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Proline-catalyzed facile access to Mannich adducts using unsubstituted azoles ☆

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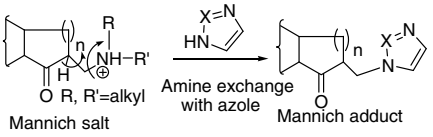
ABSTRACT

A novel and facile method for the direct construction of C–C–N bond with unsubstituted azoles under Mannich conditions is developed for the first time. The reaction is catalyzed efficiently by L-proline to give the Mannich adducts **1a**–**10b** in DMSO, whereas in water, insertion of two successive bonds, C–C–N and C–C–O occurred to give compounds **11a**–**20b**. The latter are deformylated readily into the desired products **1a**–**10b** under basic conditions. Mechanistic aspects for the formation of these products are discussed.

The Mannich reaction is extremely useful for the construction of nitrogenous molecules.[1] In this transformation, three components, a ketone, an aldehyde, and an amine react to form a β-amino-ketone. A large number of methods with different amines are reported in the literature which involve conjugate addition of an enol to a preformed iminium ion.[2] To date no direct Mannich adduct from unsubstituted azoles (C–C–N bond) has been reported, as these are unreactive under normal Mannich conditions[3] and are not able to form iminium ions with aldehyde. Andreani et al.[4] have prepared Mannich adducts of imidazoles indirectly by amine exchange reactions, with Mannich salts (Scheme 1). The same method has been followed for synthesis of related compounds for various applications.[5]

As is widely known, azoles are potential targets for drug discovery,[6] because of their diverse biological properties such as antiparasitic, antibacterial, antiviral, antiepileptic, anti-allergic, and others.[7] More recently, we have demonstrated the high antileishmanial activity of novel benzocycloalkyl azoles, which makes these compounds promising targets for the development of effective therapeutic agents. We have synthesized N-substituted azoles[8] by the reported amine exchange method. Attempts have been made to introduce such bonds directly, and in this Letter we report the details of our investigations and proposed mechanisms involved in the formation of these products.

Recent literature reports show the success of organo catalysts in the formation of α,β-unsaturated ketones.[9] Based on this precedent



Scheme 1. Mannich adducts of azoles via amine exchange.

we hypothesized that, generation of an α,β-unsaturated carbonyl intermediate in situ, formation of the Mannich adduct (C–C–N bond) would be possible by reaction with unsubstituted azoles (by aza-Michael addition).[10] For this, we chose cheap and readily available L-proline as the organo catalyst. We initially investigated the reaction of a ketone (1.0 equiv), imidazole (1.0 equiv), paraformaldehyde (1.0 equiv), and L-proline (0.3 equiv) in DMSO at 60 °C. As expected, the Mannich adduct **1a** was obtained in 96% yield Table 1. Subsequently, we found that on increasing the quantity of paraformaldehyde, product **1a** condensed with excess formaldehyde and afforded the Mannich-aldol-type product **11a** (Table 2). In order to show the generality and scope of this transformation, different ketones were used. As shown in Table 1, a wide range of ketones were suitable. Five- to seven- membered cyclic ketones participated efficiently in the process to furnish products **1a–7b** in high yields. Acyclic ketones were also good substrates affording **8a–10b** with moderate yields. The substituents on the phenyl ring did not have any significant effect on the reaction (Table 1, **3a–5a** and **9a–10b**). Further, imidazole was found to be more reactive than triazole which can be attributed to its higher pK_a value (14.5) in aqueous media compared to triazole (9.4).[11]

