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Regioselective Mannich reaction of phenolic compounds and its application to the synthesis of new chitosan derivatives

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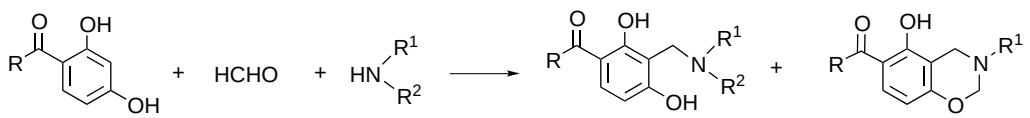
Abstract—A regioselective aminomethylation of 2,4-dihydroxybenzoyl compounds at the C(3) position was accomplished through a Mannich reaction of phenolic substrates with formaldehyde and secondary amines in methanol, whereas the reaction with primary amines included a subsequent cyclization step to yield the 1,3-benzoxazine derivatives. This sequence was successfully applied to the one-pot introduction of *N*-benzyl side chains to chitosan, a natural polyaminosaccharide, to afford a new chitosan derivative with improved solubility in an organic solvent.

Because the coupling of three components (substrate, formaldehyde, and amine) can be achieved in a one-pot reaction, a Mannich-type aminomethylation has been an attractive method for introducing a side chain to various phenols.[1,2] We have previously reported on the regioselective aldol-type reaction of phenolic enolates in water and alcohols.[3] Herein we report on the regioselective C–C bond formation at the C(3) position of resorcinol derivatives **1** via Mannich reaction, as shown in Scheme 1. Furthermore, we report on its application to the chemical modification of chitosan, a biodegradable polyaminosaccharide.

As shown in Table 1 (entries 1, 4, and 5), treatment of 2′,4′-dihydroxyacetophenone (**1a**) with formaldehyde and various secondary amines in methanol at reflux temperature selectively introduced the corresponding aminomethyl group at the C(3) position of **1a** in good yields. Similarly, ester **1b** and aldehyde **1c** were converted to the 3-aminomethylated derivatives **2b** and **2c** (entries 2 and 3), respectively. The regioselective C–C bond formation at the C(3) position of phenol **1** was estimated by the ^{1}H NMR analysis of product **2**, which showed two doublet signals corresponding to the aromatic protons having an *ortho*-coupling constant.[4]

In contrast, the reaction of phenol **1b** and formaldehyde (2 equiv.) with a primary amine, hexylamine, yielded 3-hexyl-3,4-dihydro-5-hydroxy-6-methoxycarbonyl-2*H*-1,3-benzoxazine (**3f**) via a Mannich-type aminomethylation, followed by cyclization (entry 6). The selective incorporation of the *p*-hydroxy group of **1b** into the newly formed oxazine ring of product **3f** was confirmed by ^{1}H NMR analysis, in which a singlet peak corresponding to the unreacted *o*-hydroxy proton was observed at 11.11 ppm. This phenomenon was similarly observed for reactions involving other primary amines, such as cyclohexylamine, benzylamine, and *o*-toluidine (entries 7, 8, and 9, respectively). For these one-pot reactions of phenol **1b**, formaldehyde, and primary amines (entries 6–9), it is noteworthy that simultaneous mixing resulted in poor yields; however,



1 **2** **3**

Scheme 1.

Keywords: Mannich reactions; benzoxazines; phenols; chitosan.

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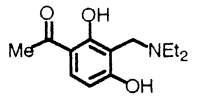
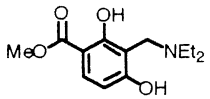
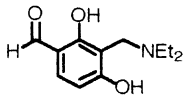
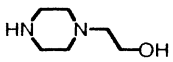
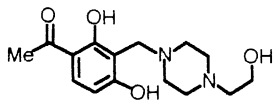
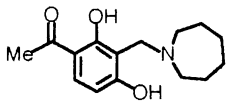
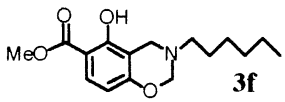
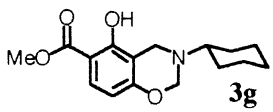
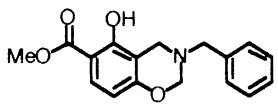
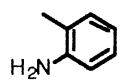
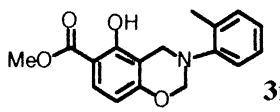
Table 1. Aminomethylation of 2,4-dihydroxybenzoyl compounds[a]

