Direct Conversion of Amidoximes to Amidines via Transfer Hydrogenation

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Received 25 June 2003

Abstract: Amidoximes, O-alkylamidoximes, and O-acylamidoximes are directly converted to amidines by reaction with ammonium formate and Pd/C in acetic acid.

Keywords: amidines, amidoximes, reductions, hydrogen transfer, protecting groups, ammonium formate

The amidine unit is the key functional group in a wide range of biologically active molecules, including a variety of serine protease inhibitors and antimicrobial agents. Amidines are typically made from nitriles by one of several routes such as the Pinner method, conversion to a thioimidate or by direct reaction with alkylchloroalumminium amides. These processes, however, are often time consuming and require the careful exclusion of water. More conveniently, amidines can be obtained by reduction of amidoximes, which in turn are readily prepared by the reaction of a nitrile with hydroxylamine. Although amidoximes have been reduced directly to amidines by transition-metal catalyzed methods, the present approaches have not seen widespread use as they typically require high hydrogen pressure and heat or the use of carbon monoxide. A more convenient approach to catalytic hydrogenation of the in situ formed O-acyl derivatives at low pressure and room temperature. First reported by Judkins and co-workers, this indirect method for reduction of amidoximes has made the two step approach to amidines from nitriles quite attractive as demonstrated by its widespread use in recent years.

As part of a program of synthesis of diamidines as antimicrobial agents, and in an effort to eliminate the need for hydrogen gas for the efficient conversion of amidoximes to amidines, we have explored the use of ammonium formate (AF) as a hydrogen transfer reagent. Indeed, AF in the presence of Pd/C has been reported to reduce a number of different functional groups. In this paper, we report that the AF/Pd/C system directly and efficiently reduces amidoximes, as well as some protected amidoximes, providing the corresponding amidines in good yield.

In initial experiments using EtOH or i-PrOH as solvent, the heating of benzamidoxime (1a) in the presence of ammonium formate (5 equiv) and Pd/C (100% by weight) for 24 hours resulted in only modest reduction of the amidoxime. In contrast, the use of refluxing acetic acid as solvent was found to give complete and clean conversion to the amidine in about 3 hours (Scheme 1). As shown in Table 1, several substituted benzamidoximes (1b–g) were subsequently reduced using this method providing the amidines in good isolated yields (66–85%). Reaction times for these examples ranged from 3–8 hours, with the progress of the reaction easily followed by TLC. In the case of amidoxime 1b, the chloro substituent was lost by hydrogenolysis, a commonly noted result for Pd/C catalyzed transfer hydrogenation reactions. In the case of the furan bisamidoxime 1h, an extended reaction time of 24 h was required for complete conversion to the bisamidine (furamidine), which is a promising antimicrobial agent.

![Scheme 1](image)

R = H, Alkyl, Acyl

The reduction of several amidoxime protecting groups by the AF/Pd/C method was also examined using compounds 1i–k. In each case, the protecting group was removed efficiently giving the amidine in good isolated yield (70–81%). The removal of the acetoxy group of 1i and the cyclic acyl group of 1j using standard catalytic hydrogenation has been previously reported. Conversion of the 1,2,4-oxazolin-5-one 1j to the amidine without the use of hydrogen makes this already extremely valuable amidine protecting group even more attractive. Finally, the O-methylamidoxime 1k and O-benzylamidoxime 1l are also efficiently reduced to the amidine using the AF/Pd/C system. This is particularly noteworthy as O-methyl protected amidoximes have recently been shown to undergo Pd-catalyzed N-arylation, while the parent amidoximes do not.

In summary, we have described the direct conversion of amidoximes, as well as some protected amidoximes, to amidines using a transfer hydrogenation approach. This process significantly simplifies amidine preparation since it neither requires the rigorous exclusion of water nor the use of hydrogen gas.

1H NMR and 13C NMR spectra were obtained on a Varian Unity+300 instrument at r.t. DMSO-d6 was used as NMR solvent, with the solvent peak serving as reference (δ = 2.49 for 1H NMR and 39.5 for 13C NMR). Mass spectra were obtained from the Georgia Institute of Technology, Atlanta, GA. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. Amidines 2a.
have been previously reported; physical and spectral data were comparable.

4-Methylbenzamidine Hydrochloride (2e); Typical Procedure
To 4-methylbenzamidoxime (1e) (1 mmol, 150 mg) dissolved in glacial HOAc (5 mL) was added slowly ammonium formate (5 mmol, 315 mg) and Pd/C (10%; 150 mg) and the mixture was heated at reflux under nitrogen. After consumption of the starting material (TLC monitoring), the mixture was cooled and filtered through Celite. The filtrate was evaporated in vacuum, and the residue was basified with aq NaOH (1 M) and extracted with EtOAc (3 × 25 mL). The combined organic layers were successively washed with H₂O (5 × 20 mL) and brine, and then dried (Na₂SO₄). Removal of the solvent under reduced pressure gave the 4-methylbenzamidine (2e) (98.5 mg, 73%), which was converted to the hydrochloride salt using anhyd HCl in EtOH.

**Table 1** Conversion of Amidoximes to Amidines using Ammonium Formate and Pd/C

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<thead>
<tr>
<th>Entry</th>
<th>Starting Amidoxime (1)</th>
<th>Product (2)</th>
<th>Reaction (h)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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<sup>a</sup> Isolated yield; all products were characterized by NMR (¹H and ¹³C), MS and elemental analysis.

2c, 2d, 2f, 2g, and 2h have been previously reported; physical and spectral data were comparable.

4-Methylbenzamidine Hydrochloride (2e); Typical Procedure
To 4-methylbenzamidoxime (1e) (1 mmol, 150 mg) dissolved in glacial HOAc (5 mL) was added slowly ammonium formate (5 mmol, 315 mg) and Pd/C (10%; 150 mg) and the mixture was heated at reflux under nitrogen. After consumption of the starting material (TLC monitoring), the mixture was cooled and filtered through Celite. The filtrate was evaporated in vacuum, and the residue was basified with aq NaOH (1 M) and extracted with EtOAc (3 × 25 mL). The combined organic layers were successively washed with H₂O (5 × 20 mL) and brine, and then dried (Na₂SO₄). Removal of the solvent under reduced pressure gave the 4-methylbenzamidine (2e) (98.5 mg, 73%), which was converted to the hydrochloride salt using anhyd HCl in EtOH.

Mp 209–212 C (lit. 210–213 C).<sup>y</sup><sup>h</sup>

¹H NMR (DMSO-d₆): δ = 2.38 (s, 3 H, CH₃), 7.41 (d, 2 H, J = 6.0 Hz, Ar), 7.77 (d, 2 H, J = 6.0 Hz, Ar), 9.26 (br, 3 H, NH, NH₂).

¹³C NMR (DMSO-d₆): δ = 20.9, 124.8, 127.8, 129.3, 144.2, 165.4.

MS (EI): m/z = 135.1 (M + 1), 108.7.
Anal. Calc'd for C₇H₈N₅.HCI.0.65 H₂O:  C, 52.69;  H, 6.79;  N, 15.39. Found:  C, 52.85;  H, 6.72;  N, 15.72.

Acknowledgment

This work was supported by awards from NIH (Grants NIAID RO1AI 46365, RO1GM61587), and the Bill and Melinda Gates Foundation.

References