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Synthesis of tricyclic units of indole alkaloids: Application of Fischer indolization and olefin metathesis

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ABSTRACT

Simple synthetic approaches to pyridocarbazole and azepinocarbazole derivatives have been reported via Fischer indolization, Grignard reaction and olefin metathesis as key steps. In addition, a combination Sonogashira coupling and Pauson-Khand reaction has been used to assemble extended pyridocarbazole derivative.

1. Introduction

Indole alkaloids with diverse biological activity has attracted the attention of the organic and medicinal chemists due to their applications in the pharmaceutical area.[1] Indole unit is an attractive building block to design new drugs based on alkaloids which are useful in the treatment of cancer. Among indole based heterocycles, pyridoindole moiety is found in many natural products (**1**–**4**) such as homofascaplysin C, canthine-6-one, (−)-goniomitine, and vincamine etc. (Fig. 1).[2] Biological activity of these natural products motivated researcher to design new routes to pyridoindole motifs. Approaches based on transition-metal-catalyzed annulations,[3] domino reactions[4] have widely been used and several methods are reported to assemble pyridoindoles.[5]

Azepinoindole skeleton, a key structural element present in many natural alkaloids (**5**–**8**) such as arborescidine B, akagerine, and appogeissoschizine etc. is worthy of synthetic investigation (Fig. 1).[6] They have been tested for different biological activities and construction of these molecules inspired organic chemists to search for efficient methods.[7] More precisely, the azepinoindole exhibiting pharmacological activities such as modulators for CNS neurotransmitter receptors (Fig. 1).[7b,8] Due to high loading of transition-metal complexes as catalyst and usage of expensive precursors, there is a need to develop simple synthetic strategies to assemble these core structures.

So, in this context, we have developed a new synthetic approach to pyridocarbazole and azepinocarbazole systems using Fischer indolization,[9] Grignard reaction[10] and ring-closing metathesis (RCM)[11] as key steps. Also, extended pyridocarbazole system has been constructed by a combination of Sonogashira coupling[12] and Pauson-Khand reaction.[13a,11f,13b-e]

2. Results and discussion

The synthesis of pyridocarbazole and azepinocarbazole derivatives begin with the preparation of tetrahydrocarbazole derivative **11** via Fischer indolization of commercially available cyclohexanone with phenylhydrazine hydrochloride **9**. Later, regioselective oxidation of **11** using periodic acid produce the keto carbazole derivative **12** (Scheme 1).[9a,14]

Further, the carbazole derivative **12** was allylated at room temperature under basic conditions to afford *N*-allyl derivative **14** because unprotected carbazole derivative **12** failed to give the Grignard addition product **13**. So, *N*-allyl carbazole **14** was prepared and then it was subjected to Grignard addition reaction using vinyl magnesium bromide to afford allyl-vinyl carbazole derivative **15**. Subsequently, RCM with the aid of Grubbs' first generation (G-I)

