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Direct reductive amination of aldehydes using lithium-arene(cat.) as reducing system. A simple one-pot procedure for the synthesis of secondary amines

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ABSTRACT

A simple one-pot procedure for the direct reductive amination of aldehydes using lithium powder and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB) or a polymer supported naphthalene as reducing system is described. The direct reductive amination of a variety of aldehydes with primary amines was achieved simply by adding a mixture of the corresponding carbonyl compound and the amine, over a solution of the lithium arenide in THF at room temperature. For most of the substrates tested the main reaction products were the secondary amines along with variable amounts of the corresponding alcohol and/or imine products. Theoretical DFT calculations have been applied in order to explain the differences in reactivity observed for aromatic substrates.

Amines and their derivatives are present in many naturally occurring bioactive molecules such as amino acids, nucleic acids and alkaloids, among others.[1] They are known to have interesting herbicidal and fungicidal activities and they are also utilised as versatile intermediates for the synthesis of pharmaceuticals, agrochemicals,[2] and as valuable building blocks for nitrogen-containing synthetic polymers. Amines can be synthesized by many different methods including: (a) reduction of nitrogen-containing functional groups such as nitro, cyano, azide, and carboxamide derivatives; (b) alkylation of ammonia, primary or secondary amines, using alkyl halides or sulfonates as alkylating agents;[1] and (c) reaction of aldehydes or ketones with ammonia, primary or secondary amines in presence of different reducing agents.[3] This latter is the so-called reductive amination reaction which is described as direct when the carbonyl compound and the amine are mixed together with a suitable reducing agent in a single operation (one-pot), without preformation of an imine or iminium salt. On the other hand, indirect reductive amination involves the preformation of an imine followed by its reduction in a second step. Direct reductive amination (DRA) offers significant advantages over other amine syntheses, including simplicity of the methodology, wide commercial availability of substrates, mild reaction conditions, and in some cases high functional group tolerance.[4] A wide variety of reducing agents and reaction conditions have been developed to perform this transformation, all of them presenting both advantages and disadvantages. The catalytic hydrogenation, for instance, is an attractive methodology from economical and ecological points of view. It can be mediated by several heterogeneous[5] and some homogeneous metal catalysts,[6] although the presence of some functional groups such as nitro, cyano and carbon-carbon multiple bonds may limit its applicability. Hydride reducing agents are also commonly used for the DRA of carbonyl compounds, among them the Borch reduction using sodium cyanoborohydride ($NaBH_3CN$), and reductive amination using sodium triacetoxyborohydride [$NaBH(OAc)_3$] have been widely used.[3,7] Sodium cyanoborohydride is stable in relatively strong acid solutions, is soluble in hydroxylic solvents such as methanol, and has different selectivities at different pH values; but it is expensive, highly toxic and may contaminate the product with NaCN, and generate toxic HCN upon work-up. Moreover, in some cases up to a fivefold excess of the amine is required in order to limit the competitive reduction of

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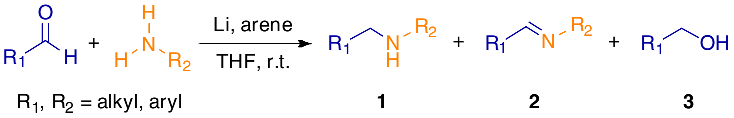
the C=O bond of the starting carbonyl compound. On the other hand, sodium triacetoxyborohydride is mild, presents a high functional group tolerance and reduces imines selectively over carbonyl compounds, but it is flammable, poorly soluble in most of the commonly used organic solvents, and has important limitations when aromatic and unsaturated ketones are used as starting carbonyl compounds. Another hydride reagent frequently used to perform the DRA reaction is sodium borohydride ($NaBH_4$). It is inexpensive, safe to handle, and can be employed for large-scale reductions,[8] nevertheless, the major drawbacks are its low selectivity, the harsh reactions conditions needed and, in many cases, the necessity of adding Brönsted acids to facilitate intermediate imine formation.[9] Many other hydride-based reducing systems have been applied to the reductive amination reaction, most of them associated with the use of complex catalysts, expensive and flammable reagents, and/or low product yield. Among them, organosilanes have the advantage to be organic-soluble reducing agents, however they present some limitations in substrate compatibility.[10] Apart from hydride-based reagents, the Hantzsch 1,4-dihydropyridine system is a mild, inexpensive and nontoxic reducing agent that has been used for the reductive amination of carbonyl compounds. Nevertheless, the reduction step proceeds in low yield, thus requiring long reaction times and the use of Lewis acids for the imine activation.[11] Some interesting related systems, using the Hantzsch ester as transfer hydrogenating agent and thioureas for selective imine activation, have recently been reported.[12]

