

## Synthesis of Carbostyryl Derivatives by Reaction of Aldehydes with Oxazolines

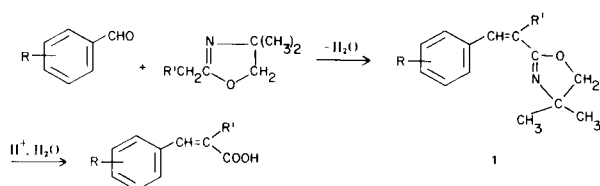
H. L. Wehrmeister

Research Department, Commercial Solvents Corporation, Terre Haute, Indiana 47808

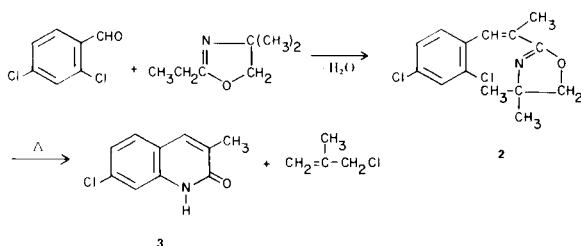
Received August 7, 1975

Carbostyryl derivatives are obtained on reaction of *o*-chlorobenzaldehyde and derivatives with 2-alkyl-4,4-dimethyl-2-oxazolines with elimination of methallyl chloride. Phenylethyloxazolines are presumed intermediates.

As previously reported (1), aromatic aldehydes react with 2-alkyl-4,4-dimethyl-2-oxazolines to yield phenylethyloxazolines (1). These phenylethyloxazolines can be hydrolyzed to the corresponding cinnamic acids. This reaction sequence constitutes a useful synthesis of cinnamic acids.



Application of this reaction to the synthesis of 2-[2-(2,4-dichlorophenyl)-1-methylethenyl]-4,4-dimethyl-2-oxazoline (2) unexpectedly gave 7-chloro-3-methylcarbostyryl (3) (Alternatively these may be named as 2(1*H*)-quinolinones.) in addition to 2.

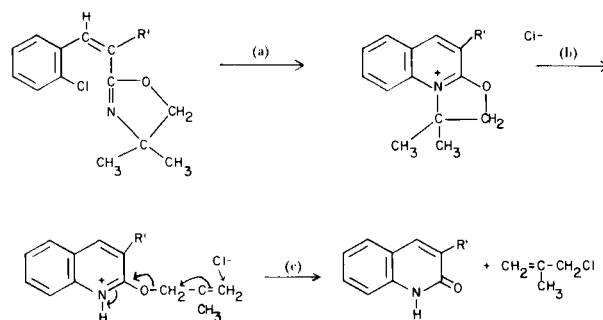


The carbostyryl may have been formed during the relatively high temperature distillation used in the workup of the product mixture. The phenylethyloxazoline could, in fact, be converted to the carbostyryl by heating at 205-295°. Methallyl chloride was obtained as a byproduct. Similarly, heating of the phenylethyloxazoline obtained by reaction of 2-chlorobenzaldehyde with 2-ethyl-4,4-dimethyl-2-oxazoline at 220-270° gave 3-methylcarbostyryl.

A convenient method for carrying out this new carbostyryl synthesis has been developed. This method consists

in heating the reactants in the presence of sodium bisulfate as catalyst in a mixture of *N*-methylpyrrolidinone and xylene at reflux under a water separator. After the water is collected, most or all of the xylene is removed by distillation and refluxing is continued at 200-220°. The cooled mixture is then poured into water and the product is collected by filtration, washed, and dried. Recrystallization from acetic acid generally has been effective for further purification. Products prepared in this manner are listed in Table I. Some of the carbostyryls were converted to 2-chloroquinolines by reaction with phosphorus oxychloride. These are listed in Table II.

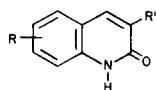
The following scheme is suggested for the carbostyryl forming reaction:



In step (a) of this scheme the -chloro group of the (*Z*)phenylethyloxazoline is displaced to give the quaternized quinoline. Large R' groups should favor formation of (*Z*)phenylethyloxazolines and thus favor carbostyryl formation. The limited data support this premise. Step (b) involves an elimination to give the imido ester hydrochloride which cleaves (step c) as expected (2) to yield the carbostyryl and methallyl chloride.

This reaction is being further studied to extend its scope and utility. Evidence for the suggested reaction scheme is being sought.

