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An efficient catalytic reductive amination: A facile one-pot access to 1,2-dihydropyrrolo[3,4-b]indol-3(4*H*)-ones by using $B(C_6F_5)_3/NaBH_4$

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Abstract. An efficient combination of $B(C_6F_5)_3$ and $NaBH_4$ was developed for direct reductive amination of aldehydes. A wide range of functional groups such as ester, nitro, nitrile, halogen, alkene, heterocycles were tolerated. Also, acid sensitive protecting groups like TBDMS and TBDPS were not affected. In addition, the present methodology was extended for tandem amination-amidation of 3-formyl-indole-2-carboxylic acids with substituted anilines to afford 1,2-dihydropyrrolo[3,4-b]indol-3(4*H*)-ones.

Keywords. Reductive amination; Lewis acid; tris(pentafluorophenyl)borane; sodium borohydride; less-toxic; tandem reaction.

1. Introduction

Substituted amines are very important industrial organic compounds owing to their widespread applications as bioactives, solvents, textile additives, raw materials for resins, rubber stabilizers, disinfectants, corrosion inhibitors and in the manufacture of detergents and plastics.[1] Furthermore, they are used as crucial organic intermediates for synthesis of natural products, pharmaceuticals and agrochemicals, and have broad applications in synthetic and combinatorial chemistry (figure 1).[2]

The simplest approach for the synthesis of amines involves imine reduction or direct reductive amination of carbonyl compounds. Metal-catalyzed hydrogenation and hydride reduction are the two strategies used for direct reductive amination of aldehydes with amines.[3a] Metal-catalyzed hydrogenation has limitations to many substrates bearing reducible functionalities apart from imines, such as compounds containing a carbon-carbon double or triple bond groups and other reducible functional groups including nitro, cyano and furyl.[3b] A variety of reagents such as $^{n}Bu_3SnH/SiO_2$[4a] and $^{n}Bu_2SnIH$[4b] or $^{n}Bu_2SnClH$,[4c] diborane/MeOH,[5a] $NaBH_4$/Bronsted acidic ionic liquid,[5b] $NaBH(OAc)_3$,[5c] hydrioiridium(III) complex,[5d] ammoniaborane/$Ti(OiPr)_4$,[5e] PMHS/$Ti(OiPr)_4$,[6a] PMHS/$ZnCl_2$,[6b] PMHS/$AlCl_3$,[6c] $ZnBH_4$,[6d] $ZnBH_4/ZnCl_2$,[6e] $ZnBH_4/SiO_2$,[7a] Zn/AcOH,[7b] $NaBH_4/ZnCl_2$,[7c] $NaBH_4/ZrCl_4$,[7d] $Ti(OiPr)_4/NaBH_4$,[8a] $NaBH_4/H_2SO_4$,[8b] $NaBH_4/Fe(OTf)_3$,[3a] $NaBH_4$/wet clay,[8c] solid acid activated $NaBH_4$,[2] $TiCl(OiPr)_3/NaBH(OAc)_3$,[9a] $LiBH_4$,[9b] $NaBH_4/H_3PW_{12}O_{40}$,[9c] $NaBH_4$/(GuHCl),[9d] $NiCl_2/NaBH_4$,[10a] pyridine/borane,[10b,c] picoline/borane,[10d] Et_3SiH/CF_3CO_2H,[11a] PMHS/$BuSn(OCOR)_3$,[11b] $PhSiH_3/Bu_2SnCl_2$,[11c] $^{n}Bu_3SnH$/DMF or HMPA,[11d] PMHS/TFA,[12a] $Zr(BH_4)_4$/piperazine,[12b] bis(triphenylphosphine)copper(I) tetrahydroborate,[12c] phosphonium borates,[12d] etc., have been employed for direct reductive amination.

