SILVER-TIN MEDIATED ALLYLATIONS IN AQUEOUS MEDIA

Eugen ANDREIADIS, George MARTON and Anca MARTON[*]

Faculty of Applied Chemistry and Materials Science, "Politehnica" University of Bucharest, Splaiul Independentei 313, 060042 Bucharest, Roumania

Silver-tin mediated allylations of several carbonylic compounds are presented. The reactions show better yields compared to other mediation systems, such as those based on Sn and/or stannous salts. Chemoselectivity of the silver-tin mediating system is much similar to that offered by other Barbier systems. Optimization of the process was also attempted by a study of the reaction parameters.

INTRODUCTION

The carbon-carbon bond formation is a subject of high interest for the organic synthesis and its achievement using certain inorganic salts and metals in aqueous media is a spectacular progress in the field.

Metal mediated allylation of carbonyl derivatives, or even of heterocycles,[1] also known as Barbier reaction, presents some important advantages when carried out in water, such as avoidance of flammable and/or anhydrous solvents, reduced aggressiveness towards the environment, easy separation of the target compounds.

The reactions of this type probably involve an organometallic reagent: it may be obtained in a previous step (case of the Grignard method), or generated "*in situ*" (present case, the Barbier variant). Besides this feature, another major difference between these two reactions is the presence of water: avoided even in traces in any Grignard synthesis, water may become the major solvent (if not the only one in most cases) in the Barbier allylations.[2]

The general reaction may be formulated:
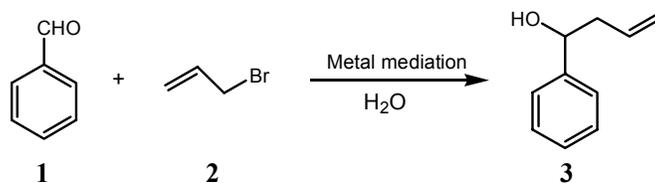
Scheme 1 – The Barbier allylation of benzaldehyde.

The metals generally used were Sn, Zn, Bi, Pb, Cd, In, which are all available, not very expensive, showing a reduced toxicity. The studies on the subject progressively added new facts: enlargement of the scale of metals, addition of supplemental powdered metals (such as aluminium[3,4]), in order to improve the yield, or the use – for the same purpose – of heat, or ultrasounds[5-7]. As a general principle, the metals used in the Barbier synthesis should be less reactive towards water, and the oxides usually formed on their surface

[*] Corresponding author: e-mail: al_marton@chim.upb.ro

should not be water insoluble, as those of Al or Ti. Still, they should be more reactive than silicon or germanium.

The organic halides are merely those with increased reactivity: allylic, propargylic, less usual the benzylic[8,9] and almost never the aliphatic ones. The nature of the halogen also counts.[10,11]

The carbonyl reagents were both aldehydes and ketones, aromatic, but also aliphatic, variously substituted. The reactivity of all major participants in the Barbier reaction – the carbonyl derivative, the halide and the metal – is governed by their reduction potential.[2,12,13]

It was also reported[14] that certain salts of transitional metals positively influence the yields of some $SnCl_2$ mediated allylations: the presence of Lewis acids ($AlCl_3$, $TiCl_4$, BF_3, $SnCl_4$, $ZrCl_4$) dramatically improved the yields of nitriles' allylation, leading to allyl ketones.[15] The use of such Lewis catalysts is also increasing the reactivity of aliphatic aldehydes, but not that of ketones, [16] in Barbier reactions.

Another influencing factor was the use of phase transfer catalysts (PTC)[7,17] that shortened the reaction time, increased the stereoselectivity of the reaction and enabled milder conditions.

All these experimental facts allowed the development of various mechanisms[8,12,16,18-20] for the Barbier reactions, the matter still being unsettled due to the multitude of arguments and counterarguments. The proposed mechanism variants are related to the chemo-and stereoselectivity of this reaction.[6,10,11,19,20]

The aim of the present research was to study the silver-tin mediated aqueous Barbier allylations as an original contribution in the field, since literature data are rather poor for such attempts (only silver-zinc and silver-magnesium mediated, and solely benzylations, were reported so far[8,9]). In this respect, silver-tin mediated systems were compared − in the same reaction conditions − to the most frequently reported tin mediated ones. Since our experiments proved to be successful, we continued the research testing the reactivity of various carbonyl derivatives. Finally, the chemoselectivity and the influence of reaction parameters (reaction time, reaction temperature, molar ratio) were also targeted.

