

TRANSFORMATIONS OF METHYL(PHENYL)- SUBSTITUTED 1,4-DIHYDRO-4- PYRIMIDINYLDENEMALONONITRILES UNDER ACTION OF NITRIC ACID

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6-*Phenyl*-, 2-*methyl-6-phenyl*-, and 2,6-*diphenyl-4-pyrimidinyldenemalononitrile* in acetic acid react with HNO_3 to form the corresponding 4-ethoxycarbonylpyrimidines in high yields after treatment of the intermediate product with ethanol. Under the same conditions 6-*methyl-2-phenyl-4-pyrimidinyldenemalononitrile* yields 6-*methyl-5-nitro-4-ethoxycarbonylpyrimidine* whereas 2-*phenyl-4-pyrimidinyldenemalononitrile* gives a mixture of 2-*phenyl-4-ethoxycarbonyl*- and 5-*nitro-2-phenyl-4-ethoxycarbonylpyrimidine*.

We have previously found that 5-*methyl(phenyl)*-substituted 1,2-dihydro-2-pyrimidinyldenemalononitriles react with fuming HNO_3 in acetic acid medium and on subsequent treatment of the formed products with ethanol give the corresponding substituted 2-ethoxycarbonylpyrimidines in high yield [1].

In continuation of the study of reactivity of tautomeric derivatives of methylenedihydropyrimidines containing various functional groups in the side chain [1, 2], we have carried out nitration of 2(6)-*methyl(phenyl)*-substituted 1,4-dihydro-4-pyrimidinyldenemalononitriles (Ia-e). The compounds Ia-c, which contain phenyl substituent in the 6-position of the heterocycle, were found to behave like the 2-pyrimidinyl analogs [1], converting into the 4-ethoxycarbonyl-substituted derivatives (IIa-c) in 80-85% yield. Nitration was carried out with fuming HNO_3 in acetic acid medium. After the reaction was complete and acetic acid was removed, the mixture was refluxed in ethanol and the products were isolated.

The corresponding 2-ethoxycarbonylpyrimidines were previously isolated in high yield from the analogous reaction of 5-*methyl(phenyl)*-substituted 1,2-dihydro-2-pyrimidinyldenemalononitriles [2].

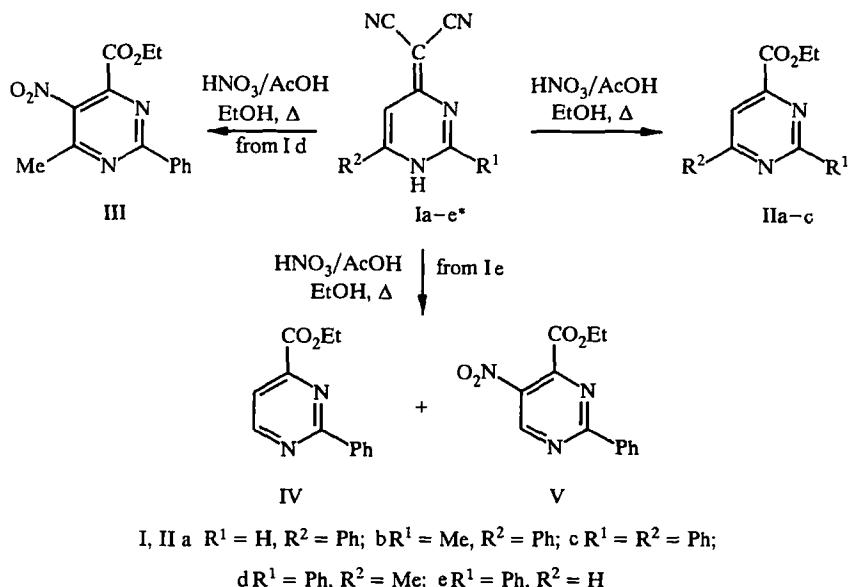
In the present work we found that 4-pyrimidinyldenemalononitriles Ia-c, which contain phenyl substituent in the 2 or 6 position behave under the same conditions like the 2-pyrimidinyl analogs [2], giving 4-ethoxycarbonyl derivatives IIa-c in 80-85% yields.

