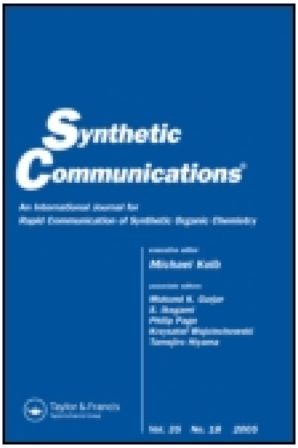

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Trifluoroacetic Acid as an Efficient Catalyst for One-Pot, Four-Component Synthesis of 1,2,4,5-Tetrasubstituted Imidazoles Under Microwave-Assisted, Solvent-Free Conditions

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Abstract: An efficient method for synthesis of various tetrasubstituted imidazoles, using trifluoroacetic acid (TFA) as a catalytic support, by four-component condensation of benzil, aldehydes, amines, and ammonium acetate under microwave-irradiated, solvent-free conditions is described.

Keywords: Four-component, microwave, solvent-free, tetrasubstituted imidazoles, trifluoroacetic acid

INTRODUCTION

The imidazole moiety, as a part of the side chain in histidine, plays a major role in the biological activity of many peptides and proteins. Functionalized imidazoles also comprise an important class of pharmacologically active compounds that have a variety of interesting properties.[1,2] Because of their widespread applications as green solvents by means of ionic liquids[3] and in organometallic chemistry as N-heterocyclic carbenes,[4] there is an increasing interest in research on imidazoles.

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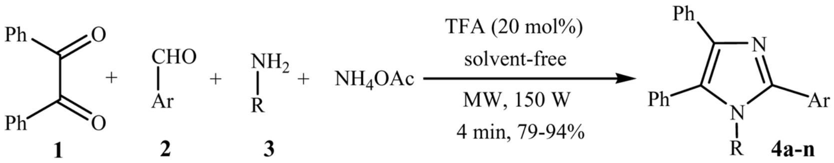
Preparation of tetrasubstituted imidazoles has been the subject of both industrial and academic studies. As a result, numerous solution-phase syntheses of these compounds have been reported.[5,6] The most well-known and classical method for preparation of these compounds involves four-component condensations of a 1,2-diketone derivative with an aldehyde, primary amine, and ammonium acetate in refluxing HOAc, which is known to have poor yields and long reaction times.[7] Improvements occurred using other acidic conditions, such as $FeCl_3 \cdot 6H_2O$,[8] heteropolyacid,[9] silica gel,[10] zeolite,[10] alumnia,[11] $HClO_4 \cdot SiO_2$,[12] molecular iodine,[13] $BF_3 \cdot SiO_2$,[14] $InCl_3 \cdot 3H_2O$,[15] $K_5CoW_{12}O_{40} \cdot 3H_2O$,[16] and copper acetate[17] under microwave-irradiated, solvent-free or classical conditions. However, most of these synthetic methods suffer from some serious drawbacks, such as laborious and complex workup and purification, significant amounts of waste materials, strongly acidic conditions, occurrence of side reactions, poor yields, and the use of expensive reagents. Therefore, the development of a new catalytic system to overcome these shortcomings and fulfill the criteria of a mild, efficient, and environmentally benign protocol for the synthesis of highly substituted imidazoles is an important task for organic chemists.

Because of its interesting properties, such as low toxicity, solubility in organic solvents, and strength, trifluoroacetic acid (TFA) is considered to be a special reagent for highly sensitive microsequencing of proteins,[18] as well as a special catalyst for promotion of numerous organic reactions.[19–30]

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. Although the basis of these practical benefits remains speculative, 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.[31]

RESULTS AND DISCUSSION

In continuing our interest on microwave-assisted synthesis of nitrogen-containing heterocycles,[32,33] we developed a one-pot reaction catalyzed by silica gel–supported sodium bisulfate for the synthesis of tri- and tetrasubstituted imidazoles.[34] In the present work, we concluded that TFA is

