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DOI: 10.1039/C6RA07660B

Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Synthesis of β-phthalimido-alcohols via regioselective ring opening of epoxide by using reusable basic magnetic nano particles and their biological investigation

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

In this work, tetra butyl ammonium hydroxide ([Bu_4N]OH) and magnetic nano particles (Fe_3O_4@SiO_2@$(CH_2)_3NH_2$) were introduced as efficient catalysts for the regioselective ring opening of epoxides including aromatic and aliphatic of epoxides to give the corresponding β-phthalimido-alcohols under mild conditions. A various range of β- phthalimido-alcohols as new compounds were prepared and fully characterized by IR, ^1H as well as ^{13}C NMR and mass spectra. Also the synthesized compounds were studied for antioxidant properties by DPPH free radical scavenging assay. The results indicated that studied β- phthalimido-alcohols derivatives have effective antioxidant functions (IC_{50}: 0.142 - 0.356 mg/mL) in compare with BHT (IC_{50}: 0.122 mg/mL) and ascorbic acid (IC_{50}: 0.146 mg/mL) as standards. This may be a new health-care food and drug supplement for special use in the future.

Introduction

Epoxides are important starting materials and useful synthetic intermediates in organic synthesis. Also, the conversion of an alkene to an epoxide is a part of a more extensive molecular transformation.[1] Since epoxide ring opening is usually stereospecific, such reactions can be used to establish stereochemical relationships between adjacent substituents.[2] For this purpose, a wide range of mono or 1,2-disubstituted products, have been synthesized via addition of various nucleophiles to epoxides and different promoters and conditions have been proposed.[3] Ring opening of epoxides have been carried out with various nucleophiles such as phenols[1, 4, 5] thiols and thiophenols[5, 11], indoles[6, 11], amines[7], sulfonamides[8], thiocyanate[9], azide[10], benzotriazole[11], alcohols[11, 12], AcOH[12], H_2O[12], cyanide[10e, 13], Sulfide[14] and a good range of anions[15]. Almost, the above mentioned ring opening of epoxides have been carried out by applying acids or bases as catalysts in the course of reactions so that literature surveys shows that there are a few reports for ring opening of epoxides under neutral conditions.[16]

Phthalimide is a very important starting synthone in organic synthetic methodology for preparing diverse functionalized molecules.[17] The most famous and oldest applications of phthalimide is Gabriel synthesis for converting halides to aliphatic and aromatic amines. Nowadays, it has been used for the synthesis of catalysts[18], complicated[19] and advanced materials.[20] Moreover, phthalimide and its analogues have been extensively used in medicinal chemistry owing to their wide range of applications for designing of diverse biologically active molecules such as anti-convulsant, anti-inflammatory, analgesic, hypolipidimic, immunomodulatory activities, antitumor drugs[21] and anti HIV.[22] Free radicals such as reactive oxygen species (ROS) are formed naturally in the body with important roles in cell signaling, however some environmental toxins may contain free radicals or stimulate the body's cells to produce free radicals.[23] High level of free radicals are hazardous to the body and damage all major components of cells, including nucleic acids, proteins and plasma membrane, may play a role in the development of cancer and other health conditions.[24] A present trend in the field of antioxidant development focuses on multipotent antioxidant agents that can prevent biological substrates from radical induced oxidative damage.[25] Antioxidants may act as free radical scavengers, reducing agents, quenchers of singlet oxygen molecules and/or activators of antioxidative defense enzyme systems to suppress the radical damages in biological systems.[26,27] Antioxidant agents such as butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) are applied as additives in foods to prevent oxidation of lipids. Also, BHA and BHT are restricted by legislative rules because of doubts over their toxic and carcinogenic effects.[28] Therefore, there is a growing request and interest for safer antioxidants in food and pharmaceutical applications.[29] Recently, phthalimide and its salts including potassium phthalimide has been also widely used as catalyst in organic synthetic chemistry.[30] Therefore, development of eco-friendly protocols using more efficient, recycle and reusable nano magentic catalysts[31] for regioselective aminolysis of epoxides under green conditions is in more demand.[32] In continuation of our previous studies on the synthesis of nano magnetic catalysts[33] and development of task specific ionic liquids (TSILs),[34] nucleophilic ability of phthalimide[35], and ring opening of epoxides[36], we found that desirable structural diversity of functionalized phthalimides could be achieved *via* joining all of these research areas to design a new reaction

