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Nucleophilic substitution on 4-hydroxymethylanilines under 'neutral' conditions via aza quinone methide intermediate

Hiroyasu Takahashi, Nobuyuki Kashiwa, Hisayoshi Kobayashi, Yuichi Hashimoto and Kazuo Nagasawa*

Institute of Molecular and Cellular Biosciences, University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan

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Abstract—Substitution reaction of 4-hydroxymethylaniline derivatives with resonance-stabilized carbon nucleophiles and an acid-labile nucleophile, including β-ketoester, 1,3-diketone, α-nitroester, and silylenolether, proceeded efficiently upon heating at 80°C in a neutral solvent system. The reaction was successfully applied to the synthesis of 4-aminophenylalanine.

The substitution reactions of aromatic rings are important in organic synthesis. We recently reported a novel substitution reaction of dialkylaniline derivatives based upon the Mannich-type condensation reaction between tertiary aromatic amines **1** and resonance-stabilized carbon nucleophiles in the presence of formaldehyde (Fig. 1).[1] In this reaction, the aza quinone methide intermediate **2** is thought to be the active intermediate, which is formed via regioselective Friedel–Crafts-type reaction with formaldehyde at the *p*-position of **1**, followed by dehydration.[2] Though this reaction is a powerful method for the formation of new carbon–carbon bonds on aromatic rings,[3] acidic conditions and a relatively high temperature (e.g. acetic acid as a solvent at 80°C) are required. Moreover, only formaldehyde (X = H in Fig. 1) can be used as an aldehyde species, i.e. other aldehydes, including acetaldehyde, do not form the intermediate **2** because of their weaker electrophilicity. Even though the aza quinone methide **2** is thought to be a useful synthetic intermediate, practical generation methods of **2** have not been well investigated. If we could generate a variety of aza quinone methide intermediates **2** (X is not only H, but also alkyl) under milder conditions, ideally 'neutral' conditions, the scope of that useful reaction would be expanded. With this in mind, we have designed **4** as a precursor of **2**. In this communication, we present our novel method for generation of the reactive aza quinone methide species **2** (X = H, Me) from **4** under 'neutral' conditions, and its subsequent substitution reaction with a variety of nucleophiles.

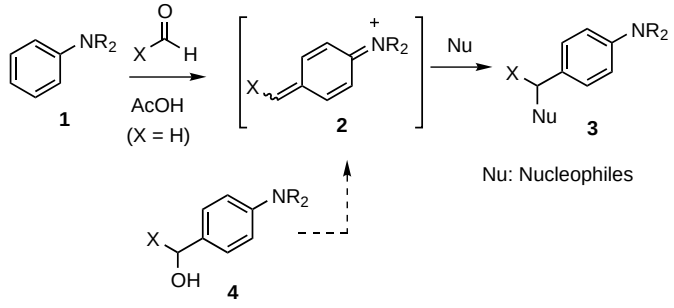

Figure 1. Novel Mannich-type condensation reaction.

To generate the aza quinone methide intermediate **2** under neutral reaction conditions, we chose the 4-hydroxymethylaniline derivatives **4**[4] as precursors for **2**. Firstly, the condensation reaction of *N*,*N*-dimethyl-4-hydroxymethylaniline (**4a**) and ethyl acetoacetate (**5a**) was investigated in various solvent systems. All reactions were run at 80°C, and 1.5 equiv. of nucleophile **5a** was added. The results are summarized in Table 1. When the reaction was performed in acetonitrile or DMSO, the desired substituted **6a** was obtained in 13–16% yield after 24 h, and the starting substrate was recovered in 63–66% yield (entries 1 and 3). However, addition of 1:1 v/v of H_2O to the reaction system resulted in a dramatic improvement of the yield. For example, addition of H_2O to the acetonitrile system enhanced the yield of **6a** from 16% to 52%, though the dimer **7a**[5] was generated in 18% yield as a by-product (entries 1 and 2). The enhancement was less masked

* Corresponding author. Tel.: +81-3-5841-7848; fax: +81-3-5841-8495; e-mail: nagasawa@iam.u-tokyo.ac.jp

