New Reactivity of Nitropyrimidinone: Ring Transformation and N-C Transfer Reactions

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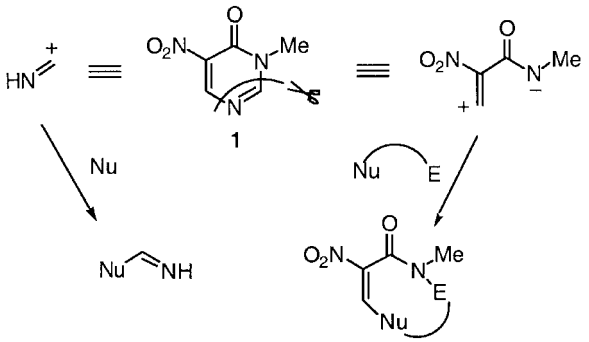
Abstract: Nitropyrimidinone **1** revealed new reactivity upon treatment with active methylene compounds **2** under basic conditions. The N1-C2-C3-C4 moiety of **1** combined with two carbon units of **2** affording polyfunctionalized pyridones **4**, which was hitherto unknown ring transformation. On the other hand, the N1-C2 moiety of **1** was transferred to the methylene group of **2** giving functionalized enamines **3**. It was also possible to modify the amino group in **3a** by reactions with primary amines. Enamines **3** reacted with hydrazines, and leading to functionalized pyrazoles **7** quantitatively. The ratios of regioisomeric pyrazoles **7**/**8** were moderately controlled by use of sterically hindered enamines **3h**, **3k** and **3l**. Furthermore, enamine **3a** was readily converted to 1,4-diazepines **9** having a functional group at the 6-position.

Key words: diazepine, functionalized enamine, nitropyrimidinone, pyrazole, pyridone

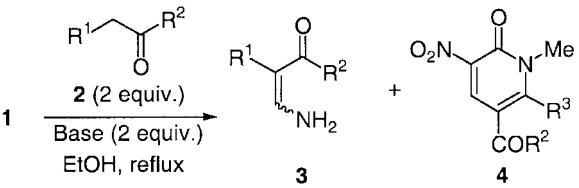
Easily available 3-methyl-5-nitropyrimidin-4(3*H*)-one (**1**)[1] has been shown as an excellent precursor for various kinds of polyfunctionalized heterocyclic compounds. Pyrimidinone **1** behaves as the synthetic equivalent of activated diformylamine when the ring transformation occurs at the 2- and the 6-positions of **1** accompanied by elimination of the N3-C4-C5 moiety as nitroacetamide. Pyrimidinone **1** actually reacted with bidentate nucleophiles to afford 4,5-disubstituted pyrimidines,[2] 3,5-difunctionalized 4-pyridones[3] and 4-aminopyridines.[4] Pyrimidinone **1** also acts as the synthetic equivalent of α-nitroformylacetic acid affording 5,6-disubstituted 3-nitro-2-pyridones[2a] as a result of the ring transformation occurring at the 4- and the 6-positions together with elimination of the N1-C2-N3 moiety (Scheme 1).



Scheme 1

Additionally, another reactivity of **1** is observed in the reaction with primary amines, and nitroenamines having a carbamoyl group are easily prepared.[5] In this reaction, the N3-C4-C5-C6 moiety is attached to amines with loss of the N1-C2 moiety. This result prompted us to develop two novel reactivity of nitropyrimidinone **1**. We considered that pyrimidinone **1** behaves as the reagent introducing an N-C unit when **1** is allowed to react with other nucleophiles than amines. Furthermore, pyrimidinone **1** is expected to be a synthetic equivalent of dipolar α-nitroacrylamide causing the ring transformation in the different mode from described above.

