THE INVESTIGATION OF PYRROLO-, THIENO- AND FURO[2,3-b]-PYRIDINE SYNTHESIS BASED ON THORPE-ZIEGLER REACTION.

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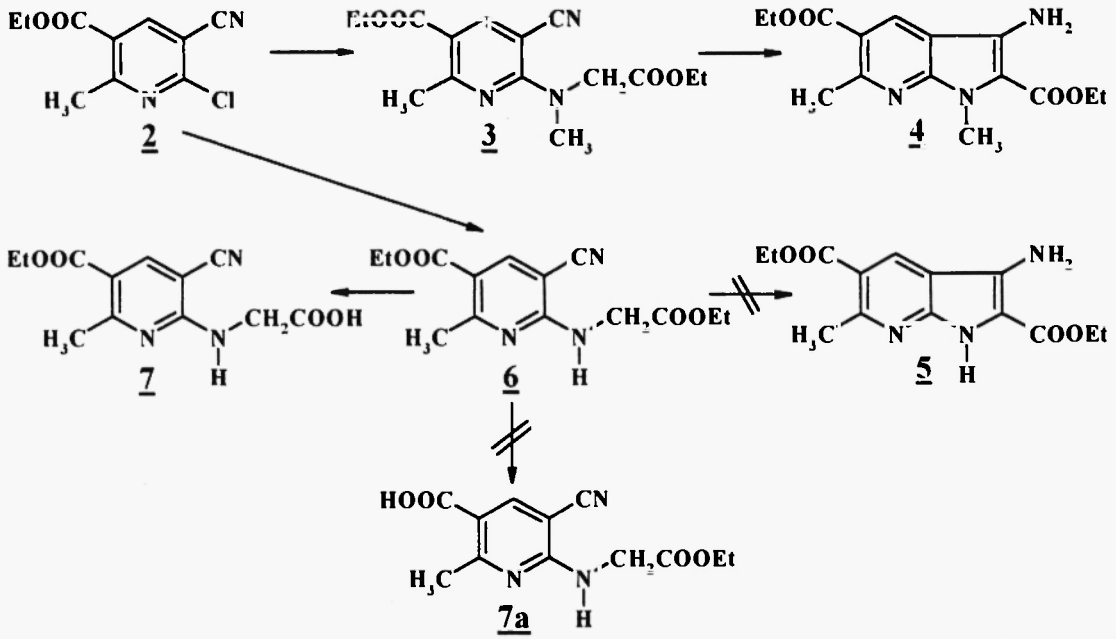
ABSTRACT: Synthesis of pyrrolo-, thieno and furo[2,3-b]pyridines has been studied under basic reaction conditions. Significant role of base catalysis as well as substituent effects in these reactions are reported. As a result of this study the best reaction conditions for the preparation of the title compounds have been found.

INTRODUCTION.

In a previous communications we have reported that 2-chloro-3-cyano-5-nitro- **1** and 2-chloro-3-cyano-5-ethoxycarbonyl- **2** pyridines are convenient synthons for Thorpe-Ziegler reaction and, as a rule, they are able to be transformed smoothly to the heterocycles having 3-aminopyrrole- and 3-aminothiophene moiety (1-3). As an extension of this work we report here new synthesis of similar heterocyclic derivatives and the results of studies of some details of Thorpe-Ziegler cyclization.

RESULTS AND DISCUSSION.

Chloropyridine **2** as well as its nitropyridine analog **1** reacted smoothly with ethyl sarcosinate and the intermediate **3** entered to Thorpe-Ziegler cyclization with the formation of 1,6-dimethyl-2,5-diethoxycarbonyl-3-aminofuro[2,3-b]pyridine **4**. It is known (4,5) that the presence of NH-group in the side chain of the intermediates similar to **3** makes difficulties for the cyclization and usually such cyclization doesn't occur. Our recent attempts to synthesize the N-unsubstituted pyrrolopyridine **5** from pyridylglycine ester **6** has failed too. In the conditions which are normally used for the synthesis of the bicycle compound **4** the saponification of one of the ethoxycarbonyl groups had place and as a result, 2-carboxymethylamino-3-cyano-5-ethoxycarbonyl-6-methylpyridine **7** has been obtained. (The second possible way of this reaction was the saponification of the ethoxycarbonyl group in position 5 of the pyridine ring with the formation of compound **7a**).



