

First Magnesium-mediated Carbonyl Benzylation in Water

DENG, Wei(邓维) TAN, Xiang-Hui(谭翔辉) LIU, Lei(刘磊)
GUO, Qing-Xiang*(郭庆祥)

Department of Chemistry, University of Science and Technology of China, Hefei 230026, China

Catalyzed by AgNO₃, Mg was found for the first time to be able to mediate the coupling reaction between aromatic aldehydes and benzyl bromide or chloride in water. The yields were slightly higher than the recent results for Mg-mediated allylation despite the fact that aqueous benzylation is intrinsically much harder than allylation. It was also found that the coupling reaction was chemoselective for aromatic aldehydes over aliphatic aldehydes, and chemoselective for aromatic aldehydes over aromatic ketones.

Keywords green chemistry, aqueous medium, Barbier reaction, Mg, chemoselectivity

Introduction

Barbier reaction, originally referred to the Mg-mediated coupling between a carbonyl compound and an organic halide, is a one-pot variant of Grignard reaction.¹ Because of its operational simplicity, Barbier reaction is very useful in synthetic organic and pharmaceutical chemistry. Recently, it was discovered that Barbier reaction can occur in aqueous media, despite that organometallic compounds are usually unstable in water.² This finding has attracted considerable attention, not only because of its intriguing mechanism, but also because of the increasing public interest in green chemistry.³

So far considerable efforts have been devoted to the Barbier reaction of allyl halides. Metals including In,⁴ Sb,⁵ Bi,⁶ Pb,⁷ Mn,⁸ Mg,⁹ Zn,¹⁰ and Sn¹¹ have been found to be able to mediate carbonyl allylation in water. Good chemoselectivity (*e.g.* aldehyde over ketone, aromatic carbonyl over aliphatic carbonyl) and stereo selectivity have also been established.⁵⁻¹¹ At this point, it is worthy to note that despite the great achievement in aqueous allylation, very little progress has been made for the aqueous Barbier-type benzylation of carbonyl compounds.¹² To our knowledge the only study on the aqueous benzylation was reported by Bieber *et al.*¹³ They found that in K₂HPO₄ buffer Zn could mediate the coupling between benzyl chloride and benzaldehyde with about 40%—60% yields.

The reason for the lack of study on aqueous benzylation is that benzylation is intrinsically much harder to achieve than allylation. In fact, in our recent studies of SnCl₂/Cu- and SnCl₂/TiCl₃-mediated allylation in water, we observed no benzylation products even though allylation was almost quantitative under the same reaction conditions.¹⁴ Despite this difficulty, in order to expand

the scope of C—C bond coupling reactions in water, we considered it to be necessary to study the Barbier-type benzylation in aqueous media.

Therefore, we recently initiated a project to study the method and mechanism of aqueous benzylation. We started our study on aqueous benzylation using the prototype metal in the classic Barbier reaction, Mg. This makes the study even more challenging because organomagnesium compounds are definitely unstable in water. Nevertheless, Li *et al.*⁹ recently showed that Mg could mediate the coupling between carbonyl compounds and allyl iodide reasonably well in aqueous NH₄Cl solutions (yield 27%—58%). Thus we wished to know if we could achieve similar or better results for the aqueous benzylation.

Results and discussion

Initially we used Li's Mg/NH₄Cl procedure to couple benzyl bromide and benzaldehyde (See Entry 1 of Table 1). However, pinacol coupling products were found to be the major products. After a careful examination of the crude extract of the reaction mixture we found a yield of only 7.3% for the desired benzylation product. We also observed a significant yield (15.6%) for benzyl alcohol, a reduced product from benzaldehyde. Thus, Li's procedure fails in the aqueous benzylation. This result shows again that benzylation is intrinsically much harder than allylation.

