SHORT PAPER

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Ion exchange resin catalysed reactions of indole with imines: formation of diindolylmethanes[†]

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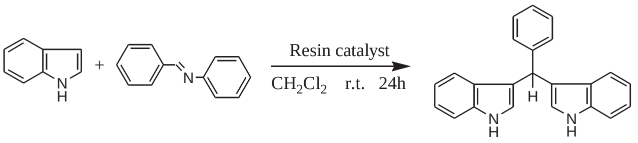
Ion exchange resins are found to catalyze the reactions of indole with imines under mild conditions, affording diindolylmethanes in good yields.

Keywords: indoles, imines, ion exchange resin, diindolylmethanes

Indole and their derivatives are used as antibiotic in the field of pharmaceuticals.[1] Diindolylmethane (DIM) is a plant compound with health-promoting properties. DIM and other plant indoles are found in all cruciferous vegetables such as cabbage, broccoli, Brussels sprouts and cauliflower.[2] These plants have been cultivated for centuries and were in early times used as medicines. About 20 years ago it was reported that when broccoli was added to the diets of study animals it could prevent certain forms of cancer. In more recent studies this same cancer protection has been shown to result from simply adding supplemental DIM or related plant indoles to the animals' diet in place of the broccoli.[3] Recently, regular use of supplementary DIM and other indole relatives has shown that many of these health-promoting effects arise from a beneficial shift in the balance of the hormones estrogen and testosterone.[4] We are therefore interested in developing new and efficient methods for the preparation of these moieties.

Traditionally, DIMs can be synthesised by condensation reactions of indoles with carbonyl compounds. Protic acids[5] as well as Lewis acids[6] are known to promote these reactions, as are also solid acid such as K10 clay.[7] Thus we are interested in exploring the use of inexpensive ion exchange resins in the synthesis of DIMs. Use of ion exchange resin catalysts offers important advantages in organic synthesis, *e.g.* simplification of reaction procedures, easy separation of products without discharge of harmful waste, repeated use of resin catalysts, and so on.

There have been limited studies on the reactions of indole with imines. It was reported that indolyl amines as the major products and DIMs as by-products were formed when catalyzed by lanthanide triflates.[8] However, we find that the DIMs are the only products when the reactions are catalysed by ion exchange resins. This may be due to the susceptibility of the imino functionality towards hydrolysis in the presence of strong protic acids.



Scheme 1 Reaction of indole with benzylideneaniline under ion-exchange resin catalysis

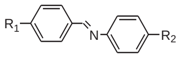
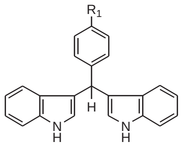
Using *N*-benzylideneaniline as the substrate (Scheme 1), we compared the catalytic activities of different resins (Table 1). It is clear that the macroporous polystyrene resins Amberlyst-35 and Amberlyst-15 (entries 3 and 1) show higher activities than other macroporous polystyrene resins (Amberlyst-16, HD82 and D001). By contrast, the catalytic efficiency of the gel-type polystyrene resin Dowex50 (entry 6) was the lowest, producing a yield of only 16%. Amberlyst-35 was further tested in the reactions of indole with five other imines. These results are summarised in Table 2.

Table 1 Catalytic efficiency of ion exchange resins in the reaction shown in Scheme 1

Entry	Catalyst	Yield[a]/%
1	Amberlyst-15	89
2	Amberlyst-16	78
3	Amberlyst-35	94
4	HD82	84
5	D001	67
6	Dowex 50	16

[a]isolated yield.

Table 2 Amberlyst-35 catalysed reactions of indole with imines

Entry	Imines 		Time /h	Products 	Yield[a] /%
1	R_1=H	R_2=H	24	R_1=H	94
2	R_1=NO_2	R_2=H	20	R_1=NO_2	79
3	R_1=NO_2	R_2=Cl	6	R_1=NO_2	51
4	R_1=Cl	R_2=CH_3	24	R_1=Cl	80
5	R_1=Cl	R_2=Cl	17	R_1=Cl	84
6	R_1=H	R_2=CH_3	24	R_1=H	76

[a]isolated yield.

Experimental

Indole was purchased from commercial sources and was recrystallised before use. Imines were synthesised according to the literature.[9] Ion exchange resins were purchased from Rohm & Hass and Shanghai Resin Factory Co. Ltd., Shanghai, China. Melting points were determined by XT-4 apparatus. IR spectra were recorded on a Perkin-Elmer spectrometer. ^{1}H NMR spectra were recorded on a Varian Mercury plus 400 MHz spectrometer and compared with authentic compounds.

Typical procedure: to a granular ion exchange resin (50mg) was added indole (110 mg, 1 mmol), *N*-benzylidene aniline (1 mmol) and CH_2Cl_2 (5ml) as solvent. The mixture was stirred at room temperature until the conversion of indole (monitored by TLC) was complete. The resin was then filtered off and washed with ethyl acetate three times. The combined solution was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether:ethyl acetate 4 : 1) to give product di-3-indolylphenylmethane (R = H) in 94% yield, m.p. 89–91 °C (lit.[6g] 88~90 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.89 (1H, s), 6.69 (2H, d, J = 3.2 Hz), 7.00 (2H, t, J = 8 Hz), 7.17 (2H, t, J = 8 Hz), 7.30 (9H, m) and 7.93 (2H, brs, NH); IR (KBr): 3412, 3046, 1637 and 746 cm^{-1}.

Product (R_1 = Cl): m.p. 77-81 °C. ^{1}H NMR: δ 5.86 (1H, s), 6.64 (2H, s), 7.02 (2H, t, J = 8.0 Hz), 7.18 (2H, t, J = 8.0 Hz), 7.25 (2H, m),

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[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

7.27 (2H, m), 7.36 (4H, d, J = 8.0 Hz) and 7.93 (2H, brs, NH); IR (KBr) 3441, 2929, 1635, 1088 and 750cm^{-1}.

Product (R_1 = NO_2): m.p. 220–222 °C (lit.[10] 220–222 °C). IR (KBr):3478, 3046, 1637, 1513, 1341, 1217 and 734 cm^{-1}.

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