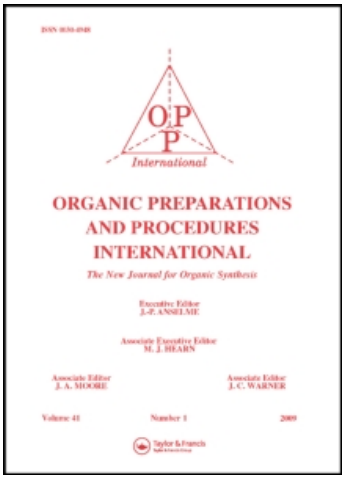

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SYNTHESIS OF OXYGEN HETEROCYCLES FROM 2-ARYLIDENE-1,3-D1 KETONES

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SYNTHESIS OF OXYGEN HETEROCYCLES FROM 2-ARYLIDENE-1,3-DIKETONES

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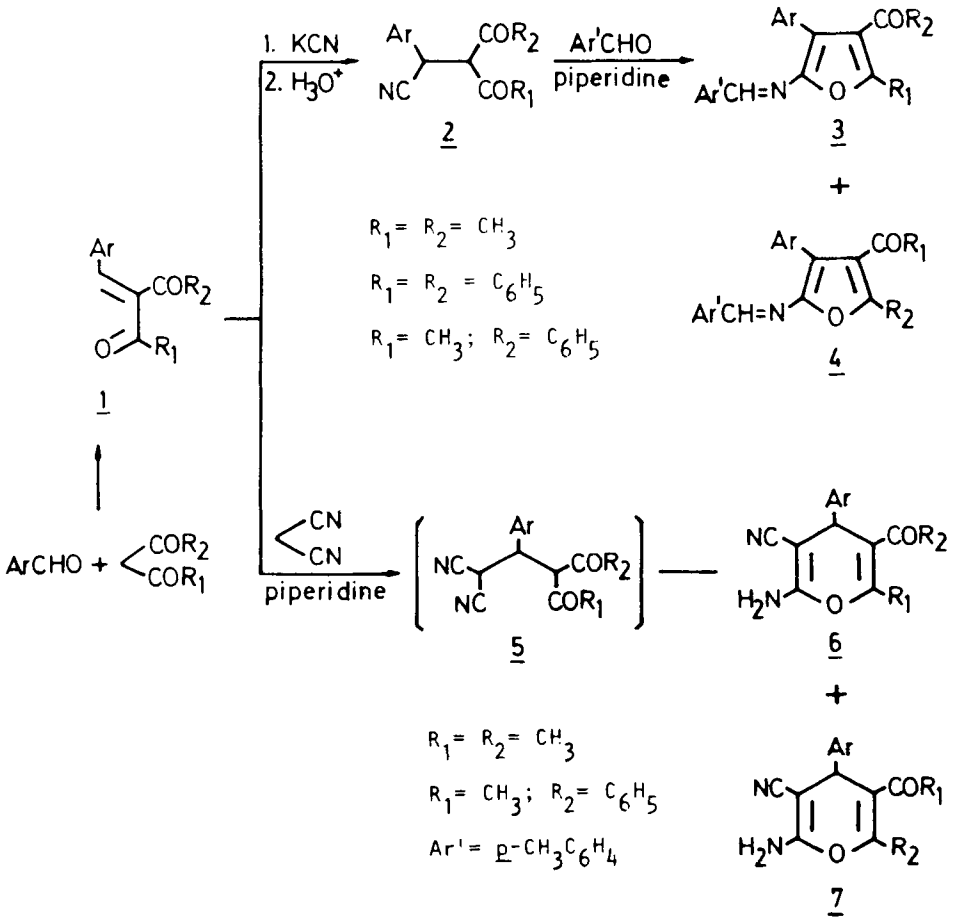
Although 2-arylidene-1,3-diketones can be useful starting materials for the preparation of heterocyclic compounds, there are only a limited number of literature references describing their use in heterocyclic synthesis. Thus, reactions of 2-arylidene-1,3-diketones with ammonia or benzamidine lead to pyrimidine derivatives.[1,2] Pyrrolines are obtained by treatment with imines derived from α-aminoacids[3] and dihidropyridines result from the reaction of ß-aminocarbonyl compounds with 2-arylidene-1,3-diketones.[4] On the other hand, 2-arylidene-1,3-diketones can also afford pyrazoles and other heterocycles by 1,3-dipolar cycloaddition reactions with diazomethane[5] or hetero Diels-Alder cycloaddition with 1,2-dimethoxyethane.[6] This paper, describes the synthesis of furans and 4H-pyrans by reaction of either hydrogen cyanide or malononitrile with 2-arylidene-1,3-diketones (1), which are easily obtained by the Knoevenagel condensation of aromatic aldehydes with 1,3-diketones.

