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Proline catalyzed, one-pot three component Mannich reaction and sequential cyclization toward the synthesis of 2-substituted piperidine and pyrrolidine alkaloids

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ABSTRACT

A very effective one-pot three component reaction of 4-bromobutanal or 5-bromopentanal, acetone, and *p*-anisidine catalyzed by proline is reported. A three component Mannich reaction followed by cyclization leading to the synthesis of 2-substituted pyrrolidine and piperidine derivatives through simultaneous formation of two C–N and one C–C bond is reported. The usefulness of the reaction is demonstrated by the synthesis of (±)coniine, (±)pelletrine, (±)sedridine, and (±)allosedridine.

2-Substituted piperidine and pyrrolidine subunits are widely found in natural products and synthetic compounds of pharmacological importance.[1] Various synthetic routes are available for synthesizing these classes of compounds and the available strategies are largely based on, but not limited to cycloaddition reactions, iminium-ion cyclization, ring closing metathesis, and Mannich type of reactions.[2] We report an organocatalytic one-pot three component reaction to achieve the synthesis of 1-(piperidin-2-yl)propan-2-one and 1-(pyrrolidin-2-yl)propan-2-one in excellent yields. The products thus obtained have the potential to be very useful synthetic precursors for 2-substituted piperidine alkaloids such as coniine, pelletrine, sedridine, and allosedridine and 2-substituted pyrrolidine alkaloids such as hygrine, norhygrine, and hygroline (Fig. 1).[3] The reaction is based on the proline catalyzed three component asymmetric Mannich reaction reported by List et al.[4] One-pot three component Mannich reactions have been used for the effective generation of amino ketones, which are further transformed to alkaloids, sugar derivatives, amino acids, and amino alcohols.[5] Multicomponent reactions in general have received recent attention in synthetic organic chemistry for providing simpler and milder procedures to synthesize complex products along with the added advantages of atom efficiency and waste reduction.[6] Organocatalytic Mannich reactions leading to asymmetric[7] and racemic[8] products have thus become an active area of research.[9]

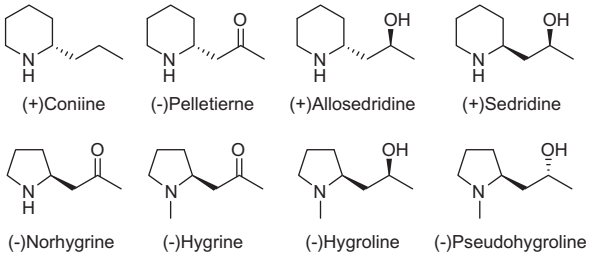

Figure 1. 2-Substituted piperidine and pyrrolidine alkaloids.

We assumed that a proline catalyzed three component reaction of 5-bromopentanal, a primary amine and acetone could result in an organocatalytic Mannich reaction followed by a cyclization through nucleophilic attack of the secondary amine on the bromide to yield 2-substituted piperidine derivatives. Accordingly, when 5-bromopentanal (1 equiv), *p*-anisidine (1 equiv), and acetone (1 equiv) were treated with proline (10 mol %) in CH_2Cl_2 (30 °C), the piperidine derivative, **1** was obtained albeit in low yield (6%, Scheme 1). However, the yield increased substantially (78%), on using triethylamine (1 equiv) to neutralize the HBr generated during the course of the reaction (Scheme 1). This is the first Letter of an organocatalytic Mannich reaction, followed by cyclization to give piperidine derivatives.

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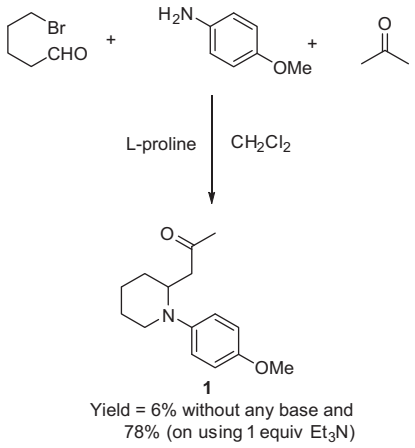
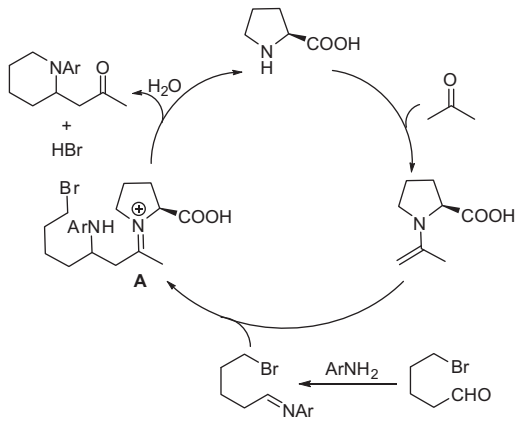


Scheme 1. One-pot three component reaction leading to 2-substituted piperidine derivatives.

