# A simple, highly regioselective and efficient reaction of indole with epoxides under solvent-free conditions

**Najmedin Azizi, Shokopheh Mehrazma, and Mohammad R. Saidi**

**Abstract:** Lithium perchlorate has been found to be an inexpensive and efficient catalyst for the ring opening of epoxides by indole and *N*-methylindole, which provides an environmentally friendly method for the synthesis of substituted indoles. A complete regioselectivity in favor of nucleophilic attack at the benzylic carbon atom of aromatic epoxides, such as styrene oxide, is observed. However, aliphatic unsymmetrical alkene oxides undergo selective nucleophilic attack at the sterically less-hindered carbon atom. This catalyst offers several advantages, such as short reaction time, high yields, lower catalytic loading, simple experimental procedure, and easy isolation of the products, under solvent-free conditions.

*Key words:* indole, epoxide, regioselectivity, solvent-free.

**Résumé :** On a observé que le perchlorate de lithium est un catalyseur peu dispendieux et efficace pour l'ouverture des cycles époxydes par l'indole et le *N*-méthylindole et la synthèse dans un environnement écologique d'indoles substitués. Les réactions sont complètement régiosélectives en faveur d'une attaque nucléophile au niveau de l'atome de carbone benzylique d'époxydes aromatiques tels que l'oxyde de styrène. Toutefois, avec les oxydes d'alcènes aliphatiques non symétriques, l'attaque nucléophile se fait sélectivement au niveau de l'atome de carbone le moins encombré. Ce catalyseur présente plusieurs avantages, tel son court temps de réaction, des rendements élevés, une quantité plus faible de catalyseur, une procédure expérimentale simple et une méthode facile d'isoler les produits dans des conditions sans solvant.

*Mots clés :* indole, époxyde, régiosélectivité, sans solvant.

[Traduit par la Rédaction]

## Introduction

Epoxides have been recognized as important and versatile synthetic intermediates in organic synthesis (1) because they are susceptible to attack by several nucleophiles and readily accessible in pure form (2). Therefore, there is a significant current interest in the ring opening of epoxides with a large variety of reagents such as electrophiles, nucleophiles, acids, bases, reducing agents, and some oxidizing agents. However, the epoxide ring-opening reaction with certain nucleophiles is generally performed with acid or base catalysis, with a large excess of nucleophiles at elevated temperature, and often fails when poor nucleophiles such as indole and hindered epoxides are used. Few procedures for the ring-opening reaction of epoxides with indole are reported in the literature by using high pressure or $SiO_2$ (3), $InCl_3$ (4), and $InBr_3$ (5) as catalysts. While the employment of high pressure requires the use of special equipment, for a catalyst such as $SiO_2$, although simple, several days were necessary to obtain good yields of products. Indium salts are expensive and indoles were only reactive toward vinyl epoxides. Furthermore, all of these reactions have been extensively investigated in toxic organic solvents, and to the best of our knowledge, reactions of indole with epoxides under solvent-free conditions have not been reported. Thus, there is a need to develop a convenient and efficient protocol for the regioselective ring opening of epoxides with indole to produce 3-alkylindole derivatives of biological importance.

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## Results and discussion

As part of our research on organic synthesis under solvent-free conditions (6), in this paper we describe a simple and practical method for the synthesis of indole derivatives using a catalytic amount of lithium perchlorate. To find out the best reaction conditions for the ring opening of epoxide with indole in the presence of $LiClO_4$, styrene oxide was reacted with 1-methylindole in a common organic solvent and under solvent-free conditions with a different amount of solid lithium perchlorate. A series of experiments carried out on epoxide and indole indicated that the best yields were obtained in the presence of 20 mol% anhydr. $LiClO_4$ and 1.0 equiv. of epoxide at 60 °C under neat conditions (Table 1). In the absence of lithium perchlorate, only the starting material was obtained after prolonged reaction times. As was expected, conducting the same reaction with 20 mol% of anhydrous lithium perchlorate in common organic solvents such as THF, diethyl ether, petroleum ether, dichloro-

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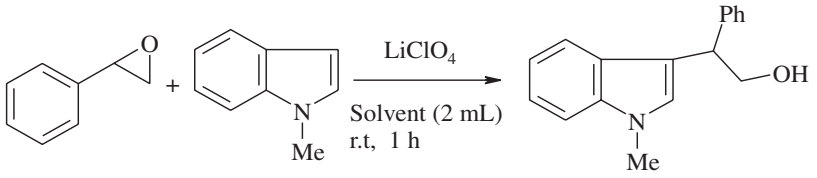
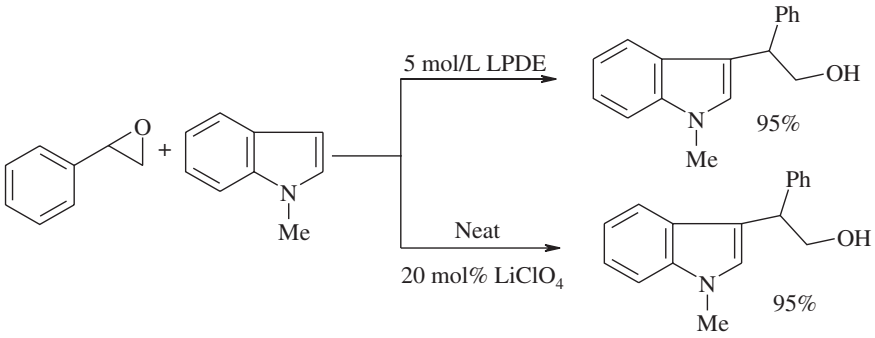
**Table 1.** Reactions of 1-methylindole and styrene oxide under different conditions.