Treatment of 3-arylidene-2,4-pentanediones 1a-d (R_1= R_2= CH_3) with potassium cyanide followed by acid treatment, affords the products resulting from the conjugate addition, 3-acetyl-2-aryl-4-oxopentanonitriles (2a-d) in good yields. These compounds cyclize upon basic treatment in the presence of an aromatic aldehyde to 4-acetyl-N-arylidene-2-aminofurans 3a-d, in a reaction involving a carbonyl and the nitrile group; the alde-

hyde is added as a trap for the unstable 2-aminofuran, which are isolated as stable Schiff bases. On the other hand, 3-benzylidene-2,4-pentanedione 1a undergoes Michael addition with malononitrile to yield in a single step

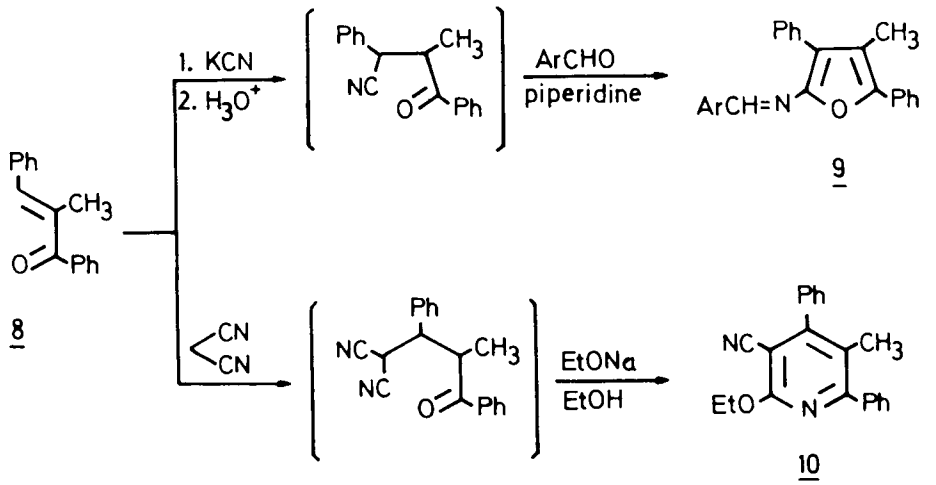


a 2-amino-4H-pyran (6a) through spontaneous cyclization of intermediate 5. 2-Arylidene-1,3-diphenyl-1,3-propanediones 1e-i (R_1= R_2= C_6H_5) behave in a similar manner, leading to pyranamines 6b-f and reaction of compounds 1e-i[7] with hydrogen cyanide, followed by cyclization in the presence of an aromatic aldehyde has also lead to the corresponding furan derivatives.

When the starting 2-arylidene-1,3-diketones (1) bear two different

acyl groups ($R_1 \neq R_2$), two different cyclization products are possible and a mixture is obtained. Thus, conjugate addition of hydrogen cyanide to 2-arylidene-1-phenyl-1,3-butanediones 1j-l (R_1= CH_3; R_2= C_6H_5) leads to 2-aryl-3-benzoyl-4-oxopentanenitriles 2e-g which undergo a base promoted cyclization, in the presence of an aromatic aldehyde, to a mixture of furans 3e-g and 4a-c. In the same way, a mixture of pyrans 6g and 7 is obtained by reaction of diketone 1j with malononitrile.

