

# Caro's Acid-Silica Gel Catalyzed Regioselective Ring Opening of Epoxides with Indoles and Imidazoles under Solvent-Free Conditions

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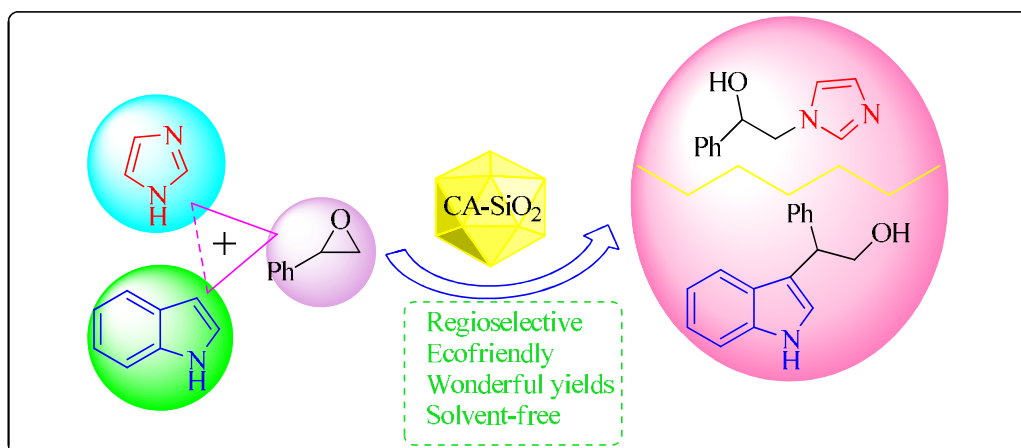
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## ABSTRACT

An efficient and facile procedure has been developed for the ring opening of epoxides with nitrogen heterocycles such as indole and imidazole in the presence of Caro's acid-silica gel (CA-SiO<sub>2</sub>) as catalyst in solventless system. The reactions were administered underneath Solvent-free conditions. The current methodology offers many benefits like good yields, easy procedure, simple work-up and ecofriendly reaction condition. The catalyst is well ready, stable and economical underneath the reaction conditions.

**Keywords:** Regioselectivity, Indole, Imidazole, Epoxide, Caro's acid-silica gel.

## GRAPHICAL ABSTRACT



## 1. Introduction

The indole nucleus is usually found in some medicines, especially those have an origin of natural products and agrochemicals [1]. Substituted indoles are capable of binding to many receptors with high affinity. Therefore, the synthesis and selective functionalization of the synthesis and selective functionalization of indoles have been always attracted the attention of synthetic organic chemists, over the years [2-4].

3-Substituted indoles are essential building blocks for the synthesis of various active molecules. Consequently, its synthesis has stirred up the interest of synthetic organic chemists for development of and introduction of new methodologies towards 3-substituted indoles [5]. Among heterocycles, the presence of 1,3-azole moieties seems vital in order to give biological activity and potency to some certain drugs [6]. The synthesis of this family of heterocyclic

compounds mainly achieved either via ring closure reactions of appropriate acyclic precursors or by substituent modification of heterocyclic systems. These compounds are worthwhile being evaluated and screened under medicative analysis systems [7]. Epoxides are recognized an important and versatile synthetic intermediates in organic synthesis [8] due to their exceptional reactivity, especially being receptive to nucleophilic attack. They are also commercially available and readily accessible in pure form [9]. Therefore, there is continuous and current interest in the ring opening of epoxides with several kinds of different reagents such as electrophiles, nucleophiles, acids, base, reducing agents, and a few oxidizing agents. Several procedures for the catalyzed ring-opening reaction of epoxides with indole have been reported in the literature using Lewis acid such as  $\text{SiO}_2$  [10],  $\text{InCl}_3$  [11] and  $\text{InBr}_3$  [12] or being performed under high pressure. One special but rare case of 3-azoles are the 1-(2-hydroxyalkyl)imidazole derivatives. Several of them are showing antifungal properties [13]. These compounds have been synthesized via epoxides ring opening upon reaction with imidazole derivatives. To perform this reaction, obtaining good yields a harsh conditions (such as strong base/high temperature [14] or high pressure [10]) are required. Since these compounds are interesting from both chemical and biological points of view, developments and modifications are still in much demands. Recently, the applications of Caro's acid-silica gel ( $\text{CA-SiO}_2$ ) as catalysts or promoters in organic synthesis has attracted much interest of synthetic organic chemists.  $\text{CA-SiO}_2$  catalyzed reaction, enhancing the reactivity and

