Synthesis of 1-substituted indoles by the vapour phase reaction of *N*-substituted anilines with glycols and epoxides over a solid catalyst and a vapour phase dealkylation of 1-alkylindole

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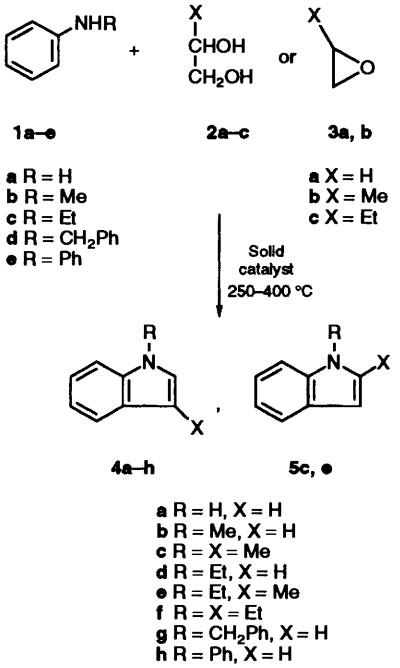
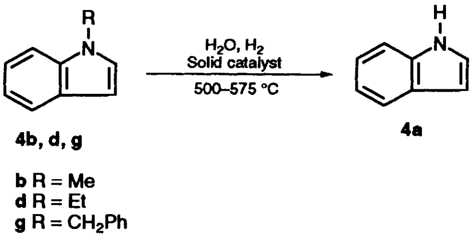
1-Substituted indoles **4b–h**, **5c**, **e** were synthesized in good yields by the vapour phase reaction of *N*-substituted anilines **1b–e** with glycols **2a–c** and epoxides **3a**, **b** at 250–400 °C over a solid catalyst, Neobead P (Al_2O_3:SiO_2:Na_2O = 88:9:3), at atmospheric pressure. 1-Alkylindoles **4b**, **d**, **g** were converted into indole (**4a**) in good yields by a vapour phase reaction with steam and hydrogen gas over ZnO (10%) supported on Neobead C (Al_2O_3) at 500–575 °C. These reaction pathways are discussed.

Indole and 1-substituted indoles are biologically and pharmacologically important compounds.[1] A large number of methods have been developed for the synthesis of the indole heterocycle.[2] From an industrial point of view the vapour phase reaction is often advantageous over the conventional liquid phase reaction in that the products can be obtained continuously with ease of operation. Several vapour phase methods of forming the indole heterocycle have been reported.[3] These methods include those based on the direct reactions of styrene with ammonia,[4] aniline with alcohols,[5] ethylene[6] and acetylene,[7] and *N*-ethylaniline,[8] in which inexpensive and readily available compounds are used as starting materials. In these reactions, however, the yields of indoles were unsatisfactory, probably due to the decomposition of the starting materials and the products which would be induced by the extremely high reaction temperature.

In this paper,[9] we report an efficient synthesis of 1-substituted indoles **4b–h**, **5c**, **e** by the vapour phase reactions of *N*-substituted anilines **1b–e** with glycols **2a–c** and epoxides **3a**, **b** at a relatively low temperature over a solid catalyst which does not contain a noble or heavy metal (Scheme 1).[10] The transformation of 1-alkylindoles **4b**, **d**, **g**, which are obtained by this method, to indole (**4a**) using a vapour phase reaction is also described (Scheme 2). In addition, these reaction pathways are discussed.



Scheme 1



Scheme 2

Results and discussion

We first examined the vapour phase reaction of aniline (**1a**) with ethylene glycol (**2a**) at atmospheric pressure in order to select a solid catalyst by using the continuous flow-system apparatus (see Fig. 7). Table 1 summarizes the results of the vapour phase reaction of **1a** with **2a** using a variety of solid catalysts such as alumina gel (runs 1 and 2), silica gel (run 3) and zeolite (run 4) which are generally used as solid acid catalysts, MgO (run 5) generally used as a solid base catalyst, silicon carbide (run 6) and active carbon (run 7). As the product distributions were considerably influenced by the reaction temperature using the individual catalyst, the yield and selectivity of **4a** were compared at the temperature where the catalytic activity for the formation of **4a** was highest. The yield of **4a** is calculated on the basis of the amount of **1a** supplied using GC. Neobead P (Al_2O_3:SiO_2:Na_2O = 88:9:3) was the most effective of the catalysts shown in runs 1–7; **4a** was obtained in 13.5% yield and 26.3% selectivity. To improve the catalytic properties of Neobead P, several metal oxides were supported with Neobead P (runs 8–12). However, the yield and selectivity of **4a** were not so good as those using Neobead P. In the reaction of **1a** with **2a**, the yield and selectivity of **4a** were low because of the production of a number of by-products such as 1-ethylindole (**4d**), 3-methylindole (**7**) and 2-methylquinoline.

Next, the vapour phase reaction of *N*-ethylaniline (**1c**) with **2a** was carried out using alumina gels which were useful in

Table 1 Effect of catalysts on the vapour phase reaction of **1a** with **2a**

			Product (**4a**)	
Run	Catalyst[a]	T/°C	Yield[b] (%)	Selectivity[b] (%)
1	Neobead P	350	13.5	26.3
2	Neobead C	300	4.9	12.8
3	Silica gel (white)	350	5.5	12.8
4	F-9	350	1.0	1.8
5	MgO	300–400	0	0
6	TSS-99205	250–400	0	0
7	Active carbon	400	5.1	17.0
8	Fe_2O_3–Neobead P	300	13.4	14.9
9	Cr_2O_3–Neobead P	350	10.5	14.1
10	Sb_2O_3–Neobead P	300	5.6	6.7
11	CoO–Neobead P	350	11.9	18.0
12	WO_3–Neobead P	300	7.3	8.0

[a] The chemical compositions of the catalysts are described in the Experimental section. [b] Yield and selectivity were defined as follows: yield (%) = (mol of **4a** formed/mol of **1a** supplied) × 100; selectivity (%) = (mol of **4a** formed/mol of **1a** reacted) × 100.

