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ARTICLE TYPE

Water-promoted *ortho*-selective monohydroxymethylation of phenols in $NaBO_2$ system

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Water-promoted *ortho*-selective monohydroxymethylation of phenols in $NaBO_2$ system generates salicyl alcohols in 65–97% yields. A remarkable rate-enhancement by water was observed, and $NaBO_2$ appeared to serve the dual role of the suitable base and the efficient chelating reagent. This protocol possesses many advantages such as short reaction times, expanding substrate scope, and high mono- and region-selectivities. The experimental results were explained by the calculations based on local ionisation energy minima, leading to a possible reaction mechanism.

Introduction

Hydroxymethylation is one of the most important carbon–carbon bond-forming reactions, which has been widely applied in the syntheses of many natural products and biologically active compounds[1]. The obtention of high selectivity in a hydroxymethylation reaction is a long-standing challenge for organic chemists. For example, hydroxymethylation of a phenol usually occurs to the positions that are *ortho* and *para* to the site of the phenolic hydroxyl group[2], in instances where the *para* position is blocked, hydroxymethylation occurs to the *ortho* positions with respect to the phenolic hydroxyl group[3]. Bishydroxymethylation of *para*-substituted phenols went smoothly under many basic conditions, whereas, as mentioned by Bew, the corresponding *mono*-specific hydroxymethylation using seemingly straightforward procedures proved problematic[3c,4], which was verified in our synthesis of 4-*tert*-butyl salicyl alcohol that was a key intermediate for the preparation of a mono-arm-Trost-type ligand[5]. Hydroxymethylation of phenols have gained some success in the synthesis of salicyl alcohols[2-4,6], which have found widespread utility as substrates for the synthesis of a large number of pharmaceuticals, natural products, functional materials, and so forth[7]. However, it is still a challenge to develop a direct approach for the efficient and fast hydroxymethylation of phenols under mild conditions with high selectivity and expanding substrate scope.

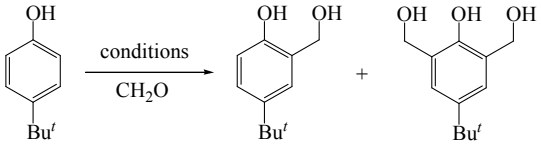
On the other hand, a huge amount of effort has been dedicated to the development of chemical reactions in agreement with the principles of green chemistry. Water is a unique green solvent for chemical transformations in view of its low cost, safety, and environmentally benign properties[8]. Organic reactions performed in water have made great progress since the concept of on-water reaction was presented by Sharpless in 2005, and this new concept has been used to explain the unusual reaction rate enhancement compared to the same reaction in an organic solvent or under solvent free conditions[9]. Various water-promoted reactions help to narrow the gap between the use of water as a reaction medium and practical green chemistry[10]. However, pursuing practical organic reactions in water is still in early stages and further research is needed to fully understand the role that water plays. In connection with our consistent interest in aqueous reaction and selective reaction[4,11], herein we would like to report a water-promoted mono- and *ortho*-selective hydroxymethylation of phenols in $NaBO_2$ system.

Results and Discussion

The hydroxymethylation 4-*tert*-butylphenol (**1a**) with formaldehyde was used as a probe for evaluating the reaction conditions, and the representative results are summarized in Table 1. Bishydroxymethylation of phenol **1a** went smoothly under basic conditions. By treating **1a** with excess formaldehyde in sodium hydroxide aqueous solution, bishydroxymethylated product **3a** was obtained in 98% yield within 0.5 day (entry 1)[5], which in turn facilitated our synthesis of a semi-crown Trost-type ligand[5]. In contrast, treatment of formaldehyde with excess phenol **1a** under the same conditions did not ensure the isolation of monohydroxymethylated product **2a** with a satisfactory yield (entry 2)[5]. Monohydroxymethylation of **1a** with formaldehyde can be possibly took place in the presence of excess phenylboronic acid[2a-b] or orthoboric acid[2c,2g] at high temperatures in benzene, toluene or xylene, and the potential bishydroxymethylation could be suppressed by chelating **2a** with the acidic boron reagent[2a-c,2g]. The reaction can be also performed in water at 110 °C, which afford **2a** in 41% yield within one and a half days, along with bishydroxymethyled product **3a** (5% yield, entry 3). However, the reaction could not be completed in many days, and low selectivity was observed when the reaction was performed at a higher temperature. When sodium tetraborate ($Na_2B_4O_7$), a basic boron reagent, was used as the chelating reagent, monohydroxymethylation of **1a** with aqueous formaldehyde could take place at room temperature (entry 4). An

