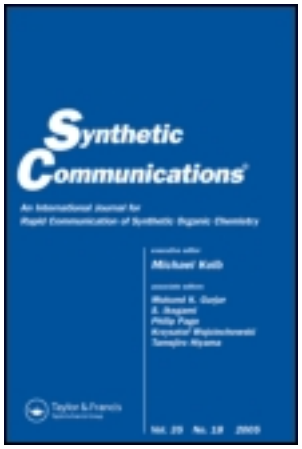

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Convenient and Scalable Process for the Preparation of Indole via Raney Nickel-Catalyzed Hydrogenation and Ring Closure

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CONVENIENT AND SCALABLE PROCESS FOR THE PREPARATION OF INDOLE VIA RANEY NICKEL–CATALYZED HYDROGENATION AND RING CLOSURE

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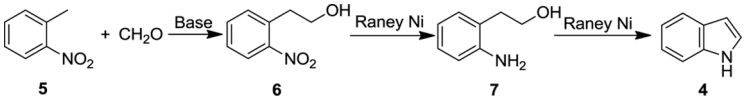
GRAPHICAL ABSTRACT



Abstract *An efficient and practical method for the synthesis of indole as a key starting material for many useful chemicals is described. Using 2-nitrotoluene as starting material, hydroxymethylation with formaldehyde under alkaline conditions gave 2-(2-nitrophenyl) ethanol on a large scale. Raney Ni catalyst was used for both reduction of the nitro group as well as for the indole formation. The overall yield was 78% from 2-nitrotoluene.*

Keywords Indole synthesis; 2-nitrotoluene; Raney Ni

INTRODUCTION

Indole (**4**) is widely used for the syntheses of pharmaceuticals, agrochemicals, perfumes, dyes, and additives to foods and feed stocks.[1–3] Although indole could be obtained by distillation from tar, the method suffered from low indole content (usually 0.2%) and increasing energy cost. Therefore, facile and economical syntheses of indole are intensively pursued. There have been papers dealing with indole ring syntheses,[4–10] but only a few are of industrial significance. According to our knowledge, three methods are currently being used to produce indole: from aniline,[11–13] 2-methylaniline,[14–16] and 2-ethylaniline.[17–23]

Unfortunately, there are some problems with present indole syntheses. Preparation of indole from 2-ethylaniline involves high temperatures (usually 600 °C)

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and expensive platinum catalyst, and the yield and selectivity are poor. Synthesis of indole from 2-methylaniline employs temperatures as high as 350 °C, and lots of thick polymer are produced in the process, which is difficult to handle and exerts a huge burden on environment. Indole synthesis from aniline and glycol developed by Mitsui Toatsu Chemicals in 1980s[11] is a good method and deserves further development, but the efforts are compromised by severe reaction conditions, nonstoichiometric molar ratio of aniline to glycol (usually 7–10:1), poor selectivity, and short catalyst life. We have now developed a new process that was successfully implemented to produce kilogram quantities of indole and is efficient and cost-effective. The details of our development work are described herein.

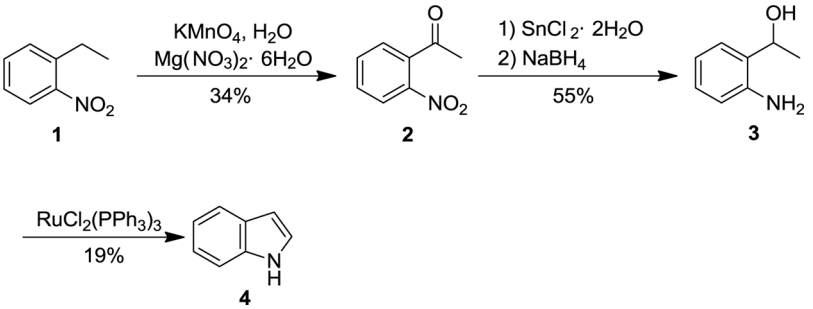
RESULTS AND DISCUSSION

At the beginning of our work, we wanted to take advantage of the superfluous supply of 2-nitroethylbenzene (**1**), a by-product from the production of chloramphenicol.[23,24] We presumed that functionalization of the ethyl side chain on the benzene ring might help to moderate the cyclization temperature and consequently increase the selectivity of indole. Upon this assumption, a route to indole (Scheme 1) was designed. Starting from 2-nitroethylbenzene, a conventional sequence of oxidation and reduction was expected to give a good yield of 2-(1-hydroxyethyl)-aniline (**3**), which was then subjected to indole synthesis. However, experimental results from every step fell short of our expectations, and the last step to indole **4** gave a yield of only 19%.

