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Reductive amination of ketones: novel one-step transfer hydrogenations in batch and continuous-flow mode

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ABSTRACT

Various ketones were efficiently transformed into the corresponding amines using ammonium formate in the presence of Zn dust or 10% Pd/C. The low-cost Zn dust method proved to be effective in amine formation from carbonyl groups at the benzylic side-chain position of aromatic systems, whereas 10% Pd/C was an efficient catalyst in the reductive aminations of carbonyl groups non-conjugated with any π-system. The 10% Pd/C-catalyzed reductions were performed more effectively in a continuous-flow X-Cube reactor than in the batch system.

Amines are indispensable building blocks in numerous drugs,[1,2] pesticides[3], and color pigments.[4] Thus, development of general and efficient methods to prepare amino compounds is still required. One of the most convenient methods to synthesize amines is the reductive amination of carbonyl compounds.[5] The classical Leuckart–Wallach (LW)[6] reaction is clean and very simple, but it has several drawbacks such as the requirement of harsh conditions, formation of *N*-formyl derivatives, and the difficulty of selective synthesis of primary amines from ammonia.

Nowadays, reductive transformations of ketones into amines are performed in the presence of catalysts. A wide range of metal-containing catalysts, usually as metal complexes, such as Pd,[7–9] Ir,[10] Rh,[10] Ru,[10] and Ti[11] are utilized in these processes. Although some of these catalysts are widely used, they have limitations with regard to chemoselectivity, recyclability, safety, and costs.

Metals (Na,[12] Ni,[13] Raney-Ni,[14] Pd,[15] Pt[16] or Ru[15]), or metals on activated charcoal (Pd/C,[15] Ru/C[15]) are also used in reductive aminations of ketones. In these cases, either the metal is dissolved in a protic solvent in the presence of an ammonia source, or the metal serves as the catalyst under an H_2 atmosphere in the presence of NH_3 or other ammonia source.[17] Sometimes, these processes result in various side reactions such as formation of alcohols, Schiff-bases, imines, and bis-amines.[15]

Amines can be formed stereoselectively by employing chiral complexes[18–21] or enzymes.[22,23] In many cases, however, cost, recyclability or environmental issues make such methods unsuitable for large scale production.

As the formation of oximes from carbonyl compounds is a well established process,[12,24] and that amines can be prepared by reduction of oximes with $LiAlH_4$,[25] or by various metals such as Zn[26–28] or Mg,[29] the combination of these two methods can provide a synthetic pathway to amines from ketones.

Metals or metal-containing catalysts can be applied for reductive aminations with various reducing agents.[5] In these processes, molecular hydrogen,[13–16,18] metal hydrides such as $NaBH_4$[11,30] or $NaBH_3CN$,[31] or various transfer hydrogenating agents such as Hantzsch esters[19] can serve as the reducing agents. In addition, reductive amination of ketones requires a nitrogen source such as ammonia,[13–16,20,32] ammonium salts (NH_4Cl,[15,16,30] NH_4OAc[31]), L-alanine[22,23] or isopropylamine.[23a,b]

Ammonium formate is an inexpensive, non-toxic, and environmentally safe reagent, and could serve as both the nitrogen source and the transfer hydrogenating agent simultaneously.[7,8,10,20,21] Ammonium formate was successfully applied previously in metal

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complex catalyzed[10,20,21] or Pd/C-catalyzed[7,8] reductive aminations of ketones.

The development of novel synthetic techniques influences not only the large scale production of pharmaceuticals, fine chemicals, and agrochemicals but also provides efficient methods for research laboratories to be able to prepare increased numbers of compounds. Despite the strong trend for automation, the majority of amine chemistry at the research phase is still carried out in batches, whereas flow processes are restricted to production processes.[2,5] Consequently, exploitation of the main advantages of the flow approach in the discovery phase, such as facile automation, reproducibility, safety, and process reliability, has gained significant interest.[33]

In this Letter, the reductive amination of ketones was investigated with ammonium formate and various metals/metal catalysts in one-pot and one-step reactions using both batch and continuous-flow methods.