Table 2 Effect of catalysts on the vapour phase reaction of **1c** with **2a**

		Product (**4d**)	
Catalyst	T/°C	Yield (%)	Selectivity (%)
Neobead P	300	42.2	71.9
Neobead D	250	12.7	22.3
Neobead C	250	9.2	19.8
K_2O (1%)–Neobead C	300	26.7	35.2
K_2O (3%)–Neobead C	300	25.5	45.5
K_2O (5%)–Neobead C	300	27.8	73.9
K_2O (7%)–Neobead C	350	31.8	62.8
K_2O (10%)–Neobead C	350	16.1	47.6

the reaction of **1a** with **2a** (Table 2). The best result was also obtained with the use of Neobead P as a catalyst. The yield of **4d** remarkably increased compared with that of **4a** which was obtained by the reaction of **1a** with **2a**; **4d** was obtained in 42.2% yield with a good selectivity. In this reaction, 1-ethyl-3-methylindole (**4e**) and 1,3-diethylindole (**4f**) were formed as by-products in 1.5% and 11% yields, respectively. On the other hand, in the use of Neobead C (Al_2O_3 = 100) and Neobead D ($Al_2O_3 : SiO_2$ = 90:10) **4d** was obtained in a low yield. Neobead P is an alumina gel in which acidity is neutralized on the surface of Neobead D. Thus, the low activities of these catalysts are probably due to the high acidity of the surface. In fact, when the reaction was carried out by using the Neobead C treated with 7% potassium oxide, the yield of **4d** increased up to 31.8%. However, treatment with more potassium oxide did not give a good result. Therefore, this vapour phase reaction is thought to proceed effectively over alumina or aluminosilicate with a moderate surface pH.

Using Neobead P, we next examined the effect of the molar feed ratio of **2a** to **1c** (p^0_{2a}/p^0_{1c}) on the product yield of **4d** as shown in Fig. 1(*a*), where p^0_{1c} and p^0_{2a} stand for the initial partial pressure of **1c** and **2a**, respectively. The total yield of indole derivatives (**4d** + **4e** + **4f**) increased remarkably with the molar ratio of p^0_{2a} to p^0_{1c}, and the yields of **4d**, **e** and **f** did not depend on the molar ratio of p^0_{2a} to p^0_{1c} when p^0_{2a}/p^0_{1c} was $\geqslant 2$. Because a small amount of **1a** was formed when p^0_{2a}/p^0_{1c} was < 1, it is thought that the deethylation of **1c** is depressed in the presence of excess **2a**. Fig. 1(*b*) also illustrates the effect of the contact time (W/F) on the product yields when $p^0_{2a}/p^0_{1c} = 2$; W is the weight of catalyst (g-cat) and F is the total (mol) of the starting compounds and the diluents supplied per hour (mol h^{-1}). The yield of **4d** gradually increased with W/F, and became nearly constant when W/F was $\geqslant$49.6 g-cat h mol^{-1}, while the selectivity of **4d** decreased slightly with increasing W/F. Moreover, when W/F was small, **4e** and **f** were not obtained. These facts suggest that **4e** and **f** may be produced *via* **4d**.

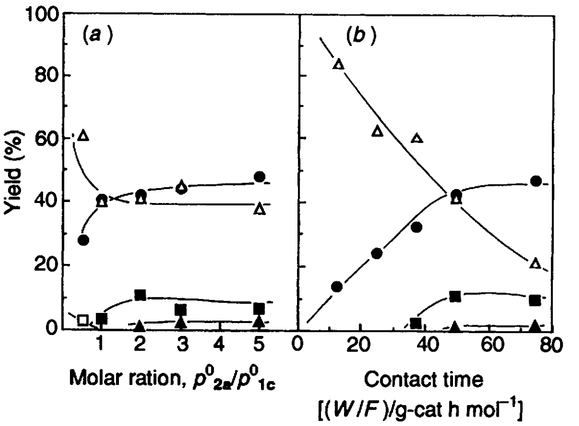


Fig. 1 Effects of the molar feed ratio of **2a** to **1c** (*a*) and the contact time (*b*) on the product distribution in the reaction using Neobead P at 300 °C. Symbols: ●, **4d**; ▲, **4e**; ■, **4f**; □, **1a**; △, **1c**. Reaction conditions: (*a*) W/F = 49.6 g-cat h mol^{-1}, $p^0_{1c} = 0.0205$, $p^0_{N_2} = 0.161$, $p^0_{H_2O}$ = 0.808, 0.798, 0.778, 0.757, 0.716 atm; (*b*) $p^0_{1c} = 0.0205$, $p^0_{2a} = 0.0409$, $p^0_{N_2} = 0.161$, $p^0_{H_2O} = 0.778$ atm.

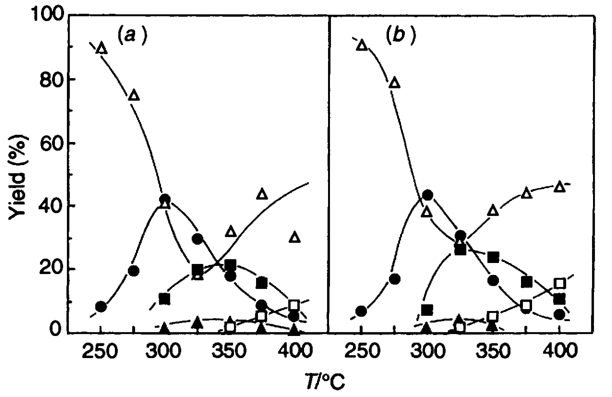


Fig. 2 Effect of the reaction temperature on the vapour phase reaction of **1c** with **2a** (*a*) and **3a** (*b*) over Neobead P. The symbols are the same as those described in Fig. 1.

From these results, it was found that the reaction should be carried out by the use of Neobead P under the reaction conditions where p^0_{2a}/p^0_{1c} was $\geqslant 2$ and W/F was 49.6 g-cat h mol^{-1}. Under this reaction condition, the product **4d** was isolated by distillation in 34% yield based on **1c**. This method was applied to the synthesis of the other 1-substituted indoles. As shown in Table 3 (runs 1–3, 6–8), the 1-substituted indoles **4b**, **g**, **h** and 2- and 3-alkyl-1-substituted indoles **4c**, **e**, **f**, **5c**, **e** were obtained in good yields by the reaction of *N*-substituted anilines with glycols **2a**–**c**.

