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A Novel Method for Biomimetic Synthesis of Mannich Bases

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Since the early studies of Mannich, Mannich reaction has become an important tool for the synthesis of new compounds. Mannich bases can be either directly employed or used as intermediates. In this work, the one-carbon unit transfer reaction of tetrahydrofolate coenzyme was initiated. 1,3-Dimethylimidazolidine as a new tetrahydrofolate coenzyme model at formaldehyde oxidation level was used to react with ketone having active hydrogen atoms and amine to give the corresponding Mannich base in good yield by a covert Mannich reaction. A novel method for biomimetic synthesis of various Mannich bases is provided.

Keywords 1,3-dimethylimidazolidine, tetrahydrofolate coenzyme model, Mannich reaction, biomimetic synthesis

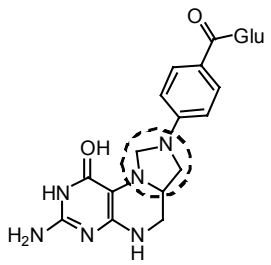
Introduction

The chemistry of Mannich bases, first studied by Mannich, has been the subject of investigations by an ever increasing number of researchers.[1] The most important application of Mannich bases is in pharmaceutical chemistry and a large number of the papers concerning Mannich bases are published in pharmaceutical journals. Particularly noteworthy are some general studies such as those regarding Mannich base derivatives possessing anticancer,[2] antivirus,[3] antimicrobial,[4] antiinflammatory,[5] or cardiotonic[1d] activity. Additionally, Mannich bases represent easily obtainable intermediates for the synthesis of other compounds such as heterocycles, amino-alcohols, *etc*.[1d]

Recently, the function of tetrahydrofolate coenzymes for organisms and the use in biomimetic synthesis have been an important subject of biochemistry.[6] Many researchers have tried to discover the mechanism of various coenzymes related to tetrahydrofolate coenzymes that lead in the biochemical transfer of a one-carbon fragment at different oxidation levels.[7] The role of six one-carbon derivatives of tetrahydrofolic acid in the enzyme-catalyzed transfer of a one-carbon unit at the level of formate, formaldehyde, and methanol has been determined.[8] When the one-carbon unit is at formaldehyde oxidation level, the imidazolidine with a five-membered ring structure is the active site (Scheme 1).[9]

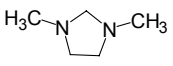
We now use 1,3-dimethylimidazolidine (**1**) containing a five-membered imidazolidine ring as the tetrahydrofolate coenzyme model at formaldehyde oxidation level (Scheme 2), which can be prepared from 1,3-dimethyl-2-imidazolidinone by reduction reaction with lithium aluminum hydride in ether.[10] The compound

Scheme 1 Tetrahydrofolate coenzyme at formaldehyde oxidation level



(**1**) was identified by ^{1}H NMR, MS, elemental analysis and IR spectra. If we make the coenzyme model (**1**) react with ketone which can provide active α-hydrogen and amine as nucleophile reagent, the one-carbon unit at the formaldehyde oxidation level will be transferred to the amine and a covert Mannich reaction will be accomplished. So a novel method for biomimetic synthesis of Mannich base is provided. The route of the new synthetic method is shown in Scheme 3.

Scheme 2 1,3-Dimethylimidazolidine as a new tetrahydrofolate coenzyme model at formaldehyde oxidation level



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Experimental

TLC analysis was carried out on glass plates coated with silica gel-G, and spots were visualized using an

