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Aminomethyl Derivatives of Furancarboxylic Acids in the Paal–Knorr Reaction

I. M. Lapina, L. M. Pevzner, and A. A. Potekhin

St. Petersburg State University,
Universitetskii pr. 26, St. Petersburg, 198504 Russia

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Abstract — Aminomethyl derivatives of furancarboxylic acids react with 1,4-dicarbonyl compounds under Paal–Knorr reaction conditions to form the pyrrole ring. It is found that α-aminomethyl derivatives of furancarboxylic acids react faster than their β analogs. The carboxy group adjacent to the aminomethyl fragment decelerates the process.

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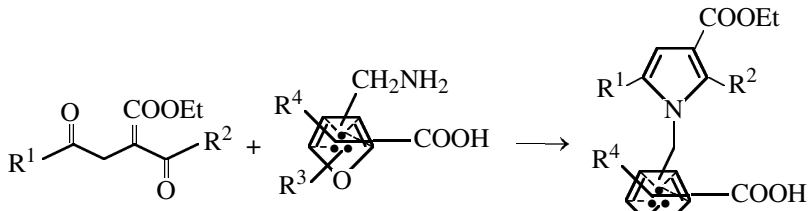
Furan derivatives bound with a nitrogen-containing heterocycle by a methylene bridge are present among quinolizidine alkaloids of the nupharidin group [1]. Some biologically active compounds contain in their stucture an N-alkylated hydrogenated pyrrole ring [2]. Therefore, compounds having both these fragments in one molecule can present interest for searching for new biologically active substances.

We recently [3] prepared a series of aminomethyl derivatives of furancarboxylic acids (compounds **I**–**IV**) and used them as amino components in the Paal–Knorr synthesis [4].



VII–**IX** **I**–**VI**

I–**IV**, R^3, R^4 = H, CH_3; **VII**, $R^1 = R^2 = CH_3$; **VIII**, $R^1 = C(CH_3)_3$, $R^2 = CH_3$; **IX**, $R^1 = CH_3$, R^2 = H.

Ethyl 2-acetyl-4-oxopentanoate (**VII**), ethyl 2-acetyl-5,5-dimethyl-4-oxopentanoate (**VIII**), and ethyl 2-formyl-4-oxopentanoate **IX** were chosen as 1,4-dicarbonyl components.

The reaction was carried out in glacial acetic acid at 100–110°C. The reagent molar ratio was 1 : 1. The reaction progress was monitored by means of TLC. Presence or absence of the 1,4-dicarbonyl compound was controlled.

The character of the process was determined by the position of the aminomethyl group in the furan ring (α or β) and with respect to carboxyl. The reaction times and the yields of the final products are presented in the table.

As seen from the table, the reaction time increases in going from furancarboxylic acids with a remote α-aminomethyl group to those having the aminomethyl group adjacent to the carboxyl, and further to β-(aminomethyl)furancarboxylic acids.

For example, ester **VII** reacts with 5-(aminomethyl)-furan-2-carboxylic acid within 40 min, while the reaction with 5-(aminomethyl)furan-3-carboxylic acid (**II**) proceeds 60 min. The reactions of 2-(aminomethyl)-5-methylfuran-3-carboxylic acid (**III**), 4-(aminomethyl)-2,5-dimethylfuran-3-carboxylic acid (**V**), and 3-(aminomethyl)furan-2-carboxylic acid (**VI**) with the above-mentioned carbonyl component are com-

Reaction time and yield of final product

Comp. no.	(Aminomethyl)furancarboxylic acid	1,4-Dicarbonyl compound		
		VII	**VIII**	**IX**
I	5-(Aminomethyl)furan-2-carboxylic acid	40 min, 81%	45 min, 70%	
II	5-(Aminomethyl)furan-3-carboxylic acid	60 min, 74%		
III	2-Aminomethyl-5-methylfuran-3-carboxylic acid	150 min, 74%		150 min, 46%
IV	4-Aminomethyl-5-methylfuran-2-carboxylic acid		180 min, 55%	
V	4-Aminomethyl-2,5-dimethylfuran-3-carboxylic acid	420 min, 69%	960 min, 60% [a]	260 min, 48% [b]
VI	3-(Aminomethyl)furan-2-carboxylic acid	620 min, 78%		

[a] Conversion of (aminomethyl)furancarboxylic acid 75%. [b] Conversion of (aminomethyl)furancarboxylic acid 82%.

plete in 150, 420, and 620 min, respectively. 1,4-Dicarbonyl compounds **VIII** and **IX** react analogously.

