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# A NOVEL AND FACILE ONE STEP PROCEDURE FOR THE SYNTHESIS OF 2-SUBSTITUTED BENZIMIDAZOLES FROM O-NITRO ANILIDES IN AQUEOUS MEDIA

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## ABSTRACT

A new method for the synthesis of 2-substituted N-H benzimidazoles was achieved in one step by reaction with $Na_2S_2O_4$ via a reductive cyclo dehydration of o-nitro anilides in water. It was observed that Methanol or Ethanol could also be used as co-solvent. This method provides facile access to a series of 2-substituted N-H benzimidazoles (**la-ln**) containing various functional groups in good to excellent yields.

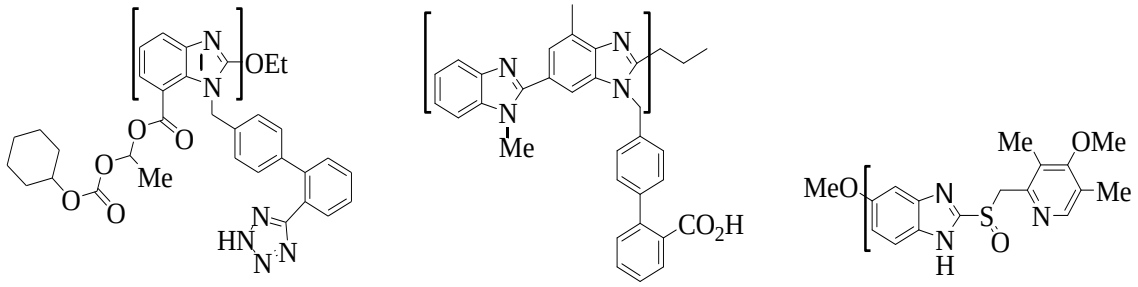
**KEY WORDS:** Benzimidazoles, water, cyclodehydration, sodium dithionite.

## 1. INTRODUCTION

Heterocyclic compounds are known to play an important role in drug invention, since the majority of therapeutic drugs contain a heterocyclic unit. Within the vast range of heterocyclic, benzimidazole privileged scaffolds have shown potential application in a variety of pharmacological targets[1]. The most prominent benzimidazole compound in nature is *N*-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin $B_{12}$.[2] Benzimidazoles are of wide interest because of their diverse biological activity and clinical applications, such as antiviral (Hep-c, HIV etc), analgesics (opioids, cannabinoids), antispasmodic, antihistaminic, anti tumor, antimicrobial, and anti fungal activities, etc.

The substituted benzimidazoles have been reported as valuable bio active structures, such as specific angiotension II receptor type 1 selective antagonists[3], for example, the anti hypertensive marketed under trade names Atacand (candesartan) and Micardis (telmisartan),

potent inhibitors of Parietal cell proton pump, the H+/K+ ATPase, example anti ulcers with trade name Nexium (esmeprazole), a proton pump inhibitor used to treat peptic ulcers and gastro esophageal reflux disease (Figure 1).




Candesartan Telmisartan Eso meprazole

**Figure 1.** The drugs that contain benzimidazole pharmacophore

Undoubtedly, benzimidazoles are important scaffolds. Hence substantial efforts have been made to search for new synthetic strategies, which could render accessible chemistry space currently not attainable by existing methods and would be of considerable importance to the synthetic chemist. However, methods to prepare substituted benzimidazoles have tremendously increased during the last few years.