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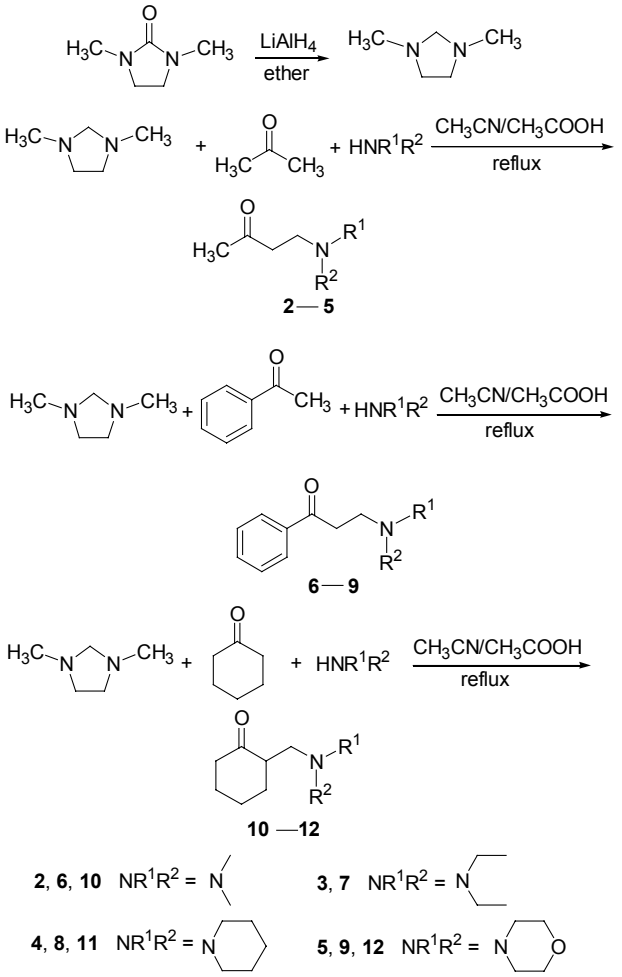
Scheme 3 The route of the new synthetic method of Mannich bases



ultraviolet (UV) lamp. Infrared (IR) spectra in cm^{-1} were recorded on a Bruck EQUIOX-55 spectrometer (Germany). The proton magnetic resonance spectra (^1H NMR) were recorded at 400 MHz on a Varian INOVA-400 spectrometer (USA), and chemical shifts were reported relative to internal Me_4Si; GC/MS analyses were performed on a Shimadzu GCMS2010 Plus spectrometer equipped with an Rxi-5ms capillary column at an ionization voltage of 70 eV.

Synthesis of 1,3-dimethylimidazolidine (1)

A mixture of 1,3-dimethylimidazolidin-2-one (1 mmol) and pure lithium aluminum hydride (approximately 5 mmol) in anhydrous ether (6 mL) was stirred for 1 h at 25 ℃. The reaction was quenched with water (0.19 mL), 15% aqueous NaOH (0.19 mL) and water (0.57 mL). The precipitate was removed by filtration and washed with ether. Evaporation of the ether afforded compound **1**.

1,3-Dimethylimidazolidine (**1**) Colorless oil, yield 55%; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.39 (s, 6H, CH_3), 2.79 (s, 4H, CH_2CH_2), 3.32 (s, 2H, CH_2); MS (70 eV) *m*/*z* (%): 100(18) $[M]^+$, 99(100), 57(53), 42(60); IR (KBr) *v*: 3420, 2938, 2850, 2804, 1663, 1457, 1395, 1286, 1233, 1125, 1081, 1038, 956, 653 cm^{-1} (According with lit.[11]).

General procedure for the synthesis of compounds 2—5

To a 50 mL flask was added 1,3-dimethylimidazolidine **1** (2 mmol), secondary amines (2 mmol), acetone (4.4 mmol), acetic acid (2—3 drops) and acetonitrile (10 mL). The mixture was refluxed for 10 h with stirring. Acetonitrile was removed by distillation. The residue was basified with 5% $NaHCO_3$ solution to make its pH 10 and then extracted with CH_2Cl_2 (10 mL×5). The organic layer was dried over anhydrous K_2CO_3 and concentrated *in vacuo* to obtain the crude product, which was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH, 20∶1, volume ratio).

4-(Dimethylamino)butan-2-one (**2**) Colorless oil, yield 83.1%; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.18 (s, 3H, $COCH_3$), 2.23 (s, 6H, NCH_3), 2.579—2.60 (m, 4H, $COCH_2CH_2N$); IR (KBr) *v*: 2946, 2863, 2820, 2770, 1713, 1463, 1379, 1358, 1039, 956, 813, 772, 587, 520 cm^{-1} (According with lit.[12]).

4-(Diethylamino)butan-2-one (**3**) Colorless oil, yield 83.1%; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.02 (t, J= 7.4 Hz, 6H, CH_2CH_3), 2.17 (s, 3H, $COCH_3$), 2. 52 (q, J=7.1 Hz, 4H, CH_2CH_3), 2.59 (t, J=7.6 Hz, 2H, $COCH_2$), 2.76 (t, J=7.4 Hz, 2H, NCH_2); IR (KBr) *v*: 2970, 2931, 2810, 1712, 1452, 1422, 1360, 1163, 1069, 759, 592 cm^{-1} (According with lit.[12]).