Table 1 Reactions of Pyrimidinone **1** with Active Methylene Compounds Leading to Enamines **3** and Polyfunctionalized Pyridones **4**



R^1	R^2	R^3		Yield (%) of **3**	Yield (%) of **4**
MeCO	OEt	Me	**a**[a]	70	0
			[b]	0	67
PhCO	OEt	Ph	**b**[a]	41	0
			[b]	0	84
MeCO	Me	Me	**c**[a]	38	0
			[b]	0	0
PhCO	Me	Ph	**d**[a]	12	0
			[b]	0	0
COOEt	OEt	OH	**e**[a]	41	78
			[b]	0	31
CN	OEt	NH_2	**f**[a]	47	70
			[b]	0	67

[a] Base: NaOEt, time: 4 h.
[b] Base: piperidine, time: 24 h.

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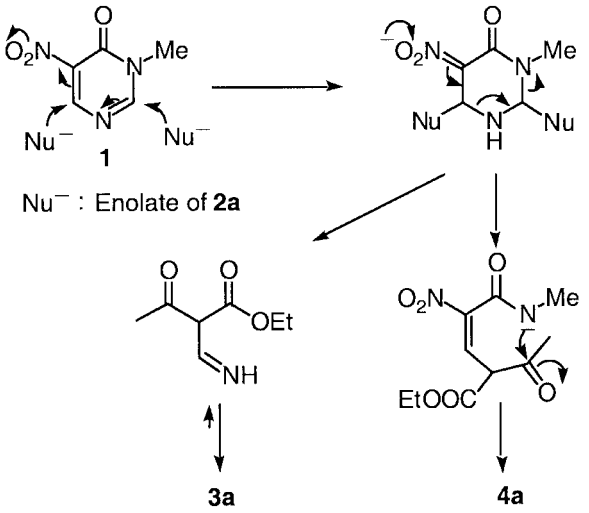
To a solution of pyrimidinone **1** (3 mmol) in ethanol (40 mL), were added a solution of ethyl 3-oxobutanoate (**2a**, 3 mmol) and sodium ethoxide (3 mmol) in ethanol (20 mL) under reflux over 1 hour, and the resultant mixture was heated at 80 °C for 4 hours. After quenching the reaction with 1 M hydrochloric acid, the solvent was removed under reduced pressure. The residue was treated with column chromatography on silica gel to afford functionalized enamine **3a** in 38% yield.[6] When two equivalents of sodium enolate were used, the yield of **3a** was improved to 70%. Pyrimidinone **1** similarly reacted with other active methylene compounds **2b**–**f** leading to corresponding enamines **3b**–**f** in moderate yields (Table 1). In cases of **2e** and **2f**, ring transformed products **4e** and **4f** were additionally isolated, however **4a**–**d** were not detected in reactions using **2a**–**d**. Since pyridones **4a**–**d** are electron-deficient as well as pyrimidinone **1**, further reactions such as ring transformation or decomposition might proceed under the present conditions. When less basic piperidine was employed instead of sodium ethoxide, it was achieved to isolate pyridones **4a** and **4b** derived from keto esters **2a** and **2b** (Scheme 2).[7,8]



Scheme 2 A plausible mechanism for the ring opening reaction of **1**

The present reaction is initiated with addition of the enolate at the 2- and the 6-positions of pyrimidinone **1**. The following ring opening reaction divides the pyrimidinone ring, and these two components furnished **3** and **4**, respectively. As another possibility, the ring opening reaction might occur after addition of first molecule of enolate at the 6-position, and the methaneimidoyl group on the nitrogen is eliminated by the attack of second enolate, which leads to same products **3** and **4**.

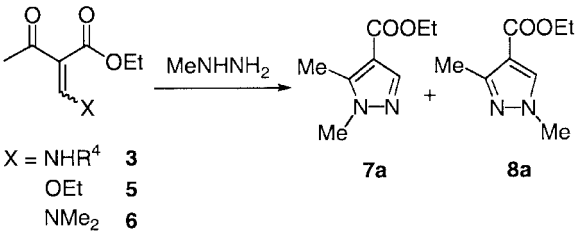
Modification on the amino group of enamine **3a** was easily performed. To a solution of **3a** in ethanol, propylamine was added, and the solution was stirred at room temperature for 1 day. The ^{1}H NMR of the reaction mixture after concentration showed signals for only modified enamine **3i**. Reactions of **3a** with aromatic amines readily proceeded to give corresponding enamines **3g** and **3h**. Sterically hindered alkyl groups such as *tert*-butyl and adamantyl groups could be also introduced though elevated temperature was necessary for effective conversion (Table 2).

