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Efficient one-pot synthesis of anti HIV and antitumor compounds: harman and substituted harmans

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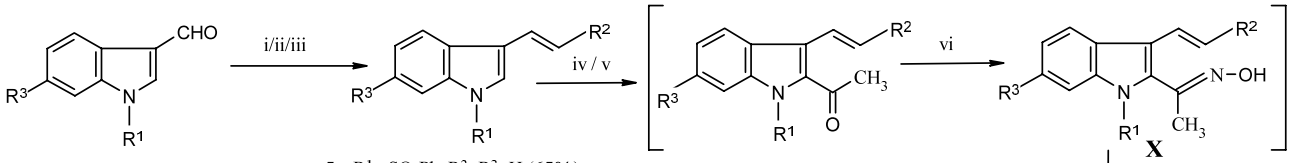
Abstract—Anti HIV and antitumor compounds, harman and substituted harmans have been synthesized using electrocyclization reactions as key steps. A one-pot reaction sequence was used to furnish these compounds in good overall yield.

The β-carboline ring system is present in many naturally occurring alkaloids which exhibit[1] interesting biological activities. Harman **9** has been reported[2] to show mutagenic and co-mutagenic properties and to inhibit topoisomerase I. Harmine **12** showed[2] significant antitumor activity. Recently harman, harmine and their derivatives were shown[3] to possess potent anti HIV activity.

Amongst the variety of methods available for the synthesis of β-carboline alkaloids, the most extensively used[1] are the Pictet–Spengler and Bischler–Napieralski condensations. However, there are a few routes in which electrocyclization reactions have been used[4a–d] for the synthesis. In the present paper, we describe the use of electrocyclization reactions of monoazahexatriene systems as key steps for the synthesis of harman, harmine and their derivatives. A similar strategy was used[4a,c,d] earlier for the synthesis of other compounds.

The key intermediate for the electrocyclization step was the azatriene **X**. The synthesis of **X** was envisioned as



1. R^1=SO_2Ph,R^3= H
2. R^1= CH_3, R^3= H
3. R^1= CH_2OCH_3, R^3= H
4. R^1= SO_2Ph, R^3= OCH_3

5a. R^1= SO_2Ph, R^2=R^3=H (**65%**)
5b. R^1= SO_2Ph, R^2=OCH_3, R^3=H (**77%**)
5c. R^1= SO_2Ph, R^2=NO_2, R^3=H (**63%**)
6a. R^1= CH_3, R^2=R^3=H (**65%**)
6b. R^1= CH_3, R^2=OCH_3, R^3=H (**68%**)
6c. R^1= CH_3, R^2=NO_2, R^3=H (**70%**)
7a. R^1= CH_2OCH_3, R^2= R^3=H (**64%**)
7b. R^1= CH_2OCH_3, R^2=OCH_3, R^3=H (**68%**)
7c. R^1= CH_2OCH_3, R^2=NO_2, R^3=H (**50%**)
8. R^1=SO_2Ph, R^2=H, R^3=OCH_3 (**57%**)

9. R^1=R^3=H (**46%** from **5a**, **53%** from **5b**, **45%** from **5c**)
10. R^1=CH_3, R^3=H (**45%** from **6a**, **46%** from **6b**, **45%** from **6c**)
11. R^1=CH_2OCH_3, R^3=H (**37%** from **7a**, **47%** from **7b**, **45%** from **7c**)
12. R^1=H, R^3=OCH_3 (**56%**)

Scheme 1. *Reagents*: (i) $(Ph)_3PCH_3I$, *t*-BuOK, THF; (ii) $(Ph)_3PCH_2OCH_3Cl$, *t*-BuOK, THF; (iii) CH_3NO_2, AcOH, AcONa; (iv) LDA, THF, *N*,*N*-dimethyl acetamide (for **5a**, **5b**, **5c**, **7a**, **7b**, **7c** and **8**); (v) *n*-BuLi, THF, *N*,*N*-dimethyl acetamide (for **6a**, **6b** and **6c**); (vi) $NH_2OH{\cdot}HCl$, AcONa, *o*-dichlorobenzene.

Keywords: Harman; harmine; β-carboline; electrocyclisation.

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involving functionalizing the indole ring at the 3-position initially and subsequently at the 2-position as shown in Scheme 1.

