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Mannich-Type Reaction for Synthesis of 3-Methyl-4-nitroimino-tetrahydro-1,3,5-oxadiazine

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MANNICH-TYPE REACTION FOR SYNTHESIS OF 3-METHYL-4-NITROIMINO-TETRAHYDRO-1,3,5-OXADIAZINE

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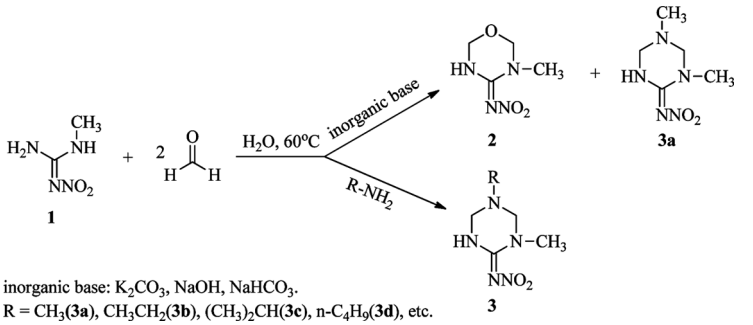
GRAPHICAL ABSTRACT



Abstract *The reaction of N-methyl-N′-nitroguanidine with 3-methyl-4-nitroimino-tetrahydro-1,3,5-oxadiazine is a Mannich-type reaction. The reaction was catalyzed by several organic and inorganic bases at different reaction times and temperatures. Three inorganic base catalysts [potassium carbonate (K_2CO_3), sodium hydrogen carbonate ($NaHCO_3$), and sodium hydroxide (NaOH)] and several organic bases (methylamine, ethamine,* iso-*propylamine, and* n-*butylamine) have been studied. The results showed that both the inorganic and organic base catalysts can be used as catalysts, with the organic bases performing better. N-Methyl-N′-nitroguanidine reacts to give the title compound* **2** *and is catalyzed by both acids and bases. The intensity of inorganic base catalysts, reaction temperature, and reaction time had significant effects on the products.*

Keywords Formaldehyde; Mannich reaction; 3-methyl-4-nitroimino-tetrahydro-1,3,5-oxadiazine; N-(1,5-dimethyl-1,3,5-triazinan-2-ylidene)nitramide; N-(5-ethyl-1-methyl-1,3,5-triazinan-2-ylidene)nitramide; N-methyl-N′-nitroguanidine

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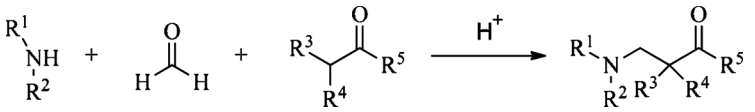
INTRODUCTION

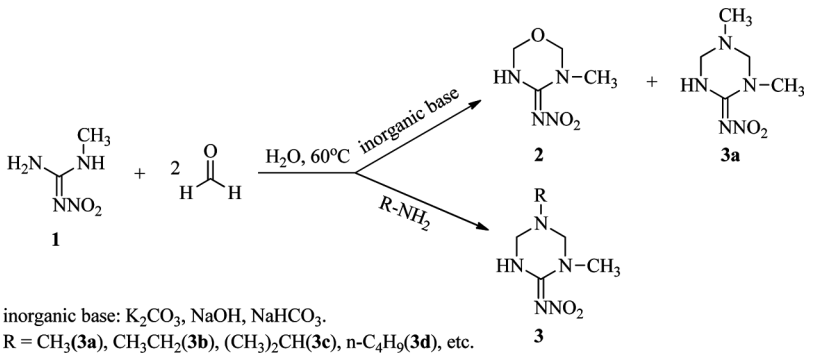
The Mannich reaction, which was developed early last century, is also known as the amine methylation reaction (aminomethlylation)[1,2] and been widely used in the synthesis of alkaloids (e.g., tropinone) and medicine (e.g., fluxetine, tramadol, and tolmetin). Commonly, the Mannich reaction has three components: amine, formaldehyde, and compound with least one active hydrogen for the condensation process (Scheme 1). Different from the general Mannich reaction, the reaction of N-methyl- N′-nitroguanidine (compound **1**) with 3-methyl-4-nitroimino-tetrahydro-1,3,5-oxadiazine (compound **2**) is a two-component process; the formaldehyde is played as aldehyde and compound **1** is played as an active hydrogen compound (Scheme 2).

