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Regioselective Preparation of Aminomethylphenols by Reduction of Mannich bases of Halophenols with Raney Cu-Al Alloy in 10% Aqueous Sodium Hydroxide

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Dedicated to Professor Otohiko Tsuge on the occasion of his retirement

It was developed a selective preparative method of aminomethylphenols by reducing Mannich bases of bromophenols with Raney Cu-Al alloy in 10% aqueous sodium hydroxide.

Aminomethylphenols are important as an intermediate for pesticides, fungicides, and drugs. Mannich reaction¹⁾ is useful for introducing an aminomethyl group in the aromatic ring of phenol. But, when ortho- and para-positions are open, all possible mono-substituted isomers and, depending upon the reaction conditions, poly-substituted products are formed.

Recently, we have demonstrated²⁾ that halogen atoms on aromatic nucleus are easily removed by treatment with Raney alloy in an alkaline media, thus working as a positional protecting group.

We here report regioselective preparation of aminomethylphenols by reduction of Mannich bases of halophenols by Raney alloy in an alkaline solution.

Results and discussion

First, Mannich bases, **1a**³⁾ and **b**, of 4-chloro- and 4-bromophenol were treated with Raney Ni-Al, Co-Al, Fe-Al, and Cu-Al alloy in aqueous NaOH and the results are given in Scheme 1 and Table 1.

As expected, Raney Ni alloy removed reductively both chlorine and bromine atom and, at the same time, cleaved C-N bond, giving cresol (**2**) in a high yield. On the other hand, reductive C-N bond fission did not occur when Cu alloy was used in place of Ni alloy. Furthermore, Cu alloy removed only bromine but not chlorine atom under the above conditions. Raney Co

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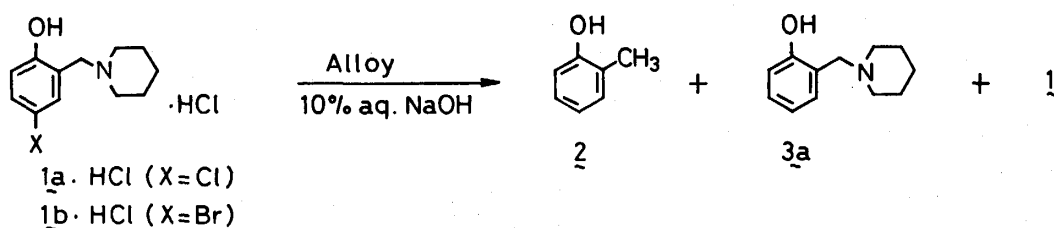
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Table 1. Treatment of **1a** · HCl and **1b** · HCl with Raney alloy¹.

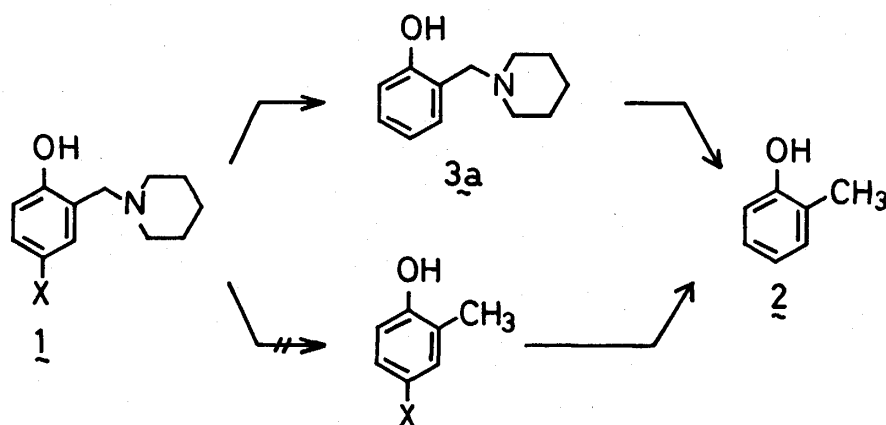
Substrate	Alloy	Alloy/1 (mg/mmol)	Product Yield (%)		
			1	2 ²	3a
1a	Ni-Al	200	—	92	—
1a	Ni-Al	100	—	55	—
1a	Ni-Al	75	(1	49	50) ³
1a	Ni-Al	50	(28	19	53) ³
1a	Cu-Al	100	84	—	—
1a	Co-Al	100	(73	0	26) ³
1a	Fe-Al	100	88	—	—
1b	Ni-Al	100	—	72	—
1b	Ni-Al	50	(28	52	14) ³
1b	Cu-Al	200	—	—	48
1b	Co-Al	200	(10	4	87) ³
1b	Fe-Al	200	(51	1	48) ³

