J. Chem. Sci. Vol. 128, No. 4, April 2016, pp. 565–572. © Indian Academy of Sciences.
DOI 10.1007/s12039-016-1056-6

One pot synthesis of 1-substituted tetrahydro-β-carbolines by Bischler–Napieralski cyclization

THOKCHOM PRASANTA SINGH and OKRAM MUKHERJEE SINGH*
Chemistry Department, Manipur University, Canchipur 795 003, Manipur, India
e-mail: ok_mukherjee@yahoo.co.in

MS received 4 September 2015; revised 26 December 2015; accepted 3 February 2016

Abstract. A novel and facile one-pot synthesis of 1-substituted tetrahydro-β-carbolines by cyclocondensation of ketene *S,S*–acetals with tryptamine in presence of $InCl_3$ and TFA as co-catalysts by Bischler-Napieralski cyclization is described. The reaction involves formation of one C-N bond, one C-C bond and a new ring annulation over an indole moiety.

Keywords. Bischler–Napieralski reaction; tetrahydro-β-carboline; ketene *S,S*–acetals; $InCl_3$; one-pot.

1. Introduction

The 1,2,3,4-tetrahydro-β-carboline (THβC) ring system is a key motif in a diversity of biologically and pharmacologically significant alkaloids, and a subject of recent reviews.[1] THβCs act as potent neuroactive alkaloids.[2] It also can bind to GABA, a receptor ion channel and modulate molecular mechanisms controlling anxiety, convulsions, and sleep.[3] THβCs exhibit many important biological activities like antimicrobial,[4] antitumor,[5] antimalarial,[6] and anti-leishmanial activity.[7] Thus, studies on the synthesis and bioassay of various THβCs derivatives have attracted increasing attention of synthetic chemists recently. It is known that, the introduction of appropriate substitutions at position-1 significantly enhanced the medicinal activities of β-carbolines.[8] Figure 1 shows some important representatives of this heterocyclic system.

Several reports for the preparation of 1-substituted THβCs are available in the literature which involves traditional Pictet–Spengler reaction[9] using activated aldehyde or ketones. However, the synthetic methods of these compounds using Bischler–Napieralski reaction[10] have been reported very rarely. Moreover, many of these reported reactions[10,11] involved multi steps and results in poor yields. Based on these findings, we were interested in designing new reactions using simple and easily accessible starting materials to expand the structural diversity of the target compounds (THβCs).

As a part of our ongoing interest in the development of bioactive heterocycles,[12] we have reported the synthesis of tetracyclic indole derivatives **3** using β-oxodithioesters **2** in In/TFA combination as catalyst (scheme 1).[13] In fact, this unexpected tetracyclic indole was prepared during the course of our various trial experiments to prepare the newly reported THβCs. Interestingly, it was found that replacement of the substrate β-oxodithioesters by its ketene *S,S* acetal derivatives **4**, we could get our desired products under similar reaction conditions. Herein, we wish to report a one-pot facile synthesis of 1-substituted THβCs **5** using ketene *S,S*–acetals **4** in presence of In/TFA combination as catalyst as depicted in scheme 1.

2. Experimental

2.1 *General procedure for the synthesis of (E)-3-(2-(1H-indol-3-yl)ethylamino)-3-(methylthio)-1-phenylprop-2-en-1-one (**5aa**)*

To a solution of the 3,3-bis(methylthio)-1-phenylprop-2-en-1-one **4a** (3 mmol) and tryptamine (3 mmol) in CH_2Cl_2 (15 mL), $InCl_3$ (2 mol%) was added and the reaction mixture was refluxed for 2 h (monitored by TLC). The reaction mixture was poured into ice-cold water and extracted with CH_2Cl_2 (30 mL). The combined organic layer was washed with H_2O (25 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to afford the crude product which was purified by column chromatography over silica gel using hexane–EtOAc (8:2) as eluent.

2.2 *General procedure for the synthesis of 1-(substituted)methylene-1,2,3,4-tetrahydro-β-carbolines (**5a-l**)*

To a solution of the ketene *S,S*-acetal (3 mmol) and tryptamine (3 mmol) in CH_3CN (15 mL), $InCl_3$ (2 mol%)

*For correspondence

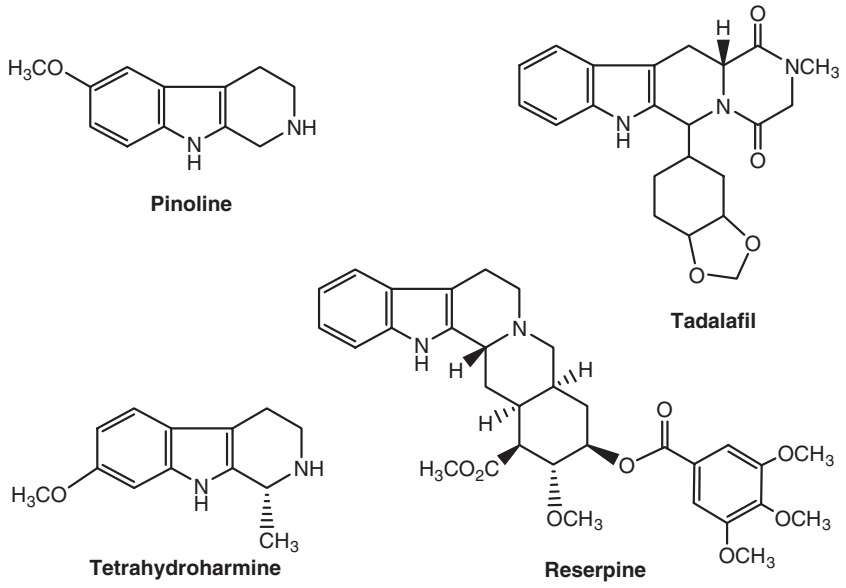
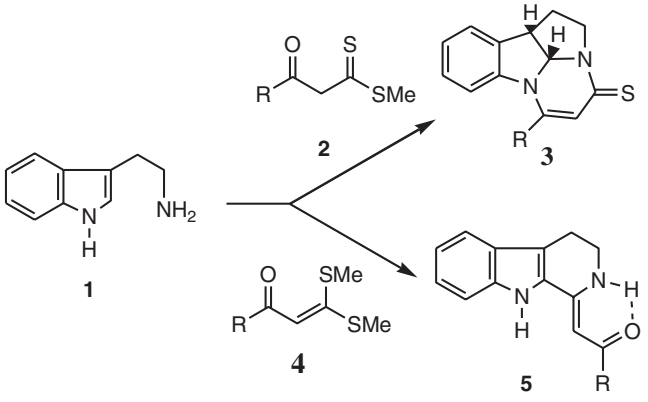


Figure 1. Some important representatives of tetrahydro-β-carbolines.



Scheme 1. Reaction of tryptamine with β-oxodithioesters and ketene *S,S*-acetals.

was added and refluxed. After refluxing for 2 h, TFA (15 mol %) was added to the reaction mixture and refluxing was continued for 1–2 h (monitored by TLC). Then, the reaction mixture was poured into ice-cold water and extracted with CH_2Cl_2 (30 mL). The combined organic layer was washed with H_2O (25 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to afford the crude product which was purified by column chromatography over silica gel using hexane–EtOAc (8:2) as eluent.

