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Silver catalyzed zinc Barbier reaction of benzylic halides in water

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Abstract: Benzylic chlorides react in aqueous dibasic potassium phosphate under silver catalysis with aromatic aldehydes in the presence of zinc dust to give 1,2-diaryl alcohols in moderate to good yields. Dimerization to bibenzyls and reduction of the halide are important side reactions. A wide range of substituted aromatic and heteroaromatic aldehydes and of substituted benzylic chlorides can be used. Aliphatic aldehydes and ketones are unreactive. A mechanism of two SET on the metal surface is discussed. © 1998 Elsevier Science Ltd. All rights reserved.

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Since the surprising discovery of the direct allylation of aldehydes and ketones by a Zn-Barbier reaction in aqueous solvents,[1] similar one step procedures using different types of organic halides have attracted growing interest during the past decade.[2] Cinnamyl [3] and propargyl halides,[4] α–bromo ketones [2d, 5] and esters [2c,d, 6] have been added sucessfully to aldehydes in the presence of zinc, tin, aluminium or indium. Analogous reactions of saturated halides have not been reported in the literature, except the 1,4-addition of secondary and tertiary alkyl halides to α,β–unsaturated carbonyl compounds.[7] Benzylic halides are known to react via cationic, radical or carbanionic intermediates with exceptional resonance stabilization, so it is surprising that no Barbier-type reaction in water has been reported.

Our first attempts with benzyl bromide, benzaldehyde and zinc dust in aqueous ammonium chloride/THF were rather disappointing: zinc dissolved in a few minutes in a slightly exothermic reaction, but toluene (**5**) was the only product and most of the aldehyde was recovered unchanged. In the absence of ammonium ions and organic cosolvent, 31 % of bibenzyl (**4**) was formed confirming the tendency of benzyl bromide to dimerize already observed in the absence of aldehyde.[8] However, careful examination of the crude extract of the reaction revealed the presence of 3 % of the expected 1,2-diphenylethanol (table 1, entry 1). In the hope to reduce the dimerization, benzyl chloride was reacted under the same conditions. Although large amounts of halide and

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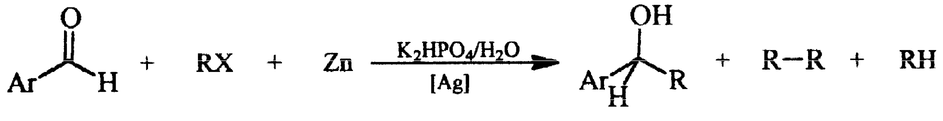

1 2 3 4 5

Table 1. Zn-Barbier reaction of benzylic halides and aromatic aldehydes in water at 30°C.[a]