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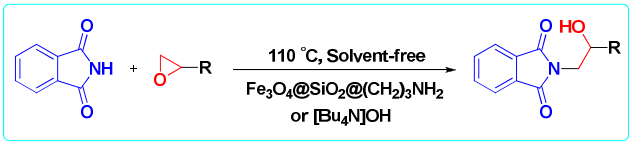
procedure for the synthesis of *β*- phthalimidoalcohols under solvent-free conditions (Scheme 1). Also results indicated that *β*- phthalimido-alcohols derivatives studied have remarkable antioxidant functions.



Scheme 1: The reaction of phthalimide with epoxide catalyzed by $Fe_3O_4@SiO_2@(CH_2)_3NH_2$ or $[Bu_4N]OH$.

Development of task specific catalysts and their structural diversity could be achieved *via* a combination of the desired structural moiety or functional group within a catalyst core. On the other hand, development of task specific ionic liquids (TSILs) and their structural diversity could be achieved *via* designing and synthesis of novel cationic cores with suitable anionic counterparts. By considering the above mentioned synthetic strategy, in the course of our investigation we decided to use tetra butyl ammonium hydroxide ($[Bu_4N]OH$) as a commercially available IL and $Fe_3O_4@SiO_2@(CH_2)_3NH_2$ as basic magnetic nano particles for the ring opening of epoxides with phthalimide under solvent free-conditions (Scheme 1).

At first, the SEM micrographs of prepared $Fe_3O_4@SiO_2@(CH_2)_3NH_2$ as basic magnetic catalyst was investigated to show that the particles were obtained in nano size (Figure 1).

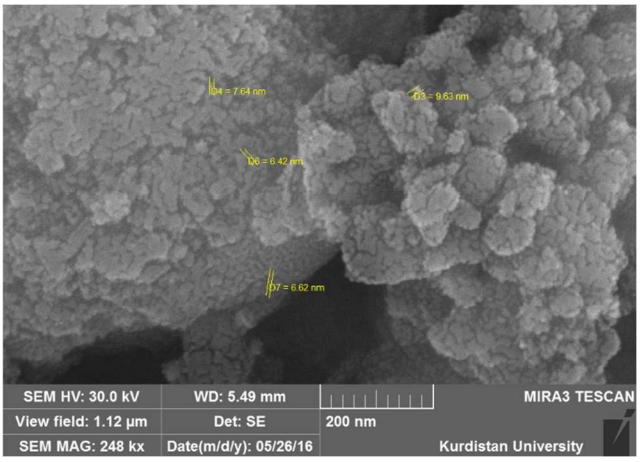


Figure 1. SEM micrographs of $Fe_3O_4@SiO_2@(CH_2)_3NH_2$.

Then, as a model reaction, the condensation of phthalimide (**1**) (1 mmol) with 2-phenyl oxirane (1 mmol) was selected in the presence of different amounts of the tetra butyl ammonium hydroxide, at range of 80-110 °C under solvent-free conditions. The results are summarized in Table 1. As it is shown at Table 1, indicates that 15 mol% of $[Bu_4N]OH$ was sufficient to afford the desired product in excellent yield and in very short reaction time at 110 °C (Table 1, entry 2). No improvement in the reaction results was observed by increasing the amount of the catalyst and the temperature. The solvent-free condensation was also tested at 110 °C without catalyst in which the reaction was not progressed even after long reaction time (2 h). Also, the solvent-free reaction of phthalimide with 2-phenyl oxirane was tested using $Fe_3O_4@SiO_2@(CH_2)_3NH_2$ at 110 °C. The best result was given by 1 mg of catalyst after 15 minutes (Table 1, entry 7).

