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Report

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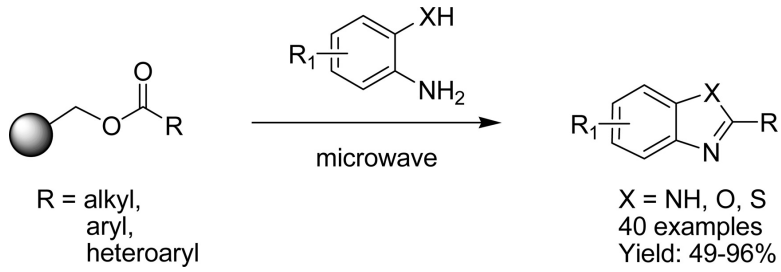

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Microwave-Assisted Synthesis of Benzimidazoles, Benzoxazoles, and Benzothiazoles from Resin-Bound Esters

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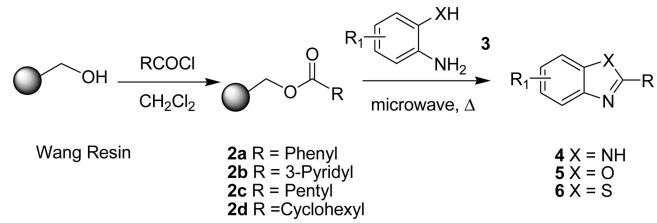
Polymer-supported combinatorial chemistry is an efficient methodology for the construction of compound libraries and has been applied to drug discovery, catalyst development, and material science.[1] The employment of a polymeric support in combinatorial chemistry facilitates handling and purification of polymer-bound intermediates and separation of products.[2] However, solid-phase organic reactions usually require rather long reaction times to drive chemical transformations to complete conversion because of heterogeneous reaction conditions. Therefore, any process accelerating solid-phase organic reactions would be desirable for high-throughput synthesis and combinatorial chemistry. Numerous reports have been demonstrated that microwave irradiation can be used to speed up solid-phase organic reactions in a variety of chemical transformations.[3] In a program aimed at finding efficient methods suitable for solid-phase reactions, we explored the microwave-assisted cleavage reaction of resin-bound esters **2** with various amine based nucleophiles **3** for the synthesis of benzofused azoles such as benzoxazoles, benzothiazoles, and benzimidazoles, which could be utilized in high-throughput solid-phase organic synthesis, as outlined in Scheme 1.

Benzimidazoles, benzoxazoles, and benzothiazoles are important scaffolds found in a variety of biologically active molecules.[4] Several reported methods for the conversion of esters into benzofused azoles generally required long reaction time in the presence of strong acid at high temperature,[5] thereby rendering them unsuitable for solid-phase chemistry. A milder procedure, mediated by Lewis acid, for the conversion of resin-bound esters into benzimidazoles and benzothiazole was disclosed recently, but it required long reaction times and failed the conversion into the corresponding benzoxazole products.[6] Recently, microwave irradiation has been exploited for condensation reactions of acid, acid chloride, and β-keto esters into benzimidazoles, benzoxazoles, and benzothiazoles.[7] However, a generalized method for the construction of all representative benzofused azole scaffolds from carboxylic acid derivatives has been rarely reported.[8] In this letter, we report a more effective condensation process which gives all of these compound types from resin-bound esters under microwave irradiation conditions.

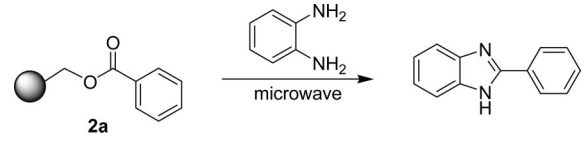
Scheme 1



As a starting point for optimizing reaction conditions for this transformation, resin bound esters **2a**−**d** were prepared from acid chloride by loading on Wang resin. Various conditions including solvent, catalyst, and reaction temperature were examined for microwave-assisted condensation of resin-bound ester **2a** with 1,2-phenylenediamine to give 2-phenylbenzimidazole, and the results are summarized in Table 1. Among the reaction conditions tested, it was found that stepwise microwave irradiation in the presence of polyphosphoric acid (PPA) in 1-methyl-2-pyrrolidinone (NMP) at 150 °C for 10 min and then at 230 °C for 30 min provided the highest yield of 2-phenylbenzimidazole (Table 1, entry 3). At 150 °C, the reaction was incomplete with a significant amount of **2a** remaining (Table 1, entry 1). At 230 °C, only a trace amount of the product was isolated due to the decomposition of 1,2-phenylendiamine (Table 1, entry 2). The employment of methanesulfonic acid under the same reaction conditions led to a poor yield of the product (Table 1, entry 4). The use of nonpolar solvents was also found to be ineffective for this reaction because of the insufficient solubility of 1,2-phenylendiamine (Table 1, entries 5 and 6).

