Catalysis Letters Vol. 98, Nos. 2–3, November 2004 (© 2004)

Bis(cyclopentadienyl)zirconium dichloride for alkylation of heteroaromatics and synthesis of bis(indolyl)methanes

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Received 30 April 2004; accepted 02 August 2004

Bis(cyclopentadienyl)zirconium dichloride catalyzed alkylation of heteroaromatics with epoxides results in the formation of 3-alkylated heteroaromatics in high yields. Cp_2ZrCl_2 is also found to be an efficient catalyst for the electrophilic substitution reaction of indoles with aldehydes and ketones to afford the corresponding bis(indolyl)methanes in high yields with complete regioselectivity.

KEY WORDS: bis(cyclopentadienyl) zirconium dichloride; epoxide; indoles; bis-(indolyl)methane.

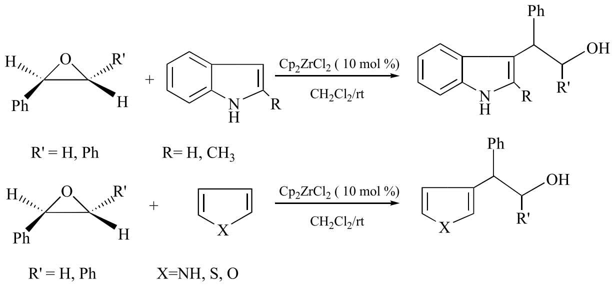
1. Introduction

Functionalized indoles and analogous heteroaromatics are the building blocks for pharmaceuticals [1]. But due to their sensitivity to acids and air, the preparation of these various derivatives poses problems to synthetic chemists. A thorough literature survey has revealed that few Lewis acid catalyzed acetylation reactions of heteroaromatics have been reported but the drawbacks of those reactions are potential side reactions [2]. At present, the largest use of zirconocenes and their analogues is as polymerization catalysts [3] and the other applications in organic synthesis is limited [4].

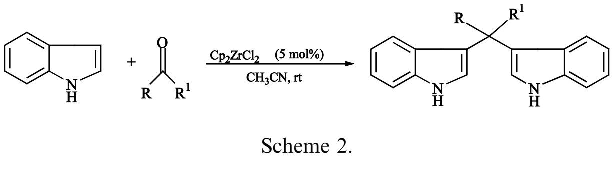
Alkylation of heteroaromatics with epoxide has been reported using lanthanide triflates [5] or silica gel under high pressures [6] and indium trichloride [7]. Major demerits of these methods involve the use of expensive reagents, drastic conditions, prolonged reaction times, and unsatisfactory yields especially in the case of aliphatic epoxides accompanied by undesirable side reactions due to polymerization or rearrangement of oxiranes.

A large number of natural products containing bis(indolyl)methanes have been isolated from marine sources during the past few years. Some of these have been found to have biological activity [8]. The reaction of electron rich heterocyclic compounds with *p*-dimethylaminobenzaldehyde under acid catalysis is well known as Ehrlich test for identifying the π-electron heterocycles such as pyrroles and indoles [9]. The analogous reaction of indoles with other aromatic/aliphatic aldehydes and ketones leads to the formation of azafulvenium salts. The azafulvenium salts undergo further addition with another indole molecule to afford bis(indolyl)methanes. Protic acids [10], Lanthanide triflates [11] and other Lewis acids [12] were found to catalyze this reaction; however, more than stoichiometric amounts of the Lewis acids are required because the acids are deactivated as they are trapped by nitrogen [13].

In continuation of our interest in the use of bis(cyclopentadienyl)zirconium dichloride as catalyst in the ring opening of epoxides [14], we herein report a convenient and efficient method for the regioselective ring opening of epoxides with different heteroaromatics to produce the corresponding 3-alkylated heteroaromatic derivatives of biological importance (Scheme 1) and the synthesis of bis(indolyl)methanes by the reaction of indoles with substituted benzaldehydes and ketones (Scheme 2) using bis(cyclopentadienyl)zirconium dichloride as a catalyst.



Scheme 1.



Scheme 2.

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2. Experimental

2.1. Preparation of the catalyst

The catalyst bis(cyclopentadienyl)zirconium dichloride was synthesized following the reported literature procedure [15]. Sodium metal (2.4 g, 0.1 mol) was dispersed in 15 mL of toluene at 115 °C to obtain particle size ca. 50 μm under a blanket of nitrogen. To this dispersion the cyclopentadiene monomer (10 mL, 0.12 mol) was added dropwise at 0 °C over a period of 15 min and then allowed to stir at room temperature for 4 h under nitrogen atmosphere to obtain sodium cyclopentadienide. A suspension of zirconium tetrachloride (11.6 g, 0.05 mol) was prepared by using dry THF (10 mL) under nitrogen atmosphere and the formed sodium cyclopentadienide was added to it dropwise over a period of 20 min and then allowed to stir for 4 h. The reaction mixture was concentrated by rotovapor and the solid obtained was subjected to Soxhlet extraction with chloroform, saturated with HCl gas, for 6 h. The chloroform extract was concentrated to ca. 10 mL and crystallized at −30 °C (dry ice/acetone) to get the pure catalyst (9.1 g, 62% Yield).