On the other hand, in terms of reaction conditions, functional group tolerance and side reactions, most of these reagents have one or more drawbacks. Earlier, $NaBH_4$ has been used with various Brønsted acids, which facilitates Brønsted imine formation for successful reductive amination. Brønsted catalysts such as H_2SO_4 or *p*-toluenesulfonic acid are commonly used, even though these are corrosive, toxic and difficult to separate from the reaction solution.[9c] Hence, there is an interest to substitute these acids with more environment-friendly Lewis acids. Lately, various research groups are engaged in investigating the potential efficacy of tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] as it is non-conventional, less-toxic, air-stable, water-tolerant and thermally stable Lewis acid.[13a,b] Recently, our group reported an efficient protocol involving the use of $B(C_6F_5)_3$ as an activator in acylation of a variety of alcohols, phenols, thiophenols, and amines.[13a]

In continuation to our interest in developing novel synthetic methodologies, herein we report a facile and rapid approach for reductive amination of aldehydes in the presence of sodium borohydride and catalytic amount of $B(C_6F_5)_3$ at room temperature. Most significantly, $B(C_6F_5)_3/NaBH_4$ can also be employed

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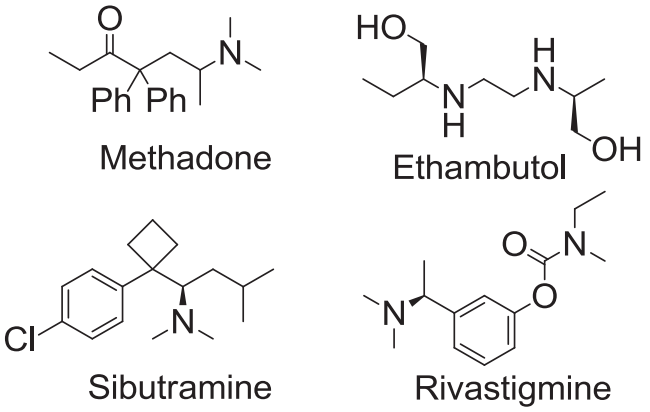


Figure 1. Selected examples of pharmaceutically important substituted amines.

for efficient one-pot synthesis of substituted 1,2-dihydropyrrolo[3,4-b]indol-3(4*H*)-ones (scheme 1).

Molecules comprising this scaffold exhibit potent biological activities mainly renin-inhibition[13c] and CNS depressant activity (figure 2).[13d] In 1967, Owellen, *et al*., demonstrated the first method for synthesis of 1,2-dihydropyrrolo[3,4-b]indol-3(4*H*)-one skeleton, it was achieved by refluxing 3-amino-4-(2-aminophenyl)-1-cyclohexyl-1*H*-pyrrol-2(5*H*)-one in acetic acid.[14a] Later in 1990, Kempf, *et al.,* reported a multi-step approach to synthesize this scaffold, involving Pd/C hydrogenation as a crucial step.[14b] Hence, an efficient and convenient synthesis of this scaffold is not yet reported. To the best of our knowledge, the present protocol is the first demonstration of Lewis acid catalyzed one-pot synthesis of 1,2-dihydropyrrolo[3,4-b]indol-3(4*H*)-ones.

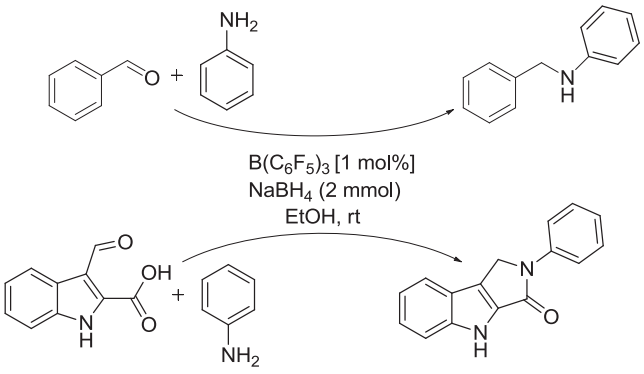
2. Experimental

2.1 *General procedure*

To a stirred solution of aldehyde/3-formyl-indole-2-carboxylic acid (1.0 mmol) and amine/aniline (1.0 mmol) in ethanol (4 mL), tris(pentafluorophenyl)borane (1 mol%) was added. After 15 min, $NaBH_4$ (2.0 mmol) was added at room temperature. On completion of the reaction (as monitored by TLC), the reaction mixture was quenched with water, later extracted with ethyl acetate. Organic layer was dried under vacuum and column chromatography was carried out for the purification product (Silica gel, *n*-hexane/ethyl acetate).

