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Superoxide Ion Promoted Synthesis of 2-Arylbenzimidazoles from Schiff Bases

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Abstract:

Background: Benzimidazoles exhibit a wide range of biological activities, including antiparasitic, antiulcer, antihypertensive, antihistaminic, anticancer, antiemetic and antiinflammatory agents.

Methods: Tetraethylammonium superoxide has been generated *in situ* by the phase transfer reaction of potassium superoxide and tetraethylammonium bromide in dry dimethylformamide at room temperature and subsequently allowed to react with a number of Schiff's bases.

Results: The Synthesis of 2-arylbenzimidazoles from Schiff bases using *in situ* generated tetraethylammonium superoxide in dry DMF, at room temperature.

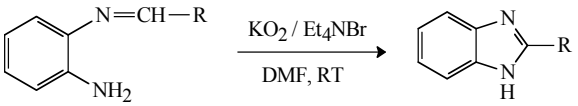
Conclusion: The role of *in situ* generated Et_4NO_2 as an efficient agent to promote the synthesis of 2-arylbenzimidazole from Schiff base has been demonstrated under mild conditions.

Keywords: Benzimidazole, oxidative cyclization, superoxide.

INTRODUCTION

Benzimidazoles exhibit a wide range of biological activities, including antiparasitic, antiulcer, antihypertensive, antihistaminic, anticancer, antiemetic and antiinflammatory agents [1-5]. There exist two general methods for synthesizing 2-substituted benzimidazoles. One is the coupling of *o*-phenylenediamines and carboxylic acids or their derivatives, which often required strong acidic conditions at high temperature or under microwave irradiation [6-11]. The other method involves oxidative cyclization of Schiff bases, derived from the condensation of *o*-phenylenediamines and aldehydes, using various oxidants such as lead tetraacetate [12, 13], nickel peroxide [14], active manganese dioxide [15] and barium manganate [16]. However, second method usually involves use of transition metals that require tedious chromatography purification of the desired product. Recently, some other methods for the preparation of benzimidazole derivatives have been reported [17].

In light of the above and as a part of the ongoing research on superoxide chemistry [18], herein a mild and efficient protocol is reported for the synthesis of 2-arylbenzimidazoles from Schiff bases using *in situ* generated tetraethylammonium superoxide in dry DMF, at room temperature (Scheme **1**).



1a - h **2a - h**

Scheme 1.

RESULTS AND DISCUSSION

Tetraethylammonium superoxide has been generated *in situ* by the phase transfer reaction of potassium superoxide and tetraethylammonium bromide in dry dimethylformamide at room temperature and subsequently allowed to react with a number of Schiff's bases viz., N-benzylidene-*o*-phenylenediamine **1a**, N-*p'*-chlorobenzylidene-*o*-phenylenediamine **1b**, N-*m'*-nitrobenzylidene-*o*-phenylenediamine **1c**, N-*p'*-nitrobenzylidene-*o*-phenylenediamine **1d**, N-*p'*-hydroxybenzylidene-*o*-phenylenediamine **1e**, N-*p'*-methylbenzylidene-*o*-phenylenediamine **1f**, N-*p'*-methoxybenzylidene-*o*-phenylenediamine **1g**, N-2-furylmethylene-*o*-phenylenediamine **1h** to bring out an oxidative cyclization to give the corresponding benzimidazoles **2a-h** in reasonably good to excellent yields (Table **1**).

The reaction was accomplished by using a 3.0 fold molar excess of KO_2 and 1.5 fold molar excess of Et_4NBr with respect to substrate **1**. Generally, the substrate was allowed to react with Et_4NO_2 for 3-6 hrs at room temperature. The reaction was then quenched with cold brine solution followed by work-up to afford the products. The total disappearance of the starting material was checked by thin layer chromatogra

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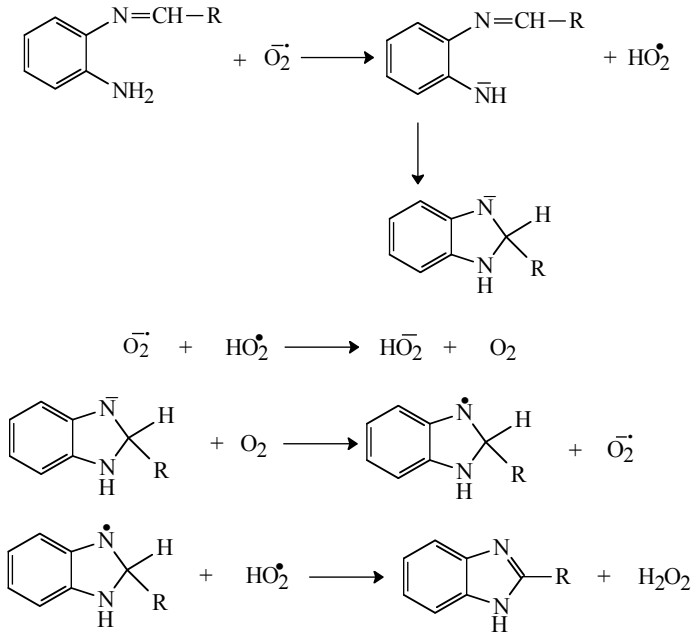
Table 1. Reaction of *in situ* generated Et_4NO_2 with various Schiff bases (1a-h).

Entry	Substituent (R)	Substrate (1)	Product (2)	Yield (%)
A	Ph	**1a**	**2a**	83
B	*p*-ClC_6H_4	**1b**	**2b**	72
C	*m*-$NO_2C_6H_4$	**1c**	**2c**	68
D	*p*-$NO_2C_6H_4$	**1d**	**2d**	80
E	*p*-OHC_6H_4	**1e**	**2e**	81
F	*p*-$CH_3C_6H_4$	**1f**	**2f**	77
G	*p*-$CH_3OC_6H_4$	**1g**	**2g**	74
H	2-Furyl	**1h**	**2h**	69



Scheme 2.

phy (TLC). The identity of all known compounds was confirmed by IR, ^{1}H NMR and comparison with literature spectral and m.p. values [12,13,16,19-21].

