

Mohammad M. Al-Arab

Department of Chemistry, Yarmouk University,
Irbid, Jordan

Received January 19, 1989

A new synthesis of substituted pyridine is reported. The base catalyzed reaction of substituted chalcones with malononitrile using sodium ethoxide in ethanol at room temperature afforded 2,4-diaryl-5-cyano-6-ethoxypyridine. Similarly, 2,4-diaryl-5-cyano-6-methoxypyridine have been prepared in presence of sodium methoxide in methanol as a catalyst.

J. Heterocyclic Chem., **26**, 1665 (1989).

Reactions of unsaturated ketones with malononitrile in the presence of ammonium acetate to give pyridines was first reported by Sakurai [1] and Midorikawa [2] and applied by some other authors [3-5]. However, in all cases, the reported yield of the pyridines did not exceed 30%. In addition, other authors [6] have reported that unsaturated ketones with electron donating substituents in the 3-position which enhance polarization of the unsaturated system, undergo reaction in ethanolic solution to give pyridines in much higher yields and provided support to a possible reaction pathway which proceeds through conjugate addition of the active methylene compound to the unsaturated ketone system. In a recent publication [7] we reported that the reaction of α,β -unsaturated cinnamionitriles with substituted arylacetone nitriles afforded a single diastereomer of 2,3-diarylglutaronitriles. Our interest in this laboratory in the condensa-

tion [8-13] of α,β -unsaturated systems with compounds having active methylene prompted us to study the reaction of different chalcones **1** and malononitrile. As a result of this reaction 6-alkoxy-2,4-diaryl-5-cyanopyridines **8** and **9** are obtained in good yield (Table II). Although we have not undertaken a mechanistic investigation of the reaction, the reaction should be considered to begin with a

Scheme I

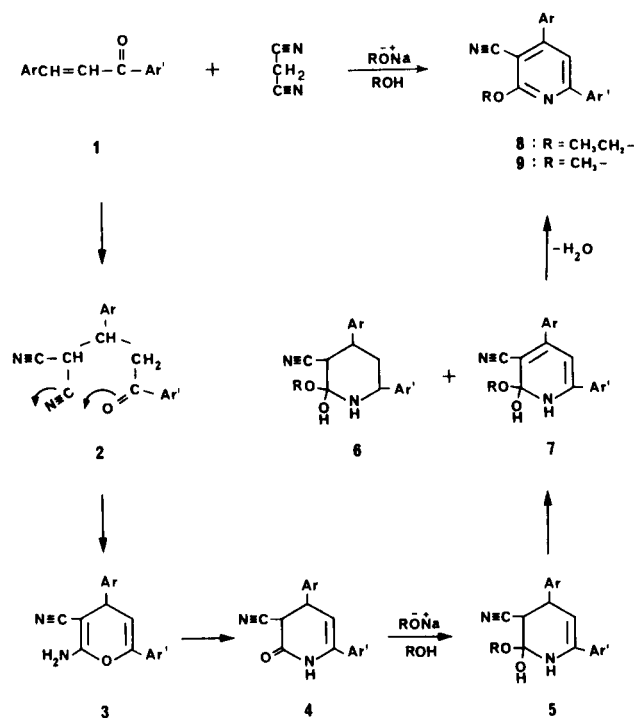


Table I

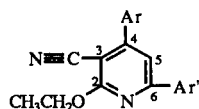
Starting chalcone	Ar	Ar'	Pyridine
Ia	Phenyl	Phenyl	8a
Ib	4-Tolyl	4-Tolyl	8b
Ic	4-Tolyl	4-Chlorophenyl	8c
Id	4-Tolyl	4-Bromophenyl	8d
Ie	4-Tolyl	2-Naphthyl	8e
If	4-Anisyl	2-Naphthyl	8f
Ig	4-Anisyl	Phenyl	8g
Ih	4-Chlorophenyl	2-Naphthyl	8h
Ii	3-Bromophenyl	2-Naphthyl	8i
Ij	3-Chlorophenyl	2-Naphthyl	8j
Ik	2,4-Dichlorophenyl	Phenyl	8k
Il	3,4-Dichlorophenyl	Phenyl	8l
Im	4-Chlorophenyl	4-Bromophenyl	9m
In	4-Tolyl	4-Anisyl	9n
Io	4-Tolyl	Phenyl	9o
Ip	4-Anisyl	2,4-Dimethoxyphenyl	9p
Iq	2,4-Dimethoxyphenyl	4-Chlorophenyl	9q
Ir	3,4-Dichlorophenyl	4-Anisyl	9r
Ia	Phenyl	Phenyl	9a
Ic	4-Tolyl	4-Chlorophenyl	9c
Ie	4-Tolyl	2-Naphthyl	9e
If	4-Anisyl	2-Naphthyl	9f
Ig	4-Anisyl	Phenyl	9g

