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A Straightforward Entry to 7-Azabicyclo[2.2.1]heptane-1-carbonitriles in the Synthesis of Novel Epibatidine Analogues

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This paper presents the synthesis of epibatidine analogues by a straightforward one-pot method for the synthesis of 7-azabicyclo[2.2.1]heptane-1-carbonitriles, starting from cyclohexanones bearing a leaving group at the 4-position. In situ imine formation, followed by reversible cyanide addition, allows complete conversion of 4-(mesyloxy)cyclohexanone to the bicyclic core. Elaboration of the introduced nitrile functionality and deprotection of the tertiary amine leads to five new epibatidine analogues.

Introduction

The alkaloid epibatidine (**1**) was first isolated in 1974 by Daly and Myers from the skin of the Ecuadorian frog *Epipedobates tricolor*.[1] Its remarkable analgesic potency was shortly afterwards shown to be about 200-fold higher than that of morphine. Unfortunately, however, the toxicity of epibatidine is too high for any human therapeutic use. The unveiling of epibatidine's mode of action has sparked the interest of many medicinal chemists: epibatidine is a highly potent nicotinic acetylcholine receptor agonist.[2] This membrane-bound pentameric ion channel has been associated with many neurological disorders such as Alzheimer's Disease, Parkinson, neuropathic pain and schizophrenia.[3] For each of these, there is a shift in the prevalence of the different nicotinic acetylcholine receptor subtypes. Currently, the search for more subtype-selective and as such less toxic epibatidine analogues continues in an effort to provide treatment for these neurological diseases. Many analogues have been synthesized, among which epiboxidine[4] (**2**) and ABT-594[5] (**3**) are the most successful examples (Figure 1).

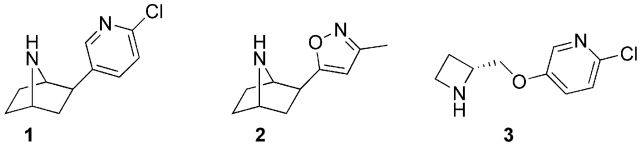

Figure 1. Epibatidine and analogues.

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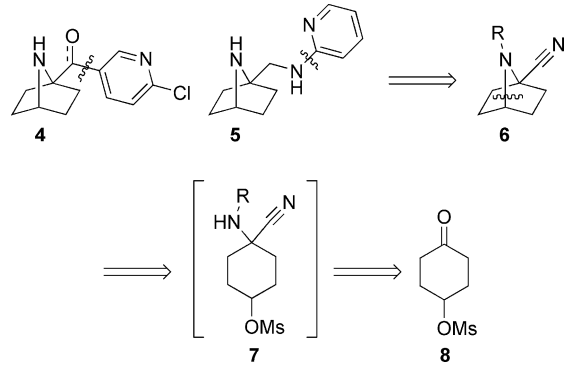
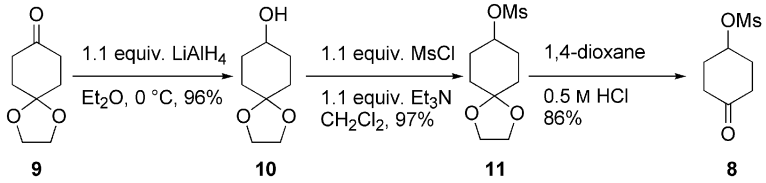
Results and Discussion

In spite of the high activity in this field, few analogues bearing the pyridyl moiety at the 1-position of the bicycle have been reported.[6] We therefore devised a retrosynthetic approach to compounds **4** and **5** (Scheme 1). To preserve epibatidine's highly important internitrogen distance of approximately 5.5 Å, an extra carbon atom is introduced between the pyridine substituent and the azabicycle.



Scheme 1. Retrosynthetic approach.