1) Temp : 80°C, Time : 2h. 2) Purity determined by vpc is >99%.

3) Relative yield determined by vpc.



Scheme 1



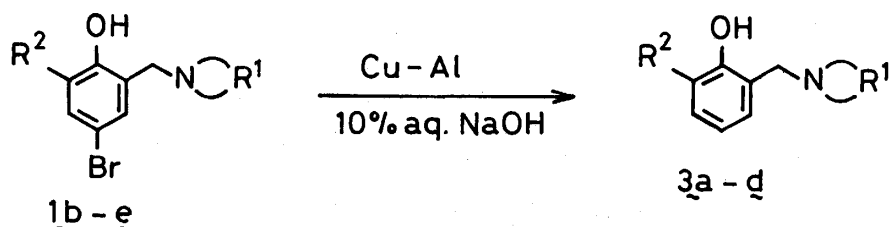
Scheme 2

and Fe alloy gave a mixture of **1**, cresol (**2**), and 2-(1-piperidinylmethyl) phenol³⁾ (**3a**). It is noted that Raney Cu alloy removed bromine more effectively than Fe and Co did. From Table 1, it is clear that reductive dehalogenation precedes C-N bond fission (Scheme 2).

From the above results, it is now expected that 2-aminomethylphenols and their chloro derivatives could be prepared by treatment of Mannich bases of bromo- and bromo-chloro-phenols, respectively, with Raney Cu-Al alloy without being contaminated by regioisomers. This is realized in Scheme 3 and Table 2. Aminomethylphenols **3a-b** and chloro derivatives **3c-d** were

Table 2. Preparation of aminomethylphenol 3.

Substrate	Product	R ¹	R ²	Yield (%)
1b	3a	-(CH ₂) ₅ -	H	57
1c	3b	-(CH ₂) ₂ O(CH ₂) ₂ -	H	75
1d	3c	-(CH ₂) ₅ -	Cl	16
1e	3d	-(CH ₂) ₂ O(CH ₂) ₂ -	Cl	63

