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Mannich Reaction of Indole with Cyclic Imines in Water

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ABSTRACT

An efficient MsOH promoted direct Mannich reaction of indoles with α-nonsubstituted aliphatic cyclic imines has been developed. The reactions were performed in water and the obtained piperidin-2-yl-indoles act as a useful precursor for the synthesis of various alkaloid-like derivatives.

Introduction

The Mannich reaction is an important reaction for the direct construction of new C—C and C—N bonds. Its endproducts, Mannich bases have attracted more and more attention of chemists due to their specific biological activities, such as antiviral,[1] acetylcholinesterase inhibitory,[2] antioxidant,[3] antiproliferative.[4] What's more, Mannich bases are also key precursors to access amino alcohols, peptides, lactams and optically active amino acids.[5,6]

On the other hand, saturated nitrogen heterocycles are also important structural elements that exist in many bioactive compounds.[7] In recent years, more than half of the FDA approved small-molecule drugs contain nitrogen heterocycles.[8] We noticed that the less studied aliphatic cyclic imines might act as starting point to simplify the preparation of various alkaloid-like saturated nitrogen heterocycles. For example, the Mannich reaction of cyclic imines with indole derivatives might provide a direct way to piperidinyl-substituted indoles, whose core structure was present in many bioactive compounds (Fig. 1).[9–12] This new methodology might also be used for the easy synthesis of some important drugs as **BCX4430** and **Veliparib** (Fig. 2).

The indole moiety is a privileged structural motif in many biologically active and medicinally valuable molecules,[13] such as anticancer drugs,[14] anti-inflammatory agents,[15] antibacterials,[16] and anti-HIV drugs.[17] Although Mannich reaction of indole with aromatic cyclic imines has already been reported,[18–20] aliphatic cyclic imines were rarely used owing to their low activities and stabilities.[21] In 1954, van Tamelen and co-workers reported the direct synthesis of β-(2-piperidy)-indoles by aliphatic cyclic imines with low yields (40–55%).[22] Recently, Shevchenko and co-workers described the Mannich reaction of indole with aliphatic cyclic imines. In their catalytic system, moisture-sensitive catalyst was used, and cyclic imines were limited to α-polyfluoroalkylated (CF_3- and C_2F_5-substituted) cyclic imines, while non-fluorinated cyclic imines that containing a phenyl or butyl moiety didn't work at all in the same reaction. Later, Monaco and co-workers reported the Mannich reaction of ketones with aliphatic cyclic imines,[23] albeit the reaction time was extremely long and the yield was quite low. In this sense, low reactivity is a huge challenge for the direct Mannich reaction of aliphatic cyclic imines. Herein, we are devoted to exploring the reactions between α-nonsubstituted aliphatic cyclic imines and indole under the appropriate conditions, our aim is to provide a general synthetic methodology for these saturated nitrogen heterocycles.

Cyclic imine **1a** and indole **2a** were chosen as representative substrates in our initial survey of reaction conditions. In the absence of any activator, no reaction was observed (Table 1, entry 1). So our efforts were concentrated on the looking for a proper activator for this transformation. We first tried different Brønsted acids, and found that MsOH was the best acid (Table 1, entry 2), other Brønsted acids such as CF_3COOH, CH_3COOH, CF_3SO_3H, PhCOOH, H_3PO_4, HCl, H_2SO_4 and Amberlyst 15 resulted in lower

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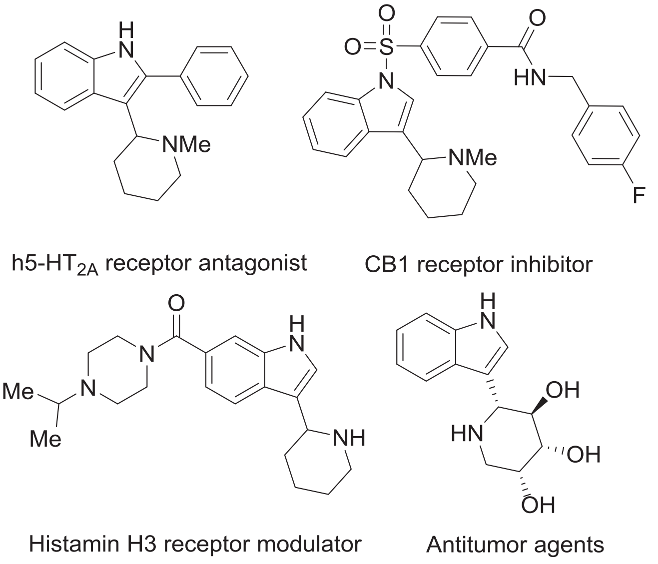


Fig. 1. Bioactive compounds containing piperidinyl-substituted indoles.

