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Microwave-Assisted Synthesis of 2,4,5-Triaryl-imidazole; A Novel Thermally Induced *N*-Hydroxyimidazole N–O Bond Cleavage

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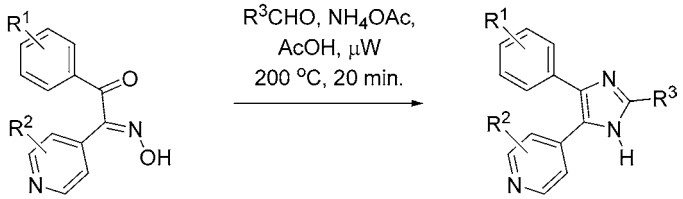
ABSTRACT



2,4,5-Triaryl-imidazoles were synthesized directly from the keto-oxime in moderate to good yields via cyclization to the *N*-hydroxyimidazole and an unprecedented in situ thermal reduction of the N–O bond upon microwave irradiation at 200 °C for 20 min.

Microwave-assisted organic synthesis (MAOS) has proven to be a valuable tool for the efficient synthesis of heterocyclic compounds with biological activities.[1,2] Many reviews have been published recently that detail its utility.[3,4] The ability to rapidly heat reactions significantly above the boiling point of the solvent has resulted in dramatic decreases in reaction times and increases in reaction yields for a variety of chemical transformations.[5,6] In addition, new synthetic transformations induced by high temperatures have been discovered.[7,8]

We report herein a novel multicomponent, one-pot, two-step microwave-assisted synthesis that provides an efficient route to diverse arrays of 2,4,5-triarylimidazoles, such as known P38 map kinase inhibitor **1**.[9] The generality of this new methodology was demonstrated by the automated microwave synthesis and automated preparative LCMS purification of a small library of these compounds.

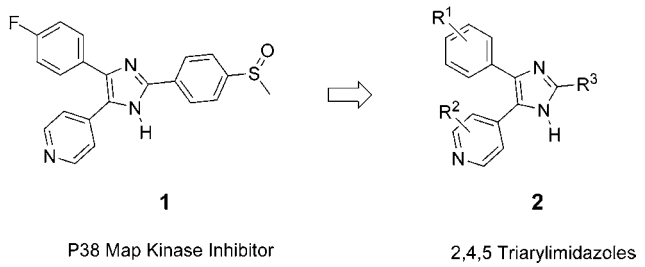


Figure 1. 2,4,5-Triarylimidazoles kinase inhibitors.

Several solution-phase and solid-phase routes to the 2,4,5-triarylimidazole scaffold have been described in the literature,[10−11] including a recent report[12] during the preparation

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(2) Kaddar, H.; Hamelin, J.; Benhaoua, H. *J. Chem. Res.* **1999**, 718−719.
(3) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199−9223.
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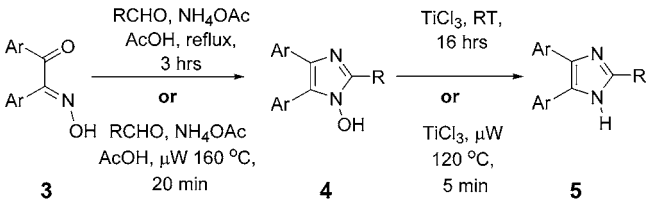
of this manuscript of the microwave-assisted synthesis of 2,4,5-imidazoles directly from 1,2-diketones, aldehydes, and ammonia. We chose to investigate the use of microwave irradiation to promote and accelerate the [3 + 2] cycloadditon of keto-oximes **3** with aldehydes[13] to yield hydroxyimidazoles **4**, primarily because of the diversity of unsymmetrical keto-oxime **3** building blocks that are readily available compared to the 1,2-diketones. We then envisioned that reduction of the hydroxyimidazoles **4** with titanium trichloride[14] could also be facilitated by microwave irradiation to provide diverse subsets of the desired imidazole **5** in two steps (Scheme 1).

