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PII: S0040-4039(16)30081-8
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.01.081
Reference: TETL 47245

To appear in: *Tetrahedron Letters*

Received Date: 19 November 2015
Revised Date: 21 January 2016
Accepted Date: 22 January 2016

Please cite this article as: Hati, S., Sen, S., N-bromo-succinimide promoted synthesis of β-carbolines and 3, 4-dihydro-β-carbolines from tetrahydro-β-carbolines, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.01.081

Graphical Abstract

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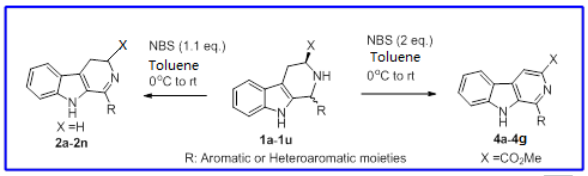
Santanu Hati and Subhabrata Sen*



Tetrahedron Letters
journal homepage: www.elsevier.com

N-bromo-succinimide promoted synthesis of β-carbolines and 3, 4-dihydro-β-carbolines from tetrahydro-β-carbolines

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
β-carboline
Tetrahydro-β-carboline
N-bromosuccinimide
3, 4-dihydro-β-carboline
Harmine

ABSTRACT

Here in, we report a facile synthesis of 3, 4-dihydro-β-carbolines and aromatic β-carbolines from tetrahydro-β-carbolines, mediated by N-bromosuccinimide in toluene at 0 °C to room temperature (rt), in good to moderate yield.

1. Introduction

Aromatic β-carboline moieties are present in a variety of biologically active alkaloidal natural products as well as pharmaceutically relevant compounds.[1a-c] Diverse β-carboline drivatives have exhibited various biological activities such as antitumor, antimalarial, antileishmanial, antibacterial and etc.[1a-c] For example Harmine (a fluorescent alkaloid with known telepathine properties), Harmaline (a reversible MAO-A inhibitor [RIMA]), Harmalol, Isoeudistomin U (DNA binding agents), 3, 4-dihydro-5(S)-5-carboxystrictosidine, Eudistomin are few of the aromatic β-carboline derivatives showing pronounced biological activity. Additionally compounds possessing these ring systems have also been used as building blocks in the generation of pharmaceutically relevant molecules.[2-6]

By virtue of wide range of biological applications, aromatic β-carbolines have become an important target of synthesis. In general, these molecules are synthesized *via* a Pictet-Spengler reaction followed by oxidative decarboxylation or dehydrogenation.[7-13] Oxidative decarboxylation strategies are tedious and required high temperature with reagents like potassium dichromate ($K_2Cr_2O_7$) in acetic acid (AcOH) and persulphates with catalytic silver or copper salts, until recently when Kamal et al. reported a mild diacetoxyiodobenzene (DIB) mediated decarboxylative oxidation of terahydro-β-carbolines.[8c, 9-12] Additionally dehydrogenation strategies typically involved large quantities of oxidants such as DDQ, SeO_2, and IBX/TBAB (Scheme 1a).[8 and 12] Interestingly, Stahl. et al. reported a bioinspired aerobic oxidation of tetrahydro-β-carbolines with bifunctional quinone catalyst to generate 3,4-dihydro-β-carbolines.[7a] Few alternative strategies to access aromatic β-carbolines involved elimination of N-tosyltetrahydro-β-carbolines by sodium hydroxide and ring closure of β-aryl amides with phosphorus oxychloride ($POCl_3$).[11 and 13]

Drawing inspiration from these reports and in continuation to our endeavor to develop practical synthetic strategies for pharmaceutically relevant compounds, a trial reaction of **1a** with catalytic NBS in THF resulted in the formation of 3, 4-dihydro-β-carboline **2a** and unreacted **1a** in the ratio of 20:80 (Scheme 1b). This result indicated that NBS is capable to promote the oxidative dehydrogenation of the tetrahydro-β-carboline 1**a**. We optimized this protocol and here in we report a facile synthesis of β-carbolines and 3, 4-dihydro-β-carbolines starting from tetrahydro-β-carbolines with NBS in appropriate solvent at 0 °C to rt (Scheme 1c).