In contrast to this, 6-*methyl-2-phenyl-1,4-dihydro-4-pyrimidinyldenemalononitrile* (Id) produces 4-ethoxycarbonyl-6-*methyl-5-nitro-2-phenylpyrimidine* (III) in 50% yield. The yield reaches 75% if a two-fold excess of HNO_3 is used. This difference in the behavior of Ic and Id is apparently due to the presence in the 6-position of methyl group, which exhibits electron-donating properties and also is less bulky than phenyl substituent in Ic and so does not hinder introduction of the nitro group in the neighboring 5-position of the pyrimidine ring.

Under analogous conditions, 2-*phenyl-1,4-dihydro-4-pyrimidinyldenemalononitrile* Ie gives a mixture of 4-ethoxycarbonylpyrimidine (IV) and its 5-nitro derivative V in a 2:1 ratio (according to PMR data). The ratio changes if an excess of HNO_3 is used.

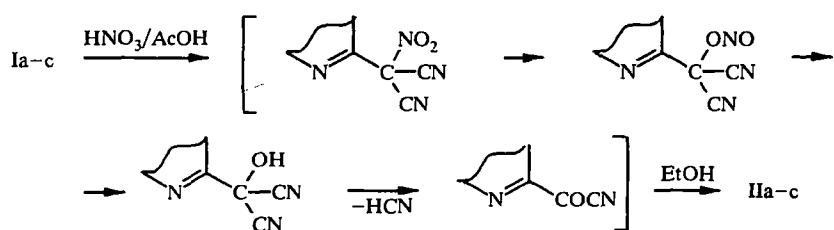
The preferred formation of the 5-nitro-substituted 4-ethoxycarbonylpyrimidine III from the 6-methyl derivative Id, in contrast to Ie, which gives a mixture of IV and V, may be caused by the influence of the methyl substituent.

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It should be noted that the reaction of 2-phenyl-1,4-dihydro-4-pyrimidinylidenecyanoacetic ester with HNO_3 in media of varying acidity results in nitration at the exocyclic double bond [2].

The probable mechanism of transformation of the malononitrile group of Ia-c into the ethoxycarbonyl group under the conditions used is analogous to that proposed by us previously for 5-substituted 2-pyrimidinylidenemalononitriles [1]. The mechanism involves nitration at the α -carbon atom of the ylidene tautomer. According to quantum-chemical calculations for the related 4-pyrimidinylidenecyanoacetic esters [3], the electron density at the α -carbon atom in the ylidene tautomer is significantly greater than in the aromatic form. The α -nitromalononitriles that are then formed convert into the corresponding α -hydroxy derivatives. The latter, being cyanohydrins, react with loss of HCN to give α -ketonitriles, which readily react with alcohol to replace the mobile CN group with ethoxy group [4].



The malononitrile moiety in Id and Ie probably reacts in a similar manner. However, the heterocycle is also nitrated.

In our opinion, the formation of 5-nitrosubstituted III and V may be caused by nitration of the ring of the starting malononitriles Id and Ie, the ylidene form of which is activated to electrophilic attack at the 5-position. Compounds Id,e apparently enter into the nitration in acetic acid as the unprotonated form, similar to 2-hydroxypyrimidines [5].

The composition and structure of the obtained products were confirmed by PMR, IR spectra and high-resolution mass spectrometry.

*The structural formula of the predominant tautomer of Ia-e is given.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument in KBr pellets (0.25% concentration). PMR spectra were recorded on a Bruker WP-200 SY (200.13 MHz) instrument. Chemical shifts were measured relative to residual protons in the solvent (acetone-d₆, δ 2.04 ppm). High-resolution mass spectra were recorded on a Finnigan MAT-8200 spectrometer. The course of the reactions and the purity of the products was monitored using TLC on Silufol UV-254 plates.

The starting 4-pyrimidinylidenemalononitriles Ia-e were synthesized from the corresponding chloropyrimidines by the literature method [1].