The above mentioned synthesis were also applied to 1,3-diphenyl-2-methylpropenone 8, which has a methyl group instead of an acyl group in compounds 1. Reaction of hydrogen cyanide with 8 in the presence of an aromatic aldehyde leads to the expected methyl substituted aminofuran 9 in low yield. However, treatment of propenones 8 with malononitrile and piperidine does not afford any isolable compound. When the latter reaction is carried out in sodium ethoxide/ethanol, an ethoxide promoted cyclization occurs, followed by an spontaneous aromatization to pyridine 10.



EXPERIMENTAL SECTION

Melting points were determined in a Buchi apparatus in capillary tubes and are uncorrected. Infrared spectra were recorded on Perkin-Elmer 257 and

TABLE 1. Physical Data of Compounds 2-4,6

Comp.	Ar	R_1	R_2	Yield (%)	mp.[a] (°C)	Elemental Analysis: Calcd. (Found) C	H	N
2a	C_6H_5	CH_3	CH_3	86	124-126		Ref. 15	
2b	p-$CH_3C_6H_4$	CH_3	CH_3	86	85-86	73.34	6.59	6.11
						(72.94)	(6.86)	(6.22)
2c	p-$CH_3OC_6H_4$	CH_3	CH_3	80	95-96	68.54	6.16	5.71
						(68.25)	(5.86)	(6.00)
2d	p-ClC_6H_4	CH_3	CH_3	87	106-107	62.53	4.85	5.61[b]
						(62.28)	(4.92)	(5.64)
2e	C_6H_5	CH_3	C_6H_5	88	110-112	77.95	5.45	5.05
						(77.64)	(5.42)	(4.70)
2f	p-$CH_3OC_6H_4$	CH_3	C_6H_5	59	122-124	74.25	5.58	4.56
						(74.47)	(5.51)	(4.59)
2g	p-ClC_6H_4	CH_3	C_6H_5	70	116-119	69.34	4.53	4.49[b]
						(69.51)	(4.73)	(4.57)
3a	C_6H_5	CH_3	CH_3	52	70-72	79.46	6.03	4.41
						(79.28)	(6.22)	(4.36)
3b	p-$CH_3C_6H_4$	CH_3	CH_3	61	98-99	79.73	6.39	4.23
						(79.79)	(6.12)	(4.50)
3c	p-$CH_3OC_6H_4$	CH_3	CH_3	45	116-117	76.06	6.09	4.03
						(76.02)	(6.19)	(3.90)
3d	p-ClC_6H_4	CH_3	CH_3	73	132-133	71.69	5.16	3.98[b]
						(72.00)	(5.23)	(3.76)
4a	C_6H_5	C_6H_5	CH_3	70[c]	148-150	82.29	5.58	3.69
						(82.37)	(5.60)	(3.98)
4b	p-$CH_3OC_6H_4$	C_6H_5	CH_3	41[c]	145-147	79.19	5.66	3.42
						(79.39)	(5.74)	(3.63)
4c	p-ClC_6H_4	C_6H_5	CH_3	74[c]	154-156	75.45	4.87	3.38[b]
						(75.30)	(5.02)	(3.23)
6a	C_6H_5	CH_3	CH_3	66	162-164	70.87	5.51	11.02
						(70.97)	(5.57)	(10.46)
6b	C_6H_5	C_6H_5	C_6H_5	89	204-206	79.34	4.79	7.41
						(78.85)	(4.48)	(7.81)
6c	p-$CH_3C_6H_4$	C_6H_5	C_6H_5	76	208-210	79.59	5.10	7.14
						(79.76)	(5.03)	(7.15)

TABLE 1 (continued)

Comp.	Ar	R_1	R_2	Yield (%)	mp.[a] (°C)	Elemental Analysis: Calcd. (Found) C	H	N
6d	p-$NO_2C_6H_4$	C_6H_5	C_6H_5	73	208-210	70.91 (70.63)	4.04 (4.00)	9.92 (10.06)
6e	p-ClC_6H_4	C_6H_5	C_6H_5	64	224-226	72.72 (72.85)	4.15 (3.95)	6.78[b] (6.30)
6f	3,4-$Cl_2C_6H_3$	C_6H_5	C_6H_5	90	216-218	67.11 (67.66)	3.58 (3.52)	6.28[b] (6.32)

a) All compounds were recrystallized from ethanol.

b) Cl: Calcd. (Found); 2d: 14.20 (14.20); 2g: 11.37 (11.15); 3d: 10.08 (9.97); 4c: 8.57 (8.88); 6e: 8.59 (8.90); 6f: 15.88 (15.53).

c) These reactions afford compounds 4a-c together with its 4-benzoyl substituted isomer (3e-g). The figure given is the total yield. The ratio 4/3 is 85/15 in 4a, 77/23 in 4b and 50/50 in 4c.