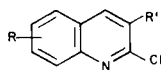
Table I



R	R'	Yield %	M.p. °C	Formula	Calcd.			Analyses, %				
					C	H	N	Cl	C	H	N	Cl
5-Cl	H	21	289-291	C <sub>9</sub> H <sub>6</sub> ClNO	60.18	3.37	7.80	19.74	60.00	3.17	7.67	19.78
7-Cl	H	12	295.5-297.5(a)	C <sub>9</sub> H <sub>6</sub> ClNO	60.18	3.37	7.80	---	60.24	3.30	7.62	---
5-Cl	Ph	91	261.5-262.5	C <sub>15</sub> H <sub>10</sub> ClNO	70.45	3.94	5.48	13.87	70.53	3.97	5.32	13.43
7-Cl	Ph	84	252-255	C <sub>15</sub> H <sub>10</sub> ClNO	70.45	3.94	5.48	13.87	70.36	3.73	5.51	13.60
6-NO <sub>2</sub>	Ph	95	299-302	C <sub>15</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub>	67.65	3.79	10.52	---	67.73	3.89	10.30	---
7-(CH <sub>3</sub> ) <sub>2</sub> N	Ph	33	249-255°	C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> O	77.24	6.10	10.60	---	76.73	6.02	10.78	---
									76.78	5.89	10.25	
7-Cl	<i>p</i> -MeOPh	67	261-263	C <sub>16</sub> H <sub>12</sub> ClNO <sub>2</sub>	67.26	4.24	4.90	12.41	66.92	4.09	4.87	12.54
7-Cl	2,4-Cl <sub>2</sub> PhO	19	290-291	C <sub>15</sub> H <sub>8</sub> Cl <sub>3</sub> NO <sub>2</sub>	52.89	2.37	4.11	31.23	52.65	2.30	3.96	31.09

(a) Lit. (3), m.p. 296-297°.

Table II



R	R'	M.p. °C	Formula	Calcd.			Analyses, %				
				C	H	N	Cl	C	H	N	Cl
5-Cl	H	78-78.5°	C <sub>9</sub> H <sub>5</sub> Cl <sub>2</sub> N	54.58	2.54	7.07	35.80	54.91	2.69	7.02	35.64
H	Ph	56-56.5 (a)	C <sub>15</sub> H <sub>10</sub> ClN	75.16	4.21	5.84	14.79	75.21	4.51	5.36	14.79
5-Cl	Ph	133-134	C <sub>15</sub> H <sub>9</sub> Cl <sub>2</sub> N	65.72	3.31	5.11	25.87	65.85	3.35	5.29	26.20
7-Cl	Ph	102-103	C <sub>15</sub> H <sub>9</sub> Cl <sub>2</sub> N	65.72	3.31	5.11	25.87	65.70	3.26	5.05	26.14
6-NO <sub>2</sub>	Ph	218-221	C <sub>15</sub> H <sub>9</sub> ClN <sub>2</sub> O <sub>2</sub>	63.28	3.19	9.84	12.46	63.30	3.36	9.66	12.34
7-Cl	<i>p</i> -MeOPh	126-127.5	C <sub>16</sub> H <sub>11</sub> Cl <sub>2</sub> NO	63.18	3.65	4.61	23.31	63.48	3.58	4.47	23.03

(a) Lit. (4), m.p. 54-55°.

## EXPERIMENTAL

Aromatic aldehydes, carboxylic acids, solvents, and other reagents were laboratory-grade products used without further purification. The oxazolines were prepared by reaction of 2-amino-2-methyl-1-propanol (AMP, Commercial Solvents Corporation) with the appropriate acid. All but one of these have been described previously (1,5,6). 2-Acetamidomethyl-4,4-dimethyl-2-oxazoline was obtained as a viscous oil, b. p. 95-99° (0.09 mm.), by reaction of *N*-acetyl glycine with 2-amino-2-methyl-1-propanol.

Boiling points are uncorrected. Uncorrected melting points were obtained with a Fisher-Johns apparatus. Elemental analyses were obtained from Micro Analyses Inc., Wilmington, Del. All ir and nmr spectra are considered consistent with assigned structures.

7-Chloro-3-phenylcarbostyryl. Standard Procedure.