increased yield was observed when the reaction was performed at 40 °C, reflecting the temperature factor effect on this reaction (entries 4–5). As expected, the reaction in $Na_2B_4O_7$ reaction system at 60 °C afforded **2a** in 84% yield within one and a half days, along with bishydroxymethyled product **3a** (4% yield, entry 6). When one equivalent of NaOH was added, the reaction went smoothly at 50 °C under otherwise identical conditions (entry 7). With the basic chelating reagent of sodium metaborate ($NaBO_2$) in comparison to $Na_2B_4O_7$, a shorter reaction time, a higher yield and a lower reaction temperature were observed (entries 6–8). With the use of organic solvents such as toluene, dichloromethane, acetonitrile and tetrahydrofuran, no reaction took place and the starting material was recovered (entries 9–12). Use of ethanol only afforded a trace amount of **2a** (entry 13). It is particularly noteworthy that the yield of **2a** rose dramatically with the increase of proportion of water in the co-solvent of EtOH–H_2O (entries 14–16). The $NaBO_2$ system was chosen in our investigations because of its relatively high yield, low reaction temperature, and short reaction time. It was found that 8 equivalent of boron chelating reagent was needed to ensure the excellent *ortho*-selectivity.

Table 1 Survey of conditions for hydroxymethylation of 4-*tert*-butylphenol (**1a**) with aqueous formaldehyde[a]



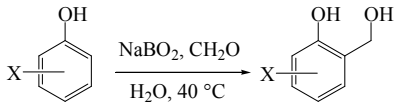
1a **2a** **3a**

Entry	Conditions	Solvents	Time	Yield of **2a**
1	2 equiv. NaOH, R.T.	H_2O	0.5 d	0 (98%)[b]
2[c]	2 equiv. NaOH, R.T.	H_2O	0.5 d	15% (72%)[b]
3	8 equiv. H_3BO_3, 110 °C	H_2O	1.5 d	41% (5%)[b]
4	2 equiv. $Na_2B_4O_7$, R.T.	H_2O	1.5 d	trace
5	2 equiv. $Na_2B_4O_7$, 40 °C	H_2O	1.5 d	20%
6	2 equiv. $Na_2B_4O_7$, 60 °C	H_2O	1.5 d	84% (4%)[b]
7[d]	2 equiv. $Na_2B_4O_7$, 50 °C	H_2O	1.5 d	85%
8	8 equiv. $NaBO_2$, 40 °C	H_2O	1 d	86%
9	8 equiv. $NaBO_2$, 40 °C	$PhCH_3$	1 d	0
10	8 equiv. $NaBO_2$, 40 °C	CH_2Cl_2	1 d	0
11	8 equiv. $NaBO_2$, 40 °C	CH_3CN	1 d	0
12	8 equiv. $NaBO_2$, 40 °C	THF	1 d	0
13	8 equiv. $NaBO_2$, 40 °C	EtOH	1 d	8%
14	8 equiv. $NaBO_2$, 40 °C	EtOH–H_2O (3 : 1)	1 d	23%
15	8 equiv. $NaBO_2$, 40 °C	EtOH–H_2O (1 : 1)	1 d	46%
16	8 equiv. $NaBO_2$, 40 °C	EtOH–H_2O (1 : 3)	1 d	65%

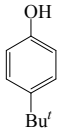
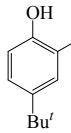
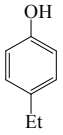
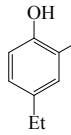
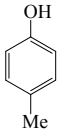
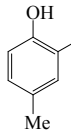
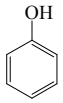
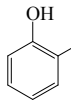
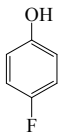
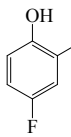
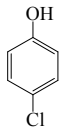
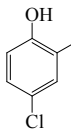
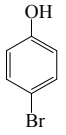
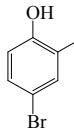
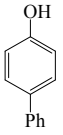
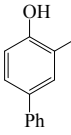
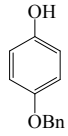
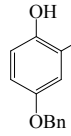
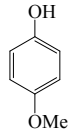
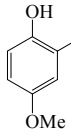
[a] General conditions: **1a** (1.0 equiv.), promoter (2.0–8.0 equiv.) and aqueous formaldehyde (37%, 5.0 equiv.) in solvent (c = 0.2 M). R.T.: room temperature.
[b] Yield of **3a**.
[c] Aqueous formaldehyde (37%, 0.05 equiv.) was added to the mixture of **1a** (1.0 equiv.) and sodium hydroxide (2.0 equiv.) in water (c = 0.2 M), and the yield was calculated based on formaldehyde.
[d] NaOH (1.0 equiv.) was added.

The procedure turned out to be applicable to a wide range of phenols, and the results are summarized in Table 2. With weak electron-donating groups, *tert*-butyl, ethyl and methyl, at the *para* position of phenols, hydroxymethylation of phenols **1a–c** with aqueous formaldehyde under the standard conditions afforded salicyl alcohols **2a–c** in high yields within 20–28 hours, demonstrating a high mono-selectivity (entries 1–3). Non-substituted phenol **1d** reacted with aqueous formaldehyde uneventfully to afford salicyl alcohol **2d** in 93% yield under the

Table 2 Water-promoted hydroxymethylation of phenols **1** with aqueous formaldehyde in $NaBO_2$ system[a]

