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Novel Mannich-type nucleophilic substitution reaction with tertiary aromatic amines

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Abstract—A novel formaldehyde-mediated condensation reaction of *N*,*N*-dialkyl aromatic amines and resonance-stabilized carbon nucleophiles is described. A condensation reaction between *N*,*N*-dimethylaniline (**4**) and ethyl acetoacetate (**8**) in the presence of formaldehyde in acetic acid took place to give 2-(4-dimethylaminobenzyl)-3-oxo butyric acid ethyl ester (**9**) together with the dimerization product **7** in 73 and 21% yields, respectively. This condensation reaction was further applied to the synthesis of 4-substituted dialkylaniline derivatives. © 2002 Elsevier Science Ltd. All rights reserved.

The Mannich reaction is a classical and useful carbon–carbon bond-forming reaction that involves the addition of resonance-stabilized carbon nucleophiles to iminium salts and imines, and this method is widely applied as a key step in the synthesis of numerous pharmaceuticals and natural products.[1] In the first step of the Mannich reaction, a primary or secondary amine **1** is reacted with a nonenolizable aldehyde, usually formaldehyde, to form the iminium salt intermediate **2**, and this electrophilic species **2** reacts with various kinds of nucleophiles, such as carbanion, amine, thiol, phenol, arylamines, and heterocycles to give condensed products **3**, known as 'Mannich bases'. Under the usual conditions of the Mannich reaction, tertiary amines cannot be employed, since the formation of the iminium salt with aldehyde at the first step of the Mannich reaction is impossible. On the other hand, the tertiary aromatic amine *N*,*N*-dimethylaniline (**4**) is known to dimerize to give biphenylmethane **7** in the presence of formaldehyde under acidic conditions.[2] In this formaldehyde-mediated dimerization reaction, aza quinone methide **5** is thought to be the active intermediate, which is formed via regioselective Friedel–Crafts-type reaction with formaldehyde at the *p*-position of **4**, followed by dehydration.[3] We regarded this aza quinone methide intermediate **5**, generated from the tertiary aromatic amine and formaldehyde, as the iminium salt equivalent of **2**, and expected it to react with various resonance-stabilized carbon nucleophiles to provide a variety of aniline derivatives **6** which would be useful intermediates for pharmaceuticals (Fig. 1).[4] Though reactions of a quinone methide intermediate with various nucleophiles have been reported,[5] the reactions of the aza quinone methide intermediate **5** have not been well examined to our knowledge.[6] In this communication, we describe a novel Mannich-type condensation reaction of tertiary aromatic amines and nucleophiles mediated by formaldehyde.

Initially the condensation reaction of *N*,*N*-dimethylaniline (**4**) and ethyl acetoacetate (**8**) in the presence of formaldehyde was investigated (Table 1). Under neutral

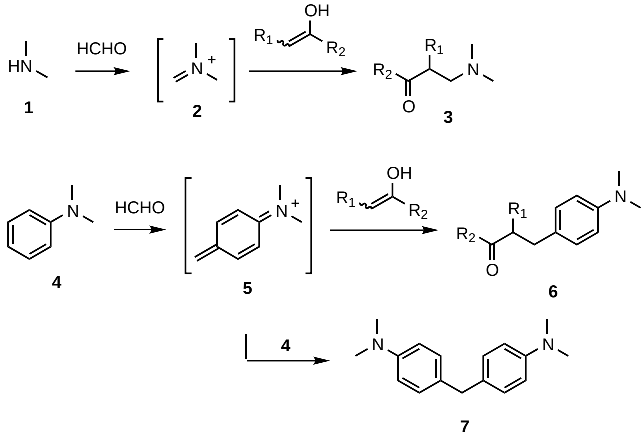

Figure 1. Typical Mannich reaction and our novel Mannich-type reaction with tertiary aromatic amine.