The most popular methods to assemble benzimidazoles involve the condensation of o-aryldiamines and aldehyde in refluxing nitrobenzene[4], the condensation of o-aryl diamines with carboxylic acids or their derivatives in the presence of strong acids such as PPA or mineral acids[5] and thermal. Direct condensation of o-aryldiamines and aldehydes is not a good synthetic reaction, as it is well known to yield a complex mixture of 1, 2-disubstituted benzimidazoles, the bis anil and dihedral benzimidazoles as the main side products.[7] In this case, however, the addition of a transition metal, namely cupric acetate, mercuric oxide or lead tetra acetate allows a partial selective synthesis of benzimidazoles.[8]

An other method is a two step procedure, including oxidative cyclo dehydrogenation of Schiff bases prepared in turn by condensation of o-phenylene diamines with aldehydes. Various oxidants and catalysts such as sulfamic acid[7], molecular iodine[9], DDQ[10], oxone[11], $FeCl_3.6H_2O$[12], $In(OTf)_3$[13] and $KHSO_4$[14] have been used. In recent years, solvent free synthesis of benzimidazoles under microwave irradiation using KSF clay[15], $Yb(OTf)_3$[16] and metal

halide supported alumina[17] have been reported. Unfortunately, despite the reported efficiency in some of the published methods, a few of these suffer from one or more disadvantages such as drastic reaction conditions, low yields, tedious work up procedure and co-occurrence of several side reactions.

Herein, we report a new method for the preparation of benzimidazoles using single substrate, i.e. o-nitro anilides which on reaction with sodium dithionite through reductive cyclodehydration offer added advantages of no by-product formation, selective 2-substituted benzimidazoles formation, use of cheap reagent and water as solvent.

## 2. RESULTS AND DISCUSSIONS

### 2.1. Synthetic results

The results of in situ reduction and cyclodehydration of a variety of o-nitro anilides are summarized in table 1. The reaction of reductive cyclodehydration is carried out at temperature ranging from 80-100 °C. A co-solvent is selected from alcohols such as methanol; ethanol can also be used to increase the solubility of the organic compounds. Water and water: alcohol systems ensured fast conversion, high yields and less toxicity.Sodium dithionite is added to the heating reactant solution in portions to minimize its spontaneous decomposition in aqueous solution to chiefly thiosulfate and sulfite. There is abundant evidence that $S_2O_4^{-2}$ rapidly fragments in aqueous solution. The kinetic schemes are complicated and the product balances are often not complete. In neutral or mild acidic solution eq.2 and eq.3 have been suggested as important contributors to the overall decomposition[18].

$$S_2O_4^{-2} + H_2O \longrightarrow HSO_2^- + HSO_3^- \qquad \text{eq.2}$$

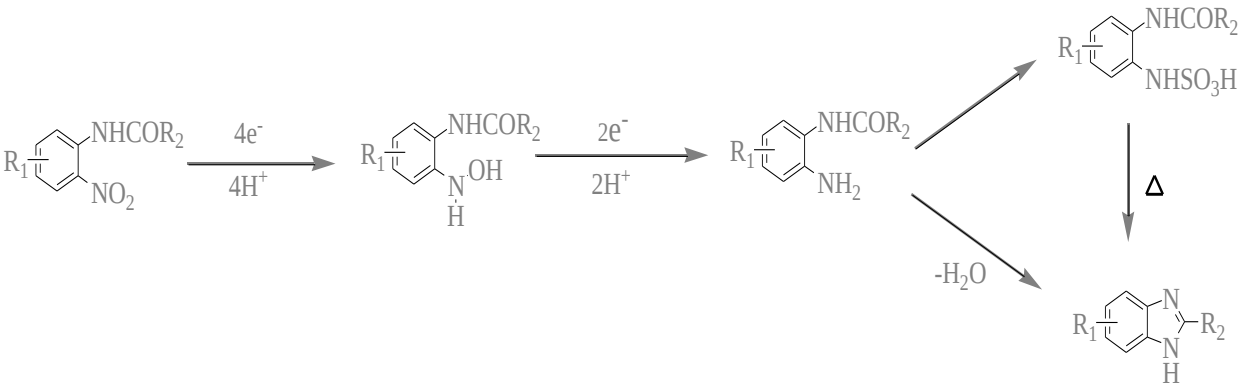
$$HSO_2^- + S_2O_4^{-2} \longrightarrow HSO_3^- + S_2O_3^{-2} \qquad \text{eq.3}$$

Decomposition as shown in eq.3 could account for the need of 3.5 equivalents necessary for complete reduction of nitro compounds.