781 spectrophotometer. ^{1}H-NMR spectra were determined in a Varian T-60 A instrument and mass spectra were measured with a Varian MAT 711 spectrograph. Reactions were monitored by TLC, using silica gel as the adsorbent and toluene-ethyl acetate as the eluent. 2-Arylidene-1,3-diketones 1[9-13] were prepared following the method described by Pratt[8] and purified by vacuum distillation or recrystallization.

3-Acetyl-2-aryl-4-oxopentanenitriles (2a-d). General Procedure.- To a solution or suspension of 30 mMol of the corresponding 3-arylidene-2,4-pentanedione (1a-d) in 40 ml of ethanol, was added a solution of excess potassium cyanide (ca. 90 mMol) in water with stirring at room temperature. After 1 hr., the reaction mixture was poured into 200 ml of 5% hydrochloric acid, whereupon a solid separated after a short period of time.[14] It was collected and washed with large amounts of water and recrystallized from ethanol.

2-Aryl-3-benzoyl-4-oxopentanenitriles (2e-g). General Procedure.- To a suspension of 65 mMol of the corresponding 2-arylidene-1-phenyl-1,3-butanedi-

one (1j-l) in 20 ml of ethanol, was added a solution of 67 mMol of potassium cyanide in water. The mixture was stirred continuously for 1 hr. and added to 150 ml of 5% hydrochloric acid. After a few minutes, a solid or an oil separated. The residue was recrystallized from ethanol.

4-Acetyl-3-aryl-5-methyl-N-(p-methylbenzylidene)-2-furanamines (3a-d). General Procedure.- A mixture of ca. 6 mMol of 3-acetyl-2-aryl-4-oxopentanenitrile (2a-d) and ca. 6 mMol of p-methylbenzaldehyde in 20 ml of absolute ethanol and a few drops of piperidine was refluxed until TLC shows no starting material remaining (1-2.5 hr.). The reaction mixture was cooled to room temperature and the furanamine precipitated in the reaction medium. It was collected by filtration and recrystallized from ethanol.

TABLE 2. Spectral Data of Compounds 2

	NMR[a]				IR	
Comp.	ArH	CH_3-CO	CH-CH[b]	Other	CN	C=O
2a	7.5-7.2	2.32(s)	4.60(d)		2240	1720
	(m,5H)	1.98(s)	4.30(d)			1700
2b	7.3-7.0	2.28(s)	4.47(d)	2.28(CH_3)	2240	1720
	(m,4H)	1.95(s)	4.10(d)			1700
2c	7.4-6.6	2.31(s)	4.52(d)	3.78(CH_3O)	2240	1720
	(m,4H)	2.0 (s)	4.26(d)			1700
2d	7.23	2.30(s)	4.56(d)		2250	1715
	(bs,4H)	2.0 (s)	4.30(d)			1700
2e	8.1-7.0	2.25(s)	5.2 (dd)[16]		2240	1720
	(m,10H)	1.93(s)	4.8 (dd)			1680
2f	7.6-6.9	2.2 (s)	5.2 (d)	3.7(CH_3O)	2260	1710
	(m,9H)		4.7 (d)			1680
2g	8.1-7.1	2.0 (s)	5.1 (d)		2250	1720
	(m,9H)		4.8 (d)			1680

a) NMR spectra of all compounds were recorded in $CDCl_3$.

b) The coupling constant is 10 Hz for all compounds.