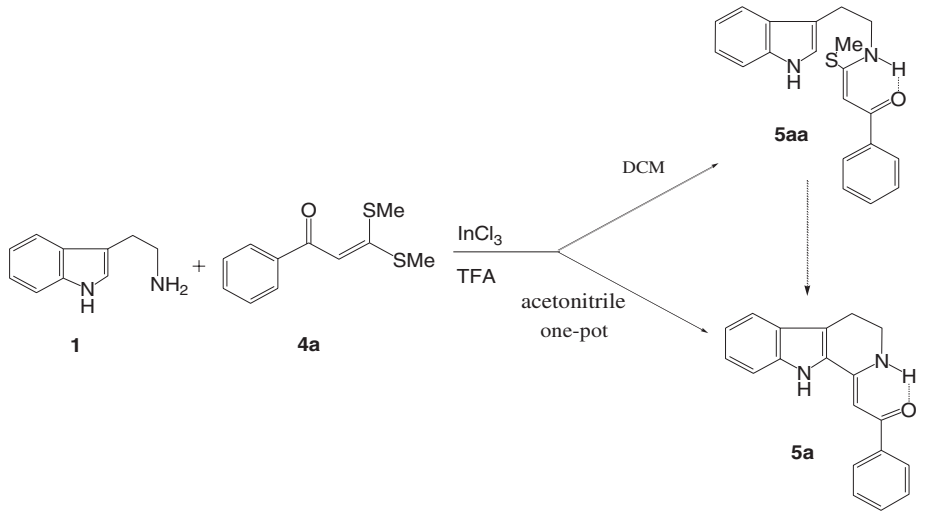
3. Result and Discussion

Encouraged by our recent findings on one-pot synthesis of indole derivatives,[13] we attempted several hit and trial methods for getting our desired tetrahydro carbolines using dithiocarboxylates (scheme 2). In an initial experiment, tryptamine **1** was reacted with 3,3-bis (methylthio)-1-phenylprop-2-en-1-one **4a** using $InCl_3$ (10 mol%) without TFA in dichloromethane at refluxing condition for 24 h. But, the reaction gave only the corresponding (*E*)-3-(2-(1*H*-indol-3-yl)ethylamino)-3-(methylthio)-1-phenylprop-2-en-1-one **5aa** in 70% yield (table 1, entry 1). In another experiment, the reaction was carried out with TFA (10 mol%) with other parameters remaining constant; the intermediate **5aa** was isolated in improved yield of 75% (entry 2). Further investigations using different organic solvents like ethanol, methanol, benzene, toluene and DMF in refluxing conditions yielded only the thioamide. It was also observed that no reaction occurred in the absence of solvent.

Next, the reaction was performed in acetonitrile as solvent with In/TFA combination as catalyst. To our delight, the reaction proceed well to give the final product (*Z*)-1-phenyl-2-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-ylidene)ethanone (**5a**) in 4 h of refluxing. Moreover, the intermediate **5aa** was also converted to the desired carboline (**5a**) by refluxing in acetonitrile using TFA as catalyst.

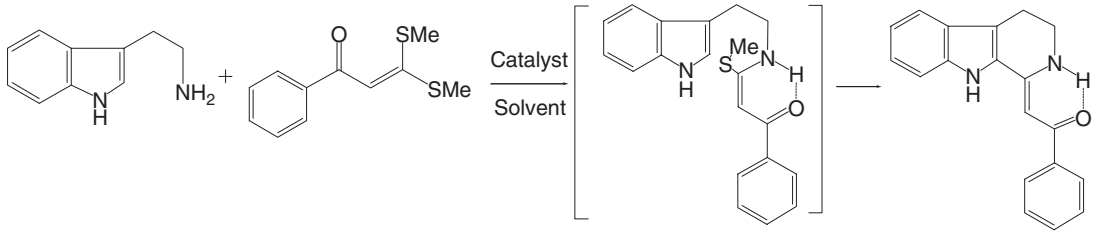
Then optimization of the product was explored by using different amounts of TFA keeping the catalytic amount of $InCl_3$ constant (2 mol%). The amount of TFA was explored by using 10, 15 and 20 mol%, and it was found that 15 mol% of TFA was sufficient for the reaction. The reaction also fails to proceed in the absence of $InCl_3$. The structures of the newly synthesized compounds were confirmed by spectral and analytical data (see Supporting Information).

Having established the optimal reaction conditions, we tested the scope of the substrates and found that various ketene *S,S*–acetals **4b-i** react with tryptamine **1**



Scheme 2. Reaction of tryptamine with ketene *S,S*-acetals catalyzed by In/TFA using various solvents.

Table 1. Optimization of reactions[a].