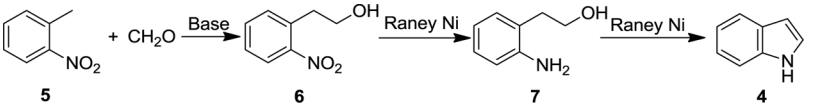
We then changed our starting material to 2-nitrotoluene (**5**), and hydroxymethylation with paraformaldehyde under alkaline conditions gave 2-(2-nitrophenyl) ethanol (**6**) (Scheme 2).[25,26] In this study, we used Raney Ni catalyst both for reduction of the nitro group as well as for the indole production in the last step. The overall yield for the three consecutive steps came as 78% based on 2-nitrotoluene.

Preparation of 2-(2-Nitrophenyl)ethanol 6

Step 1 involved base-catalyzed condensation of 2-nitrotoluene and paraformaldehyde. The main by-product is the diol **8** (Scheme 3). Different catalysts were used in this reaction,[25,27–31] and some catalysts are strongly basic anion exchange resins



Scheme 1. Synthesis of indole from 2-nitroethylbenzene.



Scheme 2. Synthesis of indole from 2-nitrotoluene.

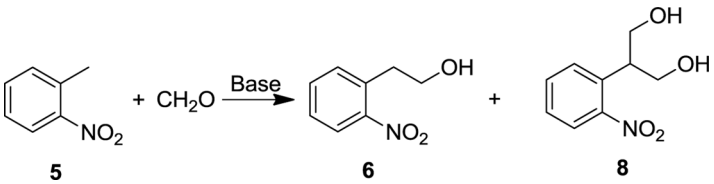
(Amberlite IRA-401, IRA-900 and IRA-900C), but no exceptional result came out (Table 1). It was decided that a 20% aqueous NaOH solution, which exhibited better balance among yield, selectivity, and economy, was the most preferable catalyst for this study.

The effect that the reaction temperature had on the hydroxymethylation is shown in Table 2, where a maximum yield of **6** was acheived at the temperature of 50 °C. The relatively narrow temperature range (40–60 °C) was used, because beyond this temperature range the rate of hydroxymethylation was too low or decreased selectivity was observed.

The effect of molar ratio of formaldehyde to **5** was studied over the range of 0.2–0.6 under the standard reaction conditions. The results are shown in Table 3. As seen from these data, a molar ratio of 0.4–0.5 gave the best results. Further increase of molar ratio of formaldehyde to 2-nitrotoluene resulted in a rapid increase of by-product **8** without substantially improving the yield.

We were frustrated that the yield of 2-(2-nitrophenyl)ethanol **6** could not be improved under the aforementioned conditions. Most of our results gave yields of **6** around 30%. In the process of optimization, we noticed a gradual reduction of alkalinity during the hydroxymethylation reaction, which could be explained by formaldehyde undergoing a Cannizzaro reaction to form formic acid, which neutralized the catalyst NaOH. It suggested to us that gradual disappearance of the catalyst might be the reason that we cannot achieve a better result. An experiment was set to explain this question. After 1.5 h of reaction under standard conditions, when pH changed from 9.4 to 7.4, a second batch of catalyst was added to the reaction mixture, and the reaction was continued for another 1.5 h. High-Performance Liquid Chromatographic (HPLC) analysis showed that contents of **6** and **8** in the reaction mixture were 35.8% and 8.5% respectively. Although the yield of **6** was increased from 31.6% to 35.8%, the content of **8** was increased more quickly from 1.8% to 8.5%.

