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Synthesis of 2-amino alcohols from imidazole derivatives: Experimental and *in silico* study

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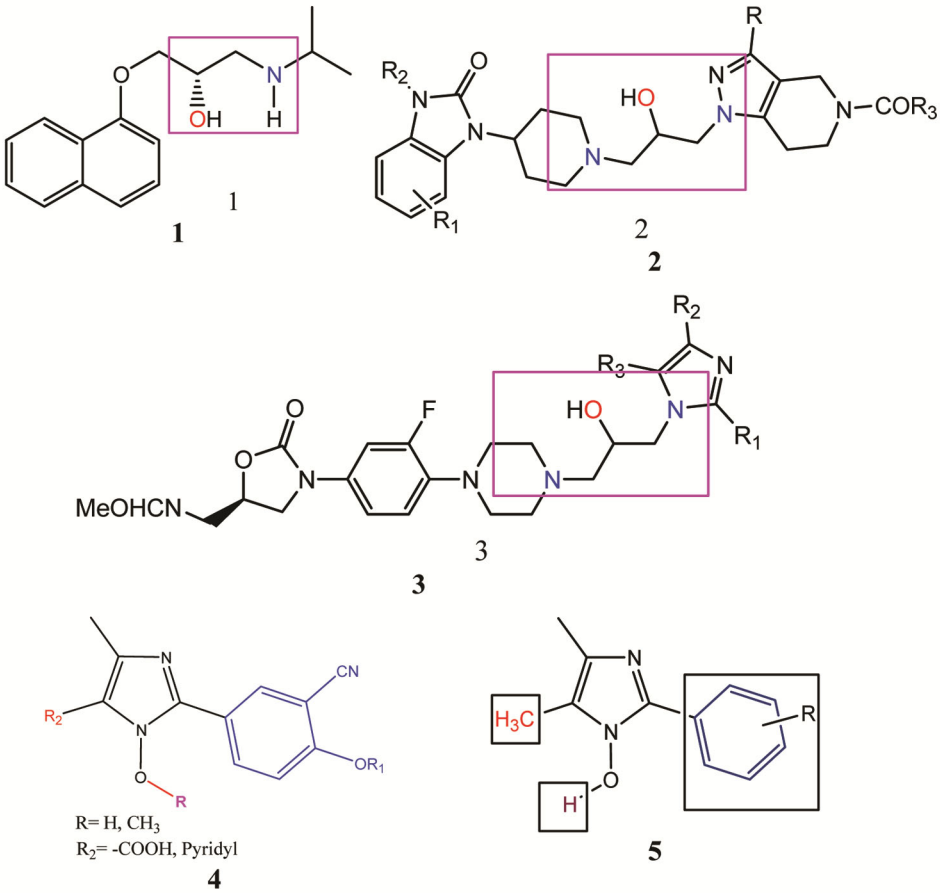
β-Amino alcohols are promising molecules as synthons and also possess significant biological activity. The synthesis of β-amino alcohols mainly involves reaction of epichlorohydrin with various amines. Most of the reported work ignores the side products formed during the course of the reaction. In an ongoing effort to discover newer imidazole-based compounds, which can act as synthon for the synthesis of β-amino alcohols, a novel series of imidazole based epoxides have been designed and synthesized using a mild, efficient, and metal free approach. Starting from N_1-hydroxy-2,4,5-trisubstituted-imidazoles and epichlorohydrin as precursor compounds, a series of molecules have been obtained which may have higher potential to show biological activity. We have come across two different products which might have significant importance for the derivatization leading to the formation of biologically active molecules. To support the experimental findings, we have also performed Density Functional Theory (DFT) calculations. On the basis of the experimental findings and theoretical calculations we have proposed a possible reaction pathway that can lead to the desired product formation.

Keywords: N_1-Hydroxy-imidazole, Oxiranes, Epichlorohydrin, DFT, β-Amino alcohols

Concern has been raised over the increasing trend for drug resistant diseases which had reached 7 lakhs by 2020. If it continues like that it will reach to 10 million per year by 2050, which is more than the number of people is struggling to survive cancer worldwide every year. With respect to the demand there is a drastic reduction of new drugs coming to the market because of several reasons[1]. In this regard development of new anti-microbial drugs play a paramount role.

