Communication

Chemoselective Benzylation and Allylation of 4-Nitrobenzaldehyde Promoted by Phase Transfer Catalyst and Metal in Aqueous Media

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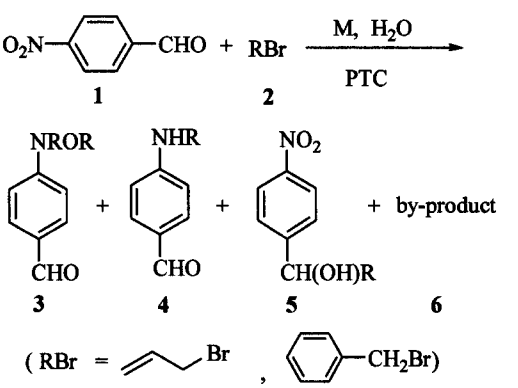
The benzylation and allylation of 4-nitrobenzaldehyde (1) could be controlled chemoselectively by using different phase transfer catalyst (PTC) and different metal catalysts. And then, benzylation and allylation of 1 with various organic halides has been realized in high yields in aqueous media.

Keywords benzylation, allylation, 4-nitrobenzaldehyde, phase transfer catalyst, selectivity, aqueous media

Over the past ten years, the pursuit of synthetic targets with increasing complexity has resulted in the development of reactions that emphasize chemo-, regio-, diastereo- and enantioselectivity.[1-4] The additions of organic halide to carbonyl compounds, promoted by various metals and acid conditions in aqueous media,[5] have been found increasing applications even for the synthesis of complex molecules. However, the chemists researching in this area confronted a kittle problem that nitrobenzaldehyde has both nitrogen electrophiles[6] and carbon electrophiles, and the reduction product and the polymer were formed when it reacted with organic halide in aqueous media. In order to construct complex molecules and evaluate the synthetic potential of such simple and environmentally clean reactions the chemoselective addition of nitrobenzaldehyde with organic halide in water is vitally required. In our investigation, phase transfer catalyst (PTC) effectively promoted allylation of carbonyl compounds,[7] the benzylation and the allylation of 4-nitrobenzaldehyde (1) with different organic halides could be controlled chemoselectively by using different PTC and different metal catalysts in aqueous media.

At first, when 4-nitrobenzaldehyde was employed as electrophile for the reaction, the products were the mixture formed from the benzylation and allylation and reduction in nitro-group, along with a little allyation of aldehyde group. Many attempts of chemoselectivity of benzylation and allylation of 4-nitrobenzaldehyde was succeeded by exerting phase transfer catalyst and various metals in aqueous media. As far as we know, this is the first example that chemoselectivity of benzylation and allylation for 4-nitrobenzaldehyde can be effected by PTC.

Scheme 1



To begin the investigation, a mixture of 4-nitrobenzaldehyde (1) with allyl bromide (**2a**) was stirred in the

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presence of PTC and zinc dust in water to afford the alkylation product in nitro group (**3a**). Herein the PTC is β-cyclodextrin (β-CD), sodium tetrafluoroborate ($NaBF_4$), tetra-4-butylammoniumbromide (n-Bu_4NBr), and polyethylene glycol 2000 (PEG 2000) respectively. It was found that β-CD, $NaBF_4$, n-Bu_4NBr and PEG 2000 promoted the allylation of 4-nitrobenzaldehyde occurring in nitro group selectively at room temperature to different extent. The consequences were listed in Table 1.

In terms of Table 1, the reaction catalyzed by β-CD, $NaBF_4$, n-Bu_4NBr and PEG 2000 individually gave the product **3a** in the yields of 84%, 73%, 92% and 50%, respectively. Among them, the reaction rate catalyzed by $NaBF_4$ proceeded faster than that of others. The reactions catalyzed by the PTC gave the products (**3a**) in the yields of 50%—92% (Entries 1—4) while no reaction occurred in the absence of PTC (Entry 5). The reduction products of the starting materials and the polymeric intermediate from the starting material or from the reduction products can lead to the complication of the products and the decrease of the conversion. When the reactions were catalyzed by β-CD or by β-CD mixed with $NaBF_4$ or n-Bu_4NBr, it was found that raising the reaction temperature could result in the increase of both reaction yields and rate (Entries 6—8). 4-(*N*-Benzyl-*N*-benzyloxy)aminobenzaldehyde (**3b**) predominated in the yield of 95% when the reaction was heated to 40 ℃ and catalyzed by the mixture of β-CD and n-Bu_4NBr (Entry 12). Also, it was found that different PTC had different influence on the distribution of product. The ratio of **3b**: **4b** was 64/36, 72/28 and 90/10, respectively when β-CD, $NaBF_4$, n-Bu_4NBr was used to catalyze the reaction respectively.

Also, the conversions were affected by PTC significantly. Nevertheless the influence on conversion was hard to be consistent with that on the distribution of products. For example, the 4-nitrobenzaldehyde was converted into the products completely when it reacted with benzyl bromide. But the product was the mixture of 4-(*N*-benzyl-*N*-benzyloxy) aminobenzaldehyde (**3b**) and 4-(*N*-benzyl)-aminobenzaldehyde (**4b**) concomitant with some side products (Entries 9—11).