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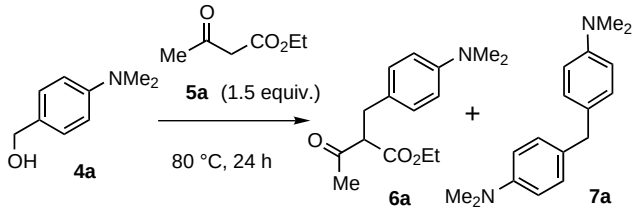
Table 1. Substitution reaction of **4a** with **5a** under neutral conditions



Entry	Solvent	**6a** (%)	**7a** (%)	Recovery of **4a** (%)
1	CH_3CN	16	9	63
2	CH_3CN/H_2O[a]	52	18	22
3	DMSO	13	12	66
4	$DMSO/H_2O$[a]	25	19	56
5	THF	6	8	81
6	THF/H_2O[a]	8	21	70
7	2-Propanol	5	17	73
8	Toluene	4	20	75

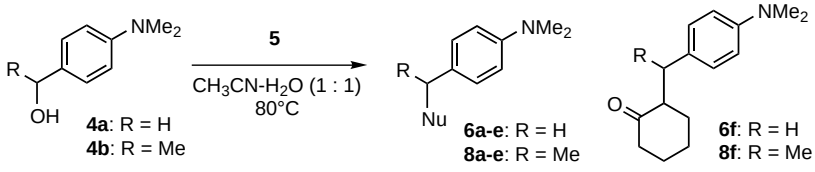
[a] 1 equiv. volume of H_2O was used.

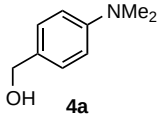
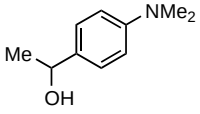
with DMSO (entries 3 and 4). The addition of H_2O is thought to be effective to accelerate the generation of the aza quinone methide intermediate **2** by protonation of the hydroxyl group of **4a**. The other solvents examined, THF, 2-propanol and toluene, gave poor results (entries 5–8).[6]

Using the 'neutral' solvent system, acetonitrile:H_2O = 1:1, we next examined the scope and limitations of this substitution reaction of the *N*,*N*-dimethyl-4-hydroxymethylaniline derivatives **4a** and **4b**, which have primary and secondary hydroxyl groups, respectively, with various resonance-stabilized carbon nucleophiles **5a–e** and the acid-labile nucleophile **5f** (Table 2). Reactions of **4a** and **4b** with nucleophiles **5a–d** in acetonitrile/H_2O (1:1) at 80°C gave 4-substituted aniline derivatives **6a–d** and **8a–d** in moderate to good yields, respectively.[7] In the case of the secondary alcohol **4b**, the dimerization reaction of **4b** was completely suppressed. When dimethyl malonate (**5e**) was used as the nucleophile, substitution reaction did not take place with **4a** and **4b**, which is presumably due to the weaker nucleophilicity of **5e** compared with the others.[1] It is noteworthy that the acid-labile nucleophile 1-cyclohexenyloxy-trimethylsilane (**5f**) reacted with **4a** and **4b** to provide the condensed products **6f** and **8f** in 50 and 14% yields, respectively.

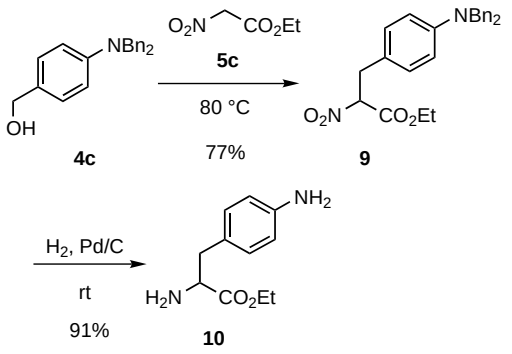
This 'neutral' substitution reaction of *N*,*N*-dialkyl-4-hydroxyanilines was successfully applied to the synthesis of amino acid derivatives **10** (Scheme 1). *N*,*N*-Dibenzyl-4-hydroxymethylaniline **4c** was reacted

