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Synthesis of 2-Aminomethyl-5-*tert*-butylphenols

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Mannich-type aminomethylation of *m-tert*-butylphenol (1) with a variety of secondary amines and formalin was carried out in ethanol at 70-80 °C for 2 h. The reaction with amines such as pyrrolidine, piperidine, *N*-methylpiperazine, and *N*-benzylpiperazine gave the expected products, 2-pyrrolidinomethyl- (2b), 2-piperidinomethyl- (2d), 2-(*N*-methylpiperazino)methyl- (2e), and 2-(*N*-benzylpiperazino)methyl-5-*tert*-butylphenol (2f) in high yields. In the reaction with piperazine, the desired compound, 2-(piperazinomethyl)-5-*tert*-butylphenol (2g) was not formed and *N,N'*-bis(2-hydroxy-4-*tert*-butylbenzyl)piperazine (3) and bis[*N,N'*-di(2-hydroxy-4-*tert*-butylbenzyl)]piperazinomethane (4) were produced in 52% and 38% yields, respectively. 2-(Dimethylamino)methyl-5-*tert*-butylphenol (2a) was obtained, albeit in a poor yield, when aqueous 10 % potassium hydroxide solution was added to the reaction mixture with dimethylammonium chloride to generate the free amine. Addition of the base was effective in the Mannich condensation with morpholine, giving the desired 2-(morpholino)methyl-5-*tert*-butylphenol (2c) in a moderate yield. Without the base, the reaction did not occur.

Introduction

The fungistatic activities toward *Aspergillus niger* of pyrazoles¹⁾ and phenol derivatives¹⁻²⁾ such as halophenols³⁾ and salicylic acids²⁾ have been reported. In the study³⁾, it was found that the fungistatic activities of halophenols were promoted by *t*-butyl group at the meta-position of the phenol ring. In continuation of our research on the relationship between fungistatic activity toward *Aspergillus niger* and the chemical structures of the tested compounds, it seemed of interest to investigate the activity of amino-substituted *m-tert*-phenol derivatives. In the studies, systematic synthesis of the tested compounds is important. However, there seems no systematic synthesis of *o*-aminomethyl-*m-t*-butylphenols. The present paper describes the synthesis of 2-aminomethyl-5-*tert*-butylphenols by the Mannich reaction.⁴⁻⁵⁾

Results and Discussion

Reaction of 5-*tert*-butylphenol (1) with secondary amines and formalin was carried out at 70-80 °C for 2 h and the results are summarized in Scheme 1 and Table 1. The aminomethylation reaction of 1 with pyrrolidine,

piperidine, *N*-methylpiperazine, and *N*-benzylpiperazine afforded the corresponding aminomethylphenols, 2-pyrrolidinomethyl- (2b), 2-piperidinomethyl- (2d), 2-(*N*-methylpiperazino)methyl- (2e), and 2-(*N*-benzylpiperazino)methyl-5-*tert*-butylphenol (2f) in high yields. In the reaction with dimethylammonium chloride, a complex mixture of unidentified products was obtained and 2-(*N,N*-dimethylamino)methyl-5-*tert*-butylphenol (2a) was not isolated from the mixture. When the reaction was carried out with an addition of aq. 10% potassium hydroxide in order to free the amine, the desired compound 2a was obtained only in a poor yield (5%). Furthermore, it was found that the reaction with weakly basic morpholine could occur in the presence of potassium hydroxide, a strong base, yielding 2-morpholinomethyl-5-*tert*-butylphenol (2c) in 25% yield. The reaction with piperazine did not afford the expected 2-piperazinomethyl-5-*tert*-butylphenol (2g). In the reaction, *N,N'*-di(2-hydroxy-4-*tert*-butylbenzyl)piperazine (3) was obtained in 58% yield, together with an unexpected product, Bis[*N,N'*-di(2-hydroxy-4-*tert*-butylbenzyl)piperazino]-methane (4), in 38% yield.