Multifunctional β-amino alcohols which are well-known versatile synthons and important reagents in the field of organic synthesis has attracted attention in recent years. Because of its common structural features widely present in a vast group of naturally occurring and synthetic molecules and amino acids[2], is a great advantage in the synthesis of several natural products. The presence of amino alcohol moiety and the relative stereo-chemistry are generally important for the biological activity of molecules used as drug or pharmacological agents including antimalarial drugs[2], HIV protease inhibitors[3], adjuvant in cancer treatment[4], inhibitor in multidrug resistance (MDR) in drug resistance cancer cells[5], antiasthmatic agents[6], anti HBV agents[7], antihypertensives[8] and antianginal agents[9]. In addition, they are widely used as β-blockers[8,10] as well as insecticidal agents[11] and chiral auxiliaries[12] which act as key synthetic intermediate for the complex compound and synthetic intermediate for complex compounds and synthetic drug candidates acting as a hydrogen bonding site in a single molecule along with substituents at α and β positions which might be so effective in enantioselective reactions. More reports of synthesis of new amino alcohols have been well documented[13–15]. This pandemic situation led to experiment out some molecules against SARS Covid-19 starting from quinoline to many molecules which are reported to be anti-cancer or anti-HIV agents. Molecules which have 2-amino alcohols are enlisted below (Scheme 1).

Similarly, oxime ethers have drawn lot of interest because of their versatile biological activity. Application of oxime ethers in organic synthesis is well documented. As a synthon, they are utilized for the synthesis of substituted heteroaromatic compounds, amino alcohols[16] and amines[17]. Enantioselective synthesis of arylalkyl amine Calcimimetics R (+)-NPSR-568 and its thio analogous were reported to be effective against hyperparathyroidism[18]. Spirocyclic NH-Azetidines were synthesized starting from oxime ether and an alkyl Grignard reagent[19].



Scheme 1 — Structure of various amino alcohols as HIV inhibitors and active against SARS Covid-2 virus

Recently, catalytic asymmetric cyclopropanation of diazo oxime ethers with olefins was reported[20]. Thus, there is a broad interest in several reactions of oxime ethers with epichlorohydrin in search of new scaffolds of medicinal interest. Angelone *et al.*[21] have reported the synthesis and cardiac activity of new β-blockers. Similarly, Martin and coworkers[22] have synthesized enantiopure isooxazolidin-4-ol by the reaction of (S)-epichlorohydrin with N-hydroxy phthalimide in the presence of base through the formation of an oxime ether analogue.

In general, synthesis of amino alcohol is done simply by opening of epoxide by excess of amines[23]. Though, the acute reaction conditions such as excess necessity of amines, high boiling temperature, prolonged reaction time and use of heavy metal catalysts would hamper the concept of green chemistry, the finding of a simple and compatible method for the synthesis of amino alcohol would be more beneficial.

Recently, catalytic asymmetric cyclopropanation of diazooxime ethers with olefins was reported[20]. Thus, there is a broad interest on several reactions of oxime ethers with epichlorohydrin in the search of new scaffolds of medicinal interest.

Chen and coworkers[24] have reported structure **4** to be a non-purine xanthine oxidase inhibitor which was modified by Zhang *et al.*[25] at the later stage by changing R_2 from a carboxylic acid moiety to pyridyl.

As we have in hand the imidazole derivative **5**[23], which is analogous to **4**; however, there is no report on studies of oxime ether widely. Thus, here we report the first synthesis of imidazole-based oxime ether derivatives with a view to explore their medicinal application and as a synthon for new molecular scaffolds.

Experimental Section

All the chemicals are procured from Sigma Aldrich India Pvt. Ltd. and all the solvents are purchased from Merck and used without further purification unless otherwise stated. All reactions were monitored by thin-layer chromatography (TLC) on Silica gel 60 F_{254} Plate. Column chromatography purifications were

performed with silica gel (100−200 mesh) as well as trituration were performed. Melting points were determined in open capillary tubes on an electrically heated block uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded with Bruker NMR spectrometer operating at 300 MHz and 400 MHz Deuterated chloroform ($CDCl_3$) was used as solvent for the measurements and the calibration performed using the residual peak of the deuterated solvents with TMS as an internal reference (chemical shifts δ in ppm, *J* in Hz). (δ 7.26 for ^{1}H; 77.0 for ^{13}C) in deuterated solvents. High-resolution mass spectra (HRMS) were recorded on a 6520 Agilent Q-TOF instrument using chloroform solution.