TABLE 3. Spectral Data of Compounds 3-4

	NMR[a]						IR
Comp.	CH=N	ArH	CH_3-CO	CH_3(Ar')	CH_3	Other	C=O
3a	8.55(s)	7.7-7.0 (m,9H)	2.05(s)	2.37(s)	2.56(s)		1665
3b	8.53(s)	7.8-7.0 (m,8H)	2.05(s)	2.35(s)	2.55(s)	2.4(CH_3)	1660
3c	8.52(s)	7.7-6.7 (m,8H)	2.08(s)	2.38(s)	2.56(s)	3.85(CH_3O)	1660
3d	8.53(s)	7.7-7.0 (m,8H)	2.06(s)	2.37(s)	2.55(s)		1665
4a[b]	8.73(s)	7.9-6.9 (m,14H)	2.20(s)	2.38(s)			1670
4b	8.7 (s)	7.9-6.7 (m,13H)	2.18(s)	2.36(s)		3.8(CH_3O)	1690
4c	8.7 (s)	7.9-7.05 (m,13H)	2.18(s)	2.38(s)			1690

a) NMR spectra of all compounds were recorded in $CDCl_3$.

b) ^{13}C-NMR ($CDCl_3$): 198.85 ($COCH_3$), 154.93 (CH=N), 150.07 (C_2 or C_5), 147.93 (C_5 or C_2), 141.59, 133.59, 131.31, 129.54, 129.37, 129.32, 128.95, 128.56, 128.31, 127.26, 127.06 (Arom.), 125.53 (C_4 or C_3), 119.64 (C_3 or C_4), 31.60 (CH_3CO), 21.38 ($CH_3C_6H_4$).

TABLE 4. Spectral Data of Compounds 6

	NMR[a]				IR		
Comp.	ArH	NH_2	CH	Other	NH_2	CN	C=O
6a[b]	7.12(s,5H)	6.62(bs)	4.38(s)	2.2(CH_3) 2.02(CH_3)	3380,3200	2200	1690
6b	7.47-6.67(m,15H,NH_2)		4.5 (s)		3470,3330	2200	1690
6c	7.50-6.75(m,14H,NH_2)		4.47(s)	2.15(CH_3)	3480,3330	2200	1690
6d	7.87-7.0 (m,14H,NH_2)		4.8 (s)		3480,3380	2210	1690
6e	7.60-6.93(m,14H,NH_2)		4.63(s)		3470,3350	2190	1685
6f	7.63-6.98(m,13H,NH_2)		4.7 (s)		3470,3300	2200	1685

a) NMR spectra of all compounds were recorded in DMSO-d_6.

b) MS:m/e = 254(M^+,39), 253(44), 212(15), 211(80), 177(100), 160(26),135(32).

3-Aryl-4-benzoyl-5-methyl-N-(p-methylbenzylidene)-2-furanamines (3e-g) and 4-acetyl-3-aryl-5-phenyl-N-(p-methylbenzylidene)-2-furanamines (4a-c). General Procedure.- A mixture of equimolar amounts of 2-aryl-3-benzoyl-4-oxopentanenitrile (2e-g) and p-tolualdehyde (ca. 5 mMol) in 15 ml of absolute ethanol with a few drops of piperidine was refluxed for 1.5 hr. Then, it was allowed to cool at room temperature and the mixture of the corresponding both isomeric furanamines precipitated after a few hours. They were collected by filtration. Fractional recrystallization from ethanol yield furanamines 4a-c.

6-Substituted 5-acyl-2-amino-3-cyano-4-aryl-4H-pyrans (6a-f). General Procedure.- To a solution of 10 mMol of the appropriate 3-benzylidene-2,4-pentanedione (1a) or 2-arylidene-1,3-diphenyl-1,3-propanedione (1e-i) in 20 ml of dry ethanol, 10 mMol of malononitrile was added with stirring at room temperature, together with a few drops of piperidine. After a few minutes, a precipitate separated and was collected and recrystallized from ethanol.

2-Amino-5-benzoyl-3-cyano-6-methyl-4-phenyl-4H-pyran (6g) and 2-amino-5-acetyl-3-cyano-4,6-diphenyl-4H-pyran (7).- To a solution of 10 mMol of 2-benzylidene-1-phenyl-1,3-butanedione (1j) in 20 ml of dry ethanol, 10 mMol of malononitrile was added with stirring at room temperature, together with a few drops of piperidine. After a few minutes, the mixture of the corresponding both isomeric pyranamines which had precipitated from the reaction medium, was collected by filtration and recrystallized from ethanol (60% yield). The results of HPLC show a 90:10 ratio, mp. 182-184°.