The major problem for the construction of the bicyclic ring by intramolecular ring closure starting from cycloalkanones **8** relates to the fact that the nucleophilic functionality and the leaving group in compound **7** need to be positioned in a *trans* relationship. Mostly this requires a number of steps including protection, deprotection strategies or difficult separation steps in order to avoid that 50% of the material cannot ring-close. Even in the best enantioselective syntheses, 25% of starting material is lost due to this *cis*/*trans* selectivity issue.[7]

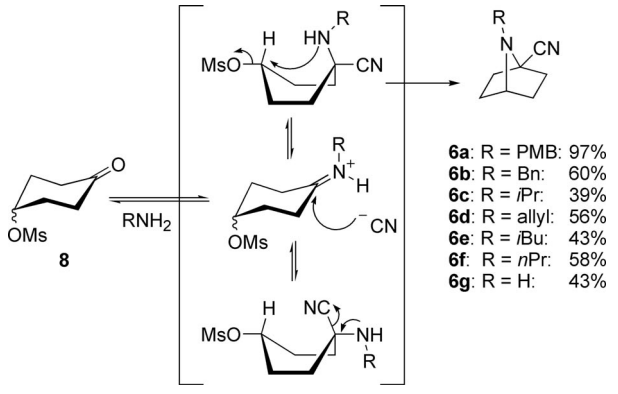


Scheme 2. Precursor synthesis.

Therefore, the reversible dynamic addition of cyanide to an imine function, developed in our laboratory, is very advantageous to convert all starting material into the ring-closed product.[8] In this paper, we wish to disclose this strategy for the construction of the 7-azabicyclo[2.2.1]heptane-1-carbonitrile skeleton (from a cyclohexanone precursor) as the key step in the synthesis of epibatidine analogues.

Starting from the commercially available protected cyclohexanone **9**, the oxo function was reduced with lithium aluminium hydride in good yield, followed by the activation of the hydroxy function as the corresponding mesylate. After deprotection of acetal **11** in 86% yield, the precursor for ring closure was obtained in three steps (Scheme 2).

The key step involves the one-pot procedure of imine formation, addition of cyanide to the imine function, followed by intramolecular nucleophilic substitution (Scheme 3). This could be performed by treating the mesyloxy ketone **8** with 1 equiv. of primary amine, 2 equiv. of triethylamine (1 equiv. is needed to trap the methylsulfonic acid after ring closure) and 2 equiv. of acetone cyanohydrine, the cyanide source, in a closed vessel in methanol for 2 d. The conversion of the mesyloxy ketone **8** to the 7-azabicyclo[2.2.1]hexane-1-carbonitrile (**6**) is complete; however, the purification of the compound by flash chromatography lowers the reaction yield considerably. The polar compounds **6** have a high affinity for silica gel, leading to product loss during the purification. Seven 7-azabicyclo[2.2.1]heptane-1-carbonitriles could be obtained in reasonable yield after purification.



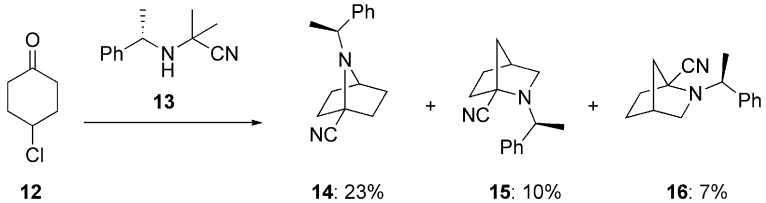
Scheme 3. Synthesis of bicycles **6a**–**6g** through reversible cyanide addition.

Our method is closely related to a recently reported enantiospecific entry to 1-cyano-azabicycles, in which 4-chlorocyclohexanone (**12**) was treated with an adduct of phenethylamine and acetone cyanohydrine (**13**) (Scheme 4).[9]

