



Preparation of 2(3H)-Benzimidazolone and its Derivative Under Aqueous Condition As a Potential Agent for Antidiabetic Compounds

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A focused library of 2(3H)-benzimidazolone and its derivatives has been synthesized in an attempt to identify their antidiabetic potential. All the products have been synthesized under aqueous conditions in lesser time with better yield and purity. A new effective and convenient method for *in situ* synthesis of five member heterocyclic ring by reaction of phenylene diamine with urea in solvent phase. All the synthesized compounds were characterized by modern spectroscopic techniques.

Key Words: Benzimidazolone, Cyclic urea, Antidiabetic potential, Phenylene diamine, Heterocyclic ring.

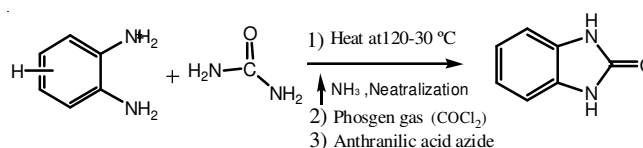
INTRODUCTION

There is an emergent interest over the last many years for the synthesis of benzimidazole-based heterocycles due to its importance in functioning of biologically important molecules in displaying wide range of biological properties^{1,2}. Benzimidazolonic scaffolds and their related cyclic urea derivatives are important heterocyclic building blocks for the species involved in inhibition of aldose reductase, antagonism of neurotransmitter receptors, antiulcer activity³, antimicrobial activity and modulation of ion channels⁴. Such spectrum of biological activity has attracted considerable attention for these compounds. The synthesis of these heterocyclic compounds having privileged structures has been reported in literature by different methods of synthesis, solid phase synthesis, from phosgene gas⁵ and from anthranilic acid azides⁶. After the comprehensive survey, it has been observed that the methods, which are still used are not simple and also give low yield with complex work up of the reaction mixture. The methods that enable the simple and rapid production of these compounds are very useful for the identification of new lead structures and have importance in pharmaceutical industry. Although some advancement in synthetic methods were achieved, but there is no improvement in yields. To improve the yield and simplify the reaction procedure, alternative method is schemed for the preparation of these pharmacological active compounds.

Among the five and six membered nitrogenous heterocyclic compounds the greatest enzyme-inducing activity is found and such properties are observed in these compounds

demonstrating a wide variety of biochemical and pharmacological properties⁷.

There are several synthetic routes to 2(3H)-benzimidazolones⁸ which involve *o*-phenylenediamine as the starting material. In literature it is found that benzimidazolone was synthesized by different methods as shown in **Scheme-I**, but there is no convenient way to achieve better yield by easy workup. These compounds are versatile key intermediates in the synthesis of our target antidiabetic compounds.



Scheme-I: Methods of benzimidazolone preparation (reported in literature)

The structure of the target compound and intermediates were confirmed by using the ¹H and ¹³C NMR, FT-IR, MS and elemental analysis (CHNS) techniques.

EXPERIMENTAL

Melting points of the compounds were determined using Gallenkamp melting point apparatus. FT-IR spectra were recorded on a Hitachi model 270-50 spectrophotometer either as KBr discs or as neat liquids; ¹H NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrophotometer in CDCl₃ solutions using TMS as an internal standard; and EIMS

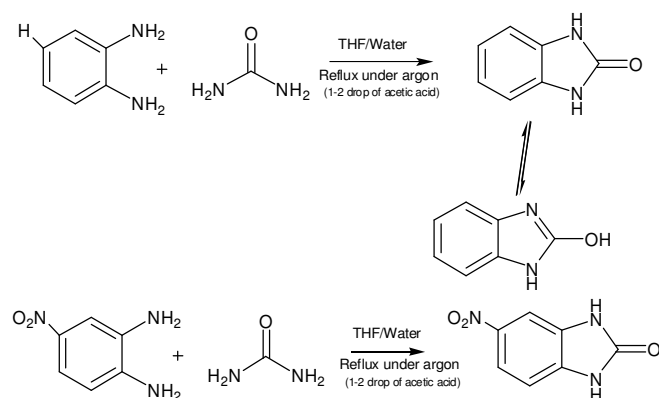
on a MAT-112-S machine at 70 eV. All the reactions were monitored by TLC using Pre-coated Kieselgel-60 HF₂₅₄ TLC plates.

