

Semisynthetic cephalosporines

I. An improved synthesis of 5-aryl-2-furancarboxylic acids

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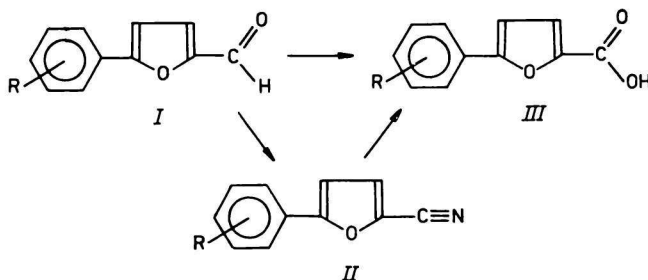
5-Aryl-2-furancarboxylic acids were prepared in substantially higher yields via oxidation of the corresponding furaldehydes, or by basic hydrolysis of 5-aryl-2-furonitriles. The starting aldehydes were obtained by Meerwein arylation of 2-fural.

5-Арил-2-фуранкарбоновые кислоты были получены с существенно более высокими выходами посредством окисления соответствующих фуральдегидов или щелочным гидролизом 5-арил-2-фуронитрилов. Исходные альдегиды были получены арилированием 2-фураля по Meerвейну.

5-Aryl-2-furancarboxylic acids *III* were prepared as intermediates for the synthesis of 5-(5-aryl-2-furyl)-tetrazol-1-ylacetic acids, which served for acylation of 7-aminocephalosporanic acid giving thus new semisynthetic cephalosporines.

Acids *III* are most frequently prepared by Meerwein arylation of 2-furancarboxylic acid [1—6]. This method, however, afforded the required compounds in low yields only, and therefore, several authors oxidized the corresponding aldehydes *I* by silver oxide at 25 °C [7—9] in 20 to 78 % yield. Increase of the yield of acids by oxidation of liquid aldehydes, or those having m.p. < 60 °C up to 77 to 86 % was achieved by raising the reaction temperature to 50—60 °C and adding ethanol to the reaction mixture in which these aldehydes and sodium salts of the corresponding acids are better soluble. Oxidation of crystalline aldehydes *I*, having melting point above 75 °C, failed by this method even after addition of ethanol and therefore, the corresponding 5-aryl-2-furonitriles *II* were prepared through oximes by dehydration with acetic anhydride in pyridine at temperatures not exceeding

95 °C [10—12]; nitriles *II* were hydrolyzed in basic medium to acids *III*. This procedure has so far been reported for preparation of 5-(4-nitrophenyl)-2-furancarboxylic acid (*IIIi*) [13] and 5-(4-chlorophenyl)-2-furancarboxylic acid (*IIIb*) [4]. The starting 5-aryl-2-furaldehydes *I* were obtained by Meerwein arylation of 2-furaldehyde [14—21] in aqueous medium; the temperature increase to 28—30 °C after addition of all reaction components resulted in purer products, higher yields, and simpler isolation (Scheme 1).



Scheme 1

Experimental

Melting points were determined on a Kofler micro hot-stage apparatus, the i.r. spectra of acids (in KBr) were recorded with a Perkin—Elmer, model 457, spectrophotometer at the concentration $c = 2.5 \times 10^{-6}$ mol dm⁻³, those of aldehydes and nitriles (in chloroform) at $c = 2.0 \times 10^{-2}$ mol dm⁻³ in a 1 mm NaCl cell.

5-Aryl-2-furaldehydes Ia—In

2-Furaldehyde (123 g; 1.28 mol) in water (650 cm³) was poured at temperatures not exceeding 10 °C into a solution of diazonium salt of the substituted aniline (1 mol), obtained by filtration of the reaction mixture 10 min after diazotization. After 30 min of stirring copper dichloride dihydrate (34.1 g; 0.2 mol) in water (80 cm³) was added at 25 °C during 30 min. The mixture was then stirred at 28—30 °C for 5 h. The substituted formaldehyde separating after 2 days was filtered off, if solid, washed with 50 % ethanol and ethanol, till oily impurities came out; finally, it was crystallized from a suitable solvent. An arylated oily furaldehyde was separated, the aqueous layer was extracted with chloroform (2 × 250 cm³), the organic layer was combined with the main portion, washed with 5 % NaOH (2 × 300 cm³) and water, the solvent was removed and sodium carbonate (1.76 g; 16.5 mmol) was added to the residue. The unwanted by-products were removed by steam distillation (8—10 h), the residue was taken out with ether (3 × 300 cm³), the extract was washed with