1 **4a** **5aa** **5a**

entry	solvent	Catalyst	time(h)	yield(%)[b]
1	$ClCH_2Cl$	$InCl_3$(10 mol%)	24	70 (**5aa**)
2	$ClCH_2Cl$	$InCl_3$(10 mol%)/TFA(10 mol%)	24	75 (**5aa**)
3	EtOH	$InCl_3$(10 mol%)/TFA(10 mol%)	24	70 (**5aa**)
4	MeOH	$InCl_3$(10 mol%)/TFA(10 mol%)	24	55 (**5aa**)
5	DMF	$InCl_3$(10 mol%)/TFA(10 mol%)	24	55 (**5aa**)
6	Toluene	$InCl_3$(10 mol%)/TFA(10 mol%)	24	55 (**5aa**)
7	No solvent	$InCl_3$(10 mol%)/TFA(10 mol%)	24	–
8	MeCN	$InCl_3$(2 mol%)/TFA(10mol%)	4	80 (**5a**)
9	MeCN	$InCl_3$(2 mol%)/TFA(15mol%)	4	85 (**5a**)
10	MeCN	$InCl_3$(2 mol%)/TFA(20 mol%)	4	85 (**5a**)
11	MeCN	TFA(10 mol%)	24	–

[a]All reactions were performed with **1** (0.5 mmol) and **4a** (0.5 mmol) under standard condition refluxing condition. [b]Yield of isolated product.

leading to the corresponding 3,3-bis(1-methyl-1*H*-indol-3-yl) derivatives **5b-i** (table 2). The results showed that the process could tolerate both aromatic ketones with electronically different substituents (entries 2–7) and even extremely electron-rich aromatic ketene *S,S*–acetals (such as 2-acetyl furan and 2-acetyl thiophene) (entries 8–9). It is observed that the substituents on the aromatic rings had some influence on the yields of products **5a-i**. The aromatic ketones with functional groups such as chloro and bromo (entries 8–10) reacted faster and gave higher yields than those with electron donating groups, such as methyl and methoxyl groups (entries 5–7).

Furthermore, ketene *S,S*–acetals derived from electron withdrawing group substituted active methylene compounds **4j-l** were reacted with tryptamine in same reaction condition to afford the corresponding THBCs **5j-l** *via* Bischler–Napieralski cyclization (table 3). The reactions were completed in 3 h of refluxing. The reactions were monitored by TLC and the structures were confirmed by ^{1}H NMR and ^{13}C NMR spectra and analytical data (see Supporting Information).

Table 2. Preparation of tetrahydro-β-carbolinesfrom ketene *S,S*–acetals.

1 **4a-i** **5a-i**

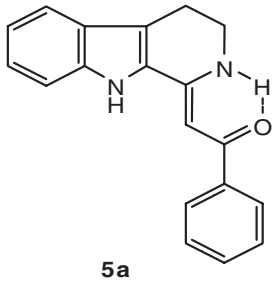
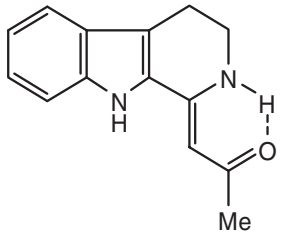
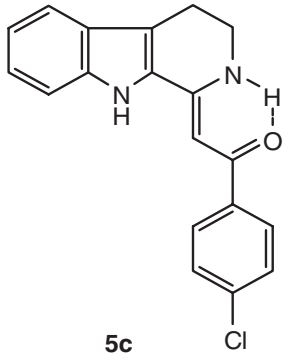
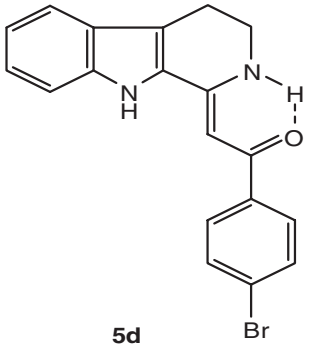
entry	R	Product	M.p. (°C)	Yield[a] (%)
1.	Ph	 **5a**	170–172	85
2.	Me	 **5b**	167–169	89
3.	4-Cl-ph	 **5c**	145–147	92
4.	4-Br-ph	 **5d**	154–157	82

