3-Methyl-5-nitropyrimidin-4(3H)-one: an excellent precursor for functionalized nitroenamines

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Abstract
The reaction of 3-methyl-5-nitropyrimidin-4(3H)-one (1) with aliphatic and aromatic primary amines effectively afforded nitroenamines 4 having a carbamoyl group. When 1,2-diaminobenzenes were used, benzimidazoles 10 were obtained besides 4. Synthetic utility of the functionalized nitroenamines was also demonstrated in the conversion of nitroenamine 4b to polysubstituted pyridone 12.

Keywords: Nitroenamines, 3-methyl-5-nitropyrimidin-4(3H)-one, benzimidazoles

Introduction

Highly electron-deficient 3-methyl-5-nitropyrimidin-4(3H)-one (1) has multifunctionality, such as nitroalkene, α,β-unsaturated amide, amidine and so on. Pyrimidinone 1 has been proved1−4 to be good synthetic equivalents of polyfunctionalized units for construction of azaheterocycles (Scheme 1).
Scheme 1

The C2-N1-C6 moiety of 1 behaved as the activated diformylamine accompanied with elimination of anionic N-methylacetamide. 3,5-Difunctionalized 4-pyridones 2 were obtained by the reaction of pyrimidinone 1 with enolate ions of 1,3-dicarbonyl compounds. Treatment of 1 with ketones in the presence of ammonia also proceeded to give 4,5-disubstituted pyrimidines 3. The yields of 3 were, however, low due to ammonolysis of 1 leading to nitroenamine 4a. Use of ammonium acetate instead of ammonia as the nitrogen source overcame this disadvantage. Pyrimidines 3 were obtained in considerably improved yields under milder conditions. In addition, 5,6-disubstituted 3-nitro-2-pyridones 5 were also produced by the alternative ring transformation of 1. In this case, the C4-C5-C6 moiety of pyrimidinone 1 acted as the equivalent of α-nitroformylacetic acid.

Meanwhile, carbamoylnitroenamine 4(see table) is an interesting as similar pattern were observed (the ratio of integrals was 73 : 23 : 2 : 2). Each structure had two broad signals in the lower field. These signals were slowly diminished in 24 h with addition of D2O. On the basis of 1H-1H COSY 2D NMR, one broad signal was related to the N-methyl group, and the other was related to both the N-methylene group and the doublet at 8.67 ppm. This olefinic proton had a large coupling constant (14.1 Hz) which was characteristic to the nitroenamine skeleton. Among six kinds of configuration and/or conformation bearing the intramolecular hydrogen bond(s) I-VI (Figure 1), I, III, IV and VI were plausible.
Reaction of 1 with sterically hindered tert-butylamine afforded nitroenamine 4c in a good yield. Treatment of 1 with aqueous ammonia solution lead to 4a. Reaction of aromatic amines with 1 gave corresponding nitroenamines 4d–f. Aminolysis of pyrimidinone 1 proceeded even at room temperature though long reaction time was required. When 1.1 equimolar of amine was used, the yield of the nitroenamine was considerably lowered. This result indicated that more than two molecules of amines were necessary to decompose 1. o-Methylaniline revealed reduced reactivity compared with p-methyl derivative, and quantitative recovery of 1 was observed in the case of less nucleophilic p-nitroaniline (Table).

Table 1

<table>
<thead>
<tr>
<th>R</th>
<th>Temp. °C</th>
<th>Product</th>
<th>Yield %</th>
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<tr>
<td>Pr</td>
<td>65</td>
<td>4b</td>
<td>94</td>
</tr>
<tr>
<td>t-Bu</td>
<td></td>
<td>4c</td>
<td>85</td>
</tr>
<tr>
<td>H</td>
<td></td>
<td>4a</td>
<td>55b)</td>
</tr>
<tr>
<td>p-Me-C₆H₄</td>
<td></td>
<td>4d</td>
<td>86</td>
</tr>
<tr>
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<td>rt</td>
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<td>26</td>
</tr>
<tr>
<td>p-Me-C₆H₄</td>
<td>65</td>
<td></td>
<td>30b)</td>
</tr>
<tr>
<td>p-Me-O-C₆H₄</td>
<td></td>
<td>4e</td>
<td>37c)</td>
</tr>
<tr>
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<tr>
<td>p-Me-O-C₆H₄</td>
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</table>

a) 25% NH₃ aq. was used. b) 1.1 mmol of amines were used.