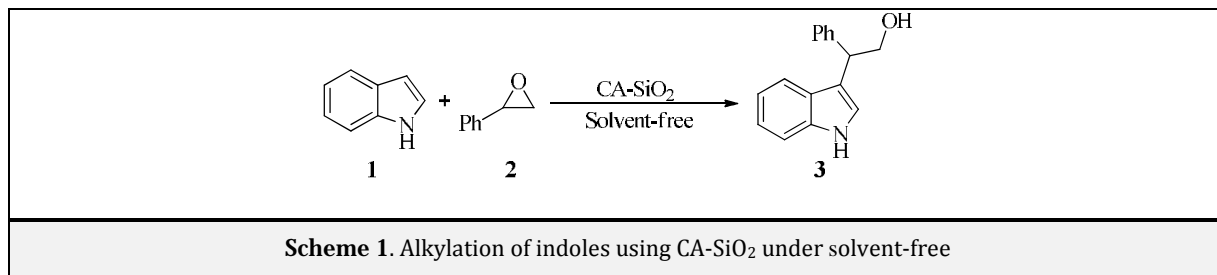
selectivity for several kind of reactions, such as oxidative coupling of thiols to disulfides [15], conversion of thioamides into amides [16], carbonyl compounds from oximes [17], synthesis xanthen [18] and synthesis tetrahydrobenzo[b]pyran [19], have been reported [20]. We are interested in heterocyclic chemistry [21-26]. We have also reported in ring opening of epoxides using different catalysts [27]. We have recently used Caro's acid-silicagel as a catalyst [28,29]. Herein we wish to disclose our result Caro's acid-silica gel catalyzed regioselective ring opening of epoxides with indoles and imidazoles under solvent-free conditions on.

## 2. Experimental

Melting points were measured by using the capillary tube technique with an electro thermal 9200 apparatus. GC-Mass analysis was performed on a GC-Mass model: 5973 network mass selective detector, GC 6890 Agilent Mass spectra were obtained with a Massens POEKTROMETER CH-7A VARIN MAT BREMEN spectrometer. IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27.  $^1\text{H}$  NMR spectra were recorded on a Bruker AQS Avance 500-MHz spectrometer using tetramethylsilane (TMS) as an internal standard.

### 2.1. General Procedure

A combination of indole(1) (1 mmol) or imidazole(4) (1 mmol) and styrene oxide(2) (1 mmol) and  $\text{CA-SiO}_2$  (0.13 mmol, 0.078 gr) was speedily stirred at room temperature for the required time (Table 2,3). After the TLC indicates the disappearance of beginning materials, EtOH (20 mL) was value-added and also the insoluble material was filtered to separate the catalyst



**Table 1.** Alkylation of indoles using CA-SiO<sub>2</sub> under Solvent-free

Entry	Nucleophile	Epoxide	Product	Mp (°C)	Time (min)	Yield (%)
1				84-85 <sup>10</sup>	20	90
2				85-86 <sup>10</sup>	40	88
3				140-142 <sup>10</sup>	60	80
4				129-131 <sup>10</sup>	60	85
5				92-95 <sup>10</sup>	64	83

then EtOH evaporated to afford the pure product **3a** and **5a**.

## 2.2. Preparation of Catalyst

In small portions of potassium persulfate (4.5 g) were added to ice-cooled 98% sulfuric acid (4.7 g) with stirring; to this, crushed ice (13 g) and water (4 g) were added. The temperature was kept below 15 °C. Silica gel (5 g, TLC grade, Kieselgel 60 G, particle size 15 mm) was added in portions to the mixture, and the mixture was

stirred for 4 h in an ice-water bath. The mixture was then filtered under suction and dried in a desiccator to give a white free-flowing power [15].