Table II

Physical Constants and Analytical Data of 6-Alkoxy-2,4-diaryl-5-cyanopyridine

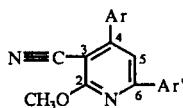
Compound No.	Yield (%)	Mp °C	Formula	C%		H%		Calcd./Found		
				C%	H%	N%	Cl%	Br%		
8a	71	103-104	C ₂₀ H ₁₆ N ₂ O	79.98	5.37	9.33	-	-		
				80.41	5.43	9.27	-	-		
8b	66	102-103	C ₂₂ H ₂₀ N ₂ O	80.43	6.14	8.57	-	-		
				80.05	6.20	8.93	-	-		
8c	74	136-138	C ₂₁ H ₁₇ ClN ₂ O	72.31	4.91	8.03	10.16	-		
				72.30	5.17	7.91	10.31	-		
8d	78	171-173	C ₂₁ H ₁₇ BrN ₂ O	64.13	4.36	7.12	-	20.32		
				64.05	4.67	7.07	-	20.15		
8e	80	138-140	C ₂₅ H ₂₀ N ₂ O	82.39	5.53	7.69	-	-		
				82.27	5.23	7.77	-	-		
8f	77	114-116	C ₂₅ H ₂₀ N ₂ O ₂	82.39	5.53	7.69	-	-		
				82.37	5.25	7.50	-	-		
8g	64	104-105	C ₂₁ H ₁₈ N ₂ O ₂	76.34	5.49	8.48	-	-		
				76.16	5.41	8.14	-	-		
8h	65	119-120	C ₂₄ H ₁₇ ClN ₂ O	74.90	4.45	7.28	9.21	-		
				75.20	4.64	7.24	9.21	-		
8i	61	109-110	C ₂₄ H ₁₇ BrN ₂ O	67.14	3.99	6.53	-	18.61		
				67.14	4.27	6.82	-	18.71		
8j	75	120-121	C ₂₄ H ₁₇ ClN ₂ O	74.90	4.45	7.28	9.21	-		
				75.07	4.21	7.00	9.22	-		
8k	58	125-126	C ₂₀ H ₁₄ Cl ₂ N ₂ O	65.06	3.82	7.59	19.20	-		
				65.02	4.15	7.41	19.41	-		
8l	60	111-112	C ₂₀ H ₁₄ Cl ₂ N ₂ O	65.06	3.82	7.59	19.20	-		
				65.22	3.96	7.75	19.35	-		
9a	58	106-107	C ₁₉ H ₁₄ N ₂ O	79.70	4.93	9.78	-	-		
				79.85	4.99	9.92	-	-		
9c	78	125-126	C ₂₀ H ₁₅ ClN ₂ O	71.75	4.52	8.37	10.59	-		
				71.83	4.61	8.25	10.62	-		
9e	56	130-131	C ₂₄ H ₁₈ N ₂ O	65.14	5.18	7.99	-	-		
				65.25	5.27	8.06	-	-		
9f	70	153-155	C ₂₄ H ₁₈ N ₂ O ₂	78.67	4.95	7.65	-	-		
				78.93	4.99	7.80	-	-		
9g	72	182-183	C ₂₀ H ₁₄ Cl ₂ N ₂ O ₂	62.35	3.66	7.27	18.41	-		
				62.53	3.76	7.35	18.42	-		
9m	72	308-310	C ₁₉ H ₁₂ BrClN ₂ O	57.10	3.03	7.01	8.87	19.99		
				57.23	3.16	7.29	8.93	20.23		
9n	76	190-191	C ₂₁ H ₁₈ N ₂ O ₂	76.34	5.49	8.48	-	-		
				76.62	5.61	8.52	-	-		
9o	62	133-134	C ₂₀ H ₁₆ N ₂ O	79.98	5.37	9.33	-	-		
				80.13	5.42	9.52	-	-		
9p	73	185-186	C ₂₂ H ₂₀ N ₂ O ₄	70.20	5.36	7.44	-	-		
				70.31	5.41	7.52	-	-		
9q	61	204-205	C ₂₁ H ₁₇ ClN ₂ O ₃	66.23	4.50	7.36	9.31	-		
				66.53	4.60	7.29	9.35	-		
9r	75	211-212	C ₂₀ H ₁₄ Cl ₂ N ₂ O ₂	62.35	3.66	7.27	18.41	-		
				62.62	3.75	7.40	18.50	-		