Table 1. Effect of different amounts of the catalysts and temperature on the reaction between phthalimide with 2-phenyl oxirane.

Catalyst	Amount of Catalyst	Temp. (°C)	Time (min)	Yield[a] (%)
$[Bu_4N]OH$	5 mol%	80	40	60
$[Bu_4N]OH$	15 mol%	110	22	91
$[Bu_4N]OH$	10 mol%	110	35	65
$[Bu_4N]OH$	20 mol%	110	21	91
$[Bu_4N]OH$	15 mol%	90	30	57
$Fe_3O_4@SiO_2@(CH_2)_3NH_2$	0.5 mg	80	17	70
$Fe_3O_4@SiO_2@(CH_2)_3NH_2$	1 mg	110	17	94
$Fe_3O_4@SiO_2@(CH_2)_3NH_2$	3 mg	110	15	94
$Fe_3O_4@SiO_2@(CH_2)_3NH_2$	0.5 mg	110	35	52
$Fe_3O_4@SiO_2@(CH_2)_3NH_2$	1 mg	90	25	65

[a]Isolated yield.

The condensation of phthalimide (1) (1 mmol) with 2-phenyl oxirane (1 mmol), as model reaction, was examined by some various organic and inorganic bases such as LiOH, KOH, NaOH, $NaCO_3$, DABCO and Et_3N to choose the best basic catalyst (Table 2). As Table 2 indicates that ($[Bu_4N]OH$) and $Fe_3O_4@SiO_2@(CH_2)_3NH_2$ are more successful than other bases.

Table 2. Evaluation of various bases on the reaction between phthalimide with 2-phenyl oxirane in comparison with $Fe_3O_4@SiO_2@(CH_2)_3NH_2$ and $[Bu_4N]OH$.

Base	Amount of Catalyst (mol%)	Temp. (°C)	Time (min)	Yield[a] (%)
LiOH	15	120	110	0
KOH	15	120	110	20
NaOH	15	120	110	30
DABCO	15	120	110	35
Et_3N	15	120	110	30
$[Bu_4N]OH$	15	110	22	91
$Fe_3O_4@SiO_2@(CH_2)_3NH_2$	1 mg	110	17	94

[a]Isolated yield.

To compare the efficiency of solution conditions versus the solvent-free conditions, a mixture of phthalimide (1 mmol) and 2-phenyl oxirane (1 mmol) in the presence of $[Bu_4N]OH$ was heated in an oil-bath (110 °C) in various solvents for 60 min. Low yields of the product was obtained, even after elongated reaction times (Table 3). In the solvent-free conditions, the starting materials (phthalimide and 2-phenyl oxirane) and the catalyst formed a homogeneous system in the reaction media. This homogeneous system was also examined using various solvents including $CHCl_3$, EtOH, EtOAC, CH_2Cl_2 and H_2O. Therefore, the catalytic activity of $[Bu_4N]OH$ decreased in the

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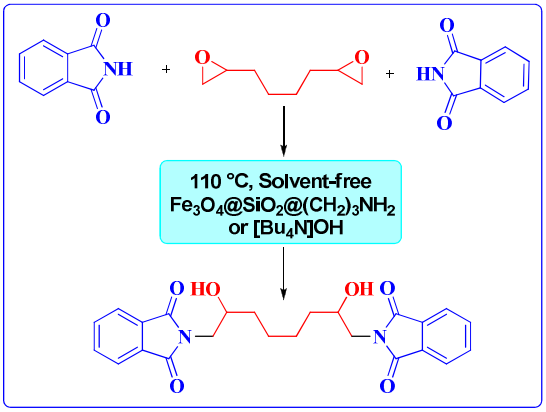
presence of these solvents. In the case of H_2O as solvent, $[Bu_4N]OH$ was soluble in water, but the starting materials were insoluble in it. Then, the yield decreased when H_2O was applied as solvent. Therefore, the solvent-free reaction was more efficient than solution conditions.

