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# Aminomethylation of organic halides promoted by zinc in protic medium

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**Abstract**—Organic halides undergo smooth aminomethylation by secondary amines and aqueous formaldehyde promoted by metallic zinc under copper(I) catalysis. Good to excellent yields are obtained with primary, secondary, and tertiary iodides, allylic, propargylic, and benzylic bromides and with α-bromoesters. In most cases, DMSO is the best solvent, but dioxane is preferable for some more reactive halides. Additional experiments with radical quenchers and promoters and the use of 'radical clocks' indicate a stepwise reaction mechanism initiated by the attack of an alkyl radical to iminium ion.

The classical Mannich reaction is still one of the most efficient strategies for the synthesis of functionalized tertiary amines.[1] The generally accepted mechanism involves iminium ions **1** as reactive intermediates, generated in acidic medium from secondary amines **2** and formaldehyde **3**, which are attacked by suitable nucleophiles. This in situ procedure is especially efficient with enolisable carbonyl compounds but has been extended to aromatic compounds[1] and terminal alkynes.[2] Although preformed stable iminium salts in aprotic solvents allow the use of organometallic nucleophiles, such complex multistep procedures are much less attractive from the experimental point of view.[3–5] The recent development of mild and efficient Mannich-type three-component reactions for the synthesis of tertiary propargylamines[6] and the growing number of Barbier-type reactions with unconventional electrophiles,[7] all performed under protic conditions, suggested the possibility to combine the generation of iminium ions and organometallic intermediates in a one-pot reaction. The validity of this approach has been reinforced by several organometallic reactions in aqueous medium: the Barbier-type alkylation of benzotriazole derivatives,[8] a source of iminium ions, and the reaction of aldehydes and amines with allylic silanes[9] or stannanes.[10] In fact, the first simultaneous in situ generation and coupling of both iminium ion and allylic intermediate in water has been accomplished recently in our laboratory.[11] In the present letter, we describe the generalization of the method for other types of activated and inactivated halides.

Already the first experiments with ethyl and isopropyl iodide under the conditions optimized for allyl bromide produced the expected tertiary amines **5**, but modest yields and formation of several side products prompted us to undertake a new systematic search for the best reaction conditions.

In principle, a multicomponent reaction with in situ formation of different intermediates increases the possibility of undesired side reactions and requires a careful optimization of all reaction parameters. In the case of the aminomethylation of alkyl halides promoted by active metals, several important alternatives must be considered (Scheme 1): direct Barbier alkylation of the aldehyde to **6**, $S_N2$ alkylation of amine **2** to **7** and reduction of iminium ion to **8** or of organic halide to **9**. Only the reaction of the iminium ion **1** with an intermediate generated by the action of the metal on the halide **4** will produce the desired product **5**. One of the most important factors is the acidity of the medium, for acid catalysis is essential for the rapid formation of the iminium species and for the activation of the metal surface, but too acidic conditions can lead to reductions of **1** and **4**

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*Keywords*: Mannich reaction; Aqueous formaldehyde; Alkyl halides; Radical mechanism.

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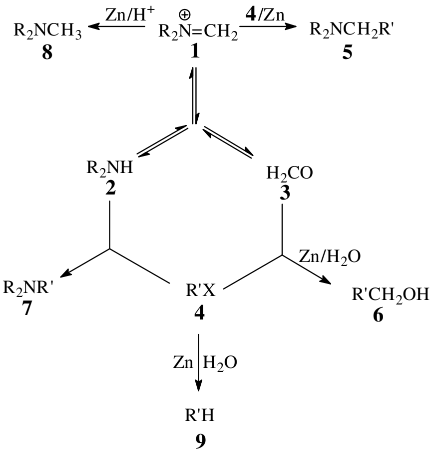


**Scheme 1.**

and dissolution of the metal. On the other hand, basic conditions can promote direct substitution by free amine. A protic solvent, ideally water, will assure rapid equilibration, but favors also reducing side reactions whereas an organic solvent may be necessary to solubilize the organic reagents. Other important factors for the control of reactivity are the temperature and the nature and active surface of the metal.

