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Reductive methylation of primary and secondary amines and amino acids by aqueous formaldehyde and zinc

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Abstract—Amines can be methylated when treated with formaldehyde and zinc in aqueous medium. Selective mono- or dimethylation can be achieved by proper choice of pH, stoichiometry and reaction time. This method can also be applied for amino acids. © 2007 Elsevier Ltd. All rights reserved.

The introduction of an amino group into an organic structure is one of the most important synthetic operations in view of the outstanding role of amines and their derivatives in biological processes and chemotherapy.¹ Unfortunately, the obvious nucleophilic substitution generally is not a useful synthetic method because polyalkylation cannot be avoided. For the introduction of only one new alkyl group reductive alkylation of amines, also known as reductive amination of carbonyl compounds, is an interesting alternative as it proceeds via reversible condensation to imines, enamines, or iminium ions which can be reduced by different methods to selectively monoalkylated products. Besides the classical Leuckart-Wallach or Eschweiler-Clarke procedures,² this reaction is normally performed in organic solvents using several borohydride reagents.^{3,4} For the simplest carbonyl compound, formaldehyde, aqueous medium is often preferred, but sometimes monomethylation cannot be controlled. However, when the dimethylation of primary amines or monomethylation of secondary amines is desired, aqueous formaldehyde is an efficient and cheap methylating agent. Instead of the expensive and sometimes toxic borohydride reagents, catalytic hydrogenation, and different reactive metals have also been used occasionally as reducing agents.²

Especially metallic zinc is a cheap and safe electron source, recently rediscovered in mild and efficient aqueous Barbier–Grignard type alkylations.⁵ During our

recent studies on the zinc promoted aminomethylation of alkyl halides,⁶ the formation of *N*-methylated tertiary amines as side products in some cases prompted us to explore this process for the simple, general, and selective *N*-methylation of primary and secondary amines. The generally accepted mechanism involves in the first step an acid catalyzed condensation of amine 1 and formaldehyde to the well-known Mannich type intermediate, iminium ion 2. The highly electrophilic carbon atom of 2 reacts easily with a hydride source to give amine 3 (Scheme 1).

An aqueous acidic medium is not only needed to solubilize all reagents and products and to catalyze the reversible condensation, but is also necessary as a proton source when zinc is used in the reduction step. In the case of cyclic amines and the lower dialkyl amines (Table 1, entries 1–6), aqueous acetic acid revealed to be the best compromise to guarantee sufficient reactivity in the electron transfer and, on the other side, to avoid unnecessary consumption of metal by hydrogen evolution. Granulated commercial zinc was completely satisfactory to achieve nearly quantitative methylation to 3 by simple stirring at room temperature. The reaction times varied from 2 to 20 h according to the steric hindrance of

Scheme 1.

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Table 1. Reductive methylation by aqueous formaldehyde and zinc^a

Entry	Substrate	Additive (equiv)	Zn	Solvent	Time	Yield (%)
1	Piperidine	HOAc (4)	Granules	2 mL H ₂ O	2 h	98
2	Pyrrolidine	HOAc (4)	Granules	$2 \text{ mL H}_2\text{O}$	2 h	82
3	Morpholine	HOAc (4)	Granules	$2 \text{ mL H}_2\text{O}$	2 h	96
4	Dibenzylamine	HOAc (8)	Granules	$2 \text{ mL H}_2\text{O}$	20 h	77
5	Dicyclohexylamine	HOAc (4)	Granules	1 mL diox.	20 h	73
6	Diethylamine	HOAc (4)	Granules	$2 \text{ mL H}_2\text{O}$	8 h	80
7 ^b	t-Butylamine	NaH_2PO_4/K_2HPO_4 (1/1)	Dust	$1 \text{ mL H}_2\text{O}$	20 h	49
8 ^b	<i>n</i> -Butylamine	HOAc (4)	Granules	$2 \text{ mL H}_2\text{O}$	2 h	97
9	<i>n</i> -Butylamine	NaH_2PO_4 (2)	Dust	1 mL H ₂ O	4 h	84
10 ^b	<i>n</i> -Propylamine	HOAc (4)	Granules	1 mL H ₂ O	2 h	98
11	n-Propylamine	NaH_2PO_4 (2)	Dust	$1 \text{ mL H}_2\text{O}$	4 h	95
12 ^b	Benzylamine	HOAc (8)	Dust	2 mL diox.	20 h	77
13 ^b	Aniline	HOAc (4)	Dust	1 mL diox.	30 min	92
14 ^b	<i>p</i> -F-aniline	HOAc (8)	Dust	2 mL diox.	4 h	96
15 ^b	p-Cl-aniline	HOAc (4)	Dust	1 mL diox.	1 h	70
16	1-aminoadamantane	NaH_2PO_4/K_2HPO_4 (1/1)	Dust	1 mL H ₂ O	20 h	85
17 ^b	1-Aminoadamantane	HOAc (4)	Dust	1 mL H ₂ O	20 h	58
18 ^b	Glycine	NaH_2PO_4 (2)	Dust	1 mL H ₂ O	1 h	94
19	Glycine	NaH_2PO_4 (1)	Dust	1 mL H ₂ O	7 min	90
20 ^b	Alanine	NaH_2PO_4 (2)	Dust	2 mL H ₂ O	20 h	92
21	Alanine	NaH_2PO_4 (2)	Dust	$2 \text{ mL H}_2\text{O}$	15 min	85
22 ^b	Isoleucine	NaH_2PO_4 (2)	Dust	4 mL H ₂ O	20 h	96
23	Isoleucine	$NaH_2PO_4(2)$	Dust	8 mL H ₂ O	15 min	90
24 ^b	Leucine	$NaH_2PO_4(2)$	Dust	8 mL H ₂ O	20 h	95
25	Leucine	$NaH_2PO_4(2)$	Dust	8 mL H ₂ O	2 h	88
26	Proline	NaH_2PO_4 (2)	Dust	$2 \text{ mL H}_2\text{O}$	20 h	92