The Mannich reaction can be catalyzed either by acid or alkali.[3–6] The acid-catalyzed reaction usually utilizes protic solvents such as methanol, water, and acetic acid. The Mannich reaction of N-methyl-N'-nitroguanidine (compound **1**) has been widely used in pharmaceuticals, pesticides, military applications, and other synthetic fields, especially in the synthesis of agrochemicals.[7]

3-Methyl-4-nitroimino-tetrahydro-1,3,5-oxadiazine (compound **2**), N-(1,5-dimethyl-1,3,5-triazinan-2-ylidene)nitramide (compound **3a**), and N-(5-ethyl-1-methyl-1,3,5-triazinan-2-ylidene)nitramide (compound **3b**) are the major products of the Mannich reaction of **1**, in which compound **2** is one of the most important intermediates in synthetic pesticides. In many reports, the major catalysts used for the transformation were acids, for example hydrochloric acid, trifluoroacetic acid, glacial acetic acid, and formic acid, which have been studied by Maienfisch et al.,[7–9] Gobel et al.,[10] Fan et al.,[11] Kang et al.,[12] Zhou et al.,[13] Tao et al.,[14]



Scheme 1. Mannich reaction general formula.



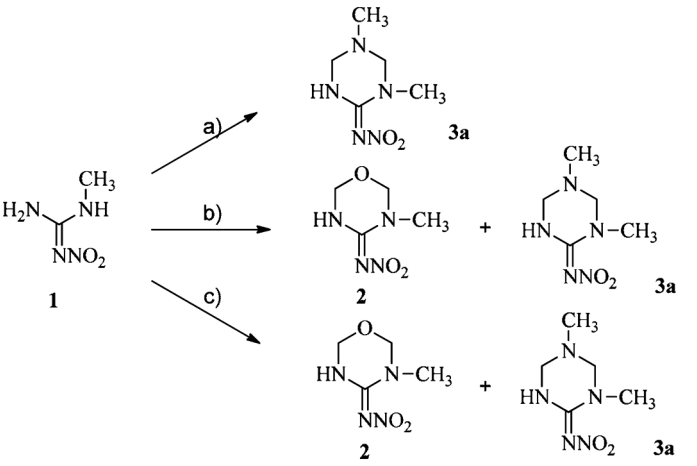
Scheme 2. Mannich reaction of N-methyl-N′-nitroguanidine in organic and inorganic bases.

Yang et al.,[15] and Metelkina.[16] They also discovered that the reaction catalyzed by formic acid gave the most satisfactory results. The reaction of N-methyl-N′-nitroguanidine (compound **1**) and formaldehyde in amine solution was mentioned by Maienfisch et al.[17]

However, these data were not reported by our labratory. Potassium carbonate (K_2CO_3), sodium bicarbonate ($NaHCO_3$), and sodium hydroxide (NaOH) have not been employed as catalysts for the Mannich reaction of **1**. In this communication, we report the synthesis of **2** using the three inorganic basic catalysts mentioned previously for the first time and the synthesis of **3** in methylamine, ethamine, *iso*propylamine, and *n*-butylamine aqueous solution. We also explored the formation of products at the different reaction temperatures and times under the inorganic base catalyst conditions.

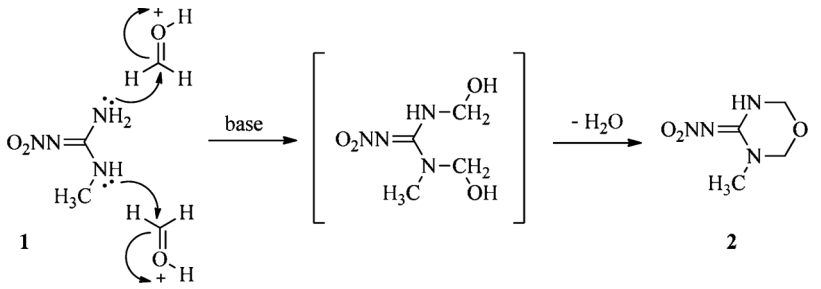
RESULTS AND DISCUSSION

Product of reaction of **1** with formaldehyde is different when using different catalysts. For example, when using NaOH, only compound **3a** was detected, but both compound **2** and compound **3a** were formed when $NaHCO_3$ and K_2CO_3 were used (Scheme 3). This phenomenon may due to the intensity of base catalysts. When the inorganic bases were not added to the reaction mixture, compounds **2** and **3a** were not detected. The appearance of **3a** after the inorganic bases were added to the reaction mixtures may be result from the decomposition of **1** in the alkali conditions, especially in the high-intensity alkali conditions. The synthesis of **2** may be more suitable in an appropriate alkali condition, and the detailed mechanism is shown in Scheme 4.



a) 1 eq. NaOH, 2 eq. HCHO, H_2O, 60°C
b) 1 eq. $NaHCO_3$, 2 eq. HCHO, H_2O, 60°C
c) 0.5 eq. K_2CO_3, 2 eq. HCHO, H_2O, 60°C

Scheme 3. Reaction of N-methyl-N′-nitroguanidine in different catalysts under 60 °C condition.