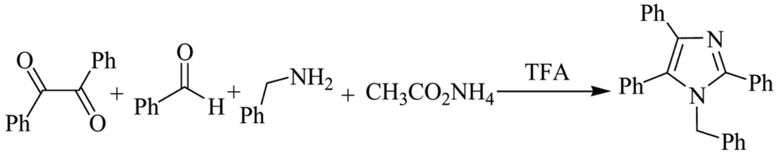


Scheme 1. TFA-catalyzed, microwave-assisted, solvent-free synthesis of 1,2,4,5-tetrasubstituted imidazoles **4a–n.**

a highly efficient catalyst for the one-pot synthesis of tetrasubstituted imidazoles **4** from benzil **1**, aldehydes **2**, amine **3**, and ammonium acetate under microwave-assisted, solvent-free conditions (Scheme 1). The multicomponent nature of the procedure together with the existence of a wide variety of commercially available aldehydes and amines make this reaction an ideal candidate for the combinatorial synthesis technology.

To achieve the best conditions for this reaction (Scheme 1), we examined the efficiency of different reaction media and catalyst amounts for the condensation reactions of benzil, benzaldehyde, benzylamine, and ammonium acetate as a model reaction (Table 1). For each reaction

Table 1. Comparison of the reaction of benzil, benzaldehyde, benzylamine, and ammonium acetate under various TFA loadings and reaction conditions



Entry[a]	Catalyst (mol %)	Conditions	Time (min)	Conversion (%)[b]
1	10	Solvent-free, 100°C	90	35
2	20	Solvent-free, 100°C	90	35
3	30	Solvent-free, 140°C	90	68
4	20	DMF, 110°C	90	20
5	0	MW (150 W), solvent-free	15	35
6	10	MW (150 W), solvent-free	6	52
7	20	MW (150 W), solvent-free	4	100
8	30	MW (150 W), solvent-free	4	100

[a] All reactions were run using benzil/benzaldehyde/benzylamine/ammonium acetate, molar ratio of 1/1/1/1.

[b] All measured by GC.

condition, conversion of initial reactants to 1-benzyl-2,4,5-triphenylimidazole was measured by gas–liquid chromatography using 0.01 M solution of the product[35] in chloroform as a standard. Reactions at different conditions and various molar ratios of substrates in the presence of TFA revealed that the best conditions were a molar ratio of benzil/aldehyde/amine/ammonium acetate/TFA of 1:1:1:1:0.20 under microwave-assisted, solvent-free conditions.

The optimal conditions were then applied for the preparation of a series of 1,2,4,5-substituted imidazoles **4a–n**. The product yields are shown in Table 2. It should be noted that this method is effective for the preparation of tetrasubstituted imidazoles from both aliphatic and aromatic amines. In each case, no side product formation (for example, 2,4,5-trisubstituted imidazoles) was observed, as is normally the case in such reactions under the influence of strong acids. This method not only affords the products in excellent yields but also avoids the problems associated with catalyst cost, handling, safety, and pollution.

It is worth mentioning that the desired products could be easily separated in this condition. Trifluoroacetic acid is completely soluble in

Table 2. Synthesis of imidazoles **4a–n** under microwave-irradiated, solvent-free conditions

Product **4**[a,b]	Ar	R	Yield (%)[c]	Mp [Ref.]
a	Ph	Ph-CH_2	92	157–159[17]
b	Ph	Ph	88	216–217[10]
c	4-Me-Ph	Ph-CH_2	94	166–167[10]
d	4-Me-Ph	Ph	85	186–188[10]
e	4-Cl-Ph	Ph-CH_2	89	163–165[14]
f	4-Cl-Ph	Ph	83	148–151[14]
g	4-Me-Ph	Ph-CH_2-CH_2	88	126–127[12]
h	3-Cl-Ph	Ph-CH_2	80	147–150[14]
i	Ph	*iso*-Bu	85	134–136[10]
j	4-Me-Ph	*iso*-Bu	85	151–152[10]
k	4-Me-Ph	Et	79	122–123[10]
l	2-Me-Ph	Ph	88	145–147
m	2-Me-Ph	4-Cl-Ph	91	165–166
n	2-Me-Ph	4-Br-Ph	90	190–192

[a] Benzil–aldehyde–amine–ammonium acetate–catalyst (1:1:11:1:0.2).