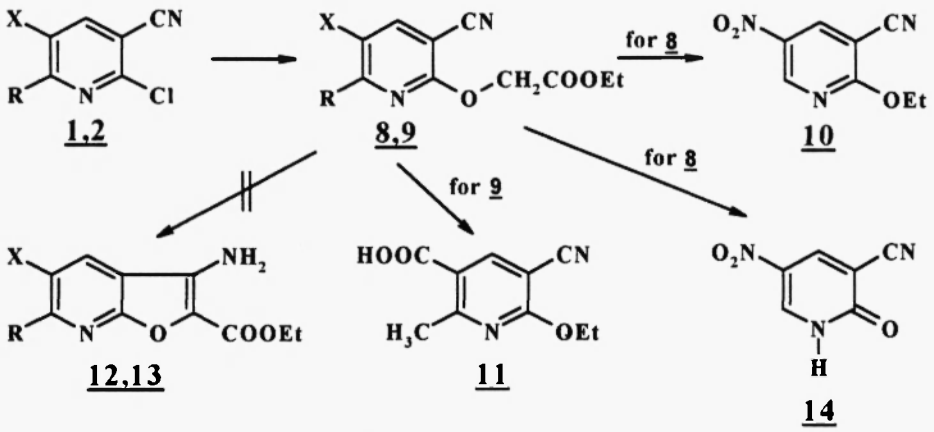
The structure of 7 was proved unambiguously from ^{1}H NMR spectral data. In the spectra of the starting compound 6 in d_6-DMSO the signals of two ethoxycarbonyl groups were observed at δ 1,17 (CH_3, tr.), 4,11 (CH_2, q.) and 1,29 (CH_3, tr.), 4,22 (CH_2, q.) p.p.m. The signals of other groups were found at 2,58 (6-CH_3, s.), 4,09 (NH$\underline{CH_2}$, d., $^3J_{CH_2NH}$ = 6 Hz), 8,15 (NH, tr.) and 8,33 (4-H, s.) p.p.m. In the spectra of 7 where one of COOEt group has been transformed to COOH group (M^+ 263), the signals of the remaining COOEt group were found at 1,29 (CH_3, tr.) and 4,22 (CH_2, q.) p.p.m. The chemical shifts of other signals practically remained unchanged (see experimental part).

The spectra of compound 7 has also been studied in d_6-DMSO-1N $NaOH_{aq}$ system. It is clear that the ionization of COOH group affects the NMR spectrum depending on position of COOEt group in molecule (whether in position 5 or in the side chain). In the recorded spectra the only significant shift has been observed for CH_2-group (Δδ=0,38ppm) whereas other protons did not change their chemical shifts (Δδ =<0,04ppm). Therefore these results confirm the presence of CH_2-COO^- anion moiety and prove the structure of obtained compound 7.

Thus the presence of NH-group hindered to Thorpe-Ziegler cyclization (probably because of formation of amide-anion) and the rate of saponification of COOEt-group was higher than the rate of pyrrole cycle closure. Evidently that the COOEt→COO^- transformation diminished CH-acidity of CH_2-group and inhibited the cyclization.

It is well known (6,7) that furan cyclization proceeds with considerable complications in comparison with pyrrole and especially thiophene cyclization. We have made attempts to obtain furo[2,3-b]-pyridines based on compounds 1 and 2. In both cases the interaction of the

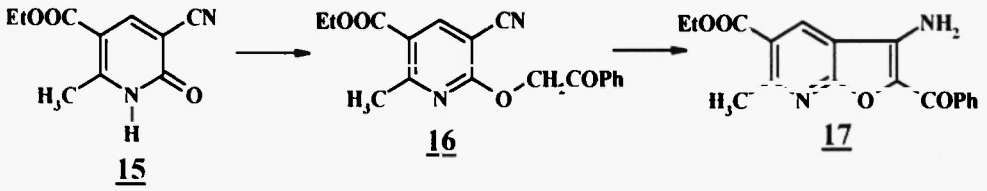
chloropyridines **1** and **2** with ethyl glycolate proceeds smoothly and ethoxycarbonylhydroxy derivatives **8, 9** were obtained with good yields (according to the method (8)). But the furan cyclizations of these esters were failed. The heating of **8, 9** in ethanol in the presence of EtONa was accompanied by the transformation of ethoxycarbonylmethoxy-groups to ethoxy-group. When nitro-derivative **8** was used for this reaction, 2-ethoxy-3-cyano-5-nitropyridine **10** has been obtained, as described before (9). In the case of compound **9** the saponifation of COOEt-group has also been observed (because of the presence of traces of water in EtOH) and as a result of the reaction 2-ethoxy-3-cyano-5-carboxy-6-methylpyridine **11** has been isolated. The desired furopyridines **12, 13** were not detected neither by isolating nor by recording of mass-spectra of the reaction mixture. The reaction of compound **8** with sodium hydroxide in ethanol proceeded similarly. In this case instead of furopyridine **12** the 3-cyano-5-nitropyridone-2 **14** has been obtained.