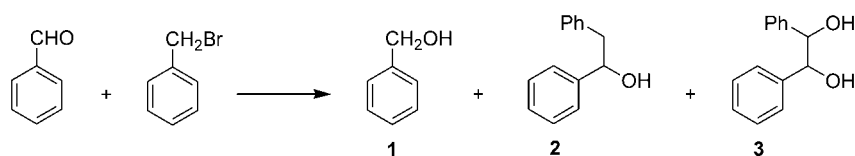
Lowering the reaction temperature, results in more pinacol coupling products but less benzylation product (Entry 2). Ultrasonic radiation¹⁵ does not improve the benzylation, either (Entry 3). Nevertheless, addition of ethanol slightly increases the yield of benzylation product to 19.5% (Entry 4).

Lewis acids are known to be able to promote aque-

* E-mail: qxguo@ustc.edu.cn

Received September 16, 2003; revised March 9, 2004; accepted March 29, 2004.

Project supported by the National Natural Science Foundation of China (No. 20332020).

Table 1 Products of the Mg-mediated benzylation under different conditions

Entry	Condition	Yield/%				
		Benzaldehyde (unchanged)	1	2	3-threo	3-erythro
1	Mg+NH ₄ Cl	8.0	15.6	7.3	38.2	30.8
2	Mg+NH ₄ Cl (0 °C)	2.4	7.8	4.6	46.2	38.9
3	Mg+NH ₄ Cl+ultrasonic	3.3	8.1	6.7	46.5	35.4
4	Mg+NH ₄ Cl+EtOH/H ₂ O (1 : 1)	8.8	14.3	19.5	33.7	23.7
5	Mg+NH ₄ Cl+BiCl ₃	6.8	20.4	9.8	34.3	28.6
6	Mg+NH ₄ Cl+FeSO ₄	2.2	13.1	7.9	43.6	33.2
7	Mg+NH ₄ Cl+ZnCl ₂	3.9	16.4	6.1	43.7	29.8
8	Mg+NH ₄ Cl+SnCl ₂	8.4	15.9	8.1	37.8	29.8
9	Mg+NH ₄ Cl+SnCl ₂ (0 °C)	11.8	31.6	5.8	22.7	28.1
10	Mg+NH ₄ Cl+CuCl	10.7	28.7	6.3	27.4	26.8
11	Mg+NH ₄ Cl+CuCl (0 °C)	8.3	54.1	3.6	13.9	20.1
12	Mg+NH ₄ Cl+Cu	7.1	37.4	10.4	22.2	22.8
13	Mg+K ₂ HPO ₄ +AgNO ₃	6.8	28.3	9.2	30.6	25.2
14	Mg+NH ₄ NO ₃ +AgNO ₃	4.8	35.8	44.5	11.7	3.2

ous Barbier reactions.¹⁶ Therefore, we added a number of Lewis acids to the reaction mixture. We found that the addition of BiCl₃, FeSO₄, or SnCl₂ improves the benzylation slightly (Entries 5, 6, and 8). However, the addition of ZnCl₂ or CuCl decreases the yield of benzylation product (Entries 7 and 10). Moreover, it was found that addition of CuCl (or Cu) would considerably promote the reduction of benzaldehyde to benzyl alcohol. Meanwhile, CuCl (or Cu) significantly lowers the yields of pinacol coupling products.

Despite the above low yields, when we conducted the Mg-mediated benzylation in the presence of AgNO₃ in an NH₄NO₃ solution, we were very pleased to see a significant yield of the desired benzylation product (44.5%) (Entry 14). Much less pinacol coupling products were obtained under this reaction condition. Nonetheless, the reduction of benzaldehyde to benzyl alcohol is a significant side reaction (yield 35.8%).

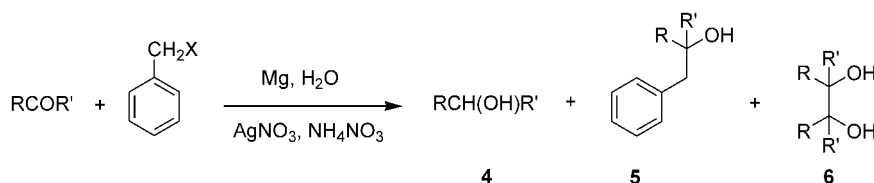
It is worthy to mention that the yield of this benzylation reaction (44.5%) is slightly lower than Bieber's result using Zn (40%—60%).¹³ However, it should be noted that Mg-mediated aqueous allylation also gives much lower yields than Zn-mediated allylation, simply because Mg is much more reactive than Zn in water.⁹ Also, Li *et al.*⁹ found that Mg-mediated allylation of benzaldehyde gives a yield of 58% of the desired product. This yield is only slightly better than that of our benzylation reaction, but one must bear in mind that benzylation is intrinsically much harder than allylation. Moreover, it should be mentioned that Li's yield of 58%