2.2 *Scale-up procedure for the synthesis of N-benzyl aniline*

To a stirred solution of benzaldehyde 5g (1.0 mmol) and aniline 4.4g (1.0 mmol) in ethanol (25 mL),



Scheme 1. $B(C_6F_5)/NaBH_4$ mediated synthesis of *N*-benzylaniline and 2-phenyl-1,2- dihydropyrrolo[3,4-*b*]indol-3(4*H*)-one.

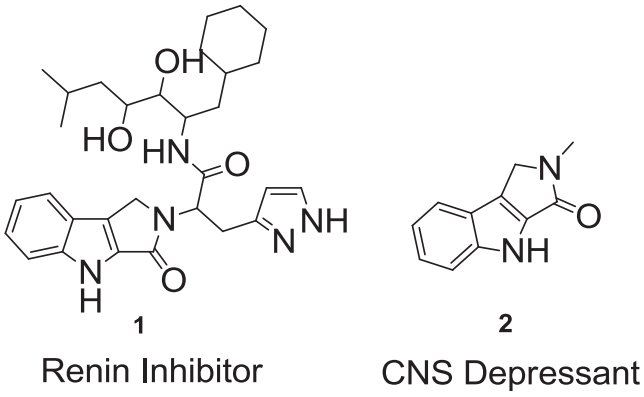


Figure 2. Bioactive molecules comprising of 1,2-dihydropyrrolo[3,4-*b*]indol-3(4*H*)-one scaffold.

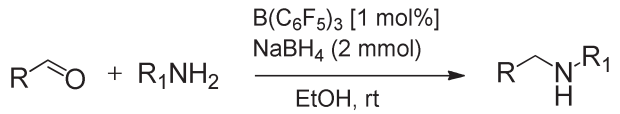
Table 1. Effect of Lewis acid concentration on yields towards reductive amination of aldehydes.[a]

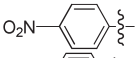
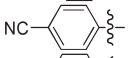
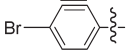
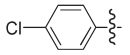
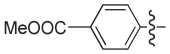
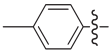
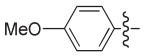
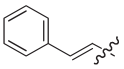
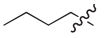
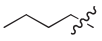
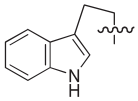
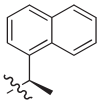
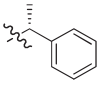
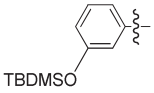
Entry	$B(C_6F_5)_3$ (mol%)	Yield (%)[b]	Time (min)
1	0.5	68	75
2	1	90	25
3	2	90	25
4	3	88	25

[a]Reaction conditions: Benzaldehyde (1 mmol), aniline (1 mmol), $NaBH_4$ (2 mmol) and ethanol (4 mL) as solvent at room temperature.
[b]Isolated yields.

tris(pentafluorophenyl)borane (1 mol%) was added. After 15 min, $NaBH_4$ 3.5 g (2.0 mmol) was added slowly at room temperature. On completion of the reaction (as monitored by TLC), the reaction mixture was quenched with water, later extracted with ethyl acetate. Organic layer was dried under vacuum and column chromatography (Silica gel, *n*-hexane/ethyl acetate) was carried out for the purification product (7.6 g, 86%).

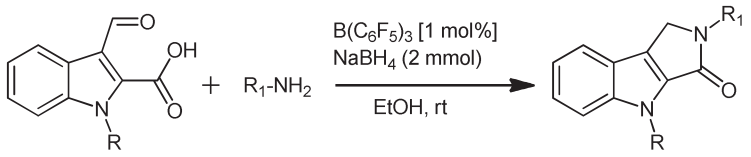
Table 2. $B(C_6F_5)_3/NaBH_4$ mediated reductive amination of aldehydes with amines.[a]



