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Hydrobromic acid-catalyzed Friedel–Crafts type reactions of naphthols†

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Catalyzed by 10 mol% of hydrobromic acid, hydroxyalkylation and allylation-iodocyclization of naphthols proceeded smoothly under mild conditions. In contrast, other Brønsted acids tested, including HCl, HI, HBF_4, HPF_6, TFA, PTSA, H_2SO_4, TfOH *etc.*, are almost ineffective under identical conditions or require harsh reaction conditions.

Acid-catalyzed/mediated Friedel–Crafts (FC) type alkylation of arenes with aldehydes, also known as hydroxyalkylation,[1,2] is one of the most important protocols for the functionalization of aromatic compounds. In this field, the reactions of electron-rich arenes with aldehydes have been well studied, for example the reaction of β-naphthols with aldehydes was successfully used for efficient synthesis of xanthenes.[3] These reactions smoothly occurred in the presence of various readily available Brønsted acids or Lewis acids through the activation of aldehydes and were found to be acidity-dependent.[3]

On the other hand, counterion effect widely exists in chemical transformations.[4] Among them, halide effect has long been recognized, especially in transition metal catalysis.[5] In the field of aromatic electrophilic substitution reactions, the physical properties of the counterion have been shown to dictate the catalytic activity in the aromatic nitration and acetylation.[6a] Counterion was also found to be able to tune both chemoselectivity and stereoselectivity of alkylation of indoles with β,γ-unsaturated α-keto esters.[6b] However, the significantly different catalysis existing between hydrobromic acid and other hydrohalic acids has never been recoganized in acid-catalyzed FC reactions. In this paper, we hope to disclose a unique catalytic performance of HBr in hydroxyalkylation and allylation-iodocyclization of naphthols.

In most cases, the reaction of naphthols with aldehydes required either at least stoichiometric amount of acid catalysts or harsh reaction conditions.[1,3,7] For example, the reaction of β-naphthol **1a** with 4-nitrobenzaldehyde **2a** had to be performed in a Teflon reaction vessel at 3.0 kbar and 60 °C for 96 h to yield benzylidene biphenol **3a** when using catalytic amounts of trifluoromethanesulfonic acid (TfOH) as catalyst.[7a] Indeed, in our experiments the hydroxyalkylation reaction of **1a** with **2a**, performed in acetonitrile at ambient conditions for 24 h (Table 1, entries 15–19), gave a trace amount of **3a** when 10 mol% of Brønsted acids, including HBF_4 (48% aqueous), HPF_6 (65% aqueous), trifluoroacetic acid (TFA, 99%), *p*-methylbenzenesulfonic acid (PTSA, 99%) or H_2SO_4 (98%), were used as catalysts, respectively. In the case of TfOH (99%) as the catalyst (10 mol%), **3a** was also isolated only in 17% yield under the identical reaction conditions (entry 20).

Surprisingly, benzylidene biphenol **3a** could be obtained in high yield by using HBr (47% aqueous, 10 mol%) as the catalyst! In this case, the reaction time was reduced to 7.0 h and the yield of **3a** reached to 76% (entry 1). In contrast, interestingly, HCl (36% aqueous, 10 mol%) and HI (45% aqueous, 10 mol%) were less effective (entries 3 and 5) even with 100 mol% of catalyst (entries 4 and 6). These results indicated that there is no essential co-relation between the acidity of the reaction solution and the efficiency of the reaction though an acidic environment proved to be necessary (entry 1 *versus* entry 21). Satisfied yield of **3a** could be obtained by using the combined HCl (36% aqueous, 10 mol%) and Bu_4NBr (10 mol%) catalytic system (entry 22). Furthermore, $CuBr_2$ was proved less effective (entry 23), and $Cu(OAc)_2$ or $CuCl_2$ was ineffective (entries 24 and 25). A comparison of different solvents indicated that acetonitrile was the best choice (entry 1 *versus* entries 7–13). It was also found that a good yield of **3a** (71%) could be obtained by using acetic acid as the solvent in the presence of catalytic amount of HBr (entry 14).