was obtained when allyl iodide was used. When allyl bromide was used, the yield decreased to 41%, a value actually lower than our benzylation using benzyl bromide. Therefore, comparing with Bieber's and Li's results we can conclude that our aqueous benzylation with Mg is successful.

We used the above procedure to benzylate a number of carbonyl compounds. The results are summarized in Table 2. According to Table 2, various substituted benzaldehydes can be well benzylated giving little or no pinacol coupling products (Entries 1—10). 2-Furaldehyde can also be successfully benzylated (Entries 11 and 12). Nevertheless, *p*-nitrobenzaldehyde or *o*-nitrobenzaldehyde, when treated with Mg/AgNO₃/NH₄NO₃, gives a complex mixture containing no desired benzylation product (results not shown in Table 2). Curiously, *p*-hydroxybenzaldehyde also does not provide any benzylation product.

Benzyl chloride was also found to be reactive under our aqueous benzylation condition. However, the yield of the benzylation product is slightly lower with benzyl chloride than with benzyl bromide.

Octanal or phenylacetaldehyde could not be benzylated under the Mg/AgNO₃/NH₄NO₃ condition (Entries 13 and 14). No pinacol coupling occurred in the two cases, either. The only observed reaction was the reduction of aldehyde to alcohol. Therefore, the Mg/AgNO₃/NH₄NO₃ procedure chemoselectively benzylates aromatic aldehydes but not aliphatic aldehydes. Aromatic ketone (Entry 15) could not be benzylated using the

Table 2 Results of the Mg/AgNO₃/NH₄NO₃-mediated carbonyl benzylation^a

Entry	X	Carbonyl compound	Yield/%			
			4	5	6-threo	6-erythro
1	Br		35.8	44.5	11.7	3.2
2	Cl		16.1	25.1	26.1	17.6
3	Br		45.1	29.3	10.5	8.8
4	Cl		26.6	15.6	31.6	20.8
5	Br		34.8	34.7	12.4	3.0
6	Cl		19.0	25.0	2.3	0.5
7	Br		28.4	41.7	8.6	4.2
8	Cl		16.6	25.6	7.6	4.3
9	Br		22.3	31.1	22.4	22.0
10	Cl		13.3	21.8	29.7	26.8
11	Br		31.0	48.4	6.4	4.0
12	Cl		25.5	44.7	11.4	9.2
13	Br		36.6	0	0	0
14	Br		69.2	0	0	0
15	Br		24.5	0	38.4	32.9

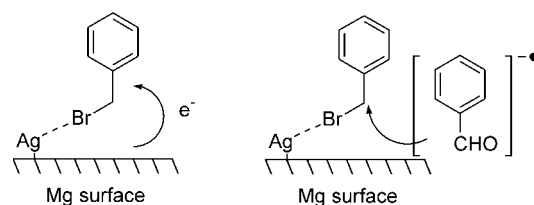
^a The products were analyzed using GC/MS.

Mg/AgNO₃/NH₄NO₃ procedure, either. However, under the reaction condition, significant amount of pinacol coupling products were obtained. Thus, the Mg/AgNO₃/NH₄NO₃ procedure chemoselectively benzylates aromatic aldehydes but not aromatic ketones.

The mechanism of the Mg-mediated Barbier reactions in water is intriguing. Clearly, a free organo-Mg species can not serve as the reaction intermediate because of its high reactivity with water. A reasonable mechanism for aqueous Mg-mediated Barbier reactions was proposed by Li *et al.*⁹ According to this mechanism, the coupling reaction should occur on the surface of Mg metal, where alkyl halide and aromatic aldehyde could be reduced to the corresponding radical anion via a single electron transfer pathway. Either alkyl halide radical anion adds to the C=O double bond of the neutral aldehyde, or aldehyde radical anion displaces the halide atom on neutral alkyl halide.