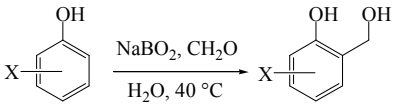


1 **2**

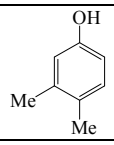
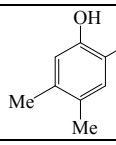
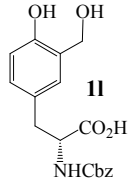
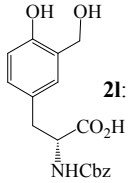
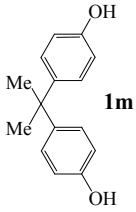
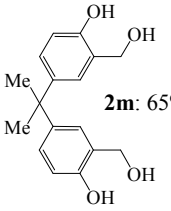
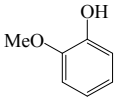
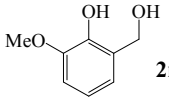
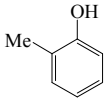
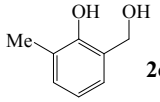
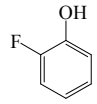
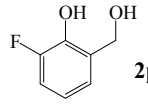
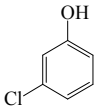
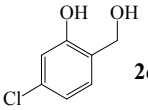
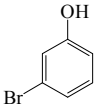
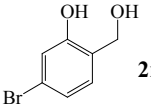
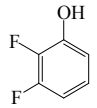
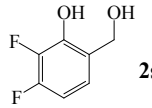
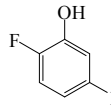
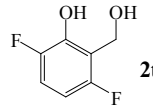
Entry	Phenols	Time	Products
1	 **1a**	28 h	 **2a**: 86%
2	 **1b**	20 h	 **2b**: 89%
3	 **1c**	20 h	 **2c**: 90%
4	 **1d**	12 h	 **2d**: 93%
5	 **1e**	30 h	 **2e**: 90%
6	 **1f**	30 h	 **2f**: 80%
7	 **1g**	16 h	 **2g**: 83%
8[b]	 **1h**	48 h	 **2h**: 95%
9[b]	 **1i**	48 h	 **2i**: 83%
10	 **1j**	12 h	 **2j**: 90%

[a] General conditions: **1a** (1.0 equiv.), $NaBO_2$ (8.0 equiv.) and aqueous formaldehyde (37%, 5.0 equiv.) in water (c = 0.2 M).
[b] The reaction was performed at 50 °C.

Table 2 (Contd.)

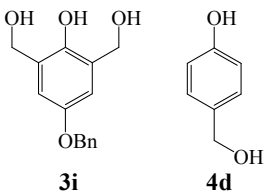


1 2

Entry	Phenols	Time	Products
11	 **1k**	10 h	 **2k**: 95%
12	 **1l**	24 h	 **2l**: 80%
13	 **1m**	36 h	 **2m**: 65%
14	 **1n**	12 h	 **2n**: 88%
15	 **1o**	12 h	 **2o**: 87%
16	 **1p**	12 h	 **2p**: 85%
17	 **1q**	12 h	 **2q**: 90%
18	 **1r**	12 h	 **2r**: 91%
19	 **1s**	12 h	 **2s**: 90%
20	 **1t**	12 h	 **2t**: 92%

[a] General conditions: **1a** (1.0 equiv.), $NaBO_2$ (8.0 equiv.) and aqueous formaldehyde (37%, 5.0 equiv.) in water (c = 0.2 M) at 40 °C.

