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An unusual Mannich type reaction of tertiary aromatic amines in aqueous micelles ☆

Atul Kumar *, Ram Awatar Maurya

Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow 226 001, India

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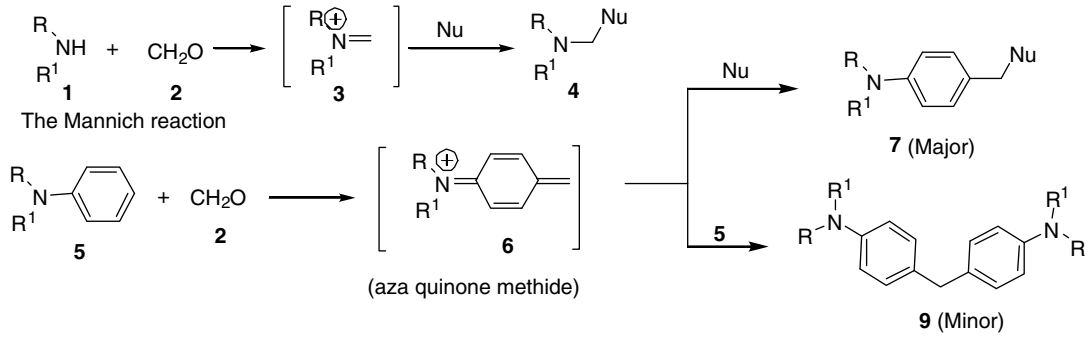
ABSTRACT

An efficient, unusual Mannich type reaction of tertiary aromatic amines, formaldehyde and 1,3-dicarbonyl compounds is described in aqueous micelles catalyzed by boric acid to afford dialkylaminoarylated 1,3-dicarbonyls. In this unusual Mannich type reaction, tertiary aromatic amines react with formaldehyde to generate an *N*-alkyl-*N*-(4-methylenecyclohexa-2,5-dienylidene)alkylaminium intermediate (aza quinone methide), which undergoes nucleophilic addition with 1,3-dicarbonyl compounds. The reaction is highly regioselective, and exclusively *para* functionalized products are formed in high yields.

The Mannich reaction is a powerful synthetic method for the preparation of β-amino carbonyl compounds, an important class of building blocks of pharmaceutically relevant compounds.[1] Due to its atom-economy, the Mannich reaction has received increasing attention, and is applied widely as a key step in the synthesis of numerous pharmaceuticals and natural products.[2] Mannich reactions are very useful for generation of diversity in order to optimize lead compounds.

The Mannich reaction proceeds with initial formation of an iminium salt (intermediate **3**) via reaction of amine **1** and aldehyde **2** (Scheme 1). The intermediate **3** then reacts with various nucleophiles to give products **4**, which are known as 'Mannich bases'. Under typical Mannich reaction conditions, simple tertiary amines cannot be employed because the iminium salt **3** cannot be generated from the aldehyde during the first step of the Mannich reaction.



Scheme 1. Unusual Mannich type reaction.

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* Corresponding author. Tel.: +91 522 2612411; fax: +91 522 2623405/2623938.
E-mail address: dratulsax@gmail.com (A. Kumar).

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However, in the present unusual Mannich type reaction, an intermediate (*N*-alkyl-*N*-(4-methylenecyclohexa-2,5-dienylidene) alkylaminium **6**, as equivalent iminium salt of **3**, is suggested to form on reaction of tertiary aromatic amines (*N*,*N*-dimethylaniline) with a non-enolizable aldehyde such as formaldehyde.[3,4] This intermediate **6** can be attacked by a number of nucleophiles to generate Mannich type products.

We report here a facile and regioselective unusual Mannich type coupling reaction of tertiary aromatic amines, formaldehyde and 1,3-diketones in the presence of boric acid in aqueous micelles via aza quinone methide intermediate **6**.

Boric acid is a useful catalyst for a number of synthetic transformations, for example, the aza Michael addition in water,[5] the thia Michael addition in water,[6] Biginelli reaction,[7] transesterification of ethyl acetoacetate[8] and decarboxylation of cyclic β-enaminoketoesters.[9] It offers milder conditions relative to common mineral acids. The selection of boric acid as catalyst was made because of one of its most fundamental properties, namely it produces a Brønsted acid $[B(OH)_3 + H_2O = H^+ + B(OH)_4^-]$ on reaction with water. The use of water as a reaction medium in organic synthesis has received much attention.[10] Water as a reaction medium conveys many important advantages; it is cheap, safe and environmentally benign. Moreover, the application of water as a solvent has led to observed differences in both reactivity and selectivity to those found in common organic solvents.[11] Thus, boric acid in water is expected to be a useful reagent for Mannich type additions. As a part of our continued efforts towards the development of environmentally friendly synthetic procedures for multi-component reactions, we report here a boric acid catalyzed unusual Mannich type coupling reaction in aqueous micelles.

Initial experiments focused on finding an efficient catalyst for coupling *N*,*N*-dimethylaniline, formaldehyde and ethyl acetoacetate (Scheme 2).

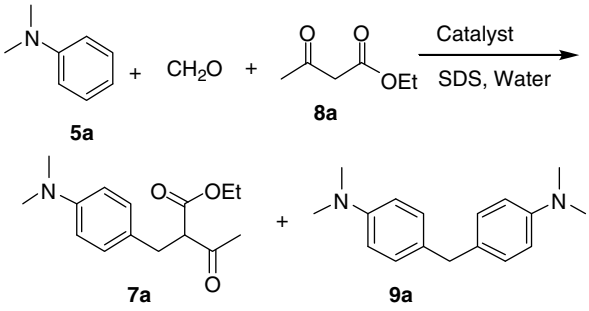
When no catalyst was used, the reaction yielded a complex mixture. Using acidic catalyst such as CF_3COOH, *para* toluene sulfonic acid (PTSA) or methane sulfonic acid (MSA), led to simplified reaction (TLC), and two major products (**7a** and **9a**) were isolated in varying ratios. Boric acid was found to be better than other acidic catalysts. Using 20 mol % of boric acid as catalyst, **7a** was obtained with high selectivity. Decreasing the amount of catalyst resulted in a poor yield of **7a** and also poor selectivity of **7a** over **9a**. The results of this study are shown in Table 1.

We also studied the effect of solvent on the boric acid catalyzed coupling reaction of ethyl acetoacetate, formaldehyde and *N*,*N*-dimethylaniline. In less polar solvents such as dichloromethane and tetrahydrofuran, poor yields of **7a** were obtained with significant formation of **9a**. However, in more polar solvents such as methanol and ethanol, **7a** was obtained with better selectivity. In neat water, the reaction gave a poor yield of **7a** but in aqueous micelles of sodium dodecyl sulfate SDS, product **7a** was formed in high selectivity. The role of SDS appears to form aqueous micelles, which increases the solubility of reactants and thus minimizes the formation of side products. The results of this study are shown in Table 2.

We studied the scope of the boric acid catalyzed unusual Mannich type reaction in aqueous micelles (Scheme 3). A number of tertiary aromatic amines reacted smoothly to yield condensed products **7a**–**n**.[12,13]

We carried out the reaction with cyclic and acyclic 1,3-dicarbonyl compounds. Reactions with acyclic 1,3-dicarbonyl compounds resulted in the formation of dimer **9a** in minor amounts, however, with cyclic 1,3- dicarbonyls **7a** was obtained exclusively. In all cases the reaction was carried out with 20 mol % boric acid in aqueous SDS (0.1 g/ml). The results of this study are shown in Table 3.

In conclusion, we have developed a boric acid catalyzed unusual Mannich type reaction of tertiary aromatic amines, formaldehyde and 1,3-dicarbonyl compounds in aqueous micelles with high regioselectivity. The reaction conditions are mild, and good to excellent yields of products are obtained in short reaction times. Further development of this unusual Mannich type reaction and its application to the synthesis of bioactive compounds are in progress.



Scheme 2.

Table 1
Screening of catalysts for coupling of ethyl acetoacetate, formaldehyde and *N*,*N*-dimethylaniline[a]

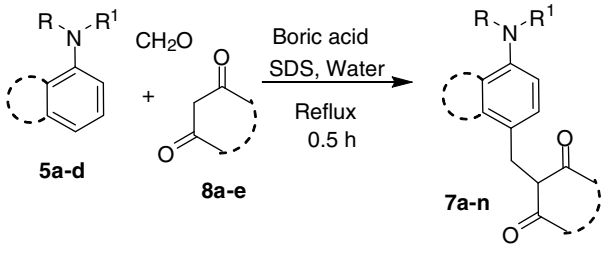
Entry	Catalyst	Catalyst (mol %)	Yield **7a**[b] (%)	Yield **9a**[b] (%)
1	None	—	<10	80
2	CF_3COOH	20	50	40
3	PTSA	20	59	41
4	MSA	20	53	35
5	H_3BO_3	20	85	<5
6	H_3BO_3	10	70	25

[a] Reaction conditions: ethyl acetoacetate (1 mmol), formaldehyde (1 mmol), *N*,*N*-dimethylaniline (1 mmol), SDS–water (1 ml, concn = 0.1 g/ml), 90 °C, 0.5 h.
[b] Isolated yield.