RESULTS AND DISCUSSION

1. Mediation system tested for benzaldehyde and allyl bromide

The study of metallic tin and silver (Sn+Ag) as mediating system, compared to systems based on tin and/or tin salts, was the main target of the present research. Metallic silver was generated *in situ* from a solution of silver nitrate, being reduced by tin. In order to activate the metallic surfaces, ammonium nitrate was added to the reaction system. The procedure involved stirring of all reagents for 24 hours followed by extraction with dichloromethane, and the extract submitted to a GC-MS analysis. The above reaction was performed in such conditions to allow a comparison with other three experiments using different systems based on tin. Using the GC data, the areas of the peaks are obtained by integration, which in turn can be roughly correlated to the number of moles of every component present in the sample. In this way, an approximate yield can be computed for each reaction. The results are presented in Table 1.

Table 1

Experimental yields for the mediation system test

No.	Mediating system	Lit.	Yield (%) (GC-MS)
1	Metallic tin in water (Sn/H_2O)	4	96
2	Stannous dichloride over copper ($SnCl_2$ + Cu)	10,11	95
3	Stannous dichloride and potassium iodide ($SnCl_2$ + KI)	21	83
4	Metallic tin and silver (Sn + Ag)	-	100[1]

[1] When this reaction was carried out again, this time using quantities four times larger (10 mmol of benzaldehyde) and the final product separated after the extraction solvent was evaporated, the practical yield of the reaction was 78%.

In order to check if it was not the influence of ammonium nitrate alone that improved the process, reaction 4 was repeated without introducing silver nitrate. All the other reaction parameters and the working-up methodology were maintained unchanged. The yield was of only 81% this time. This result may be

explained by the influence that the in-situ generated silver has upon the rate of the reaction. The experimental results might suggest (for the moment only as a hypothese) the following patterns of mechanism (Scheme 2):
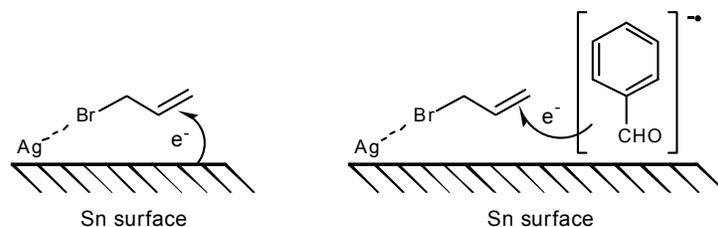
Scheme 2 – Possible effect of silver on tin-promoted allylation reactions.

The Ag atoms reduced from silver nitrate by tin on tin's surface could make the allyl halide either easier to reduce by Sn metal, or easier to be attacked by the benzaldehyde radical anion, probably by reducing the first ionization potential of the system.

2. Compared reactivity of various carbonyl reagents

The reactivity of the silver-tin mediation couple was studied using various carbonyl compounds. The reactions were run at room temperature using the same allylation reagent (3-bromoprop-1-ene).

It can be noticed that the reaction proceeds very well in most cases, giving good to excellent yields. With the exception of 2-chlorobenzaldehyde, where the yield was much lower, all the aromatic aldehydes behave similarly to benzaldehyde. It is important to note that in the reactions 2, 3 and 4, the chromatogram showed a peak due to the dehydrated reaction product, probably formed during the analysis, where extreme conditions in the MS detector favoured the dehydration. Curiously enough, the reaction with crotonaldehyde afforded a very complex chromatogram. An exact determination of the reaction products proved to be impossible with only this data. As expected from other works in the field, acetophenone gave a rather low yield compared to the rest of the compounds, because of its less active carbonyl moiety.
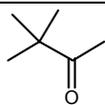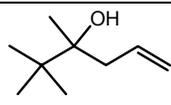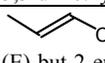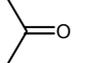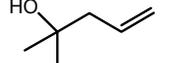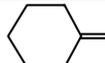
Table 2