1 (X=NO_2, R=H); 2 (X=COOEt, R=Me); 8 (X=NO_2, R=H); 9 (X=COOEt, R=Me)
12 (X=NO_2, R=H); 13 (X=COOEt, R=Me)

Based on published results (10) we made an attempt to realize the Thorpe-Ziegler cyclization in t-butanol in the presence of the potassium t-butoxide. The exchange of 2-substituent to t-BuO^- group had not took place because of large size of the latter, but the formation of furopyridine derivative had not took place too - the starting compound was isolated only. We also tried to use Vilsmaier reagent for this cyclization as it was done (although with very low yield) by authors of the publications (11,12). But the reaction didn't occur in the described conditions, the starting compounds were isolated only. Based on these results we decided to increase the electrono-negativity of the substituent in the side chain. O-alkylation of 3-cyano-5-ethoxycarbonyl-6-methylpyridone-2 **15** by bromoacetophenone (according to methods (13-15)) has been carried out

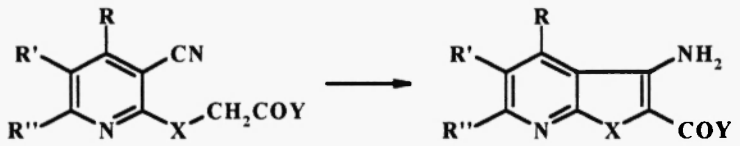
and obtained O-phenacyl derivative **16** was then refluxed in EtOH/EtONa solution. In this case 2-benzoyl-3-amino-5-ethoxycarbonyl-6-methylfuro[2,3-b]pyridine **17** has been isolated with high yield.



15 **16** **17**

Results described above and our previous investigations of Thorpe-Ziegler reaction using different starting compounds (1-3) allowed us to carry out the studies of the cyclization rate on a half-quantity level. In this work we have used TLC for this purpose. It was established that in all investigated reactions the Thorpe-Ziegler cyclization proceeded without complications. In the course of reactions the transformation of starting compounds to cyclic products was the sole direction of examined reactions (according to chromatographic data). The evaluation of the cyclization rates was fulfilled measuring the time of disappearance of the starting compounds in the chosen conditions (see **Table I**).

TABLE I



TCL control was performed using Pre-Coated TCL plates Silica Gel 60 F-254, eluent: benzene-methanol 2:1

R	R'	R''	X	Y	Time of the starting compounds disappearance (h)		
					The reaction conditions		
					DMF, Et_3N		DMF, EtONa
					20°C	DMF, boiling point	20°C
H	NO_2	H	S	OEt	0.33	no data	no data
H	NO_2	H	N(Me)	OEt	28	no data	no data
H	NH_2	H	N(Me)	OEt	reaction doesn't proceed	reaction doesn't proceed	no data
H	COOEt	Me	S	OEt	reaction doesn't proceed	2	no data
H	NO_2	H	S	NHPh	reaction doesn't proceed	no data	0,033
H	COOEt	Me	S	NHPh	reaction doesn't proceed	no data	0,15
NMe_2	H	H	S	NHPh	reaction doesn't proceed	reaction doesn't proceed	0,5
H	COOEt	Me	O	Ph	reaction doesn't proceed	reaction doesn't proceed	no data

It is clear that the presence of stronger electron-withdrawing substituent either in pyridine cycle or in the side chain lead to the acceleration of the process. In the examined range the cyclization rates have altered regarding to the substituent nature in pyridine ring:

NO_2 > COOEt > NMe_2

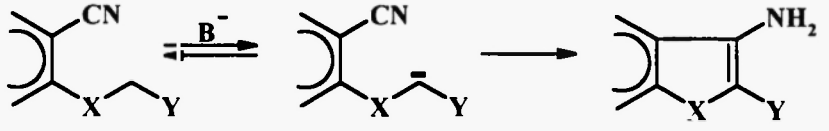
in side chain:

COOEt > CONHPh

and for furan synthesis:

COPh > COOEt (see also (16))

In accordance with the published data (6,7) the rate of thiophene cyclization was higher than that one for N-alkylpyrrole cyclization. The latter was one order higher than the rate of furan closure. Therefore we can conclude that the ionization stage **A→B** is the limiting stage of Thorpe-Ziegler cyclization.



A **B**

The similar conclusion follows also from the observed influence of the chosen base on the process rate. The rate of cyclization was significantly higher for EtONa as compared with Et_3N. More definite and detailed conclusions should be done based on «veritable» kinetic investigations.

EXPERIMENTAL.

NMR-spectra were recorded using «Unity plus 400 MHz» (Varian) with TMS as internal standard in d_6-DMSO. Mass-spectra were performed using SSQ-710 «Finnigan-MAT» mass-spectrometer with direct introduction of the samples. IR-spectra were recorded using spectrophotometer "Perkin-Elmer-457". TLC control: Pre-Coated TCL plates Silica Gel 60 F-254, eluent: benzene-methanol 2:1 UV-detection.

All physical data of synthesized compounds are presented in **Table II.**

2-[Ethoxycarbonylmethyl(N-methyl)amino]-3-cyano-5-ethoxycarbonyl-6-methylpyridine 3. Ethyl sarcosinate (1,39g, 9 mmol) and sodium acetate (1,35g, 16,4 mmol) were added to the solution of 2 (3) (1g, 4,5 mmol) in 50 ml of ethanol and the mixture was stirred for 5 h at 60°C. Mixture was cooled down, diluted with cold water, precipitate was filtered off, washed with cold water and 3 (0,95g, 69%) was obtained. M⁺ 305.

Table II: Physical data of synthesized compounds.

Comp. No.	Molecular Formula	Yield, %	m.p., °C	IR-spectra (nujol, ν, cm^{-1})	Analysis, %, Found/Calcd		
					C	H	N
3	$C_{15}H_{19}N_3O_4$	69	119-122 (ethanol)	1710 (5-COOEt), 1735 (CH_2COOEt), 2210 (CN)	58,9 / 59,0	6,4 / 6,3	13,9 / 13,8
4	$C_{15}H_{19}N_3O_4$	93	136-138 (ethanol)	1665 (2-COOEt), 1705 (5-COOEt), 3320, 3410 (NH_2)	58,9 / 59,0	6,4 / 6,3	13,8 / 13,8
6	$C_{14}H_{17}N_3O_4$	67	133-135 (ethanol)	1710 (5-COOEt), 1735 (CH_2COOEt), 2220 (CN), 3340 (NH)	57,4 / 57,7	6,1 / 5,9	14,4 / 14,4
7	$C_{12}H_{13}N_3O_4$	78	192-194 (ethanol)	1710 (5-COOEt), 1735 (CH_2COOH), 2225 (CN), 3335 (NH)	54,7 / 54,5	5,0 / 5,2	16,0 / 16,0
8	$C_{10}H_9N_3O_5$	74	92-94 (ethanol)	1750 (CO), 2230 (CN)	47,8 / 47,8	3,6 / 3,6	16,8 / 16,7
9	$C_{14}H_{16}N_2O_5$	74	91-93 (ethanol)	1710 (5-COOEt), 1730 (CH_2COOEt), 2220 (CN)	57,5 / 57,5	5,7 / 5,5	9,6 / 9,6
11	$C_{10}H_{10}N_2O_3$	77	166-168 (ethanol)	1700 (CO), 2220 (CN)	57,7 / 58,2	4,9 / 4,9	13,4 / 13,6
16	$C_{18}H_{16}N_2O_4$	69	94-95 (DMF-H_2O)	1700 (CH_2COPh), 1720 (5-COOEt), 2230 (CN)	66,9 / 66,7	5.3 / 5,0	8,7 / 8,6
17	$C_{18}H_{16}N_2O_4$	92	194-196 (DMF-H_2O)	1690 (2-COPh), 1700 (5-COOEt), 3300, 3400 (NH_2)	66,8 / 66,7	5,0 / 5,0	8,8 / 8,6

1,6-Dimethyl-2,5-diethoxycarbonyl-3-aminopyrrolo[2,3-b]pyridine 4. Small quantity of sodium ethoxide in ethanol was added to the solution of 3 (0,7g, 2,3 mmol) in 10 ml of ethanol at ethanol boiling point. Mixture was cooled down, precipitate was filtered off and 4 (1,42g, 93%) was obtained. M$^+$ 305.