Table 2. (continued)

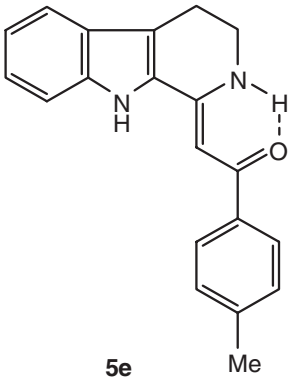
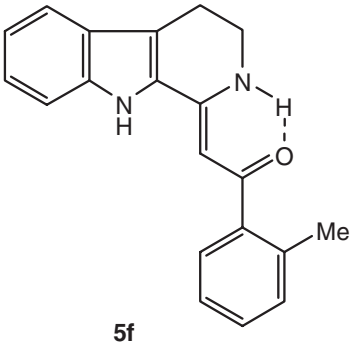
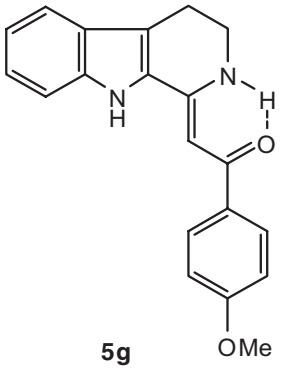
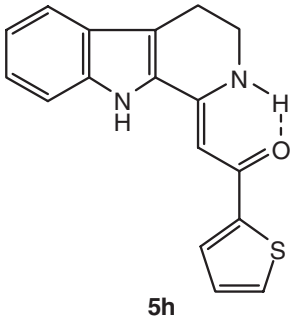
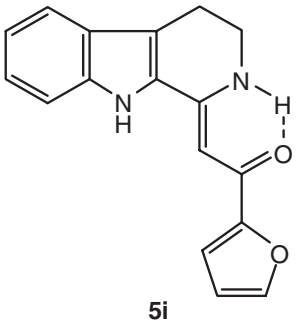
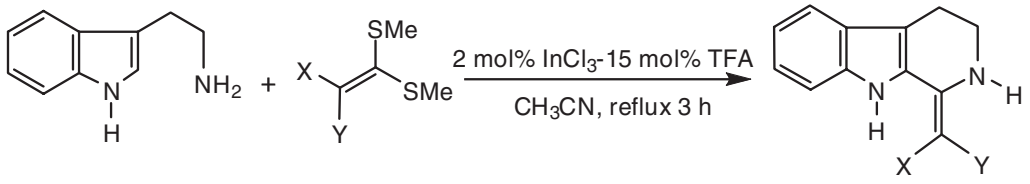
entry	R	Product	M.p. (°C)	Yield[a] (%)
5.	4-Me-ph	 **5e**	187–189	80
6.	2-Me-ph	 **5f**	145–148	75
7.	4-OMe-ph	 **5g**	162–164	82
8.	2-Thionyl	 **5h**	135–137	81

Table 2. (continued)

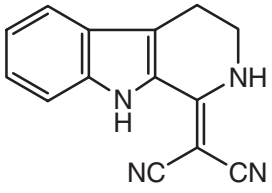
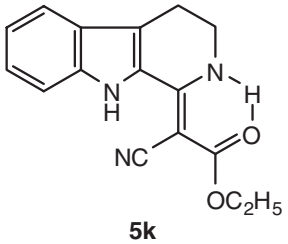
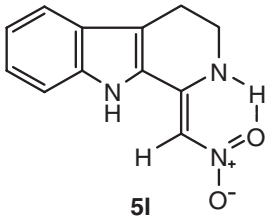
entry	R	Product	M.p. (°C)	Yield[a] (%)
9.	2-Furyl	 **5i**	129–131	74

[a]Isolated yields after silica gel column chromatography.