The above mechanism is probably adequate for aqueous allylation. However, for the benzylation reactions, use of Mg only can not sufficiently activate ben-

zyl halide. The addition of AgNO₃ was found to be crucial for the aqueous benzylation. The Ag atoms reduced from AgNO₃ by Mg on the Mg surface could make benzyl halide either easier to reduce by Mg metal, or easier to attack by benzaldehyde radical anion (See Scheme 1).

Scheme 1

We believe that the first activation pathway in Scheme 1 must be involved in the aqueous benzylation reaction, because in benzaldehyde-benzyl bromide coupling reaction we observed significant amount of PhCH₂CH₂Ph, a Wurtz-type reaction product.¹⁷ Without the addition of AgNO₃, little PhCH₂CH₂Ph could be

obtained. The importance of the second activation pathway in Scheme 1 remains unclear. Nevertheless, the presence of benzaldehyde radical anion in the reaction mixture is indicated by the reduction and pinacol coupling reactions.

Experimental

Typical procedures for the benzylation are as follows: To a mixture of carbonyl compound (2.5 mmol) and benzyl bromide (7.5 mmol) in an aqueous solution (12.5 mL) of NH_4NO_3 (0.1 mol/L) and AgNO_3 (0.01 mol/L) was added 1.25 g of Mg dust in several small portions. The mixture was vigorously stirred at room temperature for 12 h (Caution: The reaction is highly exothermic at the beginning.). 30 mL of 3 mol/L HCl were then added to the mixture to quench the reaction in an ice bath. The mixture was extracted with 3×12.5 mL of CHCl_3 . The combined organic layers were dried over anhydrous MgSO_4 and were filtered and evaporated. The residue was analyzed using GC/MS.

Conclusion

In summary, we found for the first time that catalyzed by AgNO_3 in NH_4NO_3 solution, Mg can successfully mediate the coupling reactions between aromatic aldehydes and benzyl bromide or benzyl chloride in aqueous media. This coupling reaction is chemoselective for aromatic aldehydes over aliphatic aldehydes and also chemoselective for aromatic aldehydes over aromatic ketones. These results are interesting and valuable as they clearly show that one can overcome the intrinsic lower activity of benzyl halide by using appropriate catalysts and also show for the first time that in addition to Mg-allylation, Mg-benylation reaction is also fully compatible with water. We are now working on In, Mn, and Sn-mediate aqueous carbonyl benzylation. The results will be reported in due course.