Table 3. The effect of various solvents on the reaction of phthalimide (1 mmol) with 2-phenyl oxirane (1 mmol) by method A and B in comparison with solvent-free conditions.

Solvent	Temprature	Time (min)	Yield[a] (%) A / B[b]
EtOAc	reflux	60	45 / 40
$CHCl_3$	reflux	60	55 / 33
EtOH	reflux	60	40 / 54
CH_2Cl_2	reflux	60	50 / 35
H_2O	r.t.	120	0 / 0
H_2O	reflux	120	20 / 25
-	110 °C	22/17	91 / 94

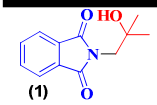
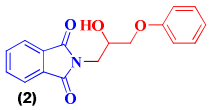
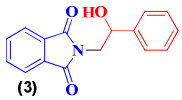
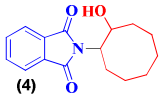
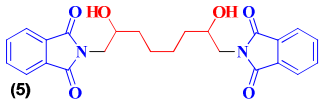
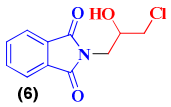
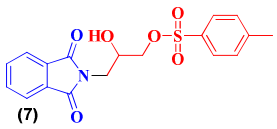
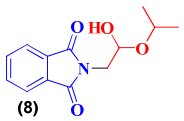
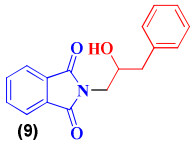
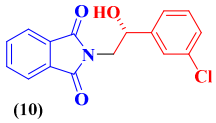
[a]Isolated yield; [b]In method A, $[Bu_4N]OH$ was used as basic catalyst and in method B, $Fe_3O_4@SiO_2@(CH_2)_3NH_2$ was used.

In order to assess the scope and the generality of the catalysts, the condensation of phthalimide with various epoxides was tested in the presence of 15 mol% $[Bu_4N]OH$ at 110 °C in the absence of solvent. The results are depicted in Table 4. As it is shown in Table 4, epoxide rings were utilized successfully in the reaction, and gave the desired products in high yields and in very short reaction times. Thus, the catalyst was general and highly efficient. Interestingly, the condensation of phetalimide (2 eq.) with 2-(4-(oxiran-2-yl)butyl) oxirane (1 eq.) in the presence of $[Bu_4N]OH$ (30 mol%) at 110 °C under solvent-free conditions, afforded (2.2'-(2,7- dihydroxyoctane-1,8-diyl)diisoindoline-1,3-dione) in 90 % of yield within 25 minutes (Scheme 2).



Scheme 2. The condensation of phthalimide with 2-(4-(oxiran-2-yl)butyl)oxirane.

Table 4. The preparation of *β*-phthaimidoalcohls using method A / B.[a]

Product	Time (min)	Yield[b] (%)	M.p. °C
 (1)	35/30	85/85[c]	103-105
 (2)	22/19	88/90	104-106
 (3)	22/17	91/94	159-161
 (4)	32/25	80/82[c]	234-238
 (5)	25/21	87/90	203-205
 (6)	45/40	81/84[d]	173-176
 (7)	25/21	72/76[d]	132-135
 (8)	30/23	80/85	125-128
 (9)	35/28	86/92	121-123
 (10)	29/21	83/89	109-112

[a]In method A, $[Bu_4N]OH$ was used as basic catalyst and in method B, $Fe_3O_4@SiO_2@(CH_2)_3NH_2$ was used as basic catalyst; [b]Isolated yield; [c]These epoxides were used 3 mmol against of 1 mmol of phthalimide; [d]These products were purified by plate chromatography.