Unlike the well known acidity-dependent Friedel–Crafts hydroxyalkylations,[1–3] the remarkable catalytic performance of HBr (entry 1 *versus* entries 3–20) indicates that the bromide anion is more than a spectator in the above HBr-catalyzed process. It may reveal that simple Brønsted acid HBr acts as a

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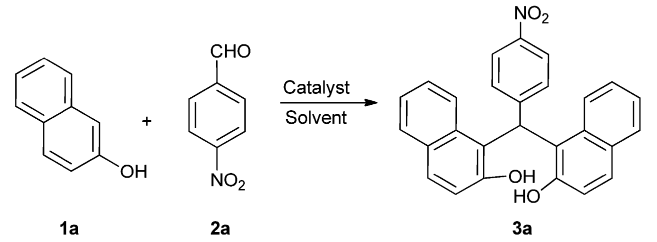
Table 1 Screening of catalysts and reaction conditions[a]



Entry	Catalyst (equiv.)	Solvent	Time (h)	Yield (%)[b]
1	HBr (0.1)	MeCN	7.0	76
2	HBr (0.05)	MeCN	24	36
3	HCl (0.1)	MeCN	24	Trace
4	HCl (1.0)	MeCN	24	30
5	HI (0.1)	MeCN	24	8.0
6	HI (1.0)	MeCN	24	43
7	HBr (0.1)	DMF	24	Nr[c]
8	HBr (0.1)	CH_2Cl_2	24	Nr[c]
9	HBr (0.1)	DCE	24	Trace
10	HBr (0.1)	Et_2O	24	5.0
11	HBr (0.1)	THF	24	6.0
12	HBr (0.1)	DME	24	13
13	HBr (0.1)	C_6H_6	24	19
14	HBr (0.1)	AcOH	16	71
15	HBF_4 (0.1)	MeCN	24	Trace
16	HPF_6 (0.1)	MeCN	24	5.0
17	TFA (0.1)	MeCN	24	Trace
18	PTSA (0.1)	MeCN	24	Trace
19	H_2SO_4 (0.1)	MeCN	24	Trace
20	TfOH(0.1)	MeCN	24	17
21	Bu_4NBr (0.1)	MeCN	24	Nr[c]
22	HCl (0.1) Bu_4NBr (0.1)	MeCN	24	68
23	$CuBr_2$ (0.1)	MeCN	24	19
24	$CuCl_2$ (0.1)	MeCN	24	Nr[c]
25	$Cu(OAc)_2$ (0.1)	MeCN	24	Nr[c]

[a] Conditions: **1a** (2.0 mmol), **2a** (1.1 mmol), solvent (10 mL), rt. [b] Isolated yields. [c] No reaction.

dual catalyst[8] in contrast to previous conventional activation pathways (activation of aldehydes with acids).[2,7] According to our work on the special catalysis of bromide anion for the condensation of ketene dithioacetals with aldehydes,[9] we envisioned that there may be exist a catalytic activation of β-naphthol by bromide anion in the present reaction though the mechanistic details are not clear at the moment.