2-Ethoxycarbonylmethylamino-3-cyano-5-ethoxycarbonyl-6-methylpyridine 6. Ethyl glycinate (0,76g, 5,4 mmol) and potassium carbonate (0,97g, 7 mmol) were added to the solution of 2 (1g, 4,5 mmol) in 15 ml of DMF and the mixture was stirred for 2 h at 60^{0}C. The mixture was cooled down, diluted with water, precipitate was filtered off and 6 (0,87g, 67%) was obtained. M$^+$ 291. ^{1}H NMR: δ 1,17 (CH_3, tr.), 1,29 (CH_3, tr.), 2,58 (6-CH_3, s.), 4,11 (CH_2, q.), 4,09 (NHCH_2, d., $^3J_{CH_2NH}$ = 6 Hz), 4,22 (CH_2, q.), 8,15 (NH, tr.), 8,33 (4-H, s.) p.p.m.

2-Carboxymethylamino-3-cyano-5-ethoxycarbonyl-6-methylpyridine 7. Small quantity of sodium ethoxide in ethanol was added to the solution of 6 (1g, 3,4 mmol) in 15 ml of ethanol at ethanol boiling point. Precipitate was filtered off, dissolved in cold water, concentrated hydrochloric acid was added until pH=5, precipitate was filtered off and 7 (0,7g, 78%) was obtained. M$^+$ 263. ^{1}H NMR: δ 1,29 (CH_3, tr.), 2,58 (6-CH_3, s.), 4,09 (NHCH_2, d., $^3J_{CH_2NH}$ =6 Hz), 4,22 (CH_2, q.), 8,15 (NH, tr.), 8,33 (4-H, s.) p.p.m.

2-Ethoxycarbonylmethylhydroxy-3-cyano-5-nitropyridine 8. Sodium hydride (0,65g, 27 mmol) was added by portions to the solution of ethyl glycolate (1,4g, 13,5 mmol) in 20 ml of benzene. After 0,5 h the solution of compound 1 (2g, 11 mmol) in 20 ml of benzene was added to the first solution, mixture was stirred for 48 h at 70^{0}C. Mixture was cooled down, filtered, mother liquor was evaporated under reduced pressure, precipitate was filtered off, washed with water and 8 (2,05g, 74%) was obtained. M$^+$ 251.

2-Ethoxycarbonylmethylhydroxy-3-cyano-5-ethoxycarbonyl-6-methylpyridine 9. Compound 9 was obtained analogously to 8 (Yield - 74%). M$^+$ 292.

2-Ethoxy-3-cyano-5-carboxy-6-methylpyridine 11. Compound 9 (1g, 0,34 mmol) was refluxed with sodium ethoxide in absolute ethanol for 6 h. Mixture was cooled down, precipitate was filtered off and 11 (0,54g, 77%) was obtained. M$^+$ 206.

2-Benzoylmethylhydroxy-3-cyano-5-ethoxycarbonyl-6-methylpyridine 16. Bromacetophenone (0,96g, 4,8 mmol) in 10 ml DMF and potassium carbonate (0,66g, 4,8 mmol) were added to the solution of 15 (3) (1g, 4,8 mmol) in 20 ml of DMF and mixture was stirred for 4 h at 16^{0}C. DMF was evaporated under reduced pressure, residue was triturated with water, precipitate was filtered off and 16 (1,07g, 69%) was obtained. M$^+$ 324.

2-Benzoyl-3-amino-5-ethoxycarbonyl-6-methylfuro[2,3-d]pyridine 17. Small quantity of sodium ethoxide in ethanol was added to the solution of **16** (1g, 3,1 mmol) in 10 ml of ethanol at ethanol boiling point. Mixture was cooled down, precipitate was filtered off and **17** (0,91g, 92%) was obtained. M' 324.

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