In Scheme 2, the preparation of 3-*tert*-butyl-4-

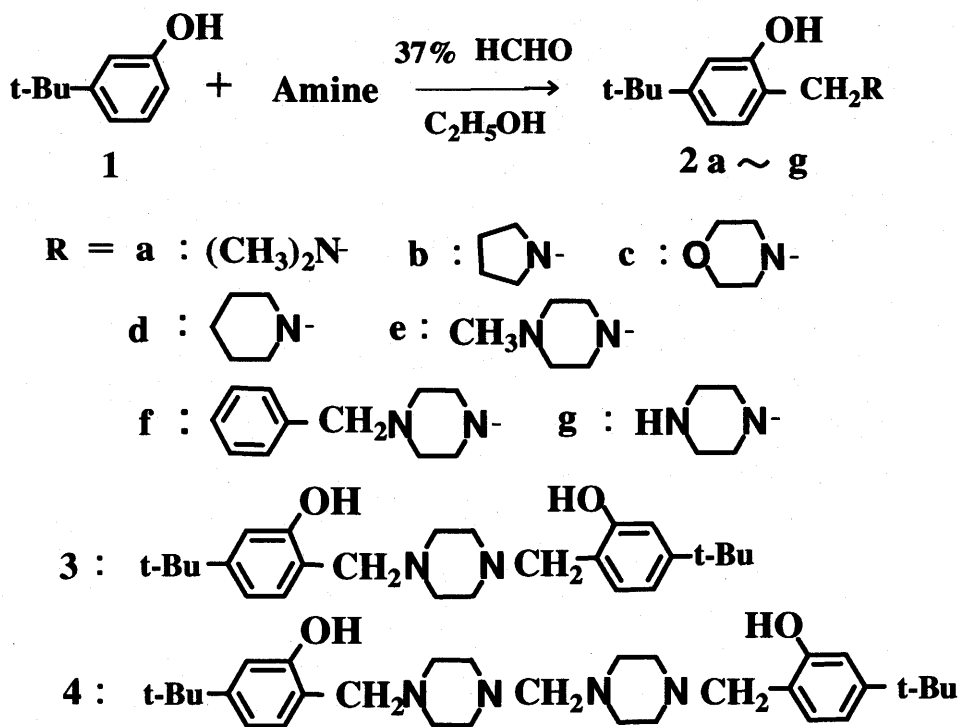
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piperidinomethylphenol (7), a positional isomer of 2d, was tried by means of reductive dehalogenation of 6,

since the aminomethylation reaction of 2-halo-5-*tert*-butylphenols (5) was expected to afford 6. The reaction of

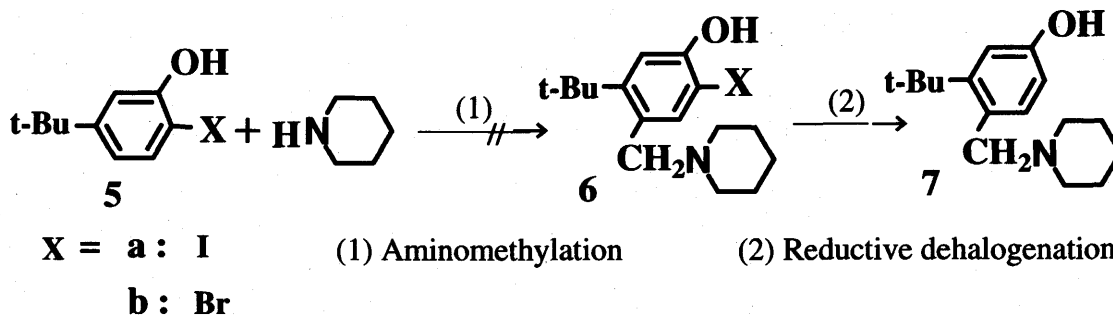


Scheme 1

2-iodo-5-*tert*-butylphenol (5a) with piperidine was carried out under the same conditions employed in the reaction of 1 with piperidine. The desired compound 6 was not obtained and, unexpectedly, 2d was produced in 32% yield. The formation pathway of 2d may be explained via a sequence of reductive deiodination of 5a with formalin and the subsequent aminomethylation of the resulted 1. The

aminomethylation of 2-bromo-5-*tert*-butylphenol (5b) did not occur.

The structures of the products were determined on the basis of their spectral data and elemental analyses (Tables 2-3).



Scheme 2

Table 1. Aminomethylation of *m-tert*-butylphenol (1) ^{a)}

Run	Amine	Product (%) ^{b)}
1	Dimethylamine ^{c)}	2a (5) ^{d)}
2	Pyrrolidine	2b (90)
3	Morpholine	2c (25) ^{d)}
4	Piperidine	2d (90)
5	<i>N</i> -Methylpiperazine	2e (96)
6	<i>N</i> -Benzylpiperazine	2f (97)
7	Piperazine	3 (52), 4 (38)

a) Reaction of 5-*tert*-butylphenol (1) (1.0×10^{-2} mol) with amines (1.1×10^{-2} mol) and formalin (2.5 ml) in ethanol (5 ml) was carried out at 70-80 °C for 2 h unless otherwise indicated. b) Isolated yields are shown. c) Hydrochloride salt .d) Aq. 10 % potassium hydroxide (2 ml) was added.

Table 2. Physical properties of aminomethylphenols 2-4.

Compd.	Mp (° C) ^{a)}	Appearance (Solvent)	Molecular formula ^{b)} (Mw)
2a	140-143	colorless cubs (methanol / water)	C ₁₃ H ₂₁ NO (207)
2b	39-41	colorless plates (methanol / water)	C ₁₅ H ₂₃ NO (233)
2c	57-58	colorless plates (methanol / water)	C ₁₅ H ₂₃ NO ₂ (249)
2d	82-84	colorless plates (methanol)	C ₁₆ H ₂₅ NO (247)
2e	56-57	colorless plates (methanol / water)	C ₁₆ H ₂₆ N ₂ O (262)
2f	83-85	colorless needles (methanol / water)	C ₂₂ H ₃₀ N ₂ O (338)
3	256-261 (decomp.)	colorless prisms (ethyl acetate)	C ₂₆ H ₃₈ N ₂ O ₂ (410)
4	184-186	colorless needles (methanol / water)	C ₃₁ H ₄₈ N ₄ O ₂ (508)

a) Uncorrected. b) Elemental analyses gave satisfactory results within the deviation of C , ±0.25, H, ±0.26, and N, ±0.16 %.

Table 3. ¹H-NMR of Aminomethylphenols 2-4.

Compd.	δ ppm in deuteriochloroform.
2a	1.27 [9H,s, <i>tert</i> -Bu], 1.45 [6H,s, (CH ₃) ₂], 3.80 [2H,s, NCH ₂], 6.70-7.05 [3H,m, aromatic H], 8.20 [1H,br s, OH, exchanged with D ₂ O]
2b	1.30 [9H,s, <i>tert</i> -Bu], 1.70~1.90 [4H,m, (CH ₂) ₂]; 2.50~2.75 [4H,m, N(CH ₂) ₂]; 3.78 [2H,s, NCH ₂]; 6.75-6.95 [3H,m, aromatic H], 9.40 [1H,br s, OH, exchanged with D ₂ O]
2c	1.27 [9H,s, <i>tert</i> -Bu], 2.55 [4H,t, J=3.5Hz, O(CH ₂) ₂], 3.66 [2H,s, NCH ₂], 3.75 [4H,t, J=3.5Hz, N(CH ₂) ₂], 6.75-6.95 [3H,m, aromatic H], 10.10 [1H,br s, OH, exchanged with D ₂ O]
2d	1.29 [9H,s, <i>tert</i> -Bu], 1.33-1.80 [6H,m, (CH ₂) ₃], 2.27-2.63 [4H,m, N(CH ₂) ₂], 3.63 [2H,s, NCH ₂], 6.70-6.93 [3H,m, aromatic H], 9.40 [1H, br s, OH, exchanged with D ₂ O]
2e*	1.27 [9H,s, <i>tert</i> -Bu], 2.30 [3H,s, CH ₃], 2.40-2.70 [8H,m, (NCH ₂ CH ₂ N) ₂], 3.66 [2H,s, NCH ₂], 6.73-6.96 [3H,m, aromatic H]
2f*	1.27 [9H,s, <i>tert</i> -Bu], 2.55 [8H,br s, (NCH ₂ CH ₂ N) ₂], 3.50 [2H,s, CH ₂], 3.66 [2H,s, NCH ₂], 6.73-6.96 [3H,m, aromatic H], 7.20-7.35 [5H,m, aromatic H]
3*	1.30 [18H,s, <i>tert</i> -Bu], 2.65 [8H,br s, (NCH ₂ CH ₂ N) ₂], 3.70 [4H,s, (NCH ₂) ₂], 6.73-7.00 [6H,m, aromatic H]
4*	1.30 [18H,s, <i>tert</i> -Bu], 2.53 [16H,br s, (NCH ₂ CH ₂ N) ₄], 2.96 [2H,s, NCH ₂ N], 3.66 [4H,s, (NCH ₂) ₂], 6.73-6.93 [6H,m, aromatic H]