2. Results and discussion

Initially for the optimization of the synthesis of 3, 4-dihydro-β-carbolines **1a** was used as the model substrate (Table 1). The reactions were conducted in various solvents such as toluene, tetrahydrofuran (THF), acetonitrile (ACN) and methanol with the reaction temperature maintained between 0 °C to rt (to inhibit any ring bromination by NBS). The average time taken for complete consumption of **1a** ranged from 3-6 h. The product conversion was monitored by LCMS. With 0.5 equivalents of NBS, the dihydro-β-carboline derivative **2a** was immediately

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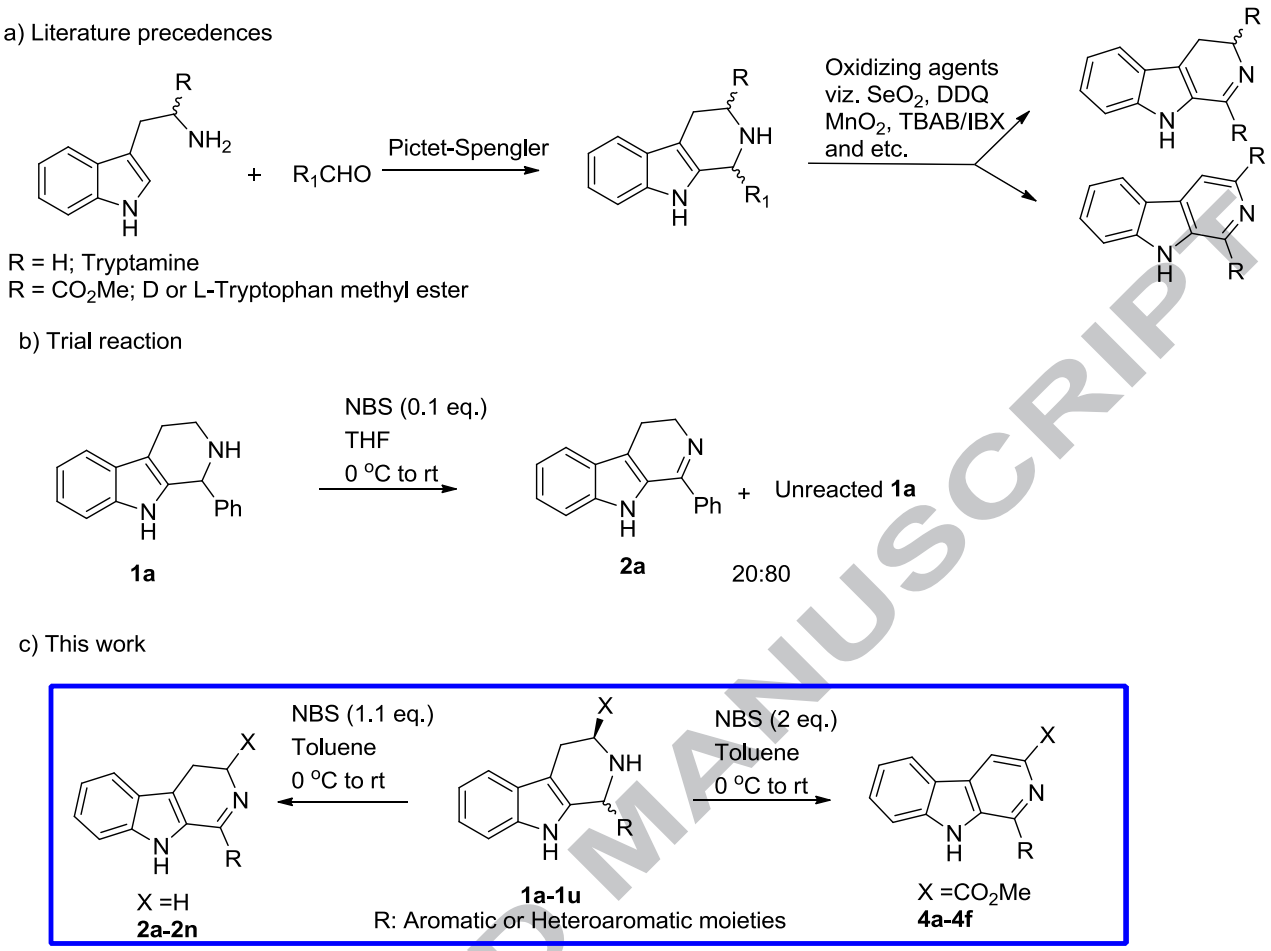
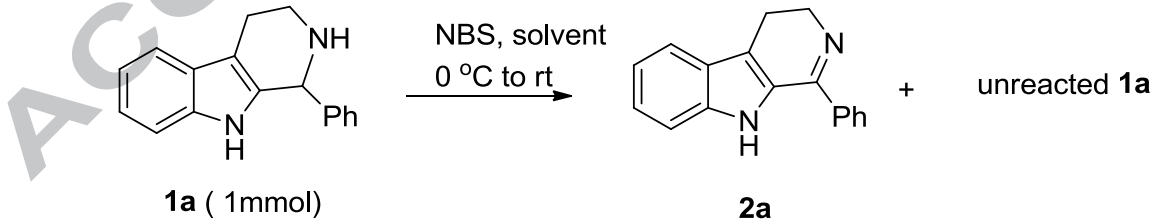
obtained in all the solvents, though in methanol the yield was lowest (entry 4,