Table III

¹³C-NMR Chemical Shifts for the 2,4-Diaryl-5-cyano-6-ethoxypyridines **8a-l**

Compound	CH ₃ -	CH ₂ -	C≡N	C-2	C-3	C-4	C-5	C-6
8a	14.3	63.3	113.3	164.8	137.6	156.7	136.6	158.0
8b	14.4	63.2	113.3	164.5	137.5	156.8	136.5	158.2
8c	14.5	63.4	113.1	164.9	136.7	156.7	136.2	157.0
8d	14.5	63.4	113.0	164.9	136.7	156.7	136.6	157.0
8e	14.3	63.5	113.2	164.5	136.7	156.2	136.5	157.3
8f	14.5	63.4	113.0	164.8	136.5	156.5	136.2	157.2
8g	14.3	63.4	113.3	164.6	136.7	156.6	136.6	157.9
8h	14.4	63.5	113.3	164.8	138.3	155.0	135.0	158.2
8i	14.5	63.6	113.4	164.9	138.3	155.1	134.7	158.4
8j	14.2	63.5	113.5	164.2	138.7	155.2	134.2	157.5
8k	14.3	63.4	113.6	164.5	137.2	155.5	134.9	157.6
8l	14.4	63.5	114.0	164.2	137.3	153.5	136.3	158.2

Table IV

¹³C-NMR Chemical Shifts for the 2,4-Diaryl-5-cyano-6-methoxypyridines **9a,c,e,f,g,m-r**

Compound	CH ₃ -	C≡N	C-2	C-3	C-4	C-5	C-6
9a	54.3	114.5	165.5	136.2	156.3	133.2	157.3
9c	54.2	114.4	165.1	135.5	156.2	133.5	157.2
9e	54.4	114.3	165.0	136.9	156.9	134.9	157.5
9f	54.5	114.6	165.3	135.0	156.3	134.4	157.8
9g	54.3	114.2	165.6	135.7	156.0	134.7	157.9
9m	54.2	114.5	165.5	135.8	156.2	133.3	157.5
9n	54.3	114.4	165.1	140.1	156.6	133.8	157.7
9o	54.4	113.4	165.1	140.2	156.8	137.8	157.9
9p	54.5	114.0	165.2	136.7	156.4	136.2	157.0
9q	54.3	114.8	164.6	136.5	156.2	136.4	157.8
9r	54.5	114.5	165.1	136.4	155.9	134.5	157.4

Table V

Reaction Conditions and Spectral Data of 6-Alkoxy-2,4-diaryl-5-cyanopyridines

Compound No.	Crystallization Solvent	Reaction time (min)	IR (Potassium Bromide)		NMR (Deuteriochloroform)	
			cm ⁻¹	v	δ	Assignment
8a	Ethanol	25	1150	C-O	1.51 (t, 3H)	CH ₃ CH ₂ -
			1435	C=C	4.66 (q, 2H)	CH ₃ CH ₂ -
			1500		7.23-8.13 (m, 11H)	Ar-H
			1575			
			1590			
			2240	C=N		
			2950	≧C-H		
3070	=CH					
8b	Ethanol	120	1145	C-O	1.48 (t, 3H)	CH ₃ CH ₂ -
			1430	C=C	2.39 (s, 6H)	Ar-CH ₃
			1505		4.61 (q, 2H)	CH ₃ CH ₂ -
			1550			
			1595			
			2230	C=N	7.19-7.99 (m, 9H)	Ar-H
			2960	≧C-H		
3060	=CH					
8c	Ethanol	30	1150	C-O	1.51 (t, 3H)	CH ₃ CH ₂ -
			1435	C=C	2.43 (s, 3H)	Ar-CH ₃
			1500		4.65 (q, 2H)	CH ₃ CH ₂ -
			1555			
			1600			
			2245	C=N	7.62-8.07	Ar-H
			2940	≧C-H		
3020	=CH					
8d	HAc/H ₂ O	25	1155	C-O	1.51 (t, 3H)	CH ₃ CH ₂ -
			1435	C=C	2.43 (s, 3H)	Ar-CH ₃
			1500		4.65 (q, 2H)	CH ₃ CH ₂ -
			1550			
			1595			
			2250	C=N	7.25-8.00 (m, 9H)	Ar-H
			2950	≧C-H		
3060	=CH					
8e	HAc	15	1140	C-O	1.51 (t, 3H)	CH ₃ CH ₂ -
			1435	C=C	2.43 (s, 3H)	Ar-CH ₃
			1505		4.65 (q, 2H)	CH ₃ CH ₂ -
			1550			
			1580			
			2230	C=N	7.25-8.07 (m, 12H)	Ar-H
			2980	≧C-H		
3080	=CH					