4-Ethoxycarbonyl-6-phenylpyrimidine (IIa). Fuming HNO₃ (0.25 ml, 5 mmol, d = 1.5) was added dropwise to suspension of Ia (1.1 g, 5 mmol) in glacial acetic acid (50 ml) under stirring. The mixture was stirred for 0.5 h until the starting dinitrile disappeared (TLC control). Acetic acid was distilled off in a rotary evaporator. Ethanol (20 ml) was added to the residue. The resulting mixture was refluxed for 2 h. Ethanol was removed in a rotary evaporator. The residue was chromatographed on silica gel column using CHCl₃-hexane (2:1) eluent. Yield 1.12 g (85%) of IIa; mp 54.5-55°C, which agrees with the literature [6].

Compounds IIb,c and III were prepared from Ib-d in a similar manner.

4-Ethoxycarbonyl-2-methyl-6-phenylpyrimidine (IIb) (see also [7]). Yield 80%; mp 60-62°C (from hexane). IR spectrum: 1725 cm⁻¹ (C=O). PMR spectrum: 1.40 (t, 3H, OCH₂CH₃), 2.76 (s, 3H, CH₃), 4.43 (q, 2H, OCH₂CH₃), 7.48-7.55 (m, 2H, CH_{arom}), 7.58 (s, 1H, H-5), 8.20-8.30 (m, 3H, CH_{arom}). Mass spectrum, *m/z*: M⁺ 242.01683. C₁₄H₁₄N₂O₂. Calculated: 242.01679.

4-Ethoxycarbonyl-2,6-diphenylpyrimidine (IIc). Yield 85%; mp 116-118°C (from hexane). IR spectrum: 1750 cm⁻¹ (C=O). PMR spectrum: 1.44 (t, 3H, OCH₂CH₃), 4.49 (q, 2H, OCH₂CH₃), 7.42-7.78 (m, 7H, H-5 and CH_{arom}), 8.30-8.71 (m, 4H, CH_{arom}). Mass spectrum, *m/z*: M⁺ 304.12117. C₁₉H₁₆N₂O₂. Calculated: 304.12115.

4-Ethoxycarbonyl-6-methyl-5-nitro-2-phenylpyrimidine (III). Yield 1.15 g (80%); mp 84-86°C. IR spectrum: 1755 cm⁻¹ (C=O). PMR spectrum: 1.38 (t, 3H, OCH₂CH₃), 2.79 (s, 3H, CH₃), 4.47 (q, 2H, OCH₂CH₃), 7.47-7.71 (m, 2H, CH_{arom}), 8.40-8.60 (m, 3H, CH_{arom}). Mass spectrum, *m/z*: M⁺ 287.12619. C₁₄H₁₃N₃O₄. Calculated: 287.12621.

4-Ethoxycarbonyl-2-phenylpyrimidine (IV) and 4-Ethoxycarbonyl-5-nitropyrimidine (V). Treatment of Ie (1.1 g, 5 mmol) with fuming HNO₃ (d = 1.5), by the method described for Ia, yields mixture of IV and V (1.03 g) in the ratio 1:2 (according to PMR data). The products were separated on silica gel column (*l* = 35 cm, d = 1 cm) using CHCl₃-hexane 1:3 eluent. Yield 0.62 g (54%) of IV and 0.36 g (27%) of V.

Compound IV. Mp 66-67°C (from hexane). IR spectrum: 1745 cm⁻¹ (C=O). PMR spectrum: 1.41 (t, 3H, OCH₂CH₃), 4.45 (q, 2H, OCH₂CH₃), 7.89 (d, 1H, 5-H, *J* = 5 Hz), 7.49-7.61 (m, 3H, CH_{arom}), 8.47-8.57 (m, 2H, CH_{arom}), 9.11 (d, 1H, 6-H, *J* = 5 Hz). Mass spectrum, *m/z*: M⁺ 228.08979. C₁₃H₁₂N₂O₂. Calculated: 228.08987.

Compound V. Mp 102-103°C (from hexane). IR spectrum: 1740 cm⁻¹ (C=O). PMR spectrum: 1.41 (t, 3H, OCH₂CH₃), 4.52 (q, 2H, OCH₂CH₃), 7.53-7.71 (m, 3H, CH_{arom}), 8.47-8.60 (m, 2H, CH_{arom}), 9.67 (s, 1H, 6-H). Mass spectrum, *m/z*: M⁺ 273.07468. C₁₃H₁₁N₃O₄. Calculated: 273.07495.

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