notably, preparation of the intermediate 2,4,5-trimethylimidazole was technically simpler, faster, and higher yielding than previous routes.[15] Based on the MAOS of imidazoles described here, lepidiline B was synthesized for the first time in 43% overall yield. This preparation, which delivered 25 mg of the natural product in 1 day, compares favorably with the reported isolation, which yielded 10 mg of lepidiline B from 10 kg of *L. meyenii* roots after multiple chromatographic separations.[6]

Scheme 1



Trifenagrel[7] (Scheme 2) is a potent 2,4,5-triarylimidazole arachidonate cyclooxygenase inhibitor that reduces platelet aggregation in several animal species and humans. Indeed, it inhibits both arachidonate and collagen-induced aggregation with equal or greater potency (5−21-fold) than in-

Scheme 2



(10) Earlier reports described microwave assisted conditions for the synthesis of imidazoles on solid support (Al_2O_3, SiO_2, and zeolite HY), and these procedures were limited to triarylimidazoles. See: Balalaie, S.; Arabanian, A.; Hashtroudi, M. S. *Monatsh. Chem.* **2000**, *131*, 945. Usyatinsky, A. Y.; Khmelnitsky, Y. L. *Tetrahedron Lett.* **2000**, *41*, 5031. In general, although solvent-free conditions were commonly used with multimode commercial microwaves ("kitchen" microwave ovens), they are incompatible with currently employed, temperature- and pressure-controlled, single-mode scientific reactors.

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domethacin and aspirin without exhibiting the gastric damage associated with these typical cyclooxygenase inhibitors. Preparation of the drug[7] (Scheme 2) using the microwave-assisted aldehyde−1,2-diketone condensation reaction proceeded smoothly and in high yield. This example highlights the speed of the method: whereas the existing optimized procedure for its preparation furnishes product after 2 h at reflux, the MAOS protocol delivers pure trifenagrel in 99% yield after 5 min.

In summary, we have developed a general microwave-assisted synthesis of 2,4,5-trisubstituted imidazoles. In addition to its speed and simple setup, the reaction is high yielding for a variety of substrates indicating its utility in a parallel synthesis format. Further, the value of this transformation in target-oriented synthesis was demonstrated in the first total synthesis of lepidiline B and a rapid, high-yielding synthesis of trifenagrel.

Acknowledgment. We thank Joan Murphy for obtaining HRMS measurements on all compounds.

Supporting Information Available: Full experimental details and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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