Although the yield of 2-(2-nitrophenyl)ethanol **6** was hard to improve, the selectivity and recycling of starting materials by distillation in vacuo endow this method with practical value. In fact, we had scaled up this preparation to produce 38.4 kg of **6** in a yield of 87% (based on reacted **5**). The decomposition temperature of **6** was about 190 °C under reduced pressure (<1 mmHg).



Scheme 3. Hydroxymethylation of 2-nitrotoluene.

Table 1. Catalysts for hydroxymethylation of 2-nitrotoluene[a]

Entry	Catalysts	Catalyst/**5** (mol/mol)	Area (%) 6 [8][b]
1	Triton B, 40% w/w in methanol	0.011	31.2 [2.1]
2	PhONa	0.017	25.3 [3.5]
3	CH_3CH_2ONa	0.029	29.8 [3.1]
4	$w(NaOH) = 10\%$ (in methanol)	0.013	29.6 [2.8]
5	NaOH	0.025	36.4 [3.3]
6	$w(NaOH) = 20\%$ (in water)	0.025	30.8 [2.2]
7[c]	Amberlite IRA-401	0.027[d]	4.2
8[c]	Amberlite IRA-900	0.025[d]	7.4
9[c]	Amberlite IRA-900C	0.025[d]	3.9

[a]Reaction conditions: 13.7 g (0.1 mol) **5**, 20 mL DMSO, 1.5 g (0.05 mol) paraformaldehyde, reaction temperature 60 °C.
[b]Area percentage by HPLC.
[c]Reaction temperatures were 40 °C.
[d]Estimated by 70% total exchange capacity.

Preparation of 2-(2-Aminophenyl)ethanol 7

Two methods were reported for the reduction of 2-(2-nitrophenyl)ethanol **6** to 2-(2-aminophenyl)ethanol **7**, including the $Zn/CaCl_2/H_2O$ system and hydrogenation under Rh/C or Pd/C.[10a] The former method was not desirable because of environmental and economic factors. The latter method was reasonable if an effective and economical catalyst was found with adequate reuse. The Rh/C catalyst was excluded because of the high cost of catalyst, so only commonly used Pd/C (5%, 10%) and Pt/C (3%) catalysts were tested under atmospheric hydrogen. It turned out that Pd/C was not an effective catalyst in this reaction, possibly because of strong hydroxyl (or amino) absoption and poisoning on palladium surface. Pt/C exhibited only low activity in this condition. After 7 h of reaction under Pt/C, by-product **7** was formed in a yield of 15%. Studies on catalytic hydrogenation with Raney Ni turned out to be successful. Simple optimized experiments showed the reaction could best be carried out under conditions of 110 °C and 2 MPa hydrogen pressure, and it could be carried out in liquid paraffin or even without a solvent as long as reaction heat was removed from system continuously. The activity of Raney nickle was rather stable (Table 4) under these conditions. It was clear from this stability data that reaction time was prolonged with each run, which could be explained

Table 2. Temperature screen for hydroxymethylation[a]

Entry	Temperature (°C)	Reaction time (h)	Area (%) 6 [8][b]
1	40	3.0	29.6 [1.6]
2	50	2.0	31.6 [1.8]
3	60	2.0	30.8 [2.2]

[a]Reaction conditions: 13.7 g (0.1 mol) **5**, 20 mL DMSO, 1.5 g (0.05 mol) paraformaldehyde, 0.5 g 20 w% NaOH aqueous solution.
[b]Area percentage by HPLC.

Table 3. Molar ratio for hydroxymethylation[a]

Entry	Molar ratios (formaldehyde to **5**)	Reaction time (h)	Area (%) 6 [8][b]
1	0.2	1.5	17.0 [1.9]
2	0.4	1.5	28.5 [2.9]
3	0.5	2.0	31.6 [1.8]
4	0.6	1.6	34.1 [6.1]

[a]Reaction conditions: 13.7 g (0.1 mol) **5**, 20 mL DMSO, reaction temperature 50 °C, 0.5 g 20 w% NaOH aqueous solution.
[b]Area percentage by HPLC.

by catalyst granules' fragmentation under strong mechanical stirring and loss in separation. In general, Raney Ni worked well in this reaction.