Table 2 Modification of the Amino Group of Enamine **3a**

R^4		Temp (°C)	Yield (%)[a]	Recovery (%) of **3a**[a]
p-$MeOC_6H_4$	**3g**	r.t.	77	23
p-$MeOC_6H_4$		80	Quant. (86)[c]	0
p-$NO_2C_6H_4$	**3h**	120[b]	15	85
Pr	**3i**	r.t.	Quant. (87)[c]	0
t-Bu	**3j**	r.t.	85	15
t-Bu		80	Quant. (93)[c]	0
Adamantyl	**3k**	80	Quant. (70)[c]	0

[a] Determined by ^{1}H NMR.
[b] In a sealed tube.
[c] Isolated yield.

Since the aminomethylene group is regarded as a synthetic equivalent of a formyl group as well as ethoxymethylene and (dimethylamino)methylene groups, enamines **3** can be used for preparation of functionalized heterocyclic compounds by condensation with bidentate nucleophiles. When enol ether **5**[9] and enamine **6**[10] are allowed to react with methylhydrazine at 0 °C, both two regioisomeric pyrazoles **7a** and **8a** were produced in 90/10 and 77/23 ratios, respectively.[11] On the other hand, enamine **3a** (R^4 = H) afforded pyrazole **7a** exclusively even at room temperature due to less steric hindrance. As shown in Table 3, the increased bulkiness on the amino group showed one possibility to control the regioselectivity in the condensation of **3** with substituted hydrazines. The ratio of **8a** in the reaction mixture was improved up to 35% when enamine **3k** was employed (Scheme 3).



Scheme 3

Reactions of enamine **3a** with other hydrazines similarly underwent to furnish corresponding pyrazoles **7l**–**p** as a single regioisomer in high yields (Table 4).[12] Sterically hindered hydrazines besides aromatic and functionalized hydrazines were applicable to the present reaction. Enamines **3b** and **3d** were quantitatively converted to pyrazoles upon treatment with methylhydrazine at room temperature. In the case of **3d** derived from diketone, two

Table 3 Steric Effects on the Ratio of **7a**/**8a**[a]

Enamine	Temp (°C)	Total yield (%)[b]	Ratio of **7a**/**8a**[b]	Recovery (%) of **3**[b]
3a	r.t.	Quant.[c]	100:0	0
3g	r.t.	Quant.	87:13	0
3j	r.t.	25	70:30	75
	80	82	70:30	18
3k	80	35	65:35	65

[a] In EtOH, time: 24 h.
[b] Determined by ^{1}H NMR.
[c] Pyrazole **7a** was isolated in 98% yield.

Table 4 Reactions of **3a** with Substituted Hydrazines R^5NHNH_2

R^5	Temp (°C)	Yield (%) of **7**[a]		Recovery (%) of **3a**[a]
H	r.t.	Quant. (97)[b]	**l**	0
t-Bu	r.t.	37	**m**	63
t-Bu	80	Quant. (88)[b]		0
Ph	r.t.	78	**n**	22
Ph	80	Quant. (71)[b]		0
p-$NO_2C_6H_4$	80	80 (65)[b]	**o**	20
CH_2COOEt	r.t.	Quant. (45)[b]	**p**	0

[a] Determined by ^{1}H NMR.
[b] Isolated yield.

kinds of pyrazoles **7d** and **7d′** were obtained in a 1/1 ratio. Amino derivative **7f**[13] was also prepared from **3f** in 60% yield at room temperature, and in a quantitative yield at 80 °C (Figure 1).

Pyrazoles could be directly prepared from pyrimidinone **1** without isolation of intermediate enamines **3**. To an ethanol solution of the reaction mixture including enamine **3a**, methylhydrazine was added and the mixture was stirred at room temperature for 1 day. After removal of the solvent, pyrazole **7a** was obtained upon treatment of the residue by column chromatography (Scheme 4). The present method was especially effective for diketone **2c** since it was somewhat troublesome to isolate enamine **3c**.

