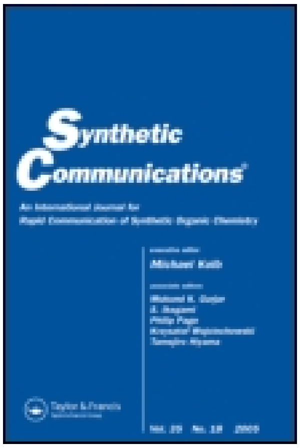

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Efficient and Practical Synthesis of Mannich Bases Related to Gramine Mediated by Zinc Chloride

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Abstract: An efficient and practical procedure for the Mannich reaction of secondary amine, formaldehyde, and indole or N-methylindole employing zinc chloride is presented. A series of gramine derivatives were obtained in 58–98% yields at room temperature in EtOH by using this method.

Keywords: Gramine, Mannich reaction, synthesis, zinc chloride

INTRODUCTION

Because of the potent biological activity exhibited by various indole derivatives,[1] the investigation of the chemistry of indoles has been and continues to be one of the most active areas of heterocyclic chemistry.[2] The Mannich reaction as a powerful carbon–carbon bond-formation process has wide application for the preparation of diverse aminoalkyl derivatives. In fact, 3-aminomethylindoles are particularly interesting on account of their biological activity and use in the total synthesis of ergot alkaloids.[3] Gramine, which occurs in sprouting barley, is a typical and simple indole alkaloid. 3-(Dimethylaminomethyl)indole is used for the synthesis of tryptophane or indole-3-acetic acid.

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Many synthetic methods for preparation of Mannich bases related to gramine have been reported.[4–9] However, in spite of their potential utility, some of the reported methods suffer from drawbacks such as long reaction times, low yields, and cumbersome product isolation procedures.

For this reason, a more accessible, convenient, and efficient mediator system is desirable.

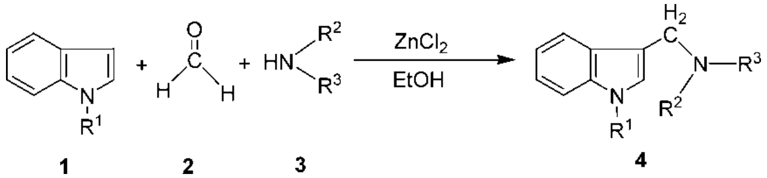
Zinc chloride has been extensively used as a catalyst for many organic reactions, such as the synthesis of 5-arylidene barbituric acid[10] and Friedel–Crafts reactions of aromatic compounds. To our knowledge, a Mannich reaction of secondary amine, formaldehyde, and indole employing zinc chloride as mediator has not been reported before. In continuation of our work in synthesis of indole derivatives,[11] we describe zinc chloride as a convenient and efficient mediator for the synthesis of Mannich bases related to gramine via Mannich reaction of secondary amine, formaldehyde, and indole (Scheme 1).

RESULTS AND DISCUSSION

We studied the influence of the grinding method on the reaction time and yield. As shown in Table 1, at room temperature, the mixture of HCHO, $HN(CH_3)_2$, $4\text{-}CH_3C_6H_4SO_3H$, and indole was ground by mortar and pestle for 5 min and indole disappeared (as indicated by TLC), but the yield of gramine was only 13% and an insoluble polymeric gum was formed. We ground the mixture of HCHO, $HN(CH_3)_2$, $4\text{-}CH_3C_6H_4SO_3H$, and indole in an icebath for 20 min and then laid the mixture for 64 min at room temperature, but the yield of gramine was only 33%.

We also examined the influence of the ultrasound irradiation on the reaction. As shown in Table 1, we found that ultrasound irradiation did not improve the yield of gramine. For example, the reaction of formaldehyde, dimethyl amine (**3a**), and indole gave 3-dimethylaminomethylindole (**4a**) in 84% yield mediated by $Ni(OAc)_2$ using stirring for 180 min, whereas under ultrasound irradiation, **4a** was obtained in 78% yield within the same time.

