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마이크로웨이브 반응조건에서 염화 테트라부틸암모늄을 촉매로 이용한 치환된 Benzimidazole화합물들의 합성

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Tetra Butyl Ammonium Chloride Catalyzed Synthesis of Substituted Benzimidazoles under Microwave Conditions

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요약. TBACl (10 mol %) 를 촉매로 사용하여 치환된benzimidazoles을 합성하는 간단하고 효율적인 합성방을 개발하였다.
주제어: 마이크로웨이브, TBACl, Benzimidazole, 톨루엔

ABSTRACT. TBACl (10 mol %) was found to be a useful catalyst for the synthesis of substituted benzimidazoles. The method was proved to be simple, convenient and the product was isolated with good yield.
Keywords: Microwave, TBACl, Benzimidazole, Toluene

INTRODUCTION

Compounds that exhibit the functionality of benzimidazoles have been used in the area of pharmaceuticals.[1-5] These high profile applications of compounds with benzimidazoles structures have prompted extensive studies for their synthesis. Methods of benzimidazole synthesis include the condensation of 1,2-phenylenediamine with carboxylic acids or their derivatives in the presence of strong acids such as poly phosphoric acids.[6] In another method, benzimidazole has been prepared by classical cyclocondensation of 1,2-phenylene diamine with the corresponding aldehydes under oxidative conditions.[7-8] Recent publications have shown synthesis of substituted benzimidazole via tosylation of N-aryl amidoxime,[9] synthesis of benzimidazole using air as an oxidant[10] and using microwave irradiation.[11] However, most of the process suffers limitations such as low yields, tedious workup procedure and co-occurrences of several side reactions. As a consequence, the introduction of novel method and further work on technical improvements to overcome the limitation is still an important experimental challenge.

In continuation of our research work on the development of useful synthetic methodologies, we have observed that benzimidazole can be synthesized efficiently by treatment of o-phenylenediamine with carboxylic acid using Tetra butyl ammonium chloride (TBACl) in good yields. Phase transfer catalyst has been recognized as a convenient and highly useful synthetic tool in both academia and industry because of several advantage of PTC (operational simplicity, mild reaction conditions with aqueous media and environmental consciousness, suitability for large scale reactions, *etc.*), which meet the current requirement for practical organic synthesis.[12-17] In this study we wished to report the use of a phase transfer catalyst for the synthesis of various benzimidazoles. During the research, we found that TBACl could catalyze the synthesis of benzimidazole in a selected pair of solvents.

EXPERIMENTAL

General

^{1}H NMR spectra were recorded on a Bruker 300-MHz spectrometer in the solvent indicated with TMS as the internal standard. All chemical shifts are given in ppm and the

coupling constants are given in Hz. For column chromatography Kieselgel 60 (ROCC, 0.040 - 0.060 mm) was used. Except TBACl (Spectrochem) and Toluene (Sonia industries), all phenylene- diamines and all carboxylic acids were obtained from Aldrich and used as such.

General experimental procedure

1,2-phenylenediamine (1 eq), carboxylic acid (1 eq) and TBACl (0.1 eq) were taken in a microwave Pyrex tube which was introduced into a Biotage Initiators 60 microwave reactor fitted with a rotational system. Toluene (10 mL) and water (10 mL) were added to it and heated in the microwave at 160 ^{o}C for the time indicated (*Table* 3). Reaction was monitored by TLC. After the completion of the reaction, reaction mixture was cooled to room temperature and ammonia solution was added to the reaction mixture to make alkaline (pH 9 - 10). It was then extracted with ethyl acetate (25 mL × 2) and separated organic layer was dried over Na_2SO_4. Organic layer was filtered and concentrated under vacuum, and the residue was purified by flash column chromatography on silica gel.

RESULT AND DISCUSSION

Early preparations of substituted benzimidazoles from phenylenediamine and carboxylic acids or carboxylic acid derivatives were carried out under vigorous dehydrating conditions.[18] Long reaction times for this reaction have been reduced by the use of microwave heating. During the course of our studies, for the preparation of different benzimidazoles we have tried with different organic solvents in conventional method, but we have not been observed much improvement in the yield and rate of reaction. Finally we have tried a biphasic system by mixing the organic solvent along with water in a microwave and we observed little change in the yield and for further increasing the yield and rate of the reaction. We tried a phase transfer catalyst, (TBACl) and we have got satisfactory yield and reduced the reaction time by using microwave conditions. With the initial success of this reaction, to test the general scope and versatility of this procedure in the synthesis of a variety of substituted benzimidazoles, we examined a number of differently substituted phenylenediamines and different carboxylic acids. We used a standard set of conditions to test this new method. We optimized a simple, microwave-based procedure for the preparation of benzimidazoles by cyclization of o-phenylenediamine and carboxylic acids, (*Scheme* 1) this we have achieved by reducing the reaction time required and enhancing the yield of the process by using phase transfer catalyst. In order to establish the optimum condition for this reaction, the effect of solvent was studied, (*Table* 1) toluene was best among the solvents tested. The best yield was obtained with water/toluene (*Table* 1). Clearly, toluene (entry 4) stands out as the solvent of choice, with its fast conversion and high yield. Next various ratios of TBACl were examined (*Table* 2). TBACl was added in different ratios in different pair of solvents (aqueous phase along with an organic phase at 160 ^{o}C in microwave as shown in the *Table* 1). Very little

