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# SYNTHESIS OF PYRIDINES BY CYCLOCONDENSATION OF ACETYL AND BENZOYL PYRUVATES WITH ENAMINES

**G. P. Sagitullina[1]**, A. K. Garkushenko[1], M. A. Dushek[1], N. V. Poendaev[1], and R. S. Sagitullin[1]***

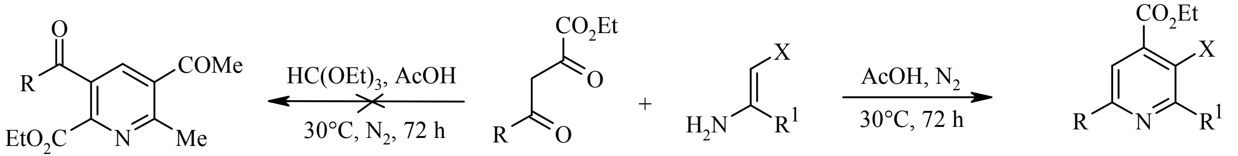
4-Ethoxycarbonylpyridines containing acetyl, benzoyl, cyclopropanoyl, and nitro groups at position 3 have been synthesized by the reaction of acetyl and benzoyl pyruvates with various enamines.

**Keywords**: enamines, pyridines with acceptor substituents, one-pot synthesis.

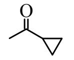
The most valuable method for the synthesis pyridines with acceptor substituents in positions 3 and 5 of the nucleus is the Hantzsch synthesis [1, 2]. In one variant of the Hantzsch synthesis for the preparation of pyridines condensation of ethyl ethoxymethyleneacetoacetate (or other products of the reaction of $\beta$-dicarbonyl compounds with ethyl orthoformate) with enamines of $\beta$-dicarbonyl compounds is used [3]. We have previously successfully used a one-pot variant of this synthesis using methylene-activated nitroacetone and nitroacetophenone [4, 5].

In a development of this work we have investigated the possibility of using a one-pot synthesis of pyridines **8** and **9** by a triple-component of acetyl and benzoyl pyruvates. However it appears that esters **1** and **2** did not react under mild conditions with ethyl orthoformate to form ethoxymethylene derivatives and consequently pyridines **8** and **9** were not formed. Under these conditions another variant of the Hantzsch synthesis – the Guareschi-Thorpe reaction – led to the formation of pyridines **5-7** in preparative yields [6-9].

The spectral data for the previously undescribed pyridines **5-7** are given in Tables 1 and 2.



**8, 9** **1, 2** **3a-e, 4a,e** **5a,e, 6a-e, 7a,e**

**1**, **8** R = Me, **2**, **9** R = Ph; **3** $R^1$ = Me, **4** $R^1$ = Ph; **5** R = $R^1$ = Me, **6** R = Ph, $R^1$ = Me,
**7** R = Me, $R^1$ = Ph; **3–7** **a** X = CN, **b** X = COMe, **c** X = COPh, **d** X =  , **e** X = $NO_2$

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* Deceased.

** To whom correspondence should be addressed, e-mail: Sagitullina@orgchem.univer.omsk.su.

[1] F. M. Dostoevsky Omsk State University, Omsk 644077, Russia.

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TABLE 1. IR and $^1$H NMR Spectra of Compounds **5-7**

| Compound | IR spectrum, ν, cm$^{-1}$ | | $^1$H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz) | | | | |
|---|---|---|---|---|---|---|---|
| | COOEt | X | $C\underline{H}_3$–$CH_2$ (t) | $CH_3$–$C\underline{H}_2$ (q) | 2(6)-$CH_3$ (s) | H-5 (s) | Other protons |
| **5a** | 1237, 1732 | 2229 (C≡N) | 1.46 (*J* = 7.1) | 4.49 (*J* = 7.1) | 2.67 (6-$CH_3$),<br>2.84 (2-$CH_3$) | 7.63 | — |
| **5e** | 1235, 1736 | 1328, 1542 ($NO_2$) | 1.35 (*J* = 7.1) | 4.37 (*J* = 7.1) | 2.59 (6-$CH_3$),<br>2.64 (2-$CH_3$) | 7.49 | — |
| **6a** | 1254, 1731 | 2227 (C≡N) | 1.50 (*J* = 7.2) | 4.54 (*J* = 7.2) | 2.95 (2-$CH_3$) | 8.20 | 7.50-7.57 (3H, m, $C_6H_5$); 8.09-8.15 (2H, m, $C_6H_5$) |
| **6b** | 1254, 1724 | 1705 (C=O) | 1.42 (*J* = 7.2) | 4.43 (*J* = 7.2) | 2.62 (2-$CH_3$) | 8.09 | 2.61 (3H, s, Ac); 7.45-7.55 (3H, m, $C_6H_5$); 8.03-8.08 (2H, m, $C_6H_5$) |
| **6c** | 1252, 1726 | 1674 (C=O) | 1.11 (*J* = 7.0) | 4.20 (*J* = 7.0) | 2.53 (2-$CH_3$) | 8.22 | 7.47-7.57 (5H, m, $COC_6H_5$); 7.60-7.65 (1H, m, $C_6H_5$); 7.81-7.88 (2H, m, $C_6H_5$); 8.12-8.15 (2H, m, $C_6H_5$) |
| **6d** | 1251, 1726 | 1688 (C=O) | 1.37-1.44 (5H, m, $C\underline{H}_3$-$CH_2$ and *c*-Pr) | 4.42 (*J* = 7.3) | 2.67 (2-$CH_3$) | 8.05 | 1.13-1.19 (2H, m, *c*-Pr); 2.20-2.28 (1H, m, *c*-Pr); 7.43-7.54 (3H, m, $C_6H_5$); 8.03-8.06 (2H, m, $C_6H_5$) |
| **6e** | 1255, 1736 | 1339, 1542 ($NO_2$) | 1.39 (*J* = 7.0) | 4.42 (*J* = 7.0) | 2.70 (2-$CH_3$) | 8.00-8.10 (3H, m, H-5 and $C_6H_5$) | 7.45-7.56 (3H, m, $C_6H_5$) |
| **7a** | 1216, 1734 | 2230 (C≡N) | 1.48 (*J* = 7.1) | 4.52 (*J* = 7.1) | 2.76 (6-$CH_3$) | 7.74 | 7.50-7.56 (3H, m, $C_6H_5$); 7.73-7.76 (2H, m, $C_6H_5$) |
| **7e** | 1217, 1737 | 1337, 1545 ($NO_2$) | 1.38 (*J* = 7.2) | 4.42 (*J* = 7.2) | 2.74 (6-$CH_3$) | 7.65 | 7.43-7.50 (3H, m, $C_6H_5$); 7.55-7.61 (2H, m, $C_6H_5$) |