standard conditions, demonstrating a high region-selectivity (entry 4). With the *para* position of phenols bearing electron-withdrawing groups such as fluoro, chloro and bromo, phenols **1e**–**g** reacted equally well with aqueous formaldehyde under the standard conditions to afford salicyl alcohols **2e**–**g** in excellent yields (entries 5–7). Hydroxymethylation of 4-phenylphenol (**1h**) and 4-(benzyloxy)phenol (**1i**) with aqueous formaldehyde afforded salicyl alcohols **2h**–**i** in good yields within 48 hours under the standard conditions, albeit at a relatively higher reaction temperature (entries 8–9). By treating 4-methoxyphenol (**1j**) with aqueous formaldehyde under the standard conditions, salicyl alcohol **2j** was obtained in 90% yield within 12 hours (entry 10). 3,4-Disubstituted phenol **1k** has also been investigated, which reacted smoothly with aqueous formaldehyde under the standard conditions to afford salicyl alcohol **2k** in 95% yield (entry 11). L-*N*-Benzyloxycarbonyl-3-hydroxymethyl-tyrosine (**1l**) reacted smoothly with aqueous formaldehyde under the standard conditions to afford salicyl alcohol **2l** in 80% yield within 1 day (entry 12). This reaction has been achieved previously in presence of borax in 5–17 days[3a,3c-d], which in turn facilitated the synthesis of methylene-bridged (*S*)-tyrosine-phenol dimers[3c], as well as the total synthesis of antitumor antibiotic jorumycin and renieramycin G[12]. Double monohydroxymethylation went smoothly between 2,2-bis(4-hydroxyphenyl)propane (**1m**) and excess aqueous formaldehyde under the standard conditions to give salicyl alcohol **2m** in 65% yield (entry 13). With a methoxyl group (a strong electron-donating group), a methyl group (a weak electron-donating group) and a fluoro group (a weak electron-withdrawing group) at the *ortho* position of phenols, hydroxymethylation of phenols **1n**–**p** with aqueous formaldehyde under the standard conditions afforded salicyl alcohols **2n**–**p** in high yields within 12 hours (entries 14–16). *meta*-Substituted phenols **1q**–**s** have also been investigated, which reacted smoothly with aqueous formaldehyde under the standard conditions to afford salicyl alcohol **2q**–**s** in 90–91% yields (entries 17–18). 2,3-Disubstituted phenol **1s** and 2,5-disubstituted phenol **1t** reacted equally well with aqueous formaldehyde under the standard conditions to afford salicyl alcohols **2s**–**t** in excellent yields (entries 19–20). It is worth mentioning that the mono- and *ortho*-selectivities of these hydroxymethylations decreased with the increase of the reaction temperature. For example, the partial *para*-hydroxymethylation of **1d**, in either $NaBO_2/H_2O$ system or $Na_2B_4O_7/H_2O$ system, was observed when the reaction was performed at 60 °C, which afforded *para*-hydroxymethyled product **4d** in about 10% yield (Fig. 1), along with salicyl alcohol **2d** (about 80% yield). The partial bishydroxymethylation of phenols **1a** and **1i**, in either $NaBO_2/H_2O$ system or $Na_2B_4O_7/H_2O$ system, was also observed when the reaction was performed at 60 °C, which afforded bishydroxymethyled products **3a** and **3i** (Fig. 1) in about 5% yields, along with salicyl alcohols **2a** and **2i** (80–85% yields). These reactions did not work in H_3BO_3/H_2O system at 60 °C. The $NaBO_2/H_2O$ system was found to be the best conditions as its lowest effective reaction temperature was the lowest one in these boron reaction systems.



3i **4d**

Fig. 1 Structures of bishydroxymethyled product **3i** and *para*-hydroxymethyled product **4d**

The high mono- and region-selectivities of these reactions

could be understood by the special properties of $NaBO_2$, which appeared to serve the dual role of the suitable base and the efficient chelating reagent. On one hand, as phenols were converted to the corresponding phenoxide anions in the basic $NaBO_2/H_2O$ system, the high *ortho*-selectivity could be explained from the calculated average local ionization energy surfaces of the phenoxide anion[13]. As shown in Fig. 2, the ionization energies (IEs) of phenoxide anion are 3.18 eV (*ortho*), 4.24 eV (*meta*) and 3.32 eV (*para*), respectively[13]. Since changes in the IEs result in exponential changes in the relative rates of reaction at different sites, the estimated regioisomer ratios, in an electrophilic substitution, are 97% (*ortho*), 0 (*meta*) and 3% (*para*), respectively[13]. It can also be proposed that similar resonant effects come into play at the *ortho* and *para* positions, but the *ortho* positions are more inductively activated than the *para* position[13]. However, a higher reaction temperature makes more collisions effective, including the collisions at the position *para* to the phenolic hydroxyl group, and thereby results in a lower *ortho*-selectivity. One resolution is to perform the hydroxymethylation at temperature as low as possible, which would make the collisions at the *para* position ineffective and thus increase the *ortho*-selectivity. The effective reaction temperature of *ortho*-hydroxymethylation in $NaBO_2/H_2O$ system (40 °C) was lower than that in $Na_2B_4O_7/H_2O$ system (60 °C) or H_3BO_3/H_2O system (110 °C), and thus could display a higher *ortho*-selectivity.

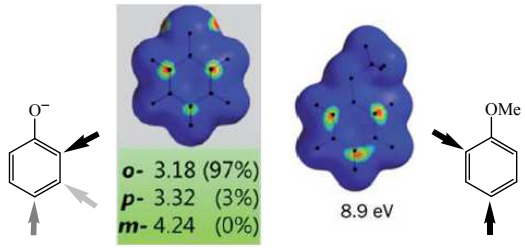


Fig. 2 Prediction of the region-selectivity with the local ionization energies (IEs) [sites of electrophilic substitution: primary (dark), secondary (gray), tertiary (light gray)][12]

On the other hand, as shown in Fig. 2, an obvious bigger ionization energy minima is required in the electrophilic substitution of anisole compared with phenoxide anion (*i.e.* 3.18 eV versus 8.9 eV, Fig. 2), indicating that phenoxide anion is far more active than anisole in an electrophilic substitution. Although a methoxyl group activates an aromatic ring toward electrophilic attack, an oxyanion substituent is an even more powerful activator because electron delocalization in phenoxide anion leads to strongly increased electron density at the aromatic ring. The possible compounds **7** (Fig. 3), resulted from the reaction of $NaBO_2$ with monohydroxymethylated products **2**, help to prevent the formation of new strongly active phenoxide anions, and thus obviate a further hydroxymethylation under mild conditions. However, the further hydroxymethylations would occur if the temperature is high enough, and thereby result in a lower mono-selectivity. The effective reaction temperature for the monohydroxymethylation in $NaBO_2/H_2O$ system was lower than that in $Na_2B_4O_7/H_2O$ system or H_3BO_3/H_2O system, and thus could display a higher mono-selectivity.