The substantial increase in yields of the reaction in the presence of equivalent amount of triethylamine was a possible indication of a base catalyzed reaction without the involvement of proline in the catalysis. However, when the reaction was carried out with triethylamine (2 equiv) and in the absence of proline, even trace amount of **1** was not formed. This has confirmed the role of proline, suggestive of an organocatalytic pathway for the reaction. It is assumed that the reaction proceeds through the formation of an enamine derived from acetone and proline, which undergoes a Michael reaction with the imine formed from *p*-anisidine and 5-bromopentanal to give the iminium ion intermediate **A**. The intermediate **A** cyclizes to give a piperidine unit, which on hydrolysis forms the piperidine derivative **1** (Scheme 2). In the absence of a base, HBr generated during the reaction maybe interfering with the reaction, either by protonating the catalyst (proline) or through acidolysis of the intermediates.

Although, the reaction was very high yielding and proceeded smoothly, no enantioselectivity was observed. Reactions catalyzed with L-proline and DL-proline proceeded with the same rate and gave racemic mixtures of the products as determined by HPLC analysis and optical rotation measurements. It was interesting to note that pyrrolidine could not catalyze the reaction and formation of **1** was not observed on using pyrrolidine (10 mol %, Et_3N, 30 °C, CH_2Cl_2) instead of proline as the catalyst. We assumed that solvents may be playing a substantial role in the catalysis and might be affecting the rate and stereoselectivity of the reaction. To determine the role of solvents we performed the reaction as in Scheme 1



Scheme 2. Proposed mechanism for the one-pot Mannich reaction and cyclization.

Table 1
Role of solvents in the one-pot Mannich reaction and cyclization

Entry	Solvent	Time	Yield (%)
1	DMF	24	0
2	DMSO	24	6
3	CH_3CN	24	0
4	THF	24	0
5	CH_2Cl_2	8	78
6	$CHCl_3$	10	81
7	$C_6H_5CH_3$	24	63
8	CH_3OH	3	99
9	C_2H_5OH	3	91
10	$(CH_3)_3COH$	4	85
11	H_2O/brine	24	0
12	Neat	18	75

(L-proline, Et_3N, 30 °C), in different solvents (Table 1). It was observed that polar aprotic solvents such as DMSO, DMF, CH_3CN, and THF gave extremely poor results, while relatively nonpolar solvents such as CH_2Cl_2, $CHCl_3$, and toluene resulted in good yields. Protic solvents such as CH_3OH, C_2H_5OH, and $(CH_3)_3COH$ yielded the best results and the reaction proceeded quantitatively in CH_3OH. However, the reaction did not work, when performed using H_2O/brine as the solvent. Doing the reaction neat, but with an equivalent of Et_3N yielded **1** in 75% yield. However, in no solvents did the reaction work with stereoselectivity and all of the reactions yielded **1** as a racemic mixture.

Identifying CH_3OH as the best solvent for this reaction, we carried out the reaction in the presence of various bases (1 equiv, L-proline, CH_3OH, 30 °C) in an effort to achieve stereoselectivity (Table 2). We observed that there was no reaction in the presence of inorganic bases such as KOH, K_2CO_3, $NaHCO_3$, and NaOAc even after 24 h. The rate and yields of the reaction were substantially high on using bases such as DBU, DABCO, DMAP, Et_3N, and DIPEA. However, none of the reaction conditions showed any stereoselectivity and **1** was isolated as a racemic mixture in all cases.[10] We assumed that the use of excess L-proline as a base to neutralize HBr, we might be able to avoid any base induced loss of stereoselectivity. Although the reaction proceeded smoothly in the presence of 1.2 equiv of L-proline and in the absence of any other base to give **1** in 80% yield, no stereoselectivity was observed.

It was very disappointing that although an ideal catalyst system for the reaction in terms of conversion could be attained, no selectivity was observed with any of the attempted reaction conditions. As an effort to achieve enantioselectivity, we carried out the reaction with various proline derivatives (Fig. 2). Although the catalysts **II**, **III**, and **IV** catalyzed the reaction, no stereoselectivity was observed. Catalysts **I**, **V**, and **VI** did not result in the formation of **1**. While L-proline (**II**) provided the best conversion (99%), catalysts **III** and **IV** yielded **1** in 82% and 78% yields, respectively and the reaction times were longer (7 h). α-Amino acids other than proline

Table 2
Role of bases in the one-pot Mannich reaction and cyclization

Entry	Base	Time	Yield (%)
1	KOH	24	0
2	K_2CO_3	24	0
3	$NaHCO_3$	24	0
4	NaOAc	24	0
5	DBU	6	45
6	DABCO	6	60
7	DMAP	6	69
8	Et_3N	3	99
9	DIPEA	4	87
10	L-Proline	8	80
11	—	24	3