### 2.2. Mechanism of reductive cyclo dehydration

Sodium dithionite is a very inexpensive but efficient reducing agent which acts as a single electron transfer donor and it has been reported to reduce aryl nitro groups to aryl amines via hydroxylamine by a six electron mechanism[19] (Scheme 1).

Sche me 1.




During benzimidazole formation from o-nitro anilides, we could detect and isolate o-amino anilide and o-amino sulphonic anilide before formation of benzimidazoles. Our initial results showed that when a solution of o-nitro anilide in water was treated with 3.5 equivalents of solid sodium dithionte at 80°C and then the reaction temperature was increased to 100 °C, formation of 2-substituted benzimidazole derivatives took place in a straight forward manner (table1) via reductive cyclo dehydration in 12-18 hrs. Slightly longer reaction time (19-20h) was necessary for some derivatives (**1d, 1h, 1i, 1l**) in order to drive the reaction to completion.

The products were easily isolated in good yields and high purity by filtration, after cooling and neutralizing (slightly basic pH 7.5-8.0) the reaction mixture with aqueous ammonia or by silica gel flash chromatography when the products did not precipitate.

The chemistry worked well with the formation of simple 2-alkyl (**1a-1d, 1m, and 1n**) and 2-aryl (**1e**) substituted benzimidazoles. Substituted o-nitro anilides also performed well (**1f-1l**). The present methodology could be very useful in telmisartan synthesis in milligram to multigram scale (Figure 2).

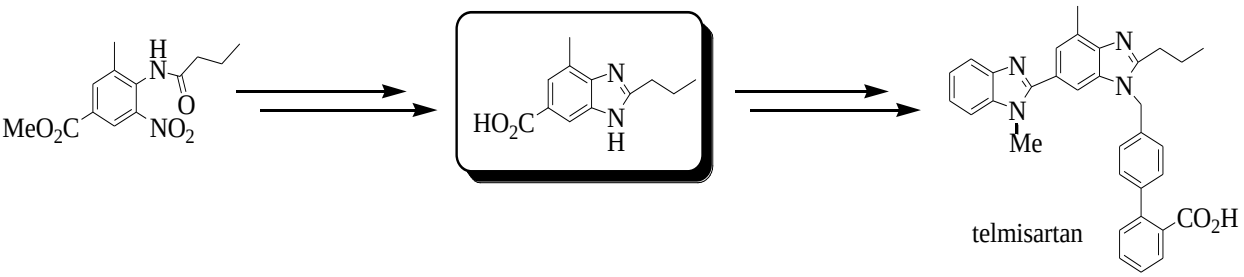
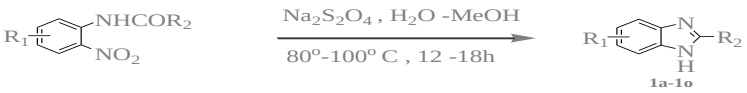