Preparation of Indole 4 (Scheme 2, Step 3)

It is known that 2-(2-aminophenyl)ethanol can be converted into indole by hydrogenation in the presence of a catalyst such as homogeneous ruthenium catalyst,[25] Raney nickel,[26] and Cu/Al_2O_3.[32] These reactions proceed readily without the aid of a hydrogen acceptor, and indole is afforded in excellent yields with spontaneous hydrogen evolution. Addition of transitional metals (with the exception of ruthenium) could enhance the Raney nickel activity, and palladium showed the greatest effect. Further addition of triphenyl phosphine enhanced the effect even more. Addition of triphenyl phosphine to the Raney Ni-Rh system showed the optimal results. However, it had no effect at all on single Raney nickel system (Table 5). It occurred to us that in using Raney nickel as catalyst for indole formation, the reaction might have proceeded first by dehydrogenation of the side chain ethanol group to form an aldehyde and then by joining with the amino group to form the ring.

It was observed that when Raney nickel was used as catalyst for this reaction, an unexpected by-product was produced (Scheme 4). We isolated this by-product, and further purification by chromatography gave this by-product as yellow solid in a yield of 15%, whose structure was assigned unambiguously as 2,3′-biindolyl **9**

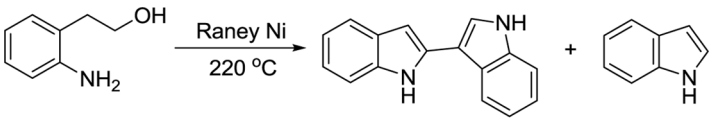
Table 4. Stability experiment (recycle) of Raney Ni catalyst[a]

Run	Reaction time (h)	Weight of product **7** (g)	Yield (%)
1	12.2	977	97.0
2	14.5	991	98.4
3	14.2	999	99.2
4	15.7	1003	99.6
5	16.3	1002	99.5
6	16.9	1000	99.3
7	18.5	997	99.0

[a]Reaction conditions: 1228 g (1.0 L) 2-(2-nitrophenyl)ethanol **6**, reaction temperature 110 °C, hydrogen pressure 2 MPa, 62.0 g Raney Ni (recycled), no solvent. Reaction time was calculated at the end of reaction.

Table 5. Effects of addition of transition metals and PPh_3

Transition metal	PPh_3	Time of cyclization (h)
N/A	N/A	5.0
	PPh_3	5.0
$RuCl_3 \cdot nH_2O$	N/A	>5.0
	PPh_3	1.75
$RhCl_3 \cdot 3H_2O$	N/A	2.75
	PPh_3	0.5
$Pd(CH_3COO)_2$	N/A	1.75
	PPh_3	1.25



7 9 8

Scheme 4. Formation of 2,3′-diindolyl **9**.

through its ^1H NMR, ^{13}C NMR, and Infrared (IR) spectra.[33] We now know the formation of **9** could be prevented by removing oxygen from the reaction system. This transformation can be a useful way to synthesize 2,3′-biindolyl and deserves further investigation (Scheme 4). Furthermore, it was observed that Raney nickel maintained a stable activity after more than 20 runs in this reaction.

EXPERIMENTAL

IR spectra (KBr pellets) were recorded on a Bio-Rad FTS 135 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV400, AV500, or Mercury 300-MHz instrument. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) used as internal standard. Organic solvents were purified by standard methods when necessary. Thin-layer chromatography (TLC) was performed on glass sheets coated with silica gel (type GF254, Qingdao Haiyang). Flash-column chromatography was carried out using silica gel (200–300) mesh. Pd on carbon (5% Pd, 10% Pd) and Pt on carbon (3% Pt) were purchased. Raney nickel was prepared according to literature methods.[34]