General Procedure for synthesis of N_1-Hydroxy-2,4,5-trisubstituted-imidazole, 5

A mixture of diacetyl monoxime (2.525 g 0.025 mol), aromatic aldehyde (0.025 mol), NH_4OAc (2 g) in acetic acid (20 mL) were stirred at RT for 24 h. The resulting solution on neutralization with liq. ammonia gave the product which was filtered, washed with distilled water, and dried[23].

General Procedure for synthesis of 4,5-dimethyl-1-(oxiran-2-ylmethoxy)-2-phenyl-1*H*-imidazole (6), 1-((4,5-dimethyl-2-phenyl-1*H*-imidazol-1-yl)-oxy)-3-methoxypropan-2-ol (7) and 1,3-bis((4,5-dimethyl-2-phenyl-1*H*-imidazol-1-yl)-oxy)-propan-2-ol (8)

To a solution of imidazole derivative (0.01 mol) in methanol (15 mL) a pinch of potassium carbonate was added and the mixture was stirred at 50ºC for 30 min. Epichlorohydrin (0.01 mol) was added over a period of 15 min with stirring. Stirring was continued at 50ºC over a period of 22 h. Then the solvent was evaporated *in vacuo* and the crude mixture was subjected to column chromatography with Hexane: Ethyl acetate (73:27 v/v) as eluent. The first phase was collected and on evaporation of the solvent gave compound **6** (1 g, 0.003 mol). The second phase was collected with the increase in polarity of the solvent mixture with a ratio of Hexane: Ethyl acetate (55:45 v/v) as eluent. Evaporation of the solvent gave the compound **7** (1.6 g, 0.005 mol). The third phase was obtained by running the column with Hexane: ethyl acetate (25:75 v/v). Evaporation of the solvent gave the desired product **8** (0.5 g, 0.001 mol).

Spectral Data

6a: ^{1}H NMR ($CDCl_3$): δ 2.19 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.40 (s, 3H, Ar-CH_3), 2.56(dd, 1H, -CH-CH_2-), 2.84 (dd, 1H, -CH-CH_2-), 3.25 (m, 1H,-CH-), 3.8(dd, 1H, -O-CH_2-CH-), 4.24((dd, 1H, -O-CH_2-CH), 7.23 (d,2H, ArH(m)), 7.42(d, 2H, ArH(o)).

6b: ^{1}H NMR ($CDCl_3$): δ 2.19 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.56(dd, 1H, -CH-CH_2-), 2.84 (dd, 1H, -CH-CH_2-), 3.25 (m, 1H,-CH-), 3.8(dd, 1H, -O-CH_2-CH-), 4.24((dd, 1H, -O-CH_2-CH-), 7.36 (d,2H, ArH(m)), 7.5(d, 2H, ArH(o)).

6c: ^{1}H NMR ($CDCl_3$): δ 2.19 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.56(dd, 1H, -CH-CH_2-), 2.84 (dd, 1H, -CH-CH_2-), 3.25 (m, 1H,-CH-), 3.8(dd, 1H, -O-CH_2-CH-), 4.24((dd, 1H, -O-CH_2-CH-), 7.4 (d,2H, ArH(o)), 7.54(d, 2H, ArH(m)).

6d: ^{1}H NMR ($CDCl_3$): δ 2.19 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.56(dd, 1H, -CH-CH_2-), 2.84 (dd, 1H, -CH-CH_2-), 3.25 (m, 1H,-CH-), 3.73(s, 3H, Ar-OCH_3) 3.8(dd, 1H, -O-CH_2-CH-), 4.24((dd, 1H, -O-CH_2-CH), 6.88(d, 1H, ArH), 6.91(m,1H, ArH), 7.19 (d,1H, ArH), 7.42(d, 1H, ArH).

6e: ^{1}H NMR ($CDCl_3$): δ 2.20 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.56(dd, 1H, -CH-CH_2-), 2.84 (dd, 1H, -CH-CH_2-), 3.25 (m, 1H,-CH-), 3.8(dd, 1H, -O-CH_2-CH-), 4.24((dd, 1H, -O-CH_2-CH-), 7.8 (d,2H, ArH), 8.32(d, 2H, ArH).