TABLE 2. $^{13}$C NMR Spectra of Compounds **5-7**

| Com-pound | Chemical shifts ($CDCl_3$), δ, ppm | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | C(2) | C(3) | C(4) | C(5) | C(6) | $\underline{C}H_3CH_2CO$ | $CH_3\underline{C}H_2CO$ | $CH_3CH_2\underline{C}O$ | 2(6)-$CH_3$ | Signals of other group |
| **5a** | 162.58 | 104.55 | 140.38 | 120.78 | 163.29 | 13.93 | 62.78 | 163.12 | 23.93 (6-$CH_3$);<br>24.88 (2-$CH_3$) | 115.73 (CN) |
| **5e** | 150.78 | 143.30 | 131.87 | 120.86 | 161.10 | 13.69 | 62.95 | 162.63 | 20.65 (6-$CH_3$);<br>24.47 (2-$CH_3$) | — |
| **6a** | 163.28 | 105.29 | 141.06 | 117.56 | 159.73 | 13.99 | 62.93 | 163.55 | 24.25 (2-$CH_3$) | 115.90 (CN), 127.42 (C(2',6')), 128.99 (C(3',5')), 130.75 (C(4')), 136.81 (C(1')) |
| **6b** | 154.22 | 135.25 | 135.40 | 117.16 | 157.72 | 13.97 | 62.33 | 165.10 | 22.50 (2-$CH_3$) | 31.74 ($CO\underline{C}H_3$), 126.98 (C(2',6')), 128.81 (C(3',5')), 129.58 (C(4')), 137.98 (C(1')), 201.13 ($\underline{C}OCH_3$) |
| **6c** | 157.82 | 136.95 | 137.15 | 117.31 | 155.97 | 13.52 | 62.14 | 164.71 | 23.03 (2-$CH_3$) | 127.04 (C(2',6')), 128.79 (C(3',5')), 128.85 (C(2'',3'',5'',6'')), 129.66 (C(4')), 132.60 (C(1')), 133.56 (C(4'')), 137.98 (C(1'')), 196.61 ($\underline{C}OC_6H_5$) |
| **6d** | 154.75 | 135.35 | 136.05 | 117.21 | 157.49 | 14.06 | 62.44 | 165.13 | 23.15 (2-$CH_3$) | 12.98 (–$CH_2$–), 23.09 (–CH–), 127.00 (C(2',6')), 128.80 (C(3',5')), 129.55 (C(4')), 138.07 (C(1')), 206.79 ($\underline{C}O$-*c*-Pr) |
| **6e** | 151.41 | 143.73 | 132.63 | 117.97 | 158.86 | 13.73 | 63.10 | 162.72 | 20.99 (2-$CH_3$) | 127.35 (C(2',6')), 129.02 (C(3',5')), 130.51 (C(4')), 136.78 (C(1')) |
| **7a** | 163.07 | 103.02 | 141.97 | 121.56 | 162.95 | 13.95 | 62.91 | 163.46 | 25.08 (6-$CH_3$) | 116.04 (CN), 128.46 (C(2',6')), 129.19 (C(3',5')), 130.09 (C(4')), 137.12 (C(1')) |
| **7e** | 151.39 | 143.68 | 135.28 | 121.81 | 161.25 | 13.70 | 63.09 | 162.47 | 24.64 (6-$CH_3$) | 127.99 (C(3',5')), 128.78 (C(2',6')), 129.92 (C(4')), 132.19 (C(1')) |