[b] The structure of known imidazoles **4a–k** were characterized by their ^1H NMR and comparison of their physical properties with reported data. For new imidazoles **4l–n,** the structures of the products were fully characterized by NMR and mass spectroscopy.

[c] All referred to isolated pure products.

water at room temperature, but the products are not. Water was added to the cooled reaction mixture, and the products were separated by simple filtration.

All known products **4a–k** were characterized by their ^{1}H NMR and comparison of their physical properties with previously reported data. For new imidazoles **4l–n,** the structures of the products were fully characterized by NMR and mass spectroscopy, (MS). Physical properties and spectral data of new compounds **4l–n** are reported.

To show the advantages of TFA as a catalyst in this reaction, our obtained results and employed reaction conditions for synthesis of 1-benzyl-2,4,5-triphenylimidazole (**4a**) were compared with previously reported data in Table 3. The results show that our method is quite comparable with the former methods in yields and reaction times.

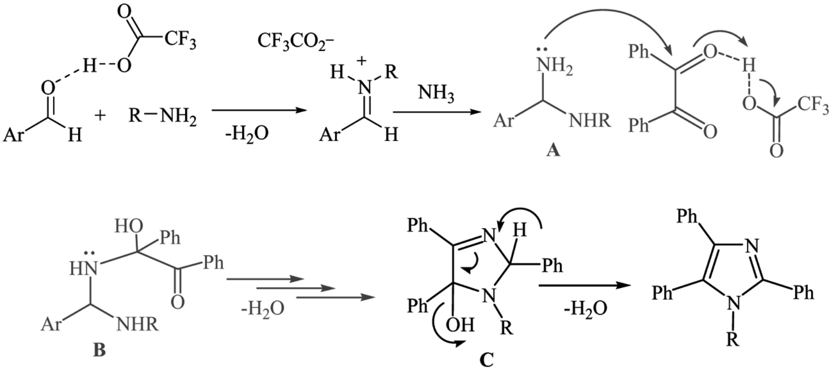
In accordance with a delineated mechanism,[35] it may be proposed that the CF_3CO_2H catalyst facilitates the formation of diamine intermediate [**A**] by increasing the electrophilicity of the carbonyl group of the aldehydes and benzil. Intermediate [**A**], in the presence of CF_3CO_2H, condenses with benzil to form imidazol-5-ol intermediate [**C**], which in turn changes to tetrasubstituted imidazoles by elimination of water (Scheme 2).

In conclusion, we have developed a simple, fast, and efficient procedure for synthesis of 1,2,4,5-tetrasubstituted imidazoles based on

Table 3. Synthesis of 1-benzyl-2,4,5-triphenylimidazole **4a** using different catalysts and reaction conditions

Entry	Solvent and catalyst (loading)	Time (min)	Yield (%)	Ref.
1[a]	Ethanol, reflux, $FeCl_3 \cdot 6H_2O$ (5 mol%),	60	98	8
2	Ethanol, reflux, $H_4[PMo_{11}VO_{40}]$ (1 mol%)	8	88	9
3	MW, solvent-free, silica gel (5 mol%)	6	87	10
4	MW, solvent-free, Zeolite HY (5 mol%)	6	83	10
5	MW, solvent-free, alumina (3.4 g per 1 mmol)	20	80	11
6	Solvent-free, $HClO_4$–SiO_2 (1 mol%)	6	96	12
7	Ethanol, reflux, I_2 (5 mol%)	—	—	13
8	Solvent-free, 140 °C, 37% BF_3-SiO_2 (0.08 g per 1 mmol)	120	80	14
9	Methanol, 25 °C, $InCl_3 \cdot 3H_2O$ (10 mol%)	360	84	15
10	Solvent-free, 140 °C, $K_5CoW_{12}O_{40} \cdot 3H_2O$ (0.1 mol%)	120	90	16
11	MW, solvent-free, TFA (5 mol%)	5	86	this work

