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PII: S0040-4039(15)30532-3
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.12.116
Reference: TETL 47163

To appear in: *Tetrahedron Letters*

Received Date: 23 November 2015
Revised Date: 28 December 2015
Accepted Date: 30 December 2015

Please cite this article as: Dey, S., Gadakh, S.K., Ahuja, B.B., Kamble, S.P., Sudalai, A., Pd-catalyzed reductive cleavage of N-N bond in dibenzyl-1-alkylhydrazine-1,2-dicarboxylates with PMHS: application to a formal enantioselective synthesis of (*R*)-sitagliptin, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.12.116

Graphical Abstract

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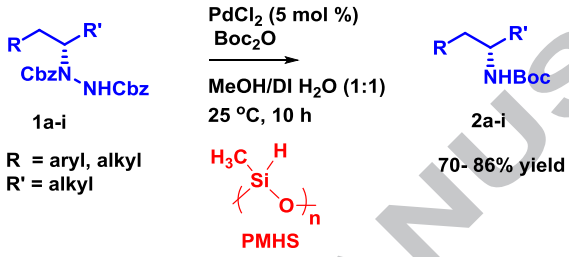

- Environmentally benign approach
- Broad substrate scope
- Formation of several useful intermediates for various drug molecules
- No racemization at the chiral centre
- Ambient reaction condition
- Use of safe, non-toxic, air and moisture stable PMHS

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Pd-catalyzed reductive cleavage of N-N bond in dibenzyl-1-alkylhydrazine-1,2-dicarboxylates with PMHS: application to a formal enantioselective synthesis of (*R*)-sitagliptin

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Envirronmentally benign
Reductive cleavage
PMHS
Hydrazine
Anti-diabetic

ABSTRACT

An environmentally benign approach involving Pd-catalyzed reductive N-N bond cleavage in dibenzyl-1-alkylhydrazine-1,2-dicarboxylates leading to the synthesis of *N*-(*tert*-butoxy)carbamates under very mild conditions has been described. PMHS serves as an inexpensive source of hydride in MeOH/deionized H_2O medium. This protocol has been successfully applied in the formal synthesis of (*R*)-sitagliptin, an *anti*-diabetic drug.

Introduction

The development of mild and efficient methods for the synthesis of amine compounds is of great importance, since these are frequently encountered as drugs in the pharmaceutical industries.[1] Some of the representative examples of the top selling drugs containing amine as a functional group include (*R*)-sitagliptine (anti-diabetic); (*S*)-benzphetamine (anorectic); (*R*)-selegiline, (anti-Parkinson's disease); and anisomysin (a psychiatric), shown in **Figure 1**. Because of the importance of amine functionnality various methods are known for its synthesis.[2] Among them reduction of nitro/azido compounds,[3a] imines,[3b] oximes[3c] and cleavage of N-N bonds[4] are the most common approaches. Especially, for the synthesis of chiral amine functionality, cleavage of N-N bonds of hydrazine groups has gained much importance in recent times, since these hydrazine compounds can be easily synthesized with high enantiopurity *via* proline catalyzed α-amination reactions of aldehydes.[5]

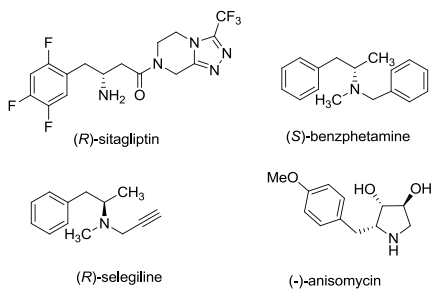
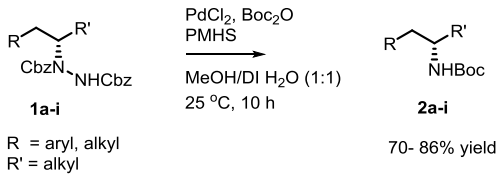


Figure 1 Representative examples of top-selling drugs cantaining amine functionality

As a consequence, a number of methods have been developed for N-N bond cleavage in hydrazine based substrates involving hydrogenation over metals,[4a] by reduction with aluminium or boron hydrides,[4b] by electroreductive process,[4c] e.g. Na or Li/NH_3 or by making use of SmI_2 with HMPA as co-solvent[4d] or by oxidative cleavage.[4e] However, these methods have been associated with certain drawbacks such as lack of reactivity, use of acidic or basic condition, sluggish reaction conditions as well as use of hazardous reagents, namely hydrogen. Therefore, the development of synthetic methodologies to cleave N-N bonds under mild, neutral reaction conditions leading to the formation of the primary amino compounds is highly desirable. Recently, Chandrasekhar *et al.* have reported reduction of simple aromatic hydrazines with Pd/C and PMHS.[4f] However, Pd catalyzed N-N bond cleavage in chiral benzyloxy carbamate protected hydrazine is not yet reported. As a part of our program aimed at the synthesis of various drug molecules using organocatalytic amination approach, the cleavage of N-N bonds is often required to get the amine intermediates.[6] Herein, we wish to report Pd catalyzed reductive cleavage of N-N bonds of dibenzyl-1-alkylhydrazine-1,2-dicarboxylate using polymethylhydrosiloxane (PMHS) as a hydride source in an environmentally attractive fashion using H_2O/MeOH medium at room temperature, which makes the present protocol highly favourable in comparison to previously reported systems (Scheme 1). PMHS is inexpensive, non-toxic and stable to air and moisture, which makes it an attractive reducing agent for environmentally benign reductive processes[7] as compared to hazardous aluminium hydrides, boranes and hydrogen.