Obolentsev and Gryazev[11] and Yur'ev *et al.*[12] reported that the vapour phase reaction of **2a** over aluminosilicate afforded acetaldehyde *via* 1,4-dioxane which probably formed *via* ethylene oxide (**3a**). Thus, we examined the synthesis of **4d** by the vapour phase reaction of **1c** with **3a**, 1,4-dioxane and acetaldehyde. As shown in Table 3, the reaction with acetaldehyde (run 12) did not afford the desired product **4d**, while the reaction using epoxides **3a**, **b** (runs 4, 5, 9, 10) and 1,4-dioxane (run 11) gave the corresponding 1-substituted indoles in poor to satisfactory yield. Fig. 2(*a*) and (*b*) show the change of the product distributions by changing the reaction

Table 3 Reaction of *N*-substituted anilines **1b–e** with glycols **2a–c**, epoxides **3a**, **b**, 1,4-dioxane, acetaldehyde and ethanol over Neobead P

Run	Aniline	Reactant	T/°C	RC[a]	Product	Yield (%)	Selectivity (%)
1	**1b**	**2a**	325	A	**4b**	47.1	55.7
2	**1d**	**2a**	300	B	**4g**	40.9	49.4
3	**1e**	**2a**	300	B	**4h**	49.2	87.9
4	**1b**	**3a**	325	A	**4b**	40.1	54.6
5	**1c**	**3a**	300	A	**4d**	43.0	69.4
6	**1b**	**2b**	300	A	**4c**	23.2	46.1
					5c	7.3	14.5
7	**1c**	**2b**	300	A	**4e**	21.4	45.8
					5e	6.4	13.7
8	**1c**	**2c**	300	A	**4f**	19.4	53.7
9	**1b**	**3b**	300	A	**4c**	19.6	38.5
					5c	4.8	9.4
10	**1c**	**3b**	300	A	**4e**	17.5	36.7
					5e	3.8	8.0
11	**1c**	1,4-Dioxane	350	A	**4d**	8.8	16.4
					4f	8.1	15.1
12	**1c**	Acetaldehyde	400	A	**1a**	3.1	12.1
13	**1c**	Ethanol	400	A	*N*,*N*-Diethylaniline	2.3	12.2
					1a	8.0	42.3

[a] RC = Reaction conditions: see in the Experimental section.

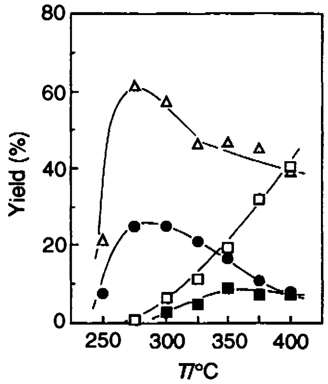


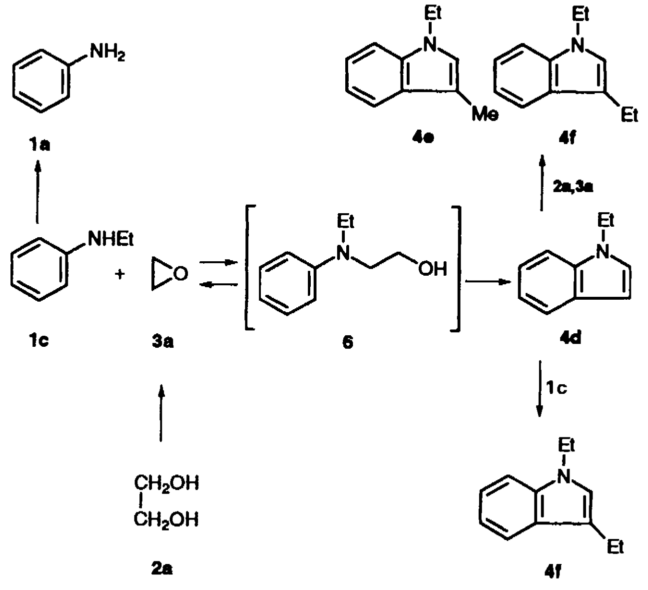
Fig. 3 Effect of the reaction temperature on the vapour phase reaction of **6** over Neobead P. The symbols are the same as those described in Fig. 1.

temperature in the vapour phase reactions of **1c** with glycol **2a** and epoxide **3a**, respectively. The yield of **4d** remarkably decreased at reaction temperatures below or above 300 °C; **4e** and **f** were formed in the highest yields at 325–350 °C; the lowest value of the residual amount of **1c** was observed at 325 °C where the total yield of indole derivatives was highest; above 350 °C, formation of a small amount of **1a** was detected due to the decomposition of **1c**. Therefore, we suppose that **1c** reacts with **3a** which is rapidly formed from **2a** over Neobead P, affording **4d**.

We next studied the reaction pathway for the formation of **4d** from **1c** and **2a**. The reaction of **1c** with ethanol over Neobead P gave an *N*-alkylated product (Table 3, run 13). We would expect 2-(*N*-ethylanilino)ethanol (**6**) to be an intermediate in this reaction although it was not detected in the reaction mixture from **1c** and **2a** (Scheme 3). In fact, **4d** was obtained by the vapour phase reaction of **6** over Neobead P at a reaction temperature in the range of 250–400 °C (Fig. 3). **4f**, **1a** and **1c** were also formed as by-products. In this reaction, the yields of **4d** and **4f** were lower and the yield of **1a** was higher compared with those of **4d**, **4f** and **1a** which were obtained by the reaction of **1c** with **2a**, and the raw material **6** was not detected at any reaction temperature due to the high reactivity. On the other hand, when the vapour phase reaction of **6** was carried out in the presence of **2a** ($p^\circ_{2a}/p^\circ_6 = 1.0$) over Neobead P, it was found that the yield of **4d** increased and the yield of **1c** remarkably decreased (see Experimental section). In the case of using **3a** instead of **2a**, the result was quite similar. The yield of **4d** also increased when the reaction of **6** was carried out in the presence of **1c** ($p^\circ_{1c}/p^\circ_6 = 1.0$). Moreover, the reaction of **6** with **1b** gave **4b** and **d**. These results indicate that **6** is an intermediate, the **6** $\rightleftharpoons$ **1c** + **2a** (or **3a**) equilibrium exists, and the reaction proceeds *via* **6**, affording **4d**.

Next, in order to clarify the production of **4e** and **f** as by-products in the reaction of **1c** with **2a**, the following reactions were investigated: the reaction of **4d** with **1c** gave **4f**, and that of **4d** with **2a** and **3a** gave **4e** and **f** (see Experimental section). On the other hand, **4e** and **f** were not formed at all from **4d** itself. Thus, it is considered that the methylation and ethylation at the 3-position of indole occurs due to the presence of excess **1c**, **2a** and **3a**.

From these facts, a plausible reaction pathway of this vapour phase reaction is shown in Scheme 3.



Scheme 3

Therefore, 1-substituted indoles were found to be synthesized in good yields by the vapour phase reaction of *N*-substituted anilines with glycols and epoxides over Neobead P catalyst. However, this method was not applicable to the straightforward synthesis of indole (**4a**).