In a plausible mechanism (Scheme 3), at first, phthalimide, as an acid, reacted with $Fe_3O_4@SiO_2@(CH_2)_3NH_2$ as a basic catalyst. The produced phthalimide anion attacked to the epoxide and opened it. Then, (**I**), as an anion, reacted with

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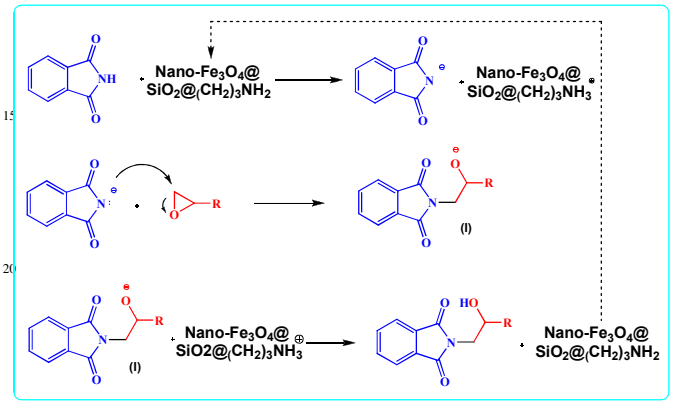
$Fe_3O_4@SiO_2@(CH_2)_3NH_3^+$ to give the desired product and the basic catalyst. The produced catalyst utilized the reaction to complete it.

The model reaction was also studied using potassium phthalimide instead of phthalimide in this reaction condition. The reaction was not carried out due to the absence of acidic hydrogen in phthalimide anion. The ring of epoxide could be opened by phthalimide anion, but in a reversible reaction the epoxide and phthalimide anion were prepared again. This observation clearly confirmed the mechanism of the reaction.



Scheme 3: The plausible mechanism for the synthesis of *β*-phthaimidoalcohls.

In another study, reusability of the catalyst was tested upon the reaction of phthalimide (1 mmol) with phenyl oxirane (1 mmol). The reaction mixture was extracted by warm ethanol to separate from the catalyst. Afterward, the reused catalyst was used for another reaction. We observed that the catalytic activity of the catalyst was restored within the limits of the experimental errors for four successive runs.

Antioxidant activity

Antioxidant properties, especially radical scavenging activities, are very important due to the deleterious role of free radicals in foods and biological systems.[37] Free radical scavenging activity of the synthesized compounds (**C_1-C_9**) assayed by 2,2-Diphenyl-1-picrylhydrazyl radical (DPPH) and comparison with ascorbic acid and BHT as a standard. Assessment of antioxidant activity showed that all compounds have effective free radical scavenging activity but in average function, compounds not showed different remarkable in amount of scavenging activity (62.92% - 73.71%), (Table **5**). The higher antioxidant activity is reflected in a lower IC_{50} value (mg/mL). The effectiveness of antioxidants as DPPH radical scavengers ranged based on the IC_{50} value in the following descending order: BHT > **C_3** = **C_6** ≥ ascorbic acid ≥ **C_2** ≥ **C_7** ≥ **C_1** > **C_5** ≥ **C_8** > **C_9** > **C_4** (Table **5**). The above results indicate that the synthesized compounds may be used in the treatment of diseases caused by free radicals. Further studies are needed to evaluate the *in vivo* potential of these compounds in animal models.

DPPH radical scavenging assay

The free radical scavenging activity of the compounds synthesized in this studied were evaluated using the stable radical DPPH.39 Briefly, 0.3 mM DMSO solution of DPPH (1 mL) was added to samples (2.5 mL) containing different synthesized compounds. The samples were first kept in a dark place at room temperature and their absorbance was read at 517 nm after 30 min. The antioxidant activity (AA) was determined using the following formula:

$$AA\ \% = 1 - [(As - Ab)/ Ac] \times 100$$

Blank samples contained 1 mL DMSO + 2.5 mL from various concentrations of synthesized compounds; control sample containing 1 mL of 0.3 mM DPPH + 2.5 mL DMSO. The optic density of the samples, the control and the empty samples were measured in comparison with DMSO. Two synthetic antioxidant, ascorbic acid and BHT were used as standards. The discoloration was plotted against the sample concentration in order to calculate the IC_{50} value, which is the amount of sample necessary to decrease the absorbance of DPPH by 50%. Experiments were carried out triplicate.

