Selective Synthesis of Phenolic Mannich Bases under Solid-Liquid Phase Transfer Conditions

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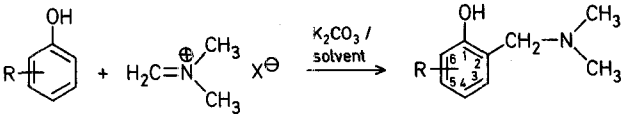
Aminomethylation of phenols is usually achieved with formaldehyde and amines in protic solvents, the classical conditions for the phenol Mannich reaction[1,2]. The reaction occurs readily in *ortho* and *para* positions, affording preferentially polysubstituted products[2].

The use of methyleneiminium salts as potential Mannich reagents in aprotic solvents has received attention, especially in the regioselective functionalization of carbonyl compounds[3] and, more recently, in the aminomethylation of indoles[4] and thiophenes[5] and has been found to be superior to the conventional Mannich reaction. Very little is known on the aminomethylation of phenols by iminium salts in aprotic media, although the possibility that this reaction can occur to give monoalkylated products in low yield has been indicated[6].

With the aim of obtaining high reactivity under mild conditions and to control at the same time polyalkylation, which is a problem for electron-rich phenolic substrates, we have explored the reaction of phenols **1** and *N*-methyl-*N*-methylenemethaniminium salts **2**. The reaction conditions employed are typical of the solid-liquid phase transfer catalysis with the phenol **1** dissolved in an organic solvent (toluene or dichloromethane) and stirred at room temperature in the presence of a solid base (potassium carbonate) and a solid methyleneiminium salt **2**.



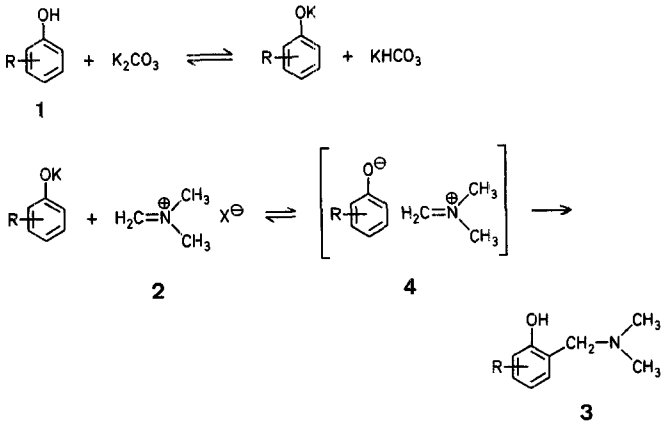
1 **2** X = Cl, J **3**

Table 1 reports data obtained with Eschenmoser's salt (**2**; X = J) but similar results were obtained with the corresponding *N*-methyl-*N*-methylenemethaniminium chloride (**2**; X = Cl). The yield of *ortho*-regiospecific monoalkylated products **3** is high (> 75%). Toluene is the solvent of choice for electron-rich phenols since it strongly decreases polyalkylation, whereas dichloromethane usually gives higher reactivity and is suitable for substrates bearing electron-withdrawing groups. *ortho*-Acetyl- and *ortho*-methoxycarbonylphenols do not react under these conditions, but the corresponding *para*-isomers give **3** in high yield. Anisole is completely unreactive towards methyleneiminium salts **2** and 2,6-dialkylphenols give *para*-alkylated products after longer reaction times and in lower yields.

Table 2 reports the effect of solvent and base on a model reaction, showing that the yield of product **3a** decreases dramatically in the absence of any base or in the presence of a soluble one such as tri-*n*-butylamine, and that it is not necessary to work in anhydrous conditions using potassium carbonate as the base (run 2).

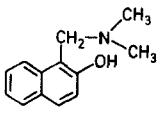
The reactions conditions are mild and crude products are isolated by simple filtration. Since methyleneiminium salts **2** can be prepared in high yields by simplified procedures[7], the proposed method for phenol *ortho*-monoaminomethylation seems to be valuable.

The results obtained suggest a possible reaction pathway in which a soluble and reactive "ion pair" **4** may form, by gegenion exchange from potassium phenolate and methyleneiminium salts, and which eventually collapses to give *ortho*-attack products **3**. The mildness of the base and the low polarity of the solvent used probably play an important role in avoiding polyalkylation. Studies are under way to clarify the reaction mechanism.



Dimethylaminomethylation of Phenols 1; General Procedure:
N-Methyl-*N*-methylenemethaniminium iodide or chloride **2** (Fluka; 10 mmol) is added to a solution of the phenol **1** (10 mmol) in toluene or dichloromethane (50 ml) in which potassium carbonate (2.1 g, 15 mmol) has been suspended. The reaction mixture is stirred at room temperature for the time required, then filtered, and the solid washed with ethyl acetate (20 ml). The solvent is evaporated in vacuo giving a residue which is either recrystallized or distilled.

