



Original article

An unusual substitution reaction of an aromatic sulfonic group based on 3-carbonyl-4-phenolsulfonic acid

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ABSTRACT

An unusual substitution reaction of an aromatic sulfonic group based on 3-carbonyl-4-phenolsulfonic acid was discovered in a diazo-coupling process. The reaction occurred under mild reaction conditions (pH 8.0–9.0, 0–5 °C, solvent: water) within a short reaction time (1 h). A plausible substitution reaction mechanism by phenol–ketone resonance was proposed.

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1. Introduction

In organic synthesis, sulfonic groups are important protecting groups and widely used for pharmaceutical and total synthesis [1]. Generally, the desulfonation and regioselective substitutions of aromatic sulfonic acids are difficult processes [2]. Stoichiometric reduction reagents (e.g., RANEY[®] Nickel) [3] and catalysts [4] are usually required to give good conversions. Harsh conditions are also needed [5], like heating with concentrated hydrochloric acid at 180 °C for many hours [6], heating with a strong base at about 200–300 °C until melting [7], or heating with strong nitric acid [8]. Under mild conditions, sulfonic groups are almost impossible to be substituted from aromatic compounds. Therefore, the desulfonation and regioselective substitutions of aromatic sulfonic acids would be very useful for the synthesis of active medicines and dyes under mild conditions.

In the present paper, we discovered a new and unexpected substitution reaction of a sulfonic group by a diazonium salt in a diazo-coupling process (Scheme 1). The substitution reaction of the aromatic sulfonic groups occurred under significantly milder conditions (pH 8.0–9.0, 0–5 °C, solvent: water) than those previously mentioned [2–8]. The novel and interesting specific substitution reaction of this aromatic sulfonic groups spurred us to determine optimal conditions and investigate the scope of the reaction. More importantly, these research results open new

possibilities for substituting aromatic sulfonic acid under mild reaction conditions (pH 8.0–9.0, 0–5 °C, solvent: water) during the synthesis of medicines and dyes.

2. Experimental

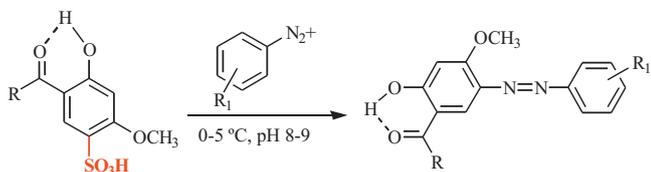
2.1. General procedures for the formation of compounds 1–3 and 8–9

A mixture of nitroaniline (1.38 g, 10.0 mmol), 3.6 mL concentrated hydrochloric acid and 25 mL H₂O was stirred vigorously for 0.5 h at 70 °C. The resultant solution was cooled below 5 °C with the aid of an ice bath and stirred as NaNO₂ (0.73 g, 10.5 mmol) in 5 mL H₂O was added rapidly. The reaction mixture was stirred at 5 °C until a clear solution was formed. This solution was added to 87 mL ethanol and 10 mL H₂O containing compound 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid (UV-284) (3.08 g, 10 mmol) and Na₂CO₃ (2.40 g, 45.4 mmol) while keeping the temperature below –20 °C. The volume ratio of ethanol and water was 2:1 in the final solution, which was stirred for 2.5 h at –20 °C. Then, the pH of the reaction solution was adjusted to 3.0 by adding 1 mol/L hydrochloric acid solution. The ethanol was distilled out from the above reaction solution, and the remaining solution was cooled to 0–5 °C. The solid was filtered and dried to yield a yellow solid. The compounds 1–3 were obtained by silica gel column chromatography using ethyl acetate/petroleum ether (60/90) mixtures as the eluent.

The compounds 8 and 9 were synthesized and purified according to the procedures described before.

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Scheme 1. The unusual substitution reaction of an aromatic sulfonic group based on 3-carboxyl-4-phenolsulfonic acid.