Statistical analysis

Data obtained from antioxidant assay is the average of triplicate analyses and recorded as means ± standard deviation. Analysis of variance was performed by Excel procedures statistical analysis was performed using student's t-test, and p value < 0.05 was regarded as significant.

Conclusions

In summary, we have introduced tetrabutyl ammonium hydroxide $[Bu_4N]OH$, as homogeneous catalyst, for the synthesis of *β*-phthalimido-alcohls under green media. Also, basic magnetic nano particles, $(Fe_3O_4@SiO_2@(CH_2)_3NH_2)$, as heterogeneous catalyst, was employed in this transformation. The promising points for the presented methodology are efficiency, generality, high yield, relatively short reaction time, low cost, cleaner reaction profile, ease work-up and finally compliance with the green chemistry protocols. Results from present study clearly demonstrated that all *β*-phthalimido-alcohols derivatives exhibit antioxidant properties that might be helpful in preventing the progress of various diseases and development of novel therapeutic agents. Of course, other effects of newly synthesized compounds in this research must be studied under *in vivo* condition.

Acknowledgements

We thank Bu-Ali Sina University and Iran National Science Foundation (INSF) (The Grant of Allameh Tabataba'i's Award, Grant Number BN093) for financial support to our research group.

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DOI: 10.1039/C6RA07660B

Table 5. Comparison of DPPH radical scavenging activity of *ß*- phthalimide alcohols derivatives and ascorbic acid as a standard.

Compounds	Concentration (mg/mL) 0.2	0.4	0.6	0.8	1	Average	IC_{50}
1	59.16 ± 2.7[a]	67.35 ± 1.5[b]	66.26 ± 1.3[b]	68.18 ± 2.6[b]	71.14 ± 3.3[b]	66.42	0.169[cd]
2	65.21 ± 2.1[a]	66.55 ± 2.2[a]	64.23 ± 2.4[a]	69.17 ± 1.2[b]	69.46 ± 1.6[b]	66.92	0.153[c]
3	70.56 ± 3.3[a]	71.23 ± 2.3[a]	70.00 ± 2.5[a]	75.13 ± 1.1[b]	78.32 ± 2.4[b]	73.05	0.142[b]
4	48.33 ± 1.8[a]	56.14 ± 1.2[b]	67.35 ± 2.4[c]	69.17 ± 2.2[c]	73.61 ± 1.5[c]	62.92	0.356[f]
5	55.45 ± 2.6[a]	67.45 ± 2.7[b]	72.25 ± 1.2[c]	78.26 ± 3.2[c]	81.51 ± 1.3[d]	71.02	0.180[d]
6	70.24 ± 1.3[a]	71.27 ± 2.1[a]	75.16 ± 1.8[a]	73.24 ± 2.6[a]	78.65 ± 3.3[b]	73.71	0.142[b]
7	61.56 ± 2.8[a]	65.23 ± 1.9[a]	73.54 ± 2.7[b]	76.34 ± 3.2[b]	76.43 ± 2.5[b]	71.22	0.162[c]
8	55.32 ± 3.1[a]	62.15 ± 2.7[b]	64.15 ± 3.1[b]	64.58 ± 2.6[b]	68.21 ± 2.4[b]	62.88	0.181[d]
9	50.62 ± 1.2[a]	53.21 ± 1.6[a]	61.41 ± 2.3[b]	69.74 ± 2.5[c]	76.25 ± 1.1[d]	62.25	0.197[e]
10	58.21 ± 2.2[a]	57.36 ± 3.1[a]	58.41 ± 1.9[a]	64.21 ± 1.4[b]	69.33 ± 2.6[b]	61.50	0.172[d]
Ascorbic acid	68.74 ± 2.7[a]	76.16 ± 3.4[b]	78.85 ± 1.4[b]	80.41 ± 2.2[b]	80.24 ± 1.6[b]	76.88	0.146[b]
BHT	82.24 ± 0.8[a]	87.65 ± 1.1[b]	89.26 ± 1.6[b]	88.12 ± 2.7[b]	92.37 ± 1.4[b]	76.88	0.122[a]

Experiment was performed in triplicate and expressed as mean ± SD. Values along column with different superscripts are significantly different (P<0.05).