Compared reactivity of various substrates in the silver mediated allylation

No	Carbonyl compound	Quantity (mmole)	Molar ratio carbonyl: halide	React time (h)	Product	Yield [1] (%)
1	Cl / —CHO **4** / 2-chlorobenzaldehyde	5.0	1: 1.5	18	Cl / OH **13** / 1-(2-chlorophenyl)-but-3-en-1-ol	35[2]
2	H₃CO—⬡—CHO **5** / 4-methoxybenzaldehyde	5.0	1: 1.5	17	H₃CO— / OH **14** / 1-(4-methoxyphenyl)but-3-en-1-ol	100
3	OH / —CHO **6** / 2-hydroxybenzaldehyde	5.0	1: 1.5	4	OH / OH **15** / 2-(1-hydroxybut-3-enyl) phenol	99

Table 2 (continues)

Table 2 (continued)

4	3,3-dimethylbutan-2-one **7**	5.0	1: 1.5	10	2,2,3-trimethylhex-5-en -3-ol	**16**	97
5	(E)-but-2-enal **8**	5.0	1: 1.5	20	several products[2]		—
6	propan-2-one **9**	5.0	1: 1.5	18	2-methylpent-4-en-2-ol	**17**	—[3]
7	cyclohexanone **10**	2.5	1 : 2	20	1-allylcyclohexanol	**18**	100
8	acetophenone **11**	2.5	1 : 2	18	2-phenylpent-4-en-2-ol	**19**	76
9	2H-chromen-2-one **12**	2.5	1 : 2	8	no product		0
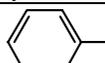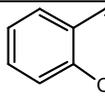
[1] the yields of the reactions are calculated by integration of GC peaks;
[2] many peaks in the GC-MS; exact assignments impossible;
[3] no acetone peak in the GC-MS due to its high volatility; chromatographic yield calculation impossible.

3. Chemoselectivity

Although the reactions occur in very good yields from aldehydes and ketones alike, as seen from the previous study on reactivity, we investigated the possibility of a chemical selectivity permitting a discrimination between these two functionalities. Crossed experiments revealed indeed that such a selectivity is easily obtained, the aldehyde being the most reactive, as expected. The observed selectivity towards the aldehyde function is probably due to a kinetic control.

Two competitive experiments have been performed, one to test the reactivity of an aldehyde together with a ketone, and another to discriminate between several ketones. All the carbonyl compounds were introduced in equimolar amounts, the same as the allylating reagent. The reactions were carried out at room temperature. The conversions (for each compound) are calculated by integration of GC-MS data (Tab. 3) .

Table 3

Experiments for testing the chemoselectivity of the Barbier allylation

No.	Carbonyl compounds	Quantity (mmole each)	Molar ratio (each carbonyl: halide)	React time (h)	Expected products of allylation	Conversion (% each)
1	Benzaldehyde + cyclohexanone	2.5	1: 1	4	1-phenyl-but-3-en-1-ol + 1-allylcyclohexanol	100 0
2	Acetone + Cyclohexanone + Acetophenone	2.5	1: 1	18	2-methylpent-4-en-2-ol + 1-allylcyclohexanol + 2-phenylpent-4-en-2-ol	10 85 5

For the first experiment, the chromatogram showed no peak corresponding to benzaldehyde, implying that the allylation occurred quantitatively. In the second experiment, the ketones gave the allylation products

in the following yields: cyclohexanone (85%), acetophenone (5%) and acetone (10%). Although further experiments are necessary for providing a consistent explanation, this result is very promising, showing that different ketones can be selectively allylated. The reason for the difference in reactivity seems to be of stereochemical nature: these results are in agreement with the dihedral angle formed by the bonds between the following atoms: oxygen – carbonylic carbon – the α sp^3 carbon and the next sp^3 carbon (in cyclohexanone) or one hydrogen atom from the same α sp^3 carbon (in acetone and acetophenone). Ab-initio computations of the molecular geometry where performed with Hyperchem 7.5 and 6-31*G basis set. The values for the above specified dihedral angle in acetone, cyclohexanone and acetophenone are of 120.84, 132.47 and 119.87 respectively. It can be seen that the larger the angle, the higher the conversion.