Scheme 4. Mechanism of compound **2** from N-methyl-N′-nitroguanidine.

The reaction of **1** and formaldehyde in organic base aqueous solutions such as methylamine, ethamine, *iso*propylamine, and *n*-butylamine also gave good yields with high purities.

The reaction conditions, results, and the yields of compounds **2** and **3** are given in Tables 1 and 2. In the inorganic base reaction, product was transformed into compound **3a** from the mixtures of **2** and **3a** when the reaction time was kept for 8 h, and the temperature was increased gradually from 40 to 90 °C. This phenomena was also observed when the reaction temperature was kept at 60 °C but the reaction times were changed from 2 to 12 h. The yields of compounds **2** and **3** under the conditions described above are shown in Table 3. When HCl, HCOOH, CH_3COOH, and F_3CCOOH and were employed in our work, no title compound was detected.

The three-component Mannich reaction mechanism[18,19] is given in Schemes 5 and 6.

Through the three-component Mannich reaction mechanism, both acid and alkaline catalysts can be used to promote reactions, and both formed enolase transition states (Schemes 5 and 6). In the two-component (**1** and formaldehyde) Mannich reaction process, no enolate transition-state compound was found. No title compound was detected in our laboratory when the acidic catalysts formic acid, acetic acid, hydrochloric acid, and trifluoroacetate were added to the mixtures (pH 1–5), reacted for several hours at 90 °C, and neutralized with 10% sodium hydroxide solution to pH 6–7. The results were different from the literature reports.[7–16] Otherwise, when alkaline catalyst instead of acidic catalyst was added, the reaction

Table 1. Final compound affected by different temperature under the catalyst conditions (reaction time 8 h)

Entry	Temperature (°C)	$NaHCO_3$	NaOH	K_2CO_3
1	40	**3a** + **2**[a]	**3a**[b]	**3a** + **2**
2	50	**3a** + **2**	**3a**	**3a** + **2**
3	60	**3a** + **2**	**3a**	**3a** + **2**
4	70	**3a** + **2**	**3a**	**3a** + **2**
5	80	**3a**	**3a**	**3a**
6	90	**3a**	**3a**	**3a**

[a]Both compounds **3a** and **2** were detected.
[b]Only compound **3a** was detected.

Table 2. Final compound affected by different reaction times under the catalyst conditions (temperature 60 °C)

Entry	Reaction time	$NaHCO_3$	NaOH	K_2CO_3
1	2 h	**3a** + **2**[a]	**3a**[b]	**3a** + **2**
2	4 h	**3a** + **2**	**3a**	**3a** + **2**
3	6 h	**3a** + **2**	**3a**	**3a** + **2**
4	8 h	**3a** + **2**	**3a**	**3a** + **2**
5	10 h	**3a** + **2**	**3a**	**3a** + **2**
6	12 h	**3a**	**3a**	**3a**
7	15 h	**3a**	**3a**	**3a**
8	20 h	**3a**	**3a**	**3a**

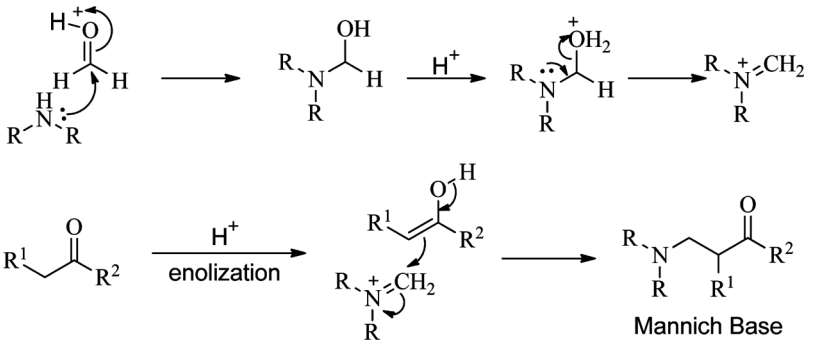
[a]Both compounds **3a** and **2** were detected.
[b]Only compound **3a** was detected.