On the other hand, alkali metals are known to be strong reducing agents, among them, lithium metal has been widely used for many reduction reactions in organic synthesis.[13] The reducing systems based on the use of alkali-metals in combination with arenes in aprotic media, with the arene acting as electron carrier via the generation of its radical anion, have received much attention. In the last years, some of us have been actively working on the preparation of transition metal nanoparticles by fast reduction of the corresponding transition metal chlorides with lithium and a catalytic amount of an arene [naphthalene, 4,4′-di-*tert*-butylbiphenyl (DTBB)] as electron carrier, for their application in many useful organic transformations.[14]

During the course of our studies on the reductive amination of aldehydes and ketones mediated by copper nanoparticles, we have found that the lithium-arene(cat.) system alone, in the absence of the copper nanoparticles, was capable of performing the desired transformation. In this work we want to introduce our results on a simple and efficient procedure for the direct reductive amination of aromatic and aliphatic aldehydes for the one-pot synthesis of secondary amines, using primary amines of several nature as starting materials in the presence of lithium powder and a catalytic amount of an arene (DTBB or a polymer supported naphthalene) in tetrahydrofuran as solvent and at room temperature (Scheme 1). The methodology reported in this work is simple, mild, economic, nontoxic, and does not need the use of any additives or acids. As far as we know, there are no reports on the direct reductive amination of aldehydes using lithium and arenes as promoters.

The direct reductive amination of a variety of aldehydes with primary amines of different nature, was achieved simply by adding a mixture of the corresponding carbonyl compound (1.0 mmol) and the amine (1.0 mmol) in THF (4 mL), over a solution of the lithium arenide obtained from the reaction of an excess of lithium powder (3.0 mmol) with a catalytic amount of DTBB (0.1 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature, under nitrogen atmosphere, until total conversion of the starting carbonyl compound (TLC, GLC).[15] For most of the substrates tested the main reaction products were the corresponding secondary amines (**1**) along with variable amounts of the direct reduction products of the starting carbonyl compounds (alcohols **3**). In some cases, the corresponding imines (**2**) were formed in very good yields but were resistant to further reduction. On the other hand, ketones remained unreacted under the same reaction conditions, even at higher reaction temperature (reflux of THF).

Table 1 summarizes the results obtained in the DRA of a series of aldehydes with different primary amines under the above described conditions. Benzylamine and *p*-methylbenzaldehyde were used as model substrates for determining the optimal reaction conditions. When DTBB was used as electron carrier the corresponding secondary amine was obtained in excellent yield and in only 1.5 h of reaction time (Table 1, entry 1). The same reaction performed below room temperature (0–15 °C) did not show conversion of the starting aldehyde. We then tested naphthalene as electron carrier in the same reaction conditions. After 1.5 h of reaction time the secondary amine was obtained in a lower yield compared with that of using DTBB (Table 1, entry 2), together with a considerable amount of 1,1′-binaphthyl as a side reaction product. These observations are in agreement with the fact that DTBB is better than naphthalene as mediator in electron transfer processes, mainly due to its lower reduction potential and its low tendency to coupling because of the steric hindrance caused by the *tert*-butyl groups. In the absence of an arene (DTBB or naphthalene), the secondary amine was obtained in much lower yield and the corresponding benzylic alcohol was formed in 20% yield (Table 1, entry 3), thus demonstrating the necessity of using an electron carrier for the DRA to occur. As reported by Compton et al.,[13b] the use of an arene as mediator in lithium reductions offers a very large rate increase over the non mediated route. On the other hand, in the last years we have been interested in the use of macromolecular structures as stabilizers for metal nanoparticles and, in connection with this goal, we have synthesized a copolymer of styrene and 2-vinylnaphthalene (PS-2VN) by anionic polymerization, which could act as a polymer supported electron carrier in the DRA reactions. Interestingly, the use PS-2VN (20 mg) and lithium (3.0 mmol) in the DRA of benzaldehyde (1.0 mmol) and cyclohexylamine (1.0 mmol) quantitatively gave the desired secondary amine (Table 1, entry 4), which was recovered from the reaction mixture simply by filtration without needing further purification. The use of the same copolymer in the DRA of *p*-methylbenzaldehyde with cyclohexylamine gave the corresponding secondary amine in a similar yield to that obtained using DTBB as electron carrier (Table 1, compare entries 5 and 14). In the optimised reaction conditions, using DTBB as arene, the DRA of benzaldehyde with aliphatic and aromatic amines such as dodecylamine, cyclohexylamine, aniline and benzylamine, gave the desired secondary amines in very good yields (Table 1, entries 6–9, respectively). Aliphatic aldehydes showed to be less reactive than their aryl counterparts, leading to the corresponding secondary amines in moderate yield and in longer reaction times (Table 1, entries 10 and 11).



Scheme 1. Reductive amination of aldehydes with primary amines.