Efficient Reductive Amination Using Hantzsch 1,4-Dihydropyrindine as Organo Reducing Agent in the Presence of $Sc(OTf)_3$ and Acidic Silica at Ambient Temperature

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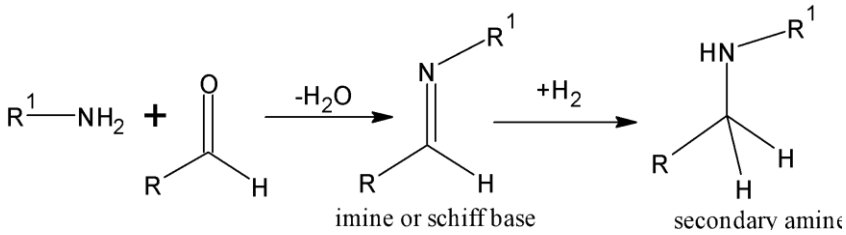
Abstract

Reductive amination of carbonyl compounds stands out as a potent method in the synthesis of structurally diverse amines. The synthesis of amine is an important reaction in drug discovery as well as in synthetic organic chemistry. It can lead to the synthesis of a variety of natural products as well as highly biologically active molecules. Present protocol deals with the reductive amination of aldehydes with aryl amines using Scandium triflate [$Sc(OTf)_3$]-acidic silica as a catalyst and Hantzsch-1,4-dihydropyridine (HDHP) as an organo reducing agent in toluene solvent at ambient temperature. Notably, the reaction demonstrates a high degree of selectivity, resulting in very good yields.

Keywords: Reductive Amination, Hantzsch-1,4-dihydropyridine, Scandium triflate, acidic silica, organo reducing agent, Ambient Temperature.

Introduction

Reductive amination[1-3] emerges as a highly effective approach for synthesizing secondary or tertiary amines in both biological and chemical systems. Typically, this method involves a two-step process: the initial synthesis of an intermediate (imine) in the first step, followed by the reduction of this imine in the second step (refer to Scheme 1). In many instances, the intermediate imine is neither stable nor isolable. Hence, the most practical and preferred approach for generating saturated amines from carbonyl compounds and amines involves the in situ formation and subsequent reduction of imines. Nature also employs reductive amination, where pyridoxal phosphate serves as a coenzyme in all transamination reactions. The natural conversion of pyridoxal phosphate into pyridoxamine phosphate in the presence of aminotransferase further exemplifies this process. [4-5]



Scheme 1: Reductive amination.

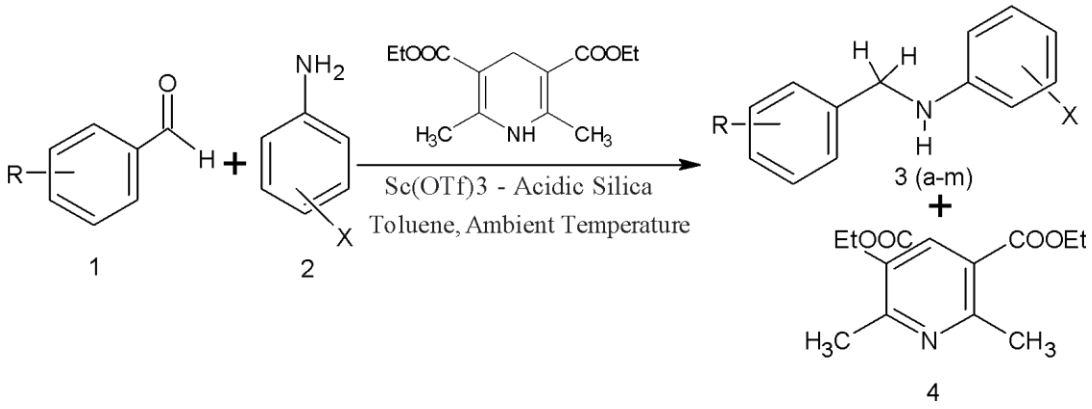
Thus, there are many approaches in literature to carry out this direct process some of these are $NaBH_3CN$, borohydride derivatives $NaBH(OAc)_3$, $Ti(O^i\text{-}Pr)_4$-$NaBH_4$, $NaBH_4$-$ZnCl_2$, $NaBH_4$-$NiCl_2$, $NaBH_4$-$H_3PW_{12}O_{40}$, $NaBH_4$ silica phosphoric acid, and *N*-methylpyrrolidine zinc borohydride, $NaBH_4$-$Mg(ClO_4)_2$, $NaBH_4$–wet clay, silica gel–$Zn(BH_4)_2$, $[Zr(BH_4)_2Cl_2(dabco)_2]$, $NaBH_4$ in micellar media, *N*–methylpiperidine zinc borohydride, Sodium cyanoborohydride and tin hydride[6-20] etc. Several previously documented methods encounter limitations, such as reliance on catalytic hydrogenation, incompatibility with compounds featuring C=C or C≡C bonds, and sensitivity to other reducible functional groups. Additionally, some reported procedures demand harsh reaction conditions and the necessity for an Argon or Nitrogen atmosphere, contributing to increased process costs.[21-24] Thus, the development of novel and simple catalytic method for a mild direct reductive amination is still an important research objective for researchers.