2.2. Typical experimental procedure for alkylation of heteroaromatics with epoxides

A mixture of styrene oxide (5 mmol), indole (5 mmol) and bis(cyclopentadienyl)zirconium dichloride (10 mol%) in dichloromethane (15 mL) was stirred at ambient temperature for an appropriate time. After the completion of reaction, as indicated by TLC, the reaction mixture was diluted with water (2 mL × 10 mL) and extracted with dichloromethane (2 mL × 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated in vacuum and purified by column chromatography on silica gel (Merck, 60–120 mesh, ethyl acetate-hexane 2:8) to afford the pure product (Table 1, entry 1). 2-(3-indolyl)-2-phenylethanol: Solid, m.p. 122 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.5(s, 1H,OH), 4.15(dd, 1H, J = 10.5, 6.95 Hz), 4.20(dd, 1H, J = 10.5, 6.95 Hz), 4.45(t, 1H, J = 7.82 Hz), 6.95–7.3(m, 9H) 7.44(d, 1H, J = 7.8 Hz), 8.05(brs, NH, 1H); IR (KBr): 3520, 3050, 1640, 1500, 1240, 770 cm^{-1}; EIMS m/z:237(M$^+$).

2.3. Typical experimental procedure for synthesis of bis(indolyl)methanes

To a mixture of indole (2.5 mmol), benzaldehyde (1.25 mmol) in acetonitrile (7 mL), bis(cyclopentadienyl)zirconium dichloride (5 mol%) was added and stirred for the appropriate time. When the reaction was completed, water (10 mL) was added to quench the reaction and extracted with CH_2Cl_2(3 mL × 10 mL). The combined organic layers were dried using anhydrous Na_2SO_4, filtered and the solvent evaporated. The crude product was purified by column chromatography, eluted with ethyl acetate-petroleum ether mixture to afford the pure product Table 2, entry 1). 3, 3'-Bis-indolylphenylmethane: Solid (pink color); mp126 °C; ^{1}H NMR (200 MHz, CDCl3):δ, 5.8(s, 1H), 7.3(m, 9H), 6.6(s, 2H), 6.99(t, 2H, J = 9.09 Hz), 7.80(br, 2H), 7.1 (t, 2H, J = 9.09 Hz); IR(KBr) 3416, 1630, 1376, 740; EIMS m/z: 322 (M$^+$).

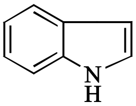
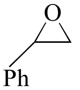
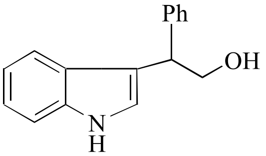
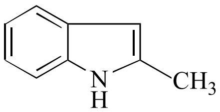
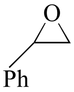
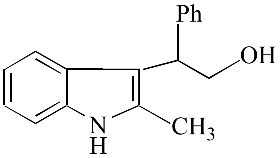
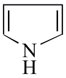
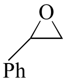
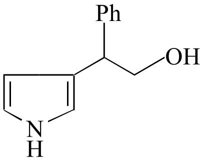
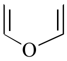
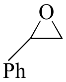
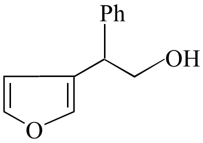
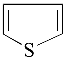
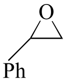
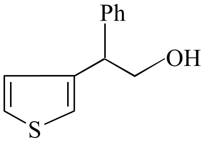
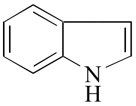
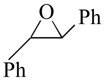
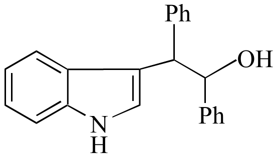
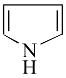
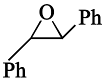
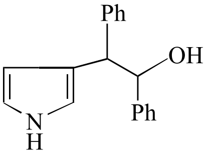
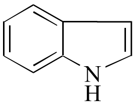
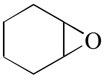
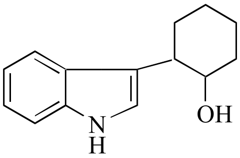
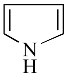
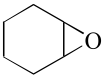
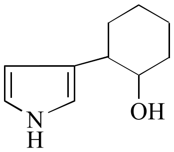
3. Results and discussion

The results obtained in alkylation of heteroaromatics with epoxides are summarized in the table 1. Aryl epoxides underwent cleavage by indole, pyrrole, furan and thiophene with preferential attack at the benzylic position resulting in the formation of primary alcohol. Since 3-position of indole is the preferred site for electrophilic substitution reactions, 3-alkyl indole derivatives were obtained as a single regio-isomer, similarly in case of five member heteroaromatics, 3-alkyl heteroaromatic derivatives were obtained as a single regio-isomer exclusively in all the reactions and characterized by ^{1}H NMR, IR and Mass spectra. This method is extended to 1,2-disubstituted and alicyclic epoxides with heteroaromatics, only *N*-heteroaromatics yield ring opened products. The reactions proceeded smoothly at ambient temperature with high regioselectivity. The process is convenient and simple, as it does not involve any drastic reaction conditions table 1).