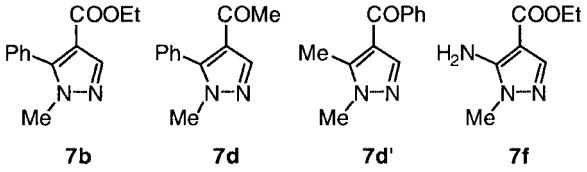
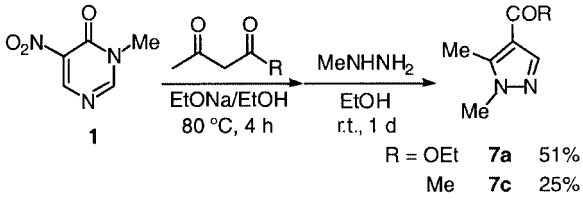
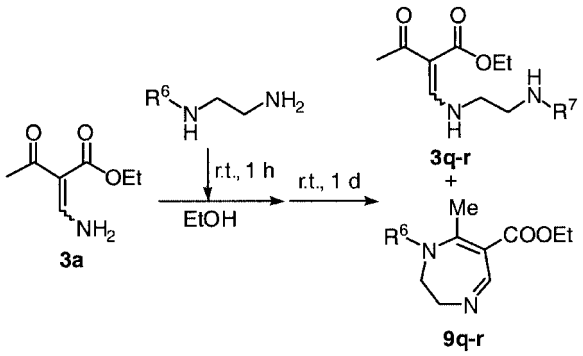


Figure 1



Scheme 4

Synthesis of 1,4-diazepine having an ethoxycarbonyl group was studied by using 1,2-diamines as bidentate nucleophiles. To a solution of enamine **3a** (1 mmol) in ethanol (20 mL), a solution of *N*-ethyl-1,2-diaminoethane (1.1 mmol) in ethanol (20 mL) was added at room temperature over 1 hour, and the mixture was stirred for 1 day (Method A, Table 5). Although consumption of **3a** was confirmed with TLC, residual product after evaporation was not diazepine **9q**. In the ^{1}H NMR a doublet having a large coupling constant was observed, which was characteristic feature for enamines substituted with an electron-withdrawing group at the β-position, thus the product was assigned as enamine **3q**.[14] Heating a solution of **3q** in ethanol under reflux for 3 days realized the ring closure to afford diazepine **9q**[15] in 80% yield (Scheme 5).



Scheme 5

Table 5 Reaction of Enamine **3a** with Diamine (Method A)

R^6	Solvent (mL)	R^7		Yield (%) of **3**[a]	Yield (%) of **9**[a]
Et	40	Et	**q**	Quant.	0
H	40	CH=CAcCOOEt	**r**	Quant.	0
H	200	CH=CAcCOOEt		49	51

[a] Determined by ^{1}H NMR.

In the case of unsubstituted diamine, double substitution exclusively proceeded to afford **3r**[16] under the same conditions. Dilution and slow addition of a diamine solution enabled the intramolecular cyclization giving diazepine **9r** in 51% yield. Furthermore, quantitative conversion from **3a** to **9r** was successful when a solution of **3a** was slowly added to a diamine solution under reflux (Method B, Table 6).

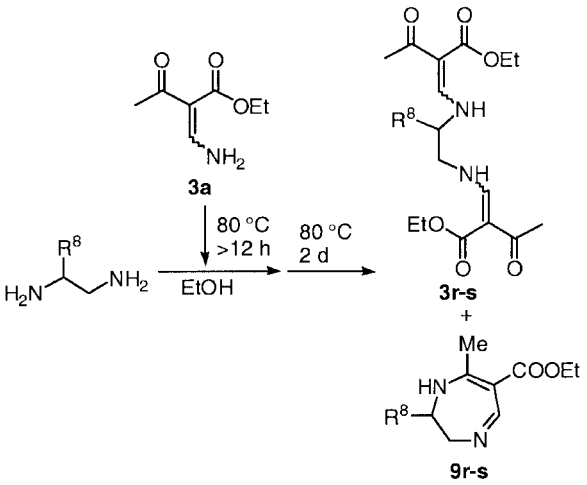
Table 6 Reaction of Enamine **3a** with Diamine (Method B)

R^8	Solvent (mL)		Yield (%) of **3**[a]	Yield (%) of **9**[a]
H	200	**r**	0	Quant.
Me	200	**s**	52	48
Me	1200		27	73

[a] Determined by ^{1}H NMR.