The two-step production of oximes from ketones and their reductive transformation into amines are well known.[24–29] Although simple metal-promoted transfer hydrogenations of oximes using ammonium formate and Zn[26] or Mg[29] in methanol have been developed, the oxime formation and reduction steps have not been combined into a one-pot process. Since oxime reduction with $HCOONH_4$ and Zn in methanol[26] proved to be reproducible and effective, we first investigated a one-pot method using these reagents for different aliphatic, cycloaliphatic, and aromatic ketones **1a–i**. Thus, ketones **1a**–**i** were treated with $H_2NOH{\cdot}HCl$, $HCOONH_4$, and Zn dust in methanol under reflux until disappearance of the starting ketones by TLC (Method A, Fig. 1 and Table 1). The one-step reductive amination of ketones with the carbonyl group α to the aromatic ring yielded the desired amines in moderate to good yields (**2e**–**i**, Method A in Table 1). On the other hand, aliphatic and cycloaliphatic ketones (**1a**–**d**) could not be aminated under these conditions (Method A, Table 1).

The one-pot process (Method A, Fig. 1 and Table 1) may not necessarily proceed via an oxime intermediate if the imine formed from ammonium formate could be reduced. Therefore, we omitted toxic $H_2NOH{\cdot}HCl$, and studied the formation of 1-phenylethylamine (**2g**) from acetophenone (**1g**) as a model experiment to test if using only $HCOONH_4$ in the presence of various metals or metal catalysts was a viable method. Preliminary screens were carried out in methanol (with 6 equiv of $HCOONH_4$), or in methanol–water 9:1 mixture (with 10 equiv of $HCOONH_4$) at room temperature (16 h) or under reflux (5 h). While Raney-Ni, Mg dust, and Cu dust were not effective under either conditions, Zn dust and 10% Pd/C proved to be effective in reductive aminations under certain conditions. Zn dust promoted reactions did not occur at room temperature, whereas at reflux, 1-phenylethylamine (**2g**) was produced in 60–71% yields (the highest yield was observed when the solvent was pure methanol). In the 10% Pd/C-catalyzed reactions, room temperature was sufficient to reduce acetophenone (**1g**). Besides formation of the desired amine **2g** in 17% yield, an almost 1:1 mixture of racemic and *meso* bis(1-phenylethylamine) as undesired side products was isolated (50%).[34] The yield of amine **2g** and the side products were virtually unaffected by the presence of water (10%) and a larger excess of $HCOONH_4$ (10 equiv) in methanol.

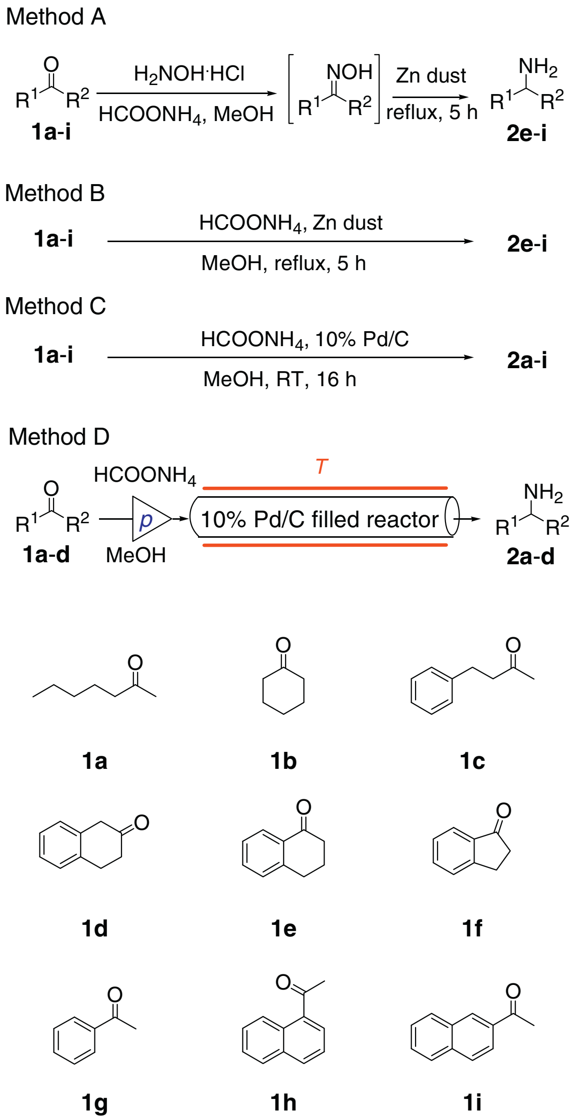

Figure 1. Reductive aminations of ketones **1a**–**i**.