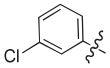
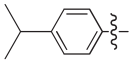
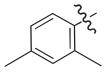
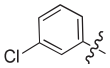
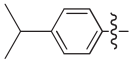
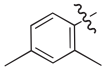
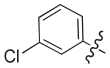
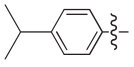
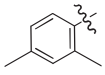
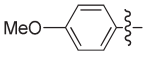
Entry[ref]	R	R_1	Yield (%)[b]	Time (min)
1[4a]			90	25
1a			86	30[c]
2[9c]			88	35
3[11d]			75	35
4[11d]			87	32
5[15a]			89	24
6[12b]			88	25
7[2]			82	31
8[5b]			88	28
9[15b]			83	22
10[15b]			75	25
11[15c]			90	25
12[15d]			89	25
13[9c]			88	30
14[15e]			85	22
15[15f]			87	25
16[15g]			90	30
17[15h]			89	30
18[15h]			88	25
19			85	25
20			83	28

[a]Reaction conditions: Aldehyde (1 mmol), amine (1 mmol), $B(C_6F_5)_3$ (1 mol%), $NaBH_4$ (2 mmol) and ethanol (4 mL) as solvent at room temperature.
[b]Isolated yields.
[c]Reaction scaled-up to 5g.

Table 3. $B(C_6F_5)_3/NaBH_4$ mediated one-pot synthesis of substituted 1,2-dihydropyrrolo[3,4-b]indol-3(4*H*)-ones.[a]



a b c

Entry[ref]	R (a)	R_1 (b)	Product (c)	Yield(%)[b]	Time (min)
1[15i]	H		**1c**	86	45
2	H		**2c**	83	52
3	H		**3c**	82	38
4	H		**4c**	80	35
5	H		**5c**	82	37
6	Ethyl		**6c**	85	40
7	Ethyl		**7c**	82	45
8	Ethyl		**8c**	81	48
9	Ethyl		**9c**	79	43
10	Ethyl		**10c**	83	45
11	Benzyl		**11c**	85	38
12	Benzyl		**12c**	82	42
13	Benzyl		**13c**	81	35
14	Benzyl		**14c**	84	40
15	Benzyl		**15c**	80	42
16	Benzyl		**16c**	89	40

[a]Reaction conditions: 3-Formyl-indole-2-carboxylic acid (1 mmol), aniline (1 mmol), $B(C_6F_5)_3$ (1 mol%), $NaBH_4$ (2 mmol) and ethanol (4 mL) as solvent at room temperature.
[b]Isolated yields.

3. Results and Discussion

Present strategy was tested with the help of a model study involving direct reductive amination of benzaldehyde with aniline using 1 mol% of $B(C_6F_5)_3$ and 2 mmol of $NaBH_4$, which proceeded smoothly with excellent yield (scheme 1). To study the effect of change in concentration of catalyst, we kept the same reaction using different concentration of $B(C_6F_5)_3$ (table 1). With 0.5 mol% concentration, 68% yield was obtained (table 1, entry 1) whereas, 1 and 2 mol% afforded 90% yield (table 1, entries 2 and 3). With further increase in concentration of $B(C_6F_5)_3$ there was no improvement in yield and reaction time (table 1, entry 4). Hence, we

moved forward taking into account 1 mol% as optimum catalyst concentration for the reaction.

To further examine the generality and scope of the present protocol, diverse range of aldehydes were subjected to reductive amination by using sodium borohydride as reductant and $B(C_6F_5)_3$ (1 mol%) as a catalyst (table 2). Reaction with substrate having no reducible functionalities gave excellent yield (table 2, entry 1). Substrates bearing potentially reducible functional groups including nitro (table 2, entries 2 and 3), cyano (table 2, entry 4), cinnamyl (table 2, entry 13) and ester (table 2, entry 7) afforded the anticipated products in the absence of detectable reduction side products. Reaction with substrates having electron donating group proceeded smoothly with good yields (table 2, entries 8 and 9). Substrates substituted with halogens like bromo, chloro and iodo (table 2, entries 5, 6 and 10) provided good yields. Heterocyclic substrates like furan-2-carbaldehyde (table 2, entry 11), 1*H*-indole-3-carbaldehyde and tryptamine (table 2, entries 12 and 16) reacted smoothly to afford desired products in excellent yields. In case of aliphatic aldehyde and amine, reaction preceded smoothly giving commendable yields (table 2, entries 14 and 15). Substrates bearing acid sensitive protecting groups like TBDMS and TBDPS afforded products in good yields without any deprotected side products (table 2, entries 19 and 20). Substrates containing chiral centres such as (*R*)-1-(naphthalen-1-yl)ethanamine and (*R*)-1-phenylethanamine (table 2, entries 17 and 18) gave desired products in 89% and 88% yields, respectively, without any detrimental effect on chirality.