***Table* 1.** Effect of solvent in cyclization of o-phenylenediamine and carboxylic acid

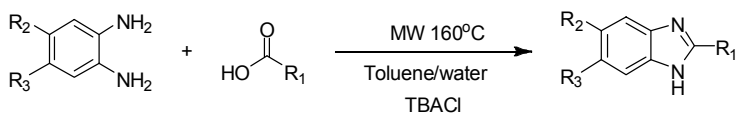
Entry	Solvent[a]	Avg: time(min)*	yield[b]
1	CCl_4	35	35
2	THF	28	42
3	Xylene	40	45
4	**Toluene**	**10**	**89**
5	DMF	25	65
6	Dichloroethane	28	64
7	Benzene	25	70
8	water[d]	90	40
9	None[e]	20	15

[a]Organic solvent/water; [b]Isolated yield after silica gel chromatography; [d]Only in aqueous phase; [e]Solvent free condition; *All reactions carried out with 10% TBACl at 160 ^{o}C.

***Table* 2.** Various ratios of TBACl for the synthesis of benzimidazoles

Entry	TBACl (mol %)	Avg: time (min)	yield[a]
1	0	15	55
2	5	15	70
3	**10**	**15**	**89**
4	20	15	85
5	40	15	85
6	50	15	85
7	100	15	85

[a]All yields refer to isolated product.



Scheme 1. Synthesis of benzimidazoles.

***Table* 3.** Synthesis of benzimidazoles catalyzed by TBACl[a]

Entry	R_1	R_2	R_3	Reaction time (min)	Yields[b] (%)
1	Br	H	H	10	86
2	H	NO_2	H	12	90
3	H	NH_2	H	10	81
4	H	Cl	H	15	89
5	$ClCH_2$	H	H	12	92
6	$CH_3(CH)CH_3$	H	H	15	75
7	CH_3	COOH	H	20	78
8	H	CH_3	CH_3	10	93
9	$(CH_2)_3OH$	H	H	15	80
10	Cl	H	H	17	85
11	C_6H_5	H	H	18	90
12	NO_2PhOCH_2	Br	H	20	92
13	$C_6H_4NH_2$	H	H	20	81
14	C_6H_5	SO_3H	H	17	76
15	$OCH_3C_6H_4$	NO_2	H	23	80
16	H	H	H	12	92

[a]The reaction was carried out with 1.0 eq of phenylenediamine, 1.0 eq of carboxylic acid and 10 mol % TBACl in 10 mL of Toluene and 10 mL of water; [b]Isolated yield after silica gel chromatography.

of the desired product was obtained in the absence of TBACl and the best yield were obtained with 10% TBACl. The study revealed that even 10 mol % of the catalyst was sufficient to carry forward the reaction with minimal time period. The above conditions show that the diamine and acid bearing both electron donating and electron withdrawing substituents gave the desired benzimidazole in good yields. Thus equal moles of phenylenediamines and carboxylic acids were heated to 160 ^oC in Microwave in Toluene/water in presence of TBACl (10 mol %) as phase transfer catalyst.

The products were confirmed by the characterization studies like ^{1}H-NMR, ^{13}C-NMR FT-IR and Mass spectrometry. All the products exhibited physical and spectral properties in accord with the structures.

Table 3 shows both phenylenediamine and carboxylic acid bearing electron donating (entry 3, 6&8) and electron withdrawing (entry 2, 4, 12&15) substituents gave desired benzimidazole in excellent yield.

In conclusion, an easier approach for the synthesis of substituted benzimidazoles has been explored by using TBACl in catalytic amount. The salient features of this method include: comparatively simple procedure, easy purification and high percentage of conversion. Work aimed at investigating further the scope of the reaction is currently being pursued.

The following compounds were prepared in this manner.