Table 4 Effects of catalysts and reaction conditions on the yield of **4a** by the dealkylation of 1-alkylindoles **4b**, **d**, **g**

Run	Catalyst	Substrate	Reaction conditions	Product (**4a**) yield (%)
1	Neobead C	**4b**	H_2O, N_2	13.6
2	Neobead C	**4b**	H_2O, benzene	20.3
3	Neobead C	**4d**	H_2O, benzene	40.8
4	Neobead C	**4b**	H_2	23.4
5	Neobead C	**4b**	H_2, benzene	28.0
6	Neobead C	**4b**	H_2O, H_2, benzene	36.7
7	Pt (0.3%)–Neobead C	**4b**	H_2O, H_2, benzene	37.6
8	Pd (0.3%)–Neobead C	**4b**	H_2O, H_2, benzene	36.6
9	Rh (0.3%)–Neobead C	**4b**	H_2O, H_2, benzene	31.1
10	Rh (0.1%)–ZnO (10%)–Neobead C	**4b**	H_2O, H_2, benzene	43.0
11	ZnO (5%)–Neobead C	**4b**	H_2O, H_2, benzene	48.9
12	ZnO (10%)–Neobead C	**4b**	H_2O, H_2, benzene	58.7
13	ZnO (20%)–Neobead C	**4b**	H_2O, H_2, benzene	53.0
14	NiO (5%)–Neobead C	**4b**	H_2O, H_2, benzene	42.2
15	NiO (5%)–Neobead C	**4g**	H_2O, H_2, benzene	43.4
16	Fe_2O_3 (5%)–Neobead C	**4b**	H_2O, H_2, benzene	46.9
17	NiO (5%)–ZnO (5%)–Neobead C	**4b**	H_2O, H_2, benzene	54.9
18	V_2O_5 (23%)–MoO_3 (4.7%)–Neobead C	**4b**	H_2O, H_2, benzene	45.5

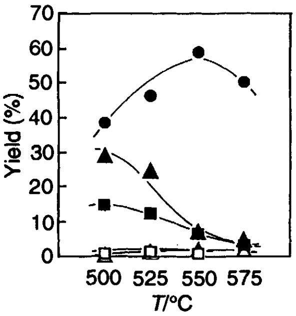


Fig. 4 Effect of reaction temperature on the demethylation of **4b** over ZnO (10%)–Neobead C. Symbols: ●, **4a**; ▲, **4b**; □, **4c**; ■, **7**; △, **1a**.

In order to synthesize **4a** efficiently, we next investigated a method for the removal of an alkyl group on the 1-alkylindoles **4b**, **d**, **g** which were obtained by the vapour phase reaction of *N*-alkylanilines **1b–d** with glycol **2a** and oxide **3a** (Scheme 2). Debenzylation of 1-benzylindole **1g** by using metal in liquid ammonia has been reported,[13] but it is difficult to remove the other alkyl groups from 1-alkylindoles by this method.[14] It is also reported that **4a** was contained in the products which were obtained by the thermal reaction of **4b**,[15] but the yield and selectivity of **4a** were not so high as to be useful for a practical preparation. On the other hand, it is well documented that the vapour phase reaction of alkylbenzenes and alkylpyridines in the presence of steam,[16] hydrogen gas[17] or oxygen gas (air)[18] gives rise to the corresponding dealkylated products. Thus, we examined the removal of the methyl group of 1-methylindole (**4b**) with steam, hydrogen or oxygen over alumina gel (Neobead C: Al_2O_3 = 100%; 6–10 mesh) at 550 °C. The reactions were conducted at atmospheric pressure using the above mentioned apparatus. As shown in Table 4, **4a** was obtained from **4b** in the presence of steam or hydrogen gas over Neobead C (runs 1, 2, 4, 5). On the contrary, **4a** was not formed from **4b** in the presence of oxygen gas because of the instability of the indole heterocycle. The reaction conditions could be varied as shown in runs 1, 2, 4–6. The results indicate that benzene as a diluent is advantageous compared with the use of nitrogen. The reaction in the presence of hydrogen gas together with steam was found to be most efficient for this demethylation (run 6).

We next examined the effect of catalysts, which contain various metals or metal oxides supported on Neobead C, on the reactions in the presence of steam, hydrogen gas and benzene vapour (runs 7–14, 16–18). The catalysts containing zinc oxide were of advantage over those containing other metals or metal oxides. The yield of **4a** was found to be highest at the supported amount of 10 wt%. This method was applied to the dealkylation of the other 1-substituted indoles **4d**, **g** (runs, 3, 15).

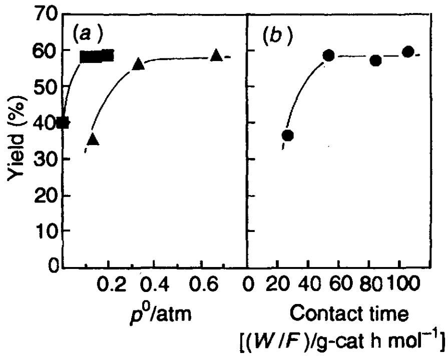


Fig. 5 Effects of the initial partial pressure of steam (■) and hydrogen gas (▲) (*a*) and the contact time (*b*) on the yield of **4a** from **4b** over ZnO (10%)–Neobead C at 550 °C. Reaction conditions: (*a*) W/F = 53.2 g-cat h mol^{-1}, $p^o_{\mathbf{4b}}$ = 0.004 90, $p^o_{benzene}$ = 0.130, $p^o_{H_2}$ = 0.666, $p^o_{H_2O} + p^o_{N_2}$ = 0.199 atm; W/F = 53.2 g-cat h mol^{-1}, $p^o_{\mathbf{4b}}$ = 0.004 90, $p^o_{benzene}$ = 0.130, $p^o_{H_2O}$ = 0.199, $p^o_{H_2} + p^o_{N_2}$ = 0.666 atm; (*b*) $p^o_{\mathbf{4b}}$ = 0.008 63, $p^o_{benzene}$ = 0.130, $p^o_{H_2O}$ = 0.198, $p^o_{H_2}$ = 0.664 atm.

We also examined the effect of the reaction temperature on the product yields from **4b** by using zinc oxide (10%) supported on Neobead C [ZnO (10%)–Neobead C] as a catalyst. As shown in Fig. 4, **4a** was obtained at 550 °C in a good yield (59%) with a good selectivity (63%). At a reaction temperature below or above 550 °C, the yield remarkably decreased; in this reaction, 3-methylindole (**7**), 1,3-dimethylindole (**4c**) and **1a** were obtained as by-products.

