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NITROPYRIDINES. 7*. SYNTHESIS OF NITROPYRIDINES FROM NITRO-MALONIC DIALDEHYDE

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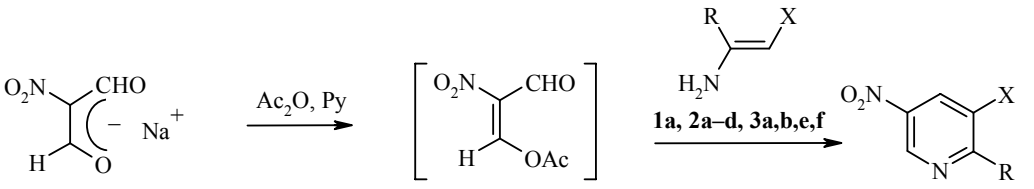
Cyclocondensation of sodium nitromalone dialdehyde with different enamines gave 3-acetyl(benzoyl, cyano, cyclopropanoyl, carbethoxy)-2-methyl(phenyl)-5-nitropyridines. With the aim of increasing the yield of pyridines we have activated the nitromalonic dialdehyde through acylation of its enol form.

Keywords: enamines, nitromalonic dialdehyde, nitropyridines.

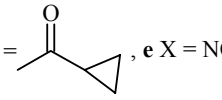
Aliphatic nitro compounds are widely used in the synthesis of nitropyridines unavailable by direct nitration of pyridines and by other known methods [2-5]. Nitromalone dialdehyde is one of the most available of the nitro ketones used but examples of nitropyridines obtained in this way are few [6-10].

The aim of this work was to synthesize 5-nitropyridines by cyclocondensation of nitromalone dialdehyde with different enamines.

Analysis of the experimental work has shown that an activated form of the nitromalone dialdehyde is most efficiently used in the cyclocondensation. With this in view, tosylation and acetylation of its enol form have been carried out [9, 10]. We have checked both variants of the acylation of nitromalone dialdehyde in the synthesis of nitropyridines experimentally and found that use of acetic anhydride for elimination of a molecule of water from the sodium malone dialdehyde monohydrate salt with simultaneous acetylation is more



1, **4** R = H, **2**, **5** R = Me, **3**, **6** R = Ph

a X = COPh, **b** X = CN, **c** X = COMe, **d** X =  , **e** X = NO_2, **f** X = CO_2Et

* For Communication 6 see [1].

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convenient practically. The nitropyridines **4-6** were prepared in 40-85% yields. Lowering of the yield of the nitropyridines is seen with an increase in the acceptor property of the X substituent in the enamine causing a decrease in the nucleophilicity of the amino group. With use in the cyclocondensation of the nitroacetophenone enamine the 3,5-dinitro-2-phenylpyridine (**6e**) was obtained in 40% yield but with the nitroacetone enamine the 2-methyl-3,5-dinitropyridine was not detected, even in trace amounts. A side reaction of the acylation of the enamines can also affect the yield of the nitropyridines [11].

The structures of the compounds **2d, 4a, 5a,d, 6a** and **6f** synthesized for the first time were confirmed from ^{1}H NMR and IR spectroscopic (Table 1), from mass-spectrometric (Table 2) data and from elemental analysis. The elemental analytical data is given in the Experimental section.

TABLE 1. Spectroscopic Characteristics of Compounds **2d, 4a, 5a,d,** and **6a,f**

