Tetrahedron 69 (2013) 4938–4943

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Solvent- and catalyst-free direct reductive amination of aldehydes and ketones with Hantzsch ester: synthesis of secondary and tertiary amines

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ARTICLE INFO

Article history:
Received 11 October 2012
Received in revised form 8 April 2013
Accepted 11 April 2013
Available online 16 April 2013

Keywords:
Free catalyst
Free solvent
Reductive amination
Aldehydes
Ketones

ABSTRACT

A facile and rapid method for the parallel synthesis of a series of secondary and tertiary amines by the direct reductive amination of aldehydes and ketones with Hantzsch ester under solvent- and catalyst-free has been developed. The scope and limitation of this method are described.

1. Introduction

Amines are important in natural products, pharmaceuticals, and agrochemicals.[1] Reductive amination is one of the oldest but most powerful used methods of accessing different kinds of amines. In particular, a one-pot reaction, in which a carbonyl compound and an amine is treated directly with a suitable reductant, is very attractive from the synthetic viewpoint since it avoids the isolation of unstable imine or iminium intermediate.[2] Catalytic hydrogenation and metal hydride reduction are the two most commonly used direct reductive amination methods. However, catalytic hydrogenation can be incompatible with the polyfunctional substrates that contain olefins or alkynes, nitro, cyano, and furyl groups. Metal hydrides, such as cyanoborohydride ($NaBH_3CN$) and various borohydride derivatives, are expensive, highly toxic and have some drawbacks, such as long reaction time, require acidic and inert conditions, produce toxic by-products, and low selectivity.[3] Furthermore, in most of these reductive conditions, the complete removal of toxic metal impurities is often difficult but essential, especially in the production of pharmaceutical intermediates. This renders the development of metal-free reductive processes a very important research goal. For this reason, Hantzsch ester (HEH), a biomimetic, inexpensive, stable, and safe reducing agent, is of great interest.[4] The direct reductive amination of aldehydes and ketones using HEH has been extensively developed, together with effective catalysts, such as $Sc(OTf)_3$,[5] $ZnCl_2$,[6] $ZrCl_4$,[7] TMSCl,[8] HCl,[9] binol phosphoric acid,[10] gold (I) complex,[11] single nucleotide,[12] thioureas,[13] and most recently, *S*-benzyl-isothiouronium.[14] But all of these methods suffer some limitations, such as the need for inert reaction conditions, hazardous solvents and catalysts, long reaction times, tedious workups, low yields, and lack of generality. Herein, we wish to introduce a facile and rapid method for the parallel synthesis of a series of secondary and tertiary amines by the direct reductive amination of aldehydes and ketones with HEH under solvent- and catalyst-free conditions (Scheme 1).

2. Results and discussion

Initially, the direct reductive amination of aldehydes was performed with benzaldehyde (1 equiv), 4-methoxyaniline (1.2 equiv), HEH (1.2 equiv), and 5 Å MS, which were mixed together in air and then heated at 100 °C for 5 h without stirring to give the required product **4a** in 59% yield (Table 1, entry 1). Heating up to 150 °C dramatically shortened the reaction time to 15 min and afforded **4a** in nearly quantitative yield (Table 1, entry 2). In addition, 5 Å MS has commonly been introduced to remove water, which has

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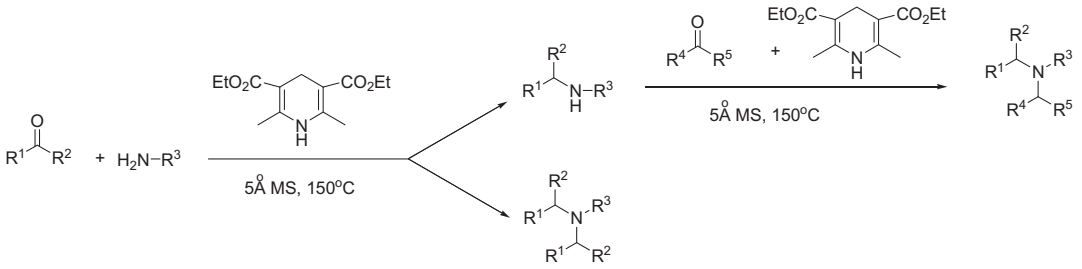
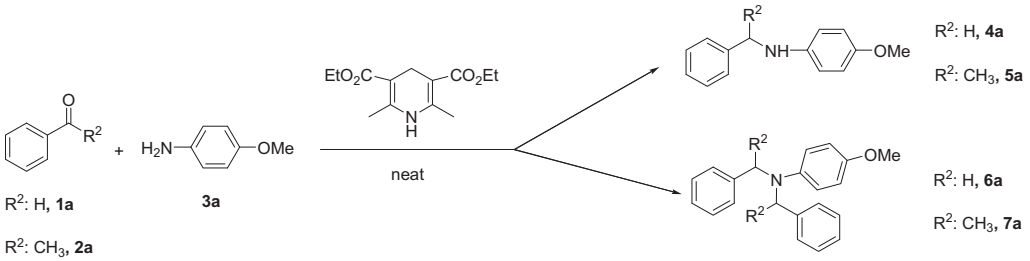
http://dx.doi.org/10.1016/j.tet.2013.04.046



Scheme 1. Direct reductive amination of aldehydes and ketones.