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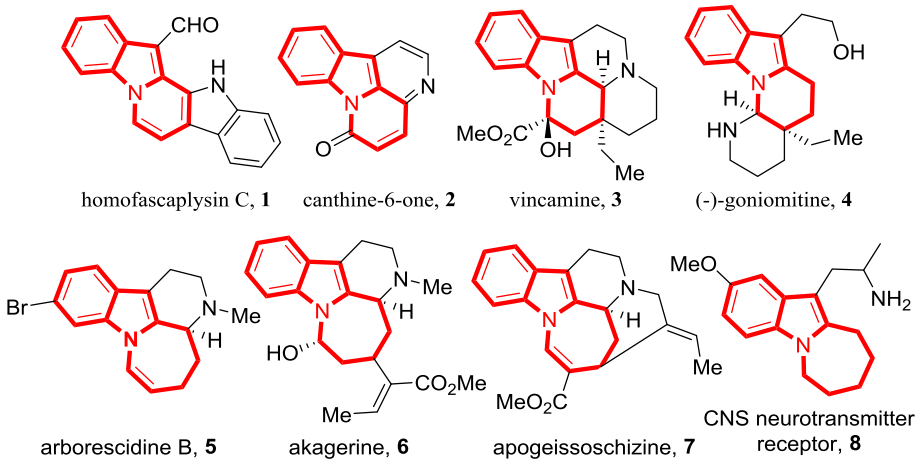
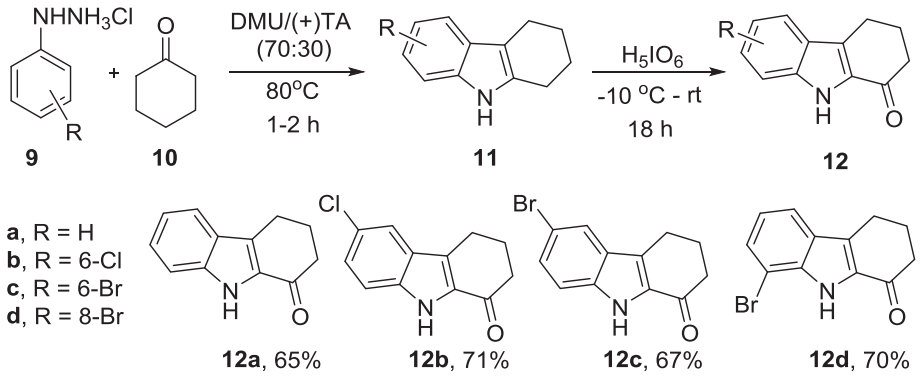


Fig. 1. Biologically active alkaloids with pyrido and azepino indole core unit.



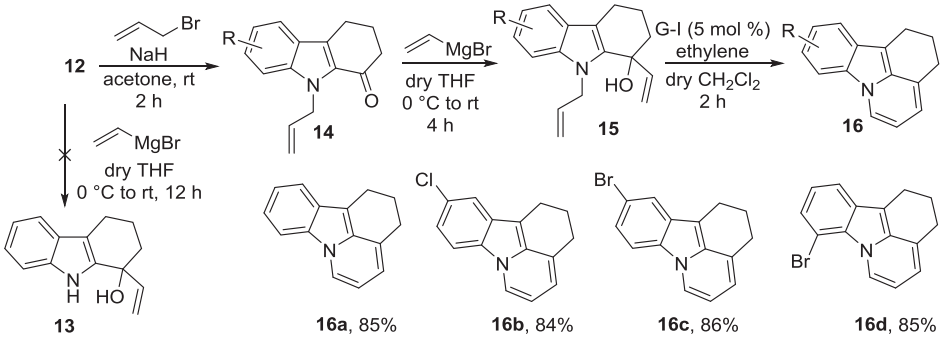
Scheme 1. Prepration of regioselective keto carbazoles.

catalyst (5 mol %) under ethylene atmosphere in dry CH_2Cl_2 delivered the pyridocarbazole derivative **16** in good yield (Scheme 2). Along similar lines, pyridocarbazole derivatives **16a-d** were also synthesized.

Next, the azepinocarbazole derivative **18** was synthesized via Grignard reaction followed by RCM. Allyl magnesium bromide addition to **14** gave diallyl carbazole **17** which was then subjected to RCM with Grubbs' second generation (G-II) catalyst to give the azepinocarbazole skeleton **18**. The G-I catalyst (5 mol %) failed to give the desired azepinocarbazole derivative **18** (Scheme 3).

In addition, another pyridocarbazole derivative **24** was synthesized by a combination of Sonogashira coupling and Pauson-Khand reaction. In this context, the synthesis of enyne building block **21** was started with bromo carbazole **11d** which on Songashira coupling sequence gave the acetylenic carbazole **19**. Further, deprotection of TMS derivative **19** was carried out with tetra-*n*-butylammonium fluoride (TBAF)/THF conditions to deliver acetylenic derivative **20**, which on *N*-allylation under basic condition produced the enyne building block **21**. Alternatively, bromo carbazole **11d** was treated with allyl bromide to afford the *N*-allyl carbazole **22**. Next, Sonogashira coupling reaction was carried out to afford the enyne **23**. Finally, removal of the TMS group using TBAF furnished the enyne building block **21** (Scheme 4).

It is interesting to note that, allyl installation followed by



Scheme 2. Synthesis of pyridocarbazoles via Grignard and RCM sequence.