| Entry | Solvent | $LiClO_4$ (g) | Yield (%) |
|---|---|---|---|
| 1 | $CH_2Cl_2$ | 0.2 | 15 |
| 2 | $CH_2Cl_2$ | 0.5 | 32 |
| 3 | THF | 0.2 | 23 |
| 4 | Diethyl ether | 1 | 95 |
| 5 | $CH_3CN$ | 0.2 | 35 |
| 6 | Petroleum ether | 0.2 | 20 |
| 7 | Methanol | 0.2 | 0 |
| 8 | Water | 0.2 | 0 |
| 9[a] | — | 0.1 | 95 |

[a]Reaction run at 60 °C.

**Scheme 1.** Reactions of indole and styrene oxide in 5 mol/L LPDE and neat conditions.

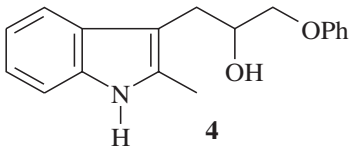



methane, acetonitrile, methanol, and water resulted, for the most part, in the recovery of the starting materials.

This shows that the solvent-free conditions play an essential role in facilitating the desired epoxide ring-opening reaction in the presence of anhydr. $LiClO_4$. On the other hand, our study shows that by increasing the amount of lithium perchlorate to 200 mol% in diethyl ether (5 mol/L solution of lithium perchlorate in diethyl ether, LPDE), the direct nucleophilic addition of indole to styrene oxide is faster than the rearrangement of the epoxide to the corresponding carbonyl compounds (Scheme 1). It also indicates that the solvent-free condition is a superior method owing to low loading of catalyst.

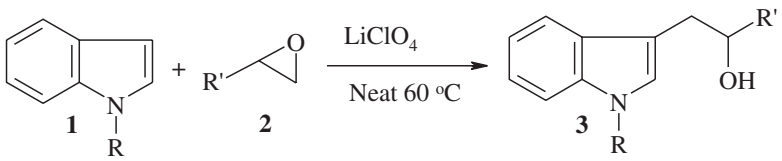
Lithium perchlorate is an extraordinarily efficient catalyst for the highly regioselective ring-opening reaction of epoxides. To show the generality and scope of the $LiClO_4$-promoted ring opening of epoxide with indole, the reaction was examined with various structurally diverse epoxides. The data in Table 2 clearly show that all reactions proceed smoothly under these reaction conditions to afford the desired indolyl alcohols in good yields with high regioselectivity. This method is also effective with aliphatic oxiranes. No precaution is needed to exclude moisture from the reaction media. The regioselectivity in the reaction for unsymmetrical epoxides is governed by both steric and electronic effects. The regioselectivity was determined by $^1H$ NMR and by comparison with the known samples. Aliphatic oxiranes underwent cleavage by indole and *N*-methylindole with the preferential attack at the less-substituted carbon atom. On the other hand, in the case of styrene oxide and other aromatic oxiranes, the reaction likely proceeds partly through an attack by the indole on the more stabilized "carbocation" with participation of phenyl groups. The role of $LiClO_4$ in catalyzing the opening of epoxide rings with indole may be realized through the coordination of $Li^+$ with epoxide oxygen and rendering the epoxide more susceptible to nucleophilic attack by indole, followed by hydrogen transfer to form the indolyl alcohols. The comparison of the present methods with respect to the amount of the catalyst used, reaction time and requirement of solvent, products yield and regioselectivity with those reported in the literature, reveals that this newly developed method is superior to the previous procedures.

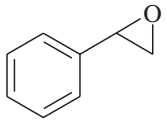
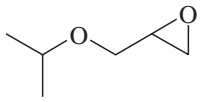
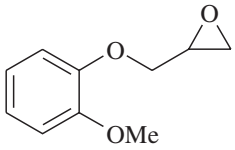
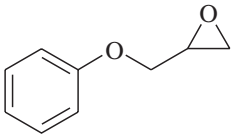
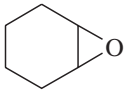
Reaction of 2-methylindole with 2,3-epoxypropyl phenyl ether proceeds efficiently at 60 °C in the presence of 20 mol% of anhydr. $LiClO_4$ under neat conditions and gave the corresponding 3-substituted 2-methylindole (**4**) in 60% yield after 1.5 h.