6f: ^{1}H NMR ($CDCl_3$): δ 2.21 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.56(dd, 1H, -CH-CH_2-), 2.85 (dd, 1H, -CH-CH_2-), 3.25 (m, 1H,-CH-), 3.85(dd, 1H, -O-CH_2-CH-), 4.26((dd, 1H, -O-CH_2-CH-), 7.61 (t,1H, ArH), 8.15(m, 1H, ArH), 8.36(m, 1H, ArH), 8.89 (s, 1H, ArH).

6g: δ2.19 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.56(dd, 1H, -CH-CH_2-), 2.84 (dd, 1H, -CH-CH_2-), 3.25 (m, 1H,-CH-), 3.82(dd, 1H, -O-CH_2-CH-), 4.24(dd, 1H, -O-CH_2-CH-), 8.15(d, 2H, ArH), 8.69 (d, 2H, ArH).

7a: ^{1}H NMR ($CDCl_3$): δ 2.19(s, 3H, -CH_3), 2.27 (s, 3H, -CH_3), 3.37 (s, 3H, -OCH_3), 3.52 (dd, 2H, -CH_2-), 3.73(s, 3H, Ar-CH_3) 4.04(m, 2H, -CH_2-), 4.15(m, 1H, -CH-), 7.21(m, 2H, ArH),7.58(m, 2H, ArH).

7b: ^{1}H NMR ($CDCl_3$): δ 2.19(s, 3H, -CH_3), 2.27 (s, 3H, -CH_3), 3.37 (s, 3H, -OCH_3), 3.52 (dd, 2H, -CH_2-), 4.04(m, 2H, -CH_2-), 4.15(m, 1H, -CH-), 7.19(m, 2H, ArH),7.7(m, 2H, ArH).

7c: δ 2.19(s, 3H, -CH_3), 2.27 (s, 3H, -CH_3), 3.37 (s, 3H, -OCH_3), 3.52 (dd, 2H, -CH_2-), 4.04(m, 2H, -CH_2),

4.15(m, 1H, -CH-), 7.19(m, 2H, ArH),7.62(m, 2H, ArH).

7d: ^{1}H NMR ($CDCl_3$): δ 2.19(s, 3H, $-CH_3$), 2.27 (s, 3H, $-CH_3$), 3.37 (s, 3H, $-OCH_3$), 3.52 (dd, 2H, $-CH_2$-), 3.8 (s, 3H, Ar-OCH_3), 4.04(m, 2H, $-CH_2$-), 4.15(m, 1H, -CH-), 7.19(m, 2H, ArH),7.62(m, 2H, ArH).

7e: ^{1}H NMR ($CDCl_3$): δ 2.19(s, 3H, $-CH_3$), 2.27 (s, 3H, $-CH_3$), 3.37 (s, 3H, $-OCH_3$), 3.52 (dd, 2H, $-CH_2$-), 3.8 (s, 6H, Ar-OCH_3), 4.04(m, 2H, $-CH_2$-), 4.15(m, 1H, -CH-), 7.19(d, 1H, ArH), 7.51(s, 1H, ArH), 7.62(d, 1H, ArH).

7f: ^{1}H NMR ($CDCl_3$): δ 2.19(s, 3H, $-CH_3$), 2.27 (s, 3H, $-CH_3$), 3.37 (s, 3H, $-OCH_3$), 3.52 (dd, 2H, $-CH_2$-), 4.04(m, 2H, $-CH_2$-), 4.15(m, 1H, -CH-), 7.61 (t,1H, ArH), 8.15(m, 1H, ArH), 8.36(m, 1H, ArH), 8.89 (s, 1H, ArH).

7g: ^{1}H NMR ($CDCl_3$): δ 2.19(s, 3H, $-CH_3$), 2.27 (s, 3H, $-CH_3$), 3.37 (s, 3H, $-OCH_3$), 3.52 (dd, 2H, $-CH_2$-), 4.04(m, 2H, $-CH_2$-), 4.15(m, 1H, -CH-), 8.15(d, 2H, ArH), 8.69 (d, 2H, ArH).

Theoretical Calculations

Theoretical calculations were carried on a representative system in the framework of density functional theory, introducing the popular B3LYP functional with triple–ζ def2-TZVP basis set, as implemented in the ORCA 5.0.1 and Avogadro software package. CPCM model has been used for the solvent correction and D3 for dispersion correction. The def2/J keyword is used to select general auxiliary basis set and RIJCOSX approximation has been taken in to account for Coulomb and numerical integrals.