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 69.94; H, 4.03; N, 18.83

Found: C, 69.62; H, 4.00; N, 19.00

IR (KBr): 3440, 3400, 3315, 3200, 2210, 2200, 1675, 1665, 1635, 1595, 1320, $cm.^{-1}$ H-NMR (DMSO-d_6): δ 7.3-6.8 (m,arom.), 6.66 (br s,NH_2), 4.31 (s,CH), 4.28 (s,CH), 1.70 (s,CH_3), 1.60 (s,CH_3).

4-Methyl-3,5-diphenyl-N-(p-methylbenzylidene)-2-furanamine (9).- A mixture of equimolar amounts of 2-methyl-1,3-diphenylpropenone (8),[17] potassium cyanide and p-tolualdehyde was kept stirring at room temperature for 5 days. The precipitate was collected and recrystallized from ethanol. After a few days a second crop of furanamine, mp. 135-136°, was collected (total 20% yield).

Anal. Calcd. for $C_{25}H_{21}NO$: C, 85.47; H, 5.98; N, 3.98

Found: C, 85.69; H, 6.14; N, 4.04

IR (KBr): 1600, 1490, 1440, 1300, 1170, 1020, 810, 760, 690 $cm.^{-1}$

H-NMR ($CDCl_3$):δ 8.6 (s,1H,CH=N), 7.8-7.0 (m,14H,arom.), 2.31 (s,3H,CH_3), 2.28 (s,3H,CH_3).

3-Cyano-2-ethoxy-5-methyl-4,6-diphenylpyridine (10).- To a solution of 4.3 mMol of 2-methyl-1,3-diphenylpropenone (8)[17] in ca. 10 ml of dry ethanol, 4.3 mMol of sodium ethoxide was added with stirring at room temperature. After several weeks standing, a precipitate separated. It was collected, washed with ethanol and recrystallized from ethanol (5% yield), mp. 128-130°.

Anal. Calcd. for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.93

Found: C, 80.14; H, 5.96; N, 8.83

IR (KBr): 2220, 1560, 1490, 1420, 1380, 1345, 1160, 760, 715, 705 $cm.^{-1}$

H-NMR ($CDCl_3$):δ 7.5-7.0 (m,10H,arom.), 4.43 (q,2H,CH_3-CH_2O), 2.0 (s,3H, CH_3), 1.4 (t,3H,CH_3-CH_2O).

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REFERENCES

+ Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alcalá de Henares, Madrid, Spain.

1. S. Ruheman and E. R. Watson, J. Chem. Soc., 85, 465 (1904).

2. S. Ruheman, ibid., 83, 1373 (1903).

3. M. Joncla and J. Hamelin, Tetrahedron Lett., 2885 (1978).

4. E. Knoevenagel, Ber., 36, 2188 (1903).

5. R. Danion-Bougot and R. Carrie, Bull. Soc. Chim. Fr., 3511 (1972).

6. R. R. Schmidt and M. Maier, Tetrahedron Lett., 1789 (1982).

7. J. A. Ciller, C. Seoane and J. L. Soto, Ann., 51 (1985).

8. E. F. Pratt and E. Werble, J. Am. Chem. Soc., 72, 4639 (1950).

9. M. Sekiya and K. Suzuki, Chem. Pharm. Bull. Jpn., 18, 1530 (1970).

10. E. Knoevenagel and N. Ruschhanpt, Ber., 31, 2775 (1898).

11. R. F. Silver, C. E. Louch, H. L. Holmes and D. T. Currie, Can. J. Chem., 45, 1001 (1967).

12. E. Hase and G. Stejernvall, Suomen Kem., 21B, 42 (1948), Beilstein III 7, 617.

13. M. Calmon, B. Arnaud-Lehujeur and J. P. Calmon, Bull. Soc. Chim. Fr., 179 (1972).

14. Sometimes a soft solid separates, but after standing (minutes to hours) it crystallized and may be collected.

15. S. Ruheman, J. Chem. Soc., 85, 1456 (1904).

16. The presence of two peaks is due to the presence of two diasteromers.

17. R. D. Abell, J. Chem. Soc., 79, 929 (1901); E. P. Kohler, Am. Chem. J., 31, 656 (1904).

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