A New Application of Mannich Bases

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Mannich bases are an important class of compounds which can easily be transformed into numerous other compounds[1]. The reactivity of Mannich bases accounts for several interesting microbiological properties[2]. More recently, the Mannich bases of various cyclic ketones have been shown to have antibacterial and antifungal activity[3]. α-Methylene ketones, very often obtained by the deamination of Mannich bases, are widely used in organic synthesis as Michael acceptors[4,5]. Also the substitution of dialkylamino groups in Mannich bases by amines and thiols has been extensively utilized[1]. However, no examples of the reaction of Mannich bases with azole nucleophiles have been reported so far.

As part of a program aimed at designing new antifungal agents we explored the reaction of Mannich base hydrochlorides derived from thiochromanone and other cyclic ketones with azoles. 3-Dimethylaminomethylthiochromanone (**1**) is unstable and known to form the dimeric product **3**[6] presumably via the intermediate **2**. In this communication we wish to report that the intermediate **2** which could not be isolated was trapped with imidazole and triazole giving the stable 3-(*N*-azolemethyl)-thiochromanones (**4**, **5**, and **5'**).

A typical procedure involves treatment of Mannich base hydrochlorides with azoles (5 eq.) in water for 12 h or in refluxing ethanol/water (1 : 1) for 2–4 h to give the products in good to excellent yield. The reaction with triazole produces two isomeric products which are separated by column chromatography.

The reaction can be extended to Mannich bases of other cyclic ketones. The results are summarized in the Table. All new compounds are fully characterized by spectroscopic methods, accurate mass measurements, and/or microanalyses.

Using azole nucleophiles, the reaction probably proceeds via elimination of the dialkylamino group followed by a Michael addition or via a nucleophilic substitution mechanism[7].

We consider that the reaction of Mannich bases with azoles is of practical interest because the resultant products cannot be prepared by the standard Mannich reaction. The azole compounds **4**–**11'** showed good antifungal properties which will be reported elsewhere.

Mannich bases of thiopyranone[8], thiochromanone[6], chromanone[9], and α-tetralone[10] are prepared by literature procedures.

α-(*N*-Azolemethyl)-cyclic Ketones (4–11'); General Procedure:
The Mannich base hydrochloride (1 eq.) and azole (5 eq.) are stirred at room temperature in water for 12 h. or refluxed in ethanol/water (1/1) for 2–4 h. The reaction mixture is extracted with chloroform and washed with water. After drying with anhydrous sodium sulfate, the solvent is removed to give a single product in the case of imidazole, and two isomeric products in the case of triazole which are separated on a silica gel column eluting with chloroform containing 1% methanol.