Synthesis of 2(3*H*)-benzimidazolone: 1,2 Phenylene diamine (0.05 mol) and urea (0.015 mol) were placed in a 100 mL round bottom flask, dissolved in 25 % THF/water solution and stir vigorously, then added 1-2 drops of acetic acid as a catalyst. The reaction mixture was refluxed on oil bath at 100-120 °C for 4.5 h and then for 0.5 h at 135 °C to remove the remaining ammonia gas. Completion of the reaction was continuously checked by TLC. After completion of the reaction, the mixture was stayed for a long time near 5 h at room temperature. The resulting precipitates were filtered and washed with ethanol thrice and then recrystallized in methanol. The precipitates were filtered, dried (anhydrous MgSO₄) for overnight. The product obtained was pale yellow in colour with good yield and sharp m.p. Elemental analysis: C₇H₆N₂O (134): calcd. C 62.68, H 4.51, N 20.89; found C 62.70, H 4.53, N 20.91.

Synthesis of 5-nitro-2(3*H*)-benzimidazolone: 5-Nitro-1,2-phenylene diamine (0.05 mol) and urea (0.015 mol) were placed in a 100 mL round bottom flask, dissolved in 25 % THF/water solution and stir vigorously, then added 1-2 drops of acetic acid as a catalyst. The reaction mixture was refluxed on oil bath at 100-120 °C for 4.5 h and then for 0.5 h at 135 °C to remove the remaining ammonia gas. Completion of the reaction was continuously checked by TLC. After completion of the reaction, the mixture was stayed for a long time near 5 h at room temperature. The resulting precipitates were filtered and washed with ethanol 3 times and then recrystallized in methanol. The precipitates were filtered, dried (anhydrous MgSO₄) for overnight. The product was yellowish brown in colour. Elemental analysis: C₇H₅N₃O₃ (179.13): calcd. C 46.92, H 2.81, N 23.46; found C 46.88, H 2.86, N 23.54.

RESULTS AND DISCUSSION

2-(3*H*)-Benzimidazolone and its derivative 5-nitro-2(3*H*)-benzimidazolone were synthesized in liquid phase of THF/water by the reaction of *o*-phenylene diamine with urea in the presence of acetic acid as a catalyst as shown in **Scheme-II**. The contrasting results were obtained by this attempt as compared to reported methods. A number of such compounds with different substitution patterns have been synthesized^{9,10} to check their medicinal properties.



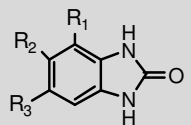
Scheme-II: Synthesis of 2(3*H*)-benzimidazolone and 5-nitro-2(3*H*)-benzimidazolone

If comparison is made between the synthetic route available in literature and new proposed method, very encouraging results are achieved and it is found to be a very facile method for preparation of biological active benzimidazolone and its derivative.

The methods found in literature to obtain benzimidazolone by the reaction of phosgene with *o*-phenylenediamine has some disadvantages due to formation of hydrochloric acid, which requires special safety arrangements due to its toxic nature. Similarly the method with urea in solid phase reaction has also some disadvantages, like the use of high temperature, continuous removal of ammonia gas and difficulty in stirring the reaction mixture.

Discrepancies have been eliminated in our proposed new and convenient method for the preparation of benzimidazolone with better yield. The products obtained in result of this most promising synthetic approach are in good yield (Table-1).

TABLE-1
PHYSICAL DATA OF 2(3*H*)-BENZIMIDAZOLONES
AND 5-NITRO-2(3*H*)-BENZIMIDAZOLONE

						
Entry	Compound name	R ₁	R ₂	R ₃	Yield ^a (%)	m.p. (°C)
1	2(3 <i>H</i>)-benzimidazolones	H	H	H	93.7	310
1	5-Nitro-2(3 <i>H</i>)-benzimidazolone	H	NO ₂	H	87	306

^aGiven yield after column chromatography; R_f value = 42 (in pure ethyl acetate)

The structures of all the synthesized compounds were established by modern spectroscopic techniques and purity ascertained by elemental analysis which supports the idea of this work. The reaction **Scheme-II** elaborates the synthesis method.

The FT-IR spectra showed a bond at 1740 cm⁻¹ and 1110 cm⁻¹ for -NCO stretching and C-H aromatic vibration as shown in Table-2. On the other hand when H is replaced by NO₂ group at position No. 5 of benzene ring then it is observed an Ar-NO₂ asymmetric stretching at 1520 cm⁻¹ which give the clear indication of introduction of -NO₂ group as shown in Table-3.