Table V (continued)

Compound No.	Crystallization Solvent	Reaction time (min)	IR (Potassium Bromide)		NMR (Deuteriochloroform)	
			cm ⁻¹	v	δ	Assignment
8f	HAc	20	1150	C-O	1.53 (t, 3H)	CH ₃ CH ₂ -
			1435	C=C	3.86 (s, 2H)	Ar-OCH ₃
			1500		4.63 (q, 2H)	CH ₃ CH ₂
			1570			
			1590			
			2240	C≡N	6.99-8.14 (m, 12H)	Ar-H
			2975	≧C-H		
3070	=CH					
8g	Ethanol	35	1160	C-O	1.54 (t, 3H)	CH ₃ CH ₂ -
			1435	C=C	3.88 (s, 3H)	Ar-OCH ₃
			1505		4.62 (q, 2H)	CH ₃ CH ₂ -
			1580			
			1590			
			2235	C≡N	7.05-8.17 (m, 10H)	Ar-H
			2980	≧C-H		
3075	=CH					
8h	HAc/H ₂ O	45	1150	C-O	1.52 (t, 3H)	CH ₃ CH ₂ -
			1430	C=C	4.65 (q, 2H)	CH ₃ CH ₂ -
			1505		7.22-8.54 (m, 12H)	Ar-H
			1570			
			1585			
			2240	C≡N		
			2980	≧C-H		
3080	=CH					
8i	Ethanol	50	1160	C-O	1.55 (t, 3H)	CH ₃ CH ₂ -
			1435	C=C	4.69 (q, 2H)	CH ₃ CH ₂ -
			1500		7.25-8.55 (m, 12H)	Ar-H
			1570			
			1590			
			2250	C≡N		
			2950	≧C-H		
3060	=CH					
8j	Ethanol	70	1150	C-O	1.55 (t, 3H)	CH ₃ CH ₂ -
			1435	C=C	4.70	CH ₃ CH ₂ -
			1500		7.43-8.54 (m, 12H)	Ar-H
			1550			
			1590			
			2250	C≡N		
			2950	≧C-H		
3050	=CH					

Table V (continued)

Compound No.	Crystallization Solvent	Reaction time (min)	IR (Potassium Bromide)		NMR (Deuteriochloroform)	
			cm ⁻¹	v	δ	Assignment
8k	Methanol	40	1160	C-O	1.52 (t, 3H)	CH ₃ CH ₂ -
			1430	C=C	4.68 (q, 2H)	CH ₃ CH ₂ -
			1505		7.25-8.13 (m, 9H)	Ar-H
			1570			
			1595			
			2240	C≡N		
			2960	≧C-H		
3060	=CH					
8l	Ethanol	45	1145	C-O	1.52 (t, 3H)	CH ₃ CH ₂ -
			1430	C=C	4.61 (q, 2H)	CH ₃ CH ₂ -
			1500		7.24-8.12 (m, 9H)	Ar-H
			1555			
			1600			
			2245	C≡N		
			2970	≧C-H		
3080	=CH					
9a	Ethanol/H ₂ O	15	1150	C-O	4.20 (s, 3H)	pyr.-OCH ₃
			1435	C=C	7.25-8.16 (m, 11H)	Ar-H
			1505			
			1560			
			1595			
			2240	C≡N		
			2950	≧C-H		
3090	=CH					
9c	HAc	35	1155	C-O	2.40 (s, 3H)	Ar-CH ₃
			1440	C=C	4.20 (s, 3H)	pyr.-OCH ₃
			1500		7.26-8.67 (m, 9H)	Ar-H
			1570			
			1600			
			2245	C≡N		
			2985	≧C-H		
3085	=CH					
9e	HAc/H ₂ O	50	1145	C-O	2.42 (s, 3H)	Ar-CH ₃
			1435	C=C	4.18 (s, 3H)	pyr.-OCH ₃
			1505		7.34-8.85 (m, 12H)	Ar-H
			1565			
			1605			
			2240	C≡N		
			2990	≧C-H		
3090	=CH					

