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Direct Leuckart-type reductive amination of aldehydes and ketones: a facile one-pot protocol for the preparation of secondary and tertiary amines

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ABSTRACT

A high-yielding and facile one-pot Leuckart-type reaction for rapid access to a number of 2° and 3° amines is described.

In modern organic synthesis, the *direct* reductive amination (DRA)[1] of aldehydes and ketones is a powerful and highly attractive protocol for the synthesis of primary, secondary, and tertiary amines.[2] Its one-step procedure offers operational convenience and avoids preformation or isolation of the imine or iminium intermediates prior to their reduction. The selective reduction of the in situ formed C=N bond and the stability of the reducing agent under the reaction conditions, which are often acidic, are critical to the overall success of the process. Catalytic hydrogenation methods,[3] both economical and eco-friendly, are effective for DRAs but are not compatible with substrates with reducible moieties, such as cyano[4] and nitro[5] groups, and may yield alcohols as by-products. Among metal hydride reducing agents, sodium cyanoborohydride ($NaBH_3CN$)[6] and sodium triacetoxyborohydride ($NaBH(OAc)_3$),[7] both commercially available, have been widely used. Sodium cyanoborohydride is highly toxic and formation of toxic by-products, such as HCN and NaCN create problematic disposal issues and may contaminate the product.[8] Other drawbacks include the need to use a fivefold excess of the amine and slow reaction rates with aromatic ketones and amines of lower basicity. Sodium triacetoxyborohydride, though less toxic, is flammable and water-reactive, and similar limitations are encountered with aromatic, α,β-unsaturated, and sterically hindered ketones.[7a] To overcome such limitations, a variety of other reductant systems, though not as widely used, have been developed. The majority of these reagents employ a catalyst combined with a reducing agent.[9]

An alternative DRA approach for the preparation of amines is the Leuckart reaction,[10] whereby an aldehyde or a ketone is heated in the presence of ammonium formate[11] or formamide,[12] or mixtures of formamide and formic acid.[13,14] The product of the Leuckart reaction is often the formyl derivative of the desired amine,[11–13] which must be hydrolyzed with acid. This requirement makes the Leuckart reaction unsuitable for substrates with acid-sensitive moieties. Ingersoll et al.[15] improved the original Leuckart procedure and expanded the scope of the reaction by developing an ammonium formate-formamide reagent that, when combined with a ketone and heated in the range of 160–185 °C for several hours followed by acid hydrolysis, afforded 1° amines in 60–80% yield.

Over the years, different mechanisms have been suggested for the Leuckart reaction;[16] imines, iminium ions, *N*-formyl imines, or *N*-formyl iminium cations have been implicated as intermediates in the process.

As part of our continued efforts on the use of simple ammonium salts in synthetic transformations,[17] we recently reported a high-yielding one-pot procedure for the preparation of a wide range of iminium salts (**1**) by direct combination of an aldehyde or a ketone with a 2° amine free base in the presence of ammonium tetrafluoroborate, ammonium perchlorate, or ammonium hexafluorophosphate (Scheme 1).[18]

Since iminium ions are possible intermediates in the Leuckart reaction, we envisioned that reduction of the in situ formed C=N bond of **1** should occur readily by substituting ammonium formate[19] for the ammonium salts previously used for the preparation of iminium salts **1**. Therefore, we decided to explore the preparation

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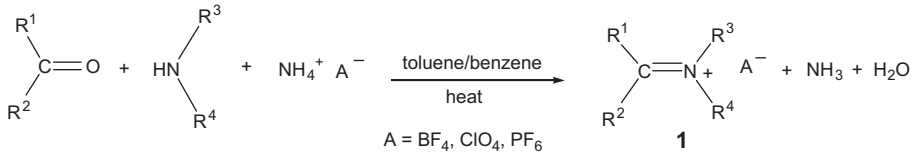
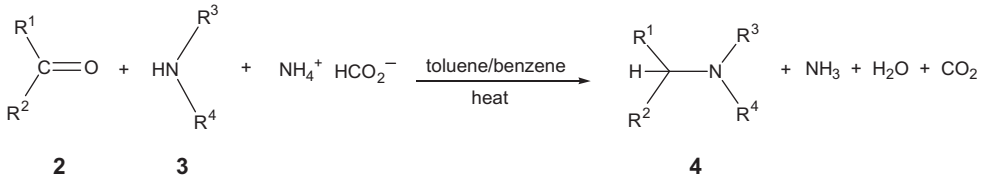
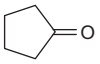
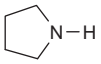
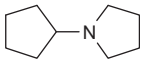
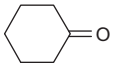
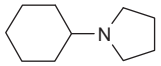
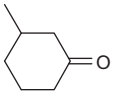
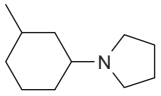
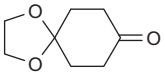
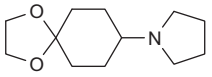
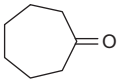
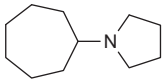
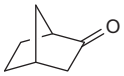
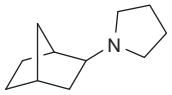
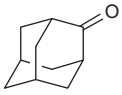
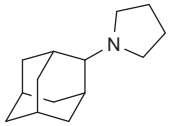
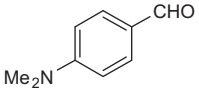
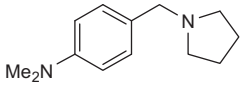
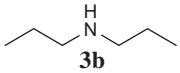
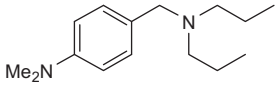
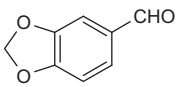
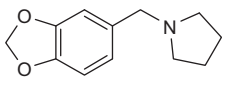
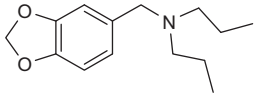


Scheme 1. One-pot preparation of iminium salts **1**.



Scheme 2. One-pot Leuckart-type preparation of amines **4**.

Table 1
One-pot preparation of 2° and 3° amines (**4**)

Entry	Aldehyde/ketone	Amine	Product	Yield (%)		Time (h)
				Benzene	Toluene	
1		 **3a**		84	54	1.5
2		**3a**		89	72	1.5
3		**3a**		80	73	1.5
4		**3a**		87	75	1.5
5		**3a**		82	71	1.5
6		**3a**		79	71	1.5
7		**3a**		66	75	1.5
8	 **2a**	**3a**		89	70	1.5
9	**2a**	 **3b**		85	75	1.5
10	 **2b**	**3a**		76	73	1.5
11	**2b**	**3a**		73	72	1.5