Intrigued by the above results, we further investigated condensation reaction of four different resin-bound esters with three differently substituted 1,2-phenylendiamines. From the results shown in Table 2,[9] it can be seen that moderate to high yields of the corresponding 2-substituted benzimidazoles were obtained in all cases. 1,2-Phenylenediamine gave the desired products in excellent yield (entries 1, 7, and 10), whereas substituted 1,2-phenylenediamine resulted in moderate to good yields of the products. Unlike other

Table 1. Investigation of the Condensation Reaction of Ester **2a** with 1,2-Phenylenediamine under Microwave Irradiation



entry	catalyst/solvent	temperature/time	yield (%)
1	15%PPA/NMP	150 °C/30 min	20
2	15%PPA/NMP	230 °C/30 min	trace
3	15%PPA/NMP	150 °C/10 min; 230 °C/30 min	94
4	4 equiv CH_3S0_3H/NMP	150 °C/10 min; 230 °C/30 min	5
5	15%PPA/1,2-$Cl_2C_6H_6$	150 °C/10 min; 230 °C/30 min	0
6	1M $AlCl_3$/nitrobenzene[a]	150 °C/10 min; 230 °C/30 min	0

[a] Reaction mixture was decomposed.

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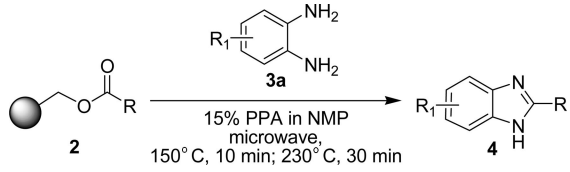
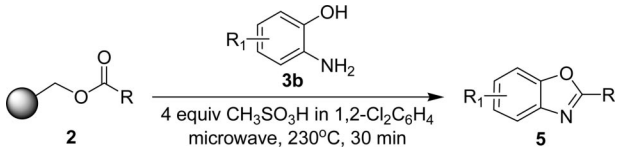
Table 2. Synthesis of Benzimidazoles (**4**) under Microwave Conditions[a]



entry	ester (**2**)	R_1	product[b] (% yield)	entry	ester (**2**)	R_1	product[b] (% yield)
1	**2a**	H	**4a** (94)	7	**2c**	H	**4g** (96)
2	**2a**	4-Me	**4b** (67)	8	**2c**	4-Me	**4h** (76)
3	**2a**	4-F	**4c** (92)	9	**2c**	4-F	**4i** (58)
4	**2b**	H	**4d** (75)	10	**2d**	H	**4j** (92)
5	**2b**	4-Me	**4e** (47)	11	**2d**	4-Me	**4k** (76)
6	**2b**	4-F	**4f** (69)	12	**2d**	4-F	**4l** (63)

[a] All reactions were carried out on a 0.3 mmol scale of ester **2** with 4 equiv of 1,2-phenylenediamine **3a** in 3 mL of NMP. [b] Isolated yield.

Table 3. Synthesis of Benzoxazoles (**5**) under Microwave Conditions[a]



entry	ester (**2**)	R_1	product[b] (% yield)	entry	ester (**2**)	R_1	product[b] (% yield)
1	**2a**	H	**5a** (96)	9	**2c**	H	**5i** (96)
2	**2a**	3-Me	**5b** (71)	10	**2c**	3-Me	**5j** (90)
3	**2a**	5-Me	**5c** (74)	11	**2c**	5-Me	**5k** (62)
4	**2a**	4-Cl	**5d** (83)	12	**2c**	4-Cl	**5l** (84)
5	**2b**	H	**5e** (84)	13	**2d**	H	**5m** (83)
6	**2b**	3-Me	**5f** (63)	14	**2d**	3-Me	**5n** (59)
7	**2b**	5-Me	**5g** (71)	15	**2d**	5-Me	**5o** (74)
8	**2b**	4-Cl	**5h** (51)	16	**2d**	4-Cl	**5p** (75)

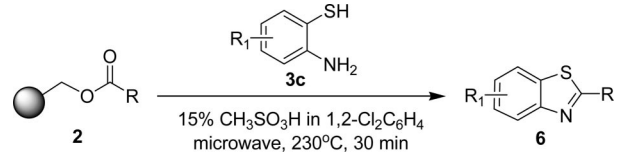
[a] All reactions were carried out on a 0.3 mmol scale of ester **2** with 4 equiv of 2-aminophenol **3b** and 4 equiv of methanesulfonic acid in 3 mL of 1,2-dichlorobenzene. [b] Isolated yield.

esters, nicotinate ester **2b** was converted to the products in moderate yields (entries 4−6).