In the light of above findings, we extended the scope of present protocol in the synthesis of 1,2-dihydropyrrolo [3,4-b]indol-3(4*H*)-ones (table 3). To begin with, 3-formyl-1*H*-indole-2-carboxylic acid was synthesized by using reported procedure.[14c] Under the optimized reaction conditions, a wide range of substituted amines were investigated for tandem amination–amidation of 3-formyl-1*H*-indole-2-carboxylic acid to synthesize the corresponding 1,2-dihydropyrrolo[3,4-b]indol-3(4*H*)-ones. Interestingly, it was observed that only aniline derivatives produced the subsequent 1,2-dihydropyrrolo[3,4-b] indol-3(4*H*)-ones in good yields (table 3, entries 1–5). The present protocol was unfruitful when the reactions were carried out using benzyl and aliphatic amines. The reactions with aniline derivatives bearing electron donating groups like methyl (table 3, entries 4 and 5), isopropyl (table 3, entry 3) proceeded with good yields. Aniline having chloro substitution (table 3, entry 2) afforded the desired product in good yield whereas, anilines substituted with electron withdrawing groups like nitro and cyano failed to provide the desired products. Thus, it can be assumed that electron donating and electron withdrawing groups have a significant influence on the reactivity of aniline.

Table 4. Comparative study using different Lewis acids towards synthesis of 1,2-dihydropyrrolo[3,4-b]indol-3(4H)-ones.[a]

Entry	Lewis acid	Yield (%)[b]	Time (min)
1	$Fe(OTf)_3$	69	60
2	$AlCl_3$	77	50
3	I_2	36	120
4	$BF_3.OEt_2$	78	60
5	$B(C_6F_5)_3$	86	45

[a]Reaction conditions: 3-Formyl-1*H*-indole-2-carboxylic acid (1 mmol), aniline (1 mmol), 1 mol% Lewis acid, $NaBH_4$ (2 mmol) and ethanol (4 mL) as solvent at room temperature.
[b]Isolated yield.

To include more diversity in substrates, we used different *N*-substituted 3-formyl-indole-2-carboxylic acids. NH proton of these 3-formyl-indole-2-carboxylic acids were substituted with ethyl[14d] (table 3, entries 6–10) and benzyl (table 3, entries 11–16). Interestingly, reactions using these substrates proceeded smoothly and afforded fine yields (79–89%). *p*-anisidine gave high yield (table 3, entry 16).

Presumably, $B(C_6F_5)_3$ activates the carbonyl functionality to afford very reactive electrophile source. Amine used as substrate reacts with the activated aldehyde to provide hemiaminol equivalent followed by dehydration episode that regenerates the catalyst. *In situ* generated imine is further reduced with sodium borohydride affording the secondary amine which later reacts with activated acid to undergo amidation to afford the 1,2-dihydropyrrolo[3,4-b]indol-3(4*H*)-one.

We also compared the efficiency of $B(C_6F_5)_3$ with other Lewis acids such as $Fe(OTf)_3$, $AlCl_3$, I_2 & BF_3 etherate for one-pot synthesis of 1,2-dihydropyrrolo [3,4-b]indol-3(4*H*)-one (table 4). It was found that $B(C_6F_5)_3$ was superior than other Lewis acids in terms of yield as well as reaction time.

4. Conclusion

In summary, we have demonstrated a facile and novel method for reductive amination of aldehydes using $B(C_6F_5)_3/NaBH_4$ as an efficient combination. Additionally, we developed a novel protocol for onepot synthesis of substituted 1,2-dihydropyrrolo[3,4-b]indol-3(4*H*)-ones *via* Lewis acid catalyzed tandem amination-amidation method. Striking advantages of present method are functional group tolerance, environmental benignness, rapid reaction, high yields of desired products, low

catalyst loading, less-toxicity of catalyst, and simple experimental procedure.

Supporting Information

Spectral data (^{1}H and ^{13}C) are available as part of the supporting information at www.ias.ac.in/chemsci.

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