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Barbier-type allylation of iminium ions generated in situ in aqueous medium

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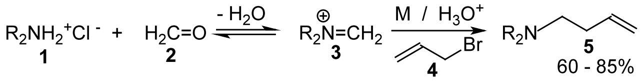
Abstract—Iminium ions, generated in aqueous solution from secondary amines and formaldehyde, undergo a Barbier-type allylation mediated by tin, aluminum and zinc. The reaction is catalyzed by copper and produces tertiary homoallylamines in up to 85% yield. © 2003 Elsevier Science Ltd. All rights reserved.

Iminium ions are well known as intermediates in the Mannich reaction, commonly applied to the synthesis of β-aminoketones, aldehydes and other derivatives.[1] They also react with Grignard reagents and other organometallic compounds giving secondary[2] and tertiary[3] amines, and have been used successfully in cyclization reactions for the synthesis of piperidines[4] and in Diels–Alder reactions[5] in aqueous solution. Iminium ions can be generated classically by condensation between an ammonium salt and formaldehyde. The protonation or alkylation of imines and enamines also results in iminium ions. A different method is the acid-catalyzed rearrangement of benzyl azide.[6]

On the other hand, many organometallic reactions have been demonstrated to proceed in aqueous media in recent years.[7] This is possible when the organometallic reagent has low reactivity towards water and is formed in the reaction medium by mixing the metal, halide and electrophilic substrate in a one-pot reaction, commonly known as Barbier-type reaction.

There is general agreement about the advantages of the use of water as solvent. Water is the cheapest and safest solvent available. In the presence of reactive functional groups, protection and deprotection processes are often unnecessary and frequently better selectivity is obtained. The use of water as solvent can reduce or eliminate environmental damage by organic wastes.[8] Therefore, organic reactions in aqueous media have attracted great interest. Barbier-type reactions have been used to allylate aldehydes and ketones promoted by zinc,[7,8] tin,[9] indium[10] and magnesium.[11] Propargyl halides add to aldehydes in the presence of tin,[12] indium,[13] and zinc.[14] Benzylic halides[15] and halo esters[16] also react with aldehydes and zinc. Even unconventional substrates such as nitrobenzene[17] and diphenyldiselenide[18] undergo Barbier-type alkylations in aqueous medium.

Most frequently, as in the Mannich reaction, iminium ions are generated in the reaction medium and react in situ with suitable nucleophiles. Nevertheless, only few examples with organometallic reagents in aqueous medium have been described.[19–22] Homoallylic amines have been obtained in a three-component reaction of aldehydes, amines and allyltributylstannane in the presence of sodium dodecylsulfate and scandium trifluoromethanesulfonate as Lewis acid.[19] Katritzky[20] has used a bimetallic system, Bi(III)/Al(0), in aqueous medium in the allylation and alkylation of 1-



Scheme 1. Barbier-type homoallylation of secondary amines by allylation of iminium ions generated in situ. M = Sn, Al, Zn; R = (**a**) -CH_3, (**b**) -CH_2CH_3, (**c**) -$CH(CH_3)_2$, (**d**) -CH_2-$(CH_2)_3CH_2$-, (**e**) -$CH_2(CH_2)_2CH_2$-, (**f**) -$CH_2CH_2OCH_2CH_2$-, (**g**) -$CH_2CH_2SCH_2CH_2$-.

Keywords: Barbier reaction; allylation; iminium salts; aqueous solvent.

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(aminoalkyl)benzotriazoles to give homoalkylated amines in high yield; the reaction probably involves dissociation of the benzotriazole to iminium ion which is attacked by the organometallic intermediate.[21] Iminium ions generated from primary amines and formaldehyde in situ have been reported to react with allyl trimethylsilane in water to give bis-homoallylamines.[22] In this paper we report the allylation of iminium ions, generated in situ, promoted by zinc in aqueous medium.