We next examined the effect of the initial partial pressure of steam ($p^o_{H_2O}$) and hydrogen gas ($p^o_{H_2}$) over ZnO (10%)–Neobead C on the yield of **4a** [Fig. 5(*a*)]. The yield of **4a** became almost constant when $p^o_{H_2O}$ was above 0.1 atm and $p^o_{H_2}$ was above 0.3 atm.† Fig. 5(*b*) also shows the effect of W/F on the yield of **4a** when $p^o_{H_2O}$ is 0.198 atm and $p^o_{H_2}$ is 0.664 atm. The yield increased with W/F. They became almost constant when W/F was above 50 g-cat h mol^{-1}. From these results, this demethylation was found to proceed effectively when the reaction was carried out over

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† 1 atm = 101 325 Pa.

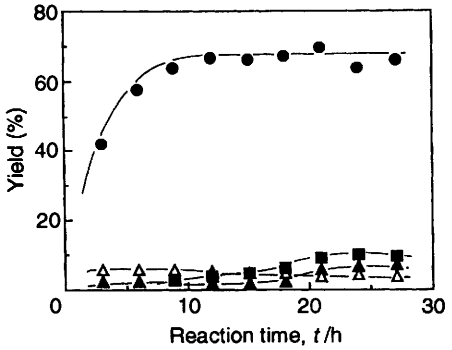


Fig. 6 Activity change of ZnO (10%)–Neobead MSC-3 on the vapour phase reaction of **4b** at 550 °C. The symbols are the same as those described in Fig. 4.

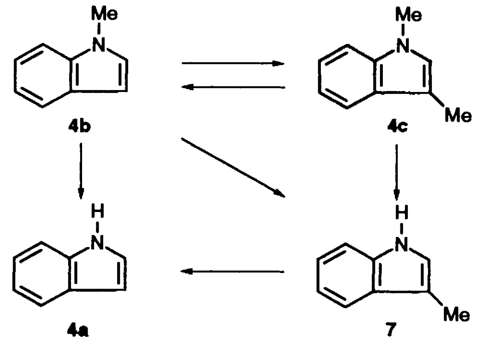
ZnO (10%)–Neobead C under the following reaction conditions: the reaction temperature was 550 °C; $p^{\circ}_{H_2O}$ was over 0.1 atm; $p^{\circ}_{H_2}$ was over 0.3 atm; W/F was over 50 g-cat h mol^{-1}.

In order to increase the activity of the catalyst, the demethylation of **4b** was carried out by using a ZnO (10%)–Neobead MSC-3 catalyst having the same composition as that of ZnO (10%)–Neobead C; the particle size of the former catalyst is smaller than that of the latter one. Fig. 6 shows the activity of the catalyst at 550 °C. The yield and selectivity of **4a** increased with the passage of time and reached up to 64–67% and 65–69%, respectively, at 12 h. Moreover, deactivation of the catalyst was not observed even after 28 h of running.

Thus, **4a** could be efficiently obtained from **4b** in the presence of steam and hydrogen gas by using ZnO (10%)–Neobead MSC-3. This vapour phase reaction is one of the most useful methods for the removal of the alkyl group from 1-alkylindole.

Finally, in order to study the reaction pathway for this dealkylation, we examined the vapour phase reaction of **7** or **4c** obtained as by-products (see Experimental section). As the result of the reaction, **4a** and **1a** were obtained from **7**. The demethylation temperature of **7** was higher than that of **4b** and the yield of **4a** was as good as that of **4a** which was obtained from **4b**. On the other hand, **4a**, **4b**, **7** and **1a** were obtained from **4c**. In this reaction, the yield of **4a** was rather low compared with that obtained from **4b**. **7** was produced in better yield than **4b**. This result indicates that the cleavage of the C–N bond of 1-methyl group proceeds more easily than the C–C bond of 3-methyl group.

From these facts, a plausible reaction pathway of the demethylation of **4b** over ZnO (10%)–Neobead C is as follows (Scheme 4). **4a** is obtained mainly by demethylation of **4b**. **4a** and **c** are afforded by disproportionation of a part of **4b**. **7** is formed by transmethylation of another part of **4b**. Demethylation of **4c** gives **4b** and **7**. **4a** is also prepared by demethylation of **7**.



Scheme 4

Summary

1-Substituted indoles were found to be synthesized in good yields by the vapour phase reaction of *N*-substituted anilines with glycols and epoxides over Neobead P catalyst. A combination of this reaction with the vapour phase dealkylation of 1-alkylindoles gives an efficient method for the preparation of indole and related compounds.

Experimental

Melting points are uncorrected. IR spectra were recorded on Shimadzu IR-27G and Perkin-Elmer 1640 spectrometers. NMR spectra were obtained using Hitachi R-20A (60 MHz) and Bruker AC-200 (200 MHz) spectrometers. MS spectra or GC–MS spectra were recorded on a Hitachi M-60 and M-2000A instrument with an OV-17 or an OV-1 column. GC analyses were performed on YANACO G 1800–TCD and Shimadzu GC-3BT instruments using a 2 m stainless column with Silicon SF-96 20% on Celite 545 (80–100 mesh) and Silicon DC 550 (20%) on Celite 545 (40–60 mesh) (Nishio Industry Co. Ltd.) columns. The GC analyses were carried out using He gas as the carrier.

Materials

N-Benzylaniline (**1d**) was prepared by reduction of *N*-benzylideneaniline with NaBH$_4$.[19] Other chemical reagents were generally obtained from Katayama Chemical Industries Co. Ltd. and Tokyo Kasei Kogyo Co. Ltd. and were used without further purification.

Catalysts

Neobead C, Neobead MSC-3, Neobead D and Neobead P were made by Mizusawa Industrial Chemicals Ltd. F-9 was made by TOSOH Corporation. TSS-99205 was made by Tokai Konetsu Kogyo Co. Ltd. Silica gel (white) and active carbon were purchased from Katayama Chemical Industries Co. Ltd. and Wako Pure Chemical Industries Ltd., respectively. MgO was prepared from magnesium nitrate according to Matsuda's method.[20] The chemical compositions (% by weight) were: Neobead C and Neobead MSC-3 (Al_2O_3 = 100); Neobead D (Al_2O_3:SiO_2 = 90:10); Neobead P (Al_2O_3:SiO_2:Na_2O = 88:9:3); silica gel (SiO_2 = 100); TSS-99205 (SiC > 98); F-9 (analysis formula: $Na_2O{\cdot}Al_2O_3{\cdot}1.5SiO_4$). The particle sizes were: Neobead C (6–10 mesh); Neobead MSC-3 (14–32 mesh); Neobead D (6–10 mesh); Neobead P (4–8 mesh); silica gel (5–10 mesh); F-9 (8–12 mesh); MgO (powder); TSS-99205 (5 mm diameter); active carbon (3–4 mm diameter). K_2O supported on Neobead C was prepared at atmospheric pressure as follows. Neobead C was added to aqueous potassium hydroxide and the mixture was allowed to settle for a day. After evaporating moisture on a water bath, Neobead C impregnated with potassium hydroxide was dried at 110 °C for 5 h and then calcined in an air stream at 450 °C for 3 h.[21] The metal supported on Neobead C was prepared as follows. Neobead C was added to aqueous metal chlorides such as $H_2PtCl_6{\cdot}6H_2O$, $PdCl_2$ and $RhCl_3{\cdot}2H_2O$ (in the case of $PdCl_2$, using 0.3 wt% aqueous hydrochloride) and the mixture was allowed to settle for 20 h. The moisture was evaporated on a water bath. The mixture was dried at 110 °C for 8 h and then reduced with hydrogen gas diluted with steam at 500 °C for 4 h.[16b] V_2O_5–MoO_3 supported on Neobead C was prepared as follows. NH_4VO_3 was added to distilled water and thereto was further added gradually oxalic acid with vigorous stirring. To aqueous $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ was added the above aqueous solution. To the mixture was added Neobead C and the mixture was allowed to settle for 20 h. The moisture was evaporated on a

