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One-pot, new stereoselective synthesis of *endo*-tropanamine

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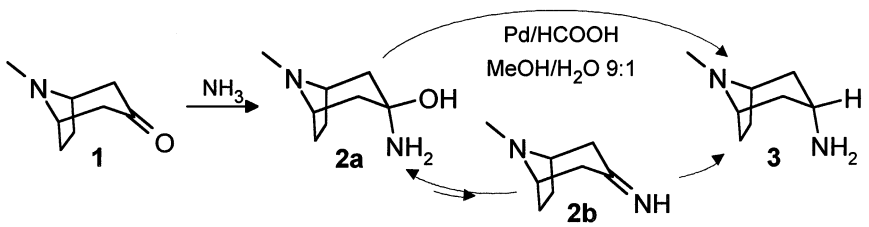
Abstract—A palladium-catalysed reduction of ketones to primary amines by reaction with ammonium formate in aqueous methanol is described. The proposed method provides a one-pot synthesis of 3-*endo*-tropanamine in high yields and stereoselectivity.

In the past few years attention has been paid to the search for an improved method leading to the formation of 3-*endo*-tropanamine **3** (Scheme 1) with high yield and stereoselectivity. The bicyclic 3-*endo*-tropanamine structure is an important intermediate in the synthesis of widely used drugs; the amide derivatives are interesting molecules as antagonists of the 5-HT_3 (5-hydroxytryptamine) receptor. 7-Azaindolylcarboxy-*endo*-tropanamide is a new antitussive drug at present involved in phase II clinical trials.[1]

The most widely used method for the introduction of the *endo*-amino group is the catalytic hydrogenation (PtO_2, EtOH, H_2) of the benzylamine Schiff's base of tropanone.[2] The hydrogenolytic removal of the benzyl group yields an unsatisfactory 8:1 mixture of *endo*/*exo* tropanamines; moreover, the formation of side products makes this process unsuitable for industrial purposes. Hutchins reported[3] that bulky reducing reagents enhance the selectivity of *exo* addition of hydrogen to the tropanone imines due to the different reactivity of the two faces. LaBell in a detailed reactivity study[4] selected a new reagent for the Schiff's base reduction from a series of bulky acyloxyborohydrides: sodium tris[(2-ethylhexanoyloxy)borohydride] provides good yields of *N*-benzyltropanamine and very high stereoselectivity (>50:1). The poor reproducibility of the debenzylation step and the high reagent cost stimulate the investigation of alternative routes.

The growing industrial request for this intermediate encouraged us to search for a competitive, highly selective procedure for the 3-*endo*-tropanamine synthesis. Unfortunately the one-step Borch's reductive amination using ammonium acetate and either $NaCNBH_3$[5] or borohydride exchange resin (BER)[6] yields the desired product with low stereoselectivity (2:1 *endo*/*exo* ratio).

We developed an alternative Pd-catalysed route for the 3-*endo*-tropanamine synthesis that employs only ammo-



Scheme 1. Suggested pathway for the reductive amination of carbonyl compounds using ammonium as nitrogen and hydrogen source.

Keywords: reductive amination; tropanamine; stereoselectivity.

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nium formate as nitrogen and hydrogen source.† Preliminary attempts to perform the reaction in methanol led to the desired product with low yield but very high stereoselectivity. This result prompted us to investigate the solvent effects and we observed that water addition (10%) to the alcoholic medium surprisingly increased the reaction yield, still maintaining a very high stereoselectivity. Therefore we worked to improve the reaction conditions in the advantageous aqueous medium.

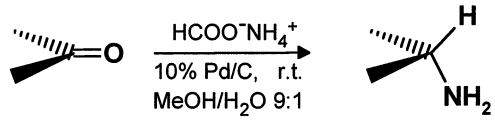
The method reported in the general procedure is optimised for the 3-*endo*-tropanamine synthesis and allowed us to obtain the product in very high yield and stereoselectivity. Nevertheless this procedure was verified with other carbonyl compounds and shown to be a general route for the synthesis of primary amines from ketones under mild reaction conditions and with high yields (Table 1).