In the reactions of 4-(aminomethyl)-2,5-dimethylfuran-3-carboxylic acid (**V**) with 1,4-dicarbonyl compounds **VIII** and **IX**. the latter are completely consumed, and some part of the starting amino acid remain unreacted . The recoveries of acid **V** in the case of 1,4-dicarbonyl compounds **VIII** and **IX** were 25 and 18%, respectively. Evidently, the formation of pyrrole is accompanied by acid hydrolysis of 1,4-dicarbonyl compounds.

Diketone **VII** is significantly more stable to heating in acetic acid than all the other diketones. The yields of the final products in its reactions with (aminomethyl)furancarboxylic acids **V** and **VI** were 69 and 78%, respectively. Hence, the use of (aminomethyl)-furancarboxylic acids in the Paal–Knorr synthesis permits to prepare compounds containing the pyrrole and furan rings simultaneously. The process is decelerated in going from α- to β-aminomethyl derivatives of furancarboxylic acids. The fraction of decomposed 1,4-dicarbonyl compound will increase with increasing reaction time with an unreactive (aminomethyl)furancarboxylic acid.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker WM-250 (250 MHz) and Bruker DPX-400 (400 MHz) instruments in $CDCl_3$ and DMSO-d_6 against TMS. Thin-layer chromatography was carried out on Silufol plates, eluent chloroform, developer iodine vapor.

Reaction of 1,4-dicarbonyl compounds with (aminomethyl)furancarboxylic acids. (Aminomethyl)furancarboxylic acid was suspended in glacial acetic acid [20 ml of glacial acetic acid per 1 g of (aminomethyl)furancarboxylic acid]. An equvalent amount of 1,4-dicarbonyl compound was added with stirring, and the reaction mixture was heated to 100–110°C for some time (see table). The reaction progress was monitored by TLC. After the reaction was complete, the solvent was removed at reduced pressure. The residue was dissolved in a little ethanol, and water was added dropwise until crystals formed. They were filtered off and dried at 40-50°C. In the reaction with (aminomethyl)furancarboxylic acid **V**, unreacted amino acid was filtered off before evaporation of the solution.

5-[3-(Ethoxycarbonyl)-2,5-dimethyl-1*H*-pyrrol-1-ylmethyl]furan-3-carboxylic acid. mp 158°C. ^{1}H NMR spectrum, δ, ppm: 1.33 t (CH_3CH_2), 2.23 s (pyrrole 5-CH_3), 2.56 s (pyrrole 2-CH_3), 4.26 q (CH_2·CH_3), 4.94 s (CH_2N), 6.29 s and 6.42 s (pyrrole H and furan H^{β}), 8.00 s (furan H^{α}), 9.56 br.s (COOH). Found, %: 61.97, H 5.94, N 4.52. $C_{15}H_{17}NO_5$. Calculated, %: C 61.85, H 5.88, N 4.81.

5-[3-(Ethoxycarbonyl)-2,5-dimethyl-1*H*-pyrrol-1-ylmethyl]furan-2-carboxylic acid. mp 172°C. ^{1}H NMR spectrum, δ, ppm: 1.33 t (CH_3CH_2), 2.20 s (pyrrole 5-CH_3), 2.52 s (pyrrole 2-CH_3), 4.24 q (CH_2·CH_3), 5.02 s (CH_2N), 5.98 d (furan H^4, J_{HH} 2.4 Hz), 6.31 s (H, pyrrole), 7.18 d (furan H^3, J_{HH} 2.4 Hz), 8.75 br.s (COOH). Found, %: C 61.99, H 5.95, N 4.71. $C_{15}H_{17}NO_5$. Calculated, %: C 61.85, H 5.88, N 4.81.

5-[5-*tert*-Butyl-3-(ethoxycarbonyl)-2-methyl-1*H*-pyrrol-1-ylmethyl]furan-2-carboxylic acid. mp 183°C. ^{1}H NMR spectrum, δ_P, ppm: 1.27 m [$(CH_3)_3C$ + CH_3CH_2], 2.42 s (pyrrole CH_3), 4.28 q (CH_2CH_3), 5.28 s (CH_2N), 5.79 d (furan H^4, J_{HH} 2.4 Hz), 6.36 s (pyrrole H), 7.22 s (furan H^3, J_{HH} 2.4 Hz), 10.30 br.s (COOH). Found, %: C 64.65, H 7.06, N 4.10. $C_{18}H_{23}NO_5$. Calculated, %: C 64.85, H 6.95, N 4.20.