Table 1. 2-[(Dimethylamino)-methyl]-phenols **3** and **5** prepared

Product No.	R	Reaction conditions: time (h)/ solvent	Yield [%]	m.p.[a] [°C] or b.p. [°C]/ torr	Molecular formula[b] or Lit. data	M.S. (70 eV) *m/e* (rel. int. %)	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm][c]
3a	H	10/toluene	85	100–101°/12	104°/13[8]	151 (32); 107 (20); 44 (100)	2.31 [s, 6H, $N(CH_3)_2$]; 3.60 (s, 2H, CH_2); 6.5–7.3 (m, 4H_{arom}); 9.70 (s, 1H, OH)
3b	6-H_3C	5/toluene	85	75–80°/0.2	91–95°/2[9]	165 (56); 164 (8); 121 (26); 44 (100)	2.3 [br. s, 9H, $ArCH_3$ + $N(CH_3)_2$]; 3.56 (s, 2H, CH_2); 6.4–7.3 (m, 3H_{arom}); 10.68 (s, 1H, OH)
3c	5-H_3C	8/toluene	84	46–47°	45–46°[10]	165 (63); 164 (8); 121 (79); 44 (100)	2.3 [br. s, 9H, $ArCH_3$ + $N(CH_3)_2$]; 3.48 (s, 2H, CH_2); 6.52 (d, 1H, 4-H, J=8 Hz); 6.60 (s, 1H, 6-H); 6.80 (d, 1H, 3-H); 10.70 (s, 1H, OH)
3d	6-*t*-C_4H_9	4/toluene	80	oil[d]	$C_{13}H_{21}NO$ (207.3)	207 (92); 192 (29); 164 (43); 147 (100); 119 (43); 44 (100)	1.46 [s, 9H, $C(CH_3)_3$]; 2.25 [s, 6H, $N(CH_3)_2$]; 3.54 (s, 2H, CH_2); 6.6–6.9 (m, 2H, 4-H + 5-H); 7.15 (dd, 1H, 3-H, J=8 Hz, 2 Hz); 11.08 (s, 1H, OH)
3e	6-Cl	2/dichloro-methane	75	100–105°/1	117°/1.7[11]	187 (25); 185 (75); 143 (7); 141 (21); 58 (92); 44 (100)	2.30 [s, 6H, $N(CH_3)_2$]; 3.58 (s, 2H, CH_2); 6.4–7.0 (m, 2H, 4-H + 5-H); 7.18 (dd, 1H, 3-H, J=8 Hz, 2 Hz); 12.08 (s, 1H, OH)
3f	4-H_3C—CO—	7/dichloro-methane	85	74°	73°[12]	193 (35); 149 (9); 58 (61); 44 (100)	2.32 [s, 6H, $N(CH_3)_2$]; 2.48 (s, 3H, CH_3CO); 3.62 (s, 2H, CH_2); 6.75 (d, 1H, 6-H, J=8 Hz); 7.4–7.9 (m, 2H, 3-H + 5-H); 10.45 (s, 1H, OH)
3g	4-H_3COOC—	7/dichloro-methane	95	89–90°	85°[13]	209 (48); 208 (14); 178 (15); 165 (18); 58 (82); 44 (100)	2.32 [s, 6H, $N(CH_3)_2$]; 3.60 (s, 2H, CH_2); 3.82 (s, 3H, OCH_3); 6.70 (d, 1H, 6-H, J=9 Hz); 7.6 (br. s, 1H, 3-H); 7.78 (dd, 1H, 5-H, J=9 Hz, 2 Hz); 10.48 (s, 1H, OH)
 **5**		0.5/dichloro-methane	98	75–76°	74–75°[14]	201 (37); 156 (28); 128 (80); 44 (100)	2.30 [s, 6H, $N(CH_3)_2$]; 3.96 (s, 2H, CH_2); 6.9–7.9 (m, 6H_{arom}); 12.45 (s, 1H, OH)

[a] Products crystallized from hexane.
[b] Satisfactory microanalyses obtained: C ±0.25, H ±0.15, N ±0.30.
[c] Measured at 60 MHz.
[d] This product was not distilled.

Table 2. Aminomethylation of Phenol **(1a)** with **2** (X=J) at Room Temperature after 5 h

Run	Solvent	Base added (1.5 eq)	Yield [%] of **3a**
1	Toluene	K_2CO_3	85
2	Toluene	K_2CO_3/H_2O (2 eq)	75
3	Toluene	none	5
4	Dichloromethane	K_2CO_3	45
5	Dichloromethane	$(n\text{-}C_4H_9)_3N$	0
6	Toluene	Na_2CO_3	45
7	Toluene	Li_2CO_3	40
8	Dimethylformamide	K_2CO_3	20

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