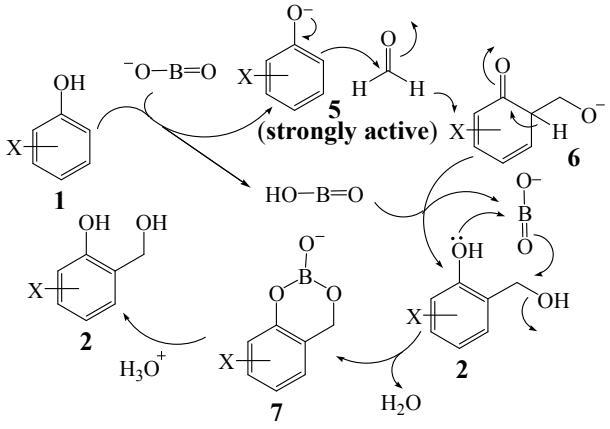


Fig. 3 A plausible mechanism for the hydroxymethylation of phenols with aqueous formaldehyde in $NaBO_2/H_2O$ system

Based on the above results, a plausible mechanism for the hydroxymethylation of phenols with formaldehyde is outlined in Fig. 3. Reaction of phenols **1** with $NaBO_2$ affords strongly active phenoxide anions **5**, which in turn would react with aqueous formaldehyde to form salicyl alcohols **2**. The produced salicyl alcohols **2** *in situ* react with $NaBO_2$ to form relatively stable compounds **7**, and thus obviate a bishydroxymethylation. Finally, acidic work-up of the reaction mixture facilitates the conversion of compounds **7** into salicyl alcohols **2**.

Conclusions

In summary, *ortho*-selective monohydroxymethylation of phenols proceeds efficiently in $NaBO_2/H_2O$ system. The reaction rate was greatly enhanced by water. The process provided a highly efficient and environmentally benign approach for the synthesis of salicyl alcohols, important substrates for the synthesis of various pharmaceutical agents and functional natural products. Applications of this hydroxymethylation protocol to the total synthesis of proanthocyanidin-type natural products are in progress in our research group.

Experimental

General procedure for water-promoted hydroxymethylation of phenols 1 with formaldehyde in $NaBO_2$ system (Table 2)

To a mixture of phenols **1** (1.0 mmol) and $NaBO_2{\cdot}4H_2O$ (98.5%, 1.12 g, 8.0 mmol) in water (5 mL) at 40 °C was added aqueous formaldehyde (37%, 372 μL, 5.0 mmol) in one portion. The mixture was stirred at 40 °C (Table 2, entries 9–10, 50 °C) for 10–48 hours, and neutralized with 3 N hydrochloric acid at room temperature until pH = 6. The resulting mixture was extracted with ethyl acetate (5 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography over silica gel to afford salicyl alcohols **2a–p**.

Salicyl alcohol 2a: Light yellow solid; m.p. = 85–86°C (lit.,[14] 84–86°C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, 1H, J = 8.4, 2.4 Hz), 7.05 (d, 1H, J = 2.4 Hz), 6.82 (d, 1H, J = 8.4 Hz), 4.84 (s, 2H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 142.9, 126.3, 124.8, 124.0, 116.0, 64.9, 34.0, 31.5; FTIR (film): 3437,

3159, 1447, 1255, 1210, 928, 870, 801 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{11}H_{15}O_2$ $[M-H]^-$: 179.1072. Found: 179.1074.

Salicyl alcohol 2b: Light yellow solid; m.p. = 83–84°C (lit.,[6a] 83°C); ^1H NMR (400 MHz, DMSO-d_6) δ 8.95 (s, br, 1H), 7.07 (d, 1H, J = 2.8 Hz), 6.80 (d, 1H, J = 8.0 Hz), 6.63 (dd, 1H, J = 8.0, 2.8 Hz), 4.85 (s, br, 1H), 4.44 (d, 2H, J = 3.6 Hz), 2.44 (q, 2H, J = 7.6 Hz), 1.08 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.1, 133.6, 128.0, 126.7, 126.3, 114.4, 58.4, 27.5, 15.9; FTIR (film): 3435, 3157, 1517, 1272, 1236, 852, 819, 794 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_9H_{11}O_2$ $[M-H]^-$: 151.0759. Found: 151.0758.

Salicyl alcohol 2c: Light yellow solid; m.p. = 104–105°C (lit.,[6a,15] 104–105°C); ^1H NMR (400 MHz, DMSO-d_6) δ 7.08 (s, br, 1H), 6.83 (d, br, 1H, J = 8.0 Hz), 6.65 (d, 1H, J = 8.0 Hz), 4.46 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.8, 128.1, 127.8, 127.5, 126.8, 114.4, 58.3, 20.2; FTIR (film): 3436, 3159, 1445, 1335, 1297, 1210, 1091, 827, 690 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_8H_9O_2$ $[M-H]^-$: 137.0597. Found: 137.0595.