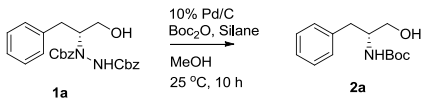


Scheme 1 Pd catalyzed reductive N-N bond cleavage

Results and Discussion

In the initial study, dibenzyl-1-(1-hydroxy-3-phenylpropan-2-yl)hydrazine-1,2-dicarboxylate (**1a**), as a model substrate, was subjected to reductive N-N bond cleavage by reacting with 10% Pd/C, Et_3SiH (2 equiv) and Boc_2O in MeOH at ambient temparature, which produced carbamate **2a** in 22% yield (entry 1; Table 1). Screening of many silanes revealed certain variations in the rate of cleavage of N-N bond (entry 1-4). For example, the rate of cleavage was found to be highest when we used PMHS (2 equiv), which gave the corresponding carbamate in 40% yield (entry 5) as compared to other silane sources. The yield of 2a was considerably improved to 78% when PMHS quantity was further increased to four equivalents under the same reaction conditions (entry 6). However, there was no significant increase in yield observed on increasing the quantity of PMHS to 8 equivalents.

Table 1 Screening of silane source[a]



entry	silanes	equiv	yields of **2a** (%)[b]
1	Et_3SiH	2	22
2	Et_3SiH	4	25
3	$PhSiH_3$	2	20
4	Ph_2SiH_2	2	15
5	PMHS	2	40
6	PMHS	4	78
7	PMHS	8	70

[a] Substrate (5 mmol), 10 mol% Pd/C, Boc_2O (5 mmol), silane, MeOH/Deionized water (1:1) (20 mL), 25 °C, 10 h; [b] isolated yields after column chromatographic purification.

Other metal salts and their complexes were also tested (Table 2) and found that Ni, Cu, and Co salts were ineffective in N-N bond cleavage (entry 1-4). However, metal salts such as $PtCl_2$, $Pd(dba)_2$, and $Pd(OAc)_2$ were found effective giving low yields (28-40%) of carbamate. Surprisingly, the use of $PdCl_2$ (5 mol%) afforded the best yield (80%) as compared to other Pd sources.

A number of organic solvents could be used to effect this reduction, as summarized in Table 3. The use of solvents like CH_2Cl_2, toluene, Et_2O and CH_3CN did not catalyze the reaction. Indeed, protic solvents like EtOH or MeOH with $PdCl_2$ produced moderate yield of carbamate (55-60%). Surprisingly, the addition of deionized water in MeOH (1:1) provided the best yield of **2a** (86%). The requirement for water in these reactions could be indicative of a transfer hydrogenation process where hydrogen gas is believed to have formed from silicon hydride and water *via* σ bond metathesis on palladium.[8] However, the yield of carbamate was reduced (30%), when deionized water was used alone as solvent. When the temperature of the reaction was increased to 60 °C, a slightly lowered yield (78%) was observed in H_2O/MeOH medium.

Table 2 Screening of metal salts[a]

entry	metal salts	mol %	yields of **2a** (%)[b]
1	$Ni(COD)_2$	5	-
2	$NiCl_2.2H_2O$	5	-
3	$Cu(OAc)_2.2H_2O$	5	-
4	$Co(NO_3)_2.6H_2O$	5	-
5	$PtCl_2$	5	28
6	$Pd(dba)_2$	5	20
7	$Pd(OAc)_2$	5	40
8	10% Pd/C	5	60
9	$PdCl_2$	5	80
10	$PdCl_2$	10	78

[a] Substrate (5 mmol), Boc_2O (5 mmol), PMHS (20 mmol), MeOH/Deionized water (1:1) (20 mL), 25 °C, 10 h; only variation in using metal salts; [b] isolated yields after column chromatographic purification; COD = 1,5-cyclooctadiene; dba = dibenzyli deneacetone.

After standardizing the reaction condition, we subjected other hydrazine compounds such as diethyl or diisopropyl-1-alkylhydrazine-1,2-dicarboxylates to the reaction conditions and found that no reaction took place, which may be due to the absence of reducible benzylic group in these substrates.