Table 2
Solvent effect on the coupling of ethyl acetoacetate, formaldehyde and *N*,*N*-dimethylaniline[a]

Entry	Solvent	Yield **7a**[b] (%)	Yield **9a**[b] (%)
1	CH_2Cl_2	25	54
2	THF	30	38
3	MeOH	70	22
4	EtOH	73	19
5	SDS–water (0.1 g/ml)	84	<5

[a] Reaction conditions: ethyl acetoacetate (1 mmol), formaldehyde (1 mmol), *N*,*N*-dimethylaniline (1 mmol), boric acid (20 mol %), reflux, 0.5 h.
[b] Isolated yield.



Scheme 3.

Table 3
Boric acid catalyzed three-component coupling of tertiary aromatic amines, formaldehyde and 1,3-dicarbonyl compounds in aqueous micelles[a]

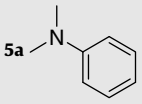
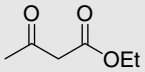
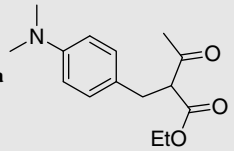
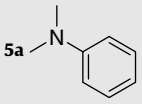
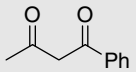
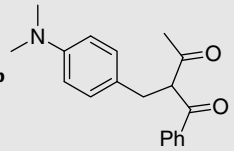
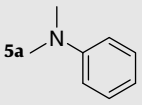
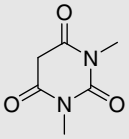
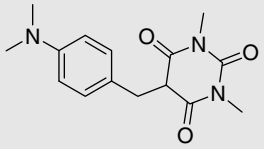
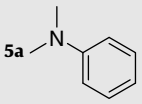
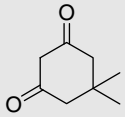
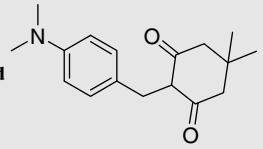
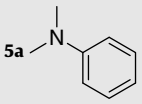
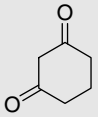
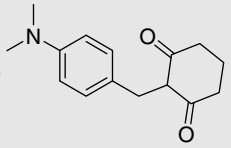
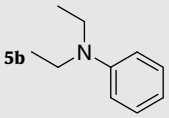
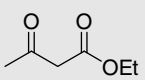
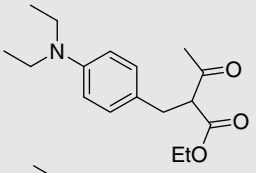
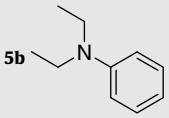
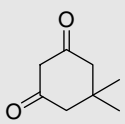
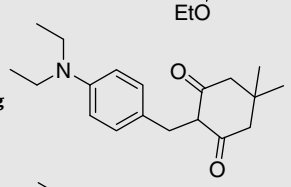
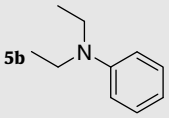
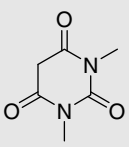
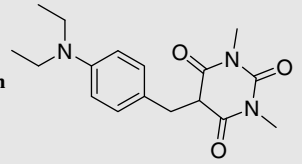
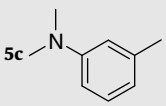
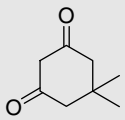
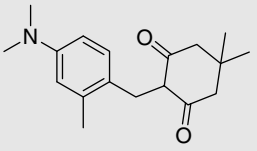
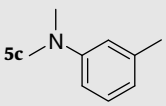
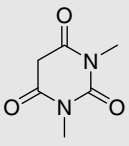
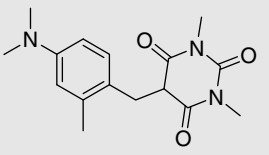
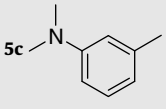
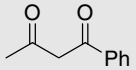
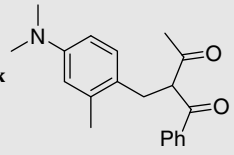
Entry	Aromatic amine	1,3-Dicarbonyl compound	Product	Time (min)	Yield[b] (%)
1	**5a** 	**8a** 	**7a** 	40	84
2	**5a** 	**8b** 	**7b** 	30	84
3	**5a** 	**8c** 	**7c** 	30	86
4	**5a** 	**8d** 	**7d** 	30	82
5	**5a** 	**8e** 	**7e** 	40	84
6	**5b** 	**8a** 	**7f** 	40	81
7	**5b** 	**8d** 	**7g** 	30	84
8	**5b** 	**8c** 	**7h** 	30	85
9	**5c** 	**8d** 	**7i** 	30	78
10	**5c** 	**8c** 	**7j** 	30	84
11	**5c** 	**8b** 	**7k** 	30	79