As shown in Table 1, the effects of different mediators, such as $4\text{-}CH_3C_6H_4SO_3H$, HCl, H_2NSO_3H, $Ni(OAc)_2$, $Cu(OAc)_2$, and $ZnCl_2$, were examined. Among these mediators, $ZnCl_2$ was found to be an excellent



Scheme 1.

Table 1. Effects of different conditions on the reaction of dimethylamine, formaldehyde, and indole[a]

Entry	Mediator	Amount of mediator (%mol)	Method	T (min)	Yield (%)[b]
1[c]	4-$CH_3C_6H_4SO_3H$	100	Grinding	5	13
2[d]	4-$CH_3C_6H_4SO_3H$	100	Grinding	20	33
3[c]	4-$CH_3C_6H_4SO_3H$	100	U.s.	120	85
4[c]	HCl	100	U.s.	120	82
5[c]	H_2NSO_3H	100	U.s.	120	53
6[c]	$Ni(OAc)_2$	100	U.s.	180	78
7[c]	$Ni(OAc)_2$	100	Stirring	180	84
8[e]			Stirring	420	65
9[e]	$Ni(OAc)_2$	100	Stirring	150	71
10[e]	$Cu(OAc)_2$	100	Stirring	150	82
11[e]	$ZnCl_2$	100	Stirring	150	91
12[e]	$ZnCl_2$	50	Stirring	90	75
13[e]	$ZnCl_2$	100	Stirring	90	81
14[e]	$ZnCl_2$	150	Stirring	90	98
15[e]	$ZnCl_2$	250	Stirring	90	93

[a] The reaction was carried out at room temperature.

[b] Isolated yields.

[c] The sequence of adding reagents was formaldehyde, dimethylamine, mediator, indole.

[d] The sequence of adding reagents was formaldehyde, dimethylamine, mediator, indole. Ground the mixture in ice bath for 20 min and then laid the mixture for 64 min at room temperature.

[e] The sequence of adding reagents was dimethylamine, mediator, formaldehyde, indole.

mediator in terms of yield and reaction time. So, $ZnCl_2$ was chosen as the mediator for the synthesis of Mannich bases related to gramine.

We studied the effect of the amount of the mediator on the reaction yield. As shown in Table 1, as the amount of $ZnCl_2$ increased, the reaction yields were improved. For example, when the amount of the mediator was 50% mol, the yield was 75% within 90 min, whereas when using 150% mol, the reaction needed only 90 min to give gramine in 98% yield.

From the results in Table 1, the reaction conditions we chose were as follows: secondary amine (**3**, 2 mmol), $ZnCl_2$ (3 mmol), formaldehyde (**2**, 2 mmol), and indole (**1**, 2 mmol). Using this reaction condition, we did a series of experiments for reactions of secondary amine, formaldehyde, and indole. The results are summarized in Table 2. It is obvious that the synthesis of Mannich bases related to gramine mediated by $ZnCl_2$ represents a better procedure in terms of higher yields, milder reaction conditions, and shorter reaction times. For example, **4a** was previously prepared by letting it sit for 10 h catalyzed by acetic acid.[4] The present procedure gave **4a** in 98% yield within 90 min.

Table 2. Synthesis of Mannich bases related to gramine mediated by zinc chloride

Entry	R^1	R^2	R^3	T (min)	Isolated yield (%)	Mp (°C) (lit)
a[a]	H	CH_3	CH_3	90	98	128–130 (127–128)[4]
b[a]	H	CH_2CH_3	CH_2CH_3	90	73	109–110
b[b]	H	CH_2CH_3	CH_2CH_3	120	85	
c[c]	H	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	90	82	Oil product
d[a]	H	$-(CH_2)_5-$		90	98	165–167
e[a]	H	$-(CH_2CH_2OCH_2CH_2)-$		120	79	121–123
e[d]	H	$-(CH_2CH_2OCH_2CH_2)-$		150	86	
f[a]	CH_3	CH_3	CH_3	150	82	Oil product
g[a]	CH_3	CH_2CH_3	CH_2CH_3	520	58	Oil product
h[a]	CH_3	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	600	58	Oil product
i[a]	CH_3	$-(CH_2)_5-$		300	88	Oil product
j[a]	CH_3	$-(CH_2CH_2OCH_2CH_2)-$		120	84	Oil product

[a] The reaction was carried out at room temperature.
[b] The reaction temperature was 2–10°C.
[c] The reaction temperature was 4–7°C.
[d] The reaction temperature was 6°C.

