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Tetrahedron Letters 47 (2006) 2883–2886
Tetrahedron Letters

Microwave-assisted one step high-throughput synthesis of benzimidazoles

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Received 8 February 2006; revised 20 February 2006; accepted 21 February 2006
Available online 9 March 2006

Abstract—One-pot synthesis of benzimidazoles from diamines and carboxylic acids was developed under microwave irradiation condition, which provided a practical and efficient method for high-throughput synthesis of this important class of heterocyclic compounds.

Microwave-assisted organic synthesis (MAOS) continues to affect synthetic chemistry significantly by enabling rapid, reproducible, and scalable chemistry development.[1] Numerous reactions including condensations, cycloadditions, heterocycle formations, and metal catalyzed cross-coupling have been explored under microwave conditions, some of which have been applied to medicinal chemistry and total syntheses of natural products.[2] MAOS can facilitate the discovery of new reactions and reduce cycle time in optimization of reactions. In addition, it serves to expand chemical space in compound library synthesis.

As it relates to our efforts to develop efficient and robust methodologies and processes for high-throughput synthesis of pharmacologically interesting libraries for drug discovery,[3] the exploration of microwave chemistry to access heterocyclic compounds has been of particular interest to us. Herein, we report a microwave-assisted approach for the synthesis of benzimidazoles in one pot from readily available starting materials.

Benzimidazole has been an important pharmacophore and privileged structure in medicinal chemistry (Fig. 1),[4] encompassing a diverse range of biological activities including antiarrhythmic, antiulcer, anthelmintical, inotropic, antihistamine, antifungal, antiviral, and cytotoxicity.[5] A recent advancement, which expands the scope of accessible benzimidazoles has been to sequence the reduction of nitroanilines and condensation with aldehydes in one-pot reactions.[6] However, many approaches for the synthesis of benzimidazoles continue to utilize the condensation reactions of arylenediamines with carboxyl equivalents such as carboxylic acids, carboxylic acid esters, lactones, anhydrides, and aldehydes.[7] These reactions require harsh dehydration conditions such as strong mineral acids, which have limited the viability of many starting materials. We envisioned that microwave irradiation could enhance this chemistry and expand the chemistry scope.

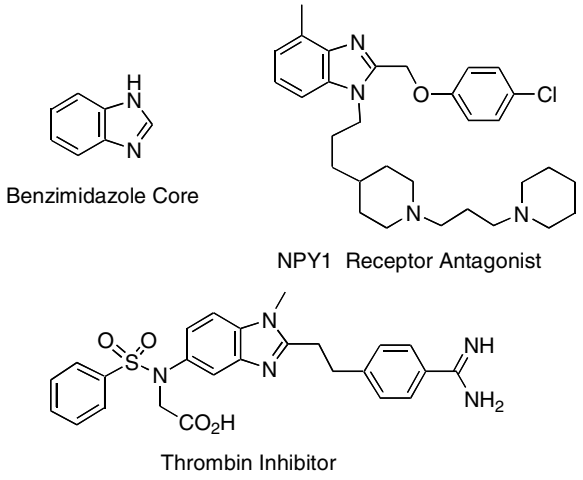

Figure 1. Biologically relevant benzimidazoles.

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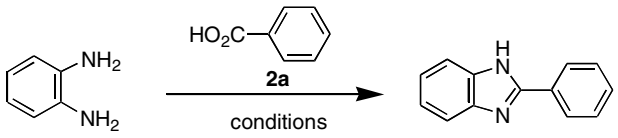
doi:10.1016/j.tetlet.2006.02.127

Table 1. Optimization of microwave-assisted benzimidazole formation



1a **3**

Temp (°C)	Reaction time (min)	**3**[a] (%)
180	10	68
200	10	79
220	10	100 (78)

[a] The conversions are determined by HPLC (ELSD) from LC–MS results of the reaction mixture. In parentheses, isolated yields by preparative TLC. The purities of the isolated products were determined by HPLC or/and ^{1}H NMRs.

