FACILE SYNTHESIS OF FUNCTIONALIZED NITROENAMINES BY AMINOLYSIS OF NITROPYRIMIDINONE

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Abstract: Aminolysis of 3-methyl-5-nitropyrimidin-4(3*H*)-one 1 readily proceeded to give nitroenamine derivatives 2 which have a *N*-methylcarbamoyl group. In the case of reaction of 1 with hydrazines at room temperature, nitroenamines 3 bearing a *N*-methanimidoyl-*N*-methylcarbamoyl group were afforded. As one of synthetic utilities, it was found that the obtained nitroenamine 2 was converted into polysubstituted pyridone 4.

Introduction

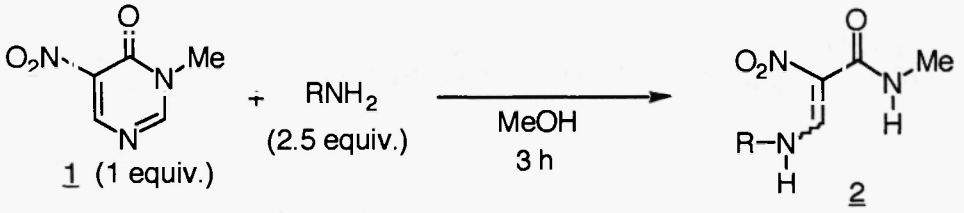
There are many reports (1, 2) dealing syntheses, properties and chemical transformations of nitroenamines. Among them, functionalized nitroenamines are highly useful synthetic intermediates of polyfunctionalized systems, but only a few preparative methods are known. To obtain nitroenamines bearing a functional group, the condensation of nitroacetic acid derivatives with amidoacetals or orthoformic esters is mainly employed. These starting materials are, however, not always readily available, so it is required to develop the facile synthetic procedure via the different path. From this point of view, aminolysis of 3-methyl-5-nitropyrimidin-4(3*H*)-one 1 (3) which is highly electron deficient was studied, since the carbamoylnitroenamine structure was masked in nitropyrimidinone 1 (N3-C4-C5-C6 moiety).

Results and Discussion

To a solution of nitropyrimidinone (1, 155 mg, 1 mmol) in MeOH (20 ml), $PrNH_2$ (206 μl, 2.5 mmol) was added and the mixture was refluxed for 3 hours. MeOH was removed, and the residue was recrystalized from hexane to furnish *N*-methyl-2-nitro-3-propylaminopropenamide 2a in 94 % yield. In the ^1H NMR spectra of 2a, a doublet signal of the olefinic proton having a large coupling constant (14.1 Hz, $NO_2C{=}C\underline{H}N\underline{H}$) was observed at 8.72 ppm. This is characteristic to the nitroenamine skeleton (4-6).

The present reaction was applicable to other primary amines (*t*-$BuNH_2$ and aromatic amines) and NH_3 to afford corresponding nitroenamines 2b-e (7) respectively. Nitropyrimidinone 1 was inactive toward *o*-$MeC_6H_4NH_2$ and *p*-$NO_2C_6H_4NH_2$ under same conditions to be recovered because of steric hindrance or low nucleophilicity (Table 1).

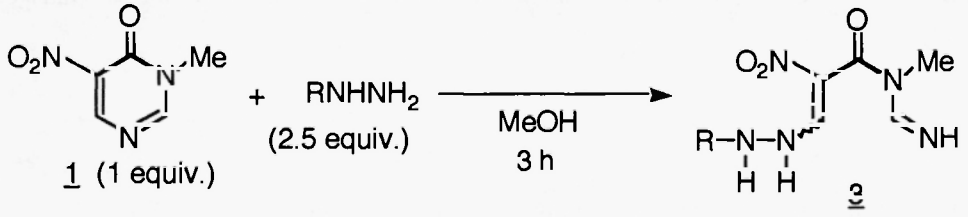
Table 1



R	Temp. (°C)	Product	Yield (%)
Pr	65	2a	94
t-Bu	"	2b	85
H	"	2c	27 [a]
p-$MeOC_6H_4$	"	2d	76
p-MeC_6H_4	"	2e	86
"	rt	"	26
"	65	"	30 [b]
o-MeC_6H_4	"	2f	4
p-$NO_2C_6H_4$	"	2g	--

a) 20 equiv. of NH_3 was used. b) 1.1 equiv. of amines were used.

Table 2



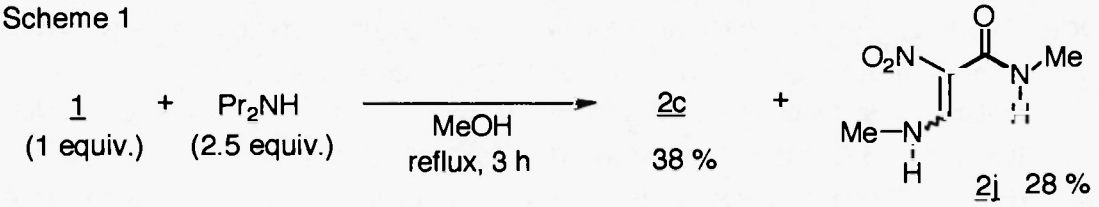
R	Temp. (°C)	Product	Yield (%)
Ph	rt	3a	71
"	65	"	– [a]
p-MeC_6H_4	rt	3b	52
p-$NO_2C_6H_4$	"	3c	76
Me	"	3d	– [a]

a) A complex mixture was obtained.