Table V (continued)

Compound No.	Crystallization Solvent	Reaction time (min)	IR (Potassium Bromide)		NMR (Deuteriochloroform)	
			cm ⁻¹	v	δ	Assignment
9f	Benzene/Hexane	35	1150	C-O	3.86 (s, 3H)	Ar-OCH ₃
			1440	C=C	4.21 (s, 3H)	pyr.-OCH ₃
			1505		7.05-8.55 (m, 12H)	Ar-H
			1570			
			1595			
			2240	C≡N		
			2950	≧C-H		
3080	=CH					
9g	Ethanol	45	1145	C-O	3.86 (s, 3H)	Ar-OCH ₃
			1435	C=C	4.18 (s, 3H)	pyr.-OCH ₃
			1500		6.99-8.15 (m, 10H)	Ar-H
			1565			
			1600			
			2245	C≡N		
			2960	≧C-H		
3060	=CH					
9m	HAc	45	1150	C-O	4.19 (s, 3H)	pyr.-OCH ₃
			1435	C=C	7.26-8.02 (m, 9H)	Ar-H
			1505			
			1560			
			1595			
			2240	C≡N		
			2970	≧C-H		
3070	=CH					
9n	Benzene/Hexane	30	1145	C-O	2.42 (s, 3H)	Ar-CH ₃
			1440	C=C	3.87 (s, 3H)	Ar.-OCH ₃
			1505		4.17 (s, 3H)	pyr.-OCH ₃
			1570		6.93-8.11 (m, 9H)	Ar-H
			1600			
			2235	C≡N		
			2985	≧C-H		
3080	=CH					
9o	Benzene/Hexane	25	1145	C-O	2.43 (s, 3H)	Ar-CH ₃
			1435	C=C	4.19 (s, 3H)	pyr.-OCH ₃
			1500		7.30-8.29 (m, 10H)	Ar-H
			1575			
			1600			
			2235	C≡N		
			2960	≧C-H		
3090	=CH					

Table V (continued)

Compound No.	Crystallization Solvent	Reaction time (min)	IR (Potassium Bromide)		NMR (Deuteriochloroform)	
			cm ⁻¹	v	δ	Assignment
9p	Benzene/Hexane	20	1150	C-O	3.98 (s, 3H)	Ar-O-CH ₃
			1440	C=C	3.95 (s, 3H)	Ar-O-CH ₃
			1505		3.87 (s, 3H)	Ar-O-CH ₃
			1570		4.18 (s, 3H)	pyr.-OCH ₃
			1595		6.90-7.75 (m, 8H)	Ar-H
			2240	C=N		
			2950	≧ C-H		
3050	=CH					
9q	Ethanol	25	1145	C-O	3.85 (s, 6H)	Ar-OCH ₃
			1435	C=C	4.16 (s, 3H)	pyr.-OCH ₃
			1500		6.60-8.06 (m, 8H)	Ar-H
			1570			
			1600			
			2235	C=N		
			2860	≧ C-H		
3090	=CH					
9r	Benzene/Hexane	40	1155	C-O	3.87 (s, 3H)	Ar-OCH ₃
			1440	C=C	4.18 (s, 3H)	pyr.-OCH ₃
			1505		6.95-7.89	Ar-H
			1565			
			1605			
			2240	C=N		
			2890	≧ C-H		
3095	=CH					

Michael addition of malononitrile to the α,β -unsaturated ketone to yield the adduct **2**, followed by cyclization to **3** through a nucleophilic attack by the carbonyl oxygen at the cyano group and then followed by Dimroth rearrangement [14] to **4**. A nucleophilic attack by the alkoxide anion to the lactam carbonyl group of **4** leads to **5** (Scheme I).