Table 3 Variation of reaction medium and temperature[a]

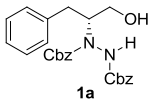
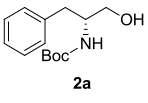
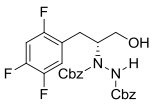
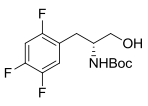
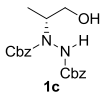
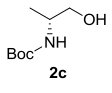
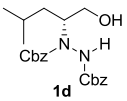
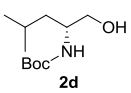
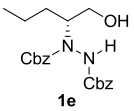
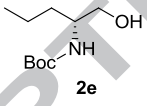
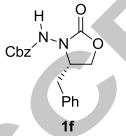
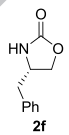
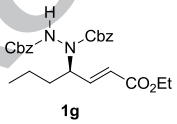
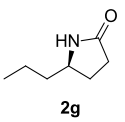
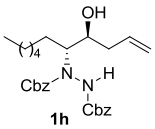
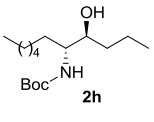
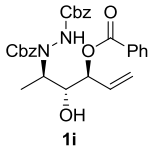
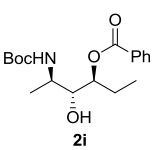
entry	medium	*t* (°C)	yields of **2a** (%)[b]
1	MeOH	25	60
2	MeOH	60	30
3	EtOH	25	50
4	DMF	25	10
5	DI water[c]	25	30
6	DI water[c] / MeOH (1:1)	25	86
7	DI water[c] / MeOH (1:1)	60	78

[a] Substrate (5 mmol), $PdCl_2$ (5 mol %), Boc_2O (5 mmol), PMHS (20 mmol), 10 h; only variation in reaction medium and temperature; [b] isolated yields after column chromatography; [c] DI water = deionized water

We have then applied the optimized procedure of Pd catalyzed reductive N-N bond cleavage to a variety of substrates, which were prepared using α-amination of carbonyl compounds following literature procedure (Table 4).[5] As can be seen, several chiral dibenzyl-1-alkylhydrazine-1,2-dicarboxylates underwent reductive cleavage to furnish carbamates in excellent yields (70-86%). It may be noted that carbamates like **2a-b** serve as builing blocks in various drug molecules.[9] The present protocol was found to be quite effective in the case of different substituted chiral hydrazines **1c-e**. Oxazolidinone **2f** was obtained in 80% yield using this protocol and can be used as chiral auxiliary in organic synthesis. Again, reductive cleavage of chiral α,β-

unsaturated hydrazide **1g** under the standard reaction condition, led to the formation of lactam **2g** in 76% yield. Also, the more functionalized hydrazine derivatives **1h-i** underwent reductive cleavage smoothly to produce functionalized carbamates **2h-i** in moderate yields. In all cases studied, the optical purity of each substrate was found to be preserved in the respective products.

Table 4 Reductive cleavage of N-N bond: Substrate scope[a]

entry	substrates	products	yields (%)[b]
1	 **1a**	 **2a**	86
2	 **1b**	 **2b**	83
3	 **1c**	 **2c**	70
4	 **1d**	 **2d**	72
5	 **1e**	 **2e**	72
6[c]	 **1f**	 **2f**	80
7[c]	 **1g**	 **2g**	76
8	 **1h**	 **2h**	76
9	 **1i**	 **2i**	74

[a] Substrate (5 mmol), $PdCl_2$ (5 mol %), Boc_2O (5 mmol), PMHS (20 mmol), MeOH/Deionized water (1:1) (20 mL), 25 °C, 10 h; [b] isolated yields after column chromatography; [c] No Boc_2O was used here.

The catalytic cycle for Pd-catalyzed reductive N-N bond cleavage is shown in Fig. 2 based on literature precedence.[10] The first step of catalytic cycle involves the reduction of $PdCl_2$ with PMHS to give active metallic Pd(0) species. This is followed by the oxidative addition of H_2 generated by PMHS to Pd(0) leading to the formation of palladium dihydride reactive species **I**. Pd(II) of species **I** co-ordinates with nitrogen atom of hydrazine to generate intermediate **II** followed σ-bond migration that leads to formation of intermediate **III**. Subsequent reductive elimination of **III** regenerates active metal species Pd(0) for the next catalytic cycle along with free amine, which was *in situ* protected with Boc_2O to furnish the carbamate **2**.