A stirred mixture of 2-benzyl-4,4-dimethyl-2-oxazoline (18.9 g., 0.1 mole), 2,4-dichlorobenzaldehyde (17.5 g., 0.1 mole) and 1 g. of sodium bisulfate in 50 ml. of *N*-methylpyrrolidinone and 30

ml. of xylene was heated at reflux under a short column, water separator (20 ml.), and condenser. Distillation to the separator occurred at a pot temperature of 177-199°. A total of 18 ml. of distillate was then drained from the separator intermittently during 1.25 hours, with the pot temperature ultimately reaching 218°. Refluxing near 218° was continued an additional 15 minutes. The cooled reaction mixture was diluted with 300 ml. of water and filtered. The solid product after washing with 2 x 100 ml. water and 2 x 50 ml. of methanol was dried in a vacuum desiccator. There was obtained 21.4 g. (84%) of 7-chloro-3-phenylcarbostyryl, m.p. 252-253°. Recrystallization from 200 ml. of acetic acid gave 15.1 g., m.p. 252-255°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>10</sub>ClNO: C, 70.45; H, 3.94; Cl, 13.87; N, 5.48. Found: C, 70.36; H, 3.73; Cl, 13.60; N, 5.51.

The other carbostyryl derivatives listed in Table I were prepared similarly with only minor modifications.

The compounds listed below were obtained in preliminary experiments by the same general reaction but not by the standardized procedure. No details are given since these materials

presumably could be prepared more readily by the standard procedure.

#### 7-Chloro-3-methylcarbostyryl.

7-Chloro-3-methylcarbostyryl was obtained by reaction of 2,4-dichlorobenzaldehyde with 4,4-dimethyl-2-ethyl-2-oxazoline. The product was recrystallized from methanol to a melting point of 242-243°.

*Anal.* Calcd. for C<sub>10</sub>H<sub>8</sub>ClNO: C, 62.04; H, 4.16; Cl, 18.31; N, 7.24. Found: C, 62.35; H, 4.37; Cl, 18.18; N, 7.49.

Methallyl chloride was isolated from the distillate collected during the reaction and identified by its b.p. (70.5-72.0°), ir and nmr spectra, and refractive index.

#### 3-Methylcarbostyryl.

3-Methylcarbostyryl was obtained by heating 2-[2-(2-chlorophenyl)-1-methylethenyl]-4,4-dimethyl-2-oxazoline (**1**) at 195-270° for 1.5 hours. The product was recrystallized from ethanol to a m.p. of 240-241° [Lit. (7), m.p. 238°].

*Anal.* Calcd. for C<sub>10</sub>H<sub>9</sub>NO: C, 75.44; H, 5.70; N, 8.80. Found: C, 75.50; H, 5.99; N, 8.68.

#### 3-Phenylcarbostyryl.

3-Phenylcarbostyryl was prepared in 68% yield by reaction of 2-chlorobenzaldehyde with 2-benzyl-4,4-dimethyl-2-oxazoline. The product was recrystallized from ethanol to a m.p. of 229-231° [Lit. (8), m.p. 231-232°].

*Anal.* Calcd. for C<sub>15</sub>H<sub>11</sub>NO: C, 81.42; H, 5.01; N, 6.33. Found: C, 81.43; H, 4.95; N, 6.31.

3-Phenylcarbostyryl was also prepared in 31% yield by reaction of 2-bromobenzaldehyde with 2-benzyl-4,4-dimethyl-2-oxazoline by the standard procedure. Further work is needed to determine if the relatively low yield indicates that *o*-chlorobenzaldehydes are more suitable than *o*-bromobenzaldehydes for this type of reaction.

#### 2,7-Dichloro-3-phenylquinoline.

A stirred mixture of 5.0 g. of 7-chloro-3-phenylcarbostyryl and 25 ml. of phosphorus oxychloride was heated at reflux for 3 hours and then evaporated on a rotary evaporator, finally at 90°, 20 mm. The residue in 200 ml. of benzene was washed with 150 ml. 3% (w/v) aqueous sodium bicarbonate solution, dried with sodium sulfate, and evaporated to yield 5.3 g. of product, m.p. 99-101°. Recrystallization from hexane-benzene gave 4.1 g. of 2,7-dichloro-3-phenylquinoline, m.p. 102-103°. The elemental analyses are given in Table II.

All the other 2-chloroquinolines listed in Table II were prepared similarly.

#### REFERENCES AND NOTES

- (1a) H. L. Wehrmeister, *J. Org. Chem.*, **27**, 4418 (1962); (b) H. L. Wehrmeister, U.S. Patent 3,466,308 (1969).
- (2) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds", Vol. 1, W. A. Benjamin, Inc., New York, N.Y., 1965, p. 169.
- (3) R. E. Lutz, G. Ashburn, and J. Rowlett, Jr., *J. