Microwave-induced Mannich reaction —
Synthesis of some Mannich derivatives of
p-aminophenol

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Mono and bis substituted dialkylamino alkyl-p-aminophenol 3 are prepared by treating paracetamol 1 with formaldehyde and appropriate secondary amines followed by deacetylation using 6 M HCl in unmodified domestic microwave oven in unsealed borosil vessels. The compounds are obtained within a short duration of time (3 min). The rate of the reaction is found to be accelerated by about 60 fold when compared to conventional heating.

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Microwave-induced Organic Reaction Enhancement [MORE] chemistry has received considerable attention in the recent years due to several advantages like short reaction time, ease of work-up, excellent yields and this method is more cost-effective [only simple glassware needed]. Moreover it is an environmentally friendly [no or less solvent needed] technique and is believed to be a step towards green chemistry. Microwave reactions involve selective absorption of MW energy by polar molecules and non-polar molecules are inert to MW dielectric heating. The initial experiments with microwave techniques concerned around the use of high dielectric solvents such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF). The rate enhancements in such reactions are now believed to be due to rapid superheating of the polar solvents. For example acetonitrile reaches 105°C (38°C higher than its boiling point). Since the appearance of two pioneering reports 3, 4 on the application of microwaves for chemical synthesis in polar solvents, the approach has blossomed into a useful technique for a several reactions of synthetic importance. However, microwave-induced Mannich reaction has not been reported so far. Keeping in view the utility of MORE chemistry and in continuation of our interest in Mannich reaction, herein we wish to report the microwave-induced Mannich reaction of paracetamol, followed by deacetylation of p-acetamidoo group to primary amine.

Results and Discussion
Mannich reaction of p-acetamidophenol 1 with formaldehyde and appropriate secondary amine in ethanol (as energy transfer medium), afford 2. The solvent was removed by rotary evaporator and without isolating the compound, the resulting viscous residue was treated with 6 M HCl to decacetylate the acetamido group to primary amine 3 (Scheme I). The reaction is fairly general, facile and it is interesting to note that this reaction is more effective when compared to conventional heating. The reaction time has been brought down from hours to minutes using microwave irradiation. In conventional heating, 6 equimolar quantities of paracetamol 1 with formaldehyde and diethylamine in ethanol were refluxed for 3 hr. After isolating the compound, it was refluxed with 6 M HCl for 1 hr. Then it was basified and converted to hydrochloride salt to afford 3b in 96% yield. In the present work, the aforesaid contents were heated for 3 min at 60% microwave energy. After removing the solvent, the residue was dissolved in 6 M HCl and again heated in the microwave oven for 3 min at 80% microwave energy. Similar to conventional method the resulting mixture was basified and converted to hydrochloride salt to obtain 3b in 96% yield. It was observed that the rate of the reaction in the presence of microwaves, increased by 60 fold when compared to conventional heating.

In conclusion, a simple and efficient method has been developed for the Mannich reaction of paracetamol followed by deacetylation to obtain mono and bis substituted Mannich derivatives of p-aminophenol. This technique could be useful to synthetic and medicinal chemist to carry out Mannich reaction to synthesize various potent biologically active compounds.

Experimental Section
Melting points were determined on Buchi 530 apparatus and are uncorrected. The purity of the com-
pounds was checked by TLC using silica gel coated Al plates (Merck). Microwave irradiations were carried out in domestic microwave oven (LG Electronics, model MG-605AP, 2450 MHz, 900 W). IR spectra (νₘₐₓ in cm⁻¹) were recorded on a Jasco IR Report-100 infrared spectrophotometer.

**General procedure for the synthesis of 2-[(dialkylamino)methyl]-4-aminophenol 3a-3g.** A mixture of 1 (3.02 g, 20 mmoles), 37% formaldehyde (2.4 mL) and appropriate secondary amine (20 mmoles) in ethanol (3 mL) were taken in a 100 mL Erlenmeyer flask covered with a small funnel. This system was then placed in an alumina bath inside the microwave oven and zapped the contents for 3 min at 60% microwave energy. Upon completion of the reaction (monitored by TLC), the solvent was removed on a rotary evaporator. The residue was dissolved in 16 mL of 6 M HCl and again zapped in the microwave oven for 3 min at 80% microwave energy. The mixture was cooled and the pH was adjusted to alkaline with ammonia solution, extracted with dichloromethane (4×30mL), washed with water, dried (MgSO₄) and evaporated to give the free amine. Then it was converted to its salt by dissolving the free amine in ether and treating with excess of alcoholic hydrogen chloride by which solid separated out. Results are summarized in the Table I.

**General procedure for the synthesis of 2,6-bis[(dialkylamino)methyl]-4-aminophenol 3h-3j.** Prepared in the same manner as 3a-3g using a mixture of 1 (2.95g, 19.5mmoles), 37% formaldehyde (6.5 mL) and appropriate secondary amine.

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>R'</th>
<th>m.p. (lit.m.p.)¹⁰,¹¹ (°C)</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>3a</td>
<td>-N₂CH₃</td>
<td>H</td>
<td>239-40</td>
<td>74</td>
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<tr>
<td>3b</td>
<td>-N₂C₆H₅</td>
<td>H</td>
<td>217-20 (218-20)</td>
<td>96</td>
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<tr>
<td>3c</td>
<td>-N₂C₆H₅</td>
<td>H</td>
<td>221-22</td>
<td>77</td>
</tr>
<tr>
<td>3d</td>
<td>-N₂C₆H₅</td>
<td>H</td>
<td>159-60</td>
<td>67</td>
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<tr>
<td>3e</td>
<td>-N₂C₆H₅</td>
<td>H</td>
<td>153-55 (153-55)</td>
<td>92</td>
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<tr>
<td>3f</td>
<td>-N₂C₆H₅</td>
<td>H</td>
<td>260-61 (259-60)</td>
<td>52</td>
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<tr>
<td>3g</td>
<td>-N₂C₆H₅</td>
<td>H</td>
<td>160-62</td>
<td>62</td>
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<tr>
<td>3h</td>
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<td>H₂C₆H₅</td>
<td>132-34</td>
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<tr>
<td>3i</td>
<td>-N₂C₆H₅</td>
<td>H₂C₆H₅</td>
<td>218-19 (219-21)</td>
<td>54</td>
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<tr>
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<td>H₂C₆H₅</td>
<td>209-11</td>
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Table I — Physical data of compounds 3a-3j
(54 mmol) in ethanol (3 mL). Results are summarized in the Table I.

Acknowledgement
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References
2 Varma R S, Green chem, 1999, 43.