Salicyl alcohol 2d: Light yellow solid; m.p. = 82–84°C (lit.,[16] 81–84°C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (s, br, 1H), 7.20 (t, 1H, J = 8.1 Hz), 7.04 (d, 1H, J = 8.1 Hz), 6.87 (d, 1H, J = 8.1 Hz), 6.85 (t, 1H, J = 8.1 Hz), 4.82 (s, 2H), 2.71 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 129.4, 127.9, 124.8, 120.1, 116.4, 64.3; FTIR (film): 3155, 1596, 1483, 1461, 1417, 1291, 1256, 1217, 1115, 1044, 995, 938, 774, 753, 735, 714 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_7H_7O_2$ $[M-H]^-$: 123.0441. Found: 123.0439.

Salicyl alcohol 2e: Light yellow solid; m.p. = 67–69°C (lit.,[17] 68–70°C); ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 6.78–6.68 (m, 3H), 4.61 (s, 2H), 4.46 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0 (d, 1C, $J_{C\text{-}F}$ = 235.1 Hz), 151.5, 127.5 (d, 1C, $J_{C\text{-}F}$ = 6.6 Hz), 116.3 (d, 1C, $J_{C\text{-}F}$ = 7.9 Hz), 114.2 (d, 1C, $J_{C\text{-}F}$ = 22.5 Hz), 113.9 (d, 1C, $J_{C\text{-}F}$ = 23.1 Hz), 62.0 (d, 1C, $J_{C\text{-}F}$ = 3.5 Hz); FTIR (film): 3174, 1512, 1455, 1415, 1373, 1307, 1277, 1197, 1155, 1008, 883, 822, 760, 697 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_7H_6O_2F$ $[M-H]^-$: 141.0346. Found: 141.0344.

Salicyl alcohol 2f: Light yellow solid; m.p. = 89–90°C (lit.,[6a,15] 90–93°C); ^1H NMR (400 MHz, DMSO-d_6) δ 7.27 (d, 1H, J = 2.4 Hz), 7.06 (dd, 1H, J = 8.8 Hz), 6.76 (d, 1H, J = 8.8 Hz), 4.45 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 129.1, 127.4, 126.0, 124.7. 117.9, 64.0; FTIR (film): 3435, 3156, 1497, 1205, 1177, 1117, 873, 807, 761 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_7H_6O_2Cl$ $[M-H]^-$: 157.0051. Found: 157.0048.

Salicyl alcohol 2g: Light yellow solid; m.p. = 109–111°C (lit.,[6a,18] 109–114°C); ^1H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.14 (d, 1H, J = 2.1 Hz), 7.05 (dd, 1H, J = 8.4, 2.1 Hz), 6.60 (d, 1H, J = 8.1 Hz), 4.54 (s, 2H), 4.50 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 130.5, 130.0, 128.7, 117.2, 110.8, 61.2; FTIR (film): 3436, 3159, 1434, 1406, 1302, 1243, 1217, 1177, 1126, 1012, 999, 898, 877, 819, 776, 743, 706 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_7H_6O_2Br$ $[M-H]^-$: 200.9546. Found: 200.9545.

Salicyl alcohol 2h: Light yellow solid; m.p. = 215–216°C; ^1H NMR (400 MHz, DMSO-d_6) δ 7.60–7.34 (m, 6H), 7.27 (t, 1H, J = 7.6 Hz), 6.85 (d, 1H, J = 8.4 Hz), 4.55 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.0, 140.5, 130.5, 128.8, 128.6, 125.8, 125.5, 125.4, 115.0, 58.2; FTIR (film): 3435, 3156, 1451, 1267, 834, 762 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{13}H_{11}O_2$ $[M-H]^-$: 199.0754. Found: 199.0752.

Salicyl alcohol 2i: Light yellow solid; m.p. = 135–136°C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.89 (s, br, 1H), 7.45–7.31 (m, 5H), 7.03 (s, br, 1H), 6.72 (s, br, 2H), 5.00 (s, br, 3H), 4.51 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.2, 148.0, 137.6, 129.5, 128.2, 127.5, 127.4, 115.0, 114.0, 113.2, 69.7, 58.3; FTIR (film): 3436, 3158, 1513, 1256, 838, 778 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{14}H_{13}O_3$ $[M-H]^-$: 229.0865. Found: 229.0868.

Salicyl alcohol 2j: Light yellow solid; m.p. = 74–76°C (lit.,[19] 75–76°C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.08 (s, br, 1H), 6.78–6.70 (m, 2H), 6.59 (d, 1H, J = 2.4 Hz), 4.74 (s, 2H), 3.72 (s, 3H), 2.98 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 149.5, 125.8, 116.9, 114.3, 113.6, 64.0, 55.8; FTIR (film): 3181, 2961, 1516, 1461, 1412, 1316, 1280, 1211, 1164, 1041, 1009, 999, 930, 865, 819, 758, 701 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_8H_9O_3$ $[M-H]^-$: 153.0546. Found: 153.0543.

