Preparation of Amidines by Amidoxime Reduction with Potassium Formate

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Abstract: Amidines can be prepared by reducing acylated amidoxime with potassium formate. The method has proved to be very simple and effective.

Key words: palladium, reductions, amidines, green chemistry

The amidine group is present in many compounds acting on a wide range of biological targets. It is an important pharmacophore in serine protease inhibitors,[1] and fibrinogen receptor antagonists,[1,2] nitric oxide synthase inhibitors[3] or tyrosine kinase inhibitors.[4] Amidine derivatives also possess antimicrobial activity.[5]

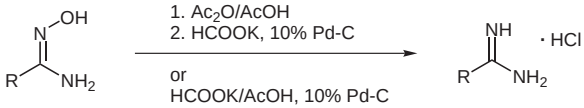
Several routes to amidines from nitriles have been published, such as conversion via amination of imidates (Pinner reaction)[6] or thioimidates,[7] addition of aluminum amide to nitriles,[8] reduction of 1,2,4-oxadiazoles,[9] and reduction of amidoximes.[10–13]

These procedures involve harsh reaction conditions, reagents that are difficult to handle, use hydrogen gas, some are water-sensitive, the isolation is fairly complicated and the yields are variable.

In search of new integrin receptor antagonists we sought for a new environmentally friendly method to prepare amidines in a straightforward and efficient way using recyclable reagents, minimizing operational hazards and giving constant yields.

Formic acid and its salts are well-known hydrogen donors and are frequently used in reductive chemistry. Many reactions have been described: reduction of aromatic nitro groups to arylamines,[14] dehalogenation of arylhalides,[15] deprotection of benzyl or benzyloxycarbonyl groups,[16] and removal of peptides from solid-phase resins.[17] The advantage of using formate salts instead of hydrogen gas is safety and easier handling of reactants, which is therefore easier to implement in industrial synthesis.

As a reducing agent we chose potassium formate over ammonium formate for a number of reasons. First, the amidine hydrochloride salt is easier to isolate and purify, since potassium chloride formed is insoluble in ethanol and other organic solvents and can simply be filtered off. When using ammonium formate or other organic amine formate salts, the resulting amine hydrochloride is partially soluble in ethanol or methanol, making isolation and purification of the amidine salt problematic. Secondly, it has been demonstrated that HCOOK, unlike ammonium formate, is a true hydrogen donor, since no hydrogen gas is released in the course of the reaction, making it safer for large-scale synthesis. Thirdly, it is recyclable, either by hydrogenation or simply by adding HCOOH. Fourthly, potassium formate is a more active donor of hydrogen than sodium or ammonium formate.[14]



Scheme 1 Reduction of amidoximes

We prepared several amidoximes by reacting the starting nitrile with hydroxylamine hydrochloride in the presence of a base and employed two approaches to reduce them to amidines (Scheme 1), one under slightly basic and acidic conditions, the second by acylating the amidoximes and reducing them under acidic conditions.

Reduction of amidoximes with HCOOK in acetic acid proceeded slowly and was complete in 24 hours (data not shown). When using HCOOK in MeOH, however, the reaction was incomplete even after 24 hours, indicating that the acidic medium accelerates the reduction.

Since amidoxime was not a very good substrate for reduction we tried to activate it by using the procedure of Judkins et al.,[11] in which the amidoxime is transformed into the more reactive acylated intermediate. Amidoximes were acylated in less than ten minutes, as reported.[11] The subsequent reduction was complete within 10 to 30 minutes, as shown in Table 1 (entries 1–4).

Surprisingly, an aliphatic amidoxime took much longer to reduce than the aromatic amidoximes (entry **5**). This is attributed to the reduction step, since acylation was complete in less than ten minutes in both cases.