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Table 3 (*continued*)

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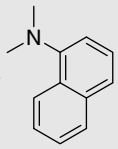
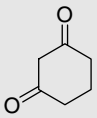
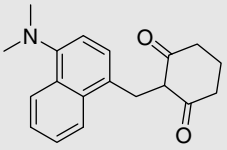
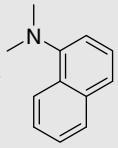
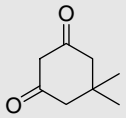
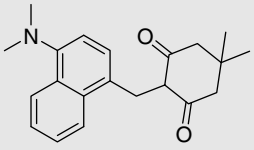
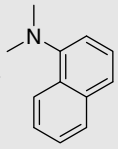
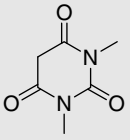
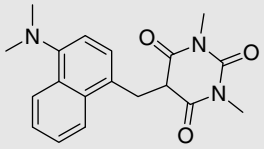
12	**5d** 	**8e** 	**7l** 	30	82
13	**5d** 	**8d** 	**7m** 	30	85
14	**5d** 	**8c** 	**7n** 	30	81

[a] Reaction conditions: 1,3-diketone (1 mmol), formaldehyde (1 mmol), tertiary aromatic amine (1 mmol), boric acid (20 mol %), SDS–water (1.5 ml, *c* = 0.1 g/ml), reflux.
[b] Isolated yield.