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
2d	1606 (C=C), 1659 (CO), 3297, 3142 (NH_2)	0.67-0.79 (2H, m, CH_2); 0.91-0.96 (2H, m, CH_2); 1.68 (1H, m, CH); 5.00 (1H, br. s, NH_2); 5.18 (1H, s, H-2); 9.65 (1H, br. s, NH_2)
4a	1355, 1528 (NO_2), 1654 (CO)	7.45–7.85 (5H, m, COC_6H_5); 8.86 (1H, m, H-4); 9.29 (1H, d, *J* = 1.7, H-2), 9.62 (1H, d, *J* = 2.4, H-6)
5a	1342, 1526 (NO_2), 1658 (CO)	2.67 (3H, s, CH_3); 7.51-7.81 (5H, m, COC_6H_5); 8.42 (1H, d, *J* = 2.4, H-4); 9.44 (1H, d, *J* = 2.4, H-6)
5d	1352, 1519 (NO_2), 1682 (CO)	1.17-1.30 (2H, m, –CH_2–); 1.34-1.42 (2H, m, CH_2); 2.43 (1H, m, CH); 2.83 (3H, s, CH_3); 8.72 (1H, d, *J* = 2.4, H-4); 9.39 (1H, br. s, H-6)
6a	1352, 1520 (NO_2), 1666 (CO)	7.24-7.68 (10H, m, C_6H_5, COC_6H_5); 8.62 (1H, d, *J* = 2.6, H-4); 9.61 (1H, d, *J* = 2.6, H-6)
6f	1342, 1592 (NO_2), 1710 (CO)	1.13 (3H, t, *J* = 7.1, CH_2–C$\underline{H}_3$); 4.24 (2H, q, *J* = 7.1, C$\underline{H}_2$–CH_3); 7.45-7.63 (5H, m, C_6H_5); 8.86 (1H, m, H-4); 9.55 (1H, d, *J* = 2.2, H-6)

TABLE 2. Mass Spectra of Compounds **2d, 4a, 5a,d, and 6a,f**

Compound	*m*/*z* (*I*, %)*
2d	125 $[M]^{+\bullet}$ (47.63), 110 $[M-CH_3]^+$ (14.41), 84 $[M-CH_3-C_2H_2]^+$ (100), 42 (18.15)
4a	228 $[M]^{+\bullet}$ (34.86), 211 $[M-OH]^+$ (25.89), 105 $[C_6H_5CO]^+$ (100), 77 $[C_6H_5]^+$ (69.91), 51 (15.84)
5a	243 $[M+1]^{+\bullet}$ (11.45), 242 $[M]^{+\bullet}$ (64.02), 240 $[M-H_2]^{+\bullet}$ (65.95), 105 $[C_6H_5CO]^+$ (100), 77 $[C_6H_5]^+$ (97.67), 51 (24.69), 50 (16.17)
5d	206 $[M]^{+\bullet}$ (55.40), 191 $[M-CH_3]^+$ (33.68), 189 $[M-OH]^+$ (11.78), 178 $[M-CO]^{+\bullet}$ (25.57), 165 $[M-CH_3-C_2H_2]^+$ (100), 160 $[M-NO_2]^{+\bullet}$ (13.02), 153 (37.14), 91 (15.43), 69 (65.23), 63 (10.91), 50 (18.52), 41 (29.34), 39 (16.23)
6a	305 $[M+1]^{+\bullet}$ (13.33), 304 $[M]^{+\bullet}$ (65.66), 276 $[M-CO]^{+\bullet}$ (26.41), 258 $[M-NO_2]^{+\bullet}$ (19.68), 229 (14.44), 105 $[C_6H_5CO]^+$ (88.00), 77 $[C_6H_5]^+$ (100), 51 (20.98)
6f	272 $[M]^{+\bullet}$ (28.38), 244 $[M-CO]^{+\bullet}$ (14.28), 243 $[M-C_2H_5]^+$ (100), 227 $[M-C_2H_5O]^+$ (13.42), 198 $[M-CO-NO_2]^{+\bullet}$ (10.03), 197 $[M-C_2H_5-NO_2]^+$ (38.16), 181 $[M-C_2H_5O-NO_2]^+$ (12.62), 153 $[M-C_2H_5O-NO_2-CO]^+$ (17.13), 127 (11.33), 77 $[C_6H_5]^+$ (18.61), 29 $[C_2H_5]^+$ (18.68), 28 [CO] (11.10)

* *I* is the percentage of the maximum peak intensity and is quoted for peaks with *I* > 10%.

The nitropyridines **4-6** obtained in this work are key compounds in the synthesis of nitroanilines and indoles [12-14].

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer (200 MHz) using $CDCl_3$ solvent with TMS as internal standard. IR spectra were obtained on a Specord IR-75 instrument in $CHCl_3$. Mass spectra were recorded on an Agilent 5973N mass spectrometer (electron ionization energy 70 eV, evaporator temperature 230-250ºC) and on a Finnigan MAT-8200 (electron ionization energy 70 eV, evaporator temperature 270-300ºC) Molecular weights and elemental compositions for compounds **4a, 6a,f** were determined mass spectrometrically. Elemental analysis of the remaining compounds was performed on a Perkin-Elmer analyzer. Monitoring of the reaction course and purity of the compounds obtained was carried out by TLC on Silufol UV-254 plates.