**4**

**Table 2.** Reactions of indoles with epoxide under solvent-free conditions.




| Entry | Epoxides | | Time (min) | Yield (%) |
|---|---|---|---|---|
| 1 |  | **3a** R = H | 45 | 95 |
| 2 | | **3b** R = Me | 120 | 95 |
| 3 |  | **3c** R = H | 120 | 66 |
| 4 | | **3d** R = Me | 60 | 78 |
| 5 |  | **3e** R = H | 120 | 64 |
| 6 | | **3f** R = Me | 60 | 80 |
| 7 |  | **3g** R = H | 60 | 64 |
| 8 | | **3h** R = Me | 90 | 79 |
| 9 | | | | |
| 10 |  | **3i** R = H | 180 | 45 |
| 11 | | **3j** R = Me | 180 | 62 |

In summary, we have described a new direct protocol for the preparation of indolyl alcohol derivatives by ring-opening reactions of epoxides with indole and *N*-methylindole in the presence of 20 mol% of anhydr. $LiClO_4$. The notable features of this procedure are the mild reaction conditions, high conversions, short reaction times, economic viability of the reagents, simple experimental procedure, and product isolation. Although lithium perchlorate is normally responsible for the rearrangement of aromatic epoxides to the corresponding carbonyls, the mild reaction conditions allowed the isolation of the desired compounds in high yields and without rearrangement, when a 5 mol/L solution of LPDE was used.

## Experimental

### General procedure for the preparation of tryptophol derivatives

To a mixture of indole (4 mmol) and epoxide (4 mmol), anhydrous lithium perchlorate (0.1 mmol) was added and stirred at 60 °C for 1–4 h. When the reaction was completed, as indicated by TLC or GC, the reaction mixture was diluted with diethyl ether or ethyl acetate and purified by flash column chromatography ($Et_2O$–hexanes, 30:70) to give the desired products. All compounds were characterized on the basis of NMR spectroscopic data.

### Selected spectroscopic data

***3a***

$^1$H NMR ($CDCl_3$, 500 MHz) $\delta_H$: 2.28 (br s, 1 H, OH), 4.03–4.41 (m, 3H), 6.73–7.63 (m, 10H), 8.34 (br s, 1H, NH). $^{13}$C NMR ($CDCl_3$, 500 MHz) $\delta_C$: 45.7, 66.4, 111.2, 116.2, 119.4, 119.6, 121.9, 122.3, 126.7, 127.1, 128.3, 128.6, 136.6, 141.8.

***3b***

$^1$H NMR ($CDCl_3$, 500 MHz) $\delta_H$: 1.80 (br s, 1H, OH), 3.82 (s, 3H), 4.23–4.53 (m, 3H), 7.02 (s, 1H), 7.11–7.53 (m, 9H). $^{13}$C NMR ($CDCl_3$, 500 MHz) $\delta_C$: 33.1, 46.0, 66.9, 109.7, 114.9, 119.5, 119.9, 122.3, 126.6, 127.1, 127.9, 28.7, 128.8, 137.6, 142.3.

***3c***

$^1$H NMR ($CDCl_3$, 500 MHz) $\delta_H$: 1.17 (d, 3H, $J$ = 6.3 Hz), 1.24 (d, 3H, $J$ = 6 Hz), 2.19 (br s, 1H, OH), 3.01 (m, 2H), 3.43 (m, 1H), 3.53 (m, 1H), 3.65 (m, 1H), 4.18 (m, 1H), 6.57 (s, 1H), 6.87–7.71 (m, 4H), 8.56 (br s, 1H, NH).

***3d***

$^1$H NMR ($CDCl_3$, 500 MHz) $\delta_H$: 1.28 (d, 3H, $J$ = 6.3 Hz), 1.30 (d, 3H, $J$ = 6.3 Hz), 2.69 (br s, 1H, OH), 3.07 (d, 2H, $J$ = 6.5 Hz), 3.47 (m, 1H), 3.59 (m, 1H), 3.70 (m, 1H), 3.83 (s, 3H), 4.22 (m, 1H), 6.60 (s, 1H), 7.03–7.76 (m, 4H).

***3g***

$^1$H NMR ($CDCl_3$, 500 MHz) $\delta_H$: 2.14 (br s, 1H, OH), 3.13–3.22 (m, 2H), 3.99–4.08 (m, 2H), 4.29 (m, 1H), 6.63 (s, 1H), 6.99–7.75 (m, 9H), 8.37 (br s, 1H, NH). $^{13}$C NMR ($CDCl_3$, 500 MHz) $\delta_C$: 29.1, 71.1, 71.9, 111.1, 111.5, 114.7, 118.1, 119.9, 121.6, 122.8, 123.1, 127.9, 129.9, 136.5, 158.8.

***3h***

$^1$H NMR ($CDCl_3$, 500 MHz) $\delta_H$: 2.27 (br s, 1H, OH), 3.08–3.15 (m, 2H), 3.86 (s, 3H), 4.13–4.15 (m, 2H), 4.45 (m, 1H), 6.74 (s, 1H), 6.75–7.93 (m, 9H).

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