Scheme 1. Synthesis of aromatic β-carbolines and 3, 4-dihydro-β-carbolines

Table 1). Equimolar amount of NBS led to a considerable improvement of yield of **2a**. The toluene and acetonitrile provided the best results with 84 and 82% yield respectively. Finally a slight increase of NBS to 1.1 equivalent in toluene further improved the yield to ~95%. Based on these observations it was concluded that 1.1 equivalent of NBS in toluene at 0 °C→ room temperature (rt), is the optimal condition for the synthesis of 3, 4-dihydro-β-carbolines.

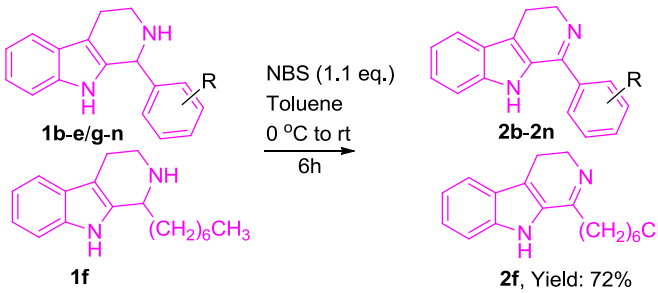
Table 1
Optimization of 3, 4-dihydro-β-carbolines



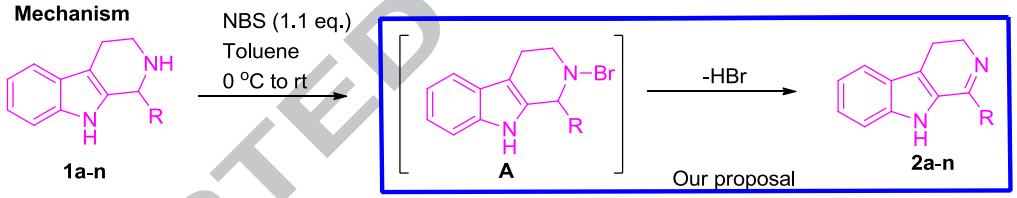
Entry	N-bromosuccinimide (mmols)	Solvents	Time (h)	Conversion (%)[a]	
				2a	**1a** (unreacted)
1	0.5	Tetrahydrofuran	4	35	45
2	″	Toluene	"	45	45
3	″	Acetonitrile	6	38	43
4	″	Methanol	"	12	43
5	1.0	Tetrahydrofuran	4	70	5
6	″	Toluene	"	84	-
7	″	Acetonitrile	6	82	3
8	″	Methanol	"	65	21
9	1.1	Toluene	"	95	-

[a] The reactions were monitored by LCMS, that provided the %ge conversion

Hence with the optimized protocol in hand, the generic nature of the process was explored. Accordingly tetrahydro-β-carbolines (**1b-n**) with a variety of functionality on the aromatic and aliphatic moiety were converted to the corresponding 3, 4-dihydro-β-carbolines (2b-n) (Scheme 2). The reactions were conducted in 100mg scale and simple purification by column chromatography afforded the desired products **2b-2n**. Irrespective of the nature of the substituents on the aromatic ring, the yields were good to moderate and ranged from 60-88% (Scheme 2). The aliphatic variant **2f** with octanal was generated in 72% yield (Scheme 2). To propose a mechanistic explanation of this transformation we postulate that the Br^+ from NBS brominates the piperidine N- (**A**) followed by elimination of HBr to afford 2 (Scheme 2).