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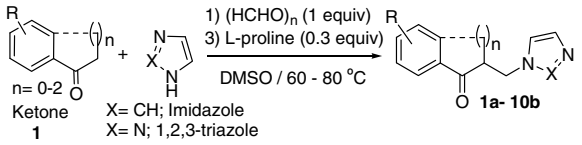
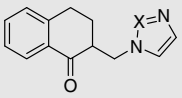
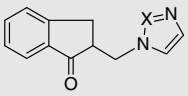
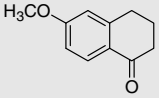
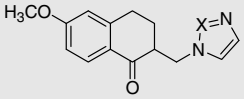
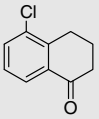
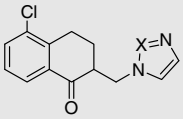
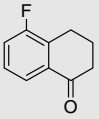
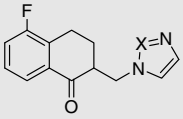
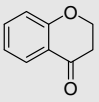
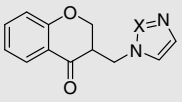
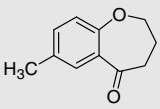
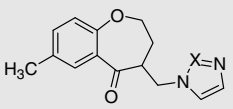
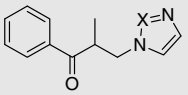
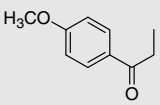
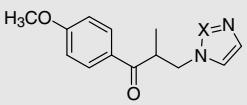
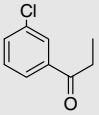
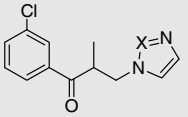
In view of the interest in reactions in aqueous medium,[12] the reaction was run in water instead of DMSO. The reaction occurred very cleanly to afford the corresponding 2-hydroxymethyl-2-azol-1-ylmethyl derivatives **11a–20b**, instead of the expected Mannich adducts **1a–10b**. However, the reaction did not reach completion (starting materials remained). Therefore, the reaction was performed with 2 equiv of paraformaldehyde and proceeded to completion to afford the Mannich-aldol-type products **11a–20b**

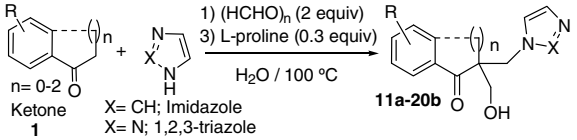
Table 1
L-Proline-catalyzed direct Mannich adducts prepared from an unsubstituted azole, paraformaldehyde, and a ketone in DMSO

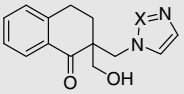
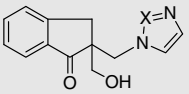
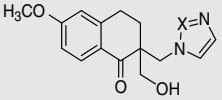
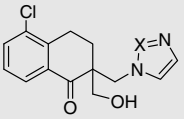
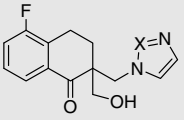
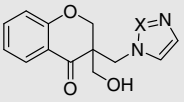
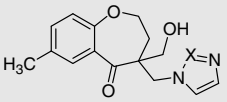
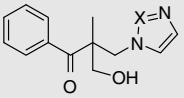
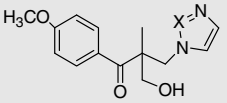
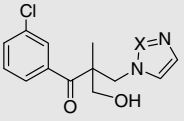


Comp. no	X	Ketone **1**	Product[a,d]	Time (h)	Yield[b,c]
1a	CH			1.5	96
1b[c]	N			2	81
2a	CH			2	93
2b[c]	N			2.5	76
3a	CH			2	91
4a	CH			3	93
5a	CH			3	89
6a	CH			2	96
6b	N			4	72
7a	CH			3	94
7b[c]	N			4.5	69
8a	CH			5.5	51
9a	CH			6	50
10a	CH			5.5	55
10b[c]	N			8	26

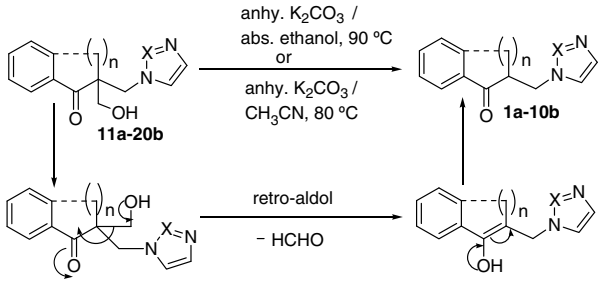
[a] Reactions of triazoles in DMSO were carried at 80 °C.
[b] Isolated yields.
[c] Less than 0.3 equiv of catalyst gave low yields, loading above 0.3 equiv gave the same yields.
[d] Reactions were not enantio selective.