Thus, indole was formylated[5] using the Vilsmeier–Haack reaction to give 3-formyl indole. *N*-Protection was carried out with benzenesulphonyl chloride using the reported[4a] procedure. The protected aldehyde **1** was converted[6] into 3-vinyl indole **5a** using methylenetriphenyl phosphorane. Compounds **1** and **5a** were characterized using spectral data. To functionalize the indole ring at the 2-position, compound **5a** was lithiated using LDA/THF at −70°C and then treated with *N*,*N*-dimethylacetamide. After work-up and washing with hexane to remove the unreacted starting materials, the reaction mixture, without further purification was treated with hydroxylamine hydrochloride and sodium acetate and was refluxed in *o*-dichlorobenzene for 8 h to furnish β-carboline alkaloid harman **9** in 46% overall yield starting from **5a**. It was characterized using ^{1}H, ^{13}C NMR and GC–MS spectral data which were consistent with the reported[7] data. Thus, in this sequence, four steps, oxime formation, electrocyclization and aromatization with deprotection occurred in a one-pot reaction sequence. Efforts to isolate the intermediate 2-keto compound were unsuccessful due to its rapid decomposition. The protected indole-3-aldehyde **1** was converted[8] to 3-vinylindole **5b** and to 3-(β-nitrovinyl) indole **5c** using nitromethane and ammonium acetate. The compounds **5b** and **5c** were characterized using spectral data. Treatment of **5b** and **5c** with LDA/THF at −70°C, followed by *N*,*N*-dimethylacetamide furnished two oily liquids. After washing with hexane to remove unreacted starting materials, the two oily compounds were treated with hydroxylamine hydrochloride and sodium acetate and refluxed in *o*-dichlorobenzene. Both of these reactions furnished harman **9** in 53 and 45% overall yields from **5b** and **5c**, respectively (Scheme 1). It was observed that the methoxy and nitro groups were eliminated during the reaction sequence, probably during the aromatization step. A similar observation has been reported earlier.[9]

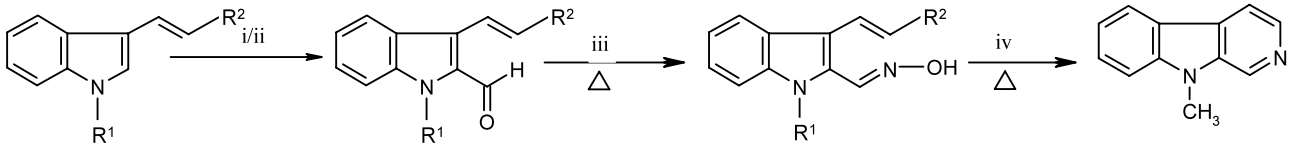
Further, using *N*-methyl and *N*-methoxymethyl indole-3-aldehydes **2** and **3**, the same sequence of reactions was followed. Reactions using 3-vinyl indoles **6a**, **6b** and **6c** afforded *N*-methylharman **10** in 45–46% overall yields and using **7a**, **7b** and **7c** afforded *N*-methoxymethyl harman **11** in 37–47% overall yields (Scheme 1). In all these reactions, the methoxy and the nitro groups were eliminated during the one-pot reaction sequence. The vinyl compounds and the β-carbolines were characterized using spectral data. The NMR data of *N*-methylharman was consistent with that reported.[7]

Using the same strategy, another antitumor and anti-HIV active β-carboline, harmine **12** was synthesized in 56% overall yield starting from 6-methoxy-3-vinylindole **8** (Scheme 1). The formation of the harmine **12** was confirmed by comparing the spectral data with that reported.[10]

Thus, harman, its derivatives and harmine were synthesized in good overall yields in a one-pot reaction sequence. In all these reactions, efforts were made to isolate the intermediate 2-keto compounds, however, all were shown to be unstable and light sensitive.

The presence of intermediate compounds was confirmed by analogy with the reaction sequence used (Scheme 2) in the synthesis of *N*-methylnorharman **17**. In this route, all the intermediates were isolated and characterized by ^{1}H NMR. Thus, lithiation of 3-vinylindole **6a** with *n*-BuLi in hexane and **7c** with *t*-BuLi in pentane, then treatment with DMF afforded the aldehydes **13** and **14**, respectively, which were converted to oximes **15** and **16**. Electrocyclization of **15** by refluxing in *o*-dichlorobenzene furnished *N*-methylnorharman **17** in poor yield as a 1:1 mixture along with the starting oxime. Moreover, electrocyclization of **16** and the one-pot reaction on **13**, failed to produce the desired product. Compounds **13**, **14**, **15**, **16** and **17** were characterized using ^{1}H NMR. The poor yields are probably due to the instability and light sensitivity of the intermediates.

In summary, biologically important, antitumor and anti-HIV β-carboline alkaloids, harman, *N*-methylharman, *N*-methoxymethyl harman and harmine were synthesized in a one-pot reaction sequence using electrocyclization reactions in good overall yields. Application of this strategy to other biologically important β-carboline alkaloids is in progress.



6a. R^1= CH_3, R^2= H
7c. R^1= CH_2OCH_3, R^2=NO_2,

13. R^1 = CH_3, R^2 = H (**80%**)
14. R^1= CH_2OCH_3, R^2= NO_2 (**88%**)

15. R^1 = CH_3, R^2= H (**85%**)
16. R^1= CH_2OCH_3 , R^2= NO_2 (**85%**)

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Scheme 2. *Reagents*: (i) *n*-BuLi, THF, DMF; (ii) *t*-BuLi, THF, DMF; (iii) NH_2OH·HCl, AcONa, MeOH; (iv) *o*-dichlorobenzene.

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