Table 1
Reductive aminations of ketones **1a**–**i** with ammonium formate in methanol

Ketone	Yield of amine **2a**–**i** (%)			
	Method A	Method B	Method C	Method D[a]
1a	[b]	[b]	52	53
1b	[b]	[b]	60	68
1c	[b]	[b]	38	41
1d	[b]	[b]	64	67
1e	69	71	5	[c]
1f	51	56	11	[c]
1g	36	71	17	[c]
1h	40	37	<5	[c]
1i	64	68	20	[c]

[a] Reaction in a packed-bed continuous-flow reactor at 40 °C and at 0.2 ml/min flow rate.
[b] No product formation was observed by TLC.
[c] Not tested.

Following these model experiments, one-step reductive aminations with the two most promising systems (Zn dust and 10% Pd/C) were performed with all the ketones **1a**–**i**. The Zn dust promoted reactions were carried out in methanol under reflux (Method B, Fig. 1 and Table 1), whereas the 10% Pd/C-catalyzed processes were performed at room temperature (Method C, Fig. 1 and Table 1). The two methods were found to be complementary, because the Zn dust promoted reactions (Method B, Fig. 1 and Table 1) of ketones with the carbonyl group at the benzylic position of an aromatic side chain, **1e**–**i**, resulted in smooth formation of the corresponding amines **2e**–**i** in moderate to good yields (37–71%, see Method B in Table 1), while the 10% Pd/C-catalyzed reactions (Method C, Fig. 1 and Table 1) were more suitable to convert aliphatic and cycloaliphatic ketones **1a**–**d** into the corresponding amines **2a**–**d** (in 38–64% yields). On the other hand, Zn dust was not effective for the transformation of aliphatic and cycloaliphatic ketones **1a**–**d** (see Method B in Table 1), while 10% Pd/C-catalysis resulted in significant formation of side products (mostly bisalkylated-amines), thereby decreasing the yields of the desired amines **2e**–**i** (see Method C in Table 1).

We also investigated the application of these methods for the reductive amination of ketones in continuous-flow systems using the X-Cube flow reactor. Since various Zn-salts were formed and precipitated during the Zn dust promoted reductive aminations (Methods A and B, Fig. 1 and Table 1), these methods were not appropriate for the continuous-flow system. As the reaction mixture remains homogeneous with the 10% Pd/C-catalyst (Method C, Fig. 1 and Table 1), reductive aminations of aliphatic and cycloaliphatic ketones **1a**–**d** were carried with the continuous-flow system using a packed-bed column containing 10% Pd/C (Method D, Fig. 1 and Table 1: 6 equiv of $HCOONH_4$ and 5 mg mL^{-1} of ketones **1a**–**d** in methanol; 40 °C; 0.2 mL min^{-1}; no measurable back-pressure). After the stationary state was reached (~8 times dead volume of the column, 40 min), feeding the reactor with the corresponding ketones **1a**–**d** was continued for 6 h. The amines **2a**–**d** were isolated from the collected homogeneous solutions (Method D, Table 1). In all cases, similar or higher yields of the amine were obtained compared to the corresponding batch reaction (53% vs 52% for **2a**; 68% vs 60% or 65%[7] for **2b**; 41% vs 38% for **2c** and 67% vs 64% for **2d**). The reactions were repeated for ketones **1a**–**d** in a second series of reductions on the same 10% Pd/C-filled column resulting in the same yields of products **2a**–**d**. The same catalyst column was used for at least 56 h of continuous reaction time with no catalyst deactivation observed. Therefore, the main advantage of the continuous-flow system with 10% Pd/C-columns is the recyclability and the efficient, safe and reproducible use of the catalyst for an extended period of time, thereby resulting in a more environmentally friendly process.

In summary, we have developed new, efficient, and convenient methods for the reductive amination of ketones. The methods use ammonium formate as the hydrogen source (similarly to the well known Leuckart reaction), but application of Zn dust or 10% Pd/C-catalyst in methanol eliminates the need for harsh conditions which can hinder industrial applications. The two methods are complementary: the Zn dust promoted reactions gave amines **2e**–**i** (in 37–71% yields) from ketones with a carbonyl group at the benzylic position of an aromatic side chain **1e**–**i**, while the 10% Pd/C-catalyzed reactions were more suitable for the conversion of aliphatic and cycloaliphatic ketones **1a**–**d** into the corresponding amines **2a**–**d** (in 38–64% yields).

Retention of the homogeneous phase for the 10% Pd/C-catalyzed transfer hydrogenations of aliphatic and cycloaliphatic ketones **1a**–**d** allowed the recyclable, efficient, and reproducible use of this catalyst in a continuous-flow reactor.

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Supplementary data

Supplementary data (experimental details) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.062.

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