The reaction of 1 with hydrazines under the conditions as employed above gave only complex mixture. It was found that room temperature was enough for this reaction to proceed affording nitroenamines 3a-c bearing a methanimidoyl substituent at the carbamoyl group (8). In each case, we did not detect any formation of triazole derivative which was supposed product of the ring transformation (3). The isolation of 3 suggests that aminolysis of pyrimidinone 1 is initiated with nucleophilic attack at the 6-position followed by the cleavage of the N1-C6 bond. When aliphatic hydrazine, $MeNHNH_2$, was employed, the reaction mixture was complicated under the same conditions (Table 2).

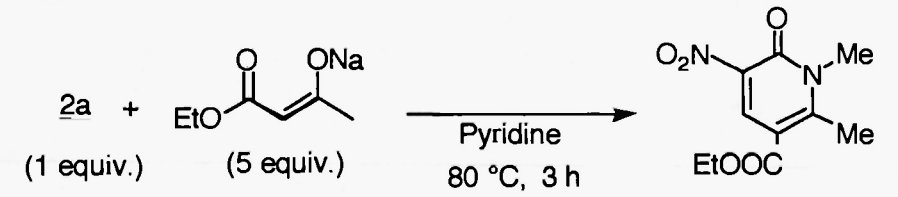
On the other hand, secondary amine such as Pr_2NH afforded amino and methylamino derivative 2c and 2j (7) instead of dipropylamino derivative, although the mechanism has not been clarified. While PhMeNH gave no positive result, and recovery of pyrimidinone 1 was observed (Scheme 1).

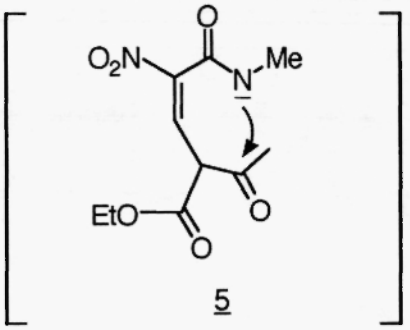
Scheme 1



As mentioned above, nitropyrimidinone 1 was found to be an excellent precursor of functionalized nitroenamines. In addition, synthetic value of prepared nitroenamines would be expected. As one of example, it was found that treatment of 2a with enolate ion of $AcCH_2COOEt$ furnished polysubstituted pyridone 4 (9). It is considered that Michael type attack of the enolate anion occurred at the electrophilic site of enamine 2a, and succeeding elimination of $PrNH_2$ afforded the intermediate 5, which is converted into pyridone 4 by ring closure (Scheme 2). Further chemical transformations of obtained nitroenamines are now under investigation.

Scheme 2





References and Notes

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(7) All of nitroenamines afforded satisfactory spectral data. The spectral data of 2j, for example, are as follows. 2j: pale yellow needles; mp 177-179 °C, IR (Nujol / cm^{-1}) 3365, 1676, 1534; ^1H NMR (60 MHz, $CDCl_3$, TMS) δ 2.95 (d, J = 5.0 Hz, 3H), 3.31 (d, J = 5.4 Hz, 3H), 8.70 (d, J = 14.0 Hz, 1H), 9.7-11.2 (br, 2H); Anal. Calcd. for $C_5H_9N_3O_3$; C: 37.72, H: 5.71, N: 26.41, Found; C: 38.05, H: 5.69, N: 26.05.

(8) The spectral data of 3a, for example, are as follows. 3a: yellow needles; mp 129-133 °C, IR (Nujol / cm^{-1}) 3322, 3305, 1643, 1592, 1350; ^1H NMR (60 MHz, d_6-DMSO, TMS) δ 3.53 (s, 3H), 5.4-5.9 (m, 2H), 6.4-7.4 (m, 5H), 8.59 (s, 1H), 8.87 (s, 1H), 8.94 (s, 1H); Anal. Calcd. for $C_{11}H_{13}N_5O_3$; C: 50.19, H: 4.98, N: 26.60, Found; C: 50.13, H: 4.97, N: 26.70.

(9) 4: pale yellow powder; mp 99-100 °C, IR (Nujol / cm^{-1}) 1720, 1693, 1527, 1336; ^1H NMR (60 MHz, $CDCl_3$, TMS) δ 1.43 (t, J = 7.3 Hz, 3H), 2.97 (s, 3H), 3.78 (s, 3H), 4.43 (q, J = 7.3 Hz, 2H), 9.02 (s, 1H); Anal. Calcd. for $C_{10}H_{12}N_2O_5$; C: 50.00, H: 5.04, N: 11.66, Found; C: 50.00, H: 4.99, N: 11.57.

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