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FORMAMIDINE AS A VERSATILE PROTECTING GROUP FOR PRIMARY AMINES: A MILD PROCEDURE FOR HYDROLYTIC REMOVAL.

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ABSTRACT: A mild, zinc chloride-promoted cleavage of N,N-dimethylformamidine derivatives of primary amines to the free amines is described. Under slightly different hydrolytic conditions the corresponding N-formyl derivatives can be isolated.

We have recently been interested in developing an efficient route to 6-substituted indoles in continuation of our work toward the synthesis of marine alkaloids.[1] As part of this work, we prepared the formamidine **2** by the reaction of the substituted aniline **1** in refluxing N,N-dimethylformamide dimethyl acetal (DMF-DMA).

Many unsuccessful attempts have been made to cyclize **2** to 6-nitroindole under a variety of basic and acidic conditions as well as under thermolytic

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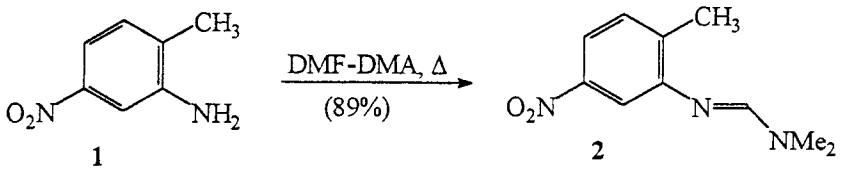
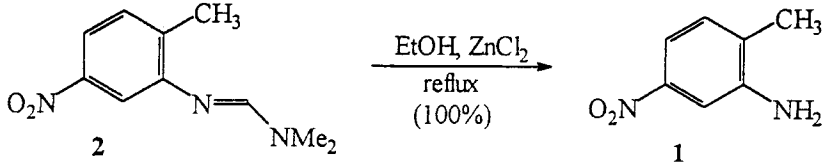


1 2

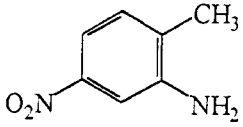
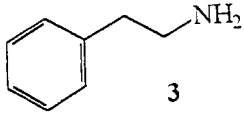
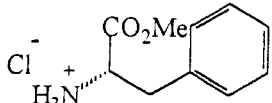
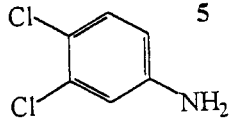
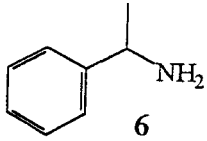
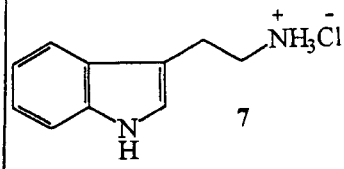
conditions (> 200°C). Although the anion of **2** appeared to be formed under basic conditions, it did not cyclize and compound **2** was usually recovered from the reaction mixture. When we tried to cyclize **2** in the presence of the Lewis acid zinc chloride in refluxing absolute ethanol the product isolated instead was the deprotected aniline **1**.



2 **1**

We decided to investigate the scope of this reaction, since known methods (LAH/Et_2O/reflux, NH_2NH_2/HOAc/MeOH, KOH/MeOH/reflux)[2] for removing formamidine protecting groups are much harsher. A number of formamidine derivatives have been prepared from the aliphatic and aromatic primary amines listed in the Table and subjected to our reaction conditions. No deprotection occurs in the absence of zinc chloride and at least a stoichiometric amount of zinc chloride is required for quantitative removal of the formamidine group. It should also be noted that evolution of dimethylamine was detected during the reaction.

Table

Entry	AMINE	Isolated Yield[a] (%) of Formamidine	Isolated Yield (%) of Deprotected Amine
1	 1	89	100
2	 3	81	90
3	 4	95	78[b]
4	 5	93	97[c]
5	 6	94	83[c]
6	 7	100	90

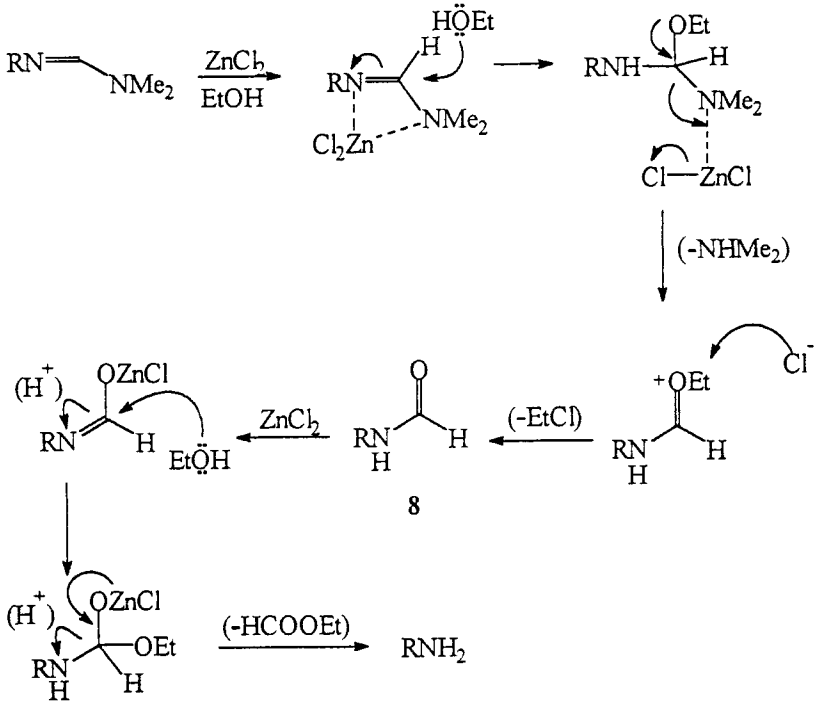
a. All formamidines gave satisfactory HR-EIMS, ^{1}H-NMR and IR data.

b. Isolated as N-formyl ethyl ester HR-EIMS; found, 221.1063: calcd. for $C_{12}H_{15}NO_3$, 221.1052.

c. Deprotected in methanol.

