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Friedel–Crafts alkylation of indoles with epoxides catalyzed by nanocrystalline titanium(IV) oxide

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Abstract—Friedel–Crafts alkylation of indoles with epoxides to afford 3-alkyl indole derivatives at room temperature with moderate to good yields and high regioselectivity using nanocrystalline titanium(IV) oxide catalyst is described.

3-Alkylindole derivatives have significant biological and pharmacological importance[1,2] and can be prepared by Friedel–Crafts alkylation of indoles using epoxides. Epoxide ring opening with different nucleophiles[3] is generally carried out with acid or base catalysts.

Epoxide ring opening with indoles has been reported using high-pressure conditions[4] or SiO_2[5] or lanthanide triflate catalysts.[6] In recent years, indium reagents have emerged as mild Lewis acids, which can promote several organic transformations. $InCl_3$[7] as well as $InBr_3$[8] have been used in the Friedel–Crafts addition of indoles with epoxides. Recently, highly enantioselective addition of indoles with aromatic epoxides catalyzed by chromium salen complexes was reported.[9]

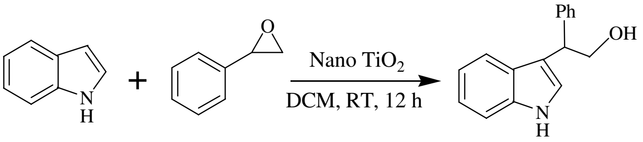
Industry favors catalytic processes induced by heterogeneous catalysts over homogeneous processes in view of the ease of handling, simple work-up, and regenerability. Nanocrystalline metal oxides have attracted attention due to their unusual magnetic, physical and surface chemical and catalytic properties.[10–12] These materials can exist with numerous surface sites with enhanced surface reactivity such as crystal corners, edges or ion vacancies.[13] Recently, Choudary et al. reported asymmetric Henry and Michael addition reactions catalyzed by nanocrystalline magnesium oxide (MgO) with good to excellent enantioselectivity.[14]

Titanium dioxide is a prominent material for various kinds of industrial applications related to catalysis, e.g. in the selective reduction of NO_x in stationary sources, photocatalysis for pollutant elimination or organic synthesis, photovoltaic devices, sensors, and paints.[15]

We herein report the use of recyclable, nanocrystalline titanium(IV) oxide (nano TiO_2) catalyst for the Friedel–Crafts alkylation of indoles with epoxides affording 3-alkyl indole derivatives at room temperature with moderate to good yields and high regioselectivity. Treatment of indole with styrene oxide resulted in the formation of 2-(3-indolyl)-2-phenylethanol in 64% yield using 10 mol % nano TiO_2 (Scheme 1).

Various types of nanocrystalline metal oxides (nano TiO_2, nano ZnO, nano CuO) as well as commercially available bulk TiO_2 were evaluated for the Friedel–Crafts alkylation of indoles with styrene oxide. Nano TiO_2 was found to be more active when compared to the other metal oxides tested (Table 1, entries 5–8). Among the different solvents used, dichloromethane gave the optimum yield (Table 1, entries 1–5).

To test the generality and scope of this nano TiO_2 catalyzed reaction, an array of structurally divergent



Scheme 1. Nano TiO_2 catalyzed Friedel–Crafts alkylation reaction of indole with styrene oxide.

Keywords: Nano TiO_2; Epoxide; Indole; Heterogeneous catalyst.

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epoxides and substituted indoles were tested. From NMR spectral data it was evident that aryl epoxides underwent cleavage by indole with preferential attachment at the benzylic position, resulting in the formation of primary alcohols (Table 2, entries 1–10) or secondary alcohols (Table 2, entries 11 and 12). Since the 3-position of indole is the preferred site for electrophilic substitution reactions, 3-alkyl indole derivatives were obtained exclusively in all reactions.