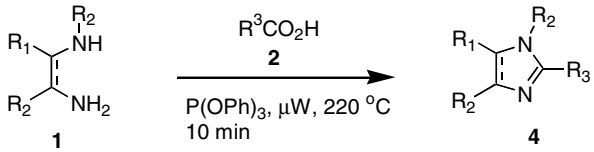
Initial efforts focused on optimizing microwave conditions for the formation of **3** employing our 'standard' microwave conditions (Table 1).[3a] Although reaction of benzene-1,2-diamine (**1a**, 1.0 equiv) with benzoic acid (**2a**, 1.0 equiv) in the presence of $P(OPh)_3$ (1.2 equiv) in pyridine under microwave irradiation at 180 °C successfully generated desired product **3**, the reaction could not go to completion even at 200 °C for 10 min. However, microwave irradiation of the reaction mixture at 220 °C for 10 min triggered the effective amidation–cyclization reaction, which resulted in formation of the desired product **3** in 100% conversion with 78% isolated yield. It was noted that pyridine was a better solvent for a broad range of diamines and carboxylic acids with a variety of functional groups than others such as glacial acetic acid, hydrochloric acid, sulfuric acid, and polyphosphoric acid.

Our preliminary success prompted an evaluation of the reaction scope aimed at achieving the ultimate goal of applying this method to high-throughput synthesis. The optimized conditions above were applied to various diamines **1** and carboxylic acids **2**, as shown in Table 2.[8] Aliphatic diamines and aromatic diamines as well as heterocyclic diamines (entries 1–4) generally provided good to excellent conversion (82–100%) with moderate to good isolated yields (32–58%). It is noteworthy that heteroaromatic diamine (entry 3) also worked well under this set of conditions. In addition, an aliphatic cyclohexyl diamine (a mixture of cis/trans, entry 4) underwent the effective cyclization to elaborate the hexahydrobenzimidazole products. These microwave results demonstrated a broad range of diamines applicable to this chemistry.

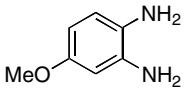
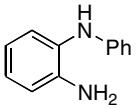
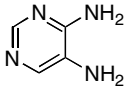
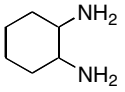
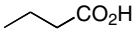
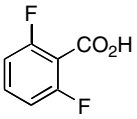
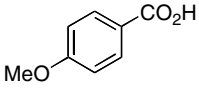
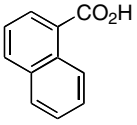
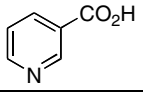
The carboxylic acid component of this reaction was also examined (entries 5–9) under the conditions. Aliphatic (entry 5), aromatic (entries 6–8), and heterocyclic carboxylic acids (entry 9) all worked well, providing overall conversions from 78% to 100% with corresponding isolated yields ranging from 58% to 86%.

To further explore the scope of the conditions, synthesis of a small library of 42 compounds was carried out with a crossing of six diamines and seven acids (Table 3). The

Table 2. Evaluation of diamines **1** and carboxylic acids **2**



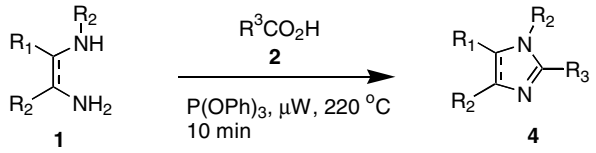
1 **4**

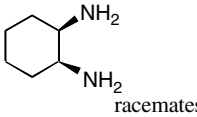
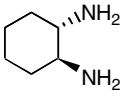
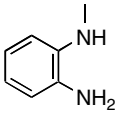
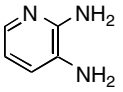
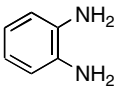
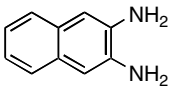
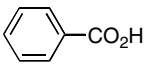
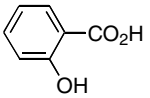
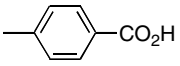
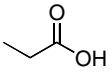
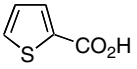
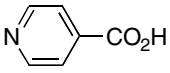
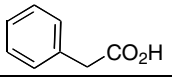
Entry	Diamines, **1**	Acids, **2**	Yield[a] of **4** (%)
1		**2a**	100 (58)
2		**2a**	100 (49)
3		**2a**	100 (32)
4[b]		**2a**	82 (55)
5	**1a**		100 (86)
6	**1a**		89 (58)
7	**1a**		78 (58)
8	**1a**		100 (67)
9	**1a**		100 (58)