c) 5.5 mmol of amines were used.
A plausible mechanism of the present aminolysis is illustrated in Scheme 3. The aminolysis of 1 is initiated with nucleophilic attack of amine at the 6-position, and the cleavage of the N1–C6 bond successively occurred. Deprotonation at the 6- or the 2-positions is considered not to occur since no product was detected on treatment of 1 with triethylamine under same conditions. The methanimidoyl group is eliminated as the amidine to yield nitroenamine 4 when intermediate 8 is attacked by a second molecule of the amine.

**Scheme 3**

Reactions of pyrimidinone 1 with diamines showed somewhat different reactivity. White precipitates were formed during the reactions using aliphatic diamines such as 1,2-diaminoethane or 1,3-diaminopropane. As there was no solvent dissolving these white solids, the structures have not been determined yet. In the reaction of isomeric pyrimidinone 6 with diamines, we isolated macrocycles which were formed by dimerization of aminolysis products. In consideration with this fact, there is possibility of these products to have similar large rings like 9 (Figure 2).

**Figure 2**

On the contrary, nitroenamine 4h was obtained in the reaction of 1 with 1,2-diaminobenzene (Scheme 4). Benzimidazole 10h was also obtained in addition to 4h; it is obvious that pyrimidinone 1 behaved as the transferring agent of a C1 unit to dianimobenzene. Since isolated 4h was not converted to 10h under the same conditions employed for aminolysis, benzimidazole 10h may be formed by the competitive intramolecular cyclization of the intermediate 8. 5,6-Dimethyl benzimidazole 10i and corresponding nitroenamine 4i were similarly prepared from 1,2-diamino-4,5-dimethylbenzene.
Reactions of pyrimidinone 1 with aromatic and aliphatic secondary amines were also studied. N-Methylaniline gave no positive result, and 1 was totally recovered. In the case of dipropylamine, unexpected products 4a and 4j (R = Me) were obtained in 38 and 28% yields instead of dipropylamino derivative 11 (Figure 3). It seems that the nitroenamine 4j is derived from the reaction of 1 with methylamine generated by the decomposition of 1. If this is true, the yield of 4j is 56% based on 1. However, we have not found plain explanation for the isolation of 4j. On the other hand, it is considered that the amino derivative 4a is produced under the mechanism shown in Scheme 5. Sterically hindered secondary amine attacks the less crowded 2-position of 1 to give adduct 12. The fission of N1–C2 bond and following methanolysis give nitroenamine 4a.

Scheme 4

<table>
<thead>
<tr>
<th>R</th>
<th>Yield %</th>
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<tbody>
<tr>
<td>H</td>
<td>30</td>
</tr>
<tr>
<td>Me</td>
<td>31</td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
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</table>

Figure 3

Scheme 5
As described above, nitropyrimidinone 1 was shown to be an excellent precursor of functionalized nitroenamines 4. In the present reaction, modification of amino group is readily achieved by choosing required amine. Obtained nitroenamines 4 are useful synthetic intermediates for polyfunctionalized compounds. As one application to organic syntheses, conversion of 4b to polyfunctionalized pyridone 13 was studied. Treatment of nitroenamine 4b with enolate ion of ethyl 3-oxobutanoate afforded 5-ethoxycarbonyl-1,6-dimethyl-3-nitropyridin-2(1H)-one (13). Pyridone 13 was formed by a series of Michael addition of the enolate ion to the electrophilic site of 4b, elimination of propylamine and intramolecular attack of the carbamoyl anion to the acetyl group (Scheme 6). Investigations of other chemical transformations of nitroenamine 4 are in progress, and the results will be reported in due course.

Scheme 6

Experimental Section

General Procedures. 3-Methyl-5-nitropyrimidin-4(3H)-one 1: Pyrimidinone 1 was obtained from 2-thiouracil by reduction, methylation, and nitration with fuming HNO₃ in 18 M H₂SO₄ at 100 °C for 7 h in 43% overall yield.

