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Zinc Barbier Reaction of Propargyl Halides in Water

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Abstract: The reaction of propargyl halides and carbonyl compounds with zinc powder proceeds in concentrated aqueous salt solutions affording with high selectivity homopropargylic alcohols. Preparatively useful yields are obtained with aromatic and aliphatic aldehydes. Ketones and 2-hydroxybenzaldehydes react partially. A surface process of two SET is discussed.

The *in situ* reaction of organic halides and carbonyl compounds in the presence of magnesium metal, described by Barbier in 1899,[1] was the precursor of the well known two-step Grignard reaction [2] which remained the dominant procedure for almost one century. In the last decades, the original one-step Barbier procedure has been performed with a wide variety of metals because of higher reactivity or better yields in many cases.[3] More recently, similar reactions in aqueous solvents using zinc, tin and indium produced surprisingly good preparative results.[4] The obvious advantages are the experimental safety and simplicity as well the possibility to use unprotected hydroxylated substrates such as sugars. However, most of the work was directed to the reaction of allylic halides which give, in general, excellent yields and high regio- and stereoselectivity with aldehydes and ketones.[4a] A few other publications refer to bromo ketones [4d, 5] and, more recently, to bromo esters.[4c,d, 6]

Propargyl bromide has been reported to add to aldehydes in the presence of tin in water,[7] but in all cases complex mixtures of acetylenic and allenic alcohols together with isomeric unsaturated ketones were obtained thus limiting the preparative utility of the procedure. The same problem of allene/acetylene isomerism has been observed in the indium mediated reaction, but in most examples one of the isomers was predominant.[8] Also the lead promoted Barbier reaction in DMF solution produced isomer mixtures.[9] Similarly, preformed allenic tin reagents reacted with aldehydes in water to give mainly the acetylenic alcohols together with 5-10 % of the allenic isomer.[10] On the other hand, organometallic reagents of titanium,[11] aluminium, magnesium and zinc [12] under anhydrous conditions and the Barbier procedure in dry benzene [13] have been reported to give only acetylenic products. These findings suggested that a lower oxidation potential of the metal favours the acetylenic product. We decided to examine in more detail the reactivity of zinc, historically the first metal used for the preparation of isolated, stable organometallic compounds [14] and for synthetically useful C-C bond forming reactions,[15] because of its impressive results in similar aqueous Barbier processes with allylic halides and bromo esters.[4,6]

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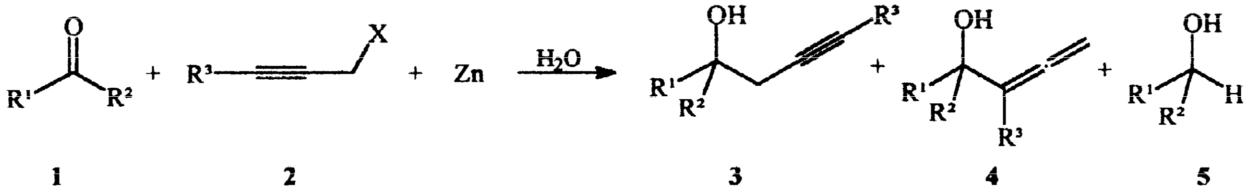

Table 1. Zn-Barbier reaction of carbonyl compounds and propargyl halides in aqueous medium.[a]

