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Use of "Homeopathic" molecular iodine as a catalyst for green and direct reductive amination of aldehydes

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ABSTRACT

A novel green and rapid approach for the direct reductive amination of aldehydes using molecular iodine as catalyst under neutral conditions is described. The mild, acid- and metal-free process can be effected using even homeopathic level (as low as 100 ppm) of molecular iodine as catalyst and utilizes the Hantzsch dihydropyridine (DHP) ester for transfer hydrogenation. The method allows the efficient synthesis of structurally diverse secondary amines and turnover number of up to 3000 has been achieved with activated substrates.

KEYWORDS

Green approach;
Homeopathic;
Biomimetic;
Molecular iodine;
Hantzsch dihydropyridine ester;
Reduction.

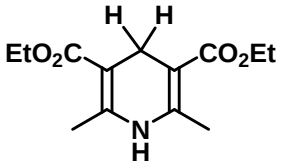
INTRODUCTION

Reductive amination of aldehydes and ketones, in which a mixture of a carbonyl compound and an amine is treated with a reductant in a "one-pot" fashion, is one of the most useful methods for the preparation of secondary or tertiary amines and related functional compounds[1]. The amines are structural element in a multitude of biologically active natural products and pharmaceuticals and therefore their synthesis has become an objective of high priority from the perspective of medicinal chemistry and organic synthesis[2]. The most commonly employed procedures for reductive aminations of carbonyls utilises boranes or metal hydrides such as $NaBH_3CN$, $NaBH_4$ as reducing agents[3] and rely on Bronsted or Lewis acids for selective activation of imine in the presence of carbonyls. However these methods suffer from the limitations such as incompatibility with acid labile functionalities, use of hazardous and/or expensive catalysts, inconvenience of handling and excess use of amines.

To circumvent these drawbacks, one of the best alternatives is to apply organo reductants that possess excellent reproducibility.

In recent years, the natural product enzyme cofactor NAD(P) and NAD(P) H have been a stimulus for investigating the use of Hantzsch ester 1 and other 1,4-dihydropyridine derivatives as attractive biomimetic reducing agent for the applications in synthetic and physical organic chemistry[4]. This conceptual blueprint of biochemical hydride reduction, wherein an enzyme and cofactor are replaced by catalysts and dihydropyridine analogues respectively, has been employed in chemical reduction of many double bond containing compounds such as imines, α,β-unsaturated carbonyl compounds etc[5-8]. Though, Hantzsch ester alone is not suitable for reductive amination, many Lewis acids such as Mg(II)[9], SiO_2[10], Al_2O_3[10], and $Sc(OTf)_3$[11] have been reported to be effective catalysts for the direct reduction amination of aledhyde or ketones using Hantzsch ester as biomimitic hydride transfer agent. The asymmetric variants of this concept has also been recently

reported independently by Reuping et al.[12], List et al.[13] and MacMillan et al.[14] using Bronsted acid catalys. For instance, the efficient effenantioselective synthesis of chiral secondary amines has been reported using BINOL based chiral phosphoric acid catalyst. Recently, Menche et al. reported a novel biomimitic hydrogen bond catalysed approach for direct reductive amination of aldehyde[15] and ketones[16] invoving Hatzsch ester as biomimitic hydride transfer agent and thiourea as hydrogen bond doner.



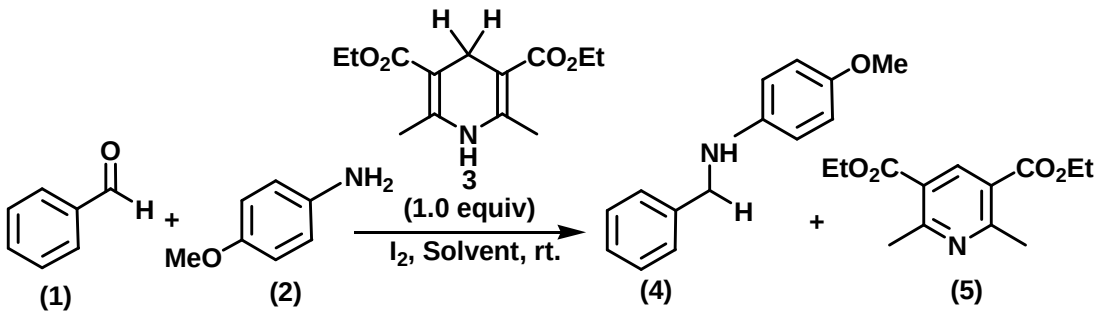
(1)

Though all these methods provides an efficient synthesis of structurally diverse amines, many of these procedures they suffer from the limitations such as use of expensive or hazardous catalysts, longer reaction times (up to 24 h), use of excess reagents and low yields. Thus, still there is a further scope to develop an improved protocol for reductive amination process.