This reaction was highly sensitive to a steric factor, and 1,2-diaminopropane afforded double substituted enamine **3s** in a considerable yield due to the prevention of cyclization by a methyl group. Using a more diluted solution improved the yield of diazepine **9s** to 73%.

In summary, nitropyrimidinone **1** revealed new reactivity with cleavage of both N1-C6 and C2-N3 bonds. The N3-C4-C5-C6 moiety behaves as the synthetic equivalent of dipolar α-nitroacrylamide to cause new-type ring transformation, and the N1-C2 moiety is used for introducing agent of an aminomethylene group. When pyrimidinone **1** was treated with active methylene compounds under basic conditions, polyfunctionalized pyridones **4** and enamines **3** were readily prepared. The latter compounds were effectively converted to pyrazoles **7/8** and 1,4-diazepines **9** having a functional group (Scheme 6). All of the reactions required only simple experimental manipulations, and no by-product was formed in the ring construction reactions. Hence, these reactions will provide a new methodology for the preparation of functionalized heterocyclic compounds.



Scheme 6

References

(1) Pyrimidinone **1** is readily prepared from 2-thiouracil by reduction, methylation and nitration[2b] in 43% overall yield.

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(7) **Typical Procedure**: To a solution of pyrimidinone **1** (155 mg, 1 mmol), in EtOH (20 mL), were added **2a** (253 μL, 2.0 mmol) and piperidine (198 μL, 2.0 mmol), and the mixture was heated under reflux for 1 d. After removal of the solvent, the residue was extracted with benzene (20 mL × 3), and the extract was concentrated. The residual red oil was treated with column chromatography on silica gel to afford **4a**[5] (eluted with chloroform/EtOAc = 7:1, 162 mg, 0.67 mmol, 67%).

(8) Pyridone **4f**: Colorless needles (recrystallized from EtOH); mp 253–255 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.32 (t, *J* = 7.1 Hz, 3 H), 3.37 (s, 3 H), 4.29 (q, *J* = 7.1 Hz, 2 H), 8.72 (brs, 1 H), 8.84 (s, 1 H), 9.28 (brs, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.0 (q), 28.9 (q), 60.8 (t), 89.3 (s), 123.4 (s), 140.0 (d), 153.7 (s), 156.9 (s), 165.2 (s). Anal. Calcd for $C_9H_{11}N_2O_5$: C, 44.82; H, 4.60; N, 17.42. Found: C, 44.70; H, 4.50; N, 17.41.

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(12) Pyrazoles having an ethoxycarbonyl group are widely used for synthetic intermediates of agrochemicals such as insecticides, fungicides, herbicides and so on, see: (a) Kitajima, T.; Tomiya, K.; Kodaka, K. Jpn. Kokai Tokkyo Koho, JP 2000212166, **2000**; *Chem. Abstr*., **2000**, *133*, 120326. (b) Okimura, N.; Tanaka, T.; Fukuchi, T.; Okada, I. Jpn. Kokai Tokkyo Koho, JP 04021671, **1992**; *Chem. Abstr*., **1992**, *117*, 2830. (c) Ishii, T.; Kuwazuka, T.; Shimotori, H.; Tanaka, Y.; Ishikawa, K. Jpn. Kokai Tokkyo Koho, JP 01106866, **1989**; *Chem. Abstr*., **1989**, *111*, 194759. (d) The NOESY spectrum of **7o** showed correlation between the phenyl group and the methyl one that was derived from the acetyl group of **3a**.

