Synthesis of 2-Substituted 4-Oxo-5-nitropyrimidines from Methyl 3-Ethoxy-2-nitroacrylate and Other Reactions

E. de la Cuesta and C. Avendaño*

Departamento de Química Orgánica y Farmaceútica, Facultad de Farmacia,
Universidad Complutense, Madrid-3, Spain

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Methyl 3-ethoxy-2-nitroacrylate (MENA) (**1**) has been the subject of study for the development of new syntheses leading to nitro-substituted heterocycles.

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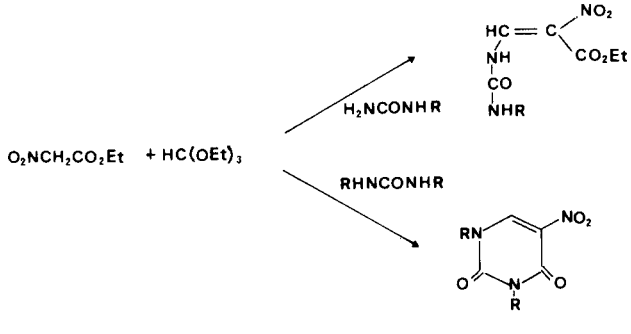
The presence in **1** of two electrophilic centers at the one and three positions allows cyclization reactions with bidentate nucleophiles. These reactions have been described in heterocyclic synthesis, especially to obtain pyrimidine derivatives, using other ethoxy methylene analogs such as those derived from diethyl malonate, ethyl cyanoacetate, acetylacetone and malononitrile [1-8].

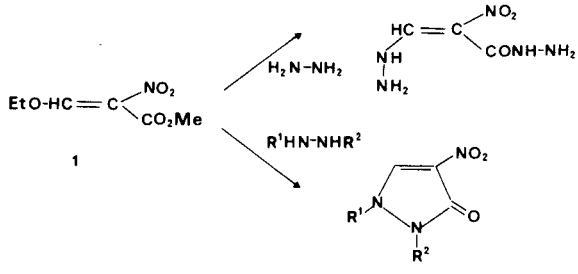
Although the ethoxy group in **1** is readily displaced by nucleophiles [9-14] the information about these cyclization reactions is brief. Ethoxymethylenenitroacetate (**1**) reacts with some hydrazines to give 4-nitro-3-pyrazolones [15] and the reaction with 2-aminopyridine followed by cyclization with polyphosphoric acid gave 3-nitro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine [13]. Ethyl 3-ethoxy-2-nitroacrylate (EENA) has been used to prepare 1-carboethoxy-3-nitro-4*H*-quinolizin-4-one [16] but the attempts to prepare 5-nitrouracil directly and its 2-thio analog using EENA and ureas or thioureas with sodium ethoxide catalysis gave very low yields [17]. The reaction of EENA with sulfamide in basic medium afforded 4-nitro-3-hydroxy-6*H*-1,2,6-thiadiazine 1,1-dioxide isolated as the alkaline salt [18,19].

The ethoxycarbonyl group in aminomethylenenitroacetates seems to be less easily attacked to give heterocycles than other aminomethylene analogs especially when the nitrogen atom on the olefinic system has an hydrogen atom. Thus, Prystăs and Gut [17] have reported that while condensation of ethyl nitroacetate with ethyl orthoformate and urea or its *N*-monosubstituted derivatives gave the ureidomethylenenitroacetates, the analogous reaction with *N,N'*-dimethylurea yielded 1,3-dimethyluracil (Scheme 1). Likewise Wolfbeis [15] obtained 1,2-disubstituted 4-nitro-3-pyrazolones with yields above 70% by reaction of **1** with *N,N'*-disubstituted hydrazines while reaction with unsubstituted hydrazine gave the open chain hydrazide (Scheme 2).

Scheme 1



Scheme 2

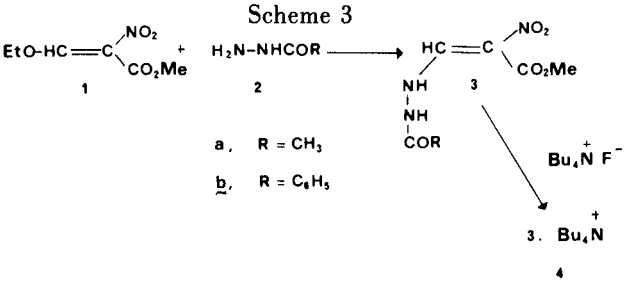


In this work we report the results obtained in the reactions of MENA (**1**) with hydrazides and amidines.