4-(Piperidin-1-yl)butan-2-one (**4**) Colorless oil, yield 82.0%; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.41—1.45 (m, 2H, piperidine-H), 1.54—1.60 (m, 4H, piperidine-H), 2.17 (s, 3H, $COCH_3$), 2.37 (br, 4H, piperidine-H), 2.61—2.63 (m, 4H, $COCH_2CH_2N$); IR (KBr) *v*: 2934, 2853, 2799, 1714, 1442, 1356, 1303, 1155, 1119, 1041, 953, 863, 772, 609, 549 cm^{-1} (According with lit.[12]).

4-Morpholinobutan-2-one (**5**) Colorless oil, yield 70.3%; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.18 (s, 3H, $COCH_3$), 2.44 (t, J=4.0 Hz, 4H, $N(CH_2)_2$), 2.60—2.67 (m, 4H, $COCH_2CH_2N$), 3.70 (t, J = 4.0 Hz, 4H, $O(CH_2)_2$); IR (KBr) *v*: 2956, 2854, 2810, 1712, 1453, 1360, 1296, 1273, 1116, 1070, 1012, 912, 867, 612 cm^{-1} (According with lit.[12]).

General procedure for the synthesis of compounds 6—9

To a 50 mL flask was added 1,3-dimethyl-imidazolidine **1** (2 mmol), secondary amines (2 mmol), acetophenone (2 mmol), acetic acid (2—3 drops) and acetonitrile (10 mL). The mixture was refluxed for 12—14 h with stirring. Acetonitrile was removed by distillation. The residue was basified with 5% $NaHCO_3$ solution to make its pH 10 and then extracted with CH_2Cl_2 (15 mL ×3). The organic layer was dried over anhydrous K_2CO_3 and concentrated *in vacuo* to obtain the crude product, which was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH, 20∶1, volume ratio).

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3-(Dimethylamino)-1-phenylpropan-1-one (**6**) Colorless oil, yield 75.6%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.32 (s, 6H, $N(CH_3)_2$), 2.80 (t, J=7.6 Hz, NCH_2), 3.20 (t, J=7.2 Hz, $COCH_2$), 7.47 (t, J=7.7 Hz, 2H, *m*-ph-H), 7.57 (t, J=7.4 Hz, 1H, *p*-ph-H), 7.97 (d, J=7.2 Hz, 2H, *o*-ph-H); IR (KBr) ν: 3061, 2972, 2943, 2861, 2819, 2768, 1684, 1597, 1581, 1451, 1379, 1330, 1286, 1206, 1068, 1040, 979, 869, 747, 692, 653, 572 cm^{-1} (According with lit.[13]).

3-(Diethylamino)-1-phenylpropan-1-one (**7**) Colorless oil, yield 72.1%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.06 (t, J=7.4 Hz, 6H, CH_2CH_3), 2.58 (q, J=7.5 Hz, 4H, CH_2CH_3), 2.94 (t, J=7.8 Hz, 2H, NCH_2), 3.16 (t, J=7.6 Hz, 2H, $COCH_2$), 7.46 (t, J=7.6 Hz, 2H, *m*-ph-H), 7.56 (t, J=7.2 Hz, 1H, *p*-ph-H), 7.95 (d, J=8.0 Hz, 2H, *o*-ph-H); IR (KBr) ν: 3061, 2969, 2930, 2872, 2808, 1683, 1597, 1448, 1378, 1281, 1219, 1069, 997, 744, 692, 653, 571 cm^{-1} (According with lit.[7a]).

1-Phenyl-3-(piperidin-1-yl)propan-1-one (**8**) Colorless oil, yield 62.3%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.44—1.48 (m, 2H, piperidine-H), 1.58—1.64 (m, 4H, piperidine-H), 2.47 (br, 4H, piperidine-H), 2.82 (t, J=7.4 Hz, 2H, $COCH_2$), 3.22 (t, J=5.4 Hz, 2H, NCH_2), 7.46 (t, J=7.6 Hz, 2H, *m*-ph-H), 7.56 (t, J=7.6 Hz, 1H, *p*-ph-H), 7.97 (d, J=7.6 Hz, 2H, *o*-ph-H); IR (KBr) ν: 3060, 2934, 2852, 2798, 1684, 1597, 1580, 1447, 1377, 1353, 1241, 1206, 1115, 1040, 977, 865, 745, 692, 569 cm^{-1} (According with lit.[14]).