Table 2. Substitution reaction of **4** with nucleophiles **5** under neutral conditions



4	**5**	equiv	Time (h)	Products	Yield (%)
 **4a**	$MeCOCH_2CO_2Et$ (**5a**)	3.0	27	**6a**	74 (13)[a]
	$MeCOCH_2COMe$ (**5b**)	2.3	24	**6b**	66 (28)[a]
	$EtO_2CCH_2NO_2$ (**5c**)	2.3	3	**6c**	98
	$NCCH_2CN$ (**5d**)	2.3	18	**6d**	80
	$MeO_2CCH_2CO_2Me$ (**5e**)	2.0	48	**6e**	0 (12)[a]
	1-Cyclohexenyloxy-trimethylsilane (**5f**)	2.3	24	**6f**	50 (30)[a]
 **4b**	$MeCOCH_2CO_2Et$ (**5a**)	1.5	24	**8a**	58
	$MeCOCH_2COMe$ (**5b**)	1.5	18	**8b**	54
	$EtO_2CCH_2NO_2$ (**5c**)	1.5	4	**8c**	97
	$NCCH_2CN$ (**5d**)	2.0	48	**8d**	93
	$MeO_2CCH_2CO_2Me$ (**5e**)	2.0	48	**8e**	complicated
	1-Cyclohexenyloxy-trimethylsilane (**5f**)	1.6	120	**8f**	14

[a]The yields in the parentheses are those of the dimers of the tertiary amines.



Scheme 1. Synthesis of 4-aminophenylalanine (**10**).

with ethyl nitroacetate (**5c**) to give the condensed product **9**, which was subsequently reduced with hydrogen in the presence of palladium on carbon to give the 4-aminophenylalanine ethyl ester (**10**)[8] in a high yield.

In conclusion, we have developed a practical method for generation of the reactive aza quinone methide intermediate **2** from *N*,*N*-dimethyl-4-hydroxymethylaniline derivatives **4**. We also have demonstrated that substitution reaction of **4** with a variety of nucleophiles **5** under 'neutral' conditions via the aza quinone methide intermediate **2**. This reaction provides an efficient method for the synthesis of β-aromatic amine-substituted ketone or ester derivatives **6** and **8**, which are useful intermediates for syntheses of pharmaceuticals[9] and natural products. Further development and applications of this reaction are under study in our laboratories.

Acknowledgements

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4. *N*,*N*-Dimethyl-4-hydroxymethylaniline derivatives **4a**, **4b** were prepared from the corresponding aldehyde, 4-(dimethylamino)benzaldehyde, by reduction with $LiAlH_4$ or methylation with methylmagnesium bromide.
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6. When the reaction was performed in acetic acid as a solvent, the dimer **7a** was obtained in 30% yield, and the starting **4a** was recovered in 50% yield.
7. Procedure for **6a**: A mixture of **4a** (100 mg, 0.66 mmol) and ethyl acetoacetate (**5a**) (0.25 mL, 2.0 mmol) in acetonitrile and H_2O (1:1 v/v, 2 mL) was heated at 80°C for 27 h. After cooling, the reaction mixture was concentrated in vacuo and the residue was purified by silica gel chromatography with hexane/ethyl acetate as the eluent to give **6a** (130 mg, 74%). Spectral data for **6a**: IR (neat) 1722, 1698 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.04 (d, $J=8.5$ Hz, 2H), 6.65 (d, $J=8.5$ Hz, 2H), 4.15 (m, 2H), 3.73 (t, $J=7.5$ Hz, 1H), 3.07 (d, $J=7.5$ Hz, 2H), 2.90 (s, 6H), 2.17 (s, 3H), 1.22 (t, $J=7.2$ Hz, 3). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.99, 169.30, 149.41, 129.36, 125.78, 112.81, 61.65, 61.26, 40.63, 33.19, 29.59, 14.00. HRMS (FAB, M^+) calcd for $C_{15}H_{21}NO_3$ 263.1521, found 263.1473.
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