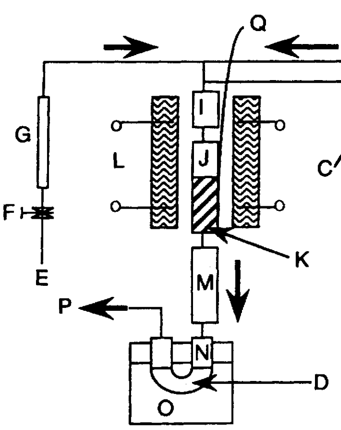


Fig. 7 Schematic diagram of the continous flow-system apparatus: C, reactants; D, products; E, nitrogen gas; F, valve; G, flow meter; H, pump; I, vaporizer; J, reactor; K, catalyst; L, furnace; M, cooler; N, trap of products; O, ice-water; P, to dry ice–MeOH trap; Q, thermocouple

water bath and the mixture was dried at 110 °C for 5 h and then calcined in an air stream at 500 °C for 8 h.[18] The other metal oxide supported on Neobead C, Neobead MSC-3 or Neobead P was prepared as follows. Neobead C, Neobead MSC-3 or Neobead P was added to an aqueous solution of $Zn(NO_3)_2 \cdot 6H_2O$, $Ni(NO_3)_2 \cdot 6H_2O$, $Fe(NO_3)_3 \cdot 9H_2O$, $(NH_4)_2Cr_2O_7$, $SbCl_3$, $Co(NO_3)_2 \cdot 6H_2O$ and/or $5(NH_4)_2O \cdot 12WO_3 \cdot 5H_2O$ and allowed to settle for 20 h. After evaporating moisture on a water bath, the mixture was dried at 110 °C for 5 h and then calcined in an air stream at 500 °C for 4 h.[21] Rh–ZnO supported on Neobead C was prepared as follows. To an aqueous $RhCl_3 \cdot 2H_2O$ and $Zn(NO_3)_2 \cdot 6H_2O$ solution was added Neobead C. The mixture was allowed to settle for 20 h and the moisture was evaporated on a water bath. The mixture was dried at 70 °C for 5 h and then calcined in an air stream at 150 °C for 1 h and at 450 °C for 1 h. The resultant solid was reduced with hydrogen gas diluted with steam at 450 °C for 1 h and at 500 °C for 3 h.[16c]

Apparatus and general procedure for vapour phase reactions

Fig. 7 shows a schematic diagram of the continuous flow-system apparatus.

The catalyst was packed into a tubular quartz-reactor (22 mm i.d. × 30 cm) connected with a vaporizer (12 mm i.d. × 15 cm). The apparatus was heated with an electric furnace. Aniline derivatives (or aniline derivatives dissolved in benzene) and glycols (or epoxides) in water were introduced with nitrogen gas into the vaporizer packed into glass beads (1.5 mm diameter). A mixture of gases was heated at 250–400 °C over a catalyst at atmospheric pressure. The products were collected as a condensed solution by cooling with ice–water and then dry ice in methanol. The solution at about 3 h after the reaction was initiated was analysed by GC. The yields of the products were calculated on the basis of the aniline derivatives **1a–e** supplied.

The dealkylation of 1-alkylindole **4b**, **d**, **g** was carried out in a similar manner to that described above. 1-Alkylindole **4b**, **d**, **g** was introduced with steam, hydrogen gas, nitrogen gas and/or benzene vapour into the vaporizer. A mixture of gases was heated at 500–575 °C over a catalyst. The condensed solution of the reaction mixture, after *ca.* 5 h [in the case of Neobead C (6–10 mesh) catalyst] after the reaction was initiated was analysed by GC. The yields of the products were calculated on the basis of 1-alkylindole **4b**, **d**, **g** supplied.

Reaction conditions of the vapour phase reaction of anilines with glycols and epoxides

The reaction of aniline (**1a**) with ethylene glycol (**2a**) (Table 1) was carried out in the range 250–400 °C under the following reaction conditions: (runs 1–7) $W/F = 49.6$ g-cat h mol^{-1}, $p^{\circ}_{\mathbf{1a}} = 0.0205$, $p^{\circ}_{\mathbf{2a}} = 0.0409$, $p^{\circ}_{N_2} = 0.161$, $p^{\circ}_{H_2O} = 0.778$ atm; (runs 8–12) $W/F = 74.4$ g-cat h mol^{-1}, $p^{\circ}_{\mathbf{1a}} = 0.0205$, $p^{\circ}_{\mathbf{2a}} = 0.0819$, $p^{\circ}_{N_2} = 0.161$, $p^{\circ}_{H_2O} = 0.737$ atm. The reaction of *N*-ethylaniline (**1c**) with **2a** or ethylene oxide (**3a**) (Table 2, Table 3 run 5, Fig. 2) was carried out in the temperature range 250–400 °C over a Neobead catalyst (20 g) under the following reaction conditions: $W/F = 49.6$ g-cat h mol^{-1}, $p^{\circ}_{\mathbf{1c}} = 0.0205$, $p^{\circ}_{\mathbf{2a},\mathbf{3a}} = 0.0409$, $p^{\circ}_{N_2} = 0.161$, $p^{\circ}_{H_2O} = 0.778$ atm. The reaction of *N*-substituted aniline **1b–e** with glycols **2a–c**, epoxides **3a**, **b**, dioxane, acetaldehyde or ethanol (Table 3) was carried out in the temperature range 250–400 °C over Neobead P (20 g) under the following reaction conditions: $W/F = 49.6$ g-cat h mol^{-1}: (A) $p^{\circ}_{\mathbf{1b,c}} = 0.0205$, $p^{\circ}_{\mathbf{2a\text{–}c},\mathbf{3a,b},\text{dioxane,acetaldehyde,ethanol}} = 0.0409$, $p^{\circ}_{N_2} = 0.161$ atm, $p^{\circ}_{H_2O} = 0.778$; (B) $p^{\circ}_{\mathbf{1d,e}} = 0.0205$, $p^{\circ}_{\mathbf{2a}} = 0.0409$, $p^{\circ}_{N_2} = 0.161$ atm, $p^{\circ}_{H_2O} = 0.659$, $p^{\circ}_{\text{benzene}} = 0.119$ atm. The yields of the products were determined by GC.