In general, indoles bearing electron-donating groups furnished higher reaction rates, affording the alcohols in moderate to good yields. On the other hand, the presence of electron withdrawing groups on the indole significantly decreased the rate of the reaction and a low yield of product was obtained even after prolonged reac-

Table 1. Screening of reaction parameters for addition of indoles to aromatic epoxides[a]

Entry	Solvent	Time (h)	Catalyst	Yield (%)[b]
1	MeCN	24	Nano TiO_2	43
2	CH_3NO_2	24	Nano TiO_2	30
3	THF	24	Nano TiO_2	20
4	Toluene	24	Nano TiO_2	52
5	CH_2Cl_2	12	Nano TiO_2	64, 62[c]
6	CH_2Cl_2	24	Commercial TiO_2	Trace
7	CH_2Cl_2	24	Nano ZnO	>5
8	CH_2Cl_2	24	Nano CuO	10

[a] Reaction conditions: Indole (2.25 mmol), styrene oxide (1 mmol), catalyst (10 mol %), solvent (3 mL), room temperature.

[b] Isolated yields.

[c] Isolated yield after the fifth cycle.

Table 2. Alkylation of indoles with epoxides using nano TiO_2[a]

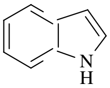
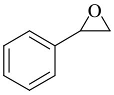
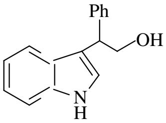
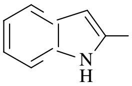
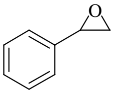
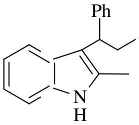
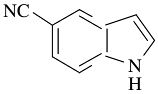
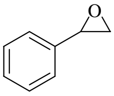
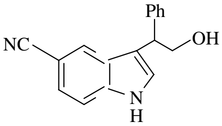
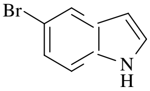
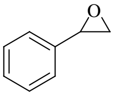
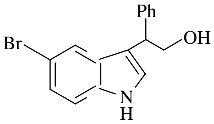
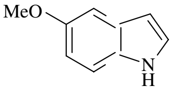
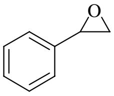
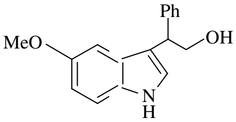
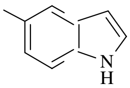
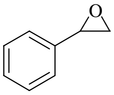
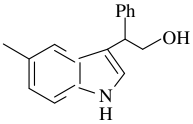
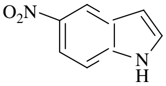
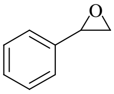
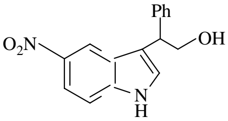
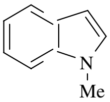
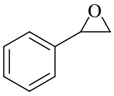
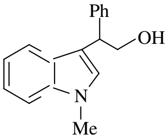
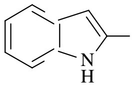
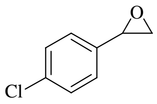
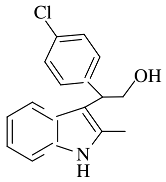
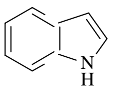
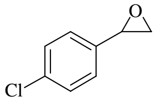
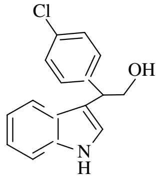
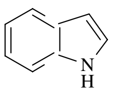
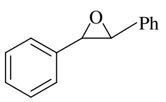
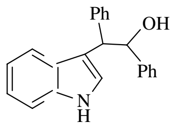
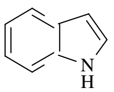
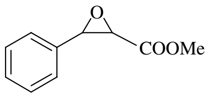
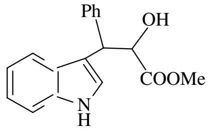
Entry	Nucleophile	Epoxide	Product	Time (h)	Yield (%)[b]
1				12	64, 62[c]
2				10	68
3				32	43
4				18	68
5				10	62
6				12	67
7				62	21
8				12	68

Table 2 (*continued*)

Entry	Nucleophile	Epoxide	Product	Time (h)	Yield (%)[b]
9				10	72
10				12	66
11				18	68
12				21	61

[a] Reaction conditions: Indole (2.25 mmol), epoxide (1 mmol), all the reactions were carried out in anhydrous dichloromethane (3 mL) at room temperature, employing 10 mol % of nano TiO_2.

[b] Isolated yields.

[c] Isolated yield after the fifth cycle.

tion time. In the case of 5-nitro- and 5-cyanoindoles very low yields of the product were observed. In all cases, a single regioisomer was obtained and the structure was established by IR, ^1H NMR and mass spectroscopic studies. This method does not require anhydrous solvents or stringent reaction conditions. The reactions were highly regioselective affording good yields of products in a short period of time. It is interesting to note that the presence of strongly coordinating groups in this reaction is well tolerated (Table 2, entries 3 and 7).