In the case of the L-phenylalanine methyl ester **4**, the transesterified ethyl ester was isolated under our usual conditions. We later found that dry methanol can be substituted for ethanol thus avoiding this complication (see entries 4 and 5). The only other difficulty occurred with benzylamine. Formamidine preparation proceeded smoothly but deprotection in this case yielded a significant amount of benzaldehyde, presumably due to the well documented formamidine-imine tautomerism.[3] This problem was not observed with the benzylic formamidine derivative from **6**, which was deprotected smoothly without any trace of the corresponding ketone being observed. The formamidine of tryptamine **7** showed ^{1}H-NMR evidence for both the cis and trans stereoisomers, presumably because the cis isomer is stabilized by H-bonding to the indole NH.[4] In all cases, the mass spectral information indicated that a small amount of the formamidine exchange product[2] (RN=CHNH-R) was also formed during reaction in refluxing DMF-DMA. These impurities caused no significant problems, as they were also readily deprotected to the corresponding free amines under our conditions.

Interestingly, when the formamidine **2** was subjected to the same reaction conditions but at 25°C, the corresponding N-formyl derivative **8** (R = 5-nitro-2-methylphenyl) was isolated. This result was later observed to occur with the formamidine from **4** and therefore appears to be general. The N-formyl compounds, which of course are also accessible by other means, are useful



Scheme 1

intermediates for preparing N-methyl analogues by lithium aluminum hydride reduction.

We postulate that N-formyl derivatives such as **8** are intermediates in the reaction mechanism, as described in Scheme 1. To confirm that N-formyl derivatives were indeed cleaved by zinc chloride-catalyzed hydrolysis, the N-formyl derivatives of **2** and aniline were prepared independently by refluxing the free amines in formic acid. Both N-formyl amines were deprotected to the corresponding amines in near quantitative yields, by refluxing in alcoholic zinc

chloride. Interestingly, attempts to deprotect the corresponding N-acetyl derivatives under the same reaction conditions proved unsuccessful, yielding unreacted starting material.

While Meyers and co-workers have made extensive use of chiral formamidines[5] in the asymmetric synthesis of alkaloids, their preferred method for cleavage of the chiral formamidine auxilliary utilizes hydrazinolysis. The use of zinc chloride offers a useful alternative for amidine cleavage, particularly in cases where hydrazine might adversely affect other functionality present in the substrate. There has been considerable interest in the recent literature in developing useful amine protecting groups[6,2c], although work on the use of formamidines appears to have been mainly limited to the nucleotide field.[7] We feel that our study shows that the formamidine group serves as a useful primary amine protecting group due to its ease of introduction, stability to a wide variety of reaction conditions and efficient removal with zinc chloride as described.

EXPERIMENTAL

All chemicals were obtained from Aldrich and used as obtained. Absolute ethanol and methanol were distilled from magnesium turnings. DMF was dried from P_2O_5 and stored over activated 3Å sieves.

Representative procedures

N'-(2-Methyl-5-nitrophenyl)-N,N-dimethylformamidine, **2**

2-Methyl-5-nitroaniline **1** (3.04 g, 20.0 mmol)and DMF-DMA (20 mL) were refluxed with stirring under nitrogen for 21 h. After removal of the

solvent[8] the orange solid was recrystallised from 95% ethanol, giving **2** (3.68 g, 89%); m.p. 86-87°C, lit.[9] 89-90°C. The ^{1}H-NMR and IR spectra were identical with those reported.[9]

2-Methyl-5-nitroaniline, 1

Compound **2** (0.50 g, 2.41 mmol), zinc chloride (1.43 g, 10.5 mmol) and absolute ethanol (10 mL) were refluxed for 20 h. Work-up of the product from CH_2Cl_2:water[10] gave 0.38 g (100%) of the deprotected aniline **1**.

N-Formyl-2-methyl-5-nitroaniline, **8**

Compound **2** (0.50 g, 2.41 mmol) and zinc chloride (0.65 g, 4.82 mmol), in absolute ethanol (10 mL), were stirred at 25°C for 24 h. After removal of the ethanol, work-up from CH_2Cl_2:water gave 0.30 g (81%) of **8**; HR-EIMS: found, 180.0523; calcd for $C_8H_8N_2O_3$, 180.0535. ^{1}H-NMR and IR spectra were identical with those in the literature.[9] Removal of the N-formyl group was subsequently carried out with refluxing ethanolic zinc chloride (22 h), as above, yielding 100% of the aniline **1**.

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4. Two signals for the indole NH were observed (δ 5.8 and 8.5 ppm) in a 2:3 ratio in the ^{1}H-NMR spectrum of the formamidine.

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8. In the cases of the hydrochloride salts (**4** and **7**), the DMF-DMA was first removed, then the resulting solid worked up from ether-water.

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10. In some cases (e.g., entries 2 and 5 in Table) 2M NaOH was used instead of water.

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