Based on product isolation and existing chemistry [22-24] of $O_2^{\bullet}$, a plausible mechanism is outlined for the oxidative cyclization observed (Scheme **2**).

CONCLUSION

In conclusion, the role of *in situ* generated Et_4NO_2 as an efficient agent to promote the synthesis of 2-arylbenzimidazole from Schiff base has been demonstrated under mild conditions.

EXPERIMENTAL

Potassium superoxide and tetraethylammonium bromide were procured from E. Merck, and were used as received. Dry DMF from Aldrich, was stored over molecular sieves (4Å) prior to use. Schiff bases were prepared according to a literature procedure [13]. Melting points were measured in open capillaries and are uncorrected. IR spectra were recorded on a Jasco FT/IR-5300 spectrophotometer. NMR spectra were run on a Jeol AL300 FT-NMR and chemical shift is expressed as δ(ppm), using TMS as internal reference.

General Procedure for the Reaction of *in situ* Generated Tetraethylammonium Superoxide with Schiff Bases 1a-h

Potassium superoxide (0.43 g; 6 mmol) and tetraethylammonium bromide (0.63 g; 3 mmol) were weighted under nitrogen atmosphere using an atmosbag and were transferred into a two-necked round bottom flask, equipped with magnetic stirrer, nitrogen inlet and a Liebig condenser protected by calcium chloride drying tube. Dry dimethylformamide (25 mL) was added to it and the mixture was agitated magnetically for 15 min to facilitate the formation of tetraethylammonium superoxide. Finally, the Schiff base **1a-h** (2

mmol) was admitted to it and the stirring was continued at room temperature for 3-6 hrs in the presence of nitrogen to avoid atmospheric moisture until the complete loss of the starting material was indicated by TLC. After the reaction was over, the mixture was treated with brine solution (20 mL) to decompose the unreacted potassium superoxide. The solution was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extract was washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated to furnish a residue which was passed through silica gel column or recrystallized from ethanol to afford the corresponding benzimidazole **2a-h**.

2-Phenylbenzimidazole (2a)

M.p. 298°C (lit.[16] 299°C); IR (KBr, cm^{-1}) 3452, 3046, 2966, 1444, 1410; ^1H NMR (DMSO-d_6): δ = 12.7 (s, 1H), 7.9 (m, 2H), 7.2-7.3 (m, 5H), 7.1 (m, 2H).

2-(4-Chlorophenyl)benzimidazole (2b)

M.p. 290°C (lit.[18] 288-291°C); IR (KBr, cm^{-1}) 3446, 3040, 1451, 1404; ^1H NMR (DMSO-d_6): δ = 12.6 (s, 1H), 8.2 (d, 2H), 7.6 (m, 2H), 7.4 (m, 2H), 7.1 (m, 2H).

2-(3-Nitrophenyl)benzimidazole (2c)

M.p. 209°C (lit.[13] 207-208°C); IR (KBr, cm^{-1}) 3446, 3065, 1520, 1445, 1358; ^1H NMR (DMSO-d_6): δ = 12.9 (s, 1H), 8.9 (s, 1H), 8.6 (m, 1H), 8.1 (m, 1H), 7.7 (m, 1H), 7.5 (m, 2H), 7.1 (m, 2H).

2-(4-Nitrophenyl)benzimidazole (2d)

M.p. 320-321°C (lit.[19] 318-320°C); IR (KBr, cm^{-1}) 3445, 1628, 1588, 1529, 1356; ^1H NMR (DMSO-d_6): δ = 12.3 (s, 1H), 8.6 (d, 2H), 7.5-7.6 (m, 2H), 7.4 (m, 2H), 7.2 (d, 2H).

2-(4-Hydroxyphenyl)benzimidazole (2e)

M.p. 290°C (lit.[19] 288-290°C); IR (KBr, cm^{-1}) 3563, 3435, 1620, 1465; ^1H NMR (DMSO-d_6): δ = 12.4 (s, 1H), 9.6 (s, 1H), 8.5 (d, 2H), 7.7 (m, 1H), 7.3-7.4 (m, 3H), 7.2 (d, 2H).

2-(4-Methylphenyl)benzimidazole (2f)

M.p. 268°C (lit.[16] 269°C); IR (KBr, cm^{-1}) 3430, 1624, 1455; ^1H NMR (DMSO-d_6): δ = 12.8 (s, 1H), 8.1 (d, 2H), 7.6 (m, 1H), 7.3-7.5 (m, 3H), 7.2 (d, 2H), 2.4 (s, 3H).

2-(4-Methoxyphenyl)benzimidazole (2g)

M.p. 228°C (lit.[18] 228-230°C); IR (KBr, cm^{-1}) 3445, 1627, 1460; ^1H NMR (DMSO-d_6): δ = 12.9 (s, 1H), 7.9 (d, 2H), 7.5-7.7 (m, 2H), 7.3 (m, 2H), 7.2 (d, 2H), 3.8 (s, 3H).

2-(2-Furyl)benzimidazole (2h)

M.p. 288°C (lit.[18] 284-286°C); IR (KBr, cm^{-1}) 3440, 3095, 1624, 1521, 1440, 1358; ^1H NMR (DMSO-d_6): δ = 12.9 (s, 1H), 8.1 (d, 1H), 7.7 (d, 2H), 7.2-7.3 (m, 2H), 6.9-7.1 (m, 2H).

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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