Further, the use of triflate salts holds distinct advantages; they exhibit enhanced stability compared to traditional catalysts, are recoverable and reusable, and can function effectively in aqueous conditions. In the current literature, triflates have proven their versatility as catalysts in various organic transformations, encompassing reactions such as Aldol reactions, Diels-Alder reactions, Mukaiyama aldol reactions, Ugi condensation reactions, alkylations, Prins-type cyclization reactions, and the synthesis of benzodiazepines, Friedel-Crafts Acylation Reactions, Michael additions, among others.[25-31] Metal triflate catalyzed reductive amination procedures are also well documented in.[32-33] By keeping all these facts in considerations, this method employs Scandium triflate $[Sc(OTf)_3]$-acidic silica as a catalyst and Hantzsch-1,4-dihydropyridine (HDHP) as an organo reducing agent in toluene solvent at ambient temperature. Significantly, the reaction demonstrates a high degree of selectivity, selectively reducing only the C=N

functionality, with no observed reduction of C=C and -CHO functions and obtained amines are very good in yields.

Results and Discussion

First of all we synthesized fresh Hantzsch 1,4-dihydropyridine (HDHP) as per standard procedure reported in literature, after that, we initially examined a direct reductive amination reaction of benzaldehyde with aniline using scandium triflate [$Sc(OTf)_3$] and acidic silica as catalyst and freshly prepared, well dried, Hantzsch 1,4-dihydropyridine (HDHP) as reducing agent. The reaction was carried out by directly mixing a 1:1:1.2 mixture of benzaldehyde, aniline, HDHP and catalytic amount of $Sc(OTf)_3$-acidic silica (0.1:0.5) in 20.0 mL of toluene at ambient temperature. Progress of reaction was monitored via TLC until complete disappearance of benzaldehyde in TLC occurred. It afforded the expected *N*-benzylaniline **3a** in very good yield, without reduction of benzaldehyde and HDHP was oxidized quantitatively to the corresponding pyridine derivative (**Scheme 2**).



Scheme 2: Reductive Amination using HDHP and $Sc(OTf)_3$-Acidic silica at Ambient Temperature.

The use of a less amount of catalyst led to a decrease in product yield, whereas an increase in the catalyst amount did not exhibit a significant impact on either the reaction rate or overall yields. In a similar fashion, it was observed that 1.2 mmol of Hantzsch 1,4-dihydropyridine (HDHP) is needed for 1.0 mmol of aldehyde to get best results. After optimization of reaction condition, a diverse range of secondary amines was successfully synthesized employing functionally diverse amines and aldehydes, as detailed in **Table-1**. The presence of electron-withdrawing or electron-donating substituents on the aromatic ring exhibited no impact on the reaction's progression. Notably, sensitive functionalities such as -CHO, C=C, OMe, and NO_2 were well-tolerated under

these mild reaction conditions. The clean reaction profile, coupled with the mild nature of HDHP, showcased high selectivity, exclusively reducing the C=N bond. This resulted in the production of the desired amines in high yields without compromising other sensitive functional groups.

Table 1: Synthesis of secondary amines via Reductive Amination using HDHP and $Sc(OTf)_3$-Acidic silica at Ambient Temperature.

S.N.	R	X	Product[a]	Time (h)	Yield[b] (%)
1	H	H	**3a**	45	86
2	4-MeO	H	**3b**	55	83
3	2-Cl	H	**3c**	50	86
4	4-Cl	H	**3d**	50	82
5	2-NO_2	H	**3e**	55	80
6	4-NO_2	H	**3f**	55	82
7	H	4-Cl	**3g**	50	83
8	H	4-NO_2	**3h**	55	80
9	H	4-MeO	**3i**	55	84
10	H	4-Me	**3j**	40	83
11	4-NO_2	4-MeO	**3k**	55	84
12	2-Me	4-Cl	**3l**	45	84
13	H	2-OH	**3m**	55	80

[a]All the products were identified by comparison of their physical and spectral data with those of authentic samples.
[b]Isolated yields.