Table 2
Insertion of two consecutive (C–N, C–O) bonds on reaction with an unsubstituted azole, paraformaldehyde, and a ketone in water catalyzed by L-proline

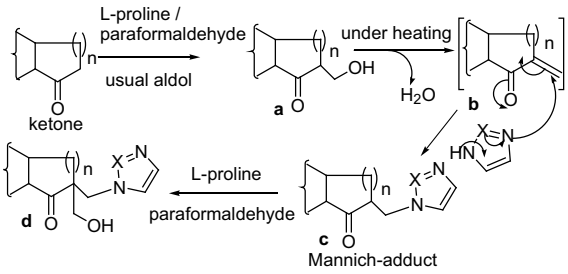


Comp. no.	X	Product[a,b,d]	Time (h)	Yield[c]
11a	CH		4.5	95
11b	N		7	82
12a	CH		6	92
12b	N		8.5	79
13a	CH		4	90
14a	CH		4	92
15a	CH		3.5	88
16a	CH		2.5	92
16b	N		6	82
17a	CH		5	92
17b	N		9	61
18a	CH		12	36
19a	CH		11.5	39
20a	CH		13	33
20b	N		24	12

[a] Unless specified, a mixture of ketone **1** (100 mg, 1 equiv), imidazole (46 mg, 1 equiv), paraformaldehyde (132 mg, 2 equiv), and L-proline (0.3 equiv) in water (0.5–1.5 mL) (for detailed procedure see Supplementary data) were stirred at 100 °C (at 60 °C the product conversion was very slow).
[b] The same ketones as in Table. 1 were used.
[c] Isolated yields.
[d] No enantio selectivity was observed.



Scheme 2. Conversion of Mannich-aldol-type products into Mannich adducts.

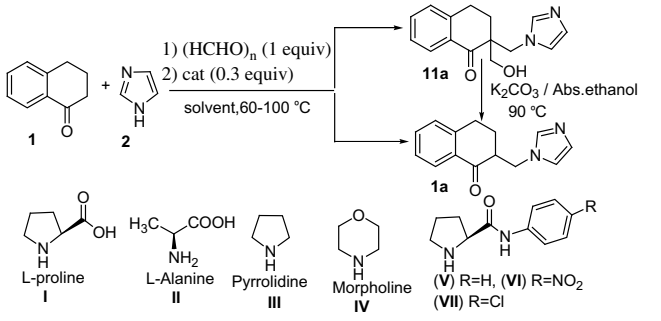


Scheme 3. L-Proline-catalyzed aldol/aza-Michael addition pathway.

(Table 2) in good to excellent yields typically. Moreover, the reaction in water comprised a highly efficient one-pot insertion of two successive bonds, that is, C–C–N and C–C–O. Further, we were excited to find that the Mannich-aldol-type products **11a–20b** were converted smoothly to the corresponding Mannich adducts **1a–10b** with anhydrous K_2CO_3 in absolute ethanol. On replacing ethanol with acetonitrile, the rate of transformation in the case of acyclic compounds was better than with the corresponding cyclic compounds. We propose a retro-aldol deformylation[13] mechanism for this transformation Scheme 2.

To demonstrate the feasibility of the proposed organo catalytic Mannich reaction, we carried out a model reaction of α-tetralone 1 (1 equiv) with imidazole (1 equiv) and paraformaldehyde (1 equiv) in the presence of different catalysts (0.3–0.5 equiv) and solvents (Table 3). Examination of the results of the catalyst screening revealed that the catalyst activities varied significantly. L-Proline-anilide **V** and L-proline-chloro anilides **VII** were found to be ineffective catalysts for the process (entries 12 and 15) and furnished **1a** and **11a** in almost equal ratios. Satisfactory yields with L-proline-nitro anilide **VI** (entries 13 and 14) were observed.