^a Typical procedure: A mixture of amine (1 mmol), additive, 37% aqueous formaldehyde (50% excess), zinc dust or granules (100% excess) and the indicated solvent was stirred at 30 °C. After completion of the reaction aqueous ammonia was added and yields were determined directly in the aqueous solution (amino acids) or in the HCCl₃-extract of the bases in relation to an internal standard. Analytical samples were obtained as picrates or oxalates in the case of amines; amino acids were isolated at the isoelectrical point by traditional methods.

the starting material. Only in the case of dicyclohexylamine the use of 1,4-dioxane gave better results than the use of a completely aqueous medium (entry 5).

Under the same acidic conditions, in the presence of a higher excess of reagents, monoalkylamines were cleanly dimethylated; only trace amounts of monomethyl amines could be detected by GC or ¹H NMR in the crude products which were easily removed by crystallization of the picrates or oxalates (entries 7, 8, and 10-12). All yields were nearly quantitative, except for amines bearing tertiary alkyl groups (entries 7 and 17) which required zinc dust and, in the case of t-butyl amine, a neutral phosphate buffer; the rather low yield of our procedure in the latter case is comparable to that reported in the literature⁷ and can be attributed to the ease of elimination in the product. In other cases, the use of phosphate buffer allowed selective monomethylation of the same starting materials (entries 9, 11, 16), a rather difficult transformation for which only a multistep procedure has been reported before.8

Anilines are expected to give polycondensation with formaldehyde by electrophilic aromatic substitution; indeed, no defined low molecular weight product was isolated in water as a solvent. However, when dioxane was used with a small excess of aqueous formaldehyde, acetic acid and zinc powder, good yields of several dimethyl anilines could be obtained (entries 13–15); only anilines substituted with electron donors, such as methyl

and methoxy groups, polymerized even under these conditions.

These surprisingly selective reactions encouraged us to apply our method to the synthesis of N-methyl amino acids, exciting starting materials for the synthesis of modified proteins. Most of the literature procedures based on reductive methylation are described to give inseparable mixtures of mono- and dimethylated products and good yields and selectivities have been achieved only by indirect multistep procedures. ¹⁰ To our surprise, careful acidity control by monobasic sodium phosphate in aqueous solution allowed to obtain N-monomethyl amino acids in high yield and purity in reaction times which varied from 7 min to 2 h (entries 19, 21, 23, and 25), depending on the steric hindrance and solubility of the starting material. When longer reaction times and higher excess of reagents were employed, the N,Ndimethyl amino acids were produced also in preparative yields (entries 18, 20, 22 and 24). Under these conditions even proline, the only natural secondary amino acid, could be methylated (entry 26). In all amino acid methylations zinc dust proved to be superior to the granulated metal.

In summary, the described procedure allows the selective preparation of mono- or dimethylated amines and amino acids. It is characterized by high yield, selectivity, and atom economy and uses simple, non-toxic, and inexpensive reagents in water, a solvent which exhibits unique

^b Dimethylation conditions.

advantages in respect to cost, safety, experimental simplicity, and, last but not least, environmental impact.

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