Experimental

All experiments were performed in oven dried glass apparatus. Reagent-grade chemicals were purchased from a commercial source and used without further purification. Melting points were determined in labotech melting point apparatus MPA350. Infrared (IR) spectra were recorded in KBr discs on a Perkin-Elmer FTIR spectrometer. ^{1}H NMR spectra were recorded on a BRUKER AVANCE II 400 NMR spectrometer in $CDCl_3$/DMSO-d_6 using tetramethylsilane (TMS) as internal standard. The progress of the reaction was monitored by thin-layer chromatography (TLC) using silica gel G (Merck).

General procedure for the synthesis of secondary amines (3a-m).

In a typical procedure, aldehyde (1.0 mmol), aniline (1.0 mmol), freshly prepared and well dried Hantzsch 1,4-dihydropyridine (1.2 mmol) and Scandium triflate (0.1 mmol) acidic silica (0.5 mol) were stirred in dry toluene (20.0 mL) at room temperature for time see table 1 to afford desired secondary amine **3a-m**. Progress of reaction was monitored via TLC, after completion of the reaction the mixture was filtered and the residue was washed with CH_2Cl_2 (2×10 mL). Solvent was evaporated and obtained crude product was purified by column chromatography on silica (60-120 mesh) eluent ethyl acetate and petroleum ether containing 1% of triethylamine to afford the pure amine. The produced secondary amines were further characterized by comparison of their physical and spectral data with those of authentic samples.

Physical and spectral data of some selected compounds:

N-Benzylaniline 3a: Liquid. IR (KBr): 1320, 1496, 1590, 2921, 3418 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.05 (br s, 1H), 4.36 (s, 2H), 6.56-6.91 (m, 3H), 7.08-7.36 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.20, 113.39, 117.40, 126.61, 127.30, 128.41, 139.90, 142.11, 149.81. ESI-MS: *m/z* 184 $(M+H)^+$.

N-(4-Chlorobenzyl)benzenamine 3d: Liquid. IR (KBr): 1100, 1318, 1468, 1600, 2925, 3681 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.03 (br s, 1H), 4.31 (s, 2H), 6.63-6.88 (m, 3H), 7.01-7.25 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.69, 112.86, 117.47, 128.96, 129.04, 138.06, 147.81. ESI-MS: *m/z* 218, 220 $(M+H)^+$.

N-(4-Nitrobenzyl)benzenamine 3f: Liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.33 (s, 2H), 5.11 (br s, 1H), 6.45-6.61 (m, 3H), 7.01-7.29 (m, 4H), 8.04-8.09 (m, 2H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 46.22, 113.46, 117.23, 120.87, 127.86, 129.60, 146.46, 148.94. ESI-MS: *m/z* 229 $(M+H)^+$.

N-Benzyl-4-methoxybenzenamine 3i: White solid, m.p. 46-47°C. IR (KBr): 1320, 1451, 1598, 2935, 3432 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 3H), 4.03 (br s, 1H), 4.23 (s, 2H), 6.61-6.75 (m, 4H), 7.25-7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.71, 56.88, 114.37, 127.51, 128.73, 140.16, 144.12, 152.18. ESI-MS: *m/z* 214 $(M+H)^+$.

N-Benzyl-2-hydroxybenzenamine 6m: White solid, m.p. 79-80°C. IR (KBr): 1320, 1480, 1595, 2946, 3410 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.01 (br s, 1H), 4.30 (s, 2H), 5.17 (br s, 1H), 6.58-6.67 (m, 3H), 6.96–7.25 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.50, 112.41, 113.53, 118.09, 121.67, 127.44, 127.70, 129.58, 136.69, 140.31, 144.76. ESI-MS: *m/z* 200 $(M+H)^+$.

Conclusions

Present protocol is mild, wide-ranging, efficient and very selective method for reductive amination of aldehydes and amines under easygoing conditions, mediated by Scandium triflate-acidic silca in toluene at ambient temperature. Furthermore, this method has the advantages of inexpensive reagents, simple operation procedure, improved yields and simple experimental work up. It is recommended that Hantzsch dihydropyridine (HDHP) is an efficient, safe and environment friendly reducing agent for the direct reduction of imines. This method is not only of interest from ecological point of view, but also proves to be a clean, mild and very simple procedure in production of secondary amines.

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