**Figure2.** Benzimidazole formation-a key step in telmisartan synthesis

**Table 1.** Synthesis of 2-substituted N-H benzimidazoles




1a-1o

| Entry | $R_1$ | $R_2$ | Product | Reaction time | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | H | $CH_3$– | 1a | 12h | 87 |
| 2 | H | Cl-$CH_2$– | 1b | 14h | 84 |
| 3 | H | $CH_3$-$CH_2$-$CH_2$– | 1c | 15h | 83 |
| 4 | H | $(CH_3)_3CH$– | 1d | 18h | 91 |
| 5 | H | Ph– | 1e | 12h | 80 |
| 6 | 6 -Cl[b] | $CH_3$– | 1f | 14h | 86 |
| 7 | 6-Br[b] | $CH_3$-$CH_2$-$CH_2$-$CH_2$– | 1g | 14h | 85 |
| 8 | 4 -$OCH_3$[b] | Ph– | 1h | 20h | 83 |
| 9 | 6 -$CH_3$[b] | $CH_3$– | 1i | 19h | 82 |
| 10 | 4 -$CH_3$[b],6 -COOH [b] | $CH_3$-$CH_2$-$CH_2$– | 1j | 17h | 88 |
| 11 | 4 -$CH_3$[b],6 -$COOCH_3$[b] | $CH_3$-$CH_2$-$CH_2$– | 1k | 17h | 95 |
| 12 | 6 -F[b] | $CH_3$-$CH_2$-$CH_2$-$CH_2$– | 1l | 18h | 71 |
| 13 | H | $CH_3$-$CH_2$– | 1m | 13h | 81 |
| 14 | H | $CH_3$-$CH_2$-$CH_2$-$CH_2$– | 1n | 14h | 87 |
| 15 | H | H | 1o | 14h | 95 |

[a]Isolated yields. All compounds produced satisfactory $^1$H NMR and Mass spectra.

[b]Benzimidazole numbering.

## 3. Experimental section

$^1$H-NMR spectra were recorded on a Bruker, Avance 300MHz spectrometer. Low resolution mass spectra were recorded on a Quattro micro spectrometer with electron spray ionization (ESI). TLC was carried out on EM Science precoated silica gel 60$F_{254}$ plates. Flash column chromatography was performed with EM Science silica gel (230-430 mesh).]

### *General procedure*

A solution of o-nitro anilide (1.0 mmol) in water was treated with solid $Na_2S_2O_4$ (3.5 mmol) at 80°C and the reaction mixture was heated at 100°C for 18 hrs. After reaction completion, it was cooled to room temperature. After removal of co-solvent under reduced pressure, the residue was treated with drop wise addition of 5N aq.$NH_4OH$ (2 ml). A precipitate was immediately formed which was then filtered, washed with water (2x15 ml) and dried under

reduced pressure to afford the desired product in satisfactory purity. Precipitated compounds with lower purity were further purified by flash chromatography on silica gel.

***(2-Pentanamido)phenyl) sulfamic acid,*** Mp: > 300° C $^1$H-NMR (300 MHz, $D_2O$) δ ppm: 7.15-7.42 (m, 4H, ArH), 2.75 (s, 1H, NH), 2.54 (s, 1H, OH), 2.41-2.46 (m, 2H, $COCH_2$), 1.59-1.68 (m, 2H, $CH_2$), 1.29-1.39 (m, 2H, $CH_2$), 0.82-0.91 (m, 3H, $CH_3$); MS (ESI): M=272, found 271 $(M-H)^+$.

***Compound 1a,*** Mp: 174-177$^o$C; $^1$H-NMR (300 MHz, $CDCl_3$) δ 9.08 (br s, 1H, NH), 7.55-7.59 (m, 2H, ArH), 7.22-7.28 (m, 2H, ArH), 2.7 (s, 3H, $CH_3$); MS (ESI): M=132, found 131 $(M-H)^+$.

***Compound 1b,*** Mp: 146-147$^o$C; $^1$H-NMR (300 MHz, $CDCl_3$) δ 9.08 (br s, 1H, NH), 7.65-7.59 (m, 2H, ArH), 7.24-7.28 (m, 2H, ArH), 3.7 (s, 2H, $CH_2$); MS (ESI): M=166, found 167 $(M+H)^+$.

***Compound 1c,*** Bp: 152-154$^o$C; $^1$H-NMR (300 MHz, $CDCl_3$) δ 8.48 (br s, 1H, NH), 7.22-7.60 (m, 4H, ArH), 2.94 (t, 2H, *J* = 8.3 Hz, $CH_2$), 1.64-1.94 (m, 2H, $CH_2$), 0.93-1.09 (m, 3H, $CH_3$); MS (ESI): M=160, found 161 $(M+H)^+$.