In exploring the scope of this method for the synthesis of other benzofused azoles, microwave-assisted condensation reaction of resin-bound esters **2** with 2-aminophenols **3b** into the corresponding benzoxazoles **5** was attempted (Table 3). Under the above conditions, 2-phenylbenzoxazole was obtained from ester **2a** in low yield due to the decomposition of 2-aminophenol. However, the reactions were found to proceed readily to the corresponding benzoxazoles in 1,2-dichlorobenzene. The microwave irradiation of resin-bound ester **2a** with 4 equiv of 2-aminophenol in the presence of 4 equiv methanesulfonic acid in 1,2-dichlorobenzene at 230 °C for 30 min provided 2-phenylbenzoxazole **5a** in 97% yield. As shown in Table 3, most of desired benzoxazoles were obtained in good to high yield. 3-Methyl-2-aminophenol gave a slightly lower yield of the products with cyclic esters presumably because of steric demand during the condensation reaction (entries 2, 6, and 14). As found in benzimidazole preparation, nicotinate ester gave moderate yield of desired benzoxaoles (entries 5−8).

Finally, microwave-assisted condensation of resin-bound esters with 2-aminothiophenols to the corresponding benzothiazoles **6** was studied (Table 4). The condensation of ester with 2-aminothiophenol (4 equiv) in 15% of methanesulfonic acid in 1,2-dichlorobenzene system gave highest yield of 2-phenylbenzothiazoles (Table 4, entry 1). Most esters **2** including nicotinate ester were converted to the corresponding benzothiazoles **6** in high yield. Interestingly with even less nucleophilic 4-trifluoromethyl-2-aminothiophenol, the condensation reaction also gave the desired products in good yield (entries 3, 6, 9, and 12).

Table 4. Synthesis of Benzothiazoles (**6**) under Microwave Conditions[a]



entry	ester (**2**)	R_1	product[b] (% yield)	entry	ester (**2**)	R_1	product[b] (% yield)
1	**2a**	H	**6a** (93)	7	**2c**	H	**6g** (90)
2	**2a**	4-Cl	**6b** (68)	8	**2c**	4-Cl	**6h** (72)
3	**2a**	4-CF_3	**6c** (81)	9	**2c**	4-CF_3	**6i** (74)
4	**2b**	H	**6d** (88)	10	**2d**	H	**6j** (93)
5	**2b**	4-Cl	**6e** (71)	11	**2d**	4-Cl	**6k** (74)
6	**2b**	4-CF_3	**6f** (70)	12	**2d**	4-CF_3	**6l** (72)

[a] All reactions were carried out on a 0.3 mmol scale of ester **2** with 4 equiv of 2-aminothiophenol **3c** in 15% of methanesulfonic acid in 3 mL of 1,2-dichlorobenzene. [b] Isolated yield.

In conclusion, an efficient method for solid-phase synthesis of benzimidazoles, benzoxazoles, and benzothiazoles libraries by microwave-assisted condensation of resin-bound esters with 1,2-phenylenediamines, 2-aminophenols, and 2-aminothiophenols was developed. The microwave irradiation proved highly effective for these condensation reactions which proceeded with short reaction times.

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Note Added after ASAP Publication. This paper was published ASAP on June 12, 2008 with errors in Table 1, entries 5 and 6. The corrected version of the paper was published ASAP on June 17, 2008.

Supporting Information Available. Experimental procedure and compound characterization data: Copies of ^{1}H and ^{13}C NMR for new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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(9) General experimental procedure: A 5 mL Biotage vial containing a magnetic stirring bar was charged with ester **2** (300 mg, 0.3 mmol) and 1,2-phenylenediamine **3a** (60 mg, 1.2 mmol) in 15% PPA in NMP (3 mL).The vial was sealed and the resulting suspension was heated in the Biotage Initiator Synthesizer at 150°C for 10 min and then 230°C for 30 min. The reaction mixture was cooled and poured into saturated $NaHCO_3$ solution and filtered through a celite pad. The organic layer was concentrated and the remaining residue was purified by short silica gel column (ethyl acetate:hexane 2:1) to give the pure product.

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