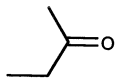
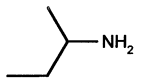
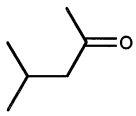
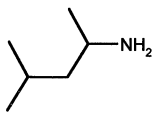
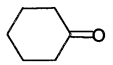
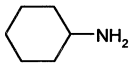
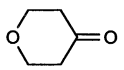
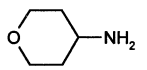
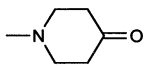
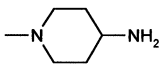
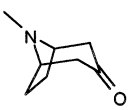
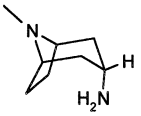
Our new method has the use of ammonium formate as the hydrogen source in common with the well-known Leuckart reaction,[7] but the palladium catalyst avoids harsh conditions (high temperatures, lack of solvent and undesired side reactions) inappropriate for industrial use. In addition we obtained unexpected results in terms of yield and stereoselectivity; the 3-*exo*-tropanamine isomer is practically undetectable (<0.1% determined on the crude residue using common analytical GC methods).

Looking at the hypothetical imine intermediate **2b**, it is not obvious what effect water has on the reaction yield because of the instability of the imine species in the aqueous medium. In our opinion water addition disfavours imine formation from the hemiaminal intermediate which, under the reaction conditions, is directly reduced to the *endo*-amine **3**. This hypothesis is in line with the observed stereoselectivity because the *endo*-aminal **2a** is the favoured one according to Alder's rule[8] (Scheme 1).

We think that the aminal reduction occurs by a direct transfer of the formate hydrogen mediated by the catalyst. To support this hypothesis we carried out a reaction replacing ammonium formate with ammonium acetate and bubbling through hydrogen gas as the hydrogen source; as expected no product formation was observed.

Table 1. Reductive amination of several ketones



	Substrate	Product	Yield*(%)
(a)			95
(b)			92
(c)			65
(d)			80
(e)			75
(f)			83

*Isolated yields from the starting ketone

In summary, we have found a simple, high yielding, one-pot, convenient procedure for the transformation of ketones into primary amines. This method, optimised for the synthesis of 3-*endo*-tropanamine from tropanone, gives useful results with several ketones. Our reaction conditions allow the desired products to be obtained in high yield and stereoselectivity. This procedure is an improved choice to Borch and Leuckart's methods commonly used for the synthesis of primary amines by reductive amination.

† **General procedure for the synthesis of 3-*endo*-tropanamine 3**: A solution of 8-methyl-8-azabicyclo[3.2.1]octan-3-one (**1**) (6 g, 43 mmol) in MeOH (112 mL) was treated, with vigorous stirring, with ammonium formate (25 g, 0.40 mol) and water (12.5 mL). After complete dissolution, 10% Pd/C (5.1 g, 4.8 mmol) was added and the reaction mixture was stirred overnight at room temperature. On completion of the reaction (TLC, eluent: EtOH/NH_4OH, 8:2), the catalyst was filtered off on Celite and the solution was concentrated under reduced pressure; the oily residue obtained was dissolved in EtOH (100 mL) and to the solution 37% HCl (7.5 mL) was added dropwise. The solution was seeded and left stirring at room temperature for 1 h and at 4°C for 5 h. The resulting white precipitate was filtered and dried at 40°C under vacuum to give *endo*-8-methyl-8-azabicyclo[3.2.1]octane bis hydrochloride (7.6 g, 35.6 mmol) in 83% yield; mp >360°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.2–11.0 (bs, 1H), 8.7–8.2 (bs, 3H), 4.0–3.8 (bs, 2H), 3.7–3.5 (m, 1H), 2.8–2.55 (m, 5H), 2.4–2.05 (m, 6H). Anal. calcd for $C_8H_{18}N_2Cl_2$ (213.48).

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