(13) Kopp, M.; Lancelot, J.-C.; Dallemagne, P.; Rault, S. *J. Heterocycl. Chem.* **2001**, *38*, 1045.

(14) Enamine **3q**: Isolated yield 91%. Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer δ = 1.11 (t, *J* = 7.2 Hz, 3 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 1.80–2.30 (br, 1 H), 2.49 (s, 3 H), 2.60–2.80 (m, 2 H), 2.84 (t, *J* = 5.6 Hz, 2 H), 3.46 (q, *J* = 7.2 Hz, 2 H), 4.19 (q, *J* = 7.2 Hz, 2 H), 8.03 (d, *J* = 13.6 Hz, 1 H), 10.90–11.20 (br, 1 H); *Z*-isomer δ = 1.11 (t, *J* = 7.2 Hz, 3 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 1.80–2.30 (br, 1 H), 2.42 (s, 3 H), 2.60–2.80 (m, 2 H), 2.84 (t, *J* = 5.6 Hz, 2 H), 3.46 (q, *J* = 7.2 Hz, 2 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 8.17 (d, *J* = 14.8 Hz, 1 H), 9.20–9.40 (br, 1 H), 8.90–9.10 (br, 1 H); *E*/*Z* = 9/1. ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer δ = 14.1 (q), 15.3 (q), 30.9 (q), 43.8 (t), 49.2 (t), 52.0 (t), 59.7 (t), 100.4 (s), 160.3

(d), 167.4 (s), 199.4 (s); *Z*-isomer δ = 14.1 (q), 15.3 (q), 30.9 (q), 41.4 (t), 49.2 (t), 52.0 (t), 59.7 (t), 100.3 (s), 160.2 (d), 169.2 (s), 195.7 (s).

(15) Diazepine **9q**: Isolated yield 30%. Dark brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.2 Hz, 3 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 2.31 (s, 3 H), 3.31 (q, *J* = 7.2 Hz, 2 H), 3.44 (t, *J* = 4.0 Hz, 2 H), 3.80–4.00 (br, 2 H), 4.19 (q, *J* = 7.2 Hz, 2 H), 7.64 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (q), 14.5 (q), 27.7 (q), 51.2 (t), 53.1 (t), 55.0 (t), 60.0 (t), 97.0 (s), 150.0 (d), 168.6 (s), 169.7 (s).

(16) Enamine **3r**: Isolated yield 82%. Colorless needles; mp 203–204 °C. ^{1}H NMR (400 MHz, DMSO-d_6): isomer A δ = 1.25 (t, *J* = 7.1 Hz, 6 H), 2.24 (s, 6 H), 3.55 (brs, 4 H), 4.16 (q, *J* = 7.1 Hz, 4 H), 7.94 (d, *J* = 14.1 Hz, 2 H), 9.12 (brd, *J* = 14.1 Hz, 2 H); isomer B δ = 1.19 (t, *J* = 7.1 Hz, 6 H), 2.30 (s, 6 H), 3.55 (brs, 4 H), 4.05 (q, *J* = 7.1 Hz, 4 H), 7.88 (d, *J* = 13.2 Hz, 2 H), 10.72 (brd, *J* = 13.2 Hz, 2 H); A/B = 1/7. Since NMR spectra suggested both isomers A and B had symmetrical structures, they were thought to be *EE* and *ZZ* isomers. ^{13}C NMR (100 MHz, DMSO-d_6): isomer A δ = 13.6 (q), 29.7 (q), 48.9 (t), 58.1 (t), 98.6 (s), 159.5 (d), 165.7 (s), 196.2 (s); isomer B δ = 13.6 (q), 29.9 (q), 48.9 (t), 58.0 (t), 98.6 (s), 159.5 (d), 165.7 (s), 196.2 (s). IR (nujol): 1648, 1699 cm^{-1}. MS (FAB): *m/z* (%) = 341 (100) [M^+ + 1]. Anal. Calcd for $C_7H_{11}NO_3$: C, 56.46; H, 7.11; N, 8.23. Found: C, 56.19; H, 7.17; N, 8.23.