Results and Discussion

Recent studies found that 2-amino alcohols found to be active in the two human cancer cell lines[24], one being gastric adenocarcinoma cells and the other lung adenocarcinoma cells (A549).

This paper deals with the studies on reaction of various 2-aryl-4,5-dimethyl-N1-hydroxyimidazole derivatives with epichlorohydrin in alkaline medium. In view of our objectives, initially reaction of 4,5-dimethyl-2-(3-nitrophenyl) imidazo-1-ol[23] **5f** was treated with epichlorohydrin in presence of potassium carbonate in methanol at RT. Interestingly it was observed that in addition to the desired product oxime-ether derivative **6f**, two other different products were formed, which were easily separated by column chromatography using hexane: ethyl acetate as eluent.

The formation of the desired oxime ether is confirmed by the analysis of ^{1}H and ^{13}C NMR, and the mass spectra. ^{1}H NMR spectra of the oxime ether shows peaks at δ 2.21 and 2.29 corresponding to the two methyl protons at 4- and 5- position of the imidazole ring respectively. Peaks at δ 2.56 and 3.85 correspond to the methylene group of the epoxide ring and the –O-CH_2-CH- respectively. Peak at δ 3.25, corresponds to the methyne proton of the epoxide ring. Peaks ranging from δ 7.6 to 8.9 correspond to the three aromatic protons of the benzene ring.

In order to ascertain the structure of the other two products in hand we have analyzed the spectroscopic data of these two compounds. Compound obtained in the second phase collection during column chromatography shows peaks at δ 2.20, 2.27, 3.37, 3.51, 4.04 and 4.15 in the aliphatic region. The total proton count indicates that there is one additional peak corresponding to three protons is being observed in comparison to the oxime ether aliphatic protons. The position and the proton count clearly indicate the presence of a $-OCH_3$ group. The possibility of existence of the $-OCH_3$ group can only be explained by the participation of the solvent in the opening of the epoxide ring giving rise to afford the new product **7e**. The mass spectra (HRMS) show the molecular ion peak at *m/z* 322.14 emphasizes our demand of solvent assisted ring opening of the epoxide ring of the oxime ether. The incorporation of the $-OCH_3$ group to the terminal carbon atom also helps in the downfield shift of the methylene protons from δ 2.56 in oxime ether to δ 3.51.

The product obtained from the last phase of the column chromatography is also analyzed for its structure using spectroscopic techniques using ^{1}H and ^{13}C NMR spectra and the mass spectra. ^{1}H NMR spectra indicate presence of peaks at δ 2.16, 2.22, 4.08 and 4.36 corresponding to the two methyl groups, methyne proton(-CH-) and methylene (-CH_2-) protons respectively. Absence of any other peak in the aliphatic region led us to analyze the mass (HRMS) spectra which indicate the existence of a peak corresponding to *m/z* 522 and a molecular ion peak at *m/z* 266 clearly suggest that the epoxide ring is being opened by another molecule of N-hydroxyimidazole giving rise to the dimer **8**.

To the best of our knowledge, in almost all cases of nucleophilic substitution reactions of epichlorohydrin with either phenol[25] or oxime[17] reported till date, it

results in the ether keeping the epoxide ring intact, which thereby reacts with amines and other nucleophiles to yield molecules of medicinal interest.

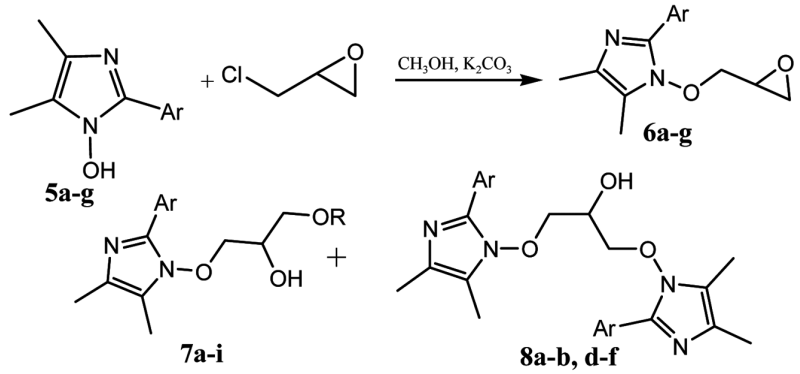
Contrary to this for the first time we have observed formation of three different products in one pot. One being the normal oxime ether **6f** (35%) as predicted earlier, the second one is the solvent assisted ring opening of the epoxide product **7f** (50%) and the third one is the nucleophilic substitution of the epoxide ring to give rise to the dimer product **8f** (13%) (Scheme 2).

The attack of epichlorohydrin with the imidazole derivative to give rise products **6f** and **7f** respectively can be explained either through S_N1 mechanism as suggested by Parker and coworkers[26] or by S_N2 mechanism on the basis of Krasuskii rule.

It has been observed that if the reaction was continued for longer times (> 24 h), the dimer could not be isolated and only compounds **6** and **7** were formed. This is probably the dimer decompose to give rise the oxime ether **6** and imidazole derivative **5** (Scheme 3). The crude reaction mixture also got decomposed if it was kept overnight after work up.

We have extended this methodology with various other substitutions over the phenyl ring at 2-position (Table 1)[31]. It worked successfully for all substituents and obtained all three products, except for 4,5-dimethyl-2-(4-Br-phenyl)-imidazole derivative **13c** and 4,5-dimethyl-2-(3,4-dimethoxy-phenyl) derivative **13g**. We were not able to isolate the dimer **16**, for **13c** and **13g**, may be due to possible decomposition of the product over the silica gel column, as a result the starting imidazole **13c** and **13g** were obtained.

Since the involvement of solvent giving rise to the product **13**, which is resulted by the solvent assisted ring opening of the epoxide ring, prompted us to explore the possibility of using other alcohol as solvent. Thus, the reaction of **13e** and **13f** was attempted in ethanol instead of methanol (Table 2). However, we got a 1.2-dihydroxy derivative instead of the solvent assisted ring opening product **15f**. The solvent assisted product formation can be explained on the basis of nucleophilicity of the solvent used[27]. It can be speculated that the formation of diol **15h-i** as the product may be the result of the water of crystallization participating as a nucleophile *via* the S_N2 mechanism.

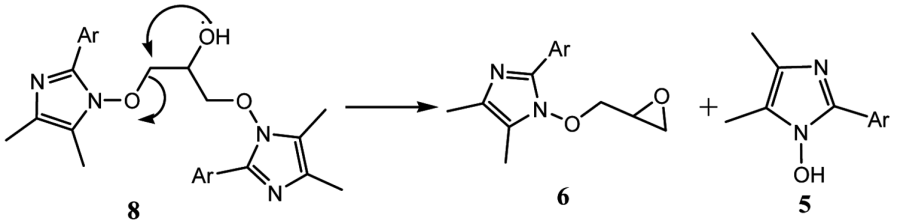


7a-g: R= CH_3 when solvent is methanol,

Ar= **a**: 4-$CH_3C_6H_4$, **b**:4-ClC_6H_4, **c**:4-BrC_6H_4, **d**: 2-$OCH_3C_6H_4$, **e**: 4-$NO_2C_6H_4$, **f**: 3-$NO_2C_6H_4$, **g**: 3,4-$(OCH_3)_2C_6H_3$

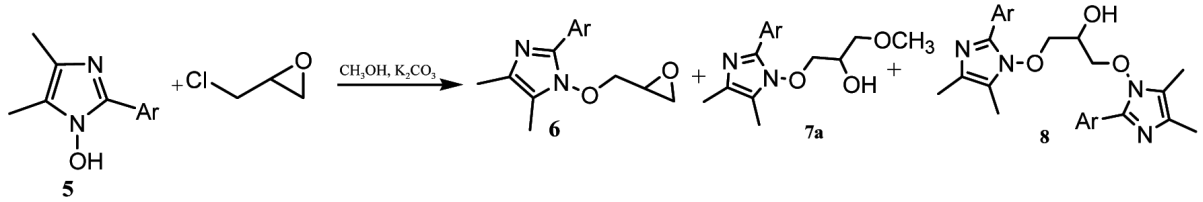
7h-i: R=H, Ar= 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$ and solvent is ethanol