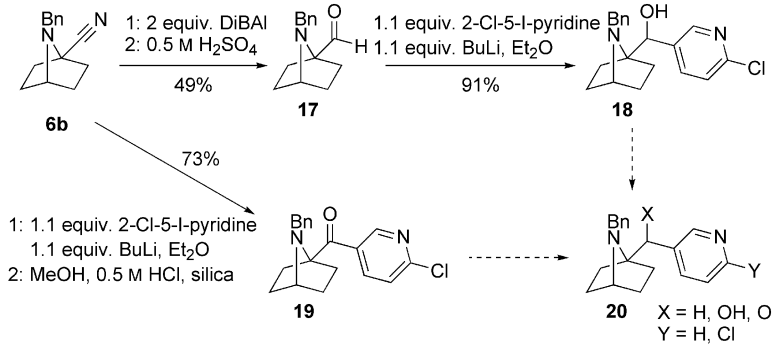
This chloro ketone, however, was shown to isomerize through a ring contraction to 3-(chloromethyl)cyclopentanone, thus yielding a mixture of 7-azabicyclo[2.2.1]heptane **14** (23%) and 2-azabicyclo[2.2.1]heptanes **15** and **16** (17%) after ring closure. The use of mesyloxy ketone **8** eliminates this side reaction and allows the quantitative formation of the desired 7-azabicycles, increasing the isolated yields considerably. Furthermore, the extra step of adduct formation is eliminated.

Compounds **6a** and **6b** were selected for the further synthesis of epibatidine analogues considering the higher yield and the possibility of oxidative and reductive removal of the N-protecting groups.

In a first attempt to obtain compound **4**, nitrile **6b** was submitted to a partial reduction by means of DiBAl (Scheme 5). Infrared analysis showed that the reduction to the aldimine proceeded cleanly. Surprisingly, however, the obtained aldimine was quite resistant to hydrolysis. Even after careful screening of hydrolysis conditions, chromatography was needed to obtain pure aldehyde **17** in 49% yield.[10] The subsequent addition of the 2-chloropyridyl group was straightforward and provided racemic alcohol **18** in excellent yields. To avoid the troublesome preparation of aldehyde **17**, the nucleophilic addition of the pyridyl group was also performed on nitrile **6b**. After hydrolysis of the resulting imine (which proceeded smoothly in this case), ketone **19** was obtained in 73% yield. Deprotection of these two substrates **18** and **19** would lead to the proposed epibatidine analogue **4**. However, in both cases the removal of the protective benzyl group proved to be extremely difficult. In



Scheme 4. Literature synthesis of 7-azabicyclo[2.2.1]heptanes.



Scheme 5. Synthesis and attempted deprotection of **18** and **19**.

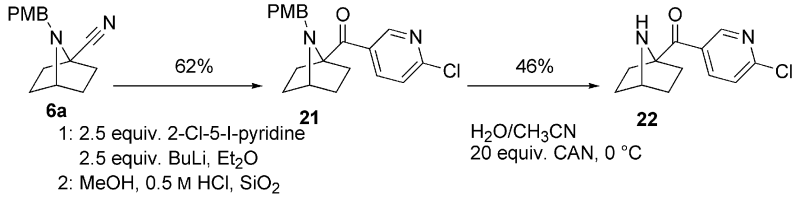
order to retain the chlorine group, a mild non-reductive deprotection by using ethyl chloroformate was evaluated. After 16 h at 55 °C, only starting material could be recovered. Switching to reductive deprotection, all attempted methods yielded a mixture of starting material, dechlorinated, and in some cases dehydroxylated degradation products. Because neither dechlorination, nor dehydroxylation nor debenzylation was obtained cleanly, this pathway was not further pursued.

Subsequently, the troublesome benzyl deprotection was circumvented by switching to oxidative deprotection strategies. The use of a *p*-MeO-benzyl protecting group allowed for the synthesis of **21**, which could be deprotected by treatment with ammonium cerium nitrate (CAN) (Scheme 6).

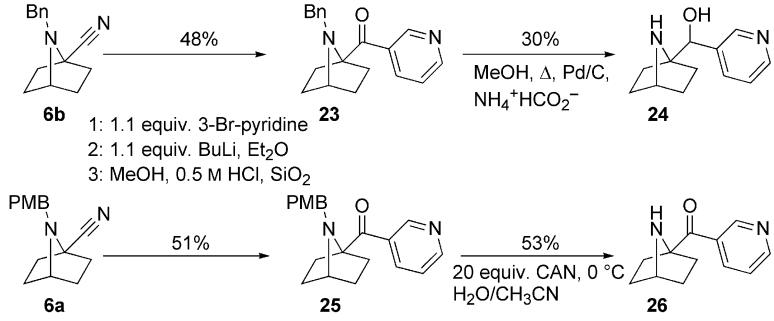
In the absence of a chlorine substituent, which is in fact not essential to epibatidine's biological activity,[11] both the oxidative and reductive deprotection strategies were successful. Ketone **23** was synthesized from 7-azabicyclo[2.2.1]-heptane-1-carbonitrile **6b** in 48% yield. Refluxing with ammonium formate in the presence of Pd/C led to complete removal of the benzyl group within 4 h, and epibatidine analogue **24** could be recovered after crystallization from diethyl ether (Scheme 7). In a similar fashion, ketone **25** was obtained from **6a** in 51% yield. Oxidative deprotection delivers epibatidine analogue **26**.