				Yields(%)[b]			
Entry	Substrate 1 (mmol)	Halide 2	Solvent	1	3	4	5
1	C_6H_5CHO (1.0)	$HCCCH_2Cl$	NH_4Cl	16	35	1	6
2	C_6H_5CHO (1.0)	$HCCCH_2Br$	NH_4Cl	22	15	trace	18
3	C_6H_5CHO (1.0)	$HCCCH_2Cl$	NaH_2PO_4	24	6	trace	3
4	C_6H_5CHO (1.0)	$HCCCH_2Cl$	K_2HPO_4	19	5	trace	1
5	C_6H_5CHO (1.0)	$HCCCH_2Br$	K_2HPO_4	20	33	1	1
6	C_6H_5CHO (1.0)	$HCCCH_2Cl$	$CaCl_2$ / NH_4Cl	7	65	2	2
7	C_6H_5CHO (1.0)	$HCCCH_2Cl$	$CaCl_2$ / NH_4Cl / THF	3	85	3	-
8	C_6H_5CHO (1.0)	$HCCCH_2Br$	$CaCl_2$ / NH_4Cl	12	78	2	5
9	C_6H_5CHO (1.0)	$HCCCH_2Br$	$CaCl_2$ / NH_4Cl / THF	3	83	3	6
10[c]	C_6H_5CHO (1.0)	$HCCCH_2Cl$	$CaCl_2$ / NH_4Cl	70	5	trace	-
11[c]	C_6H_5CHO (1.0)	$HCCCH_2Br$	$CaCl_2$ / NH_4Cl	22	59	2	2
12	C_6H_5CHO (0.5)	CH_3CCCH_2Br	NH_4Cl	5	19	53	-
13	C_6H_5CHO (0.5)	CH_3CCCH_2Br	K_2HPO_4	7	28	40	-
14	4-F-C_6H_4CHO (0.5)	$HCCCH_2Cl$	NH_4Cl / dioxane	4	70	6	5
15	4-Cl-C_6H_4CHO (0.5)	$HCCCH_2Cl$	NH_4Cl / dioxane	-	38	3	4
16	4-CH_3O-C_6H_4CHO (0.5)	$HCCCH_2Cl$	$CaCl_2$ / NH_4Cl / dioxane	39	44	trace	12
17	2,3-$(CH_3O)_2C_6H_3CHO$ (0.5)	$HCCCH_2Br$	$CaCl_2$ / NH_4Cl / dioxane				
18	3,4-$(CH_3O)_2C_6H_3CHO$ (0.5)	$HCCCH_2Br$	$CaCl_2$ / NH_4Cl / dioxane	6	54	trace	12
19	2-$C_{10}H_7CHO$ (0.5)	$HCCCH_2Cl$	NH_4Cl / dioxane	3	73	trace	6
20	2-C_4H_3OCHO (0.5)	$HCCCH_2Cl$	$CaCl_2$ / NH_4Cl / THF	-	72	trace	12
21	2-C_4H_3SCHO (0.5)	$HCCCH_2Br$	$CaCl_2$ / NH_4Cl / THF	-	74	trace	15
22	$C_6H_5CHCHCHO$ (0.5)	$HCCCH_2Br$	$CaCl_2$ / NH_4Cl / dioxane	-	66	trace	-
23	$(CH_3)_2CHCHO$ (0.5)	$HCCCH_2Br$	$CaCl_2$ / NH_4Cl	5	60	10	-
24	$C_6H_5CH_2CH_2CHO$ (0.5)	$HCCCH_2Br$	K_2HPO_4 / dioxane	12	72	3	-
25	$C_6H_5COCH_3$ (0.5)	$HCCCH_2Br$	K_2HPO_4	69	16	-	-
26	4-F-$C_6H_4COCH_3$ (0.5)	$HCCCH_2Br$	K_2HPO_4	53	10	-	-
27	$C_6H_5COCF_3$ (0.5)	$HCCCH_2Br$	K_2HPO_4 / dioxane	44	46	4	-
28	2-HO-C_6H_4CHO (0.5)	$HCCCH_2Cl$	$NH_4H_2PO_4/H_3PO_4$/MeOH	36	30	-	-
29	2-HO-3-CH_3O-C_6H_3CHO (0.5)	$HCCCH_2Cl$	$NH_4H_2PO_4/H_3PO_4$/MeOH	55	34	-	-

[a] Typical procedure: 3 mmol of zinc powder were added to 2 ml of the indicated concentrated salt solution and stirred for 5 min. A mixture of carbonyl compound, halide and (where indicated) 0.5 ml of organic cosolvent was added at once. After stirring for 1 h, the reaction was acidified with 2 N HCl and extracted with 1 ml of CCl_4 or $CHCl_3$ (entries 14, 15, 28 and 29) containing 0.05 mmol of cyclohexane as internal quantitative standard. [b] Determined by ^{1}H-NMR (**1**, **3** and **5** in relation to cyclohexane) and GC/MS (**4** in relation to **3**). [c] Granulated zinc was used.