Besides the PTC, the alternation of metal catalysts can also have a great influence on the benzylation and the allylation. When the reaction of 4-nitrobenzaldehyde (**1**) with allyl bromide (**2a**) was catalyzed by $SnCl_2$ and Zn instead of Zn alone in water, conversion of aldehyde group to corresponding homoallylic alcohol, 1-(4-nitrophenyl)-3-buten-1-ol (**5a**), was obtained. The **5a** can be increased from 50% to 70% when β-CD was employed as

Table 1 Benzylation and allylation of aldehydes in the presence of phase transfer catalyst in water

Entry	RX[a]	Metal	PTC[b]	Time (h)	Temp. (℃)	3	4	5 (Yield, %)[c]
1	**a**	Zn	A	11	25	84	—	—
2	**a**	Zn	B	11	25	73	—	—
3	**a**	Zn	C	11	25	92	—	—
4	**a**	Zn	D	20	25	50	—	—
5	**a**	Zn	—	20	25	—	—	—
6	**a**	Zn	A	10	40	90	—	—
7	**a**	Zn	A + B	5	40	92	—	—
8	**a**	Zn	A + C	5.5	40	94	—	—
9	**b**	Zn	A	24	25	58	32	—
10	**b**	Zn	B	24	25	55	22	—
11	**b**	Zn	C	24	25	61	7	—
12	**b**	Zn	A + C	6	40	95	—	—
13	**a**	Sn	A + B	24	25	—	—	—
14	**a**	Zn + $SnCl_2$	—	16	20	—	—	50
15	**a**	Zn + $SnCl_2$	A	10	20	—	—	70
16	**b**	Zn + $SnCl_2$	— or A	12	20	—	—	—
17	**b**	Zn + $SnCl_2$	—	5	40	27	66	—

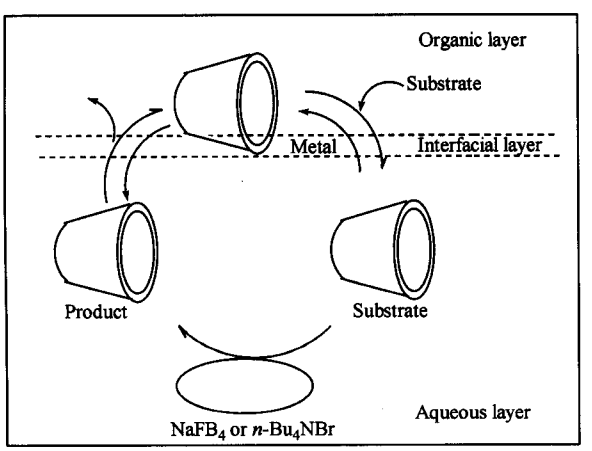
[a] **a**, allyl bromide; **b**, benzylbromide. [b] A, β-cyclodextin; B, $NaBF_4$; C, n-Bu_4NBr; D, polyethylene glycol 2000. [c] Determined by ^1H NMR analysis of the crude reaction mixture.

PTC (Entries 14 and 15). When allyl bromide (**2a**) was substituted by benzyl bromide (**2b**), the alkylation occurred to afford 4-(*N*-benzyl)aminobenzaldehyde (**4b**) as dominated product concomitant with 4-(*N*-benzyl, *N*-benzyloxy)aminobenzaldehyde (**3b**) and ratio of **4b**:**3b** was 71/29 at 40 ℃ (Entry 17). No reaction of 4-nitrobezaldehyde with benzyl bromide occurred when catalyzed by pure Sn or by $SnCl_2$ and Zn with or without PTC at 20 ℃ (Entries 13 and 16).

Based on these results, we have proposed the use of β-CD to improve the substrate transfer between the organic and aqueous phases. Cyclodextrins (CDs) are cyclic oligosaccharides composed of 6, 7 or 8 glucose units linked by a α-(1-4) glucosidic bond and traditionally been designated as α-, β- and γ-CD respectively. Their molecular geometries are characterized as the shape of a truncated cone with the 3-OH and 6-OH hydroxyl groups of each glucose unit in CD. The 3-OH and 6-OH hydroxyl groups occupied the wider and the narrower rim of the cone respectively. The CD cavity is essentially hydrophobic and can host a wide range of organic molecules.