Table 1

5-Aryl-2-furaldehydes Ia—In

Compound	R	M.p./°C		Yield/%	Solvent	M.p./°C	
		B.p./°C (p/kPa)				B.p./°C (p/kPa)	Ref.
Ia	H	144—146 (0.7)	42	—	—	145 (0.7) [19]	
Ib	4-Cl	130—131	63	Ethanol	—	129 [14]	
Ic	3-Cl	114—115	59	Ethanol	—	97.5—98 [15]	
Id	2-Cl	78—79	61	Ethanol	—	76.5—77.5 [16]	
Ie	2,6-Cl ₂ ^a	56—58	41	Ethanol	—	—	
If	4-Br	157—158	64	Ethanol	—	158 [17]	
Ig	3-CF ₃	53—54	36	50 % Ethanol	—	—	
Ih	2-CF ₃ ^b	47—48	35	50 % Ethanol	—	—	
Ii	4-NO ₂	213—214	67	Ethyl acetate	—	213—214 [18]	
Ij	2-NO ₂	98—98.5	65	Ethanol	—	98—98.5 [18]	
Ik	4-CH ₃	55—56	36	—	—	55—56 [19]	
		118—120 (0.07)	—	—	—	160 (1.1) [19]	
Il	3-CH ₃ ^c	105—106 (0.07)	32	—	—	—	
Im	4-CH ₃ O	173—175 (0.07)	25	—	—	175 (0.07) [19]	
In	2-CH ₃ O ^d	162—163 (0.07)	22	—	—	—	

a) For C₁₁H₆Cl₂O₂ (M_r=241.1) w_i(calculated): 54.80 % C, 2.50 % H, 29.41 % Cl; w_i(found): 54.12 % C, 2.30 % H, 30.08 % Cl. IR spectrum ($\tilde{\nu}/\text{cm}^{-1}$): 1679 $\tilde{\nu}(\text{C}=\text{O})$. b) For C₁₂H₇F₃O₂ (M_r=240.2) w_i(calculated): 60.01 % C, 2.93 % H; w_i(found): 60.28 % C, 3.12 % H. IR spectrum ($\tilde{\nu}/\text{cm}^{-1}$): 1681 $\tilde{\nu}(\text{C}=\text{O})$. c) For C₁₂H₁₀O₂ (M_r=186.2) w_i(calculated): 77.38 % C, 5.40 % H; w_i(found): 77.66 % C, 5.58 % H. IR spectrum ($\tilde{\nu}/\text{cm}^{-1}$): 1687 $\tilde{\nu}(\text{C}=\text{O})$. d) For C₁₂H₁₀O₃ (M_r=202.2) w_i(calculated): 71.25 % C, 4.98 % H; w_i(found): 71.12 % C, 4.98 % H. IR spectrum ($\tilde{\nu}/\text{cm}^{-1}$): 1680 $\tilde{\nu}(\text{C}=\text{O})$.

5 % sodium carbonate ($2 \times 300 \text{ cm}^3$) and water to a neutral reaction, and concentrated. The aldehyde prepared in this way is suitable for oxidation without further purification. A pure aldehyde can be obtained either by distillation under reduced pressure, or by extraction with boiling n-heptane; the latter procedure is more advantageous since no tarry products become formed upon higher temperatures during distillation.

Physicochemical characteristics of aldehydes *Ia—In* are presented in Table 1.

5-Aryl-2-furonitriles IIa—III

5-Aryl-2-furaldehyde (0.2 mol) and hydroxylammonium chloride (24.0 g; 244 mmol) were heated in pyridine (160 cm^3) at 60°C for 30 min, then acetic anhydride (110 cm^3 , 1 mol) was successively added at a temperature not exceeding 95°C , which was being kept for additional 2 h. The mixture was cooled to 20°C , poured into water (1000 cm^3) and the separated nitrile was stirred for 1 h, filtered, washed with water, dried, and crystallized.

Physicochemical characteristics of furonitriles *IIa—III* are listed in Table 2.

5-Aryl-2-furancarboxylic acids IIIa—III

Method A

Silver nitrate (67.95 g; 0.4 mol) in water (300 cm^3) was added to a stirred aqueous solution of sodium hydroxide (32 g; 0.8 mol, 200 cm^3). 5-Aryl-2-furaldehyde (0.1 mol) was at once added to the brown precipitate and the temperature was maintained within $50\text{—}60^\circ\text{C}$ for 1 h; ethanol (200 cm^3) was added, and the separated silver was filtered off after 5 min, the hot filtrate was acidified with 15 % hydrochloric acid and the freed substituted furancarboxylic acid was filtered off, washed with water, dried, and crystallized.