Experimental

All chemicals were purchased from Merck or Fluke Chemical Companies. Magnetic nanoparticles were prepared according the previous literature.[38] Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. The ^{1}H NMR (400 or 300 MHz) and ^{13}C NMR (100 or 75 MHz) were run on a Bruker Avance DPX-250 FT-NMR spectrometer (δ in ppm). Microanalyses were performed on Perkin-Elmer 240-B microanalyses. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

General procedure for the synthesis of ß-phthaimidoalcohls using $[Bu_4N]OH$

A mixture of phthalimide (0.147 g, 1 mmol), epoxide (1 mmol), and $[Bu_4N]OH$ (0.15 mol%) in a 10 mL round-bottomed flask, connected to a reflux condenser, was stirred in an oil-bath at 110°C. After completion of the reaction, as monitored by TLC, the reaction mixture was cooled to room temperature, extracted with CHCl3 (10 mL) and H2O (10 mL) to separate the catalyst. The product was recrystallized in CHCl3 to afford the pure product, which required no further purification.

General procedure for the synthesis of *ß*-phthaimidoalcohls using Nano Fe_3O_4@NH_2

A mixture of Phthalimide (0.147 g, 1 mmol), epoxide (1 mmol), and nano $Fe_3O_4@SiO_2@(CH_2)_3NH_2$ (1 mg) in a 10 mL round-bottomed flask connected to a reflux condenser, was stirred in an oil-bath (110°C). After completion of the reaction, as monitored by TLC, the reaction mixture was cooled to room temperature, extracted with Ethanol separate the catalyst. The product was recrystallized in ethanol to afford the pure product which required no further purification.

Notes and references

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‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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DOI: 10.1039/C6RA07660B

Synthesis of *ß*-phthalimido-alcohols via regioselective ring opening of epoxide by using reusable basic magnetic nano particles and their biological investigation

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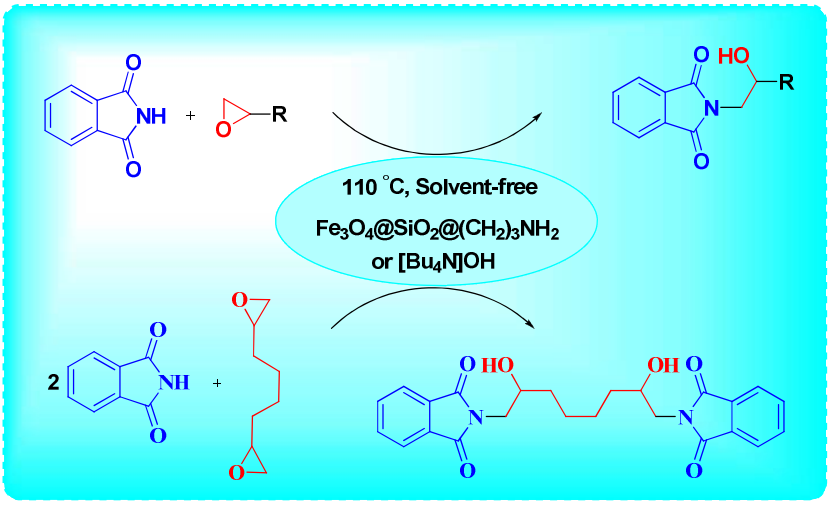

Tetra butyl ammonium hydroxide ($[Bu_4N]OH$) and magnetic nano particles ($Fe_3O_4@SiO_2@(CH_2)_3NH_2$) were introduced for the regioselective ring opening of epoxides including aromatic and aliphatic of epoxides to give the corresponding *ß*-phthalimido-alcohols. The products were studied for antioxidant properties by DPPH free radical scavenging assay.