3-Morpholino-1-phenylpropan-1-one (**9**) Colorless oil, yield 60.7%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.51 (t, J=4.0 Hz, 4H, $N(CH_2)_2$), 2.84 (t, J=7.4 Hz, 2H, $COCH_2$), 3.19 (t, J=7.6 Hz, 2H, NCH_2), 3.72 (t, J=4.4 Hz, 4H, $O(CH_2)_2$), 7.47 (t, J=7.2 Hz, 2H, *m*-ph-H), 7.57 (t, J=8.0 Hz, 1H, *p*-ph-H), 7.96 (d, J=7.6 Hz, 2H, *o*-ph-H); IR (KBr) ν: 3060, 2955, 2853, 2809, 1683, 1597, 1580, 1449, 1398, 1361, 1261, 1216, 1116, 1070, 980, 914, 869, 747, 692, 571 cm^{-1} (According with lit.[15]).

General procedure for the synthesis of compounds 10—12

To a 100 mL flask was added 1,3-dimethylimidazolidine (**1**) (5 mmol), secondary amines (5 mmol), cyclohexanone (11 mmol), acetic acid (10 drops) and acetonitrile (40 mL). The mixture was refluxed for 20 h with stirring. Acetonitrile was removed by distillation. The residue was basified with 5% $NaHCO_3$ solution to make its pH 10 and then extracted with CH_2Cl_2 (15 mL ×5). The organic layer was dried over anhydrous K_2CO_3 and concentrated *in vacuo* to obtain the crude product, which was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH, 20∶1, volume ratio).

2-(*N*,*N*-dimethylaminomethyl)cyclohexanone (**10**) Colorless oil, yield 35.6%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40—2.53 (m, 8H, cyclohexanone-H), 2.21 (s, 6H, $N(CH_3)_2$), 2.23 (d, J=6.8 Hz, 2H, NCH_2), 2.67—2.72 (m, 1H, COCH); IR (KBr) ν: 2936, 2859, 2818, 2765, 1709, 1453, 1382, 1307, 1263, 1218, 1126, 1029, 876, 669, 543 cm^{-1} (According with lit.[13]).

2-(Piperidin-1-ylmethyl)cyclohexanone (**11**) Colorless oil, yield 25.4%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35—2.58 (m, 8H, cyclohexanone-H), 1.36—1.44 (m, 2H, piperidine-H), 1.51—1.57 (m, 4H, piperidine-H), 2.17—2.42 (m, 6H, $N(CH_2)_3$), 2.75—2.80 (m, 1H, COCH); IR (KBr) ν: 2932, 2855, 2773, 1709, 1447, 1378, 1353, 1303, 1222, 1121, 1057, 995, 865, 781, 669, 532 cm^{-1} (According with lit.[16]).

2-(Morpholinomethyl)cyclohexanone (**12**) Colorless oil, yield 23.3%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.38—2.58 (m, 8H, cyclohexanone-H), 2.37—2.46 (m, 6H, $N(CH_2)_3$), 2.79—2.84 (m, 1H, COCH), 3.68 (t, J=4.0 Hz, 4H, $O(CH_2)_2$); IR (KBr) ν: 2932, 2855, 2808, 1708, 1450, 1364, 1296, 1118, 1069, 1009, 869, 669, 540 cm^{-1} (According with lit.[17]).

Results and Discussion

As shown in Scheme 3, when a mixture of 1,3-dimethylimidazolidine, secondary amines and ketones with active α-hydrogens was heated (CH_3CN, reflux) in the presence of acetic acid, the corresponding aminomethylation derivatives **2**—**12** were obtained (Table 1). All the products were characterized by ^{1}H NMR and IR spectra. The yields of **2**—**12** were listed in Table 1, wherein those of **10**, **11** and **12** were low. Thus it could be seen that the structure of ketone dominated the yield and the greater steric effect would result in the lower yield.