The reaction of MENA with **2a,b** afforded the *E*-forms of the hydrazidomethylenenitroacetate **3a,b** with good yield. The identification of the *E*-isomer was performed by assigning the ^{1}H nmr signals for the ethylenic protons at δ 8.23 (**3a**) and δ 8.49 (**3b**) [20]. The *Z,E*-isomerization of some aminomethylenenitroacetates has been previously studied [21,22]. Compounds **3a** and **3b** showed low frequency ir absorptions in the solid state assigned to the nitro group together with the low intensity of the band attributed to the asymmetric nitro mode.

Attempts to cyclise **3a** and **3b** by treatment with *p*-toluenesulfonic acid, triethylamine or sodium ethoxide failed (Scheme 3). In the treatment of **3a** with sodium ethoxide, low yields (16%) of the sodium salt of 4-nitro-3-pyrazolin-5-one were detected by ir and ^{1}H-nmr spectroscopy.

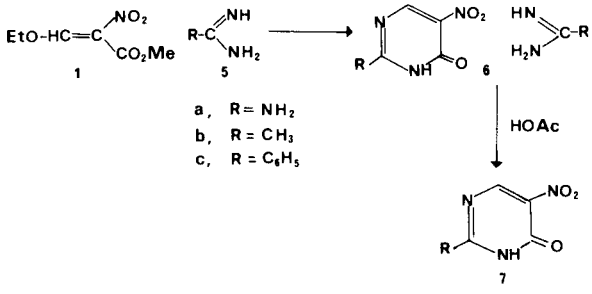
Scheme 3



The cyclisation of compounds **3a,b** was also attempted with tetrabutylammonium fluoride supported on silica gel [23] according to the method described by Pless to induce similar intramolecular cyclisations [24]. Analytical and ^{1}H nmr data revealed that tetrabutylammonium salts of **3a** and **3b** were formed under these conditions (**4**). The formation of these salts shows the ability of compound **3** to bind ions. Similarly, highly stable alkaline salts of 4-nitro- and 4-cyano-6*H*-1,2,6-thiadiazine 1,1-dioxides have also been found [19].

The above mentioned ability to form salts seemed to be useful in the reaction of **1** with a molar excess of amidine to obtain 2-substituted 4-oxo-5-nitropyrimidines as amidinium salts. Nishigaki *et al.* [5] found that in the formation of 2-substituted 4-oxo-5-cyanopyrimidines by reaction of ethyl ethoxymethylenecyanoacetate and amidines, the mole ratios of reacting components have a remarkable effect upon the yields of products. Treatment of 1 equivalent of **1** with 3 equivalents of amidines **5** gave 5-nitro-4-oxopyrimidine amidinate **6** which were quantitatively converted to 5-nitro-4-oxopyrimidines **7** by treatment with acetic acid (Scheme 4). The observed yields of 5-nitro-4-oxopyrimidines **7** are better than those described for the direct nitration of 4-oxopyrimidines [25].

Scheme 4



EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 577 spectrometer. Proton magnetic resonance spectra were carried out on Perkin-Elmer R-24, 60 MHz and Varian EM-390, 90 MHz spectrometers with TMS as internal standard.

Methyl 3-Ethoxy-2-nitroacrylate (**1**).

This reagent was prepared by condensation of methyl nitroacetate [26] and ethyl orthoformate in acetic anhydride [9].

Methyl 2-Nitro-3-acylhydrazinoacrylate (**3a,b**).

To a solution of methyl 3-ethoxy-2-nitroacrylate (**1**) (3.21 g, 0.018 mole) in 40 ml of dry ether was added dropwise the hydrazide (**2**) (0.018 mole, 1.35 g of **2a** or 2.5 g of **2b**) dissolved in 30 ml of absolute ethanol under stirring. After 24 hours under reflux the solution was cooled and the solid product was filtered and washed with ether. Recrystallization in acetone yielded pale yellow needles of pure **3a** (2.6 g, 71%), mp 118-119° dec.

Anal. Calcd. for $C_6H_9N_3O_5$: C, 35.47; H, 4.46; N, 20.68. Found: C, 35.15; H, 4.30; N, 20.63.

Pure yellow needles of **3b** were obtained from acetone (3.2 g, 55%), mp 132-133° dec.

Anal. Calcd. for $C_{11}H_{11}N_3O_5$: C, 49.81; H, 4.18; N, 15.84. Found: C, 49.86; H, 4.06; N, 15.76.

Methyl 2-Nitro-3-acylhydrazinoacrylate Tetrabutylammonium Salts (**4a,b**).

Methyl 2-nitro-3-acethydrazideacrylate (**3a**) (0.64 g, 3.1 mmoles) and 1.65 g (6.2 mmoles) of tetrabutylammonium fluoride supported on silica gel [23] were dissolved in 40 ml of tetrahydrofuran and refluxed for 14 hours. After cooling, the filtrate was washed with THF and extracted with hot ethanol. The ethanolic solution was evaporated under reduced pressure and the solid was recrystallized in ethanol to give 170 mg of **4a** as bright yellow plates (12% yield), mp 182-183°.