To understand the reason behind the increased activities of nano TiO_2 over the other nanocrystalline metal oxides used, ammonia temperature programmed desorption (TPD) tests of the samples were run. In the ammonia TPD test, nano TiO_2 (16.150 mL/g) showed greater desorption of ammonia over commercial TiO_2 (0.1422 mL/g), nano ZnO (15.5947 mL/g) and nano CuO (14.5028 mL/g).

Therefore, the increased activities of nano TiO_2 over the other samples tested may be due to increased acidity. Besides this, nano TiO_2 has higher surface area (500 m^2/g) and higher porosity than commercial TiO_2 (SA: 10.69 m^2/g), which may contribute to its increased chemical reactivity.

To conclude, we have shown that nano TiO_2 is a highly active, reusable[16] catalyst for the Friedel–Crafts reactions of indoles with epoxides. Thus nano TiO_2 with its well-defined shape and size (10–20 nm) and higher specific surface area shows higher activity than other catalysts.

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16. General experimental and recycling procedure: Nano TiO_2 (10 mol %) was added to a mixture of indole (2.25 mmol) and styrene oxide (1 mmol) in anhydrous dichloromethane (3 mL) and the mixture was stirred at room temperature for 12 h. After completion of the reaction as monitored by TLC, the catalyst was centrifuged and washed with ether and DCM. The reaction was quenched with a saturated solution of $NaHCO_3$ (3 mL) and extracted with ether. The combined organic layers were separated and dried over Na_2SO_4. The resultant organic layer was concentrated to give crude 2-(3-indolyl)-2-phenylethanol (Table 2, entry 1) and unreacted indole. Column chromatography was performed using silica gel (100–200 mesh) to afford the pure product after removing the unreacted indole.[8] Yield: 64%, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.61 (br, 1H), 4.18–4.23 (m, 2H), 4.50 (t, $J = 6.7$ Hz, 1H), 7.03–7.48 (m, 10 H), 8.11 (br, 1H); EIMS *m*/*z*: 237 (25), 206 (100), 178 (30), 128 (15), 102 (10), 77 (15), 63 (5), 51 (11). The reusability of the catalyst was assessed after activating the catalyst at 250 °C for 1 h. The nano TiO_2 was reused for five cycles with consistent activity. All the products (except those from entries 9 and 10, Table 2) are reported compounds which were identified by IR, ^{1}H NMR and mass spectroscopic data.[8,9] Spectroscopic and analytical data of new compounds. 2-(2-Methyl-1*H*-indol-3-yl)-2-(4-chlorophenyl)-ethanol (Table 2, entry 9): Yellow oil. Yield: 72%, ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.35 (br, 1H), 2.42 (s, 3H), 4.05–4.12 (m, 2H), 4.36 (t, $J = 7.5$ Hz, 1H), 6.87–7.30 (m, 8H), 7.52 (br, 1H). EI-MS *m*/*z* (relative intensity) 285 (20), 254 (100), 204 (18), 176 (28), 110 (12), 77 (15), 52 (18). IR(neat) 3530, 3397, 3055, 2924, 1616, 1590, 1566, 1488, 1459, 1300, 1092, 1015, 749. Anal. Calcd for ($C_{17}H_{16}ClNO$): C, 71.45, H, 5.64, N, 4.90. Found: C, 71.54; H, 5.67; N, 4.85. 2-(1*H*-Indol-3-yl)–2-(4-chlorophenyl)-ethanol (Table 2, entry 10): Yellow oil. Yield: 66%, ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.50 (br, 1H), 3.96–4.17 (m, 2H), 4.34 (t, $J = 6.6$ Hz, 1H), 6.86–7.40 (m, 9H), 8.08 (br, 1H). EI-MS *m*/*z* (relative intensity) 271 (6), 241 (41), 204 (25), 121 (19), 117 (64), 84 (16), 43 (100), 37 (22). IR(neat) 3544, 3411, 3055, 2879, 1619, 1547, 1490, 1456, 1415, 1340, 1249, 1092, 1045, 1012, 746 Anal. Calcd for ($C_{16}H_{14}NO$): C, 70.72; H, 5.19; N, 5.15. Found: C, 70.78, H, 5.22, N, 5.10.