As shown in Table 2, as far as some reactions are concerned, at lower temperature the yield increased. The reaction of diethylamine (**3b**), formaldehyde, and indole gave 3-diethyl aminomethylindole (**4b**) in 73% yield within 90 min mediated by $ZnCl_2$ at room temperature. However, **4b** was obtained in 85% yield using stirring for 120 min mediated by $ZnCl_2$ at 2–10°C. At lower temperature, by-products are difficult to form.

As shown in Table 2, when the amount of the mediator was 150% mol, **4a** was obtained in 98% yield within 90 min, but the reaction of diethylamine, formaldehyde, and indole gave **4b** in only 73% yield within 90 min. It is apparent that steric hindrance affects the yields.

CONCLUSION

In conclusion, zinc chloride was found to be a convenient and efficient mediator for the synthesis of Mannich bases related to gramine via Mannich reaction of secondary amine, formaldehyde, and indole or N-methylindole.

EXPERIMENTAL

Melting points were uncorrected. ^1H NMR spectra were measured on a Bruker Advance 400 (400-MHz) spectrometer using TMS as internal standard and

$CDCl_3$ as solvent. Elemental analyses were carried out using Heraeus analyzer. Sonication was performed on a Shanghai Branson-BUG ultrasonic cleaner (with a frequency of 25 kHz and a nominal power of 250 W). The reaction flask was located in the maximum energy area in the cleaner, where the surface of reactants is slightly lower than the level of the water, and addition or removal of water was used to control the temperature of the water bath.

General Procedure

A 50-mL round flask was charged with secondary amine (**3**, 2 mol), EtOH (3 mL), zinc chloride (3 mmol), formaldehyde (**2**, 2 mmol, 36% aq.), and indole or N-methylindole (**1**, 2 mmol). The mixture was stirred for a period as indicated in Table 2. After dilution with H_2O (7 mL), the mixture was made basic with NaOH (6 mmol, 20% aq.) and extracted three times with ethyl acetate (3 × 10 mL). Ethyl acetate was evaporated under reduced pressure. The residue was diluted with H_2O (8 mL) and acided with HCl (4 mmol, 20% aq.). After filtration, the mother liquor was basified with NaOH (7 mmol, 20% aq.), the resulting suspension was cooled in an ice bath. The product was collected by filtration and washed with water. If the product was oil, the product was extracted three times with diethyl ether (3 × 10 mL), the combined organic layers were dried over anhyd. $MgSO_4$, and the solvent was evaporated under reduced pressure. All the products were confirmed by comparing their melting points, element analyses, ^1H NMR data with data reported in literature.

Data

Compound 4b. Mp 109–110°C. ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 1.118$ (t, 6H, $J = 7.2$ Hz), 2.599 (q, 4H, $J = 7.2$ Hz), 3.825 (s, 2H), 7.137–7.207 (m, 3H), 7.378 (d, 1H, $J = 8.0$ Hz), 7.756 (d, 1H, $J = 8.0$ Hz), 8.163 (s, 1H). Anal. calcd. for $C_{13}H_{18}N_2$: C, 77.184; H, 8.968; N, 13.848. Found: C, 77.341; H, 8.958; N, 13.974.

Compound 4c. Oil product. ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 1.036$ (t, 6H, $J = 7.2$ Hz), 1.738 (sextet, 4H, $J = 7.2$ Hz), 2.634 (t, 4H, $J = 7.6$ Hz), 3.977 (s, 2H), 7.063 (s, 1H), 7.265–7.361 (m, 3H), 7.904 (d, 1H, $J = 7.6$ Hz), 8.743 (s, 1H). Anal. calcd. for $C_{15}H_{22}N_2$: C, 78.213; H, 9.626; N, 12.161. Found: C, 78.066; H, 9.705; N, 12.281.