Preparation of 2-(2-Nitrophenyl)ethanol 6

A 500-L reactor with internal cooling was charged with 120.0 kg 2-nitrotoluene, 200.0 kg dimethyl sulfoxide, 13.1 kg paraformaldehyde, and 4.4 kg 20% aqueous sodium hydroxide. The contents were stirred for 1 h at 50 °C (reaction is exothermic), affording a dark brown solution. The reaction was quenched with concentrated HCl solution, and then 38.4 kg 2-(2-nitrophenyl)ethanol **6** (yellow thick oil, >99.5% purity by area % HPLC) was obtained by distillation in vacuo. In the meantime, 83.5 kg 2-nitrotoluene were recovered. The yield of 2-(2-nitrophenyl)ethanol was

86.7% based on recovered starting material. IR (KBr): 3360, 2945, 2882, 1524, 1348, 1043, 742 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.90, 133.83, 133.02, 132.84, 127.65, 124.88, 62.78, 36.17; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92–7.90 (dd, $J = 1.2$, 8 Hz, 1H, ArH), 7.56–7.52 (dt, $J = 1.2$, 7.6 Hz, 1H, ArH), 7.43–7.34 (m, 2H, ArH), 3.95–3.91 (t, $J = 6.4$ Hz, 2H, CH_2), 3.17–3.14 (t, $J = 6.4$ Hz, 2H, CH_2), 1.86 (br s, 1H, OH).

Preparation of 2-(2-Aminophenyl)ethanol 7

To a 5-L reactor, 446 g 2-(2-nitrophenyl)ethanol, 2000 mL liquid paraffin, and 28 g Raney Ni were added. The solution was stirred over a period of 1.5 h at 110 °C under 2 MPa hydrogen pressure. The mixture was cooled to 20 °C, and catalyst was filtered off. The filtrate was separated by liquid separation and then dried over anhydrous $MgSO_4$ to afford burgundy 2-(2-aminophenyl)ethanol **7** 354 g (yield 97%). IR (KBr): 3361, 3252, 2943, 2879, 1625, 1498, 1043, 753 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.87, 130.49, 127.54, 124.38, 119.17, 116.23, 63.05, 34.66; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.07–7.06 (dd, $J = 1.2$, 3.2 Hz, 2H, ArH), 6.79–6.75 (dt, $J = 1.2$, 7.6 Hz, 1H, ArH), 6.79–6.75 (d, $J = 7.6$ Hz, 1H, ArH), 3.90–3.87 (t, $J = 6$ Hz, 2H, CH_2), 3.17 (br s, 3H, NH_2 and OH), 2.80–2.77 (t, $J = 6$ Hz, 2H, CH_2).

Preparation of Indole 4

To a 250-mL, four-necked flask equipped with thermometer, Dean–Stark trap, condenser, and mechanic stirrer, 80 g 2-(2-aminophenyl)ethanol, 80 mL liquid paraffin, and 10 g Raney Ni were charged. The mixture was stirred for 5 h at 220 °C under nitrogen protection. Water (16 g) was collected from the Dean–Stark trap. The mixture was cooled to 80 °C, and Raney nickel was filtered off. The filtrate was distilled in vacuo to afford 60.3 g indole as a white crystalline solid (yield 88.3%, 99.8% purity by area % HPLC). IR (KBr): 3402, 1456, 1415, 1337, 1247, 1090, 1059, 747, 725 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 136.04, 128.10, 124.47, 122.24, 121.02, 120.10, 111.34, 102.83; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.98 (br s, 1H, NH), 7.66–7.63 (dd, $J = 1.2$, 10 Hz, 1H), 7.35–7.33 (d, $J = 10.8$ Hz, 1H), 7.22–7.09 (m, 3H), 6.55–6.53 (m, 1H).

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(d, $J = 2.5$ Hz, 1H), 7.50–7.46 (q, $J = 7.5$ Hz, 2H), 7.36–7.34 (d, $J = 2.5$ Hz, 1H), 7.19–7.13 (m, 2 H), 7.04–7.01 (t, $J = 7.5$ Hz, 1H), 6.97–6.94 (t, $J = 7.5$ Hz, 1H), 6.75–6.75 (d, $J = 2.0$ Hz, 1H).

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