The electrophilic substitution reactions of indole with aldehydes or ketones proceeded smoothly at ambient temperature to afford the corresponding bis(indolyl)methane derivatives in good to excellent yields. The results are summarized in table 2. The presence of electron withdrawing and electron donating group exerted little influence on the reactivity pattern. The nitro substituted aryl aldehydes (entry 2) required longer reaction time to produce comparable yields than those of their simple and electron rich counterparts (entry 3). The reaction of indole with ketones such as cyclohexanone and cyclopentanone afforded the products in moderate yields with longer reaction times when compared to aldehydes (entries 1–4 versus 5–6). The unique activity can be contributed to its mild Lewis acidity which activates the carbonyl group as well as the indole moiety to promote the reaction.

In conclusion, this letter describes a simple, convenient and efficient protocol for the alkylation of heteroaromatics with epoxides and the synthesis of bis(indolyl)methanes by the reaction of indole with aldehydes or ketones in presence of bis(cyclopentadienyl)zirconium dichloride. The notable merits of this protocol are mild reaction conditions, high selectivity,

Table 1
Bis(cyclopentadienyl)zirconium dichloride catalyzed alkylation of heteroaromatics with epoxides[a]

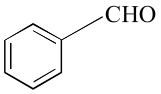
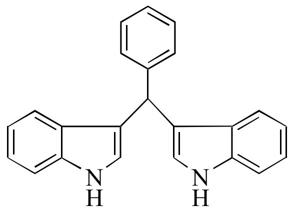
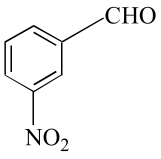
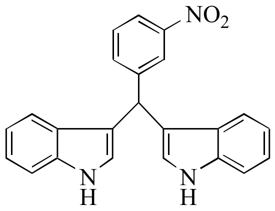
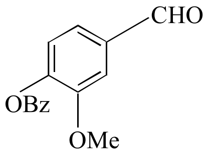
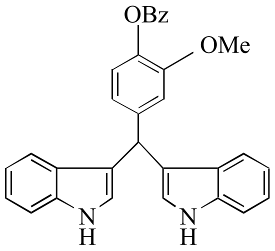
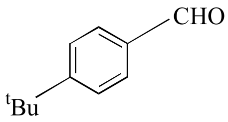
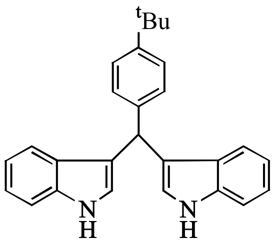
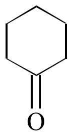
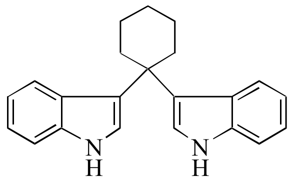
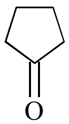
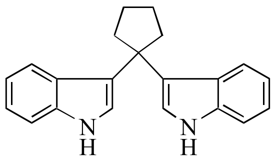
Entry	Heteroaromatics	Epoxide	Time(h)	Product[b]	Yield[c] (%)
1			4		97
2			10		85
3			18		84
4			22		77
5			18		71
6			18		82
7			20		71
8			24		68
9			22		73

[a] Reaction conditions: catalyst (10 mol%), epoxide (5 mmol), heteroaromatics (5 mmol), DCM(15 mL).

[b] All products were characterized by ^{1}H NMR, IR and Mass spectra.

[c] Isolated yields calculated based on the epoxide used.

Table 2
Bis(cyclopentadienyl)zirconium dichloride catalyzed synthesis of bis(indolyl) methanes using indole with aldehydes and ketones[a]

Entry	Aldehydes/Ketones	Time(h)	Product	Yield[b] (%)
1		36		79
2		44		70
3		40		76
4		30		85
5		55		56
6		52		60

[a] Reaction condition: catalyst (5 mol%), indole (2.5 mmol), aldehyde/ketone (1.25 mmol), acetonitrile (7 mL).

[b] All products were characterized by ^{1}H NMR, IR and Mass spectra. Isolated yields calculated based on the indole used.

cleaner reaction profiles, improved yields and simple experimental and work-up procedure.

Acknowledgment

KA thanks CSIR, New Delhi for the award of fellowship.

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