A second series of analogues could be obtained from **6b** in three steps. Reduction of **6b** to amine **27** by means of $LiAlH_4$ was performed quantitatively. Next, the pyridyl group was introduced by means of a Pd-catalyzed cross coupling. Standard Buchwald conditions[12] were used to test three different ligands: binap, dppp and di-*tert*-butyl{1-[2-(dicyclohexylphosphanyl)ferrocenyl]ethyl}phosphane (dfep)[13] provided a conversion of 48, 12 and 10%, respectively. By using binap as ligand, several conditions were tested (Table 1). The best results were obtained by using 1 equiv. of 2-bromopyridine, 1.4 equiv. of NaO*t*Bu and 4 mol-% of $(dba)_3Pd_2CHCl_3$ catalyst.

Ligand requirements for this reaction proved to be highly dependent upon the substrate. By using 2-bromopyridine the ligand of choice was binap, giving a conversion of 95% over 2 d. However, when the same reaction conditions were applied by using 3-bromopyridine, no conversion could be

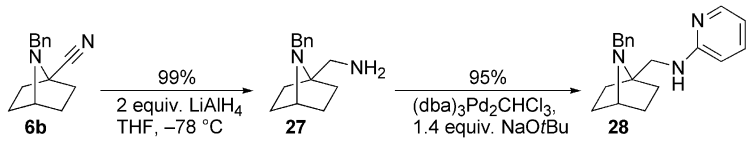


Scheme 6. Synthesis of **22**.



Scheme 7. Synthesis of **24** and **26**.

Table 1. Optimization of Pd-catalyzed cross-coupling by using binap.

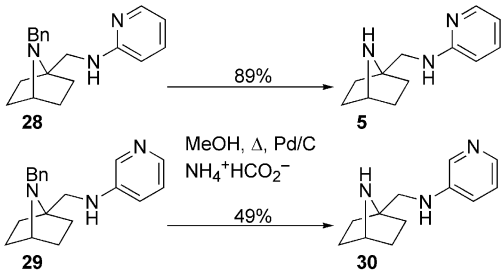


	2-Chloropyridine	2-Bromopyridine		
	1.2 equiv. amine	1.2 equiv. amine	1 equiv. amine	0.8 equiv. amine
2% cat.	56%	59%	91%	85%
4% cat.	62%	77%	95%	N/A[a]

[a] N/A: not available.

detected. Again, all three ligands were tested showing dfep to be the most efficient. A conversion of 55% could be obtained, and secondary amine **29** was isolated in 47% yield after column chromatography.

Removal of the protective benzyl group was performed by refluxing in methanol by using ammonium formate as reducing agent (Scheme 8). Compound **5** was obtained after 1 h of reflux, whereas for compound **30** a period of 2 h was necessary to bring the reaction to completion. The low yields for **30** are attributed to its troublesome purification. Compound **5** could easily be separated from the excess ammonium formate by dissolution in dry diethyl ether. Compound **30**, however, in spite of its highly similar structure, does not dissolve in diethyl ether. Eventually, this product was obtained after preparative TLC with reasonable recovery by using a highly polar mixture of chloroform/triethylamine (93:7).



Scheme 8. Synthesis of **5** and **30**.

Conclusions

We have described the preparation of five new epibatidine analogues by using a short and efficient synthesis of 7-azabicyclo-[2.2.1]heptane-1-carbonitriles.

Supporting Information (see footnote on the first page of this article): Experimental procedures, spectroscopic data and copies of ^{1}H and ^{13}C NMR spectra.

Acknowledgments

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