Salicyl alcohol 2k: Light yellow solid; m.p. = 110–112°C (lit.,[4b] 112–113°C); ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, br, 1H), 6.77 (s, 1H), 6.62 (s, 1H), 4.66 (s, 2H), 4.03 (s, br, 1H), 2.14 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 136.9, 129.0, 127.1, 122.9, 117.2, 63.0, 19.4, 18.4; FTIR (film): 3179, 2935, 1460, 1407, 1311, 1280, 1203, 1022, 988, 891, 861, 759, 706, 686 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_9H_{11}O_2$ $[M-H]^-$: 151.0754. Found: 151.0751.

Salicyl alcohol 2l: Light yellow solid; m.p. = 125–129°C; $[\alpha]_D^{25}$ = 10.6 (c = 0.8, CH_3CO_2H); ^1H NMR (400 MHz, DMSO-d_6) δ 12.67 (s, br, 1H), 9.19 (s, 1H), 7.59 (d, 1H, J = 8.4 Hz), 7.36–7.18 (m, 6H), 6.92 (d, 1H, J = 8.4 Hz), 6.66 (d, 1H, J = 8.0 Hz), 4.98 (t, 1H, J = 2.4 Hz),4.98 (d, 2H, J = 2.4 Hz), 4.45 (s, 2H), 4.12–4.08 (m, 1H), 2.94 (dd, 1H, J = 13.6, 4.0 Hz), 2.72 (dd, 1H, J = 13.6, 10.4 Hz); HRMS (ESI) m/z: Calcd for $C_{18}H_{18}NO_6$ $[M-H]^-$: 344.1134. Found: 344.1136. The analytical data were same with the reported results[3a,3c-d].

Salicyl alcohol 2m: Light yellow solid; m.p. = 105–106°C; ^1H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 2H), 7.16 (d, 2H, J = 2.4 Hz), 6.85 (dd, 2H, J = 8.4, 2.4 Hz), 6.63 (d, 2H, J = 8.4 Hz), 4.86 (t, 2H, J = 5.6 Hz), 4.43 (d, 4H, J = 5.6 Hz), 3.33 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.6, 140.9, 127.3, 125.2, 125.1, 113.8, 58.4, 30.9; FTIR (film): 3435, 3157, 1445, 1293, 987, 743 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{17}H_{19}O_4$ $[M-H]^-$: 287.1283. Found: 287.1285.

Salicyl alcohol 2n: Light yellow solid; m.p. = 60–61°C (lit.,[15] 60–61°C); ^1H NMR (400 MHz, DMSO-d_6) δ 6.90 (d, 1H, J = 7.6 Hz), 6.82 (d, 1H, J = 7.6 Hz), 6.73 (t, 2H, J = 7.6 Hz), 4.49 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.0, 143.1, 129.0, 119.4, 118.3, 110.2, 58.1, 55.7; FTIR (film): 3439, 3161, 1496, 1202, 1101, 768, 723 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_8H_9O_3$ $[M-H]^-$: 153.0546. Found: 153.0543.

Salicyl alcohol 2o: Light yellow solid; m.p. = 36–38°C (lit.,[2b] 35–36°C); ^1H NMR (400 MHz, DMSO-d_6) δ 7.04 (d, 1H, J = 7.6 Hz), 6.96 (d, 1H, J = 7.6 Hz), 6.70 (t, 2H, J = 7.6 Hz), 4.56 (s, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.6, 128.9, 127.9, 125.0, 124.1, 118.8, 59.8, 16.0; FTIR (film): 3438, 3151, 1448, 1299, 1087, 760, 721 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_8H_9O_2$ $[M-H]^-$: 137.0597. Found: 137.0595.

Salicyl alcohol 2p: Light yellow solid; m.p. = 98–100 °C; ^1H

NMR (400 MHz, DMSO-d_6) δ 7.10–6.85 (m, 3H), 4.36 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.8 (d, 1C, $J_{C\text{-}F}$= 238.7 Hz), 143.6 (d, 1C, $J_{C\text{-}F}$= 12.0 Hz), 133.8 (d, 1C, $J_{C\text{-}F}$= 5.2 Hz), 122.5 (d, 1C, $J_{C\text{-}F}$= 3.0 Hz), 117.3, 114.2 (d, 1C, $J_{C\text{-}F}$= 18.1 Hz), 62.1; FTIR (film): 3419, 2959, 1622, 1602, 1523, 1479, 1443, 1384, 1294, 1262, 1202, 1112, 1020, 933, 870, 819, 789, 741 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_7H_6FO_2$ [M-H]$^-$: 141.0352. Found: 141.0349.