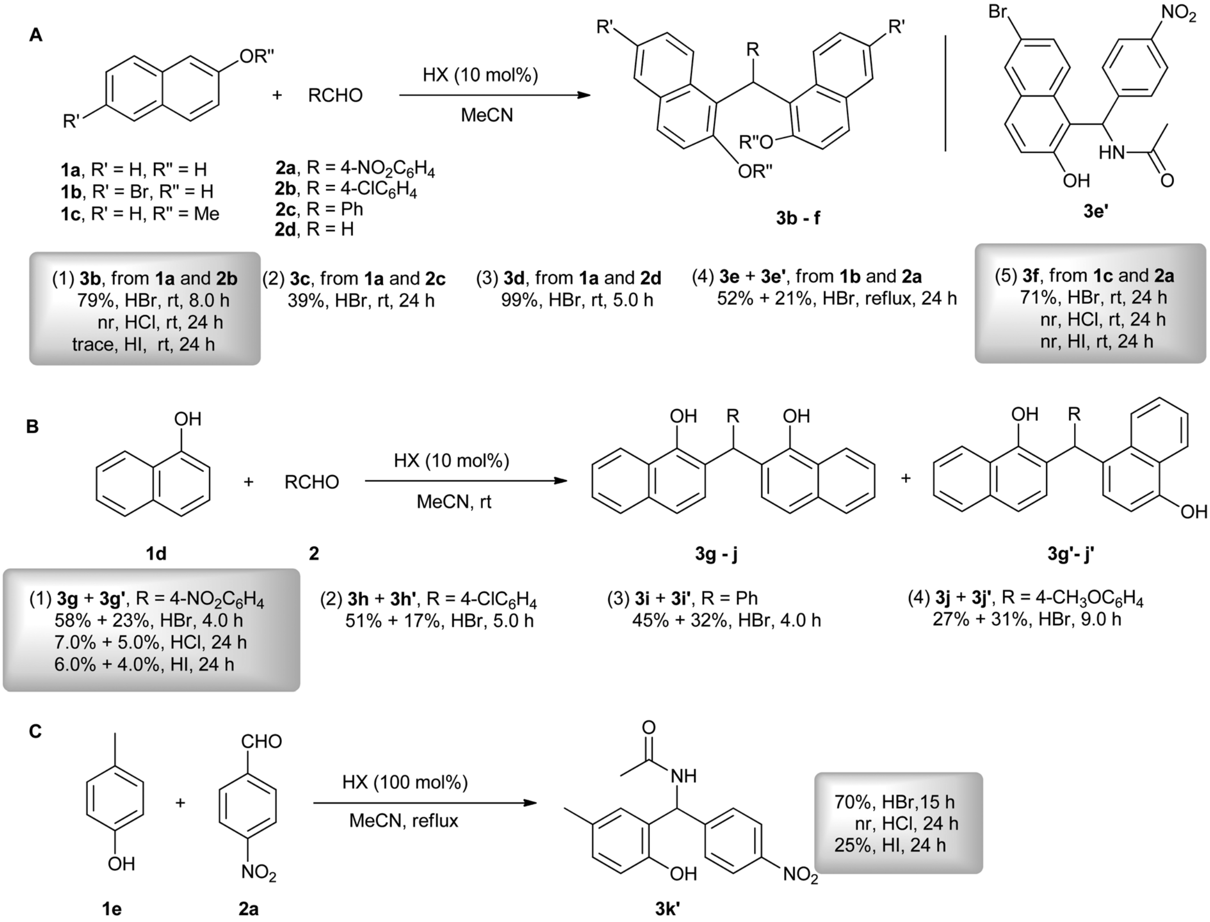
Further evidence for the unique catalytic activity was obtained by the reaction of **1a** with 4-chlorobenzaldehyde **2b**. Benzylidene biphenol **3b** was isolated in 79% yield with HBr (10 mol%) as the catalyst at room temperature for 8.0 h, while HCl (10 mol%) and HI (10 mol%) showed inefficient catalysis for this procedure even after 24 h (Scheme 1A, (1)). In addition, the catalytic activity of HBr was also observed from the reaction of **1a** with benzaldehyde **2c** and formaldehyde **2d** (Scheme 1A, (2) and (3)), respectively, although a lower yield of **3c** (39%) was obtained from less electrophilic **2c**. In the case of the reaction of less nucleophilic 6-bromo-β-naphthol **1b** with **2a**, products **3e** and **3e′** were afforded in 73% total yield at elevated temperature for 24 h (Scheme 1A, (4)). In this reaction, product **3e′** was formed in 21% yield by a hydroxyalkylation-Ritter reaction cascade.[10] Furthermore, it was noted that benzylidene biphenol **3f** could be obtained in 71% yield by the reaction of **2a** with β-methoxynaphthalene **1c** in the presence of 10 mol% of HBr for 24 h. However, no **3f** was detected when HCl or HI was used as catalyst, respectively (Scheme 1A, (5)). The successful synthesis of **3f** indicates that the free-OH of naphthols is not necessary in the HBr-catalyzed reactions. In comparison, a phenol hydroxyl group is required for the generation of, for example, reactive magnesium phenoxide in FC reactions of phenols.[11]

As presented above, we observed a significantly catalytic power of bromide anion in FC type reactions. Different from those conventional hydroxyalkylation usually involving high reaction temperature, solvent-free, microwave, or in the presence of excess amounts of acid catalysts,[3] the mild reaction conditions of our HBr-catalyzed reaction of β-naphthols with aldehydes (Scheme 1) can avoid further dehydration and thus easily afford biphenol derivatives **3** (the key skeleton of blepharismins)[12] as the products.