Scheme 2 — Reaction of imidazole derivatives with epichlorohydrin



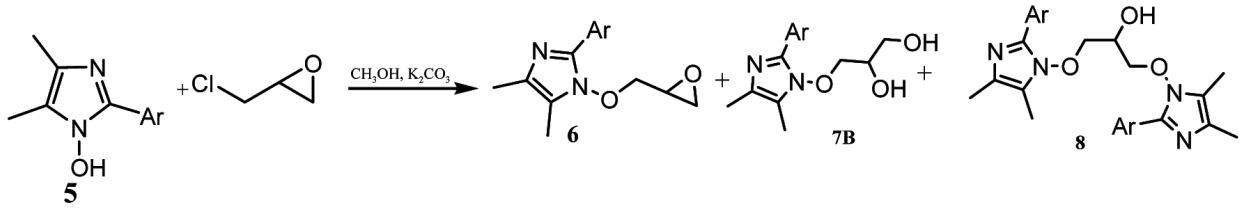
Scheme 3 — Decomposition of the dimer

Table 1 — Yield of various products in methanol



Compd	Ar=	Solvent	Yield of **12** (%)	Yield of **13** (%)	Yield of **14** (%)	Physical state		
						1	**2**	**3**
a	4-$CH_3C_6H_4$	MeOH	34	51	11	Liquid	Solid	Solid
b	4-Cl C_6H_4	MeOH	35	48	12	Solid	Solid	Solid
c	4-Br C_6H_4	MeOH	38	54.5	Not Observed	Solid	Solid	–
d	2-OCH_3 C_6H_4	MeOH	30	45	12	Liquid	Solid	Solid
e	3,4-$(OCH_3)_2$ C_6H_3	MeOH	22	57	Could not be recovered	Liquid	Solid	–
f	3-NO_2 C_6H_4	MeOH	34	55	10	Solid	Solid	Liquid
g	4-NO_2 C_6H_4	MeOH	34	51	13	Solid	Solid	Liquid

Table 2 — Yields of various products in ethanol



Compd	Ar=	Solvent	Yield of **1** (%)	Yield of **2** (%)	Yield of **3** (%)	Physical state		
						1	**2**	**3**
h	3-NO_2 C_6H_4	EtOH	24	64	6	Solid	Solid	Solid
i	4-NO_2 C_6H_4	EtOH	22	65	4	Solid	Solid	Solid

Computational Section

DFT study was carried out using the ORCA 5.0[28,29]. The B3LYP[30,31] functional and def2-TZVP[32] basis set was used for all atoms for the optimization of the geometry of the structures. Solvent effects for methanol and ethanol were taking into consideration using the CPCM model as implemented in ORCA. From the optimized structures single point energy has been calculated for all the molecules involved in the reaction in vacuum and CPCM[33,34] model. Further, frequency calculations were performed using the same level of theory to calculate the Gibbs free energy profile for each step. The presence of only one negative frequency was confirmed for the transition states.

Energy profile

The 1-hydroxy-imidazole undergoes reaction with epichlorohydrin and give three different products which pass through the formation of three Transition States such as TS1, TS2 and TS3. With progress of reaction the imidazole act as nucleophile and undergo SN_2 mechanism where it passes through a transition state TS1 where attack of nucleophile and removal of chlorine takes place simultaneously which was confirmed by vibrational frequency calculation for the predicted transition state where one and only one negative frequency was observed which suggests the imaginary mode which form **6** which is acting as an intermediate but also found at the end of reaction as second major product. As the intermediate possesses comparatively higher energy being not that much stable, it undergoes two transition states as TS2 and TS3 where the imidazole and solvent methanol act as nucleophile for SN_2 reaction. In TS2 opening of epoxide and attack of the nucleophile takes place simultaneously which was confirmed theoretically as there is found one and only one negative vibrational frequency which was visualized in Avogadro where the concerted reaction has been seen. These two transition states give two products as **7** and **8** respectively. **7** possess the lowest energy that is 4.5 kcal/mol which matches the experimental result as a major product (Fig. 1). As

complete conversion of intermediate does not take place it was observed to be second major product. The third product which was a dimeric form was found to be the minor product. From the energy level diagram, it was observed that from the intermediate, it passes through transition state TS3 which have lower energy as compare to TS2. Although, kinetically it should form the **8** more significantly as compared to **7** but experimentally it was found that **7** is more selectively formed. As we know, bulkier a nucleophile is, the more difficult it is to attack the substrate, and weaker the nucleophile becomes. In this reaction nucleophiles play the major role as the hydroxy-imidazole is bulkier as compared to methanol, for the opening of epoxide the imidazole faces steric hinderance and proper orientation is needed. Hence, **7** is formed more significantly. It suggests that the reaction is thermodynamically rather than kinetically controlled.