In recent years, molecular iodine has attracted considerable attention as an inexpensive, non-toxic, nonmetallic and readily available catalyst for effecting various organic transformations[17,18]. However, despite of several obvious advantages of molecular iodine as catalyst, to our knowledge, it has been not hitherto tested as catalyst for direct reductive amination of carbonyl compounds, particularly, using DHP ester as a reducing agent. In continuation of our interest in the development environmentally benign synthetic protocols[19], herein, we report first time that direct reductive amination of aldehydes could be achieved even using homeopathic level of molecular iodine as catalyst in good to high yields under extremely mild and essentially neutral conditions. This mild and rapid protocol requires extremely small amount of catalyst (as low as 100 ppm), utilizes Hatzsch ester as hydride source and eliminates the need for strong acid or metal catalyst.

RESULTS AND DISCUSSION

The Initial optimisation study (catalyst / reductant (DHP)loading, solvent, reaction time etc.) was carried out using a model reaction involving benzaldehyde **(1)** and *p*-anisidine **(2)** and Hantzsch dihydropyridiene ester **(3)** at room temperature to give the product amine **(4)** scheme 1.The results of this study are collected in TABLE 1. As shown in our results, the reaction hardly proceeded in the absence of catalyst (TABLE 1, entry 1), however, using 10, 5.0, 2.5 and 1.0 mol % of catalyst in methylene chloride the reaction smoothly proceeded within very short reaction time ranging from few minutes to less than an hour in a excellent yield. The effect of solvent on the present reaction was also investigated and the solvents such as THF, acetonitrile and Toluene were also found to be effective but the best results were obtained with CH_2Cl_{-2} and hence it was chosen for further study. In order to find out wheather the amount of DHP ester used hase any relavence on the outcome of the reaction, the reaction was analysed using different amount of DHP etser (TABLE 2). It was observed that the amount of DHP ester found to have crucial role on the yields and best result ware obtained using 1.2 equivalnent of reductant. Thus the best reaction conditions were aldehydes (1 .0 equiv.), amine (1.0 equiv.) Hantzsch DHP ester (1.2equiv.) in the presence of iodine 1 mol % in DCM at room temperature for 55 minutes. We have chosen these reaction conditions to explore the scope and generality of the reaction.



Scheme 1

TABLE 1 : Synthesis of diverse secondary amines via reductive amination of different aldehydes catalyzed by molecular iodine[a]

Entry	R-	R'-	Products (4a-n)	Yield (%)
1	Ph-	4-CH_3-Ph-	4a	94
2	Ph-	4-OMe-Ph-	4b	96
3	Ph-	Ph-	4c	89
4	Ph-	4-Cl-Ph-	4d	85
5	Ph-	4-Ac-Ph-	4e	72
6	Ph-	2-pyridyl	4f	90
7	4-Br-Ph-	Ph-	4g	81
8	4-Br-Ph-	3,4-Cl_2-Ph-	4h	80
9	4-NO_2-Ph-	4-OMe-Ph-	4i	94
10	4-Cl-Ph-	Ph-	4j	87
11	4Cl- Ph-	1-Napthyl-	4k	68
12	4-Cl-Ph-	4-Cl-Ph-	4l	95
13	Ph-	2-Thiophenyl-	4m	75
14	Isobutyl-	4-OMe-Ph-	4n	91

[a]Reaction conditions: 1.0 equiv. of aldehyde, 1.0 equiv of amine and 1.1 equiv. of Hantzsch ester in the presence of 1 mol % of I_2 at room temperature for 55 minutes; [b]Isolated yields; [c]The reduction of double bond was observed.

Thus the structurally diverse amines such as aromatic, heteroaromatic and aliphatic amines were allowed to react with benzaldehydes under the optimized reaction conditions scheme 2. The results are collected in TABLE 2. It is clear from our results that the reaction is general as the reductive amiantion of electron rich, neutral and electron deficient anilines proceeded rapidly and almost with equal efficiency to afford god to high yields of the products. Even sterically congested anilines such as o-chloroanilines (TABLE 1, entry- 8) reacted efficiently to give high yield of the corresponding product amine using present reaction conditions.

