Tetrahedron Letters 55 (2014) 1829–1834

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Direct reductive amination using triethylsilane and catalytic bismuth(III) chloride

Takehiko Matsumura, Masahisa Nakada *

Department of Chemistry and Biochemistry, Graduate School of Advanced Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan

ARTICLE INFO

Article history:
Received 21 December 2013
Revised 23 January 2014
Accepted 28 January 2014
Available online 6 February 2014

Keywords:
Bismuth(0)
Bismuth(III) chloride
Catalysis
Direct reductive amination
Triethylsilane

ABSTRACT

Direct reductive amination (DRA) using triethylsilane (TESH) and catalytic bismuth(III) chloride ($BiCl_3$) is described for the first time. The use of TESH and $BiCl_3$ provides easy handling, low cost, non-toxicity, and a mild Lewis acid activity, thereby meeting the demand for green and sustainable chemistry. The developed DRA is highly chemoselective and applicable to less-basic amines. The experimental results of this study revealed that the developed DRA could be catalyzed by $BiCl_3$, which was gradually reduced to Bi(0) or bismuth with a low valency by TESH, but TESCl, Bi(0), and Bi(0) with TESCl catalyzed the DRA to some extent.

Because many biologically active and pharmaceutically relevant compounds include amines and their derivatives, amine preparation methods are important.[1] Therefore, a variety of preparation methods for amines have been reported, and the direct reductive amination (DRA) of aldehydes and ketones has been widely used for the preparation of primary, secondary, and tertiary amines, because it offers compelling advantages over other synthetic methods owing to brevity, wide availability of substrates and reagents, generally mild reaction conditions, and high functional group tolerance in some cases. DRA has another advantage in that intermediate imines do not need to be isolated. Thus, a mixture of an aldehyde or ketone and an amine is treated with a reducing reagent in a one-pot fashion. Therefore, DRA is not only useful but also effective for the reaction of aromatic amines with aliphatic carbonyl compounds that produce unstable imines. However, the reducing reagent should be carefully selected for a successful reaction because the reduction of aldehydes or ketones sometimes competes under the reaction conditions.

Catalytic hydrogenation with a platinum, palladium, or nickel catalyst has been used for DRA because it is an economical and effective method and has advantages in large-scale reactions.[2] However, this method has not been applied to the reaction of compounds containing carbon–carbon multiple bonds and reducible functional groups such as nitro and cyano groups.

DRA using sodium cyanoborohydride ($NaBH_3CN$)[3] and sodium triacetoxyborohydride [$NaBH(OAc)_3$][1c,4] offers the advantages of simplicity, wide availability of substrates, mild reaction conditions, and a tolerance to other functional groups. However, the former is highly toxic and generates toxic byproducts such as hydrogen cyanide (HCN) and sodium cyanide (NaCN). Moreover, it requires large quantities of excess amine. The latter requires corrosive acetic acid to carry out the reaction,[5] and it is not compatible with aromatic and unsaturated ketones.[4,6]

Several reagents for DRA other than those mentioned above have been developed, including sodium[6] or zinc borohydride with Brønsted acid or Lewis acid,[7] nickel boride,[8] pyridine·BH_3,[9] 2-picoline·BH_3,[10] 2,6-diborane·methanol,[11] dimethylamine·BH_3,[12] *t*-BuMe*i*PrN·BH_3,[13] 5-ethyl-2-methylpyridine·BH_3,[14] benzylamine·BH_3,[15] borohydride exchange resin (BER),[16] zinc–acetic acid,[17] sodium borohydride–magnesium perchlorate,[18] zinc borohydride–zinc chloride,[19] silica gel–zinc borohydride,[7d] and dibutyltin chloride hydride.[20] However, most of the reported DRAs call for filtration, aqueous workup, evaporation, or a combination of these techniques prior to purification. These operations typically serve to remove or decompose organic-insoluble metal salts introduced as reducing reagents such as $NaBH_3CN$ and $NaBH(OAc)_3$.