The allylation was carried out in micro scale as follows: a mixture of 1 mL of water, 1 mmol of amine (**1**), 1.2 mmol of formaldehyde (**2**, 35% aq.), 2 mmol of allyl bromide (**4**) and 2.5 mmol of granulated reactive metal was stirred vigorously for 1 h at rt (30°C). The reaction was quenched by 5 mL of NaOH 10%. The product (**5**) was extracted by 1 mL of CCl_4 containing 0.2 mmol/mL of anisol as internal quantitative reference (Scheme 1). The reaction of dimethylamine hydrochloride (**1a**), formaldehyde (**2**) and allyl bromide (**4**) was used as the starting point.

Initially, three different metals, Al, Sn and Zn, were tested and all produced moderate amounts of the expected homoallylamine (Table 1, entries 1–3). However, the smooth reaction and better yield with zinc directed the following efforts to this metal. The study of granulometry of metal showed that granulated zinc is better (Table 1, entries 3 and 10). The effect of acidity is very important in this reaction to protonate the secondary amine, to drive the equilibrium to iminium formation and to avoid undesired *N*-alkylation. Organic and inorganic acids were tested (Table 1, entries 4–8). Acetic acid (AcOH) showed better yields and no byproducts were formed. In the absence of acetic acid some *N*-alkylation was observed. When the reaction was run between 40 and 50°C, the yield improved to 44% (Table 1, entries 10 and 11). At 0°C and 60°C lower yields were obtained (Table 1, entries 9 and 12). The addition of different water-miscible co-solvents brought no improvement (Table 1, entries 13–19).

In view of the still moderate yields and the possible volatility of the reaction product with dimethylamine (**5a**), we applied the methodology of entry 8 (Table 1) to morpholine, because **5f** was expected to be less volatile. Indeed, a 47% yield was obtained even at room temperature. Once more, the addition of acetic acid proved to be crucial (Table 2, entries 1 and 2). Encouraged by these results we studied the effect of catalysts using morpholine.

As can be seen from Table 2 (entries 2 and 3), $RuCl_3$ and TlI suppressed the reaction completely. Most of the other catalysts, including the Lewis acids $InCl_3$ and EuF_3, produced lower yields than the uncatalyzed reaction (Table 2, entries 5–12). $CdCl_2$ and Ag_2SO_4 brought some improvement, but only $CuCl_2$ and CuI raised the yields significantly to 63 and 72%, respectively (Table 2, entries 13 and 16). Working at 50°C brought further improvement of the yield to 67 and 76%, respectively (Table 2, entries 17 and 18). Increasing the amount of CuI to 100 mg (~1 equiv.), a 78% yield was obtained at rt (Table 2, entry 20). Again, granulated zinc showed to be more efficient than zinc powder (Table 2, entry 20).

Table 1. Reaction of dimethylammonium hydrochloride (**1a**), formaldehyde (**2**) and allyl bromide (**4**) in the presence of reactive metals

Entry	Temp. (°C)	Solvent	Metal	Yield (%)
1	30	H_2O	Al	15
2	30	H_2O	Sn[a]	10
3	30	H_2O	Zn	30 (22)[b]
4	30	1 M HCl	Zn	30
5	30	1 M F_3CCOOH	Zn	24
6	30	1 M HCOOH	Zn	25
7	30	1 M H_3PO_4	Zn	–
8	30	1 M AcOH	Zn	35
9	0	1 M AcOH	Zn	15
10	40	1 M AcOH	Zn	42 (19)[b]
11	50	1 M AcOH	Zn	44
12	60	1 M AcOH	Zn	30
13	30	H_2O:DMF[c]	Zn	32
14	30	H_2O:dioxane[c]	Zn	33
15	30	H_2O:THF[c]	Zn	31
16	30	H_2O:CH_3CN[c]	Zn	24
17	30	H_2O:DMSO[c]	Zn	34
18	30	H_2O:ethylene glycol[c]	Zn	17
19	30	H_2O:methanol[c]	Zn	16

[a] The reaction time with tin was 20 h.
[b] Yield using powdered zinc
[c] A 1:1 mixture was used.