Table 1 Synthesis of Mannich bases

Entry	Ketone	Amine	Time/h	Product	Yield/%
1	Ac[a]	DM[d]	10	**2**	83.1
2	Ac	DE[e]	10	**3**	82.0
3	Ac	PIP[f]	10	**4**	73.7
4	Ac	MOR[g]	10	**5**	70.3
5	Ap[b]	DM	12	**6**	75.6
6	Ap	DE	12	**7**	72.1
7	Ap	PIP	14	**8**	62.3
8	Ap	MOR	14	**9**	60.7
9	Ch[c]	DM	20	**10**	35.6
10	Ch	PIP	20	**11**	25.4
11	Ch	MOR	20	**12**	23.3

[a] Ac: acetone; [b] Ap: acetophenone; [c] Ch: cyclohexanone; [d] DM: dimethylamine; [e] DE: diethylamine; [f] PIP: piperidine; [g] MOR: morpholine.

Protonation of 1,3-dimethylimidazolidine (**1**) in trifluoroacetic acid produces an 82∶18 equilibrium between the monoprotonated ring form (**1**-H^+) and a second form with Schiff-base, open-chain structure (*N*-methyl-*N*-(2-methyl-amino)ethyl-*N*-methylene ammonium trifluoroacetate).[18] The described herein carbon-transfer reaction should be derived from this ring-chain tautomerism in 1,3-dimethylimidazolidine. So the mechanism of formation of the aminomethylation de-

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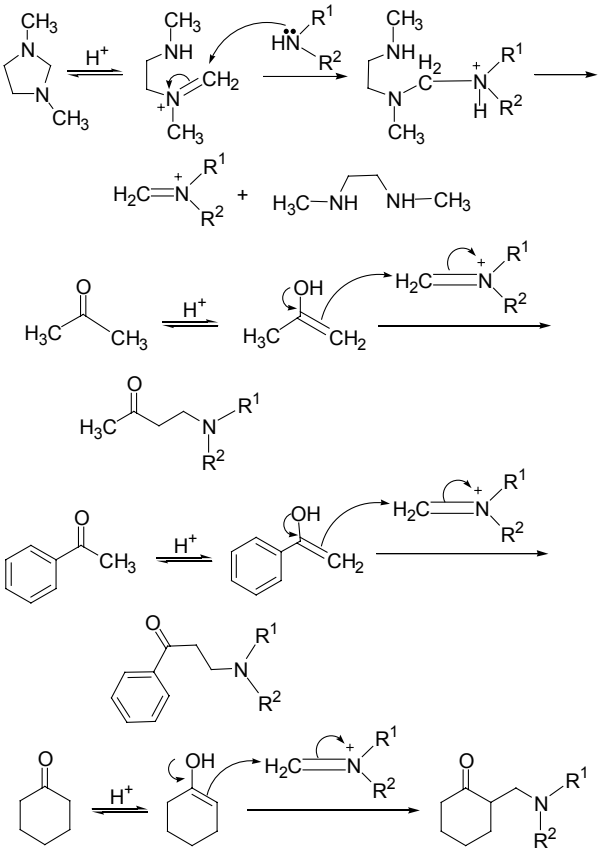
rivatives can be rationalized via the sequence described as shown in Scheme 4.

Scheme 4 Possible reaction mechanism of 1,3-dimethylimidazolidine with ketone and amine



Actually this carbon transfer reaction can be regarded as covert Mannich reaction. Furthermore it should be emphasized that the particular merit of the reported synthetic approach lies in the fact that the use of the relatively unstable aldehydes, required in the "Pictet-Spengler procedure" for related synthesis, is avoided.

The application of the methodology of Mannich bases synthesis to isoquinoline and β-carboline derivatives is being vigorously investigated and our results on these studies will be presented elsewhere.

Conclusions

In conclusion, the one-carbon unit of tetrahydrofolate coenzyme was transferred to nucleophile by using the imidazolidine as a new tetrahydrofolate coenzyme formaldehyde oxidation level model with amine as nucleophile reagents via a covert Mannich reaction. The one-carbon unit transfer reaction of tetrahydrofolate coenzyme was initiated. Biomimetic synthesis of eleven aminomethylation derivatives was accomplished. Mechanism of the reaction was proposed. A novel method for the biomimetic synthesis of Mannich bases was provided.

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