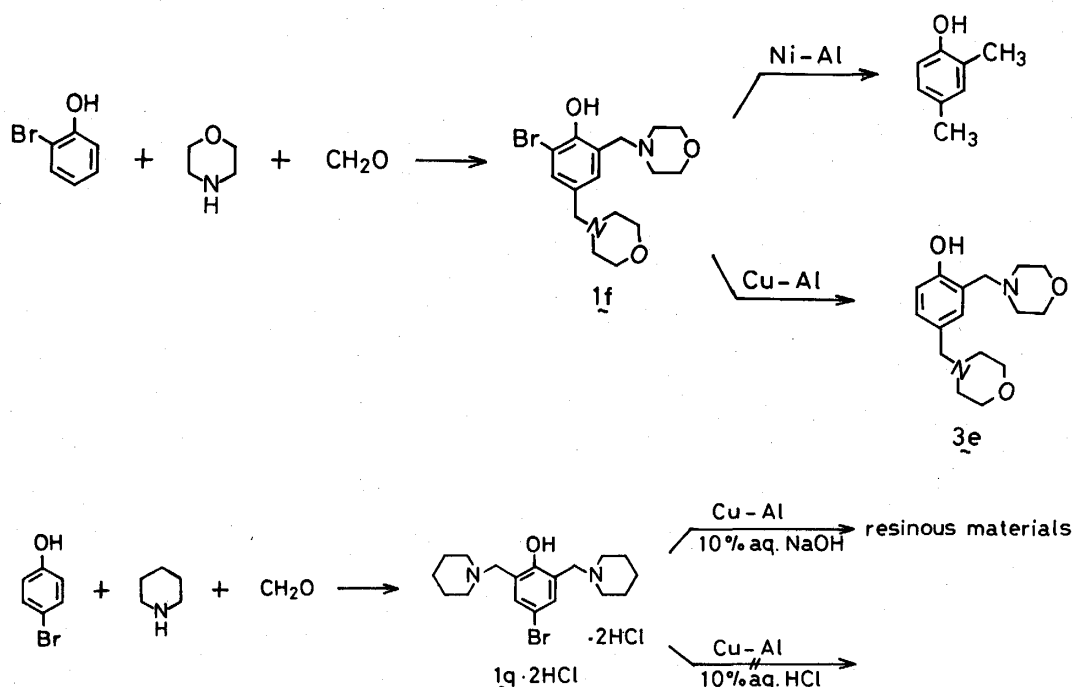


Scheme 3

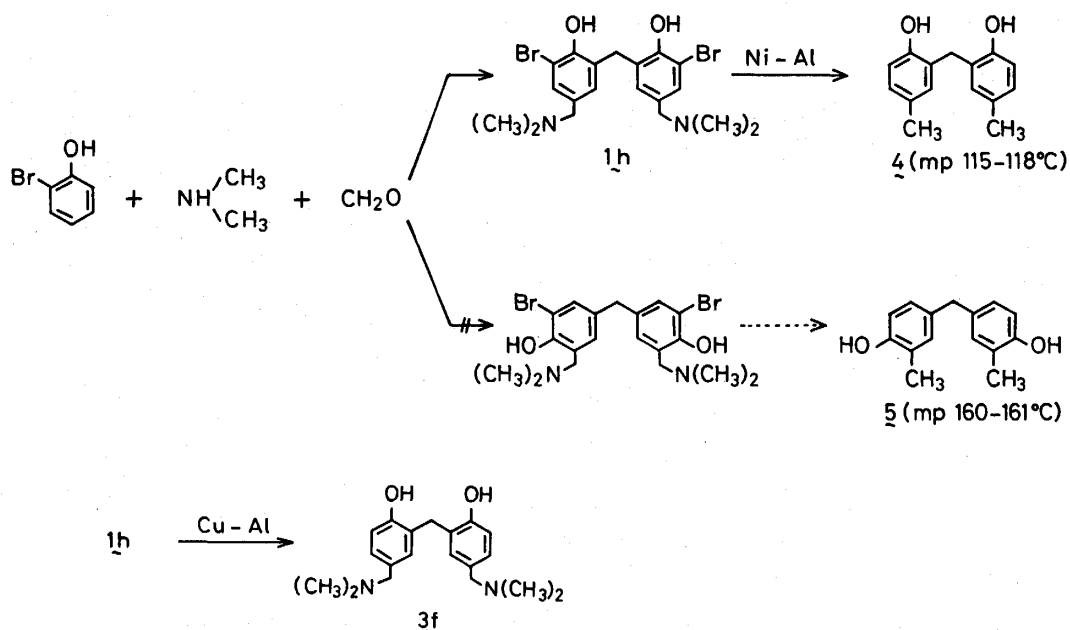
obtained in the yields shown in Table 2.

Reduction of mannich base **1f** by Ni alloy gave 2,4-xylenol in 74% yield and the reduction by Cu alloy did 2,4-di(1-morpholinylmethyl)phenol (**3e**) in 66% yield. Compound **1g** is unstable under basic conditions, forming resinous materials. Reduction of **1g** with Ni alloy in hydrochloric acid resulted in a recovery of **1g** in 80% yield.