2-bromobenzimidazole (Table 3, entry 1): Yield (1.56 g, 86%). The characterization data obtained for 2-bromobenzimidazole are identical to those previously reported in the literature.[19] ^{1}H-NMR data: δ_H (DMSO): 13.2 (1 H, s), 7.52 (2 H, d, J = 1.2), 7.2 (2 H, t, J = 4.0). ^{13}C-NMR data: δ_C (DMSO): 127.2, 122.8. MS, *m*/*z* 198.9.

5-nitrobenzimidazole (Table 3, entry 2): Yield (0.95 g, 90%). The characterization data obtained for 5-nitrobenzimidazole are identical to those previously reported in the literature.[20] ^{1}H-NMR data: δ_H (DMSO): 13.11 (1 H, s), 8.57 (1 H, s), 8.52 (1 H, s), 8.14 (1 H, d, J = 2.0), 7.79 (1 H, d, J = 8.8). ^{13}C-NMR data: δ_C (DMSO): 147.2, 143.0, and 118.0. MS, *m*/*z* 164.0.

5-aminobenzimidazole (Table 3, entry 3): Yield (0.87 g, 81%). ^{1}H-NMR data: δ_H (DMSO): 12.0 (1 H, s), 7.89 (1 H, s), 7.27 (1 H, d, J = 8.4), 6.69 (1 H, d, J = 1.6), 6.52 (1 H, d, J = 2.0), 5.0 (2H, s). ^{13}C-NMR data: δ_C (DMSO): 144.9, 139.9, and 111.9. MS, *m*/*z* 134.2.

5-chlorobenzimidazole (Table 3, entry 4): Yield (0.95 g, 89%). The characterization data obtained for 5-chlorobenzimidazole are identical to those previously reported in the literature.[20] ^{1}H NMR data: δ_H (DMSO): 12.63 (1 H, s), 8.28 (1 H, s), 7.66 (1 H, d, J = 2.0), 7.61 (1 H, d, J = 8.4), 7.23 (1 H, d, J = 2.0). ^{13}C-NMR data: δ_C (DMSO): 163.5, 143.9, 126.6, 122.5. MS, *m*/*z* 153.1.

2-(chloromethyl) benzimidazole (Table 3, entry 5): Yield (1.41g, 92%). ^{1}H NMR data: δ_H (DMSO): 12.6 (1 H, s), 7.59 (2 H, d, J = 1.2), 7.25 (2 H, t, J = 1.2), 4.95 (1 H, s). ^{13}C-NMR data: δ_C (DMSO): 150.0, 138.6, 123.0, 115.7, 38.5. MS, *m*/*z* 167.1.

2-isopropylbenzimidazole (Table 3, entry 6): Yield (1.11 g, 75%). ^{1}H NMR data: δ_H (DMSO): 12.14 (1 H, s), 7.46 (2 H, d, J = 2.4), 7.13 (2 H, t, J = 4.0), 3.37 (1 H, m), 1.35 (6 H, d, J = 7.2). ^{13}C-NMR data: δ_C (DMSO): 160.1, 121.5, 28.8, 21.8. MS, *m*/*z* 161.1.

2-methylbenzimidazole-5-carboxylic acid (Table 3, entry

7): Yield (0.90 g, 78%). The characterization data obtained for 2-isopropylbenzimidazole are identical to those previously reported in the literature.[21] ^{1}H NMR data: δ_H (DMSO): 12.63 (1 H, s), 8.07 (1 H, s), 7.78 (1 H, d, J = 6.8), 7.5 (1H, d, J = 8.0), 2.50 (3 H, s). ^{13}C-NMR data: δ_C (DMSO): 168.48, 154.5, 124.2, 123.2, and 15.2. MS, *m*/*z* 177.1.

5,6-dimethylbenzimidazole (Table 3, entry 8): Yield (0.99 g, 93%). The characterization data obtained for 5, 6-dimethylbenzimidazole is identical to those previously reported in the literature.[21] ^{1}H NMR data: δ_H (DMSO): 12.21 (1 H, s), 8.06 (1 H, s), 7.35 (2 H, s), 2.30 (6 H, s). ^{13}C-NMR data: δ_C (DMSO): 141.41, 130.49, and 20.4. MS, *m*/*z*, 147.2.

2(3-hydroxypropyl)benzimidazole (Table 3, entry 9): Yield (1.3 g, 80%). The characterization data obtained for 2(3-hydroxypropyl)benzimidazole are identical to those previously reported in the literature.[22] ^{1}H NMR data: δ_H (DMSO): 12.2 (1 H, s), 7.50 (2 H, d, J = 33.6), 7.10 (2 H, t, J = 2.8), 4.69 (1 H, s), 3.49 (2 H, t, J = 30.8), 2.86 (2 H, t, J = 7.6), 1.96 (2 H, m). ^{13}C-NMR data: δ_C (DMSO): 155.5, 143.8, 134.8, 121.8, 121.3, 118.5, 111.0, 60.6, 31.3, and 25.0. MS, *m*/*z* 177.1.