Synthesis of nitroenamines 4. To a solution of pyrimidinone 1 (155 mg, 1.0 mmol) in methanol (20 mL), propylamine (205 µL, 2.5 mmol) was added, and the mixture was heated under reflux for 3 h. After removal of methanol, the residue was extracted with hot hexane (30 mL x 3). The extract was concentrated to afford almost pure nitroenamine 4b (176 mg, 0.94 mmol, 94% yield). Further purification was performed by recrystallization from hexane. Reactions of 1 with other primary amines except for ammonia were similarly conducted.

N-Methyl-2-nitro-3-(propylamino)propenamide (4b). Colorless needles; mp 82–84 °C; IR (Nujol) 3341, 1654, 1529 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, TMS). The largest amount of product (Product A): δ 1.00 (t, J = 7.4 Hz, 3H), 1.65–1.75 (m, 2H), 2.92 (d, J = 4.9 Hz, 3H), 3.42 (dt, J = 6.7, 6.7 Hz), 8.67 (d, J = 14.1 Hz, 1H), 8.7–8.9 (br, 1H, exchangeable with D₂O, NHMe), 10.6–11.1 (br, 1H, exchangeable with D₂O, =CHNHPr). The second largest amount of product: δ 1.01 (t, J = 7.3 Hz, 3H), 1.7–1.8 (m, 2H), 2.95 (d, J = 4.7 Hz, 2H), 3.53 (dt, J = 6.7, 6.7 Hz), 8.54 (d, J = 15.2 Hz, 1H), 8.6–8.8 (br, 1H, exchangeable with D₂O, NHMe), 9.8–10.1 (br, 1H, exchangeable with D₂O, =CHNHPr). In addition, two sets of signals having a similar pattern and
chemical shifts were observed, however, they were too small to be wholly analyzed.; $^{13}$C NMR (100 MHz, CDCl$_3$, TMS) Product A: $\delta$ 165.1, 157.4, 117.2, 52.4, 25.6, 23.6, 11.0: Product B; 161.7, 154.6, 52.6, 26.4, 23.6, 10.9 (one signal was hidden by noise). Anal. Calcd. for C$_7$H$_{13}$N$_3$O$_3$: C, 44.91; H, 7.00; N, 22.45%. Found: C, 45.12; H, 7.16; N, 21.99%.

3-t-Butylamino-N-methyl-2-nitropropenamide (4c). Colorless granules; mp 62–63 °C; IR (Nujol) 1659, 1641, 1520, 1338 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, TMS) All signals of each four products A–D were obviously recognized except for the combined broad NH signal at $\delta$ 8.7–9.0. The ratio of A–D was 63 : 17 : 11 : 9. Product A $\delta$ 1.42 (s, 9H), 2.92 (d, $J$ = 4.8 Hz, 3H), 8.77 (d, $J$ = 14.6 Hz, 1H), 8.7–9.0 (br), 11.0–11.4 (br, 1H): Product B $\delta$ 1.47 (s, 9H), 2.95 (d, $J$ = 4.5 Hz, 3H), 8.66 (d, $J$ = 15.1 Hz, 1H), 8.7–9.0 (br), 10.1–10.4 (br, 1H): Product C $\delta$ 1.43 (s, 9H), 2.96 (d, $J$ value could not be measured, 3H), 8.77 (d, $J$ = 15.7 Hz, 1H), 8.7–9.0 (br), 9.8–10.1 (br, 1H): Product D $\delta$ 1.45 (s, 9H), 2.87 (d, $J$ = 4.7 Hz, 3H), 8.18 (d, $J$ = 15.3 Hz, 1H), 8.7–9.0 (br), 9.5–9.7 (br, 1H). Anal. Calcd. for C$_8$H$_{15}$N$_3$O$_3$: C, 47.75; H, 7.51; N, 20.88%. Found: C, 47.13; H, 7.50; N, 20.74%.

N-Methyl-3-(4-methylphenyl)amino-2-nitropropenamide (4d). Yellow needles; mp 118–125 °C (dec.); IR (Nujol) 1627, 1601, 1537, 1516 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, TMS) Data of the largest amount of product are shown. $\delta$ 2.37 (s, 3H), 2.98 (d, $J$ = 4.8 Hz, 3H), 7.17 (d, $J$ = 6.9 Hz, 2H), 7.21 (d, $J$ = 6.9 Hz, 2H), 8.75–8.9 (br, 1H), 9.13 (d, $J$ = 13.7 Hz, 1H), 12.4–12.7 (br, 1H, two maxima were observed). Anal. Calcd. for C$_{11}$H$_{13}$N$_3$O$_3$: C, 56.16; H, 5.57; N, 17.86%. Found: C, 56.35; H, 5.70; N, 17.79%.