Mannich base of diphenylmethane **1h** was prepared by the reaction of 2-bromophenol with dimethylamine. From ¹H-nmr data, **1h** was elucidated to have 2,2'-dihydroxy- or 4,4'-dihydroxydiphenylmethane skeleton. In order to clarify this, **1h** was reduced with Ni alloy, giving 5,5'-dimethyl-2,2'-dihydroxydiphenylmethane (**4**) whose melting point (mp 115–118°C) is different



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from that (mp 160–161°C) of isomeric 3,3'-dimethyl-4,4'-dihydroxy one **5**.⁴⁾ Raney Cu alloy reduction afforded the expected **3f** in 40% yield.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-apparatus and Mitamura-riken MELT-THERMO and are uncorrected. Mass spectra were obtained on a Nippon Denshi JMS-01SG-2 mass spectrometer at 75 eV using a direct inlet system. ¹H-nmr spectra were recorded on a Nippon Denshi JEOL FT-100 using TMS as an internal standard.

Preparation of Mannich base (1).

Preparation of Mannich base (**1**) was carried out according to the reported procedure.¹⁾ Typical procedure is as follows. To a stirred mixture of phenol (10 mmol) and secondary amine (15 mmol) was added dropwise at room temperature 37% aq. formalin (15 mmol) over a period of 30 min. The mixture was stirred at room temperature for 30 min and then in oil bath kept at 100°C for 2 h. After it was cooled to room temperature, ether (50 ml) was added. Organic layer was separated, dried over MgSO₄, and evaporated in vacuo, giving crude **1**. Hydrochloride of **1** was obtained as a white solid by introducing dry hydrogen chloride into an ether solution of crude **1**.

4-Chloro-2-(1-piperidinylmethyl)phenol (**1a**): colorless needles, mp 52–54°C (lit., mp 56–57°C).³⁾

N-(5-chloro-2-hydroxyphenylmethyl)piperidinium chloride (**1a** · HCl): colorless needles, mp 231–234°C (decomp.), Yield 90%; mass, m/e 227 (M⁺), 225 (M⁺) (Found: C, 55.16; H, 6.57; N, 5.42).

Calcd for $C_{12}H_{17}NOCl_2$: C, 54.97; H, 6.54; N, 5.34%

4-Bromo-2-(1-piperidinylmethyl)phenol (**1b**): colorless needles, mp 53–57°C; 1H -nmr ($CDCl_3$) δ 1.40–1.80 (6H, m), 2.30–2.70 (4H, m), 3.60 (2H, s), 6.70 (1H, d, $J=8.0$ Hz), 7.05 (1H, d, $J=2.5$ Hz), 7.23 (1H, dd, $J=8.0$ and 2.5Hz), 9.40–9.70 (br s, 1H); mass, m/e 271 (M^+), 269 (M^+).

Found: C, 53.14; H, 5.87; N, 5.04. Calcd for $C_{12}H_{16}NOBr$: C, 53.35; H, 5.97; N, 5.18%.

N-(5-bromo-2-hydroxyphenylmethyl)piperidinium chloride (**1b** · HCl): colorless needles, mp 245–248°C (decomp), Yield 89%; 1H -nmr (CD_3OD) δ 1.40–2.00 (6H, m), 2.80–3.20 (4H, m), 4.25 (2H, s), 6.90 (1H, d, $J=8.0$ Hz), 7.40 (1H, dd, $J=8.0$ and 2.5Hz), 7.60 (1H, d, $J=2.5$ Hz); mass, m/e 271 (M^+), 269 (M^+). Found: C, 46.83; H, 5.48; N, 4.39. Calcd for $C_{12}H_{17}NOBrCl$: C, 47.01; H, 5.59; N, 4.57%.

N-(5-bromo-2-hydroxyphenylmethyl)morpholinium chloride (**1c** · HCl): colorless crystals, mp 165–180°C (decomp.), Yield 91%; 1H -nmr (CD_3OD) δ 3.00–3.50 (4H, m), 3.60–4.20 (4H, m), 4.34 (2H, s), 6.86 (1H, d, $J=8.5$ Hz), 7.45 (1H, dd, $J=8.5$ and 2.5Hz), 7.59 (1H, d, $J=2.5$ Hz); mass, m/e 273 (M^+), 271 (M^+). Found: C, 42.73; H, 5.01; N, 4.72. Calcd for $C_{11}H_{15}NO_2BrCl$: C, 42.81; H, 4.90; N, 4.54%.

N-(5-bromo-3-chloro-2-hydroxyphenylmethyl)piperidinium chloride (**1d** · HCl): colorless crystals from hexane, mp 186–192°C (decomp), Yield 91%; 1H -nmr (CD_3OD) δ 1.30–2.20 (6H, m), 2.70–3.80 (4H, m), 4.34 (2H, s), 7.61 (1H, d, $J=2.5$ Hz), 7.65 (1H, d, $J=2.5$ Hz); mass, m/e 307 (M^+), 305 (M^+), 303 (M^+). Found: C, 42.03; H, 4.78; N, 3.53. Calcd for $C_{12}H_{16}NOBrCl_2$: C, 42.26; H, 4.73; N, 4.11%.

N-(5-bromo-3-chloro-2-hydroxyphenylmethyl)morpholinium chloride (**1e** · HCl): colorless powder, mp 170–178°C (decomp.), Yield 96%; 1H -nmr (CD_3OD) δ 3.06–3.60 (4H, m), 3.62–4.24 (4H, m), 4.88 (2H, s), 7.63 (1H, d, $J=2.0$ Hz), 7.68 (1H, d, $J=2.0$ Hz); mass, m/e 307 (M^+), 305 (M^+). Found: C, 39.09; H, 4.39; N, 4.14. Calcd for $C_{11}H_{14}NO_2BrCl_2$: C, 38.51; H, 4.11; N, 4.08%.

2-Bromo-4,6-di(morpholinomethyl)phenol (**1f**): pale pink plates from ethanol, mp 167–169°C, Yield 81%; 1H -nmr ($CDCl_3$) δ 2.20–2.80 (8H, m), 3.36 (2H, s), 3.50–3.90 (10H, m), 6.90 (1H, d, $J=2$ Hz), 7.40 (1H, d, $J=2$ Hz); mass, m/e 371 (M^+), 369 (M^+). Found: C, 51.81; H, 6.28; N, 7.43. Calcd for $C_{16}H_{23}N_2O_3Br$: C, 51.76; H, 6.24; N, 7.55%.

4-Bromo-2-hydroxy-1,3-benzobis[N-(methylene)piperidinium] dichloride (**1g** · 2HCl): pale orange crystals from acetonitrile, mp 227–229°C (decomp.), Yield 95%; 1H -nmr ($CDCl_3$) δ 0.70–1.80 (6H, m), 2.10–2.80 (4H, m), 3.54 (4H, s), 7.14 (2H, s), 9.20–10.20 (1H, br s); mass, m/e 368 (M^+), 366 (M^+). Found: C, 48.65; H, 6.60; N, 6.31. Calcd for $C_{18}H_{29}N_2OBrCl_2$: C, 49.11; H, 6.64; N, 6.36%.

3,3'-Dibromo-2,2'-dihydroxy-5,5'-di(dimethylaminomethyl)diphenylmethane (**1h**): pale yellow needles from hexane, mp 171–175°C (decomp.), Yield 24%; 1H -nmr ($CDCl_3$) δ 2.30 (6H, s), 3.58 (2H, s), 3.66 (1H, s), 6.44 (1H, d, $J=2$ Hz), 7.16 (1H, d, $J=2$ Hz), 10.20–10.50 (1H, br s). Found: C, 48.28; H, 5.12; N, 5.73. Calcd for $C_{19}H_{24}N_2O_2Br_2$: C, 48.33; H, 5.12; N, 5.93%.