***Compound 1d,*** Mp:319-321$^o$C; $^1$H-NMR (300 MHz, $CDCl_3$+DMSO-$d_6$) δ ppm: 9.05 (s, 1H, NH), 7.56 (d, *J* = 7.8Hz, 1H, ArH), 6.99 (d, *J* = 7.8 Hz, 1H, ArH), 6.73 (t, *J* = 7.5Hz, 1H, ArH), 6.64 (d, *J* =7 .5Hz, 1H, ArH), 0.912 (s, 9H, $CH_3$),MS (ESI): M=174, found 175 $(M+H)^+$.

***Compound 1e***, Mp: 289-291$^o$C; 1H-NMR (300 MHz, $CDCl_3$+DMSO-$d_6$) δ ppm: 9.25 (s, 1H, NH), 6.68-8.39 (m, 10H, ArH); MS (ESI): M=194, found 193 $(M-H)^+$.

***Compound 1f,*** Mp:204-205$^o$C; $^1$H-NMR (300 MHz, $CDCl_3$) δ ppm: 8.4 (br s, 1H, NH), 7.58 (s, 1H, ArH), 7.51 (d, *J* = 8.7Hz, 1H, ArH ), 7.23 (d, *J* = 8.4, 1H, ArH ), 2.7 (s, 3H, $CH_3$); MS (ESI): M=166, found 167 $(M+H)^+$.

***Compound 1g***, Mp:139-141$^o$C; $^1$H-NMR (300 MHZ, $CDCl_3$) δ ppm: 8.04 (br s, 1H, NH), 7.69 (s, 1H, ArH), 7.43 (d, *J* = 8.4Hz, 1H, ArH),7.35( d, *J* = 8.4Hz, 1H, ArH), 2.93-2.98 (m, 2H, $CH_2$), 1.62-1.87 (m, 2H, $CH_2$), 1.28-1.43 (m, 2H, $CH_2$), 0.89-0.95 (m, 3H, $CH_3$); MS (ESI): M=253, found 254 $(M+H)^+$.

***Compound 1h***, Mp: 219-221°C; $^1$H-NMR (300 MHz, $CDCl_3$) δ ppm: 10.1 (s, 1H, NH), 6.42-8.51 (m, 8H, ArH), 3.6 (s, 3H, $OCH_3$); MS (ESI): M=224, found 225 $(M+H)^+$.

***Compound 1i,*** Mp:195-196°C; $^1$H-NMR (300 MHz, $CDCl_3$) δ ppm: 8.40(br s, 1H, NH), 7.58 (s, 1H, ArH), 7.51 (d, *J* = 8.7Hz, 1H, ArH), 7.46 (d, *J* = 8.4Hz, 1H, ArH), 2.67(s, 3H, $CH_3$), 2.61(s, 3H, $ArCH_3$) ; MS (ESI): M=146, found 147 $(M+H)^+$.

***Compound 1j,*** Mp: 295-297°C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.81 (br, 2H, NH and COOH), 8.71 (s, 1H, ArH), 7.69 (s, 1H, ArH), 3.71 (s, 3H, $OCH_3$), 2.91 (t, *J* = 7.2 Hz, 2H, $=CH_2$), 2.64 (s, 3H, $ArCH_3$), 1.67-1.95 (m, 2H, $CH_2$), 1.10 (t, *J* = 7.0 Hz, 3H, $CH_3$); MS (ESI): M= 218, found 217 $[M-H]^+$.

## 3. CONCLUSION

In summary, the benzimidazole ring is an important pharmacophore in modern drug discovery. We have demonstrated a versatile and simple one pot procedure for the synthesis of a novel class of exclusively 2-substituted N-H benzimidazoles by sodium dithionite via reductive cyclo dehydration of o-nitro anilides. $Na_2S_2O_4$, used under proper conditions, is an effective, in expensive and safe reagent with regard to explosions. The reactions are performed under water for soluble substrates or otherwise MeOH or EtOH can be used as co solvent. These properties represent advantage over other methods.

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