[a] The conversions are determined by HPLC (ELSD) from LC–MS results of the reaction mixture. In parentheses, isolated yields by preparative TLC. These yields were not optimized. The purities of the isolated products were determined by HPLC or/and ^{1}H NMRs.
[b] cis/trans Mixture purchased from Aldrich.

selected diamines included aliphatic (cis and trans cyclohexyl diamines), aromatic (both plain and mono-substituted) as well as heterocyclic diamines. The selected carboxylic acids included aliphatic, aromatic, and heterocyclic acids. The library synthesis was performed on a solution-phase high-throughput automated synthesis platform integrated with a microwave station.[10] These compounds were then purified on an in-house high-throughput purification platform by reverse-phase HPLC with mass-triggered fraction collection,[11] quantified by weight, and characterized by LC/MS to confirm the synthesis of the desired compounds and to establish purity. Table 3 shows the results in purities and yields of all products in the combinatorial crossing of the two components using given reaction condition.

Table 3. Small library synthesis



2	1					
	 racemates					
	56[a] (100, 100)	43 (100, 100)	71 (74, 84)	43 (92, 100)	50 (100, 100)	32 (100, 100)
	72 (100, 100)	31 (86, 81)	65 (100, 100)	25 (100, 100)	43 (100, 100)	39 (100, 100)
	57 (82, 100)	59 (50, 100)	38 (63, 100)	46 (50, 86)	65 (100, 100)	67 (100, 100)
	83 (100, 100)	98 (100, 100)	66 (100, 100)	84 (100, 100)	30 (100, 100)	42 (100, 100)
	36 (100, 100)	35[b] (100, 100)	25 (100, 100)	53 (92, 100)	51 (100, 100)	36 (67, 79)
	14 (100, 100)	94 (74, 100)	41 (100, 100)	74 (100, 100)	40 (100, 100)	16 (100, 100)
	68 (100, 100)	68 (76, 100)	65 (100, 100)	73 (100, 100)	72 (100, 100)	49 (100, 100)

[a] Isolated yields by preparative HPLC. In parentheses are the UV_{214nm} and ELSD purity determined by HPLC.
[b] See Ref. 9.

In summary, a microwave-assisted one-pot synthesis of benzimidazoles from readily available starting materials has been developed. The broad chemistry scope and efficiency have been demonstrated through successful syntheses of a diverse set of benzimidazoles. The further application of this microwave methodology for the synthesis of other heterocycles will be described in due course.

References and notes

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8. General reaction procedure for the synthesis of benzimidazoles from acids and diamines are described in Table 2: In a conical-bottomed Smith Process vial, 0.5 mL of butyric acid in anhydrous pyridine (0.4 M, 200 μmol), 0.5 mL of 1,2-phenylenediamine in anhydrous pyridine (0.4 M, 200 μmol), and triphenyl phosphite (70 μL, 245 μmol) were charged. The sealed vial was irradiated in the microwave for 10 min at 220 °C. The pressure reading at this temperature was 8.1 bar. After cooling, the reaction mixture was concentrated in vacuo and the residue was purified by preparative TLC (CH_2Cl_2/MeOH, 20/1) to give the desired product **4** (Table 2, entry 5): 2-propyl-1*H*-benzimidazole; 27.5 mg (86%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98 (t, $J = 7.6$ Hz, 3H), 1.91 (m, 2H), 2.96 (t, $J = 7.6$ Hz, 2H), 7.21–7.60 (dd, $J = 3.2$, 6.0 Hz, 2H), 7.56 (dd, $J = 3.2$, 6.0 Hz, 2H), 10.9 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 22.1, 31.6, 115.0, 122.5, 138.9, 155.9; HRMS calcd for ($C_{17}H_{16}N_2O_2$+H) 161.1073, found 161.1076.
9. ^{1}H NMR (CD_3OD, 400 MHz) δ 1.37–1.43 (m, 2H), 1.51–1.57 (m, 2H), 1.85–1.88 (m, 2H), 2.24–2.27 (m, 2H), 3.18–3.21 (m, 2H), 7.16 (dd, $J = 4.0$, 4.8 Hz, 1H), 7.64 (dd $J = 3.6$, 1.2 Hz, 1H), 7.68 (dd, $J = 4.8$, 1.2 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 26.3, 31.8, 70.2, 129.5, 131.6, 132.3, 133.2, 163.8; HRMS calcd for ($C_{11}H_{14}N_2S$+H) 207.0951, found 207.0952.
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