As a result of extensive optimization experiments with representative halides of different structural types, several common features could be observed. Probably for solubility reasons, the best results were obtained in polar organic solvents mixed with a small excess of aqueous formaldehyde. In all cases, greater excess of formaldehyde or higher amounts of water increased the formation of side products **8** by reductive methylation. Copper iodide was essential for good yields, but its amount could be reduced, in comparison to the previous conditions,[11] to 0.1 equiv; other Cu(I) or Cu(II) compounds were much less effective. The addition of a proton source (4 equiv) was necessary to suppress direct N-alkylation to **7**. A general observation was the superiority of granulated zinc over zinc dust and other metals (Sn, Al, Mn, Mg, In, or Bi). Formation of alcohol **6** by Barbier addition to **3** was observed only in the reaction of allyl bromide with tin. In general, an excess of halide (2 equiv) is indicated in order to assure complete conversion of **2**; alternatively, in the case of halides of higher molecular weight or synthetic value, the amine may be used in excess.

**Table 1.** Aminomethylation of alkyl halides[a]

| Entry | Amine **2** | Halide **4** | Solvent | Acid | Temp. (°C) | Yield **5** (%) |
|---|---|---|---|---|---|---|
| 1 | Piperidine | Me-I | MeOH | HOAc | 30 | 40 |
| 2 | Piperidine | Et-I | DMSO | HOAc | 30 | 95 |
| 3 | Piperidine | *i*-Pr-I | DMSO | HOAc | 30 | 84 |
| 4 | Piperidine | *t*-Bu-I | Dioxane | HOAc | 0 | 66 |
| 5 | Piperidine | Allyl-Br | DMSO | HOAc | 0 | 75 |
| 6 | Piperidine | Propargyl-Br | Dioxane | HOAc | 0 | 76 |
| 7 | Piperidine | 1-Br-2-butyne | DMSO | HOAc | 0 | 60[b] |
| 8[c] | Piperidine | Benzyl-Br | Dioxane | HOAc | 0 | 68 |
| 9 | Morpholine | Et-I | DMSO | HOAc | 30 | 71 |
| 10 | Morpholine | *i*-Pr-I | DMSO | HOAc | 30 | 71 |
| 11 | Morpholine | *t*-Bu-I | Dioxane | HOAc | 0 | 55 |
| 12 | Morpholine | *n*-Bu-I | DMSO | $F_3CCO_2H$ | 30 | 60 |
| 13 | Morpholine | Cyclohexyl-I | DMSO | $F_3CCO_2H$ | 30 | 77 |
| 14[c] | Morpholine | $PhCH_2CH_2$-I | DMSO | $F_3CCO_2H$ | 30 | 59 |
| 15[c] | Morpholine | Benzyl-Br | Dioxane | HOAc | 0 | 68 |
| 16[c] | Morpholine | Br-$CMe_2CO_2Et$ | DMSO | $F_3CCO_2H$ | 0 | 65 |
| 17 | $Me_2NH \times HCl$ | *i*-Pr-I | DMSO | HOAc | 30 | 91 |
| 18 | $Me_2NH \times HCl$ | Cyclohexyl-I | DMSO | HOAc | 30 | 69 |
| 19[c] | $Me_2NH \times HCl$ | Adamantyl-I | Dioxane | HOAc | 0 | 69 |
| 20 | $Me_2NH \times HCl$ | Allyl-Br | DMSO | HOAc | 0 | 76 |
| 21 | $Et_2NH$ | *i*-Pr-I | DMSO | HOAc | 30 | 79 |
| 22 | $Et_2NH$ | *t*-Bu-I | Dioxane | HOAc | 0 | 57 |
| 23[c] | $Et_2NH$ | Benzyl-Br | Dioxane | HOAc | 0 | 80[b] |
| 24 | $Et_2NH$ | 1-Br-2-butyne | DMSO | HOAc | 0 | 57 |
| 25 | Pyrrolidine | Et-I | DMSO | HOAc | 30 | 68 |
| 26 | Pyrrolidine | *i*-Pr-I | DMSO | HOAc | 30 | 64 |
| 27 | Pyrrolidine | *t*-Bu-I | Dioxane | HOAc | 0 | 59 |
| 28 | Dibenzylamine | Et-I | DMSO | HOAc | 30 | 75 |
| 29 | Dibenzylamine | *i*-Pr-I | DMSO | HOAc | 30 | 63 |

[a] General procedure: To a solution of free amine or hydrochloride (5 mmol), acid (20 mmol), and halide (10 mmol) in 5 ml of the indicated solvent were added, at rt or 0 °C, aqueous formaldehyde (1 ml, 35%), CuI (100 mg), and granulated zinc (15 mmol). After 2 h of stirring, the reaction was hydrolyzed by the addition of 50 ml of aqueous NaOH (10%) and extracted with ether. The solvent was removed and the free bases were purified by short-path distillation or crystallization as picrates.