Table 3. Yields of title compounds

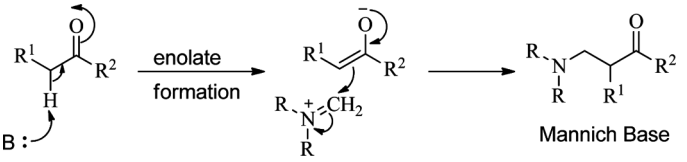
Entry	Base	Reaction time (h)	Reaction temperature (°C)	Yield (%)
1	$NaHCO_3$	6	60	33.7,[a] 37.8[b]
2	NaOH	6	60	53.2[a]
3	K_2CO_3	6	60	48.3,[a] 29.7[b]
4	CH_3NH_2	5	60	92.7[c]
5	$C_2H_5NH_2$	5	60	89.6[c]
6	$(CH_3)_2CH_2NH_2$	5	60	91.5[c]
7	n-$C_4H_9NH_2$	5	60	87.3[c]

[a]Yield of isolated compound **3a**.
[b]Yield of isolated compound **2**.
[c]Yield of isolated compound **3**.

proceed well. Meanwhile, the change of the products was also explored under the conditions shown in Tables 1 and 2. The compound **2** disappeared as temperature increased from 40 °C to 90 °C gradually and reaction time prolonged from 2 h to 20 h. Therefore, during the two-component (**1** and formaldehyde) Mannich reaction, the activity of H of compound **1** was decreased under acidic conditions and increased



Scheme 5. Mannich reaction under acidic conditions.



Scheme 6. Mannich reaction under basic conditions.

under basic conditions, which makes it difficult to react in acidic solution and easy to react in basic solution.

CONCLUSION

In conclusion, this work demonstrates a method for synthesizing **2, 3a, 3b, 3c**, and **3d** under basic conditions. The Mannich reaction of **1** and formaldehyde solution (or paraformaldehyde) can be catalyzed by alkaline catalyst but not acidic catalyst. Both organic and inorganic bases worked well in this reaction, but organic bases are better. The intensity of inorganic alkali, reaction time, and reaction temperature have great effects on the final products; high temperatures or long reaction times will cause compound **2** to be hydrolyzed.

EXPERIMENTAL

All purchased starting materials and reagents were used without further purification. ^{1}H NMR spectra were recorded on a DRX-300 FT-NMR Bruker instrument. Chemical shifts are expressed in parts per million (ppm, δ). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br s (broad singlet). Mass spectra (MS, electrospray ionization positive) were recorded on an Apex IV FTMS Bruker instrument. Infrared (IR) spectra were recorded on a Nicolet 6700 FT-IR Thermo instrument. Ultraviolet (UV) spectra were recorded on an UV-1800 Shimadzu spectrophotometer.

Preparation of N-Methyl-n′-nitroguanidine (Compound 1)[20,21]

Nitroguanidine (40.2 g, 0.39 mol) was dissolved in water (50 ml) at 60 °C, and then methylamine aqueous solution (58.1 g, 0.47 mol, 25% in water) was added to the solution over 30 min. The evolution of ammonia was observed, and the solutiion was stirred for 20 min. At the end of this time, during which the reaction mixture was stirred continuously, the clear solution was cooled in an ice-water bath to 4 °C. The white precipitation was filtered off, washed with cold water to neutral, and dried in the vacuum oven at 60 °C for 3 h to afford 38.6 g.

Data for Compound 1

N-Methyl-N′-nitroguanidine (1). Yield 84.6%; white solid; mp 155–156 °C.[22] MS m/z 118.1; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.75 (d, $J = 6$ Hz, 3H,

CH_3), 7.82 (br s, 2H, NH_2), 8.57 (br s, 1H, NH); IR 3418.20, 3252.28, 3112.44, 1642.68, 1605.35, 1294.01, 1142.08, 594.93 cm^{-1}; UV 267.80 nm.

Preparation of 3-Methyl-4-nitroimino-tetrahydro-1,3,5-oxadiazine (Compound 2)

A mixture of N-methyl-N′-nitroguanidine (4.58 g, 0.039 mol) and sodium hydrogen carbonate (3.28 g, 0.039 mol) in 50 ml of water was stirred at 60 °C. After N-methyl-N′-nitroguanidine was dissolved, formaldehyde aqueous solution (7.27 g, 0.09 mol, 37% in water) was added. The mixture was stirred for 4–6 h at 60 °C. After this period, the reaction was extracted with dichloromethane, and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated followed by column chromatography (eluted with dichloromethane–acetonitrile 5:2) to afford 2.35 g, dried in the vacuum oven at 60 °C for 3 h.