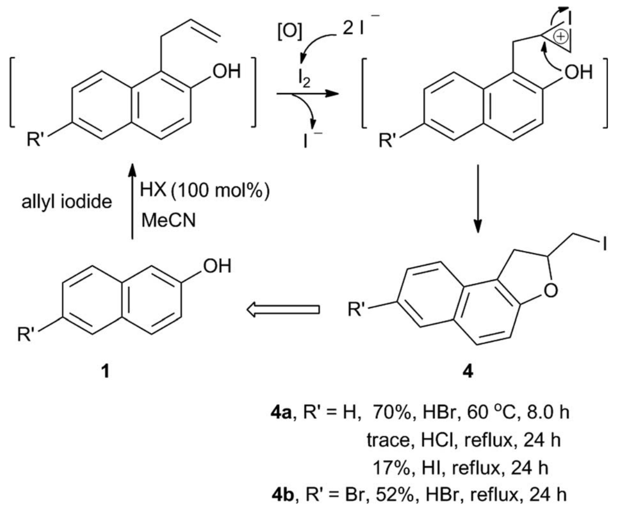
It has been proved that α-naphthol is much less reactive than β-naphthol in hydroxyalkylation and related reactions.[3a] In our research, however, α-naphthol **1d** was found to be suitable substrate for the HBr-catalyzed hydroxyalkylation. The reactions of **1d** with selected aromatic aldehydes could afford biphenol products **3g–j** and their isomers **3g′–j′** in good to high yields under the identical reaction conditions (Scheme 1B), while poor regioselectivities were observed likely due to the similar nucleophilicity of the orto- and *para*-position of phenols. On the other hand, **3g** and **3g′** were obtained in very low yields with HCl or HI as catalyst, respectively (Scheme 1B, (1)). The crucial and unique catalytic role of HBr in FC reaction could also be appreciated by other observations, for example, the hydroxyalkylation-Ritter reaction of *p*-cresol **1e** with **2a** (Scheme 1C).

To gain further insight into the unique catalytic behavior observed, a typical Friedel–Crafts alkylation of naphthols with allyl iodide was next tried under the catalysis of HBr. As a result, 2-(iodomethyl)-1,2-dihydronaphtho [2,1-*b*]furans **4** were obtained in good yields by using excess of allyl iodide (10 equiv.) in the presence of HBr (100 mol%) at 60 °C for 8.0 h (Scheme 2). By comparison, HI was a less effective catalyst and HCl was almost inefficient (Scheme 2). Fousteris and his co-workers developed a green process for the synthesis of 2-(iodomethyl) dihydro-benzofurans *via* water promoted iodocyclization of 2-allylphenols.[13] Clearly, our procedure provides a more direct route to dihydro-benzofurans *via* HBr-catalyzed allylation of commercially available phenols with allyl iodide and subsequential iodocyclization (Scheme 2).

As we known, the classical Friedel–Crafts reactions usually require an acidic catalyst for the activation of electrophiles.[1–3,7] Differently, the Friedel–Crafts type reactions of phenols presented in this communication are seem to be both proton and anion-dependent. The catalytic mechanism of HBr is not yet clear at this stage. Recently, the unique catalysis of bromide anion was also found in metal-free diamination of alkenes[14a] and copper-catalyzed oxidative aromatization of 2-cyclohexen-1-ones.[14b] The specially catalytic phenomenons of bromide anion,



Scheme 1 HBr-catalyzed Friedel–Crafts hydroxyalkylation.



Scheme 2 HBr-mediated tandem allylation/iodocyclization reaction.

less paid attention before in organic reactions, remains to be clarified.[8,15]

In summary, unprecedented Friedel–Crafts type reactions are reported to be HBr-dependent. The hydroxyalkylations of phenols with aldehydes afford biphenol derivatives in the presence of only a catalytic amount of HBr under very mild reaction conditions. In addition, 2-(iodomethyl)dihydrobenzofurans can also be synthesized in a single step directly from commercially available phenols and allyl iodide under the similar metal-free and good laboratory practice conditions. Although this catalytic procedure is still limited in scope, the special catalytic power of bromide anion may indicate a new anion catalytic version and deserves more attention in further research.

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