2.2. The procedures for the formation of compound 4

Sodium nitrite (0.69 g, 10 mmol) was dissolved in 8 mL concentrated H_2SO_4 at 70 °C, and then the reaction mixture was cooled to 0 °C. 2,4-Dinitroaniline (1.83 g, 10 mmol) was added to the above solution over 30 min. After being stirred for 6 h, the diazonium salt was added dropwise in 87 mL ethanol and 10 mL H_2O containing compound 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid (UV-284) (3.08 g, 10.0 mmol) and Na_2CO_3 (2.40 g, 45.4 mmol) while keeping the temperature below -20 °C. The resulting solution was stirred for 2.5 h at -20 °C. Then, the pH of the reaction solution was adjusted to 3.0 by adding 1 mol/L hydrochloric acid solution. The ethanol was distilled out from the above reaction solution, and the remaining solution was cooled to 0–5 °C. The solid was filtered and dried to yield a yellow solid. The compound **4** was isolated by silica gel column chromatography using ethyl acetate/petroleum ether (60/90) mixtures as the eluent.

2.3. The procedures for the formation of compounds 5–7

A mixture of aromatic amines (10.0 mmol), 2.5 mL concentrated hydrochloric acid and 20 mL H_2O was stirred vigorously. The resulting solution was cooled below 5 °C with the aid of an ice bath and stirred as NaNO_2 (0.73 g, 10.5 mmol) in 5 mL H_2O was added rapidly. The reaction mixture was stirred at 5 °C until a clear solution was formed. The solution was added to 87 mL ethanol and 10 mL H_2O containing compound 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid (UV-284) (3.08 g, 10 mmol) and Na_2CO_3 (2.40 g, 45.4 mmol) while keeping the temperature below -20 °C. The volume ratio of ethanol and water was 2:1 in the final solution, which was stirred for 2.5 h at -20 °C. Then, the pH of the reaction solution was adjusted to 3.0 by adding 1 mol/L hydrochloric acid solution. The ethanol was vacuum removed from the above reaction solution, and the remaining solution was cooled to 0–5 °C. The solid was filtered and dried to give a yellow solid. The compounds **5–7** were obtained by silica gel column chromatography using ethyl acetate/petroleum ether (60/90) mixtures as the eluent.

3. Results and discussion

Initial solvent and temperature screenings were carried out by changing the ratio of ethanol- H_2O (v/v) or the reaction temperature. The reaction between *p*-nitrobenzenediazonium ion and 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid (UV-284) was used as the model. The results were listed in Table 1.

3.1. Substitution conditions and substrate scope

The reaction system used in the usual diazo-coupling conditions (0–5 °C, in water) gave an encouraging yield of 19.2% for compound **1** (entry 1). This reaction between *p*-nitrobenzenediazonium ion and aromatic sulfonic groups cannot occur in traditional diazo-coupling reactions [9]. A remarkably improved yield was obtained when ethanol was added (entries 2 and 3) to the

Table 1
Unusual reactions of sulfonic acid substitution with *p*-nitrobenzenediazonium ion under different conditions.

Entry	Temperature (°C)	Ethanol/ H_2O (v/v)	Yield (%)
1	0–5	0/1	19.2 ^a
2	0–5	1/1	33.5 ^a
3	0–5	2/1	37.5 ^a
4	–10 to –15	2/1	40.8 ^a
5	–20 to –25	2/1	43.9 ^a , 38.3 ^b

^a Determined by HPLC analysis.

^b The obtained products were purified on silica gel column using ethyl acetate/petroleum ether (60/90) mixture as eluent.

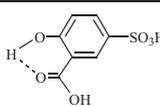
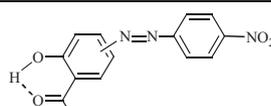
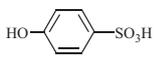
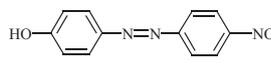
reaction. A high yield (43.9%) was also surprisingly obtained when the reaction temperature was decreased to -20 °C to -25 °C (entry 5). The yield of compound **1** was improved under reducing reaction temperature. This was caused by the stability of

Table 2
Diazonium salt diversity in the novel reaction of sulfonic acid substitution.

Entry	Diazonium salt	Product	Yield (%) ^a
1			43.9
2			10.7
3			5.1
4			9.9
5			Negligible
6			Negligible
7			13.2

^a Determined by HPLC analysis.

Table 3
Aromatic sulfonic group diversity in the substitution reaction.^a

Entry	Coupling component	Product	Yield (%) ^b
1			13.0
2			Negligible

^a Reaction conditions: the coupling reaction temperature 0–5 °C.

