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An Expeditious Synthesis of Epibatidine and Analogues

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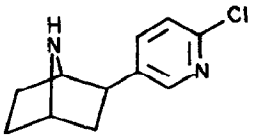
Abstract: *An efficient synthesis of Epibatidine and its analogues* via *[3+2] cycloaddition of non-stabilised azomethine ylide and substituted 6-chloro-3-vinyl pyridine.*

Epibatidine (1), a new class of alkaloid possessing a 7-azabicyclo(2.2.1)heptane ring system with 2-chloro-5-pyridyl substituent in an *exo*-orientation, isolated from the skin extract of Equadoran poison frog, *Epipedobates tricolour*, has been shown to exhibit non-opioid analgesic activity about 200-500 times more than that of morphine[1]. Owing to its intriguing pharmacological activity, interesting structural features and scarcity of 1 in nature, the total synthesis of 1 has obviously attracted considerable research interest. The basic strategy adopted so far towards the synthesis of 1 has either involved the intramolecular transannular nucleophilic displacement[2a-c] by the amine substituent at 4 position of substituted cyclohexyl ring, as reported by Fraser et.al[3], or by (4+2)-cycloaddition reaction of pyrrole with 2-chloro-5-alkyne pyridine[4]. However, these methodologies



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suffer from serious limitation due to the involvements of multiple steps, poor yields, stereoselectivity and lack of easy adaptability for the synthesis of Epibatidine analogues[5]. Recently, we have reported[6] an efficient strategy for the construction of x-azabicyclo(m.n.1) alkane ring systems by (3+2) cycloaddition of corresponding non stabilised azomethine ylides, generated by the sequential double desilylation of N-alkyl-α,α'-di(trimethylsilyl)

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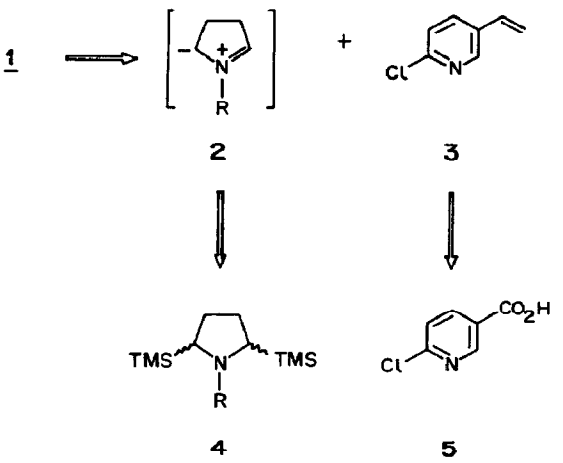
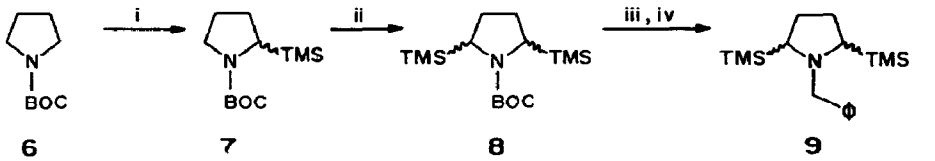
cyclic amines using Ag(I)F as one electron oxidant, with a variety of dipolarophiles. Therefore, it occurred to us that **1** can be easily synthesized by following the retrosynthetic steps as shown in **SCHEME-1**. We wish to report herein the total synthesis of **1** and its analogues which is short and efficient starting from easily available precursor compounds.

SCHEME - I



The precursor **9** was obtained in 73% yield from N-Boc pyrrolidine (**6**) by following the strategy as shown in **SCHEME-II**. Metallation of **6** (1 mole) with sec-BuLi, in the presence of TMEDA(1 mole), at -78 for three hours followed by trimethyl silyl chloride (1.2 moles) addition gave 2-trimethyl silyl N-Boc pyrrolidine (**7**) in 95% yield. Repetition of the above metallation sequence gave 2,4-di(trimethyl silyl) N-Boc pyrrolidine (**8**) in 80% yield. Deprotection of **8** with trifluoroacetic acid and subsequent N-benzylation with benzyl chloride gave **9** in 73 % yield[7].