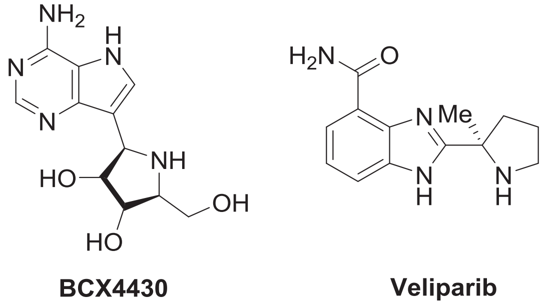
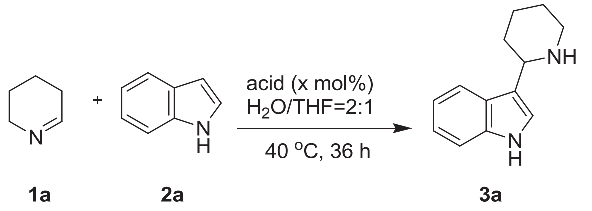


Fig. 2. Drugs containing saturated nitrogen heterocycles.

Table 1
Screening of acids for the reaction of indole with cyclic imine.[a]



Entry	Acid	x =	Yield[b] (%)
1	–	–	nd
2	MsOH	100	80
3	TsOH·H$_2$O	100	72
4	CF$_3$COOH	100	32
5	CH$_3$COOH	100	8
6	CF$_3$SO$_3$H	100	5
7	PhCOOH	100	7
8	L-proline	100	nd
9	H$_3$PO$_4$	100	16
10	HCl	100	53
11	H$_2$SO$_4$	100	46
12	Amberlyst 15	100	9
13	Cu(OTf)$_2$	100	9
14	ZnF$_2$	100	47
15	MsOH	80	15
16	MsOH	120	79
17	MsOH	150	79
18	MsOH	200	78

[a] Reaction conditions: imine **1a** (0.4 mmol), indole **2a** (0.33 mmol), solvent (5 mL) at 40 °C for 36 h.
[b] Determined by GC–MS analysis.

yields for the target product. This reaction didn't take place when L-proline was employed. We also tried several Lewis acids, but only obtained poor yields when using Cu(OTf)$_2$ or ZnF$_2$ (Table 1, entries 13–14). We speculated that the proper acidity of MsOH might be essential for this transformation, for both stronger acids (CF$_3$COOH, CF$_3$SO$_3$H) and weaker acids (CH$_3$COOH, PhCOOH) exhibited inferior catalytic activities.

The reaction was then run with different molar ratios of MsOH (80 mol%, 100 mol%, 120 mol%, 150 mol%, and 200 mol%, respectively). The optimum loading of MsOH was 100 mol% (Table 1, entry 2). The yield didn't improve when the loading of acid was higher than 100 mol% (Table 1, entries 16–18), while a decrease of MsOH to 80 mol% resulted in a significant drop in yield (Table 1, entry 15).

Next we performed the reaction in different solvents. As we know, good yield was obtained in H$_2$O/THF (2:1), whereas the yield of **3a** dropped sharply in THF (Table 2, entry 2). Carrying out the reaction in CH$_2$Cl$_2$ or CHCl$_3$ could afford **3a** with moderate yield (Table 2, entries 3–4). When the reaction was run in DCE, MeCN and MeOH, lower yields of the target products were obtained (Table 2, entries 5, 6, 8). The best result was observed in H$_2$O/MeOH (2:1) in comparison with other organic solvents (Table 2, entry 9). In view of the differences of yield among THF, H$_2$O/THF (2:1), MeOH and H$_2$O/MeOH (2:1), we also tried H$_2$O as a sole solvent, and obtained satisfactory yield (Table 2, entry 10). We assumed that MsOH in water might be beneficial for the protonation of imine **1a**.

As we all know, the use of organic solvents in organic synthesis is an incessant source of worry, since it gives rise to toxicity, hazard, pollution issues, *etc.* On the contrary, water offers many advantages because it is a cheap, readily available, non-toxic and non-flammable solvent.[24] Therefore we chose water as optimal solvent, and several common surfactants were used as additives to improve the solubility of indole in water. When 30 mol% of TBAI was used, the yield of **3a** was even higher than that in pure H$_2$O (Table 2, entries 13–16). 30 mol% was also proved to be the optimum amount of TBAI. Decreasing or increasing the amount of TBAI resulted in lower yield (Table 2, entries 17–19).

Finally, the reaction temperature was also investigated. The yield of **3a** dropped sharply due to a poor conversion when the reaction was run at 25 °C (Table 2, entry 20). Higher temperatures (40 °C, 60 °C and 80 °C) afforded comparable yields (84%) along with significantly shorter reaction time (Table 2, entries 13, 21–22, 36 h, 18 h and 12 h respectively). Interestingly, when we run