Our first attempts used benzaldehyde as carbonyl substrate which has demonstrated superior reactivity in all reactions mentioned before. When a mixture of this reagent with 1.5 equivalent of propargyl chloride was added to a vigourously stirred suspension of excess zinc powder in concentrated ammonium chloride solution, most of the metal dissolved within 1 h. After acid hydrolysis and extraction, the ^{1}H-NMR spectrum of the crude extract revealed a 35 % yield of the expected homopropargylic alcohol **3** together with 16 % of unreacted aldehyde **1** and 6 % of benzyl alcohol (**5**); 1 % of the isomeric allenic alcohol **4** could be detected by GC/MS analysis (Table 1, entry 1). The same reaction using propargyl bromide was rather exothermic and much faster, but produced more reduction and less addition (entry 2). Use of more acidic or more alkaline salt solutions also caused lower yields (entries 3-5). Best results were achieved in a solvent mixture which had already been successfully applied in the Reformatsky reaction:[6] saturated calcium chloride solution containing 10 % of ammonium chloride (entries 6 and 8); in the absence of the latter, both halides proved to be completely unreactive. Further improvement was achieved using THF as a cosolvent raising the yield of **3** to 83-85 % (entries 7 and 9); only 3 % of the allenic isomer **4** together with very small amounts of aldehyde **1** and reduction product **5** were observed. Under these conditions, even granulated zinc gave reasonable yields with the bromide, whereas the reactivity of the chloride was insufficient (entries 10 and 11). In all these experiments, the regioselectivity of the coupling was much higher than in the case of aqueous Sn or In promoted reactions.[7,8] With 1-bromo-2-butyne or other substituted propargylic halides, most of the known procedures are reported to give exclusively the allenic alcohols **4**; in our Zn promoted reaction, **4** was the major product, but considerable amounts of unrearranged acetylenic alcohol **3** were also observed (entries 12 and 13). Most interesting is the increase of **3** in basic medium.

Coming back to the reaction of the parent propargylic halides, we investigated the influence of the structure of the carbonyl compound. 4-Substituted benzaldehydes gave satisfactory yields using a threefold excess of the chloride (entries 14-16), whereas the bromide gave considerable amounts of reduction. When two methoxy groups were present (entries 17 and 18), the 2,3-substituted aldehyde produced higher transformation rates and better yields than the 3,4-substituted isomer. Naphthalenic and heteroaromatic aldehydes also reacted with good yields (entries 19-21), as well as cinnamic, hydrocinnamic and isobutyraldehyde (entries 22-24). In most of the last examples, the allenic alcohols **4** could be detected only in trace amounts with exception of 4-fluoro- and 4-chlorobenzaldehyde and isobutyraldehyde which showed isomer ratios **3** : **4** between 10 : 1 and 6 : 1. Even acetophenone, which is unreactive in the Sn and In promoted reaction, produced some addition when reacted under basic conditions (entries 25-27); introduction of an electronwithdrawing fluorine atom in the aromatic ring brought no increase of reactivity, but 2,2,2-trifluoroacetophenone gave 46 % of **3** together with 4 % of the allenic isomer **4**.

One of the most attractive aspects of organometallic reactions in water is the possibility to use unprotected substrates bearing hydroxy or other acidic groups. Unfortunately, our procedure had very restricted success with hydroxybenzaldehydes. Only salicylaldehyde and o-vanilline gave partial transformation to acetylenic alcohols **3** (entries 28 and 29); their 3- and 4-hydroxylated isomers were completely unreactive. Most surprisingly, the positive results were achieved in rather acidic medium (1 M phosphoric acid), under neutral or basic conditions no addition at all was observed.

Our results allow also some mechanistic conclusions. A free radical pathway, as recently evidenced for the Reformatsky reaction in water,[6] can be excluded because neither radical scavengers (galvinoxyl or hydroquinone) nor radical initiators (peracids or benzoyl peroxide) have any influence on the reaction. Organometallic intermediates may be involved in the Sn promoted reaction as suggested by the easy addition of preformed reagents in water,[7,9] but seem less probable in our case because of the higher reactivity of Zn-organic compounds; furthermore, the weak influence of pH observed in our reactions does not support strongly basic intermediates. Also the different reactivity of propargyl chloride and bromide points to a mechanism where the carbon-halogen bond breaks in the rate determining step. The strong decrease of yield with granulated zinc indicates that a surface process must be involved. Such a mechanism of two separate SET on the metal surface, first to the halide and then to its aggregate with the carbonyl compound, has already been proposed for similar reactions.[4a]

In summary, the zinc promoted Barbier reaction of propargyl halides proceeds in moderate to good yields with aromatic, heteroaromatic, unsaturated and aliphatic aldehydes. In many cases, the less expensive chloride can be used. Organic cosolvents like THF or dioxane enhance the yields especially with solid substrates. In all examples studied, high regioselectivity in favour of the homopropargylic alcohols **3** is observed, comparable to the addition of Mg, Zn and Al-reagents under anhydrous conditions.[12,13] Ketones and o-hydroxybenzaldehydes give only partial transformation. The most important conclusion from our experiments may be the demonstration that organometallic reactions in water are more general and useful than suggested by the predominance of work on allylic systems in the last years. It can be expected that other conjugated or even saturated halides undergo similar transformations. Also mechanistic studies seem to keep some surprise for the future.

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