SCHEME - II

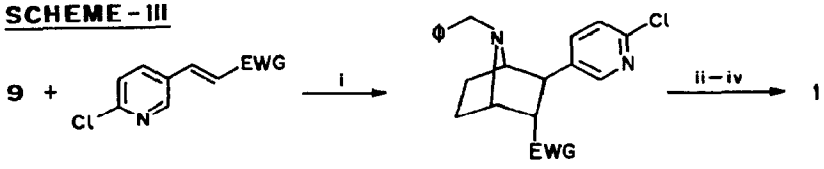


i) Ether , TMEDA , Sec - BuLi , – 78°C , TMSCl , 3h , ii) Repeat of Sequence in (i), iii) TFA , DCM , 5°, 30 MIN , iv) K_2CO_3 , CH_3CN , $PhCH_2Cl$, Δ , 8h.

Compound **10** may be obtained in 83% yield by following simple steps from commercially available 2-chloro-5-pyridine carboxylic acid (**5**). The (3+2)-cycloaddition reaction between **9** and **10a** was carried out by additon of **9** (1 mole) to a stirred mixture containing Ag(I)F (2 mole) and **10a** (1.2mole) in dry CH_3CN

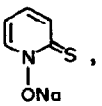
under argon atmosphere at room temperature. Instant precipitation of Ag(0) metal takes place which ultimately forms a silver mirror on the walls of the flask.

SCHEME - III



	10	11
EWG	a = $-CO_2Et$	83 %
	b = $-CHO$	70 %
	c = $-CN$	77 %
	d = $-NO_2$	80 %

i) Ag (I) F , CH_3CN ii) LiOH / MeOH , 95% , iii) $(COCl)_2$,



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t-BuSH , PhH , Δ , 75 % iv) H_2–Pd/c 90 %

The reaction is complete within 30-35 minutes, however, the stirring was continued for an additional half an hour. The reaction mixture was decanted and filtered through a plug of celite. Evaporation of CH_3CN gave cycloadduct **11a** in 82% yield which was further purified by column chromatography (silica gel, > 200 mesh ethyl acetate:pet.ether (1:10 as eluent)) and characterized by ^1H NMR, ^{13}C NMR and mass spectral data[8].

The *exo*-position of 2-chloropyridyl group in **11a** was established by proton decoupling experiment based on H-2 and H-3. For illustration H-2 at 2.55(d, J=6.16 Hz) was found to couple only with H-3 at 3.95(dd, J=6.16, 4.55 Hz) indicating the *trans* relationship between H-2 and H-3, which is in agreement with the reported values of Epibatidine ^1H NMR spectra[2a-f]. Further, this has been supported by observing no NOE between these protons. Final confirmation to our stereochemical assignment, was obtained by transforming **11a** into **1** and comparing spectral characteristics with the reported values[2a-f] of **1**. The conversion of **11a** to **1** was achieved by radical decarboxylation of corresponding thiohydroxamic ester using Bartons method[9], followed by reductive N-debenzylation carried out by hydrogenation over Pd/C as catalyst in overall 78 % yield.

The *exo*-selectivity for 2-chloropyridyl group in cycloadduct **11a** may be explained by considering the *endo*-mode of cycloaddition of **2** with **10** where the 2-chloropyridyl group adopts the *exo*-position possibly to avoid steric crowding with bulky benzyl group.

In order to generalise our strategy for the synthesis of Epibatidine analogues, identical reactions were performed by using substituted dipolarophile **10b-d** which gave corresponding cycloadducts **11b-d** in 75-80 % yield.

Our efforts to synthesize **1** in both enantiomeric forms using various chiral dipolarophiles continues and will be disclosed in full paper.