The **Nitromalone dialdehyde Salt** was prepared in two stages from furfural by the method given in [15]. 3-Amino-1-phenyl-2-propen-1-one (**1a**), 3-amino-1-phenyl-2-buten-1-one (**2a**), 3-amino-1,3-diphenyl-2-propen-1-one (**3a**), 4-amino-3-penten-2-one (**2c**), 3-amino-3-phenylacrylonitrile (**3b**), and ethyl 2-(3-amino-3-phenyl)acrylate (**3f**), were synthesized by methods [16-21]. 2-Nitro-1-phenylethyleneamine (**3e**) was prepared by transamination of N-(2-nitro-1-phenylvinyl)aniline [6, 22, 23]. The 3-amino-2-butenenitrile (**2b**) used in the work was obtained from the Fluka company.

3-Amino-1-cyclopropyl-2-buten-2-one (2d). A mixture of 1-cyclopropyl-1,3-butanedione [24] (4.4 g, 35 mmol) and a saturated alcohol solution of ammonia (125 ml) was stirred at about 20ºC for 24 h. Solvent was distilled off and the residue was recrystallized from CCl_4. Yield 80%; mp 100-101 (CCl_4). Found, %: C 67.03; H 8.96; N 11.05. $C_7H_{11}NO$. Calculated, %: 67.17; H 8.86; N 11.19.

Nitropyridines 4-6 (General Method) A mixture of sodium nitromalone dialdehyde monohydrate (2.0 g, 12.7 mmol) and acetic anhydride (13 ml) was stirred for 30 min, pyridine (7.5 ml) was added, and the product was stirred for a further 10 min. The corresponding enamine **1a, 2a-d, 3a,b,e,f** (12.7 mmol) was added and stirred for 18 h. The mixture was poured into iced water and the precipitate formed was filtered off. The yields of nitropyridines are given after column chromatographic purification (silica gel, Merck 60A, 0.060-0.200 mm, eluent benzene).

3-Benzoyl-5-nitropyridine (4a). Yield 47%; mp 96-97ºC [petroleum ether (40-70ºC)]. Found: *m/z* 228.0549 $[M]^+$. $C_{12}H_8N_2O_3$. Calculated: M 228.2036.

3-Benzoyl-2-methyl-5-nitropyridine (5a). Yield 85%; mp 55-56ºC (hexane). Found, %: C 64.82; H 4.25. $C_{13}H_{10}N_2O_3$. Calculated, %: C 64.46; H 4.16.

3-Benzoyl-5-nitro-2-phenylpyridine (6a). Yield 55%; mp 113-114ºC [petroleum ether (40-70ºC)]. Found: *m/z* 304.0848 $[M]^+$. $C_{18}H_{12}N_2O_3$. Calculated: M 304.2996.

2-Methyl-5-nitronicotinonitrile (5b). Yield 39%; mp 73-74ºC (hexane) (mp 73-74ºC [25]).

5-Nitro-2-phenylnicotinonitrile (6b). Yield 78%; mp 120-121ºC (alcohol) (mp 121-122ºC [25]).

3-Acetyl-2-methyl-5-nitropyridine (5c). Yield 52%; mp 64-65ºC (alcohol) (mp 63.5-64ºC [26]).

(2-Methyl-5-nitro-3-pyridyl)(cyclopropyl) ketone (5d). Eluent chloroform–ethyl acetate (9:1). Yield 62% as light-yellow crystals with mp 80-81ºC [petroleum ether (40-70ºC)]. Found, %: C 58.08; H 4.83; N 13.26. $C_{10}H_{10}N_2O_3$. Calculated, %: C 58.25; H 4.89; N 13.59.

3,5-Dinitro-2-phenylpyridine (6e). Yield 40%; mp 84-85ºC (80% alcohol) (mp 83-85ºC [27]).

Ethyl 5-nitro-2-phenylnicotinate (6f). Yield 68%; mp 100-101ºC (alcohol). Found: *m/z* 272.0797 $[M]^+$. $C_{14}H_{12}N_2O_4$. Calculated: M 272.2562.

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