The role played by β-CD in biphasic catalysis is attributed to their complex properties and we have proposed that β-CD operates as inverse PTC according to the mechanism depicted in Scheme 2. β-CD forms an inclusion complex with the substrate (such as 4-nitrobenzaldehyde and allyl bromide or benzyl bromide) in the organic phase and/or the liquid-liquid interface. Owing to its significant dispersion and solubility in water, the inclusion complex can migrate into the aqueous phase, allowing the substrate to react with the catalyst such as $NaBF_4$ and n-Bu_4NBr. After the reaction takes place, the product is released in the organic phase and the transfer cycle can occur.[8]

Scheme 2



In conclusion, the chemoselectivity of 4-nitrobezaldehyde reacted with allyl bromide or benzyl bromide was studied. The methodology here provides direct access to 4-(*N*-alkyl-*N*-alkyloxy) aminobenzaldehyde (**3b**), starting from organic halides by employing PTC and zinc powder, 4-(*N*-benzyl)aminobenzaldehyde (**4b**) and corresponding homoallylic alcohol starting from benzyl bromide (**2b**) or allyl bromide (**2a**) by using Zn and $SnCl_2$ in the presence of β-CD. The results showed that the benzylation and the allylation of 4-nitrobenzaldehyde could be controlled chemoselectively by using different PTC and different metal catalysts. As a result, we can extend this method to the compounds that contain both nitrogen electrophilic and carbon electrophilic centers to control the reaction chemoselectivity. The allylation can carry out in the carbonyl group of the compound that contains nitro group in water and the benzylation and allylation can carry out in the nitro group of the compound that contains carbonyl group in water, which extends the scope of organic reaction in aqueous media. More detailed studies on the mechanism and scope of the reaction are in progress.

A typical procedure of the allylation was as follows. To the solution of 0.150 g (1 mmol) of 4-nitrobezaldehyde and 20% mmol of PTC in 5 mL of distilled water (0.130—0.195 g, 2—3 mmol) of zinc powder and 0.18 mL (2 mmol) of allyl bromide was added. The reaction mixture was allowed to stir rigorously overnight and monitored by TLC. Then the solution was extracted by ethyl acetate and the organic layer was dried with anhydrous $MgSO_4$. After remove of the solvent, the residue was determined by ^1H NMR and GC-MS.

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9 IR (Perkin-Elmer, 2000 FTIR), ^{1}H NMR (CD_3Cl, 400 MHz), ^{13}C NMR ($CDCl_3$, 100 MHz) and MS-GC (HP5890 (II)/HP 5972, EI) spectroscopic data for:

4-(*N*-Allyl-*N*-allyloxy) aminobenzaldehyde (**3a**) Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.84 (s, 1H), 7.78 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 5.87—6.06 (m, 2H), 5.20—5.39 (m, 4H), 4.35—4.39 (m, 2H), 4.12—4.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.8, 155.6, 132.6, 132.2, 131.4, 129.7, 119.4, 119.0, 114.4, 74.9, 58.3; IR (NaCl) ν: 3080, 2978, 2925, 2734, 1692, 1598, 1569, 1507, 1421, 1310, 1220, 1166, 995, 928, 831 cm^{-1}; MS m/z calcd: 218.10961; found 218.1107 (CI, $M^+ + 1$)

4-(*N*-Benzyl-*N*-benzyloxy) aminobenzaldehyde (**3b**) Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.87 (s, 1H), 7.81 (d, J = 8.4, 2H), 7.27—7.42 (m, 10H), 7.18 (d, J = 8.4,2H), 4.71 (s, 2H), 4.65 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.8, 155.9, 136.4, 135.6, 131.4, 130.1, 129.1, 128.9, 128.5, 127.8, 114.8, 77.3, 60.7; IR (NaCl) ν: 3063, 3031, 2925, 2874, 2734, 1691, 1598, 1569, 1506, 1454, 1425, 1367, 1307, 1212, 1164, 1081, 1029, 829, 733, 698 cm^{-1}; MS m/z calcd: 318.1494; found 318.1490 (CI, $M^+ + 1$).

4-(*N*-Benzyl)aminobenzaldehyde (**4b**) Orange solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.75 (s, 1H), 7.66 (d, J = 8.8 Hz, 2H), 7.27—7.47 (m, 5H), 6.64 (d, J = 8.8 Hz, 2H), 4.66 (s, 1H), 4.42 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.6, 153.3, 137.9, 132.5, 128.9, 128.5, 127.8, 127.4, 112.1, 60.5; IR (KBr) ν: 3356, 3029, 2918, 2849, 2740, 1667, 1597, 1535, 1494, 1453, 1424, 1344, 1308, 1227, 1164, 1075, 1027, 826, 732, 698 cm^{-1}; MS m/z calcd: 212.1075; found 212.1075 (CI, $M^+ + 1$).

1-(4-Nitrophenyl)-3-buten-1-ol (**5a**) Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 5.73—5.84 (m, 1H) 5.20—5.22 (m, 1H), 5.15—5.20 (m, 1H), 4.86 (br, q, 1H), 2.53—2.60 (m, 1H), 2.41—2.50 (m, 1H), 2.24 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.1, 147.2, 133.2, 126.6, 123.6, 119.7, 72.2, 43.9; IR (NaCl) ν: 3404, 3080, 2920, 1642, 1604, 1519, 1347, 1108, 1056, 921, 855 cm^{-1} MS m/z calcd: 193.0739; found 193.0750 (EI, M^+).

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