2-chlorobenzimidazole (Table 3, entry 10): Yield (1.19 g, 85%). The characterization data obtained for 2-chlorobenzimidazole are identical to those previously reported in the literature.[23] ^{1}H NMR data: δ_H (DMSO): 13.3 (1 H, s), 7.48 (2 H, d, J = 4.4), 7.21 (2 H, t, J = 4.0). ^{13}C-NMR data: δ_C (DMSO): 139.1, 122.8, 120.8, and 108.9. MS, *m*/*z* 153.02.

2-phenylbenzimidazole (Table 3, entry 11): Yield (1.61 g, 90%) The characterization data obtained for 2-phenylbenzimidazole are identical to those previously reported in the literature.[24] ^{1}H NMR data: δ_H (DMSO): 12.93 (1 H, s), 8.2 (2 H, d, J = 0.8), 7.51 (5 H, m), 7.20 (2 H, t, J = 4.8). ^{13}C-NMR data: δ_C (DMSO): 151.7, 130.6, 130.31, 129.4, 126.9. MS, *m*/*z* 195.0.

2-((4-nitrophenoxy)methyl)-5-bromobenzimidazole (Table 3, entry 12): Yield (2.96 g, 92%). ^{1}H NMR data: δ_H (DMSO): 12.95 (1 H, s), 8.24 (2 H, d, J = 6.9), 7.76 (1 H, s), 7.50 (1 H, d, J = 47.1), 7.31 (1 H, d, J = 2.4), 729 (2 H, d, J = 7.2), 5.49 (2 H, s). ^{13}C-NMR data: δ_C (DMSO): 163.4, 150.9, 141.8, 126.3, 125.4, 115.8, 64.7. MS, *m*/*z* 347.7.

2-(2-aminophenyl) benzimidazole (Table 3, entry 13). Yield (1.56 g, 81%). The characterization data obtained for 2-(2-aminophenyl) benzimidazole are identical to those previously reported in the literature.[25] ^{1}H NMR data: δ_H (DMSO): 12.67 (1 H, s), 7.86 (1 H, d, J = 1.2), 7.66 (1 H, d, J = 7.2), 7.52 (1 H, d, J = 7.6), 7.26 (2 H, s), 7.24 (1 H, d, J = 6.4), 7.20 (1 H, t, J = 8.8), 7.18 (1 H, t, J = 8.0), 6.85 (1 H, t, J = 8.0), 6.65 (1 H, t, J = 7.2). ^{13}C-NMR data: δ_C (DMSO): 153.0, 148.7, 134.0, 130.8, 118.6, 116.6, 111.2, and 110.6. MS, *m*/*z* 210.1 [M^+]

2-phenylbenzimidazole-5-Sulphonicacid (Table 3, entry 14): Yield (1.10 g, 76%). ^{1}H NMR data: δ_H (DMSO): 8.2 (2 H, d, J = 1.6), 7.98 (1 H, s), 7.80 (5 H, m). ^{13}C-NMR data: δ_C (DMSO): 150.4, 146.9, 133.8, 132.4, 131.7, 130.1, 128.4, 124.5, 114.0, 111.3. MS, *m*/*z* 275.1 [M^+].

4-nitro-2(4-methoxy phenyl)benzimidazole (Table 3, entry 15). Yield (1.40 g, 80%). The characterization data obtained for 4-nitro-2(4-methoxy phenyl) benzimidazole are identical to those previously reported in the literature.[26] ^{1}H NMR data: δ_H (DMSO): 8.47 (1 H, s), 8.25 (2 H, d, J = 9.2), 8.18 (1 H, d, J = 2.0), 7.82 (1 H, d, J = 8.8), 7.20 (2 H, d, J = 8.8), 3.88 (3 H, s). ^{13}C-NMR data: δ_C (DMSO): 163.02, 154.9, 143.9, 130.0, 119.5, 118.9, 115.3, 114.9, 111.2, and 56.1. MS, *m*/*z* 270.1 [M^+].

Benzimidazole (Table 3, entry 16). Yield (1.0g, 92%). The characterization data obtained for benzimidazole are identical to those previously reported in the literature.[20] ^{1}H NMR data: δ_H (DMSO): 12.52 (1 H, s), 8.25 (1 H, s), 7.62 (2 H, d, J = 2.4), 7.20 (2 H, d, J = 3.2). ^{13}C-NMR data: δ_C (DMSO): 142.4, 138.8, 122.1, and 115.9. MS, *m*/*z* 119.1 [M^+].

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