N-Methyl-3-(2-methylphenyl)amino-2-nitropropenamide (4e). Yellow needles; mp 154–159 °C (dec.); IR (Nujol) 3379, 1626, 1539 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, TMS) Data of the largest amount of product were shown. $\delta$ 2.43 (s, 3H), 3.00 (d, $J$ = 4.9 Hz, 3H), 7.0–7.4 (m, 4H), 8.75–8.9 (br, 1H), 9.16 (d, $J$ = 13.3 Hz, 1H), 12.7–12.9 (br, 1H, two maxima were observed). Anal. Calcd. for C$_{11}$H$_{13}$N$_3$O$_3$: C, 56.16; H, 5.57; N, 17.86%. Found: C, 55.78; H, 5.61; N, 17.74%.

3-(4-Methoxyphenyl)amino-N-methyl-2-nitropropenamide (4f). Yellow needles; mp 120–124 °C (dec.); IR (Nujol) 3390, 1628, 1601, 1541 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, TMS) Data of the largest amount of product were shown. $\delta$ 2.98 (d, $J$ = 4.5 Hz, 3H), 3.83 (s, 3H), 6.95 (d, $J$ = 8.9 Hz, 2H), 7.19 (d, $J$ = 8.9 Hz, 2H), 8.75–8.9 (br, 1H), 9.03 (d, $J$ = 13.7 Hz, 1H), 12.5–12.8 (br, 1H). Anal. Calcd. for C$_{11}$H$_{13}$N$_3$O$_4$: C, 52.59; H, 5.22; N, 16.73%. Found: C, 52.38; H, 5.09; N, 16.80%.

Ammonolysis of pyrimidinone 1. To a solution of pyrimidinone 1 (155 mg, 1.0 mmol) in methanol (20 mL), 25% aqueous ammonia (170 µL, 2.5 mmol) was added, and the mixture was heated under reflux for 3 h. After removal of methanol, the residue was washed with CHCl$_3$ (30 mL) to afford almost pure nitroenamine 4a (80 mg, 0.55 mmol, 55% yield). Further purification was performed by recrystallization from ethanol.

3-Amino-N-methyl-2-nitropropenamide (4a). Orange needles; mp 179–182 °C; IR (Nujol) 3384, 3287, 1509 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$, TMS) $\delta$ 2.75 (d, $J$ = 4.5 Hz, 3H),
Reactions of pyrimidinone 1 with aromatic diamines. To a solution of pyrimidinone 1 (155 mg, 1.0 mmol) in methanol (20 mL), 1,2-diaminobenzene (119 mg, 1.1 mmol) was added, and the mixture was heated under reflux for 3 h. After removal of methanol, the residue was recrystallized from methanol to give nitroenamine 4h (73 mg, 0.31 mmol, 31% yield). The mother liquor was concentrated, and the residue was column chromatographed on silica gel yielding benzimidazole (25 mg, 0.21 mmol, eluted with ethyl acetate/ethanol = 2/1). Reactions of 1 with 1,2-diamino-4,5-dimethylbenzene was similarly conducted. Structures of benzimidazoles 10h and 10i were confirmed by comparing physical and spectral data with commercially available authentic samples.

3-(2-Aminophenyl)amino-N-methyl-2-nitropropenamide (4h). Orange needles; mp 150–151 °C; IR (Nujol) 3361, 1626, 1603, 1277 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆, TMS) Data of the largest amount of product were shown. δ 2.78 (d, J = 4.4 Hz, 3H), 5.08 (br.s, 2H), 6.67 (dd, J = 7.8, 7.8 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 6.99 (dd, J = 7.8, 7.8 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 8.75–8.85 (br, 1H, a shoulder was observed), 8.96 (d, J = 13.5 Hz, 1H), 12.34 (br.d, J = 13.5 Hz, 1H). Anal. Calcd. for C₁₀H₁₂N₄O₃: C, 50.84; H, 5.12; N, 23.72%. Found: C, 50.90; H, 5.15; N, 23.73%.