[b] The rearranged allenic compound was isolated.

[c] 10 mmol of amine and 5 mmol of halide were used.

All other parameters—solvent, temperature, and employed acid—varied for different types of halides. Primary and secondary alkyl iodides are best reacted in commercial DMSO at rt (30 °C); for small halides (R = Et, *i*-Pr) acetic acid is sufficient as proton source (Table 1, entries 2, 3, 9, 10, 17, 21, 25, 26, 28, and 29), for those of higher molecular weight trifluoracetic acid is more effective (entries 12–14 and 18). Tertiary iodides, benzyl, and propargyl bromide (entries 4, 6, 11, 15, 19, 22, 23, and 27) were too reactive under these conditions and required a less polar solvent, dioxane, at lower temperature (0 °C) in the presence of acetic acid. Allyl bromide and 1-bromo-2-butyne gave best results in DMSO at 0 °C (entries 5, 7, 22, and 24). Only for methyl iodide we were unable to obtain preparative yields, the best result (40%) was achieved in methanol at rt (entry 1).

Various cyclic secondary amines **2** were used with good results. As already observed in previous papers,[6,11] steric hindrance in acyclic amines causes loss of reactivity, but even with dibenzylamine we obtained satisfactory yields of **5** (entries 28 and 29).

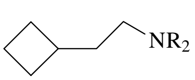
In analogy to the classical Mannich reaction,[1] the mechanism can be explained as a nucleophilic attack of an organozinc intermediate to the highly electrophilic iminium ion. There are also parallels to the aqueous Barbier addition to aldehydes and ketones.[12] However, several important differences can be observed. First, the aqueous Zn-Barbier reaction is essentially limited to allylic,[12] propargylic,[13] and benzylic halides,[14] all capable of producing resonance stabilized intermediates; saturated primary alkyl iodides react only partially with highly electron-deficient benzaldehydes.[15] By contrast, in the present reaction, all types of halides, including primary, secondary, and tertiary alkyl iodides, give comparable yields. Second, no catalyst is necessary for the aqueous allylation of carbonyl compounds, but the presence of catalytic copper(I) species improves the yields significantly in the case of iminium ions.

In order to get a better understanding of these differences, a series of competition reactions was performed using morpholine, formaldehyde, and allyl bromide in all cases and adding various additives or catalysts (Table 2). The uncatalyzed reaction produced a moderate yield of **5** (39%, entry 1). When the same reaction was conducted in the presence of one equivalent of benzaldehyde as a competitive electrophile, the yield of **5** was slightly reduced to 36%, but 60% of homoallylic alcohol **13** was also formed (entry 2). This latter product was significantly reduced to 26% in the presence of catalytic copper iodide, whereas the yield of tertiary amine increased to 60%; exactly the same yield of **5** was obtained in the absence of benzaldehyde (entries 3 and 4). In the presence of a radical quencher, 2,6-di-*tert*-butyl-4-methylphenol (BHT), the yield of **5** was also decreased to 33% (entry 5). These few experiments demonstrate clearly that carbonyl and iminium addition follow different and competitive mechanisms: the first predominates in the absence of any catalyst and is severely suppressed by CuI; the second process is enhanced by the same catalyst, but inhibited by BHT. These observations are best explained by a first single electron transfer (SET) to the halide producing a radical intermediate **10** which can add directly to iminium ion **1**, but not to benzaldehyde, generating radical cation **11** (Scheme 2). A further SET to **10** produces a carbanionic species **12**, capable to react with benzaldehyde to **13** (R = allyl) and, in minor degree, with iminium ion **1**. The role of the catalyst can be to stabilize the radical **10** or to prevent the second SET.

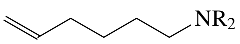
Further confirmation of this type of mechanism was obtained by use of different radical quenchers in the aminomethylation of iodocyclohexane. The presence of

**Table 2.** Reaction of morpholine and formaldehyde with different halides promoted by zinc in the presence of additives