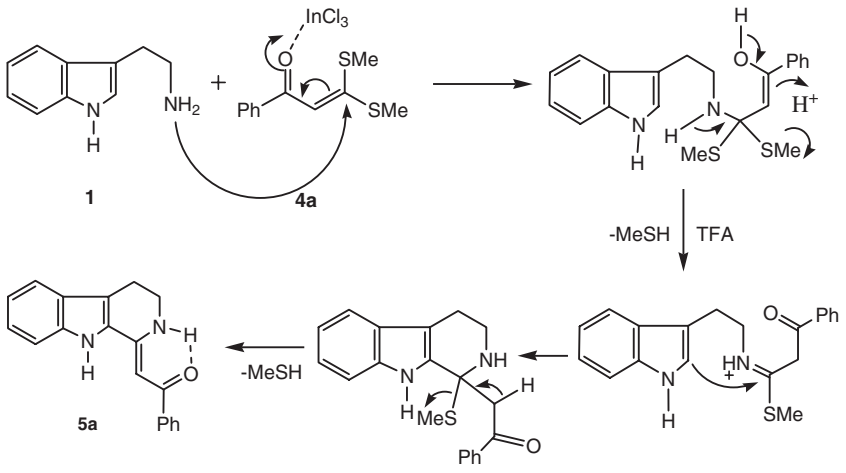
Table 3. Preparation of tetrahydro-β-carbolines from ketene *S*,*S*–acetals derived electron withdrawing substituents.



1 **4j-l** **5j-l**

entry	X/Y	Product	M.p. (°C)	Yield[a] (%)
1.	CN/CN	 **5j**	170–172	85
2.	CN/$CO_2C_2H_5$	 **5k**	167–169	89
3.	H/NO_2	 **5l**	154–157	82

[a]Isolated yields after silica gel column chromatography.



Scheme 3. Plausible mechanism.

The proton decoupled ^{13}C NMR spectrum of compound **5a** showed 19 distinct chemical shift values with reference to TMS. The spectrum showed presence of carbonyl carbon at δ 185.4 ppm. The signal due to N-H proton in the ^{1}H NMR spectra of enaminones **5a–i**, enaminonitrile **5j**, enaminoesters **5k** and nitroenamine **5l** appears between δ 10–12 ppm due to, probably, the intramolecular hydrogen bonding. The other indole N-H proton gave signals at δ 8–10 ppm.

The plausible mechanism of the reaction is depicted in scheme 3 based on the established classical mechanism of Bischler-Napieralaski. In the initial step, in the presence of Lewis acid $InCl_3$ in acetonitrile, the electron rich nitrogen atom of tryptamine **1** attack the electrophilic carbon of ketene *S,S* acetal **4a**, thereby forming a new C-N bond initially. Elimination of one molecule of methanethiol may generate an iminium intermediate. Intramolecular attack of C-2 of indole ring to the electrophilic centre to form the newly annulated six membered ring with subsequent elimination of one more molecule of methanethiol gives the final desired product **5a** (scheme 3).

4. Conclusions

A facile one-pot synthesis of 1-substituted tetrahydro-β-carbolines by Bischler–Napieralski cyclization from readily accessible ketene *S,S*–acetals and tryptamine has been described. Consequently, a library of THBCs was synthesized under mild and environmentally benign reaction conditions. The initial strategy involves the *in situ* formation of an intermediate in presence of $InCl_3$/TFA which cyclises in the presence of acteonitrile in one procedure. The alternative route, which is the major work of this investigation, involves a one-pot reaction condition using $InCl_3$/TFA and refluxing in acetonitrile.

Supplementary Information (SI)

General experimental procedures, characterization data and spectra are available in Supplementary Information at www.ias.ac.in/chemsci.

Acknowledgements

T. P. S. is grateful to DST, New Delhi for INSPIRE-Fellowship. O. M. S. is thankful to SERB, DST (Project No. EMR/2014/000331) and DBT (Project No. BT/278/TBP/2011) for financial assistance.