entry	ArCHO 1 (mmol)	RX 2 (mmol)	salt solution	catalyst	unchanged[b]		yields (%)[b]		
					1	**2**	**3**	**4**	**5**
1	C_6H_5CHO (0.5)	$C_6H_5CH_2Br$ (1.5)	$CaCl_2$	-	35	-	3	31	49
2	C_6H_5CHO (0.5)	$C_6H_5CH_2Cl$ (1.5)	$CaCl_2$	-	44	64	9	-	29
3	C_6H_5CHO (0.5)	$C_6H_5CH_2Cl$ (1.5)	K_2HPO_4	-	46	47	31	-	29
4	C_6H_5CHO (0.5)	$C_6H_5CH_2Br$ (1.5)	K_2HPO_4	-	58	-	9	14	61
5	C_6H_5CHO (0.5)	$C_6H_5CH_2Cl$ (1.5)	K_2HPO_4	$Pb(OAc)_2$	15	28	47	-	32
6	C_6H_5CHO (0.5)	$C_6H_5CH_2Br$ (1.5)	K_2HPO_4	$Pb(OAc)_2$	74	-	15	17	52
7	C_6H_5CHO (0.5)	$C_6H_5CH_2Cl$ (0.75)	K_2HPO_4	$AgNO_3$	6	-	75	36	8
8	C_6H_5CHO (0.5)	$C_6H_5CH_2Br$ (0.75)	K_2HPO_4	$AgNO_3$	55	-	22	40	28
9	C_6H_5CHO (0.5)	$C_6H_5CH_2Cl$ (0.75)	K_2HPO_4/NaH_2PO_4	$AgNO_3$	10	-	61	15	25
10	C_6H_5CHO (0.5)	$C_6H_5CH_2Cl$ (0.75)	NaH_2PO_4	$AgNO_3$	-	-	24	-	36
11	C_6H_5CHO (0.5)	$(C_6H_5)_2CHCl$ (0.75)	K_2HPO_4	$AgNO_3$	17	-	36	27	11
12	C_6H_5CHO (0.5)	$C_6H_5CHCH_3Cl$ (0.75)	K_2HPO_4	$AgNO_3$	18	-	16[c]	56[d]	6
13	C_6H_5CHO (0.5)	$C_6H_5C(CH_3)_2Cl$ (0.75)	K_2HPO_4	$AgNO_3$	-	-	-	61	32
14	C_6H_5CHO (0.5)	4-CH_3O-$C_6H_4CH_2Cl$ (0.75)	K_2HPO_4	$AgNO_3$	14	-	62	42	15
15	C_6H_5CHO (0.5)	4-F-$C_6H_4CH_2Cl$ (0.75)	K_2HPO_4	$AgNO_3$	16	-	73	35	20
16	C_6H_5CHO (0.5)	1-$C_{10}H_7$-CH_2Cl (0.75)	K_2HPO_4	$AgNO_3$	24	-	60	35	20
17[e]	C_6H_5CHO (0.5)	2-C_5H_4N-CH_2Cl (0.75)	K_2HPO_4	$AgNO_3$	-	-	66	-	51
18[e]	C_6H_5CHO (0.5)	4-C_5H_4N-CH_2Cl (0.75)	K_2HPO_4	$AgNO_3$	-	-	64	-	48
19	2-$C_{10}H_7CHO$ (0.5)	$C_6H_5CH_2Cl$ (0.75)	K_2HPO_4/dioxane	$AgNO_3$	1	-	61	14	14
20	2-C_4H_3OCHO (0.5)	$C_6H_5CH_2Cl$ (0.75)	K_2HPO_4	$AgNO_3$	-	-	87	10	27
21	2-C_4H_3SCHO (0.5)	$C_6H_5CH_2Cl$ (0.75)	K_2HPO_4	$AgNO_3$	17	-	23	13	71
22	4-F-C_6H_4CHO (0.5)	$C_6H_5CH_2Cl$ (0.75)	K_2HPO_4	$AgNO_3$	4	-	70	39	17
23	4-Cl-C_6H_4CHO (0.5)	$C_6H_5CH_2Cl$ (0.75)	K_2HPO_4/CH_3OH	$AgNO_3$	1	-	60	32	23
24	4-CH_3O-C_6H_4CHO (0.5)	$C_6H_5CH_2Cl$ (1.5)	K_2HPO_4	$AgNO_3$	29	-	51	37	26
25	2,3-$(CH_3O)_2$-C_6H_3CHO (0.5)	$C_6H_5CH_2Cl$ (0.75)	K_2HPO_4	$AgNO_3$	9	-	46	19	7
26	3,4-$(CH_3O)_2$-C_6H_3CHO (0.5)	$C_6H_5CH_2Cl$ (0.75)	K_2HPO_4	$AgNO_3$	12	-	34	15	25
27[f]	2-HO-C_6H_4CHO (0.2)	$C_6H_5CH_2Cl$ (1.0)	K_2HPO_4	$AgNO_3$	12	-	31	22	56
28[f]	3-HO-C_6H_4CHO (0.2)	$C_6H_5CH_2Cl$ (1.0)	K_2HPO_4	$AgNO_3$	17	-	27	4	32
29[f]	4-HO-C_6H_4CHO (0.2)	$C_6H_5CH_2Cl$ (1.0)	K_2HPO_4	$AgNO_3$	4	-	9	2	28
30[f]	2-HO-3-CH_3O-C_6H_3CHO (0.2)	$C_6H_5CH_2Cl$ (1.0)	K_2HPO_4	$AgNO_3$	9	-	55	8	35
31[f]	3-HO-4-CH_3O-C_6H_3CHO (0.2)	$C_6H_5CH_2Cl$ (1.0)	K_2HPO_4	$AgNO_3$	41	-	24	5	37
32[f]	4-HO-3-CH_3O-C_6H_3CHO (0.2)	$C_6H_5CH_2Cl$ (1.0)	K_2HPO_4	$AgNO_3$	7	-	-	-	27

[a] *Standard procedure:* 2 mg of the catalyst and 1.5 g of the indicated salt or salt mixture (1:1) were dissolved in 1.5 mL of water at room temperature (30°C). A mixture of aldehyde, benzylic halide and, where indicated, 0.5 mL of cosolvent was added at once. Under efficient stirring, 2 mmol of commercial zinc dust were added portionwise over a period of 10 min. After 1 h of stirring, the mixture was acidified with 2 N HCl and extracted with 1 mL of CCl_4 containing 0.05 mmol of cyclohexane as internal quantitative reference. The extracts were analyzed directly by ^1H NMR and GC/MS. [b] Based on starting materials (aldehyde for **1** and **3**, halide for **2**, **4** and **5**) and determined by ^1H-NMR in relation to cyclohexane. [c] Mixture of threo/erythro (1:1). [d] Mixture of meso/dl (1:1). [e] Hydrolysis with 5 mL of 10 % NH_4OH. [f] The aldehyde was added first; extraction with $CHCl_3$.