Reaction of *N*-ethylaniline (1c) and ethylene glycol (2a)

1c, aqueous **2a** (0.156 g cm^{-3}) and nitrogen gas were continuously introduced over 20 g of Neobead P at 300 °C under following reaction conditions: $W/F = 49.6$ g-cat h mol^{-1}, $p^{\circ}_{\mathbf{1c}} = 0.0205$, $p^{\circ}_{\mathbf{2a}} = 0.0409$, $p^{\circ}_{N_2} = 0.161$, $p^{\circ}_{H_2O} = 0.778$ atm. The reaction mixture from 2 to 11 h (for 9 h) after the reaction was initiated was collected and extracted with toluene. The extract was washed with aqueous 10% H_2SO_4 and dried ($MgSO_4$). After the solvent was evaporated, the residue was distilled under reduced pressure to obtain 1-ethylindole (**4d**) [bp 80 °C/ < 1 mmHg (lit.,[22] 83–86 °C/0.6 mmHg)] in 34% yield (3.7 g) based **1c**.[23] 1,3-Diethylindole (**4f**) was also obtained from the reaction mixture by distillation (bp 128–129 °C/18 mmHg).[23] But the isolation of 1-ethyl-3-methylindole (**4e**) as another by-product was difficult because of the small quantity obtained, so the formation of **4e** was confirmed by comparing the GC–MS and GC retention time with those of an authentic sample prepared from *N*-ethylaniline (**1c**) and propylene glycol (**2b**).

Identification of the products by the reaction of other anilines 1a, b, d, e with glycols 2a, b and epoxides 3a, b

In these reactions, the corresponding indoles obtained as the main products, were isolated from the reaction mixture by distillation or silica gel column chromatography and identified by IR, NMR and MS spectra: indole (**4a**) was obtained by steam distillation (bp 90–98 °C/65 mmHg); 1-methylindole (**4b**) was obtained by distillation [bp 118–125 °C/30 mmHg (lit.,[22] 73–75 °C/2.4 mmHg)];[24,25] 1-benzylindole (**4g**) was obtained by silica gel column chromatography (toluene–CCl_4 = 1:1) and recrystallization from ethanol [mp 43–44 °C (lit.,[23] mp 43–44 °C)];[26] 1-phenylindole (**4h**) was obtained by silica gel column chromatography (toluene–CCl_4 = 1:1);[26,27] 1,3-dimethylindole (**4c**) was obtained by distillation [bp 139 °C/30 mmHg (lit.,[28] 103–105 °C/2 mmHg)];[29] 1,2-dimethylindole (**5c**) was obtained by distillation [bp 142–143 °C/30 mmHg (lit.,[24] 85–92 °C/1.2 mmHg)]; 1-ethyl-3-methylindole (**4e**) was obtained by distillation [bp 125–126 °C/18 mmHg (lit.,[30,31] 84–86 °C/0.5 mmHg)].[32] 1-Ethyl-2-methylindole (**5e**) was not isolated from reaction mixtures; therefore, the formation of **5e** was confirmed by the GC–MS spectrum and from the result of the formation of 1,2-

dimethylindole (**5c**) from *N*-methylaniline (**1b**) and propylene glycol (**2b**).

Reaction of 2-(*N*-ethylanilino)ethanol (6)

The reaction of **6** was carried out at a temperature in the range of 250–400 °C over Neobead P (20 g) under the following reaction conditions: $W/F = 53.1$ g-cat h mol^{-1}, $p^{\circ}_{6} = 0.0219$, $p^{\circ}_{H_2O} = 0.678$, $p^{\circ}_{N_2} = 0.173$, $p^{\circ}_{\text{benzene}} = 0.127$ atm. The yields of the products were determined by GC. The result is shown in Fig. 3.

Reaction of 6 with ethylene glycol (2a)

The reaction of **6** with **2a** was carried out over Neobead P (20 g) at 300 °C under the following reaction conditions: $W/F = 53.1$ g-cat h mol^{-1}, $p^{\circ}_{6} = 0.0219$, $p^{\circ}_{2a} = 0.0219$, $p^{\circ}_{H_2O} = 0.656$, $p^{\circ}_{N_2} = 0.173$, $p^{\circ}_{\text{benzene}} = 0.127$ atm. The yields of **4d**, **4f**, **1c** and **1a** (based on **6**) were 40.6%, 3.8%, 25.4% and 0.2%, respectively (analysed by GC).

Reaction of 6 with *N*-ethylaniline (1c)

The reaction of **6** with **1c** was carried out at 275 °C over Neobead P (20 g) under the following reaction conditions: $W/F = 53.1$ g-cat h mol^{-1}, $p^{\circ}_{6} = 0.0219$, $p^{\circ}_{1c} = 0.0219$, $p^{\circ}_{H_2O} = 0.656$, $p^{\circ}_{N_2} = 0.173$, $p^{\circ}_{\text{benzene}} = 0.127$ atm. The yields of **4d** and **f** (based on **6**) and the yield of **1a** (based on **6** + **1c**) were 31.1, 1.6 and 1.0%, respectively (analysed by GC).

Reaction of 6 with *N*-methylaniline (1b)

The reaction of **6** with **1b** was carried out at 300 °C over Neobead P (20 g) under the following reaction conditions: $W/F = 53.1$ g-cat h mol^{-1}, $p^{\circ}_{6} = 0.0219$, $p^{\circ}_{1b} = 0.0219$, $p^{\circ}_{H_2O} = 0.656$, $p^{\circ}_{N_2} = 0.173$, $p^{\circ}_{\text{benzene}} = 0.127$ atm. The yields of **4b**, **d** and **1c** (based on **6**) and the yield of **1a** (based on **6** + **1b**) were 4.2, 12.4, 47.5 and 2.1%, respectively (analysed by GC).