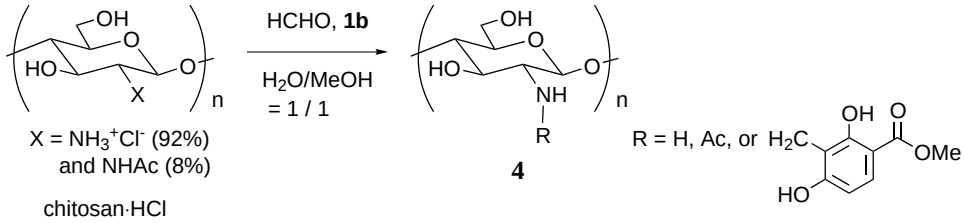
Entry	Substrate R		HCHO / equiv	Amine R^1	Amine R^2	Time / h	Product		Yield[b] / %
1	Me	**1a**	1.1	Et	Et	1 h		**2a**	79
2	MeO	**1b**	1.1	Et	Et	1 h		**2b**	76
3	H	**1c**	1.1	Et	Et	0.8 h		**2c**	67
4	Me	**1a**	1.1			0.4 h		**2d**	94
5	Me	**1a**	1.1			0.5 h		**2e**	93
6	MeO	**1b**	2	$n\text{-}C_6H_{13}$	H	0.5 h and then 3 h[c]		**3f**	61
7	MeO	**1b**	2			1 h and then 1 h[c]		**3g**	66
8	MeO	**1b**	2	$PhCH_2$	H	1.5 h and then 5 h[c]		**3h**	63
9	MeO	**1b**	4			0.2 h and then 1 h[d]		**3i**	81

[a] Molar ratio of **1**/HCHO/amine = 1:1.1:1.1; solvent, MeOH; 65°C.
[b] Isolated yield.
[c] Formaldehyde (2 equiv.) was treated with amine (1 equiv.) for 0.5–1.5 h, and then with **1b** (1 equiv.) for 1–5 h.
[d] Formaldehyde (4 equiv.) was treated with *o*-toluidine (2 equiv.) and Et_3N (0.2 equiv.) at 0°C for 0.2 h in 1,4-dioxane, and then with **1b** (1 equiv.) at 105°C for 1 h in 1,4-dioxane.

good yields were obtained by the pretreatment of formaldehyde with the primary amines to form Schiff base, followed by addition of phenol **1b**.[5]

Typical procedures are as follow: cyclohexylamine (63 mg, 0.60 mmol) was treated with paraformaldehyde (38 mg, 1.2 mmol) in methanol (1 ml) at 65°C for 1 h. To the reaction mixture, a solution of phenol **1b** (105 mg, 0.60 mmol) in methanol (2 ml) was added. After stirring for an additional 1 h at 65°C, extractive work-up yielded the crude product (178 mg), which was purified by preparative TLC (chloroform/methanol = 10:1) to afford **3g**[6] (119 mg, 66% yield).

This method was applied to the introduction of benzyl-type side chains to the amino group of chitosan, a β-(1-4)-linked natural polysaccharide composed of 2-amino-2-deoxy-β-D-glucopyranose (D-glucosamine) residues. Although chitosan is attractive as a biodegradable and biocompatible material,[7,8] poor solubility has been one of the main obstacles towards its effective utilization. As shown in Scheme 2, chitosan



Scheme 2.

hydrochloride (1016 mg, 4.7 mmol as amino group, Koyo Chemical Co. Ltd, Lot No. L0221-20FD, *M*w 4400, *M*n 1470) was treated with paraformaldehyde (151 mg, 5.0 mmol) and **1b** (840 mg, 5.0 mmol) in a mixture of water and methanol (1:1), since chitosan hydrochloride is soluble in water. After stirring at 65°C for 45 h, the *N*-selectively modified product **4** (1044 mg) was collected by precipitation using acetone (1000 ml). It is interesting to note that chitosan, which possesses primary amino groups, behaved similarly as a secondary amine to produce the acyclic side chain product, in spite of our observations that primary amines produced heterocyclic products. Any signals corresponding to the C(2) protons of the 1,3-benzoxazine skeleton (δ ca. 5) were not detected in the ^{1}H NMR (D_2O) study of the chitosan derivative. Comparison between the peak areas of the aromatic proton signals (δ 6.57 and 7.84) in the side chain and that of the C(1) proton signal (δ 4.7–4.9) of D-glucosamine residue determined the degree of substitution (DS) as 0.11 (R = H (81%), Ac (8%), and CH_2-Ar (11%) in Scheme 2), which was in good agreement with a DS value of 0.16 estimated by elemental analysis. In comparison to the starting chitosan, which dissolved in methanol at a concentration of 3.8 mg/ml, the newly synthesized derivative **4** exhibited a higher solubility in methanol (9.4 mg/ml).

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4. ^{1}H NMR ($CDCl_3$) of **2b**: δ 1.14 (t, J = 4.7 Hz, 6H), 2.67 (q, J = 4.7 Hz, 4H), 3.88 (s, 3H), 3.91 (s, 2H, Ar-CH_2N), 6.31 (d, J = 8.9 Hz, 1H), 7.63 (d, J = 8.9 Hz, 1H), 11.25 (br s, 1H), 12.40 (br s, 1H).
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6. ^{1}H NMR ($CDCl_3$) of **3g**: δ 1.0–2.0 (m, 10H), 2.6–2.7 (m, 1H), 3.90 (s, 3H), 4.05 (s, 2H, Ar-CH_2N), 5.00 (s, 2H, OCH_2N), 6.30 (d, J = 8.9 Hz, 1H), 7.59 (d, J = 8.9 Hz, 1H), 11.13 (br s, 1H, 5-OH).
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