Since the reaction takes place in acidic medium and free formic acid is formed from HCOOK, we tried using only HCOOH (data not shown), but the reaction did not even start until potassium carbonate was added. This is in agreement with the earlier finding that formic acid is practically inactive as a reducing agent.[14]

Acetic acid is expected to be superior to stronger acids for acidification, since there is equilibrium at lower pH between the active formate anion (originating from potassium formate) and the inactive formic acid (in 1 mL of glacial acetic acid the molar ratio of HCOOK/HCOOH is approximately 0.5). Stronger acids would shift the

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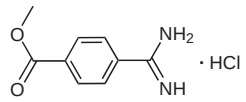
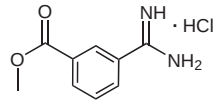
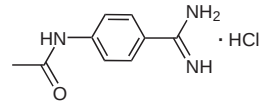
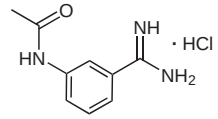
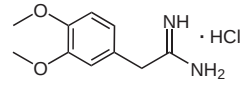
Table 1 Reaction Times and Yields

Entry	Compound	Reaction time	Yield (%)
1	 **1**	10 min	87
2	 **2**[20]	40 min	63
3	 **3**	10 min	85
4	 **4**	30 min	82
5	 **5**	12 h	88

equilibrium towards the formic acid, slowing down or stopping the reaction entirely.

The reaction proceeds readily in commercial but not in anhydrous solvents; no reaction took place in anhydrous EtOH without the addition of water. A certain amount of water is therefore essential for the reaction to take place. In fact, Wiener et al.[15] have demonstrated that water and formate are adsorbed on the Pd/C catalyst, where hydrogen is formed by combination of a hydride ion originating from formate and a proton from a water molecule. The reduction thus takes place on the catalyst surface.

We have described a simple and effective reduction of amidoximes alone[18] or preferably via an acylated intermediate,[19] i.e. via the modified Judkins[11] procedure. The reactions take place in acidic media, preferably in acetic acid, yielding amidine salts in high yields.

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(18) **Typical Procedure for Reduction of Amidoxime**: The parent amidoxime (1 mmol) was dissolved in a mixture of glacial AcOH (1 mL) and potassium formate solution in MeOH (10 mmol), followed by the addition of 10% Pd/C. The mixture was stirred at r.t. until the reaction was complete based on TLC. Isolation and purification were performed as described in ref. 19 to yield pure amidine hydrochloride.
(19) **Typical Procedure for Reduction of Amidoxime via the Acylated Intermediate**: Potassium formate was prepared in situ from HCOOH (10 mmol) and K_2CO_3 (5 mmol) in MeOH (1.5 mL). The parent amidoxime (1 mmol) was dissolved in AcOH (1 mL) and Ac_2O (1.1 mmol) was added at r.t. After 5 min, potassium formate solution in MeOH was added, followed by 10% Pd/C. The mixture was stirred at r.t. until reaction was complete based on TLC. The solids were filtered, washed with MeOH or EtOH, and the filtrate was evaporated. The residue was dissolved in anhyd EtOH and 5 M HCl in anhyd EtOH (12 equiv) was then added. The solids were filtered, washed with anhyd EtOH and the filtrate was evaporated to yield pure amidine hydrochloride.
(20) **Representative Spectroscopic Data for Compound 2**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.92 (s, 3 H, Me), 7.78 (t, *J* = 7.8 Hz, 1 H, ArH), 8.11 (d, *J* = 7.8 Hz, 1 H, ArH), 8.28 (d, *J* = 7.8 Hz, 1 H, ArH), 8.38 (s, 1 H, ArH), 9.37 (s, 2 H, NH_2), 9.58 (s, 2 H, NH_2^+). ^{13}C NMR (300 MHz, DMSO-d_6): δ = 166.1, 134.8, 133.7, 131.1, 130.5, 129.6, 53.5. HRMS: *m*/*z* [M^+] calcd for $C_9H_{10}N_2O_2$: 178.0742; found: 178.0750.