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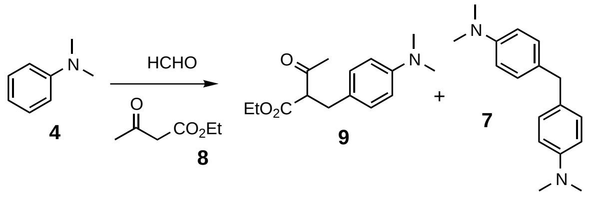
Table 1. Mannich-type condensation reaction with *N*,*N*-dimethylaniline



Entry	Solvent	**8** (equiv.)	Temp. (°C)	Time (h)	Yield (%)	
					9	**7**
i	DMF	1.5	100	4	–	6
ii	CH_3CN	1.5	80	5	24	26
iii	AcOH	1.5	80	0.5	73	21
iv	AcOH	5	80	0.5	63	7
v	TFA	1.5	80	2	29	13

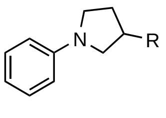
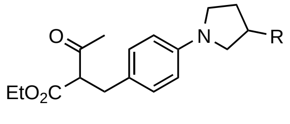
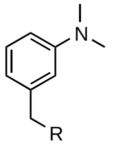
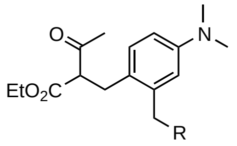
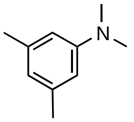
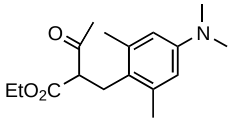
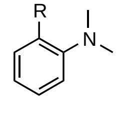
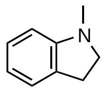
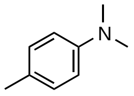
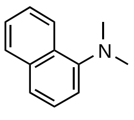
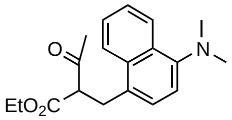
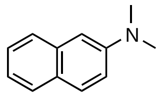
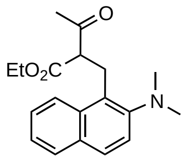
conditions (entries i and ii), the condensation reaction did not proceed or gave only a low yield of the desired **9** together with the dimer **7**. On the other hand, when the reaction was performed in acetic acid at 80°C, the reaction was completed within 30 min and gave **9** in 73% yield, together with dimerized product **7** in 21% yield (entry iii). If the amount of the nucleophile **8** was increased, the formation of the dimer **7** was suppressed (entry iv). Switching the solvent to TFA from acetic acid decreased the yield of **9** to 29% (entry v). Dimerization reaction of **4** took place quantitatively in the absence of **8** in acetic acid at 80°C.

Condensation reactions of various tertiary aromatic amines and ethyl acetoacetate (**8**) (1.5 equiv.) with formaldehyde (5 equiv.) were next examined. All reactions were run in acetic acid at 80°C, and the results are summarized in Table 2. Cyclic tertiary aromatic amine derivatives **10a** and **10b** gave the condensed products **11a** and **11b** in moderate yield. The 3-substituted aniline derivatives **10c**, **10d**, **10e** and **10f** gave the corresponding condensed products **11c**, **11d**, **11e** and **11f** in good yield with small amounts of dimers. The sterically hindered 3,5-disubstituted derivative **10g** gave **11g** in only 24% yield, and a 36% yield of the dimerization product was obtained. The 2-substituted aniline derivatives **10h** and **10i** did not react with formaldehyde and the starting amines were recovered quantitatively, whereas *N*-methylindoline **10j**, a ring-closed derivative of **10h**, was polymerized under these reaction conditions. The 4-substituted aniline **10k** gave multiple products, as detected on TLC. 1-Naphthylamine **10l** and 2-naphthylamine **10m** regioselectively gave the condensed products **11l** and **11m** in 64 and 26% yields, respectively. Thus, the condensation reaction occurred with non- or 3-substituted tertiary aromatic amines, whereas 2- or 4-substituted tertiary aromatic amines did not give the desired condensation reaction products. In the case of 2-substituted aromatic amines (**10h**, **10i**), formation of the aza quinone methide intermediate corresponding to **5** is thought to be unstable by steric repulsion between the *N*-alkyl group and the 2-substituents of the aromatic ring, and the starting aromatic tertiary amines were recovered.