Treatment of 1 or 1 HCl with Raney alloy.**Preparation of aminomethylphenol (3) by treatment of 1 or 1 HCl with Raney Cu alloy.**

Typical procedure. To a stirred mixture of **1** (5 mmol) and a 10% aqueous NaOH (20 ml) was added at room temperature Raney Cu alloy (500 mg, 100 mg of alloy/1 mmol of **1**) in five portions and it was heated in oil bath kept at 80°C for 1 h. Inorganics were filtered and the filtrate was neutralized with concentrated hydrochloric acid. White solid formed was filtered through celite and the filtrate was extracted with chloroform (150 ml), dried over MgSO₄, and evaporated in vacuo to give **3**.

2-(1-Piperidinylmethyl)phenol (**3a**): colorless liquid (lit., bp 150–152°C/12mmHg)³; ¹H-nmr (CDCl₃) δ 1.30–1.80 (6H, m), 2.30–2.60 (4H, m), 3.60 (2H, s), 6.60–7.30 (4H, m), 10.27 (1H, s); mass, m/e 191 (M⁺).

2-(1-Morpholinylmethyl)phenol (**3b**): colorless needles from hexane, m.p. 85–88°C; ¹H-nmr (CDCl₃) δ 2.40–2.80 (4H, m), 3.50–3.90 (6H, m), 6.70–7.30 (4H, m); mass, m/e 193 (M⁺).

Found: C, 68.14; H, 7.81; N, 7.12. Calcd for C₁₁H₁₅NO₂: C, 68.37; H, 7.82; N, 7.25%.

2-Chloro-6-(1-piperidinylmethyl)phenol (**3c**): colorless needles from hexane, mp 43–45°C (lit., mp 49°C).⁵

2-Chloro-6-(1-morpholinylmethyl)phenol (**3d**): colorless needles from hexane, mp 117–118°C (lit., mp 114°C).⁵

2,4-Di(1-morpholinylmethyl)phenol (**3e**): colorless needles, mp 90–93°C; ¹H-nmr (CDCl₃) δ 2.20–2.70 (8H, m), 3.36 (2H, s), 3.40–3.92 (10H, m), 6.72 (1H, d, J=8Hz), 6.90 (1H, d, J=2Hz), 7.06 (1H, dd, J=8 and 2Hz); mass, m/e 292(M⁺). Found: C, 65.93; H, 8.34; N, 9.56. Calcd for C₁₆H₂₄N₂O₃: C, 65.73; H, 8.27; N, 9.58%.

4,4'-Dihydroxy-3,3'-di(N,N-dimethylaminomethyl)diphenylmethane (**3f**): colorless needles from hexane, mp 88–91°C; ¹H-nmr (CDCl₃) δ 2.30 (12H, s), 3.59 (4H, s), 3.76 (2H, s), 6.70 (2H, d, J=6Hz), 6.76 (2H, d, J=2Hz), 6.94 (2H, dd, J=6 and 2Hz), 9.40–10.20 (2H, br s); mass, m/e 314 (M⁺). Found: C, 72.66; H, 8.58; N, 8.73. Calcd for C₁₉H₂₆N₂O₂: C, 72.58; H, 8.33; N, 8.91%.

Reduction of 1h

A mixture of **1h** (620 mg, 2 mmol) in 10% aq. NaOH (10 ml) was treated with Raney Ni-alloy (1600 mg) as described above, giving **4** (40 mg, 9%).

4,4'-Dihydroxy-3,3'-dimethyldiphenylmethane (**4**): colorless needles from hexane, mp 118–121°C; ¹H-nmr (CD₃OD) δ 2.12 (6H, s), 3.66 (2H, s), 6.40–7.00 (6H, m); mass, m/e 228 (M⁺).

Found: C, 78.43; H, 7.13. Calcd for C₁₅H₁₆O₂: C, 78.92; H, 7.06%

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