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12. *General experimental procedure for the unusual Mannich type reaction:* In a 25 ml round-bottomed flask, *N*,*N*-dimethylaniline (0.121 g, 1 mmol), 37% aqueous formaldehyde (0.081 ml, 1 mmol), ethyl acetoacetate (0.130 g, 1 mmol), boric acid (0.013 g, 20 mol %) and SDS–water (1.5 ml, *c* = 0.1 g/ml) were taken. The reaction mixture was refluxed for half an hour. The reaction was followed by TLC monitoring. After completion, the reaction mixture was diluted with 25 ml water and extracted with ethyl acetate (25 × 2). The organic layer was dried over sodium sulfate and concentrated to give a crude. The crude was subjected to column chromatography to yield compound **7a** (0.22 g, 84%).
13. Physical data for selected compounds: *ethyl 2-(4-(dimethylamino)benzyl)-3-oxobutanoate* **7a**: Physical state: oily. ESI-MAS (*m*/*z*) = 264 $(M+H)^+$. IR (Neat, cm^{-1}): 2942, 1722, 1698, 1363. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.22 (t, *J* = 7.1 Hz, 3H), 2.17 (s, 3H), 2.89 (s, 6H), 3.05 (d, *J* = 7.5 Hz, 2H), 3.72 (t, *J* = 7.5 Hz, 1H), 4.12–4.14 (m, 2H), 6.65 (d, *J* = 8.5 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 29.6, 33.2, 40.6, 61.2, 61.6, 112.8, 125.7, 129.3, 149.4, 169.3, 203.0. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.30; H, 7.92; N, 5.20. *2-(4-(dimethylamino)benzyl)-1-phenylbutane-1,3-dione* **7b**: ESI-MAS (*m*/*z*) = 296 $(M+H)^+$. IR (KBr, cm^{-1}): 3064, 2925, 1720, 1677, 1597, 1523, 1447, 1358, 1228, 756, 694. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.12 (s, 3H), 2.87 (s, 6H), 3.20 (m, 2H), 4.77 (t, *J* = 7.1 Hz, 1H), 6.60 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 8.7 Hz, 2H), 7.42–7.55 (m, 3H), 7.91–7.95 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.0, 34.4, 41.1, 65.7, 113.3, 126.5, 128.6, 129.1, 129.8, 130.6, 134.0, 137.0, 149.9, 196.4, 204.1. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.16; H, 7.12; N, 4.60. *5-(4-Dimethylamino-benzyl)-1,3-dimethyl-pyrimidine-2,4,6-trione* **7c**: Mp 236 °C. ESI-MAS (*m*/*z*) = 290 $(M+H)^+$. IR (KBr, cm^{-1}): 2928, 2815, 1683, 1613, 1526, 1449, 1381, 1360, 1301, 821, 754. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.87 (s, 6H), 3.02 (s, 6H), 3.10 (m, 3H), 6.46 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.6, 40.8, 49.6, 56.8, 112.4, 121.0, 130.0, 150.6, 150.7, 172.2. Anal. Calcd for $C_{15}H_{19}N_3O_3$, C, 62.27; H, 6.62; N, 14.52. Found: C, 62.18; H, 6.56; N, 14.46. *2-(4-Dimethylamino-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione* **7d**: Mp 155 °C. ESI-MAS (*m*/*z*) = 274 $(M+H)^+$. IR (KBr, cm^{-1}): 2959, 2928, 2874, 2547, 1569, 1522, 1451, 1378, 1252, 1214, 1154, 1042, 946, 802, 599, 487. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.03 (s, 6H), 2.26 (s, 4H), 2.85 (s, 6H), 3.15 (s, 2H), 6.59 (d, *J* = 8.6 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 26.7, 28.8, 32.3, 41.3, 47.2, 54.5, 113.2, 114.9, 129.4, 130.6, 149.1. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.61; H, 8.36; N, 5.02. *2-(4-Dimethylamino-benzyl)-cyclohexane-1,3-dione* **7e**: Mp 140 °C. ESI-MAS (*m*/*z*) = 246 $(M+H)^+$. IR (KBr, cm^{-1}): 3440, 3045, 2923, 1590, 1529, 1431, 1370, 1295, 1267, 1172, 998, 803. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.85 (quintet, *J* = 6.1 Hz, 2H), 2.35 (t, *J* = 6.1 Hz, 4H), 2.85 (s, 6H), 3.05 (s, 1H), 3.45 (s, 2H), 6.56 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.0, 26.1, 31.6, 38.4, 46.7, 117.6, 120.9, 134.4, 135.5, 153.9. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.31; H, 7.69; N, 5.64. 2-(4-(Diethylamino)benzyl)-5,5-dimethylcyclohexane-1,3-dione **7g**: ESI-MAS (*m*/*z*) = 302 $(M+H)^+$. IR (KBr, cm^{-1}): 2966, 2872, 1617, 1570, 1519, 1378, 1308, 1250, 1042. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.04–1.26 (m, 12H), 2.28 (s, 4H), 3.22–3.33 (m, 4H), 3.43–3.57 (m, 3H), 6.58 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 2H). Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.63; H, 8.94; N, 4.76. *5-(4-Diethylamino-benzyl)-1,3-dimethyl-pyrimidine-2,4,6-trione* **7h**: Mp 145 °C. ESI-MAS (*m*/*z*) = 318 $(M+H)^+$. IR (KBr, cm^{-1}): 2967, 2927, 1680, 1613, 1521, 1442, 13691355, 1267, 196, 1155, 1099, 811. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.07 (t, *J* = 7.0 Hz, 6H), 2.99 (s, 6H), 3.22–3.33 (m, 7H), 6.46 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 12.9, 28.4, 44.7, 44.8, 62.2, 112.2, 122.1, 130.5, 147.5, 151.0, 172.0. Anal. Calcd for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.22; H, 7.17; N, 13.16. *4,4′-Methylenebis(N,N-dimethylaniline)* **9a**: ESI-MAS (*m*/*z*) = 255 $(M+H)^+$. IR (KBr, cm^{-1}): 3007, 2888, 2806, 1614, 1521, 1445, 1345, 1230, 1166, 1070, 947, 796. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.81 (s, 12H), 3.73 (s, 2H), 6.58 (d, *J* = 8.5 Hz, 4H), 6.96 (d, *J* = 8.5 Hz, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 40.3, 41.4, 113.5, 129.8, 130.8, 149.5. Anal. Calcd for $C_{17}H_{22}N_2$: C, 80.27; H, 8.72; N, 11.01. Found: C, 80.20; H, 8.66; N, 11.12.