Reactions with other nucleophiles were examined using non- or 3-substituted tertiary aromatic amines **4**, **10d** and **10e** in the presence of formaldehyde (Table 3). All reactions were performed in acetic acid at 80°C, with 1.5 and 5 equiv., respectively, of nucleophiles (**12**–**14** and **8**) and formaldehyde, and the results are summarized in Table 3. When ethyl nitroacetate (**12**) and acetylacetone (**13**) were used as nucleophiles, condensed products **15a**–**c** and **16a**–**c** were obtained in 60–77% yield. On the other hand, dimethyl malonate (**14**) did not react with any of the aromatic tertiary amines **4**, **10d** and **10e** and only gave dimerization products of the tertiary aromatic amines.[7] This is probably because of the nucleophilicity of **8** and **12**–**14**. The pK_a values of the active methylene protons of the nucleophiles **8** and **12**–**14** are 11, 6, 9 and 13, respectively, in H_2O,[8] and considering the order of these values, the results in Table 3 suggest that the nucleophile in this condensation reaction requires a nucleophilicity corresponding to a pK_a value of at least 11 of the active methylene protons.

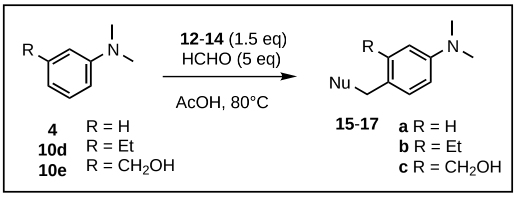
In conclusion, we have developed a novel Mannich-type condensation reaction, which is a regioselective substitution reaction of tertiary aromatic amines and resonance-stabilized carbon nucleophiles in the presence of formaldehyde. This one-pot reaction was applied to the synthesis of various β-aromatic amine-substituted ketone or ester derivatives. Further development of this reaction and application to the synthesis of natural products are in progress.

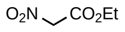
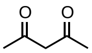
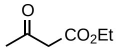
Table 2. Condensation reaction with various tertiary aromatic amines

Substrate	Products, yields
 **10a** R = H **10b** R = OH	 **11a** R = H 48% (9%)^a **11b** R = OH 45% (trace)^a
 **10c** R = H **10d** R = Me **10e** R = OH **10f** R = CO_2Me	 **11c** R = H 61% (15%)^a **11d** R = Me 83% (4%)^a **11e** R = OH 89% (trace)^a **11f** R = CO_2Me 74% (17%)^a
 **10g**	 **11g** 24% (36%)^a
 **10h** R = Me **10i** R = CO_2Et	R = Me no reaction R = CO_2Et no reaction
 **10j**	polymerized
 **10k**	complex mixture
 **10l**	 **11l** 64% (27%)^a
 **10m**	 **11m** 26% (32%)^a

^{a} The yields in parentheses are those of the dimers of the tertiary amines.

Table 3. Condensation reaction with various nucleophiles



 **12** (pKa = 6)	**15a** **15b** **15c**	R = H R = Et R = CH_2OH	62% (22%)^a 63% (20%)^a 72% (15%)^a
 **13** (pKa = 9)	**16a** **16b** **16c**	R = H R = Et R = CH_2OH	73% (19%)^a 77% (10%)^a 60% (32%)^a
 **8** (pKa = 11)	**9** **11d** **11e**	R = H R = Et R = CH_2OH	73% (21%)^a 83% (4%)^a 89% (trace)^a
 **14** (pKa = 13)	**17a** **17b** **17c**	R = H R = Et R = CH_2OH	0% (30%)$^{a,ref\ 7)}$ 0% (65%)^a 0% (60%)^a

^{a} The yields in parentheses are those of the dimers of the tertiary amines.

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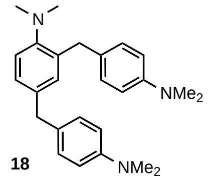
7. In the condensation reaction with **4** and **14**, **18** was also formed in 60% yield.



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