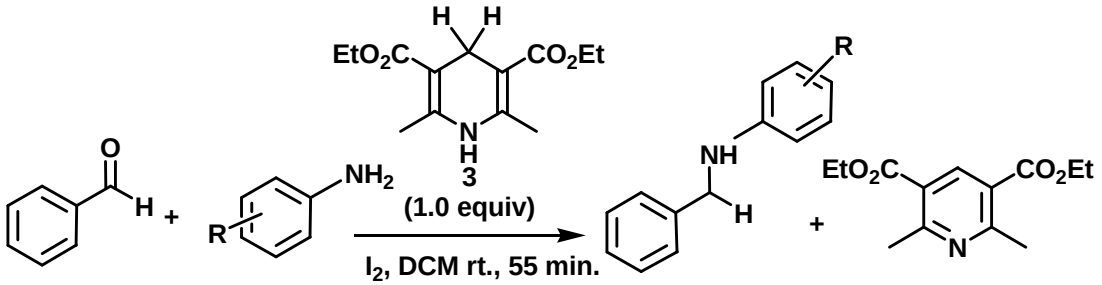
Having good results being obtained in the reactions involving diverse amines, next the scope of the present reaction for different aldehyde was explored scheme-3. The results are summarized in TABLE 2. From our results (TABLE 1, entries 9-20), it is further clear that wide variety of aldehydes underwent reductive amination smoothly under present reaction conditions. The aromatic, heteroaromatic, as well as aliphatic aldehydes reacted efficiently under the present reaction condition giving again high to excellent yield of the secondary amines[20].

TABLE 2 : Effect of DHP ester on reductive amination of benzaldehyde

Entry	DHP ester (equiv.)	Time (min)	Yield (%)[b]
1	0.5	55	52
2	1.0	55	83
3	1.2	55	94

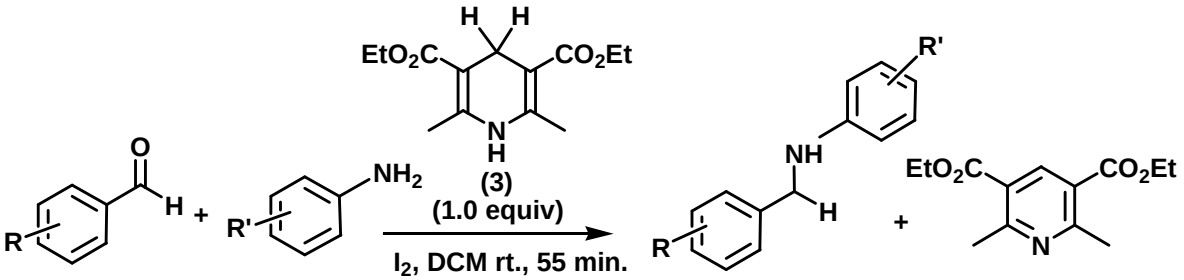
[a]Reaction conditions. 1.0 equiv. of benzaldehyde, 1.0 equiv. of p-anisidine in the presence of 1.0 mol % iodine in DCM at room temperature; [b] Isolated yields.

The extremely high efficiency of the present catalyst (I2 1 mol %; time 55 miutes; 99> % yield) as observed in model reaction (TABLE 1, entry-3) prompted us to check whether the reaction could be performed with same efficiency using even further low amount of I_2 catalyst. We set out to test this notion using same set of reaction conditions as above except using (very low) ppm level of I_2 concentration. The results of this study are presented in TABLE 3. As can be seen from our results (TABLE 3), almost similar yields were obtained using 1000, 500 and 100 ppm of I_2 within the reaction times 2.5, 4.5 and 24 h. It is to be noted that use of as low as 100 ppm of I_2 catalyst is sufficient to proceeded the reaction in high yield within reasonable time[21]. Notably, the highest reaction time required (24 h) in this case is still comparable the existing methods involving DHP ester as reducing agents. Remarkably, the turnover number of 3,500 (TABLE 1, entry-3) was achieved using this catalyst and we believe that this could be highest turnover number ever achieved for reductive



Scheme 2

amination of aldehydes employing such an approach (DHP-catalyst as a reducing system).



Scheme 3

TABLE 3 : Use of "Homeopathic" I_2 for reductive amination of aldehyde[a]

Entry	I_2 (ppm)	Time (h)	Yield (%)[b]
1	1000	2.5	87
2	500	4.0	86
3	100	24	87

[a]Reaction conditions. 1.0 equiv. of benzaldehyde, 1.0 equiv. of p-anisidine and 1.2 equiv. of Hantzsch ester in the presence of iodine at room temperature; [b] Isolated yields.