References

1. (a) Cao R, Peng W, Wang Z and Xu A 2007 *Curr. Med. Chem.* **14** 479; (b) El-Sayed M and Verpoorte R 2007 *Phytochem. Rev.* **6** 277; (c) Chen F E and Huang J 2005 *Chem. Rev.* **105** 4671; (d) Kam T S and Sim K M 1998 *Phytochem.* **47** 145
2. Tomas H 2000 *J. Agric. Food Chem.* **48** 4900
3. (a) Ninan P T, Insel T M, Cohen R M, Cook J M, Skolnick P and Paul S M 1982 *Science* **218** 1332; (b) Mendelson W B, Cain M, Cook J M, Paul S M and Skolnick P 1983 *Science* **219** 414
4. Ma Y, Wu H, Zhang J and Li Y 2013 *Chirality* **25** 656
5. (a) Akundi R S, Macho A, Munoz E, Lieb K, Bringmann G, Clement H W, Hull M and Fiebich B L 2004 *J. Neurochem.* **91** 263; (b) Zheng C, Fang Y, Tong W, Li G, Wu H, Zhou W, Lin Q, Yang F, Yang Z, Wang P, Peng Y, Pang X, Yi Z, Luo J, Liu M and Chen Y 2014 *J. Med. Chem.* **57** 600
6. (a) Brokamp R, Bergmann B, Muller I B and Stefan Bienz S 2014 *Bioorg. Med. Chem.* **22** 1832; (b) Gupta L, Srivastava K, Singh S, Puri S K and Chauhan P M S 2008 *Bioorg. Med. Chem. Lett.* **18** 3306

7. Kumar R, Khan S, Verma A, Srivastava S, Viswakarma P, Gupta S, Meena S, Singh N, Sarkar J and Chauhan P M S 2010 *Eur. J. Med. Chem.* **4** 53274
8. (a) Cao R, Peng W, Chen H, Hou X, Guan H, Chen Q, Ma Y and Xu A 2005 *Eur. J. Med. Chem.* **40** 249; (b) Zhang G, Cao R, Guo L, Ma Q, Fan W, Chen X, Li J, Shao G, Qiu L and Ren Z *Eur. J. Med. Chem.* **65** 21
9. (a) Barbero M, Bazzi S, Cadamuro S and Dughera S 2010 *Tetrahedron Lett.* **51** 6356; (b) Wanner M J, van der Haas R N S, de Cuba K R, van Maarseveen J H and Hiemstra H 2007 *Angew. Chem.* **119** 7629; (c) Bernhardt P, Usera A R and O'Connor S E 2010 *Tetrahedron Lett.* **51** 4400; (d) Larghi E L, Amongero M, Bracca A B J and Kaufman T S 2005 *Arkivoc* **xii** 98; (e) Klausen R S and Jacobsen E N 2009 *Org. Lett.* **11** 887; (f) Bondzic B P and Eilbracht P 2008 *Org. Biomol. Chem.* **6** 4059; (g) Pal B, Jaisankar P and Giri V S 2003 *Synth. Commun.* **33** 2339
10. (a) Roszkowski P, Wojtasiewicz K, Leniewski A, Maurin J K, Lis T and Czarnocki Z 2005 *J. Mol. Catal. A: Chemical* **232** 143; (b) da Silva W A, Rodrigues M T, Shankaraiah N, Ferreira R B, Andrade C K Z, Pilli R A and Santos L S 2009 *Org. Lett.* **11** 3238; (c) Meruva S B, Raghunadh A, Kamaraju R R, Kumar U K S and Dubey P K 2014 *Beilstein J. Org. Chem.* **10** 471; (d) Kumar D, Mishra B A, Shekar K P C, Kumar A, Akamatsu K, Kusakab E and Ito T 2013 *Chem. Commun.* **49** 683
11. Chakrabarti S, Panda K, Ila H and Junjappa H 2005 *Synlett* **20** 309
12. (a) Singh O M, Devi L R, Singh T P and Ila H 2011 *Arkivoc* **ii** 297; (b) Chanu L G, Singh T P, Jang Y J, Yoon Y J, Singh O M and Lee S G 2014 *Bull. Korean Chem. Soc.* **35** 994; (c) Singh T P, Khan R, Noh Y R, Lee S G and Singh O M 2014 *Bull. Korean Chem. Soc.* **35** 2950
13. Singh T P, Bhattacharya S and Singh O M 2013 *Org. Lett.* **15** 1974