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REFERENCES:

1. Spande, T. F.; Garrafo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. ***J. Am. Chem. Soc.*** **1992**, *114*, 3475.

2. a) Broka, C. A *Tetrahedron Lett.* **1993**, *34*, 3251.
   b) Fletcher, S. R.; Baker, R.; Chambers, M.S.; Hobbs, S. C.; Mitchell P. ***J. J. Chem. Soc. Chem. Commun.*** **1993**, 1216
   c) Corey, E. J.; Loh, T.; Achyuthrao,S.; Daley, D. C.; Sarshar. S. *J.Org. Chem.* **1993**, *58*, 5600.
   d) Szantay, C.; Balogh, Z.K.; Moldvai, I.; Szantay, C.; Major, E. T.; Blasko, G ***Tetrahedron Lett.*** **1994**, *35*, 3171.
   e) Clayton, S. C.; Regan, A. C. *Tetrahedron Lett.* **1993**, *34*, 7493.

3. Fraser, R. R and Swingle, R. B. *Can. J. Chem.* **1970**, *48*, 2065.

4. Huag, D. F. ; Shen, T. Y. *Tetrahedron Lett.* **1993**, *34*, 4477

5. The natural Epibatidine have been shown to be toxic (Li, T.; Eckman, J.; Huang, D.F.; Shen, T.Y. ***Bio-org and Med. Chem. Lett.*** **1993**, *3*, 2759). Therefore, synthesis of various analogues for pharmacological evaluation are desirable.

6. Pandey, G.; Lakshmaiah, G.; Ghatak, A. *Tetrahedron Lett.* **1993**, *34*, 7304.

7 Spectroscopic data for compound **9a**:
<u>^{1}*H-NMR (200 MHz, CDCl$_3$)*</u>: 7.25-7.40 (m, 5H), 3.85 (d, 1H, J=13.14 Hz), 3.40 (d, 1H J=13.02 Hz), 2.32-2.42 (m, 2H), 1.67-1.82 (m, 2H), 0.02 (s, 18H).
<u>^{13}*C-NMR (50.4 MHz, CDCl$_3$)*</u>: 141.73, 129.47, 128.17, 126.82 (Ph), 60.10 (N-CH_2), 56.05 (C-1,C-5), 26.84 (C-3, C-4), 1.71 (-CH_3).
<u>*MS (m/e)*</u>: 232, 159, 91.

8. Spectroscopic data for compound **11a**:
<u>^{1}*H-NMR (200 MHz, CDCl$_3$)*</u>: 8.25 (d, J=2.7 Hz, H_2'), 7.52-7.25 (m, 7H), 4.2 (q, J=7.21 Hz, 2H), 3.95 (dd, J=6.16, 4.55 Hz, H_3), 3.85 (d, J=4.78 Hz, H_1), 3.72 (d, J=13.70 Hz, 1H, H_7), 3.61 (d, J=13.71, 1H, H_7), 3.60 (dd, J=4.47, 4.48 Hz, H_4), 2.55 (d, J=6.16 Hz, H_2), 1.95-2.05 (m, 1H), 1.9-2.0 (m, 1H), 1.4 (m, 2H), 1.2 (t, J=7.25, 3H).
<u>^{13}*C-NMR (50.4 MHz, CDCl$_3$)*</u>: 173.12 (C=O), 149.25 (C_6'), 139.48 (C_2') 134.72 (C_4'), 128.06 & 126.75 (C_{Ph}), 123.6 (C_4'), 63.96 (C_1), 63.31 (C_4), 60.70 (-O<u>C</u>H_2-), 52.49 (C_3), 51.37 (C_7), 47.16 (C_2), 27.26 (C_5), 20.99 (C_6), 14.01 (CH_2-<u>C</u>H_3).
<u>*MS m/e*</u>: 370, 297, 159, 91.

9. Barton, D.H.R; Crich, D and Motherwell, W.B. *J. Chem. Soc. Chem. Commun.* **1983, 939.**

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