Table 1
Optimization of the reaction conditions



Entry	Carbonyl compound	Equiv of Carbonyl/Amine/HEH	Additive	Temperature (°C)	Reaction time (h)	Product	Yield (%)
1	Benzaldehyde **1a**	1/1.2/1.2	5 Å MS[a]	100	5	**4a**	59
2	Benzaldehyde **1a**	1/1.2/1.2	5 Å MS[a]	150	0.25	**4a**	99
3	Benzaldehyde **1a**	1/1.2/1.2	None	150	0.25	**4a**	98
4	Benzaldehyde **1a**	1/1.2/1.2	None[c]	150	0.25	**4a**	96
5	Acetophenone **2a**	1/1.5/1.5	5 Å MS[a]	150	14	**5a**	90
6	Acetophenone **2a**	1/1.5/1.5	None	150	24	**5a**	45
7	Acetophenone **2a**	1/1.5/1.5	5 Å MS[b]	150	14	**5a**	87
8	Acetophenone **2a**	1/1.5/1.5	5 Å MS[a,c]	150	14	**5a**	82
9	Benzaldehyde **1a**	3/1/2.5	5 Å MS[a]	130	24	**6a**	48
10	Benzaldehyde **1a**	3/1/2.5	5 Å MS[a]	150	12	**6a**	91
11	Benzaldehyde **1a**	3/1/2.5	None	150	12	**6a**	51
12	Acetophenone **2a**	5/1/4	5 Å MS[a]	200	96	**7a**	—[d]

[a] Unactivated (Sigma–Aldrich, 1.6 mm pellets, product number: 334316).
[b] Activated at 400 °C for 24 h.
[c] $NaHCO_3$ (50 mol %) was added.
[d] Only monoalkylated intermediate **5a** was formed.

a deleterious impact on both iminium formation and the reduction step,[10a] however, it had no considerable effect whatsoever upon the direct heating of all three reactants at 150 °C (Table 1, entry 3). Next, the direct reductive amination of ketones with acetophenone, 4-methoxyaniline, and HEH was investigated (Table 1, entries 5–8). Unlike with benzaldehyde, this reaction proceeded much more difficultly due to the sterical hindrance of the methyl group. Longer reaction time, a slight excess of the amine and HEH (1.5 equiv) with respect to the ketone (1 equiv) and 5 Å MS additive were found to be crucial to achieve the best yield of product **5a** (Table 1, entry 5). It might be possible that the auto-oxidation of the aldehydes involved may produce sufficient quantities of acids that could catalyze the reactions in the direct reductive amination of aldehydes and also the acidity of the molecular sieves used or of the volatile components in the molecular sieves might catalyze the reactions in the direct reductive amination of ketones.[13d] However, upon addition of excess base (50 mol % $NaHCO_3$) or activation of 5 Å MS at high temperature to eliminate the above mentioned effects, the direct reductive amination of aldehydes and ketones proceeded well under desired condition (Table 1, entries 4, 7, and 8). Therefore these reactions may proceed through thermal effect and easy removal of water with 5 Å MS. Mechanistically, at the elevated temperature, the direct reductive amination of aldehydes and ketones may involve a single-step hydride transfer from HEH to imines or iminiums, as previously reported (Scheme 2).[15]

With the optimized reaction conditions in hand, we examined the scope and limitations of aldehydes, ketones, and amines using benzaldehyde, acetophenone, and 4-methoxyaniline as representative substrates. It should be noted that 4-methoxyaniline was chosen because the 4-methoxyphenyl group can be oxidatively removed from the resulting amine to produce a primary amine, which renders the whole protocol more versatile.[16] As revealed in Table 2, entries 1–17, the direct reductive amination of aldehydes provided the secondary amines with high yields by the various combination of aromatic and aliphatic aldehydes with primary amines. In contrast, upon the direct reductive amination of ketones, the nature of the substrates had great influence compared to aldehydes (Table 3, entries 1–22). For example, the cyclic aliphatic ketone (Table 3, entry 7) was the most reactive, while the more sterically hindered ketone (Table 3, entry 11) furnished low yield. The nitro substituted aromatic amine (Table 3, entry 18) proceeded more difficultly, and the aliphatic amine (Table 3, entry 21) was completely unreactive. It was also found that the functional groups, such as OH, C=O, NO_2, and C=C were tolerated very well under our conditions (Table 2, entries 4 and 6; and Table 3, entries 4 and 8, respectively). In addition, the chemoselective reductive amination