3-(2-Amino-4,5-dimethylphenyl)amino-N-methyl-2-nitropropenamide (4i). Orange needles; mp 215–217 °C; IR (Nujol) 3383, 3327, 3250, 1628, 1541, 1290 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆, TMS) Data of the largest amount of product were shown. δ 2.23 (s, 3H), 2.24 (s, 3H), 2.94 (d, J = 4.4 Hz, 3H), 4.97 (br.s, 2H), 6.79 (s, 1H), 7.28 (s, 1H), 8.95–9.05 (br, 1H, The top of the signal was slightly splitting), 9.08 (d, J = 13.4 Hz, 1H), 12.53 (br.d, J = 13.4 Hz, 1H). Anal. Calcd. for C₁₂H₁₆N₄O₃: C, 54.54; H, 6.10; N, 21.20%. Found: C, 54.70; H, 6.09; N, 21.17%.

Reactions of pyrimidinone 1 with dipropylamine. To a solution of pyrimidinone 1 (155 mg, 1.0 mmol) in methanol (20 mL), dipropylamine (343 µL, 2.5 mmol) was added, and the mixture was heated under reflux for 3 h. After removal of methanol, the residue was extracted with hot hexane (30 mL x 3). The extract was concentrated to afford almost pure nitroenamine 4j (45 mg, 0.28 mmol, 28% yield). The residue was washed with CHCl₃ (30 mL) to furnish nitroenamine 4a (55 mg, 0.38 mmol, 38% yield). Further purification was performed by recrystallization from ethanol.

N-Methyl-3-methylamino-2-nitropropenamide (4j). Pale yellow needles; mp 177–179 °C; IR (Nujol) 3365, 3254, 1676, 1618, 1534 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, TMS) Signals of two products A and B could be assigned except for the combined broad NH signal at δ 8.65–8.85. The ratio of A and B was 78:22. Product A δ 2.92 (d, J = 4.9 Hz, 3H), 3.26 (d, J = 5.2 Hz, 3H), 8.66 (d, J = 14.1 Hz, 1H), 8.65-8.85 (br), 10.5–10.9 (br, 1H): Product B δ 2.95 (d, J = 4.8 Hz, 3H), 3.36 (d, J = 5.2 Hz, 3H), 8.54 (d, J = 15.2 Hz, 1H), 8.65–8.85 (br), 9.6–10.0 (br, 1H) Anal. Calcd. for C₅H₈N₃O₃: C, 37.72; H, 5.71; N, 26.41%. Found: C, 38.05; H, 5.69; N, 26.05%.
Reactions of nitroenamine 4b with enolate ion of ethyl 3-oxobutanoate. The sodium enolate was prepared from ethyl 3-oxobutanoate (0.64 mL, 5.0 mmol) and sodium ethoxide (5.0 mmol) in ethanol (20 mL). After removal of ethanol, the resultant enolate was dissolved in pyridine (20 mL). The solution was added to a solution of nitroenamine 4b (187 mg, 1.0 mmol) in pyridine (20 mL), and the mixture was heated at 80 °C for 3 h. 1M HCl (10 mL, 10 mmol) was added, and the mixture was extracted with CHCl3 (30 mL x 3). The organic layer was dried over MgSO4, and concentrated. The residue was column chromatographed on silica gel to afford pyridone 13 (137 mg, 0.57 mmol, 57% yield, eluent: CHCl3 / ethyl acetate = 3 / 1).

5-Ethoxycarbonyl-1,6-dimethyl-3-nitropyridin-2(1H)-one (13). Pale yellow powder; mp 99–100 °C; IR (Nujol) 1720, 1693, 1527, 1336 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆, TMS) δ 1.31 (t, J = 7.1 Hz, 3H), 2.84 (s, 3H), 3.61 (s, 3H), 4.28 (q, J = 7.1 Hz, 2H), 8.72 (s, 1H). Anal. Calcd. for C₁₀H₁₂N₂O₅: C, 50.00; H, 5.04; N, 11.66%. Found: C, 50.00; H, 4.99; N, 11.57%.

References