We use the term "homeopathic" molecular iodine, originally coined by Beletskaya for those reactions where very low loadings of palladium can be used[22].

The Hatzsch ester can be readily synthesized on multigram scale by simple approach. Molecular iodine is cheap, non toxic and environmentally benign catalyst that is available to any common laboratory. The reaction is convenient, general, and provide high to quantitative yields of the amine products with excellent functional group compatibility within very short time. A most remarkable feature of the present protocol is that the even homeopathic level of iodine concentration ((as low as 100ppm =0.004 mol % of I_2 catalyst) is effective as a catalyst for smooth proceeding of the reaction and the reduction is completely selective towards imine.

General procedure

To a mixture of aldehyde (1 mmol), amine (1 mmol) and Hantzsch Dihydropyridine ester (DHP), (1.1 equiv.) in DCM 10 ml, was added I_2 (0.01 mmol) and reaction mixture was stirred at room temperature for 55 minutes. After completion of reaction, (after this time TLC shown complete disappearance of DHP ester), the reaction mixture was quenched with 10 % solution of Na_2S2O_3 (20 ml) to destroy the iodine catalyst and organic layer was separated. The aqueous layer was further extracted with DCM (2X 15 ml). The combined organic extracted was washes water, dried over anhy. $MgSO_4$ and solvent evaporated. The residue on column chromatographic purification gave analytically pure product in high to excellent yields.

Procedure for reductive amination using "Homeopathic" iodine

To a flask charged with Benzaldehyde (1 mmol), p-anisidine (1 mmol) and Hantzsch Dihydropyridine ester (DHP), (1.1 equiv.) was added the 1000, 500 or 100 ppm solution of I_2 in DCM and reaction mixture was stirred at room temperature for the time indicated in TABLE 2. (Note: the I_2 solution of desired concentration (ppm) was made by stepwise dilution with DCM of the appropriate volume of 1000 ppm stock solution in DCM). After completion of reaction, (TLC shown complete disappearance of DHP estser after the indicated time.), the reaction mixture was quenched with 10 % solution of Na_2S2O_3 (10 ml) to destroy the iodine catalyst and organic layer was separated. The aqueous layer was further extracted with DCM (2 X 15 ml). The combined organic extracted was washed water, dried over anhy. $MgSO_4$ and solvent evaporated. The residue on column chromatographic purification gave analytically pure product in high yield.

Selected spectrel data

N-(4-nitrobenzyl)-*P*- anisidine (4k)

^{1}H NMR (400 MHz, $CDCL_3$) Δ = 3.74 (s, 3H), 4.41 (s, 2H), 6.56(d, 2H, J- 9.0 Hz), 6.75 (d, 2H, J = 9.0, HZ,) 7.54 (d, 2H, *J* = 8.8 Hz), 8.20 (d, 2H, J = 8.8 Hz).

MS (M + H): calcd for $C_{14}H_{14}N_2O_3$ 259. 27; Found: 259.2

***N*-(4-chlorobenzyl) aniline (4l)**

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.08 (broad s, 1H); 4.34 (s, 2H); 6.63-6.65 (s, d, 2H); 6.74-6.78 (ddd, 1H); 7.19-7.23 (m, 2H); 7.27-7.33 (m, 4H).

MS (M+H): calcd for $C_{13}H_{12}NCl$ 218.5 found 218.1.

***N*-(4-chlorobenzyl)-1-naphthylamine (4o)**

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.49 (s, 2H); 4.74 (broad s, 1H); 6.55-6.57 (dd 1H); 7.26-7.34 (m, 4H); 7.37-7.39 (d, 2H); 7.42-7.53 (m, 3H); 7.79-7.84 (dtd, 2H).

MS $(M+H)^+$: calcd for $C_{13}H_{12}N_2O_2$ 229; found 229, 252 (M+ Na).

N-[4'-chlorobenzyl]-4 –chloroaniline (4p)

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.96 (broad s, 1H), 4.27 (s, 2H), 6.50-6.56 (m, 2H), 6.84-6.91 (m, 2H), 7.26-7.32 (m, 4H).

MS $(M+H)^+$: calcd for $C_{13}H_{11}NCl_2$ 253, Found 253.

CONCLUSION

In conclusion, we have shown that extremely low ("homeopathic") loadings of I_2 can be used to effect the reductive amination of aldehydes leading to the efficient and rapid synthesis of structurally diverse secondary amines under mild and essentially neutral conditions in an environmentally benign and cost effective way. The adaptation of present reducing system (I_2/DHP) for reductive amination of ketones is currently underway in our laboratory.

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