In ¹H-NMR spectra of 2(3*H*)-benzimidazolone, signals for NH protons were observed in a downfield region in the range of 10.59 ppm. The protons H 4, 5, 6, 7 are appeared at

TABLE-2
FT-IR SPECTRAL DATA OF
2(3*H*)-BENZIMIDAZOLONES WHEN R=H

Entry	Functional group behaviour	ν (cm ⁻¹)
1	-NCO stretching	1740
2	C-H aromatic vib	1110
3	C-H vib deformation	830-880
4	C=C aromatic vib	1385-1395
5	=C-H aromatic stretching	3182-3190
6	-NH free group	3250-3400
7	C=O overtone	3350-3400

TABLE-3
FT-IR SPECTRAL DATA OF
2(3H)-BENZIMIDAZOLONES WHEN R=NO₂

Entry	Functional group behaviour	ν (cm ⁻¹)
1	-NCO stretching	1745
2	Ar-NO ₂	1525-1520
2	C-H aromatic vib	1110
3	C-H vib deformation	880-830
4	C=C aromatic vib	1395-1385
5	=C-H aromatic stretching	3190-3182
6	-NH free group	3400-3250
7	C=O overtone	3400-3350

6.91 ppm. In ¹³C NMR the signal in the range of 155.72 ppm was assigned to the carbonyl carbon. Carbon 4,5,6,7 appeared in the rang of 119-123 ppm (Fig. 1).

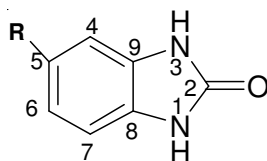


Fig. 1. Representation of benzimidazolone structure with carbon numbering

¹H NMR of 2(3H)-benzimidazolone and 5-nitro-2(3H)-benzimidazolone are shown in Tables 4 and 5 showed that the protons of H-1 and H-3 resonated in the region of 10.7 ppm and 11.40 ppm as singlet. The H-5 of 2(3H)-benzimidazolone was replaced by NO₂ group and it may change the chemical shift pattern of neighboring protons.

TABLE-4
¹H-NMR SPECTRAL DATA (DMSO) OF 2(3H)-
BENZIMIDAZOLONES WHEN R=H

Entry	No. of proton	Chemical shift δ (ppm)	Multiplicity
1	H-1,3	10.7	2H, s
2	H-4, 5, 6, 7	6.90	4H, s

TABLE-5
¹H-NMR SPECTRAL DATA (DMSO) of
2(3H)-BENZIMIDAZOLONES WHEN R=NO₂

Entry	No. of proton	δ (ppm)	Multiplicity	Coupling constant (J Hz)
1	H-1,3	11.40	2H, s	—
2	H-4	8.26	1H, dd	$J_{4,6} = 2.05$ (meta)
3	H-6	7.87	1H, d	$J_{6,7} = 8.75$ (ortho) $J_{6,4} = 2.01$ (meta)
4	H-7	7.68	1H, d	$J_{7,6} = 8.53$ (ortho)

The ¹³C NMR spectra of both the compounds showed that carbonyl carbon of heterocyclic ring appeared at 156 ppm and change in shift of C-5 is observed in case of 5-nitro-2(3H)-benzimidazolone from 121 ppm to 142 ppm listed in Tables 6 and 7, which indicate the shift towards down field region due to presence of electron withdrawing -NO₂ group.

In ¹H NMR spectra of 5-nitro-2(3H)-benzimidazolone. It is also observed the signal of H 4, 6, 7 appeared at different chemical shifts due to presence of -NO₂ group at 5-position

in their neighbor. Thus, the proton H-4 resonated at 8.26 ppm as doublet with coupling constant of 2.03 Hz and H-6 resonated at 7.87 ppm as a doublet of doublet with ortho coupling constant of 8.75 Hz and meta coupling constant of 2.01 Hz. The other proton H-7 resonated at 7.68 ppm as a doublet with coupling constant 8.53 Hz.

TABLE-6
¹³C NMR SPECTRAL DATA (DMSO) of 2(3H)-
BENZIMIDAZOLONES WHEN R=H

Entry	No. of ¹³ C	Chemical shift δ (ppm)
1	C4, 7	109
2	C5, 6	121
3	C8, 9	130
4	C2	156

TABLE-7
¹³C-NMR SPECTRAL DATA (DMSO) OF 2(3H)-
BENZIMIDAZOLONES WHEN R=NO₂

Entry	No. of ¹³ C	Chemical shift δ (ppm)
1	C2	155.91
2	C4	105.00
3	C5	141.70
4	C6	109.00
5	C7	119.00

In ¹³C NMR the signal in the range of 155.91 ppm was assigned to the carbonyl carbon and for carbon No. 5 of C-NO₂ group of aromatic ring was at 141.70 ppm. In the compound 5-nitro-2(3H)-benzimidazolone due to the presence of -NO₂ group at 5-position the chemical environment of C 4, 6, 7 was changed. Thus C-4 resonated at 105, C-6 at 109 ppm and C-7 at 119 ppm.

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