Proposed Mechanism

N1-Hydroxy imidazole in presence of base K_2CO_3 act as nucleophile and opening of epoxide as well as closer of epoxide take place with removal of chlorine[26]. Scheme 4 shows the proposed mechanism for ring opening of epoxide in presence of excess

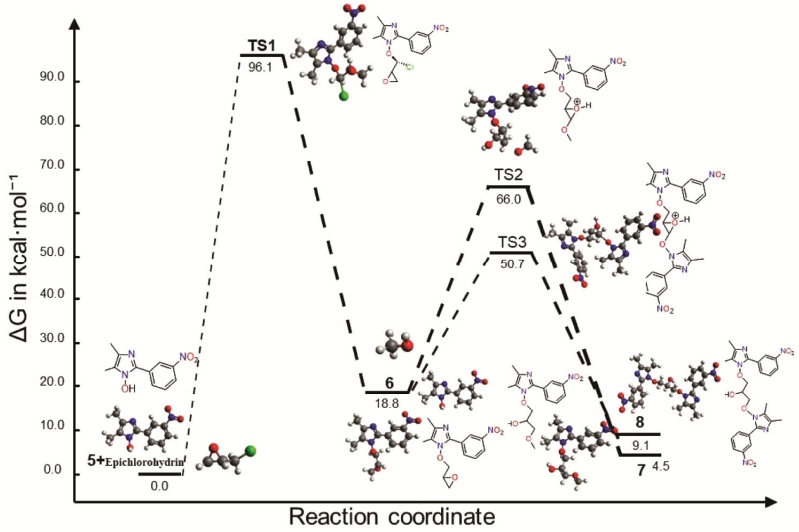
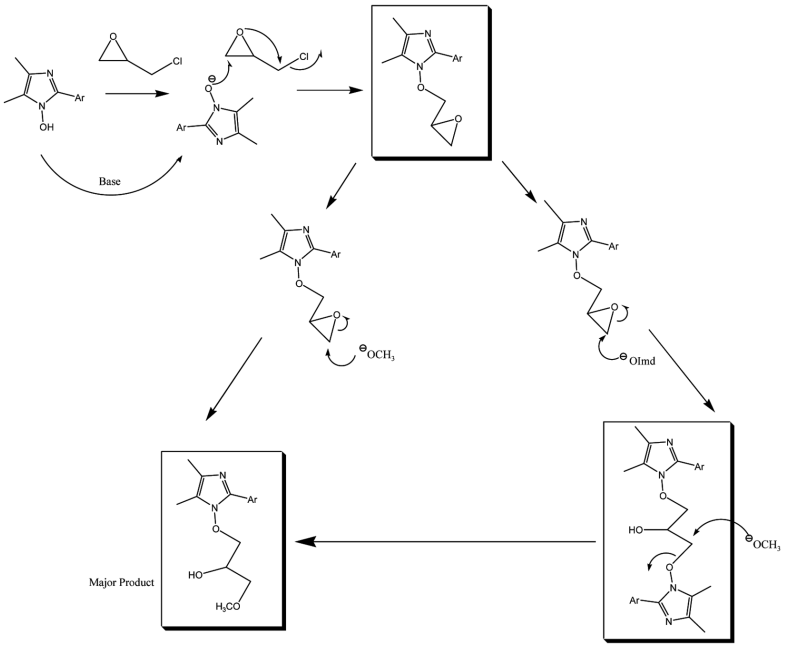


Fig. 1 — Energy level diagram showing change in free energy during the progress of reaction



Scheme 4 — Proposed mechanism for ring opening of epoxide

methanol by methoxide ion and form the **7**[27]. During this process it also forms the dimeric product which is again converted to **7** by attack of methoxide ion.

Conclusion

In conclusion, the present method is novel, mild, and efficient for the synthesis of new series of imidazole based epoxides and ring opened hydroxy imidazole derivatives accomplished by N_1-hydroxy imidazole as nucleophile. The greatest advantage of our methods, though, lies in their convenience like experimental simplicity, cost effective, mild reaction conditions, reduced reaction times, avoiding use of expensive metal catalysts, and good yields of the products where solvent itself acts as nucleophile which may also be called green synthetic approach.

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Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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