Table 2. Effect of catalysts in the reaction of morpholine, formaldehyde and allyl bromide promoted by Zn at 30°C

Entry	Catalyst[a]	Solvent	Yield (%)
1	–	H_2O	33
2	–	H_2O/2 mmol AcOH	47
3	TlI	H_2O/2 mmol AcOH	–
4	$RuCl_3$	H_2O/2 mmol AcOH	–
5	$Pb(OAc)_2$	H_2O/2 mmol AcOH	24
6	$Fe_2(SO_4)_3$	H_2O/2 mmol AcOH	35
7	RhI_3	H_2O/2 mmol AcOH	35
8	EuF_3	H_2O/2 mmol AcOH	36
9	$InCl_3$	H_2O/2 mmol AcOH	38
10	$BiCl_3$	H_2O/2 mmol AcOH	42
11	$NiCl_2$	H_2O/2 mmol AcOH	44
12	$CrCl_3$	H_2O/2 mmol AcOH	45
13	$CdCl_2$	H_2O/2 mmol AcOH	50
14	Ag_2SO_4	H_2O/2 mmol AcOH	52
15	$CuCl_2$	H_2O/2 mmol AcOH	63
16	CuI	H_2O/2 mmol AcOH	72
17	$CuCl_2$ (50°C)	H_2O/2 mmol AcOH	67
18	CuI (50°C)	H_2O/2 mmol AcOH	76
19	CuI (50 mg)	H_2O/2 mmol AcOH	76
20	CuI (100 mg)	H_2O/2 mmol AcOH	78 (54%)[b]
21	CuI (200 mg)	H_2O/2 mmol AcOH	70

[a] Unless otherwise stated, 5 mg of catalyst were used.
[b] Yield using powdered zinc.

In the latter experiments, granulated zinc was added to a suspension of CuI in water forming a black precipitate. A similar reagent has been prepared by Luche and co-workers under sonochemical conditions and used in conjugate additions to α,β-unsaturated carbonyl compounds[7c,23] and in the cleavage of epoxyalkylhalides[24] in aqueous media. Because of the strong reducing character of the zinc–copper couple,[25] a radical mechanism by a single-electron transfer is most probable in these reactions.[23–26] The same reagent has been also successfully applied in the reductive ring opening of 2-(bromomethyl)aziridines[27] and, more recently, in the Wurtz-type coupling of organic halides in water.[28]

In the following experiments the optimized conditions (Table 2, entry 20) were applied to different secondary amines (Table 3). The steric effect is evident when we compare the increase of yield from diisopropylamine to dimethylamine (Table 3, entries 1–3). The best yields were obtained with cyclic amines (78–85%, Table 3, entries 4–7). Structure and purity of the tertiary amines **5a–g** were confirmed by ^{1}H NMR spectroscopy and GC/MS[29] measurements of the crude extracts. Analytical samples were obtained by crystallization with picric acid.

Homoallylic amines are important intermediates in the synthesis of nitrogen-containing compounds such as natural products and biologically active compounds.[30,31] The most useful previously described methods for synthesizing this kind of amines are nucleophilic additions of allylic organometallic species to imines and their derivatives, such as acylimines, acyliminium ions and iminium ions,[32,33] all performed under anhydrous conditions except the reactions with preformed allyl silanes and stannanes.[19–22] The reactions reported in this paper represent a novel and practical method to obtain tertiary homoallylic amines, under very mild conditions. Both reagents, iminium salt and organometallic species are generated in situ, using water as safe and environmentally benign solvent, the only waste being non-toxic inorganic Zn and Cu salts. The possible extension of this method to other aldehydes, amines and halides is in progress in our laboratory.

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Table 3. Reaction of different amines with formaldehyde, allyl bromide and Zn in the presence of CuI at 30°C

Entry	Amine	Yield (%)
1	Diisopropylamine	20
2	Diethylamine	45
3	Dimethylamine	60
4	Morpholine	78
5	Pyrrolidine	85
6	Piperidine	78
7	Thiomorpholine	81

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