Anal. Calcd. for $C_{22}H_{44}N_4O_5$: C, 59.41; H, 9.98; N, 12.60. Found: C, 59.80; H, 10.28; N, 12.34.

Methyl 2-nitro-3-benzhydrazideacrylate (**3b**) (0.25 g, 0.94 mmole) and 0.49 g (1.8 mmoles) of TBAF-silica reagent were dissolved in 20 ml of THF and refluxed for 14 hours. After cooling and filtration, the THF solution was concentrated under reduced pressure and the residual solid was crystallized in acetone-petroleum ether to give 170 mg (36%) of **4b** as bright yellow plates, mp 104-106° dec; ^{1}H nmr (deuteriochloroform): δ 8.63 (s, HC=C, 1H), 8.05 (m, aromatic, 2H), 7.4 (m, aromatic and NH, 4H), 3.8 (s, OCH_3, 3H), 3.2 (m, CH_2-N^+, 8H), 1.8-0.7 (m, $CH_2CH_2CH_3$, 28H).

Anal. Calcd. for $C_{27}H_{46}N_5O_5$: C, 63.98; H, 9.15; N, 11.06. Found: C, 64.10; H, 9.45; N, 11.18.

5-Nitro-4-oxopyrimidine Amidinates (**6**). General Method.

To an ice-cold solution of 0.03 g-atom of sodium in 30 ml of absolute ethanol were added 0.03 mole of amidine-hydrochloride stirred for a few minutes and quickly filtered from precipitated sodium chloride. To the cooled filtrate (2-5°) was added 0.01 mole of MENA in portions under shaking to give an orange-yellow solution. After standing overnight in an icebox the products were separated as follows.

2-Amino-5-nitro-4-oxopyrimidine Guanidinate (**6a**).

The crystals which separated from the reaction mixture were collected by filtration to yield 1.58 g of crude **6a**. Recrystallization from methanol gave yellow-brown needles of pure **6a**, mp 248° dec.

Anal. Calcd. for $C_5H_9N_7O_3$: C, 27.89; H, 4.21; N, 45.57. Found: C, 28.03; H, 4.58; N, 45.62.

2-Methyl-5-nitro-4-oxopyrimidine Acetimidinate (**6b**).

The reaction solution was evaporated under reduced pressure to dryness to give a syrup that was worked up with chloroform and ethyl acetate to give 1.20 g (32%) of pure **6b**, mp 176-177° dec.

Anal. Calcd. for $C_7H_{11}N_5O_3$: C, 39.41; H, 5.20; N, 32.85. Found: C, 39.22; H, 5.48; N, 32.89.

2-Phenyl-5-nitro-4-oxopyrimidine Benzamidinate (**6c**).

The sticky residue obtained after evaporation of the reaction solution under reduced pressure was worked up with petroleum ether-acetone to give 2.9 g (59%) of crude **6c** as a yellow solid which was recrystallized in ethanol to give pure **6c** as yellow plates, mp 220-221° dec.

Anal. Calcd. for $C_{17}H_{15}N_5O_3$: C, 60.50; H, 4.48; N, 20.77. Found: C, 60.28; H, 4.44; N, 21.01.

Compounds **6** were neutralized with acetic acid to give quantitatively compounds **7**.

2-Amino-5-nitro-4-oxopyrimidine (**7a**).

Compound **7a** was obtained as a solid with mp 300° (recrystallized from water).

Anal. Calcd. for $C_4H_4N_4O_3$: C, 30.75; H, 2.58; N, 35.89. Found: C, 30.72; H, 2.76; N, 35.63.

2-Methyl-5-nitro-4-oxopyrimidine (**7b**).

This compound has mp 161° dec (recrystallized from methanol).

Anal. Calcd. for $C_5H_5N_3O_3$: C, 38.69; H, 3.25; N, 27.09. Found:

C, 38.77; H, 3.37; N, 27.45.

2-Phenyl-5-nitro-4-oxopyrimidine (**7c**).

This compound had mp 274° (recrystallized from ethanol).

Anal. Calcd. for $C_{10}H_7N_3O_3$: C, 55.28; H, 3.25; N, 19.35. Found: C, 55.06; H, 3.12; N, 19.14.

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[20] The reagent **1** showed a mixture of the *E* and *Z* isomers in a 3:7 ratio. The signal for the ethylenic proton at higher field was attributed to the *Z*-isomer by estimation of the chemical shifts of protons in olefinic systems using additive increments for the substituents.

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