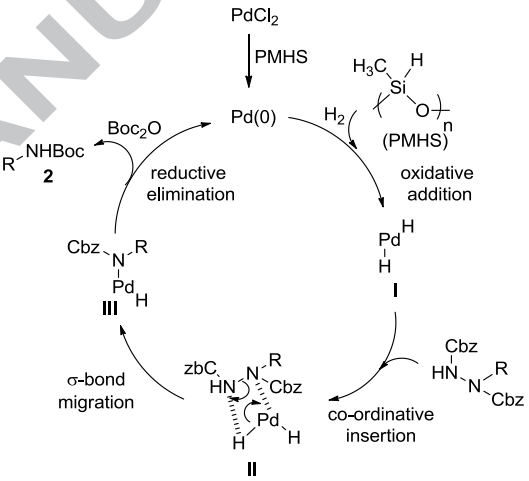
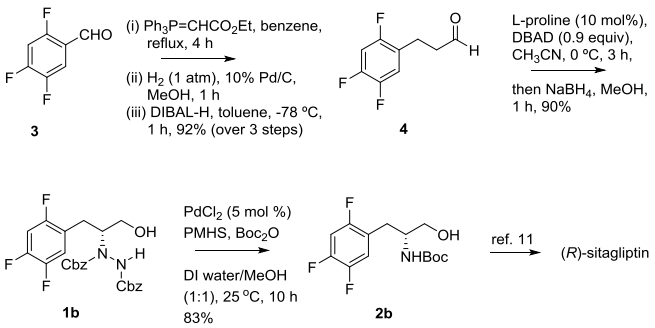


Figure 2 Proposed catalytic cycle for reductive N-N bond cleavage

Finally, its application was demonstrated in a short, fomal synthesis of (*R*)-sitagliptin, an anti-diabetic drug.[9c-d] Thus, aldehyde **4** was obtained from commercially available 2,4,5-trifluorobenzaldehyde **3** by a simple functional goup manipulation: (i) two carbon homologation with stabilized Wittig ylide; (ii) hydrogenation of the benzylic C=C bond by 10% Pd/C over H_2 (1 atm); (iii) selective reduction of ester functionality by DIBAL-H to aldehyde. The aldehyde was subjected to L-proline catalyzed α-amination reaction to afford α-amino alcohol **1b** in 90% yield, which was converted to carbamate **2b** following the present protocol. The transformation of **2b** to (*R*)-sitagliptin is well established in the literature (Scheme 2).



Scheme 2 Formal synthesis of *anti*-diabetic drug, (*R*)-sitagliptin

Conclusions

In conclusion, we have demonstrated an efficient, environmentally benign approach to cleave N-N bonds in dibenzyl-1-alkylhydrazine-1,2-dicarboxylate to furnish *N*-(*tert*-butoxy)carbamates. The method effectively cleaves N-N bond in a variety of hydrazine compounds containing a number of different functional group to their respective amines, which can be used as building blocks in medicinal chemistry. The use of polymethylhydrosiloxane (PMHS), an inexpensive, easy to handle, environmental benign reagent as reducing agent in our protocol makes it more viable than other reported methods.

Acknowledgements

SD, BBA & SKG thank CSIR, New Delhi for the award of senior research fellowships and CSIR, Indus MAGIC (CSC 0123) and DST, (No. SR/S1/OC-42/2014) New Delhi for financial support. The authors are also thankful to Dr. V.V. Ranade, Chair, Chem. Engg. & Process Develop. for his constant encouragement.

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Supplementary Material

Supplementary data (^{1}H and ^{13}C NMR spectra for all compounds, detailed experimental procedures) associated with this article can be found, in the online version.

Pd-catalyzed reductive cleavage of N-N bond in dibenzyl-1-alkylhydrazine-1,2-dicarboxylates with PMHS: application to a formal enantioselective synthesis of (*R*)-sitagliptin

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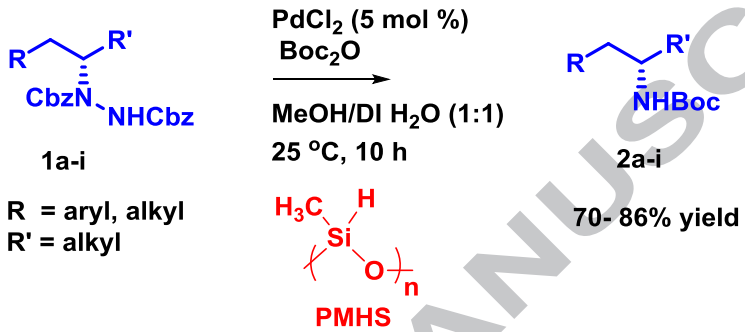
A one-step Pd-catalyzed direct conversion of dibenzyl-1-alkylhydrazine-1,2-dicarboxylates to various reactive intermediates using PMHS as a hydride source in an environmentally benign fashion is described.



- Environmental benign approach
- Broad substrate scope
- Formation of several useful intermediates for various drug molecules
- No racemization at the chiral centre
- Ambient reaction condition
- Use of safe, non-toxic, air and moisture stable PMHS