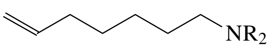
| Entry | Halide R′X (**4**) | Acid | Temp. (°C) | Additives (equiv) | Products (yield [%]) |
|---|---|---|---|---|---|
| 1 | Allyl-Br | HOAc | 0 | None | **5** (39) |
| 2 | Allyl-Br | HOAc | 0 | PhCHO (1.0) | **5** (36) + **13** (60) |
| 3 | Allyl-Br | HOAc | 0 | PhCHO (1.0) + CuI (0.1) | **5** (60) + **13** (26) |
| 4 | Allyl-Br | HOAc | 0 | CuI (0.1) | **5** (60) |
| 5 | Allyl-Br | HOAc | 0 | CuI (0.1) + BHT (1.0) | **5** (33) |
| 6 | Cyclohexyl-I | $CF_3COOH$ | 30 | None | **5** (49) |
| 7 | Cyclohexyl-I | $CF_3COOH$ | 30 | Galvinoxyl (0.1) | **5** (32) |
| 8 | Cyclohexyl-I | $CF_3COOH$ | 30 | TEMPO (0.1) | **5** (19) |
| 9 | Cyclohexyl-I | $CF_3COOH$ | 30 | $(BzO)_2O$ (0.1) | **5** (26) |
| 10 | Cyclohexyl-I | $CF_3COOH$ | 30 | CuI (0.1) | **5** (77) |
| 11 | Cyclohexyl-I | $CF_3COOH$ | 30 | CuI (0.1) + BHT (1.0) | **5** (64) |
| 12 | Cyclohexyl-I | $CF_3COOH$ | 30 | CuI (0.1) + $(BzO)_2O$ (0.1) | **5** (57) |
| 13 | Cyclobutyl-$CH_2$-I **14** | HOAc | 30 | CuI (0.1) | **15** (36) + **16** (4) |
| 14 | 6-Iodo-1-hexene **17** | HOAc | 30 | CuI (0.1) | **18** (9) + **19** (21) |
| 15 | Cyclopropyl-$CH_2$-I **20** | HOAc | 30 | CuI (0.1) | **21** (25) |



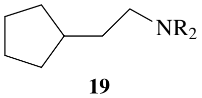
**1 5**



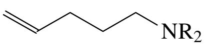
**16**



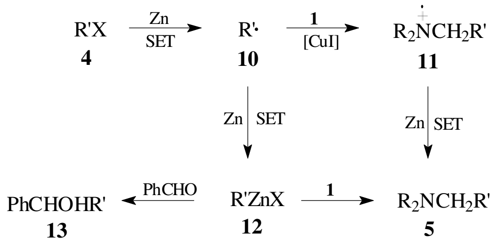
**18**



**19**



**21**



**Scheme 2.**

stable free radicals—galvinoxyl and TEMPO—or a radical source—dibenzoyl peroxide—led to a significant decrease of the yield of **5** in comparison to the uncatalyzed reaction (Table 2, entries 6–9). On the other hand, addition of CuI caused an important improvement which is only partially lost in the presence of BHT or dibenzoyl peroxide (entries 10–12).

Finally, three halides whose rearrangement can be used as a 'radical clock'[16] were reacted with morpholine and formaldehyde under non-optimized conditions. Iodomethylcyclobutane (**14**) gave a mixture of two morpholines with isomeric N-substituents, the unrearranged cyclobutylethyl (**15**) and the linear 5-hexenyl group (**15**) in a 9:1 ratio (Table 2, entry 13). A similar reaction with 6-iodo-1-hexene (**17**) produced the unrearranged linear (**18**) and the cyclized compound (**19**) in a ratio of 3:7 (entry 14). Finally, iodomethylcyclopropane (**20**) led to **21** under complete ring opening with no trace of the cyclic product. These findings are in good agreement with the relative rates of rearrangement of the three radicals known from the literature ($k_{25} = 5 \times 10^3$; $2.3 \times 10^5$ and $9.4 \times 10^7\ \mathrm{s}^{-1}$).[16] Similar rearrangement ratios have been also observed in the copper catalyzed aqueous Wurtz coupling of the same iodides.[17]

The described experiments corroborate the participation of alkyl radical intermediates in the first step of the addition to iminium ion. A similar mechanism has been already suggested in a related radical addition promoted by titanium trichloride[18] and in our previous work with terminal alkynes.[6]

In conclusion, this simple three-component, one-pot reaction allows the efficient synthesis of tertiary amines using inexpensive and environmentally benign reagents and solvents in the presence of water and atmospheric oxygen. In contrast to recently published ionic reactions with preformed iminium ions and organometallic Zn or Mg reagents under anhydrous conditions, restricted to aromatic and benzylic groups,[4,5] the present radical reaction works equally well with allyl, benzyl, propargyl, primary, secondary, and tertiary alkyl halides and α-bromoesters.

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