Method B

Potassium hydroxide (16.8 g; 0.3 mol) in water (40 cm^3) was poured into a solution of 5-aryl-2-furonitrile (0.1 mol) in hot ethanol (125 cm^3). The mixture was heated at a gentle reflux for 12 h, filtered and the filtrate was diluted with water (250 cm^3). Acidification of the filtrate with 15 % hydrochloric acid resulted in separation of the respective substituted furancarboxylic acid, which was worked up as with the method A.

Physicochemical characteristics of acids *IIIa—III* are given in Table 3.

Table 2
5-Aryl-2-furonitriles *IIa—III*

Compound	R	M.p./°C B.p./°C (p/kPa)	Yield/%	Solvent	M.p./°C Ref.
<i>IIa</i>	H	71—72	83	Ethanol	72 [10]
<i>IIb</i>	4-Cl	74—75	86	n-Hexane	76 [10]
<i>IIc</i>	3-Cl	106—107	86	n-Heptane	104—105 [11]
<i>IId</i>	2-Cl	76—77	80	n-Hexane	74—75 [11]
<i>IIe</i>	2,6-Cl ₂	39—40	81	Ethanol	—
<i>IIf</i>	4-Br	86—87	87	n-Heptane	88 [10]
<i>IIg</i>	4-NO ₂	172—173	81	Ethanol	172—173 [13]
<i>IIh</i>	2-NO ₂	97—98	86	Ethanol	97—98 [10]
<i>IIi</i>	4-CH ₃	95—96	86	n-Heptane	87 [10]
<i>IIj</i>	3-CH ₃ ^b	92—95 (0.07)	81	—	—
<i>IIk</i>	4-CH ₃ O	85—86	76	Ethanol	86 [10]
<i>III</i>	2-CH ₃ O ^c	116—118	60	Ethanol	—

a) For C₁₁H₅Cl₂NO (*M_r* = 238.1) *w_i*(calculated): 55.46 % C, 2.11 % H, 5.88 % N, 29.78 % Cl; *w_i*(found): 55.72 % C, 1.92 % H, 5.92 % N, 30.06 % Cl. IR spectrum ($\tilde{\nu}/\text{cm}^{-1}$): 2226 $\tilde{\nu}(\text{C}\equiv\text{N})$. **b)** For C₁₂H₉NO (*M_r* = 183.2) *w_i*(calculated): 78.75 % C, 4.94 % H, 7.65 % N; *w_i*(found): 78.90 % C, 4.78 % H, 7.70 % N. IR spectrum ($\tilde{\nu}/\text{cm}^{-1}$): 2228 $\tilde{\nu}(\text{C}\equiv\text{N})$. **c)** For C₁₂H₉NO₂ (*M_r* = 189.2) *w_i*(calculated): 72.41 % C, 4.53 % H, 7.08 % N; *w_i*(found): 72.56 % C, 4.45 % H, 7.12 % N. IR spectrum ($\tilde{\nu}/\text{cm}^{-1}$): 2227 $\tilde{\nu}(\text{C}\equiv\text{N})$.

Table 3
5-Aryl-2-furancarboxylic acids IIIa—IIIl

Compound	R	M.p./°C Yield/%	Solvent Method	M.p./°C Ref.	Method Yield/%
IIIa	H	147—148 82	Water A	151—152 [9]	A 78
IIIb	4-Cl	197—200 89	Ethanol B	198—201 [4]	C 20
IIIc	3-Cl	181—182 87	50 % Acetic acid B	173—176 [5]	C 17
III d	2-Cl	217—220 83	Ethanol B	219—223 [5]	C 18
IIIe	2,6-Cl ₂ ^c	204—205 84 ^a , 78 ^b	50 % Ethanol A, B	—	—
III f	4-Br	207—209 86	Ethanol B	198—200 [4]	C 18
III g	3-CF ₃	211—213 79	50 % Ethanol A	208—210 [9]	C 21.3
III h	2-CF ₃ ^d	170—173 77	50 % Ethanol A	—	—
III i	4-NO ₂	254—256 71	Acetic acid B	251—252 [4]	C 40
III j	2-NO ₂	215—218 76	50 % Ethanol B	213—215 [5]	C 33
III k	4-CH ₃	182—184 81 ^a , 79 ^b	50 % Ethanol A, B	180—183 [9]	A 20
III l	4-CH ₃ O	187—189 86 ^a , 83 ^b	Benzene A, B	172—176 [9]	A 32