Salicyl alcohol 2q: Light yellow solid; m.p. = 78–80°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (s, OH), 7.28 (d, 1H, J = 8.2 Hz), 6.82 (s, 1H), 6.74 (d, 1H, J = 8.2 Hz), 4.57 (s, OH), 4.43 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.4, 131.4, 129.3, 129.1, 115.4, 114.1, 59.8; FTIR (film): 3418, 2944, 1610, 1502, 1389, 1267, 1101, 1031, 907, 703 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_7H_6ClO_2$ [M-H]$^-$: 157.0056. Found: 157.0058.

Salicyl alcohol 2r: Light yellow solid; m.p. = 100–101°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.69 (s, 1H), 7.31 (d, 1H, J = 8.4 Hz), 6.97 (d, 1H, J = 1.6 Hz), 6.79 (dd, 2H, J = 8.4, 1.6 Hz), 5.14 (s, br, 1H), 4.43 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.0, 131.1, 129.4, 121.5, 118.6, 114.6, 62.3; FTIR (film): 3185, 2958, 1582, 1445, 1400, 1284, 1264, 1179, 1154, 1048, 992, 889, 857, 812, 694 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_7H_6O_2Br$ [M-H]$^-$: 200.9546. Found: 200.9545.

Salicyl alcohol 2s: Light yellow solid; m.p. = 129–131°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.4 (s, br, 1H), 7.00 (t, 1H, J = 8.0 Hz), 6.82 (d, 1H, J = 8.0 Hz), 5.19 (s, br, 1H), 4.43 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.5 (d, 1C, $J_{C\text{-}F}$ = 242.4 Hz), 148.4 (d, 1C, $J_{C\text{-}F}$ = 242.5 Hz), 145.6 (d, 1C, $J_{C\text{-}F}$ = 8.9 Hz), 138.1 (d, 1C, $J_{C\text{-}F}$ = 14.6 Hz), 123.0 (dd, 1C, $J_{C\text{-}F}$ = 9.9, 4.5 Hz), 112.3 (d, 1C, $J_{C\text{-}F}$ = 7.4 Hz), 56.3; FTIR (film): 3413, 2959, 1523, 1489, 1416, 1372, 1309, 1060, 998, 954, 931, 874, 812, 769, 675 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_7H_5F_2O_2$ [M-H]$^-$: 159.0258. Found: 159.0254.

Salicyl alcohol 2t: Light yellow solid; m.p. = 132–134°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, br, 1H), 7.14 (dd, 1H, J = 11.16, 7.4 Hz), 6.79 (dd, 1H, J = 11.16, 7.4 Hz), 5.30 (s, br, 1H), 4.39 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.0 (d, 1C, $J_{C\text{-}F}$ = 236.5 Hz), 147.3 (d, 1C, $J_{C\text{-}F}$ = 235.3 Hz), 144.7 (dd, 1C, $J_{C\text{-}F}$= 25.8, 11.7 Hz), 119.1 (dd, 1C, $J_{C\text{-}F}$ = 17.9, 5.4 Hz), 115.6 (dd, 1C, $J_{C\text{-}F}$ = 20.7, 7.1 Hz), 104.4 (dd, 1C, $J_{C\text{-}F}$ = 26.4, 2.9 Hz), 55.9 (d, 1C, $J_{C\text{-}F}$ = 3.0 Hz); FTIR (film): 3418, 2959, 2920, 1637, 1518, 1442, 1325, 1231, 1181, 1150, 1101, 1080, 1024, 997, 877, 844, 751 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_7H_5F_2O_2$ [M-H]$^-$: 159.0258. Found: 159.0256.

Bishydroxymethyled product 3a: Light yellow solid; m.p. = 115–116°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, br, 1H), 7.06 (s, 2H), 4.74 (d, 2H, J = 3.9 Hz), 3.05 (s, br, 2H), 1.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 142.6, 125.4, 124.8, 63.6, 34.0, 31.4; FTIR (film): 3366, 3006, 1483, 1225, 1154, 1071, 929, 860 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{12}H_{17}O_3$ [M-H]$^-$: 209.1178. Found: 209.1180.

Bishydroxymethyled product 3i: Light yellow solid; m.p. = 159–160°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.44–7.31 (m, 5H), 6.84 (s, 2H), 5.19 (t, 2H, J = 5.6 Hz), 5.00 (s, 2H), 4.53 (d, 4H, J = 5.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.4, 145.1, 137.6, 129.6, 128.2, 127.4, 127.3, 111.9, 69.5, 59.0; FTIR (film): 3368, 3008, 1510, 1255, 1172, 937, 838 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{15}H_{15}O_4$ [M-H]$^-$: 259.0970. Found: 259.0973.

***para*-Hydroxymethyled product 4d**: Light yellow solid; m.p. = 117–118°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.41 (s, br, 1H), 7.09 (d, 1H, J = 8.0 Hz), 6.72 (d, 1H, J = 8.0 Hz), 5.00 (s, br, 1H), 4.53 (d, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.2, 132.6, 127.9, 114.7, 62.7; FTIR (film): 3396, 3135, 1615, 1600, 1517, 1232, 1202, 987, 830 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_7H_7O_2$ [M-H]$^-$: 123.0441. Found: 123.0439.

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