Reaction of 1-ethylindole (4d) with ethylene glycol (2a)

The reaction of **4d** with **2a** was carried out at 350 °C over Neobead P (20 g) under the following reaction conditions: $W/F = 49.6$ g-cat h mol^{-1}, $p^{\circ}_{4d} = 0.0161$, $p^{\circ}_{2a} = 0.0805$, $p^{\circ}_{H_2O} = 0.742$, $p^{\circ}_{N_2} = 0.161$ atm. The yields of **4e** and **f** (based on **4d**) were 8.5 and 23.1%, respectively (analysed by GC).

Reaction of 1-ethylindole (4d) with *N*-ethylaniline (1c)

The reaction of **4d** with **1c** was carried out at 350 °C over Neobead P (20 g) under the following reaction conditions: $W/F = 49.6$ g-cat h mol^{-1}, $p^{\circ}_{4d} = 0.0205$, $p^{\circ}_{1c} = 0.102$, $p^{\circ}_{H_2O} = 0.716$, $p^{\circ}_{N_2} = 0.161$ atm. The yields of **4f**, **1a** and *N*,*N*-diethylaniline (based on **4d**) were 15.8, 11.2 and 1.9%, respectively (analysed by GC).

Reaction conditions of the dealkylation of 1-alkylindole 4b, d, g (Table 4, Fig. 4)

The reactions of **4b**, **d**, **g** were carried out at 550 °C (Table 4) or in the range of 500–575 °C (Fig. 4) over Neobead C (20 g) or metal or metal oxide supported on Neobead C (20 g), under the following reaction conditions: (Table 4, run 1) $W/F = 99.2$ g-cat h mol^{-1}, $p^{\circ}_{4b} = 0.0161$, $p^{\circ}_{H_2O} = 0.823$, $p^{\circ}_{N_2} = 0.161$ atm; (Table 4, run 2) $W/F = 99.2$ g-cat h mol^{-1}, $p^{\circ}_{4b} = 0.0161$, $p^{\circ}_{H_2O} = 0.823$, $p^{\circ}_{\text{benzene}} = 0.161$ atm; (Table 4, run 3) $W/F = 59.1$ g-cat h mol^{-1}, $p^{\circ}_{4d} = 0.0384$, $p^{\circ}_{H_2O} = 0.384$, $p^{\circ}_{\text{benzene}} = 0.578$ atm; (Table 4, run 4) $W/F = 198$ g-cat h mol^{-1}, $p^{\circ}_{4b} = 0.142$, $p^{\circ}_{H_2} = 0.858$ atm; (Table 4, run 5) $W/F = 59.1$ g-cat h mol^{-1}, $p^{\circ}_{4b} = 0.0425$, $p^{\circ}_{H_2} = 0.425$, $p^{\circ}_{\text{benzene}} = 0.533$ atm; (Table 4, runs 6–14, 16–18 and Fig. 4) $W/F = 53.2$ g-cat h mol^{-1}, $p^{\circ}_{4b} = 0.008\,63$ atm, $p^{\circ}_{H_2O} = 0.198$, $p^{\circ}_{H_2} = 0.664$, $p^{\circ}_{\text{benzene}} = 0.130$ atm; (Table 4, run 15) $W/F = 26.6$ g-cat h mol^{-1}, $p^{\circ}_{4g} = 0.008\,81$, $p^{\circ}_{H_2O} = 0.198$, $p^{\circ}_{H_2} = 0.663$, $p^{\circ}_{\text{benzene}} = 0.130$ atm. The yields of the products were determined by GC.

Identification of the products by the demethylation of 4b

From the condensed solution obtained by the reaction of **4b** over ZnO (10%)–Neobead C, the reaction mixture was extracted with diethyl ether. The solvent was removed under reduced pressure and the residue was crystallized with hot water. The colourless solid was identified as indole (**4a**) by comparing IR, NMR and GC–MS spectra and the GC retention time with those of an authentic sample. All other by-products [3-methylindole (**7**), 1,3-dimethylindole (**4c**) and aniline (**1a**)] were decided by GC–MS and GC retention time by comparing with those of authentic samples.

Activity change of ZnO (10%)–Neobead MSC-3 for the formation of indole (4a) from 1-methylindole (4b) (Fig. 6)

The reaction of **4b** was carried out at 550 °C over ZnO (10%)–Neobead MSC-3 (70 g) under the following reaction conditions: $W/F = 198$ g-cat h mol^{-1}, $p^{\circ}_{2a} = 0.009\,93$, $p^{\circ}_{H_2O} = 0.141$, $p^{\circ}_{H_2} = 0.718$; $p^{\circ}_{\text{benzene}} = 0.131$ atm. The yields of **4a** and by-products (**7** and **1a**) were determined by GC. The result is shown in Fig. 6.

Demethylation of 3-methylindole (7)

The reaction of **7** was carried out in the temperature range 500–575 °C over ZnO (10%)–Neobead C (20 g) under the following reaction conditions: $W/F = 53.2$ g-cat h mol^{-1}, $p^{\circ}_{7} = 0.008\,63$, $p^{\circ}_{H_2O} = 0.198$, $p^{\circ}_{H_2} = 0.664$; $p^{\circ}_{\text{benzene}} = 0.130$ atm. The yields of **4a** and **1a** were: 33.7 and 0%, respectively, at 500 °C; 35.9 and 0%, respectively, at 525 °C; 42.1 and 0%, respectively, at 550 °C; 42.9 and 0.4%, respectively, at 575 °C. The residues of **7** were 38.0 (500 °C), 32.5 (525 °C), 22.2 (550 °C) and 24.4% (575 °C), respectively (determined by GC).

Demethylation of 1,3-dimethylindole (4c)

The reaction of **4c** was carried out at the temperature in the range 525–600 °C over ZnO (10%)–Neobead C (20 g) under the following reaction conditions: $W/F = 53.2$ g-cat h mol^{-1}, $p^{\circ}_{4c} = 0.008\,63$, $p^{\circ}_{H_2O} = 0.198$, $p^{\circ}_{H_2} = 0.664$, $p^{\circ}_{\text{benzene}} = 0.130$ atm. The yields of **4a** and by-products (**4b**, **7** and **1a**) were: 27.6, 6.6, 16.1 and 1%, respectively, at 525 °C; 28.4, 5.6, 19.1 and 1.3%, respectively, at 550 °C; 31.4, 4.9, 15.7 and 1.3%, respectively, at 575 °C; 32.4, 2.9, 14.1 and 1.1%, respectively, at 600 °C. The residues of **4c** were 10.6 (525 °C), 7.0 (550 °C), 5.0 (575 °C) and 2.1% (600 °C), respectively (determined by GC).

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