A disproportionation [15] of **5** gives **7** and the not isolable pyridine derivative **6**. Subsequent dehydration of **7** leads to the aromatic cyanopyridine derivative, **8** or **9**. By this one pot simple reaction, two new series of 6-alkoxy-2,4-diaryl-5-cyanopyridines have been prepared (Table I). The structure was assigned on the basis of analytical and spectral data. The ir spectra of both series of pyridines **8** and **9** show a peak at 2240 cm⁻¹ due to the cyano stretching frequency. The pyridine ring peaks appeared at 1600, 1570, 1500 and 1435 cm⁻¹. In the ¹H-nmr spectrum of the 6-ethoxypyridine series **8a-l**, the ethoxy group gives rise to a quartet at around 4.65 ppm and a triplet at 1.51 ppm with J = 7.8 Hz. The aromatic protons including the pyridine ring proton appear as a multiplet at 7.19-8.07 ppm

(Table V).

On the other hand, the 6-methoxypyridine series **9a,c,e,f,g,l-r** show a singlet at 4.21 ppm characteristic of the methoxy group in addition to the aromatic protons at 6.99-8.15 ppm. The ¹³C-nmr spectra of these pyridines show beside a singlet at around 113.0 ppm characteristic of the cyano carbon, a singlet at 54.5 ppm due to the methoxy carbon (**9** series, Table IV) and two singlets at 14.3 and 63.4 ppm due to the ethoxy carbons (**8** series, Table III).

EXPERIMENTAL

Melting points were determined on a Electrothermal melting point apparatus and are uncorrected. The ir spectra were recorded in potassium bromide pellets on a Pye-Unicam SP3-100 instrument. ¹H-nmr and ¹³C-nmr spectra were measured on a Bruker WP 80-SY spectrometer using deuteriochloroform solutions containing TMS as internal standard. Compounds were analyzed by M-H-W Laboratories, Phoenix Arizona, U.S.A.

General Procedure.

To a freshly prepared sodium alkoxide solution (0.017 mole of sodium metal in 150 ml of the corresponding absolute alcohol), 0.017 mole of malononitrile was added with stirring. To this mixture 0.017 mole of chalcone was added with continuous stirring for the appropriate time at room temperature after which a solid separated, collected by suction filtration, washed with cold methanol and recrystallized from a suitable solvent.

Acknowledgement.

The author thanks Yarmouk University for the financial support of this work.

REFERENCES AND NOTES

[1] A. Sakurai and N. Midorikawa, *Bull. Chem. Soc. Japan*, **40**, 1680 (1967).

[2] A. Sakurai and N. Midorikawa, *Bull. Chem. Soc. Japan*, **41**, 430 (1968).

[3] A. Sammour, M. B. I. Sleim and M. S. Abdel Halim, *Egypt. J. Chem.*, **15**, 23 (1972).

[4] A. Sammour, Y. Akhnoukh, H. Jahine, *Egypt. J. Chem.*, **13**, 420 (1970).

[5] U. Basu, *J. Indian Chem. Soc.*, **7**, 818 (1930).

[6] N. Latif, N. Mishriky, and N. S. Girgis, *Indian J. Chem.*, **20B**, 147 (1981).

[7] M. M. Al-Arab, H. D. Tabbā, I. A. Abu-Yousef, and Marilyn M. Olmstead, *Tetrahedron*, **44**, 7293 (1988).

[8] M. M. Al-Arab, *Chem. Scr.*, **27**, 453 (1987).

[9] M. M. Al-Arab, *J. Chem. Eng. Data*, **31**, 261 (1986).

[10] M. M. Al-Arab and A. M. Issa, *Monatsh. Chem.*, **118**, 987 (1987).

[11] M. M. Al-Arab and A. M. Issa, *Collect. Czech. Chem. Commun.*, **52**, 1021 (1987).

[12] M. M. Al-Arab, *Collect. Czech. Chem. Commun.*, **50**, 2910 (1985).

[13] M. M. Al-Arab, *J. Chem. Eng. Data*, **31**, 376 (1986).

[14] M. Wahren, *Z. Chem.*, **9**, 241 (1969).

[15] H. H. Otto, *Arch. Pharm. (Weinheim)*, **307**, 422 (1974).