Data for compound 2. Yield 37.8%; white solid; mp 143–144 °C; MS m/z 161.06650 (M + H), 183.04850 (M + Na), 199.02246 (M + K); ^{1}H NMR[22] (300 MHz, $CDCl_3$) δ 3.03 (s, 3H, CH_3), 4.87 (s, 2H, CH_2), 5.01 (d, $J = 3$ Hz, 2H, CH_2), 9.70 (br s, 1H, NH); IR 3314.36, 2942.94, 2890.16, 1600.76, 1544.51, 1300.80, 940.14, 625.21, 602.79 cm^{-1}; UV 273.4 nm.

Preparation of N-(5-Ethyl-1-methyl-1,3,5-triazinan-2-ylidene)nitramide (Compound 3b)

N-Methyl-N′-nitroguanidine (2.0 g, 0.017 mol) was dissolved in water (8 ml) at 60 °C, and then formaldehyde aqueous solution (3.16 g, 0.039 mol, 37% in water) and ethamine aqueous solution (1.25 g, 0.018 mol, 65% in water) were added to the solution over 10 min. The mixture was stirred for 5 h at 60 °C. After this period, the reaction was extracted with dichloromethane, and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated to afford 2.84 g, which were dried in the vacuum oven at 30 °C for 3 h.

The compounds **3a, 3c**, and **3d** were synthesized according to the method of **3b**.

Data for Compounds 3a–3d

N-(1,5-Dimethyl-1,3,5-triazinan-2-ylidene)nitramide (compound 3a)[23–25]. Yield 92.7%; white solid; mp 127–128 °C; MS m/z 174.09822 (M + H), 196.08013 (M + Na), 212.05409 (M + K); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.62 (s, 3H, CH_3), 3.03 (s, 3H, CH_3), 4.25 (s, 2H, CH_2), 4.35 (s, 2H, CH_2), 9.51 (br s, 1H, NH); IR 3421.61, 3318.27, 3291.97, 2932.96, 1597.36, 1540.69, 1380.57, 996.52, 626.87 cm^{-1}; UV 273.8 nm.

N-(5-Ethyl-1-methyl-1,3,5-triazinan-2-ylidene)nitramide (compound 3b)[26]. Yield 89.6%; white solid; mp 105–106 °C; MS m/z 188.11383 (M + H), 210.09579 (M + Na), 226.06973 (M + K); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (t, $J = 3$ Hz, 3H, CH_3), 2.73 (q, $J = 9$ Hz, 2H, CH_2), 2.94 (s, 3H, CH_3), 4.25 (s, 2H, CH_2), 4.35 (s, 2H, CH_2), 9.36 (br s, 1H, NH); IR 3318.02, 2967.68, 2935.46, 2875.62, 1599.91, 1540.73, 1361.59, 995.49, and 634.35 cm^{-1}; UV 274.4 nm.

N-(5-*Iso*-propyl-1-methyl-1,3,5-triazinan-2-ylidene)nitramide (compound 3c)[27]. Yield 91.5%; white solid; mp 152–153 °C; MS m/z 202.12959 (M + H), 224.11147 (M + Na), 240.08532 (M + K); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, $J = 6$ Hz, 6H, CH_3, CH_3), 3.02 (s, 3H, CH_3), 3.07–3.16 (m, H, CH), 4.38 (s, 2H, CH_2), 4.48 (d, $J = 1.2$ Hz, 2H, CH_2), 9.45 (br s, 1H, NH); IR 3341.29, 2980.33, 2927.98, 2878.12, 2843.21, 1604.43, 1552.59, 1378.08, 1336.27, 1176.15, 1049.45, and 641.83 cm^{-1}; UV 274.3 nm.

N-(5-Butyl-1-methyl-1,3,5-triazinan-2-ylidene)nitramide (compound 3d). Yield 87.3%; yellow thick liquid; MS m/z 216.14522 (M + H), 238.12707 (M + Na), 254.10109 (M + K); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, $J = 6$ Hz, 3H, CH_3), 1.34–1.45 (m, 2H, CH_2), 1.46–1.54 (m, 2H, CH_2), 2.73 (t, $J = 7$ Hz, 2H, CH_2), 3.01 (s, 3H, CH_3), 4.29 (s, 2H, CH_2), 4.38 (d, $J = 1.2$ Hz, 2H, CH_2), 9.45 (br s, 1H, NH); IR 3332.38, 2963.56, 2924.17, 2880.61, 2861.34, 2830.75, 1601.01, 1554.19, 1378.90, 1331.46, 1190.30, 629.36 cm^{-1}; UV 274.6 nm.

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