4. Study of reaction parameters: reaction time, temperature, molar ratio

Further experiments have been performed on the tin-silver nitrate mediation couple in order to establish the best reaction conditions. Benzaldehyde was used as reference substrate, and allyl bromide as allylation agent. Experiments were performed according to the general procedure presented.

The reaction time was varied from 30 min to 1 h 45 min to 3 h at room temperature. The molar ratio benzaldehyde to allyl bromide was 1:1.5. The extracts were analysed by GC-MS and the calculated yields for each case show that after only 3 hours benzaldehyde was completely allylated.

The reaction was run for 30 min at room temperature (20°C) and at 50°C, respectively. The other parameters and the working-up of the reaction mixture were kept unchanged (same as above). At room temperature the yield was very modest, but an increase of only 30°C produced quantitative allylation.

The molar ratio benzaldehyde to allyl bromide initially used was 1:2, affording quantitative transformation. We tried to lower this ratio and observe the effect it had on the reaction yield and found that the reaction has proceeded equally well when a 1:1.5 molar ratio was employed, and even when an equimolar ratio was used (however, tin was used in a slight excess, in order to cover a possible oxidation due to storage). Silver acts as a catalyst, and its molar ratio to carbonyl was 0.1 or lower. All these results are summarized in Tab. 4.

Table 4

Influence of the reaction time, temperature and molar ratio over the yield

a) Variation of reaction time (room temp.)			b) Variation of reaction temperature (30 min)			c) Variation of molar ratio		
No.	Time (min)	Yield (%) (GC-MS)	No.	Temp.	Yield (%) (GC-MS)	No.	Molar ratio carbonyl:halide:tin	Yield (%) (GC-MS)
1	30	8	1	20°C	8	1	1:2:2	100
2	105	45	2	50°C	100	2	1:1.5:1.5	100
3	180	100				3	1:1:1.5	100

EXPERIMENTAL PART

Allylation mediated by tin and silver (Sn + Ag)[1]: In a 50 mL round bottomed flask 10 mL of an aqueous 0.01 M AgNO$_3$ and 0.1 M NH$_4$NO$_3$ solution (0.1 mmol, 0.017 g AgNO$_3$ and 1 mmol, 0.08 g NH$_4$NO$_3$) are introduced. Then 0.25 mL (0.265 g, 2.5 mmol) freshly distilled benzoic aldehyde and 0.42 mL (0.605 g, 5 mmol) allyl bromide (3-bromoprop-1-ene), followed by 0.6 g (5 mmol) tin powder, are added. The flask is loosely stoppered and the mixture is allowed to react under vigorous magnetic stirring at room temperature for 24 h.[2] The resulting mixture is quantitatively vacuum filtered using a frit, to separate the inorganic salts and break the emulsion. Both the cake and the filtrate are extracted with 2 × 5 mL dichloromethane each. The combined organic layers are washed with 2 × 20 mL of water and dried over anhydrous magnesium sulfate (MgSO$_4$). The organic phase is filtered and analysed by GC-MS without further purification.

Observation: The allylations no. 1-3 presented in Table 1, were performed according to the literature cited; the other experiments, in various conditions were performed accordingly.

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[1] For experiment no. 4 in Tab. 1

[2] The 24 hours reaction time was set only for this particular experiment, to allow a comparison with other systems also presented in Tab. 1. For other experiments described, the conditions varied, being accordingly specified.

CONCLUSIONS

The tin-silver mediation couple, used for the aqueous Barbier allylation reaction of benzaldehyde, gives an excellent yield compared to other known tin-based mediators. We tested the reactivity of this metallic system on several compounds containing a carbonyl moiety and obtained very good results on most of the substrates, regardless if they were aldehydes or ketones. A competitive experiment showed, as expected, that the mediating system exhibits a marked selectivity for the aldehydes, compared with the ketones, and moreover, that a possibility for differentiating between various ketones exists. The optimization experiments showed that equimolar amounts of benzaldehyde and allyl bromide can be successfully used, and that the reaction is complete in 3 hours at room temperature and only 30 min at 50ºC. We can therefore conclude that the tin-silver couple is a very good mediator for the aqueous allylation reaction.

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