Scheme 1. Conventional versus Microwave-Assisted Synthesis of 2,4,5-Triarylimidazoles

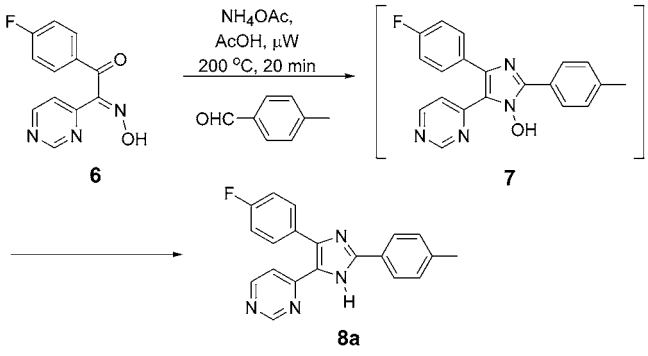


Initial experiments demonstrated that our microwave-assisted approach could be used to expedite the synthesis of imidazoles in yields comparable to those of conventional heating methods. Diaryl keto-oximes **3** were condensed with various aldehydes in the microwave at 160 °C for 15 min to give hydroxyimidazoles **4** in moderate to good yields. The solvents were evaporated to afford crude hydroxyimidazoles **4** that were used directly in the next step. Microwave-assisted reduction of the *N*-hydroxyimidazoles **4** with $TiCl_3$ at 120 °C for just 5 min gave near quantitative yields of the desired imidazoles **5**. The total reaction time for synthesis of one compound from the keto-oxime **3** was shortened from 19 h to only 25 min with this two-step microwave-assisted procedure.

Unfortunately, attempts to transition this reaction into a high-throughput method for the synthesis of diverse libraries of triarylimidizoles **5** proved problematic as a result of the laborious workup of the titanium reaction. Most notable, the aqueous base extraction was plagued with emulsions due to the resulting titanium dioxide. An alternative[15] solid-phase extraction procedure also gave low yields as a result of the inherent high aqueous solubility of imidazoles **5**.

However, careful analysis of the crude reaction products from the initial microwave-assisted [3 + 2] cycloaddition of keto-oxime **6** and 4-methylbenzaldehyde revealed that a small amount of the unexpected but desired imidazole **8a** was formed. This observation led us to investigate this reaction more closely. Subsequent variation of the solvent, temperature, and time of reaction provided optimized conditions for the synthesis of the 2,4,5-trisubstituted imidazole **8a** directly from the keto-oxime **6** (Scheme 2).

Scheme 2. Microwave-Assisted One-Pot Synthesis of 2,4,5-Triarylimidazole **8a**



We initially studied the effect of temperature on this one-pot, two-step reaction (Table 1). We observed a clear trend toward in situ cleavage of the N−O bond at higher temperatures. These results are consistent with a thermalytic cleavage mechanism of the N−O bond at extreme temperatures. Although the conversion to the imidazole **8a** was only 10% at 160 °C, heating in the microwave to 220 °C for 20 min gave complete conversion to the desired imidazole **8a**. The crude sample was filtered and purified by injection directly onto a preparative LCMS to provide the desired triarylimidazole **8a** in 44% yield. We did note that HPLC

Table 1. Temperature Study on Microwave-Assisted Cyclization/Reduction[a]

	yield (%)[b]	
temp (°C)	**7**	**8a**
160	70	8
180	45	22
200	8	44
220	0	47

[a] Conditions: 1.1 equiv of *p*-tolualdehyde, 4 equiv of NH_4OAc, AcOH, irradiation in microwave for 20 min. [b] Isolated yields.

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(15) Purification of the desired compounds using either C18 silica or Dowex 50WX8-200 resin failed because of poor retention on the solid phase.

conversions did not directly correlate to the yield with very high temperatures. For example, the isolated yield for reaction at 220 °C (100% conversion) was only marginally better than that realized at 200 °C where we achieved only 85% conversion of **6** to desired imidazole **8a**. Apparently, product **6** is unstable to the higher reaction temperatures and slightly lower reaction temperatures are required to afford the highest yields.

The intermediate *N*-hydroxyimidazole **7** was isolated in good yield (57%) to allow testing of various solvents directly in the N−O bond cleavage reaction (Table 2). The conversion of *N*-hydroxyimidazole **7** to imidazole **8a** was found to be optimal in acetic acid as compared to a variety of other solvents tested. Pyridine also gave moderate conversions to the desired imidazole **8a**, demonstrating that acidic and basic solvents are suitable.