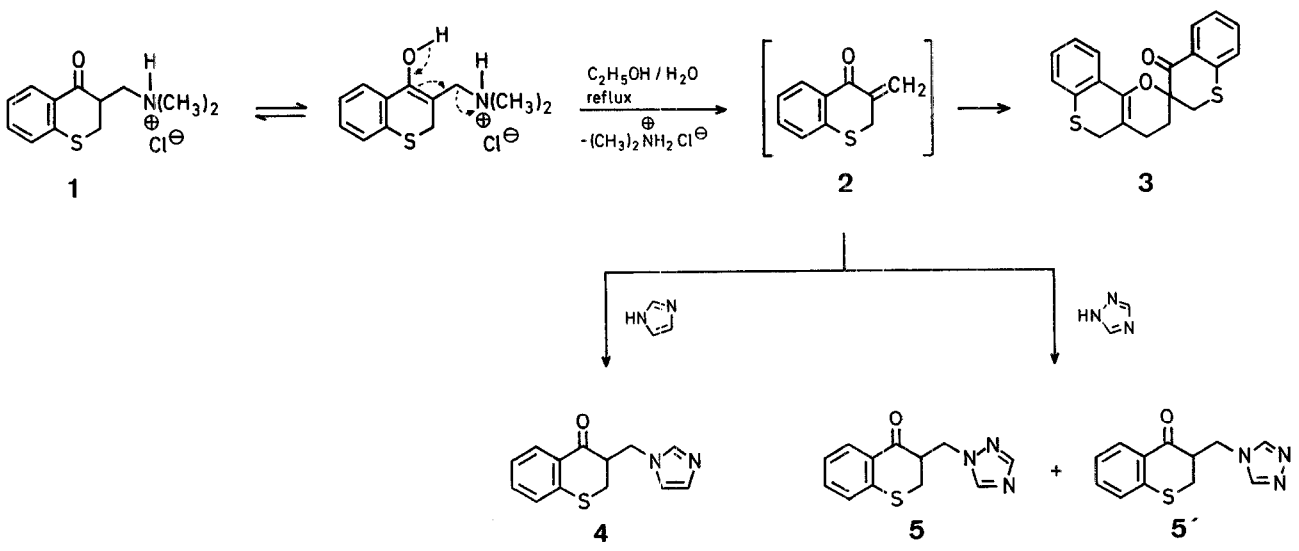
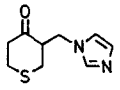
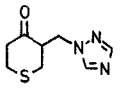
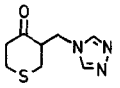
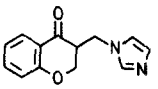
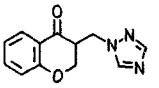
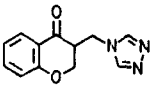
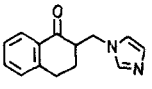
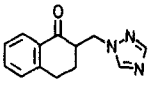
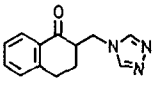


Table. α-(*N*-Azolemethyl)-cyclic Ketones **4**–**11**′ prepared

Product	Yield [%]	m.p.[a] [°C]	Molecular formula[b]	^{1}H-N.M.R. ($CDCl_3$/TMS)[c] δ (ppm)[d,e]	Mass Spectra[f] *m/e* (M^+)
4	96	105°	$C_{13}H_{12}N_2OS$ (244.3)	7.51 (H-1), 7.1 (H-2), 6.92 (H-3)	244
5	51	83°	$C_{12}H_{11}N_3OS$ (245.3)	8.25 (H-1), 7.96 (H-2)	245
5′	25	153°	$C_{12}H_{11}N_3OS$ (245.3)	8.3 (H-1, H-2)	245
6 	97	115°	$C_9H_{12}N_2OS$ (196.3)	7.5 (H-1), 7.08 (H-2), 6.94 (H-3)	196
7 	45	80°	$C_8H_{11}N_3OS$ (197.3)	8.24 (H-1), 8.0 (H-2)	197
7′ 	24	110°	$C_8H_{11}N_3OS$ (197.3)	8.24 (H-1, H-2)	197
8 	97	122°	$C_{13}H_{12}N_2O_2$ (228.2)	7.55 (H-1), 7.1 (H-2), 6.98 (H-3)	228
9 	74	65°	$C_{12}H_{11}N_3O_2$ (229.2)	8.22 (H-1), 7.94 (H-2)	229
9′ 	22	140°	$C_{12}H_{11}N_3O_2$ (229.2)	8.28 (H-1, H-2)	229
10 	96	72°	$C_{14}H_{14}N_2O$ (226.2)	7.5 (H-1), 7.06 (H-2), 6.96 (H-3)	226
11 	40	oil	$C_{13}H_{13}N_3O$ (227.2)	8.23 (H-1), 7.95 (H-2)	227
11′ 	16	158°	$C_{13}H_{13}N_3O$ (227.2)	8.22 (H-1, H-2)	227

[a] Uncorrected.
[b] Satisfactory microanalyses obtained: C ±0.4, H ±0.19, N ±0.3, S ±0.2.
[c] ^{1}H-N.M.R. spectra were taken at 100 MHz on a Varian XL-100 spectrometer.
[d] Only azole protons are reported.
[e] In the case of imidazole protons small couplings (*J* values ≤ 1 Hz) observed in the spectra are not listed.
[f] Mass spectra were performed with Varian Mat CH-5.

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