Table 3
Solvent and catalyst optimization[a]



Entry	Solvent	Catalyst	Time (h)	Temp. (°C)	Yield[b] (%)	Ratio of **11a**/**1a**[c]
1	DMF	**I**	5	60	83	6:94
2[d]	EtOH	**I**	12	90	27	0:100
3[d]	IPA	**I**	24	90	24	0:100
4[d]	*t*-Butanol	**I**	24	90	18	0:100
5	DMSO	**II**	5	60	89	12:88
6	DMF	**II**	6	60	81	21:79
7[d]	H_2O	**II**	6	70	86	100:0
8[e]	DMSO	**III**	18	100	16	100:0
9[e]	H_2O	**III**	18	100	18	100:0
10[e]	DMSO	**IV**	24	100	13	100:0
11[e]	H_2O	**IV**	24	100	12	100:0
12	DMSO	**V**	48	60	39	40:60
13	DMSO	**VI**	18	60	56	53:47
14[d]	H_2O	**VI**	24	70	67	100:0
15	DMSO	**VII**	48	60	22	45:55
16	DMSO	None	48	60	0	—

[a] A mixture of α-tetralone **1** (100.0 mg, 1 equiv), Imidazole (46.0 mg, 1 equiv), paraformaldehyde (66.0 mg, 1 equiv), and catalyst (0.3 equiv) in a specified solvent (0.5–1.5 mL) was stirred at 60–100 °C.
[b] Total isolated yield of **1a** and **11a**.
[c] Ratio with respect to isolated yield.
[d] Reaction was not complete (starting materials remained).
[e] Reaction run using 0.5 equiv of catalyst.

In order to determine whether the carboxylic function was essential, we carried out the same reaction with secondary amines, namely, pyrrolidine **III** and morpholine **IV**. The reaction conversion was high, but instead of the expected Mannich adducts, normal Mannich bases of the corresponding amines were furnished in major amounts along with product **11a** (entries 8–11). L-Alanine **II** was comparable to L-proline (entries 5–7). The best results were obtained with L-proline. In water, Mannich-aldol-type product **11a** was observed exclusively, irrespective of the catalyst used (entries 7, 9, 11, and 14). In isopropanol, ethanol, and *t*-butanol, low yields of Mannich adducts **1a** were observed (entries 2–4). However, in solvents other than water and alcohols, both products **11a** and **1a** were obtained in varying ratios. The results of this study prompted us to select DMSO to prepare Mannich adducts and water for Mannich-aldol-type products as the reaction media and L-proline as the catalyst.

To propose a possible mechanism for this process, the reaction was carried out under controlled conditions. On carefully monitoring the course of the reaction of the ketone, paraformaldehyde, imidazole, and 0.3 equiv of L-proline in DMSO, we were able to isolate a β hydroxy ketone **a** (aldol product) from the reaction mixture along with the Mannich product **c** (Scheme 3). As expected, on further reaction, the β hydroxy ketone **a** disappeared completely, and **c** was isolated as the only product.

On the basis of the above observations and literature reports,[14] it can be postulated that the reaction involves the formation of an aldol product **a** which undergoes dehydration and generates in situ, an α,β-unsaturated carbonyl intermediate **b**. This reacts readily with an azole (via aza-Michael addition) to give the Mannich adduct **c**. In the presence of excess formaldehyde, an enamine forms with the catalyst and reacts via aldol condensation to afford the 2-hydroxymethyl-2-azol-1-ylmethyl (Mannich-aldol-type) product **d**.

In summary, we have developed an efficient method for the direct construction of Mannich adducts with unreactive imidazoles and triazoles using the readily available and inexpensive catalyst, L-proline. We have also reported a method for insertion of two consecutive functional arms, that is, C–C–N and C–C–O at the α-position of a keto group. This reaction is applicable to a wide range of ketones, affording good to excellent yields of products. We are currently utilizing this method for the synthesis of bioactive molecules bearing azolylmethyl and hydroxymethyl moieties and related compounds.[15]

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, characterization data and NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.155.

References and notes

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