References and notes

- Blomberg, C.; Hartog, F. A. *Synthesis* **1977**, 18.
- (a) Li, C. *J. Chem. Rev.* **1993**, 93, 2023.
(b) Liao, L.-A.; Li, Z.-M. *Chin. J. Org. Chem.* **2000**, 20, 306 (in Chinese).
- (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*, Oxford University Press, New York, **1997**.
(b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*, John Wiley & Sons, Inc., New York, **1997**.
- (a) Chan, T. H.; Li, C. J.; Lee, M. C.; Wei, Z. Y. *Can. J. Chem.* **1994**, 72, 1181.
(b) Yuan, Y.-F.; Cao, Z.; Hu, A.-G.; Wang, J.-T. *Chin. J. Org. Chem.* **2000**, 20, 269 (in Chinese).
(c) Zhang, J.-M.; Zhang, Y.-M. *Chin. J. Chem.* **2002**, 20, 296.
- Li, L. H.; Chan, T. H. *Tetrahedron Lett.* **2000**, 41, 5009.
- (a) Wada, M.; Ohki, H.; Akiba, K. *Bull. Chem. Soc. Jpn.* **1990**, 63, 2751.
(b) Ren, P.-D.; Pan, S.-F.; Dong, T.-W.; Wu, S.-H. *Chin. J. Chem.* **1996**, 14, 462.
- Zhou, J. Y.; Sun, G.-F.; Zhang, M.-F.; Jia, Y.; Wu, S. H. *Chin. J. Chem.* **1997**, 15, 361.
- Li, C. J.; Meng, Y.; Yi, X. H.; Ma, J. H.; Chan, T. H. *J. Org. Chem.* **1999**, 64, 3230.
- (a) Li, C. J.; Zhang, W. C. *J. Am. Chem. Soc.* **1998**, 120, 9102.
(b) Zhang, W. C.; Li, C. J. *J. Org. Chem.* **1999**, 64, 3230.
- (a) Deng, D.; Lu, Z. *Chin. Chem. Lett.* **1994**, 5, 173.
(b) Deng, D.-L.; Lu, Z.-H.; Wu, K. *Chin. J. Org. Chem.* **1996**, 16, 462 (in Chinese).
- (a) Mukaiyama, T.; Harada, T. *Chem. Lett.* **1981**, 1527.
(b) Wu, S.; Zhu, T. *Acta Chim. Sinica* **1987**, 45, 1135 (in Chinese).
(c) Wu, S. H.; Huang, B. Z.; Zhu, T. M.; Yiao, D. Z.; Chu, Y. L. *Acta Chim. Sinica* **1990**, 48, 372 (in Chinese).
(d) Zhou, C.-L.; Zha, Z.-G.; Wang, Z.-Y.; Wu, J.-H.; Zhang, J.-H. *Chin. J. Chem.* **2002**, 20, 718.
(e) Zha, Z.-G.; Xie, Z.; Zhou, C.-L.; Wang, Z.-Y.; Wang, Y.-S. *Chin. J. Chem.* **2002**, 20, 1477.
(f) Wang, Z.-Y.; Yuan, S.-Z.; Zha, Z.-G.; Zhang, Z.-D. *Chin. J. Chem.* **2003**, 21, 1231.
- It should be mentioned that Barbier-type benzylation of carbonyl compounds in organic solvent is also much less efficient than allylation. See:
(a) Gao, X.; Wang, X.; Cai, R.; Wei, J.; Wu, S. *Acta Chim. Sinica* **1993**, 51, 1139 (in Chinese).
(b) Di Scala, A.; Garbacia, S.; Helion, F.; Lannou, M.-I.; Namy, J.-L. *Eur. J. Org. Chem.* **2002**, 2989.
- Bieber, L. W.; Storch, E. C.; Malvestiti, I.; da Silva, M. F. *Tetrahedron Lett.* **1998**, 39, 9393.
- (a) Tan, X.-H.; Shen, B.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2002**, 43, 9373.
(b) Tan, X.-H.; Shen, B.; Deng, W.; Zhao, H.; Liu, L.; Guo, Q.-X. *Org. Lett.* **2003**, 5, 1833.
(c) Wang, J.; Yuan, G.; Dong, C.-Q. *Chem. Lett.* **2004**, 33, 286.
- (a) Sha, Y.-W.; Wang, Y.; Ge, J.; Wang, X. *Chin. J. Org. Chem.* **2001**, 21, 102 (in Chinese).
(b) Lu, J.; Yang, B.-Q.; Bai, Y.-J.; Ma, H.-R. *Chin. J. Org. Chem.* **2001**, 21, 640 (in Chinese).
(c) Wang, J.; Jiang, F.-C. *Chin. J. Org. Chem.* **2002**, 22, 212 (in Chinese).
(d) Yang, G.-C.; Chen, Z.-X.; Hu, C.-L. *Chin. J. Org. Chem.* **2002**, 22, 289 (in Chinese).
(e) Bian, Y.-J.; Li, J.-T.; Li, T.-S. *Chin. J. Org. Chem.* **2002**, 22, 227 (in Chinese).
(f) Zhang, S.-M.; Li, H.; Zheng, X.-C.; Li, B.-Q.; Wu, S.-H.; Huang, W.-P.; Liu, Z.-G.; Feng, Y. *Chin. J. Org. Chem.* **2002**, 22, 603 (in Chinese).
- Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, 55, 11149.
- We conducted some ESR experiments to monitor the reaction intermediates. Unfortunately, we could not observe any ESR signals for benzyl radical or benzyl radical anion.