Therefore, it is reasonable that the use of organic-soluble reducing reagents such as organosilanes with efficient catalysts could streamline DRA.[21] It could also provide the advantage of multiple parallel solution phase synthesis, which requires a protocol with no pre-chromatography product manipulation. Although a variety of DRA have been reported, as described above, there have been

* Corresponding author. Tel./fax: +81 3 5286 3240.
E-mail address: mnakada@waseda.jp (M. Nakada).

http://dx.doi.org/10.1016/j.tetlet.2014.01.132
0040-4039/

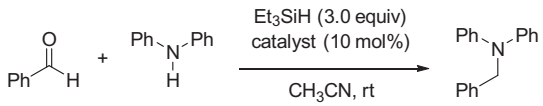
limited reports on DRA using organosilane as a reducing reagent. Organosilanes such as triethylsilane (TESH), in the presence of acid catalysts, are mild and useful reagent systems for reduction. However, trifluoroacetic acid (TFA)/TESH[22] is not compatible with acid labile functional groups. The use of $TiCl_4$/organosilane[23] is limited to aromatic aldehydes. Bu_2SnCl_2/$PhSiH_3$[24] is toxic, $Ti(OiPr)_4$/polymethylhydrosiloxane (PMHS)[25] is water-sensitive, and organosilane with a hydrio-iridium complex[26] is not compatible with substrates containing reducible functionalities. Hence, the development of improved methods using organosilanes is still anticipated. We herein report DRA using TESH and catalytic bismuth(III) chloride ($BiCl_3$).

The preparation of aryl- and diarylamine derivatives is important in research on structure–activity relationships. The DRA of aryl- and diarylamines is a rational approach from the standpoint described above, and DRAs, which use organosilane and a catalytic amount of $Ga(OTf)_3$[27] or $InCl_3$,[28] have also been reported. However, both reagents are relatively expensive, and in the latter system, the unsaturated carbonyl compounds are potentially reduced.[29] Moreover, it has been reported that In(III) results in teratogenicity in rats.[30]

It has been reported that diarylamines are included in many biologically active and pharmaceutically relevant compounds,[31] as well as new materials,[32] but DRAs of aldehydes and diphenylamine have been limited. Therefore, we started to screen various Lewis acids as a catalyst for the DRA of benzaldehyde and diphenylamine using TESH and Lewis acid.[33]

The DRA was examined using a 1:1 ratio of benzaldehyde and diphenylamine in the presence of 3.0 equiv of TESH and 10 mol % Lewis acid in acetonitrile at room temperature (Table 1). $TiCl_4$ (59%, entry 1) and $SnCl_4$ (68%, entry 2) afforded the product in good yields. $SbCl_5$ (entry 3), $ZnCl_2$ (entry 4), $PbCl_2$ (entry 5), and $CeCl_3{\cdot}7H_2O$ (entry 6) did not afford any product, and $YCl_3{\cdot}6H_2O$ was almost ineffective (10%, entry 7). The yields in the reactions with Bi(III) were high, except BiF_3 (0%, entry 8). The yield was 99% when 10 mol % of $BiCl_3$ was used (entry 9), and use of the reduced amount (5 mol %) reduced the yield to 34% (entry 10). The yields when $BiBr_3$ and BiI_3 were used were 79% (entry 11) and 81% (entry 12), respectively. Interestingly, $Bi(OTf)_3$ (74%, entry 13), which is known to be a strong Lewis acid, was less effective than the other Bi(III) reagents (entries 9, 11, 12). The DRA catalyzed by $InCl_3$[28] proceeded faster and afforded the product with 95% yield (entry 14); however, $InCl_3$ is relatively expensive and has

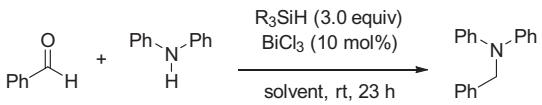
Table 1



Entry	Catalyst	Time (h)	Yield[a] (%)
1	$TiCl_4$	23	59
2	$SnCl_4$	23	68
3	$SbCl_5$	23	9
4	$ZnCl_2$	23	NR
5	$PbCl_2$	23	NR
6	$CeCl_3{\cdot}7H_2O$	13	NR
7	$YCl_3{\cdot}6H_2O$	13	10
8	BiF_3	13	NR
9	$BiCl_3$	13	99
10[b]	$BiCl_3$	13	34
11	$BiBr_3$	13	79
12	BiI_3	13	81
13	$Bi(OTf)_3$	13	74
14	$InCl_3$	10	95

[a] Isolated yield.
[b] $BiCl_3$ (5 mol %) was used.

Table 2



Entry	Organosilane	Solvent	Yield[a] (%)
1	Et_3SiH	CH_3CN	99
2	Et_3SiH	Toluene	Trace
3	Et_3SiH	Et_2O	Trace
4	Et_3SiH	CH_2Cl_2	NR
5	Et_3SiH	THF	NR
6	Et_3SiH	DMF	NR
7	Et_3SiH	DMSO	NR
8	Ph_3SiH	CH_3CN	NR
9	$(EtO)_3SiH$	CH_3CN	NR
10	$PhMe_2SiH$	CH_3CN	71
11	Et_2SiH_2	CH_3CN	72
12	Ph_2SiH_2	CH_3CN	42
13	$PhMeSiH_2$	CH_3CN	95
14	$PhSiH_3$	CH_3CN	97[b]

[a] Isolated yield.
[b] The reaction required 7 h to be completed.

disadvantages, as described above. Consequently, the results listed in Table 1 indicate that the use of $BiCl_3$ (10 mol %) is the most effective and practical for the DRA of benzaldehyde and diphenylamine using TESH.

To the best of our knowledge, DRA using organosilanes and catalytic Bi(III) has never been reported. In addition, Bi(III) has been used as an efficient green catalyst because of its many advantages, including its easy handling, low cost, nontoxic nature, and mild Lewis acid activity.[34] Hence, we decided to study DRA using organosilanes and $BiCl_3$.

The reaction conditions for DRA using $BiCl_3$ were examined (Table 2). The DRAs of benzaldehyde and diphenylamine using TESH in various solvents were screened. Trace amounts of the product were obtained in toluene (entry 2) and diethyl ether (entry 3), but no reactions occurred in dichloromethane (entry 4), THF (entry 5), DMF (entry 6), and DMSO (entry 7). Reactions with some organosilanes were also examined, but no reaction occurred with Ph_3SiH (entry 8) and $(EtO)_3SiH$ (entry 9). The reactions with $PhMe_2SiH$ (entry 10), Et_2SiH_2 (entry 11), Ph_2SiH_2 (entry 12), $PhMeSiH_2$ (entry 13), and $PhSiH_3$ (entry 14) afforded the product in yields of 71%, 72%, 42%, 95%, and 97%, respectively. The results listed in Table 2 indicate that the DRA of benzaldehyde and diphenylamine exhibited the best performance when TESH or $PhSiH_3$ in the presence of catalytic $BiCl_3$ in acetonitrile as the solvent was used.

The DRAs of various aldehydes and ketones using TESH and $BiCl_3$ were examined, as summarized in Table 3. The substituent effect of substrates was observed in the DRAs of arylaldehydes with diphenylamine (Table 3). The yield was reduced in the DRAs of *o*-chlorobenzaldehyde (entry 2) and *o*-ethynylbenzaldehyde (entry 3), which can be attributed to the steric hindrance suffered from the *o*-substituent. The yield in the DRA of *p*-nitrobenzaldehyde (entry 4) was 90%, while that of *p*-methoxybenzaldehyde (entry 5) decreased to 35% and the starting material remained. This difference can be explained by the electronic effect of the substituent, that is the electron-donating *p*-substituent deactivated the benzaldehyde. This electronic effect well explains the DRA of 3,4,5-trimethoxybenzaldehyde (entry 6) in which the product was formed with a low yield and the starting material remained again.

The above substituent effect is consistent with a reaction mechanism via the formation of iminium by the nucleophilic attack of diphenylamine to aldehyde and the subsequent reduction of the imine. Chloride, nitro group, and alkyne, which are reducible