**2-(1H-indol-3-yl)-2-phenylethanol (3a)** [10]: M.p. 121-122 °C, IR (KBr): 3412, 3321, 3056, 3027, 2926, 2874, 1601, 1491, 1453, 1306, 1223, 1054, 744, 700 cm<sup>-1</sup>, <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 1.64 (br, 1H, OH); 4.39-4.42 (dd, 2H, J = 8 and 6.5 Hz, CH<sub>2</sub>); 4.53-4.56 (t, 1H, J = 7.5 Hz,

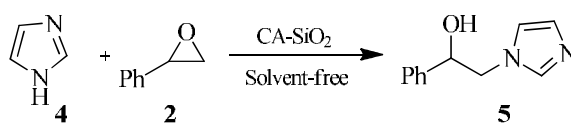
CH), 7.09-7.12 (t, 1H, J = 7 Hz, ArH); 7.15 (s, 1H, ArH); 7.17-7.20 (t, 1H, J = 7 Hz, ArH); 7.24-7.35 (m, 4H, ArH); 7.41-7.43 (d, 2H, J = 7 Hz, ArH); 7.53-7.55 (d, 1H, J = 7.5 Hz, ArH); 8.1 (br, 1H, NH) ppm, MS: m/z 237 [M<sup>+</sup>], 219, 206, 191, 178, 165, 151, 128, 115, 102, 77.

**2-(1H-imidazol-1-yl)-1-phenylethanol (5a)** [10]: M.p. 145-148 °C, IR (KBr): 3689, 2955 cm<sup>-1</sup>, <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 3.45 (s, 1H, OH); 4.10 (m, 2H, CH<sub>2</sub>); 4.86 (m, 1H, CHOH); 6.87-6.90 2

(s, 1H and 1H, NCHCHN); 7.25-7.36 (m, 6H, ArH and NCHN) ppm, MS: m/z 189 [M<sup>++1</sup>], 188, 107, 82.

### 3. Results and Discussion

In order to work out the foremost acceptable reaction conditions and to evaluate the action efficiency of CA-SiO<sub>2</sub> catalyst, at the beginning a model study was administered on the synthesis of **3a** (Scheme 1).



**Scheme 2.** Alkylation of epoxides using CA-SiO<sub>2</sub> under solvent-free

**Table 2.** Alkylation of epoxides using CA-SiO<sub>2</sub> under Solvent-free conditions

Entry	Nucleophile	Epoxide	Product	Mp (°C)	Time (min)	Yield (%)
1			<b>5a</b>	84-85 <sup>10</sup>	25	80
2			<b>5b</b>	143-144 <sup>10</sup>	65	87
3			<b>5c</b>	116-117 <sup>10</sup>	40	84
4			<b>5d</b>	117-119 <sup>10</sup>	35	86

Encouraged by these results, we have a tendency to applied reaction of imidazole with epoxide within the presence of 0.13 mmol CA-SiO<sub>2</sub> at underneath solvent-free conditions, that afforded imidazolyl alcohols in good yields among a brief amount of time (Scheme 2, Table 2). Imidazole, with a pka of 7.1 could be a

abundantly stronger base and nucleophile than indole, consequently imidazoles is alkylated on nitrogen simply. Ring opening occurred completely at less hindered carbon of the epoxide. This can be according to S<sub>N</sub>2-type attack by the imidazole nitrogen. All product (Table 1,2) obtained were totally characterised

by spectroscopical strategies as well as <sup>1</sup>HNMR, IR and spectrometry and conjointly by the comparison of the spectral information with according values.

#### 4. Conclusion

We represented herein CA-SiO<sub>2</sub> catalyzed extremely economical, protocol for preparation of reaction epoxides with nitrogen heterocycles underneath Solvent-free in good yields. simple work-up, cheap, prepared convenience of the catalyst makes the procedure a horny different to the prevailing strategies for preparation of reaction epoxides with nitrogen heterocycles.

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