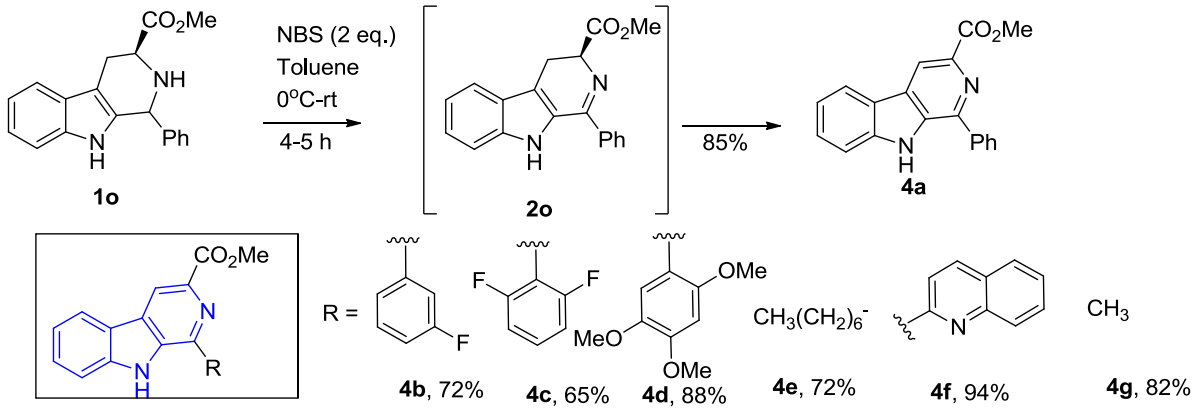


R	Substrates (#)	Products (#)	Yields (%)
3-CF_3	**1b**	**2b**	73
3,5-dimethyl	**1c**	**2c**	88
4-methyl	**1d**	**2d**	62
2-methyl	**1e**	**2e**	75
3-fluoro	**1g**	**2g**	75
2,4-ditrifluromethyl	**1h**	**2h**	59
3-methoxy	**1i**	**2i**	65
4-methoxy	**1j**	**2j**	83
2,4,5-trimethoxy	**1k**	**2k**	61
2-fluoro-4-methoxy	**1l**	**2l**	71
3-methyl-4-methoxy	**1m**	**2m**	89
2,3,5-trichloro	**1n**	**2n**	65



Scheme 2. NBS mediated synthesis of 3, 4-dihydro-β-carbolines

Next, we examined the scope of our protocol towards the synthesis of aromatic β-carboline derivatives (Scheme 3) from tetrahydro-β-carboline esters (derived from the condensation of L-tryptophan methyl ester and appropriate aldehydes). Transformation of this type has been previously conducted under mild condition by using IBX (2 equiv.) and tetrabutyl ammonium bromide (0.5 equiv.) in acetonitrile at room temperature for 2h.[8f] Hence we were hopeful that we would be able to repeat similar results with NBS, especially after obtaining the 3, 4-dihydro-β-carbolines (**2a-n**). Accordingly **1p** was chosen as the model substrate. To our pleasant surprise the reaction with two equivalent of NBS in toluene at 0 °C→rt showed ~85% conversion to aromatic β-carboline ester **4a** (Scheme 3). LCMS monitoring of the reaction indicated the formation of the 3, 4-dihydro-β-carboline intermediate **2o** which was then further oxidized to **4a**. To further confirm the formation of **2o**, it was isolated, purified and characterized by ^{1}H and ^{13}C-NMR. Additionally, **1o** was further reacted with 1.1 equivalent of NBS to generate **2o**. This methodology afforded a bevy of aromatic β-carboline esters (**4b-4g**) from their appropriate precursors in moderate to excellent yields (Scheme 3).



Scheme 3. Synthesis of aromatic β-carboline esters

3. Conclusion

In conclusion, we have devised an efficient strategy for the synthesis of aromatic-β-carbolines and its 3, 4-dihydro analogs through an efficient oxidative dehydrogenation of the corresponding tetrahydro-β-carbolines under mild condition. This strategy used NBS for the first time in such oxidative dehydrogenation reactions thereby providing the desired compounds in decent yields. Additionally this further provides a practical approach to access these classes of heterocycles that can be applied effectively in generating combinatorial libraries and will expedite compound generation during projected structure activity relationship studies.

4. Acknowledgements

The authors thank Shiv Nadar University for the support. SH acknowledges SNU for the graduate scholarship.

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