Compound 4d. Mp 165–167°C. ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 1.445$ (d, 2H, $J = 4.8$ Hz), 1.607 (qui, 4H, $J = 5.6$ Hz), 2.511 (s, 4H), 3.745 (s, 2H), 7.112–7.228 (m, 3H), 7.352 (d, 1H, $J = 8.0$ Hz), 7.758 (d, 1H, $J = 8.0$ Hz), 8.482 (s, 1H). Anal. calcd. for $C_{14}H_{18}N_2$: C, 78.463; H, 8.465; N, 13.072. Found: C, 78.676; H, 8.473; N, 13.233.

Compound 4e. Mp 121–123°C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta_H = 2.540$ (s, 4H), 3.727 (s, 2H), 3.743 (s, 4H), 7.145–7.249 (m, 3H), 7.379 (d, 1H, $J = 8.0$ Hz), 7.791 (d, 1H, $J = 7.6$ Hz), 8.207 (s, 1H). Anal. calcd. for $C_{13}H_{16}N_2O$: C, 72.194; H, 7.456; N, 12.953. Found: C, 72.243; H, 7.480; N, 13.007.

Compound 4f. Oil product. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta_H = 2.492$ (s, 6H), 3.641 (s, 3H), 3.813 (s, 2H), 7.011 (s, 1H), 7.358–7.449 (m, 3H), 7.972–7.993 (m, 1H). Anal. calcd. for $C_{12}H_{16}N_2$: C, 76.555; H, 8.565; N, 14.880. Found: C, 76.406; H, 8.589; N, 14.932.

Compound 4g. Oil product. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta_H = 1.180$ (t, 6H, $J = 7.2$ Hz), 2.647 (q, 4H, $J = 7.2$ Hz), 3.803 (s, 3H), 3.865 (s, 2H), 7.052 (s, 1H), 7.193 (t, 1H, $J = 7.2$ Hz), 7.297 (t, 1H, $J = 7.2$ Hz), 7.356 (d, 1H, $J = 8.0$ Hz), 7.808 (d, 1H, $J = 8.0$ Hz). Anal. calcd. for $C_{14}H_{20}N_2$: C, 77.732; H, 9.318; N, 12.950. Found: C, 77.806; H, 9.364; N, 12.815.

Compound 4h. Oil product. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta_H = 0.978$ (t, 6H, $J = 7.2$ Hz), 1.649 (sextet, 4H, $J = 7.2$ Hz), 2.525 (t, 4H, $J = 7.2$ Hz), 3.816 (s, 3H), 3.869 (s, 2H), 7.048 (s, 1H), 7.202 (t, 1H, $J = 7.6$ Hz), 7.310 (t, 1H, $J = 8.0$ Hz), 7.367 (d, 1H, $J = 8.0$ Hz), 7.825 (d, 1H, $J = 7.6$ Hz). Anal. calcd. for $C_{16}H_{24}N_2$: C, 78.638; H, 9.898; N, 11.463. Found: C, 78.811; H, 9.917; N, 11.667.

Compound 4i. Oil product. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta_H = 1.558$ (d, 2H, $J = 4.4$ Hz), 1.722 (t, 4H, $J = 5.2$ Hz), 2.600 (s, 4H), 3.819 (s, 5H), 7.105 (s, 1H), 7.259 (t, 1H, $J = 8.0$ Hz), 7.314–7.409 (m, 2H), 7.865 (d, 1H, $J = 7.6$ Hz). Anal. calcd. for $C_{15}H_{20}N_2$: C, 78.903; H, 8.828; N, 12.269. Found: C, 78.795; H, 8.820; N, 12.384.

Compound 4j. Oil product. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta_H = 2.597$ (s, 4H), 3.788 (s, 3H), 3.807 (s, 6H), 7.072 (s, 1H), 7.236 (t, 1H, $J = 7.2$ Hz), 7.315–7.391 (m, 2H), 7.846 (d, 1H, $J = 8.0$ Hz). Anal. calcd. for $C_{14}H_{18}N_2O$: C, 73.012; H, 7.877; N, 12.164. Found: C, 73.212; H, 7.964; N, 12.320.

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