## EXPERIMENTAL

IR spectra of compounds **5a**,**e**, **6a-c**, **7a**,**e** were measured with a Simex FT-801 in $CHCl_3$. $^1H$ NMR spectra of compounds **6a**,**b** and **7a**,**e** were recorded on a Bruker AC-250 (250 MHz) spectrometer with TMS as internal standard, and **5a**,**e** and **6c-e** on a Bruker DRX-400 (400 MHz) instrument with $CHCl_3$ as internal standard ($\delta_C$ 7.26). $^{13}C$ NMR spectra were recorded on a Bruker DRX-400 (100 MHz) spectrometer with $CDCl_3$ as internal standard ($\delta_C$ 77.00). Elemental analyses were obtained on a Perkin-Elmer CHN analyzer Merck 60A, 60-200 μm silica gel was used for column chromatography. Monitoring of reactions and purity of the compounds obtained was by TLC on Silufol UV-254 plates.

**Ethyl 2,4-Dioxopentanoate (1)** was synthesized according to [10] and **Ethyl 2,4-Dioxo-4-phenylbutanoate (2)** according to [11]. **4-Aminopent-3-en-2-one (3b), 3-Amino-1-phenyl-but-2-en-1-one (3c), 3-Amino-1-cyclo-propylbut-2-en-1-one (3d),** and **3-Amino-3-phenylacrylonitrile (4a)** were obtained as described in [3, 12-14]. **1-Methyl-2-nitrovinylamine (3c)** was obtained by the transamination of (1-methyl-2-nitrovinyl)phenylamine [15-17]. **2-Nitro-1-phenylethylenamine (4e)** was obtained by the transamination of N-(2-nitro-1-phenyl-vinyl)aniline [16, 18, 19]. **3-Aminobut-2-enenitrile** was obtained from Fluka.

**Synthesis of Pyridines 5a,e, 6a-e, and 7a,e (General Method)**. A solution of ester **1** (or **2**) (6 mmol) and corresponding enamine **3a-e**, **4a**,**e** (6 mmol) in acetic acid (5 ml) was stirred for 72 h at 30°C. The reaction mixture was diluted with water and ice and the crystals formed were filtered off.

**Ethyl 3-Cyano-2,6-dimethylisonicotinate (5a).** Yield 70%; mp 38-39°C (petroleum ether 40-70°C). Found, %: C 64.56; H 5.98; N 13.87. $C_{11}H_{12}N_2O_2$. Calculated, %: C 64.69; H 5.92; N 13.72.

**Ethyl 2,6-Dimethyl-3-nitroisonicotinate (5e).** Yield 80%; mp 54-55°C (ethanol) (mp 58-59°C [20]). Found, %: C 53.17; H 5.34; N 12.56. $C_{10}H_{12}N_2O_4$. Calculated, %: C 53.57; H 5.39; N 12.49.

**Ethyl 3-Cyano-2-methyl-6-phenylisonicotinate (6a).** Yield 75%; mp 94-95°C (ethanol). Found, %: C 72.55; H 5.33; N 10.62; $C_{16}H_{14}N_2O_2$. Calculated, %: C 72.16; H 5.30; N 10.52.

**Ethyl 3-Acetyl-2-methyl-6-phenylisonicotinate (6b).** Yield 80%; mp 64-65°C (petroleum ether 40-70°C). Found, %: C 71.79; H 6.03; N 5.23. $C_{17}H_{17}NO_3$. Calculated, %: C 72.07; H 6.05; N 4.94

**Ethyl 3-Benzoyl-2-methyl-6-phenylisonicotinate (6c).** Yield 72%; mp 111-112° (ethanol). Found, %: C 76.56; H 5.62; N 4.45. $C_{22}H_{19}NO_3$. Calculated, %: C 76.50;, H 5.54; N 4.06.

**Ethyl 3-(Cyclopropylcarbonyl)-2-methyl-6-phenylisonicotinate (6d).** Yield 60%; mp 112-113°C (ethanol). Found, %: C 73.81; H 6.32; N 4.75. $C_{19}H_{19}NO_3$. Calculated, %: C 73.77; H 6.19; N 4.53.

**Ethyl 2-Methyl-3-nitro-6-phenylisonicotinate (6e).** Yield 75%; mp 82-83°C (ethanol). Found, %: C 62.57; 4.75; 9.84. $C_{15}H_{14}N_2O_2$. Calculated, %: C 62.93; H 4.93; N 9.79.

**Ethyl 3-Cyano-6-methyl-2-phenylisonicotinate (7a).** Yield 77%; mp 75-76°C (ethanol). Found, %: C 71.92; H 5.37; N 10.61. $C_{16}H_{14}N_2O_2$. Calculated, %: C 72.16; H 5.30; N 10.52.

**Ethyl 6-Methyl-3-nitro-2-phenylisonicotinate (7e).** Yield 40%; mp 77-78°C (ethanol). Found, %: C 62.55; H 4.82; N 9.56. $C_{15}H_{14}N_2O_4$. Calculated, %: C 62.93; H 4.93; N 9.79.

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