* : The peak due to the hydroxyl group of the compound was not observed, but a singlet of the OH proton was detected at around δ 4.63 ppm after the sample was treated with deuterium oxide.

Experimental

¹H NMR spectra were determined with a Hitachi R-900 spectrometer with Me₄Si (TMS) as an internal reference. Mass spectra were obtained on a Hitachi M-80 mass spectrometer at 70 eV by using a direct-inlet system. IR spectra were measured as KBr band IR spectra were measured as KBr pellets on a Nippon Bunko (JASCO) IR-A spectrophotometer. An absorption band ascribable to ν_{O-H} in IR spectra of the products was observed at 2600~3200 cm⁻¹ as a broad peak which overlaps with the due to ν_{C-H} at 2700~3100 cm⁻¹. The products were purified by recrystallization from the solvent given in Table 2.

General Procedure for Runs 2-6 in Table 1: To a stirred solution of *m-tert*-butylphenol (1) (1.5 g, 1.0 × 10⁻² mol) in ethanol (5 ml), amine (1.1 × 10⁻² mol) and formalin (2.5 ml) were added and the mixture was heated on

a water-bath (70-80 °C) for 2 h. Then, water (about 50 ml) was added to the reaction mixture and the precipitates formed were filtered and recrystallized.

General Procedure for Runs 1 and 3 in Table 1: The reaction mixture was treated and worked up as described above, affording oily products, which were taken up with benzene (30 ml × 3). The benzene solution was dried over anhydrous magnesium sulfate and then evaporated *in vacuo* to leave white crystals, which were recrystallized.

Procedure for Run 7 in Table 1: The reaction mixture was treated and worked up as described above, affording a solid. Product 4 was isolated as an *n*-hexane soluble compound from the solids, and product 3 was obtained from the hexane insoluble solid. Products 3 and 4 were purified by recrystallization.

References

- 1 Fukata, G., Komatsu, K., Tori-i, A., Tsuzuki, H. and Tashiro, M., *J. Food Hyg. Japan*, 1993, **3 4**, 227.
- 2 Tsuzuki, H., Fukata, G., Narazaki, S., Nishi, M., Tsuruta, Y., Yonemitsu, T., Mataka, S. and Tashiro M., *J. Food Hyg. Japan*, 1993, **3 4**, 142.
- 3 Fukata, G., Miyoshi, F., Tsuda, Y., Iwata, S., Tsuzuki, H. and Tashiro, M., *J. Food Hyg. Japan*, 1990, **3 1**, 323.
- 4 Blicke, F. F., *Organic Reactions*, 1942, **1**, 303.
- 5 Pastushok, V. N., Bradshaw, J. S., Bordnuov, A. V., and Izatt, R. M., *J. Org. Chem.*, 1996, **6 1**, 6888 and references cited therein.