4-[3-(Ethoxycarbonyl)-2,5-dimethyl-1*H*-pyrrol-1-ylmethyl]-2,5-dimethylfuran-3-carboxylic acid. mp 171°C. ^{1}H NMR spectrum, δ, ppm: 1.37 t (CH_3·

CH_2), 2.13 s, 2.17 s, 2.46 s, 2.55 s (furan and pyrrole CH_3), 4.26 q (CH_2CH_3), 5.07 s (CH_2N), 6.29 s (pyrrole H). Found, %: C 64.02, H 6.36, N 4.25. $C_{17}H_{21} \cdot NO_5P$. Calculated, %: C 63.92, H 6.64, N 4.39.

4-[5-*tert*-Butyl-3-(ethoxycarbonyl)-2-methyl-1*H*-pyrrol-1-ylmethyl]-2,5-dimethylfuran-3-carboxylic acid. mp 108°C. ^{1}H NMR spectrum, δ, ppm: 1.32 m [$(CH_3)_3C$ + CH_3CH_2], 2.17 s (pyrrole CH_3), 2.40 s (furan 5-CH_3), 2.56 s (furan 2-CH_3), 4.25 q (CH_2CH_3), [5.16 d (CH_A, J_{AB} 23 Hz), 5.47 d (CH_B, J_{AB} 23 Hz)], 6.35 s (pyrrole H). Found, %: C 66.06, H 7.76, N 3.68. $C_{20}H_{27}NO_5$. Calculated, %: C 66.46, H 7.53, N 3.88.

4-[5-*tert*-Butyl-3-(ethoxycarbonyl)-2-methyl-1*H*-pyrrol-1-ylmethyl]-5-methylfuran-2-carboxylic acid. mp 187°C. ^{1}H NMR spectrum, δ, ppm: 1.32 m [$(CH_3)_3C$ + CH_3CH_2], 2.18 s (pyrrole CH_3), 2.36 s (furan CH_3), 4.25 q (CH_2CH_3), 5.05 s (CH_2N), 6.37 s, 6.72 s (pyrrole and furan H). Found, %: C 64.60, H 7.13, N 3.95. $C_{19}H_{25}NO_5$. Calculated, %: C 65.69, H 7.25, N 4.03.

3-[3-(Ethoxycarbonyl)-2,5-dimethyl-1*H*-pyrrol-1-ylmethyl]furan-2-carboxylic acid. Decomp. point 163°C. ^{1}H NMR spectrum, δ, ppm: 1.22 t (CH_3CH_2), 2.03 s (pyrrole 5-CH_3), 2.34 s (pyrrole 2-CH_3 + DMSO), 4.11 q (CH_2CH_3), 5.11 s (CH_2N), 5.67 s (pyrrole H^β), 6.18 (furan H^β), 7.32 s (furan H^α). Found, %: C 61.71, H 5.82, N 4.57. $C_{15}H_{17}NO_5$. Calculated, %: 61.85, H 5.88, N 4.81.

2-(3-Carboxy-5-methyl-1*H*-pyrrol-1-ylmethyl)-5-methylfuran-3-carboxylic acid. Decomp. point 244°C. ^{1}H NMR spectrum, δ, ppm: 2.17 s, 2.07 s (pyrrole and furan 5-CH_3), 5.33 s (CH_2N), 6.10 s, 6.32 s (furan and pyrrole H^β), 7.26 s (pyrrole H^α), 12.32 br.s (carboxyl 2H).

4-(3-Carboxy-5-methyl-1*H*-pyrrol-1-ylmethyl)-2,5-dimethylfuran-3-carboxylic acid. Decomp. point 253°C. ^{1}H NMR spectrum, δ, ppm: 2.05 s, 2.15 s (pyrrole and furan 5-CH_3), 2.49 s (furan 2-CH_3 + DMSO), 4.96 s (CH_2N), 6.09 s (pyrrole H^β), 6.99 s (pyrrole H^α), 12.11 br.s (2H, COOH).

2-[3-(Ethoxycarbonyl)-2,5-dimethyl-1*H*-pyrrol-1-ylmethyl]-5-methylfuran-3-carboxylic acid. mp 183°C. ^{1}H NMR spectrum, δ, ppm: 1.32 t (CH_3CH_2), 2.17 s (pyrrole 5-CH_3), 2.22 s (pyrrole 2-CH_3), 2.57 s (furan CH_3), 4.25 q (CH_2CH_3), 5.32 s (CH_2N), 6.26 s (pyrrole H^β). 6.31 s (furan H^β). Found, %: C 63.16, H 6.20, N 4.47. $C_{16}H_{19}NO_5$. Calculated, %: C 62.94; H 6.27, N 4.59.

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