^b Determined by HPLC analysis.

p-nitrobenzenediazonium ion was improved in low temperature. Additionally, with keeping diazonium salt at the low temperature for 1 h, the HPLC yield of compound **1** was 50.7%. Indeed, the substitution reaction of the sulfonic group in UV-284 proved to be efficient even at –10 °C to –25 °C (entries 4 and 5).

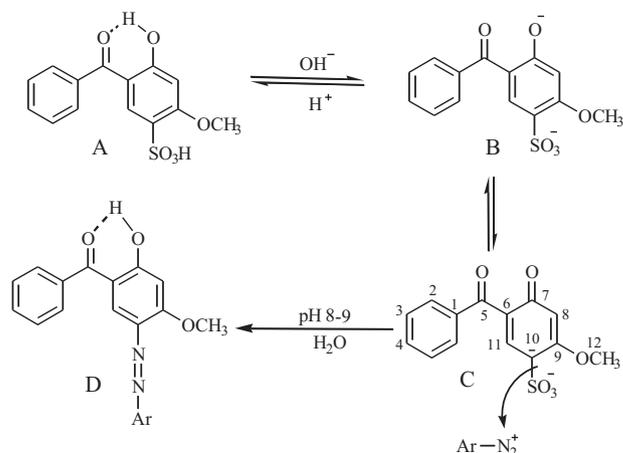
The type of diazonium salt was found to be an essential factor affecting the regioselectivity substitution of the present substitution reaction. Therefore, the effects of the type of diazonium salt was investigated using the optimal reaction conditions (pH 8.0–9.0, –20 °C in ethanol/H₂O (2/1 (v/v))). The results were summarized in Table 2.

As presented in Table 2, the sulfonic group in UV-284 was substituted by a diazonium salt containing a nitro group, then converted into the corresponding compounds **1–4** in over 5% yields (entries 1, 2, 3, and 4). With the decrease of the activity of diazonium salt, the yield of the regioselectivity substitution gradually decreased. However, the yields of compounds **4** and **7** were still low, which could be ascribed to the increased steric constraints. With aniline or 4-methoxyaniline diazonium salt, the desired products were not obtained at all (entries 5 and 6) due to the low reactive activity of this type of diazonium salt [10].

To further expand coupling components based on the diazo-coupling process, we investigated the scope of the reaction with *p*-hydroxybenzenesulfonic acid and 5-sulfosalicylic acid dihydrate under the optimized reaction conditions (Table 1). It was found that the sulfonic groups of UV-284 and 5-sulfosalicylic acid dihydrate (Table 3) had high substituents efficiency by *p*-nitrobenzenediazonium ion under the optimal reaction conditions (pH 8.0–9.0, –20 °C in ethanol/H₂O (2/1 (v/v))). But, the 4-hydroxybenzenesulfonic acid did not react in the coupling process. So, the aromatic sulfonic groups were easily replaced by diazonium salt in diazo-coupling process, based on the *o*-hydroxy position of *p*-hydroxybenzenesulfonic acid with electron-withdrawing groups.

3.2. A plausible mechanism

Based on the results of the preliminary investigations, a plausible mechanism for this substitution reaction is proposed in Scheme 2. Initially, UV-284 undergoes a deprotonation reaction in the presence of a base. UV-284 is then converted into B, which produces the resonance quinoid C (Figs. S1 and S2 in Supporting information). Subsequently, after being attacked by the positive nitrogen ions of the diazonium salt at C10 of quinoid C, the sulfonic group of UV-284 is substituted. As a result, the insoluble compound D is produced, of which these characterization was obtained by Figs. S3–S26 in Supporting information. However, we discovered that when *p*-nitrobenzenediazonium ion was used, the sulfonic group in 4-hydroxybenzenesulfonic acid cannot be substituted in the coupling process. More detailed studies regarding this mechanism are currently underway.



Scheme 2. Plausible mechanism of a substitution reaction using phenol-ketone isomers.

4. Conclusion

In summary, an unusual substitution reaction of an aromatic sulfonic group based on 3-carbonyl-4-phenolsulfonic acid was discovered under 0–5 °C in the water solution of pH 8.0–9.0. This discovery established possibilities of replacing sulfonic acids in aromatic compounds under mild conditions.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.cclet.2013.04.016>.

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