[a] Entry 1 is GC-measured yield, and all others are isolated yields.



Scheme 2. Plausible mechanism for the formation of tetrasubstituted imidazoles.

TFA-catalyzed, one-pot, four-component condensation of benzil, benzaldehydes, primary amines, and ammonium acetate under microwave-assisted, solvent-free conditions. The short reaction times, easy workup, clean reaction profiles, and good product yields make our methodology a valid contribution to the existing processes in the field of 1,2,4,5-tetrasubstituted imidazoles synthesis.

EXPERIMENTAL

General Procedure

In a typical procedure appropriate amounts of benzil **1** (1 mmol), aldehydes **2** (1 mmol), primary amine **3** (1 mmol), ammonium acetate (1 mmol), and TFA (0.2 mmol) in a beaker were mixed thoroughly and exposed to microwave irradiation (150 W, 20% power) for 4 min in a four-step mode with interval (1 min–40 s–1 min). Then the reaction mixture was allowed to cool down to room temperature, 20 mL water were added, and the resulting solid was filtered off and washed with 10 mL of hot water. Resulting products have sufficient purity, but if more purification is necessary, the products can be recrystallized from ethanol.

Spectral Data of New Compounds 4l–N

1,4,5-Triphenyl-2-o-tolyl-1 H-imidazole **4l**

Colorless solid; mp 173–174; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.28 (s, 3H, CH_3), 6.93 (m, 2H, arom), 7.11–7.30 (m, 15H, arom), 7.66 (m, 2H, arom);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.7, 125.7, 126.9, 127.8, 128.1, 128.3, 128.4, 128.5, 128.8, 129.0, 129.3, 129.7, 130.5, 131.2, 131.3, 131.5, 131.7, 135.1, 137.0, 138.2, 138.6, 147.7; MS m/z: 386 ($[M]^+$, 100), 165 (50), 77 (23).

1-(4-Chlorophenyl)-4,5-diphenyl-2-O-tolyl-1H-imidazole **4 m**

Colorless solid; mp 205–206; ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.27 (s, 3H, CH_3), 6.79 (m, 2H, arom), 7.14–7.33 (m, 14H, arom), 7.64 (m, 2H, arom); ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 20.7, 122.0, 125.9, 127.1, 127.8, 128.6, 129.1, 129.5, 129.6, 129.7, 130.7, 130.8, 131.0, 131.4, 131.6, 132.3, 134.8, 136.1, 138.4, 138.6, 147.6; MS m/z: 422 ($[M+2]^+$, 33), 420 ($[M]^+$, 100), 165 (60), 77 (24).

1-(4-Bromophenyl)-4,5-diphenyl-2-o-tolyl-1 H-imidazole **4n**

Colorless solid; mp 209–211; ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.27 (s, 3H, CH_3), 6.86 (m, 2H, arom), 7.13–7.33 (m, 14H, arom), 7.65 (m, 2H, arom); ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 20.7, 125.8, 127.1, 127.8, 128.5, 128.6, 129.0, 129.3, 129.4, 129.5, 129.6, 130.7, 130.8, 131.0, 131.4, 131.6, 133.9, 134.8, 135.6, 138.6, 147.7; MS m/z: 466 ($[M+2]^+$, 98), 464 ($[M]^+$, 100), 165 (45), 77 (25).

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