aldehyde remained unreacted after 1 h, 9 % of addition and, more importantly, no dimerization at all were observed (entry 2). Some improvement was achieved by longer reaction time, but more important was the influence of pH: in dibasic potassium phosphate (pH ~12), 31% of the addition product was obtained; however, half of both starting materials remained unchanged (entry 3). Benzyl bromide reacted completely under these conditions in 1 h, producing 14 % of dimerization and only 9 % of addition (entry 4). More alkaline solutions, tribasic phosphate or even potassium hydroxide, did not increase the yield of addition product and caused decomposition of the aldehyde. In the following experiments the influence of metal catalysts was investigated under the conditions of entry 7. While copper catalyzed the dimerization,[8] lead suppressed this reaction completely and raised the yield of **3** to 47 % (entry 5). The most impressive results, however, were achieved with silver which produced complete transformation of benzyl chloride within 1 h, yielding 75 % of addition and only 8 % of reduction, leaving unreacted 6 % of benzaldehyde; the undesired dimerization was also catalyzed but could be reduced to 36 % using a lower excess of halide (entry 7). Under similar conditions, in the presence of lead or silver, benzyl bromide produced more addition product in comparison with the uncatalyzed reaction, but dimerization always predominated and most of the aldehyde remained unreacted (entries 6 and 8). Once more the importance of basic reaction conditions was confirmed: in a buffer of mono- and dibasic phosphate (pH ~8) the yields of both adduct **3** and dimer **4** decreased significantly and in monobasic phosphate (pH ~4) only 24 % of **3** and no **4** were observed (entries 9 and 10).

Under the standard conditions of experiment 7 various benzylic chlorides **2** of different structural type were reacted. Secondary benzylic chlorides gave less addition and more dimerization than benzyl chloride and the tertiary 2-chloro-2-phenylpropane produced only the dimer **4** and cumene **5** (entries 11-13). 4-Fluoro- and 4-methoxybenzyl chloride showed results comparable to the parent compound (entries 14 and 15). Also 1-chloromethylnaphthalene and 2- and 4-picolyl chloride gave satisfactory yields of **3** (entries 16-18); most noteworthy, the two heterocyclic compounds showed no tendency to dimerize.

The influence of the structure of the aldehyde was examined under standard conditions as before using benzyl chloride in all examples. The solid 2-naphthaldehyde needed dioxane as a cosolvent to guarantee satisfactory conversion and yield of adduct **3** (entry 19). 2-Furaldehyde gave excellent yield of addition, but its less electrophilic sulfur-analogue gave only 23 % (entries 20 and 21). 4-Substituted benzaldehydes also revealed decreasing reactivity with more electron donating substituents (entries 22-24). Two methoxy groups intensified the deactivating effect, especially in meta and para position (entries 25 and 26). Hydroxybenzaldehydes, potentially interesting substrates in aqueous Barbier reactions,[2,4,6] reacted only in part: 2-hydroxylated substrates gave weak to moderate yields when a 5-fold excess of halide was used (entries 27 and 30); their 3-hydroxy analogues still produced some addition (entries 28 and 31), but with 4-hydroxyaldehydes only traces of **3** could be detected (entries 29 and 32). All attempts to react α,β-unsaturated or aliphatic aldehydes failed. Acetophenone and its 1,1,1-trifluoro analogue were also unreactive. In all these cases, bibenzyl and toluene were the only products observed.

Although all experiments of this work were realized in microscale without preparative purposes in this moment, preparatively interesting yields of adducts **3** are obtained with many aromatic aldehydes and benzylic chlorides. The byproduct **4** can be easily removed by chromatography or distillation and **5** is volatile in most cases. For its experimental simplicity and safety this aqueous Barbier procedure can be an advantageous alternative to the traditional Grignard synthesis [9] of 1,2-diaryl-alcohols and their direct derivatives such as unsymmetrical stilbenes, 1,2-diaryl-alkanes and aryl-benzyl-ketones which can be easily obtained on dehydration, catalytic hydrogenation or oxidation.

From the mechanistic point of view, our observations can, at least, exclude some alternatives. A radical chain mechanism as evidenced for the aqueous Reformatsky reaction [6] can be excluded because neither radical initiators (peroxides) nor scavengers (galvinoxyl, 2,6-di-t-butyl-4-methylphenol) had any influence on the reaction. Furthermore, the different reactivity of benzyl bromide and chloride does not support a benzyl radical as a common intermediate for addition and dimerization. For the same reason and in view of the relatively weak pH dependence, a organometallic intermediate seems unlikely. A mechanism of two single electron transfers, as proposed by Li,[2a] is more consistent with part of the experimental observations. Most probably, these SET occur on the metal surface between adsorbed molecules. The observation that reduction to **5** can be minimized when zinc is added portionwise to the mixture of all other reagents, suggests a competition between the organic reactants and water for the metal surface. Preferential adsorption of different compounds can explain the catalytic effect of copper, silver and lead. The observed failure of the addition reaction in the case of 3- and 4-hydroxybenzaldehydes may be due to a more efficient adsorption via hydroxyl group, removing thus the carbonyl group from the reactive surface. Furthermore, the reduction product may arise from a similar process between halide and water; in concentrated alkaline salt solutions most of the active sites on the surface should be occupied by hydroxyl ions and not by water, and this may reduce this side reaction. A more detailed and satisfactory elucidation of this and other similar aqueous Barbier reactions will require much experimental and theoretical effort in the future.

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