Method C = Meerwein arylation of 2-furancarboxylic acid; a) method A; b) method B; c) For C₁₁H₆Cl₂O₃ (M_r = 257.1) w_i(calculated): 51.39 % C, 2.36 % H, 27.58 % Cl; w_i(found): 51.18 % C, 2.32 % H, 27.83 % Cl. IR spectrum ($\tilde{\nu}/\text{cm}^{-1}$): 1673 $\tilde{\nu}(\text{C}=\text{O})$. d) For C₁₂H₇F₃O₃ (M_r = 256.2) w_i(calculated): 56.26 % C, 2.75 % H; w_i(found): 56.43 % C, 2.64 % H. IR spectrum ($\tilde{\nu}/\text{cm}^{-1}$): 1730 $\tilde{\nu}(\text{C}=\text{O})$.

References

1. Freund, W., *J. Chem. Soc.* 1952, 3068.
2. Marthur, K. B. L. and Mehra, H. S., *J. Chem. Soc.* 1961, 2576.
3. Khan, M. and Rolya, J., *Aust. J. Chem.* 26, 1147 (1973).
4. Krutošíková, A., Kováč, J., Rentka, J., and Čakrt, M., *Collect. Czechoslov. Chem. Commun.* 39, 767 (1974).
5. Krutošíková, A., Kováč, J., and Sýkora, V., *Collect. Czechoslov. Chem. Commun.* 39, 1892 (1974).
6. Oleinik, A. F., Voziakova, T. I., Novitskii, K. Yu., Zykova, T. N., Guskova, T. A., and Pershin, G. N., *Khim.-Farm. Zh.* 10, 46 (1976).
7. Chadwick, D., Chambers, J., and Meakins, J., *J. Chem. Soc., Perkin Trans. I* 1973, 1766.
8. Wright, G. C., Burch, H. A., and Goldenberg, M. M., U.S. 3856825; *Chem. Abstr.* 82, 139940 (1975).
9. Burch, H. A., White, R. E., Wright, G. C., and Goldenberg, M. M., *J. Pharm. Sci.* 69, 107 (1980).
10. Považanec, F., Kováč, J., and Krutošíková, A., *Collect. Czechoslov. Chem. Commun.* 41, 1692 (1976).
11. Považanec, F. and Kováč, J., *Chem. Zvesti* 33, 798 (1979).
12. Oleinik, A. F., Voziakova, T. I., Solovyeva, N. P., and Novitskii, K. Yu., *Khim. Geterotsykl. Soedin.* 1975, 1029.
13. Hahn, W. E., Krajzewicz, F., and Nowaczyk, M., *Lódž. Towarz. Nauk, Wydział III* 6, 15 (1960); *Chem. Abstr.* 55, 19891 (1961).
14. Akashi, H. and Oda, R., *Rep. Inst. Chem. Research* 19, 93 (1949); *Chem. Abstr.* 45, 7519 (1951).
15. Parke, Davis, and Co. Michigan, USA, *Brit.* 1139164 (1969); *Chem. Abstr.* 71, 77769 (1969).
16. Krutošíková, A., Kováč, J., Frimm, R., Kováč, Š., and Sticzay, T., *Chem. Zvesti* 25, 142 (1971).
17. Oleinik, A. F., Voziakova, T. I., and Novitskii, K. Yu., *Khim.-Farm. Zh.* 5, 19 (1971).
18. Frimm, R., Kováč, J., and Jurášek, A., *Zborník prác Chemickotechnologickej fakulty SVŠT.* (Collection of Communications, Section Chemistry, Slovak Technical University.) P. 35. Bratislava, 1967.
19. Frimm, R., Kováč, J., and Krutošíková, A., *Chem. Zvesti* 27, 101 (1973).
20. Pelosi, S. S., White R. E., White, R. L., Wright, G. C., and Chia-Nien You, U.S. 3906010; *Chem. Abstr.* 84, 30857 (1976).
21. Pelosi, S. S., White, R. E., White, R. L., Wright, G. C., and Chia-Nien You, U.S. 3919231; *Chem. Abstr.* 84, 59168 (1976).

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