Table 2. Solvent Study of Microwave-Assisted N−O Bond Cleavage of *N*-Hydroxyimidazole **7**[a]

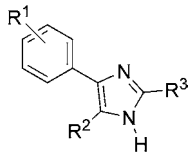
solvent	**8a** (%)[b]	temp (°C)
AcOH	56	200
pyridine	33	200
DMF	27	200
TFA	31	200
MeOH/1 N HCl	1	140
MeOH/MSA	0	160
DCE	4	180
EtOH	3	160

[a] Conditions: solvent, maximum irradiation in microwave for 20 min. [b] Conversions calculated on the basis of HPLC, UV detection at 220 nm.

A diverse set of imidazoles were synthesized with these optimized conditions.[16] Three different keto-oximes **3** were reacted with five different aromatic and aliphatic aldehydes to test the generality of this new microwave-assisted method (Table 3). The entire library was then purified by automated preparative LCMS to afford good yields (40−63%) for aromatic aldehydes R3 with all R1 and R2 substituents and moderate yields (17−37%) with aliphatic aldehydes R3.

(16) **Compound 8a.** To a small microwave tube was added keto-oxime **6**, (24 mg, 0.1 mmol), ammonium acetate (31 mg, 0.4 mmol), 4-tolualdehyde (13 uL, 1.1 mmol), and glacial acetic acid (1.0 mL). The mixture was irradiated at 200 °C in an Optimizer (Personal Chemistry) for 20 min and cooled to 50 °C. The crude sample was filtered and purified by direct injection onto a preparative LCMS to provide the desired triarylimidazole **8a** as the TFA salt (20 mg, 44% yield): ^{1}H NMR (d_6-DMSO) δ 9.08 (s, 1H), 8.79 (d, J = 5.58 Hz, 1H), 8.06 (d, J = 8.18 Hz, 2H), 7.78 (m, 3H), 7.39 (m, 4H), 2.40 (s, 3H); MS (ES+) $[M + H]^+$ 331.3.

Table 3. Automated Microwave-Assisted Synthesis and Preparative LCMS Purification of a Diverse Library of 2,4,5-Triarylimidazoles[a]



8a

8	R^1	R^2	R^3	yield (%)[b]
a	4-F	4-pyrimidyl	4-tolyl	44
b	4-F	4-pyrimidyl	4-anisoyl	56
c	4-F	4-pyrimidyl	4-Cl-phenyl	40
d	4-F	4-pyrimidyl	ethyl	21
e	4-F	4-pyrimidyl	*tert*-butyl	34
f	3-CF_3	4-pyrimidyl	4-tolyl	49
g	3-CF_3	4-pyrimidyl	4-anisoyl	51
h	3-CF_3	4-pyrimidyl	4-Cl-phenyl	37
i	3-CF_3	4-pyrimidyl	ethyl	17
j	3-CF_3	4-pyrimidyl	*tert*-butyl	29
k	3-CF_3	4-pyridyl	4-tolyl	50
l	3-CF_3	4-pyridyl	4-anisoyl	63
m	3-CF_3	4-pyridyl	4-Cl-phenyl	45
n	3-CF_3	4-pyridyl	ethyl	26
o	3-CF_3	4-pyridyl	*tert*-butyl	25

[a] Conditions: 1.1 equiv of *p*-tolualdehyde, 4 equiv of NH_4OAc, AcOH, irradiation in microwave for 20 min at 200 °C. [b] Isolated yields.

We have discovered an efficient microwave-assisted, one-pot, two-step synthesis of triarylimidazoles from keto-oximes and aldehydes. The novel thermally induced N−O reductive bond cleavage step is promoted by extreme temperatures in the microwave and is achieved in good yields. Importantly, the microwave-assisted procedure allows for the rapid synthesis, 20 min compared to 2 days by conventional methods, and direct LCMS purification, without the need for extraction, of 2,4,5-triarylimidazole libraries. These results further demonstrate the value of microwave-assisted chemistry not only to provide increased yields and shorter reaction times for known chemical transformations but also to elucidate unprecedented chemical transformations and streamlining of high throughput chemistry.

Supporting Information Available: LC/MS (ES+)and ^{1}H NMR spectra for **6**, **7**, and **8a**−**o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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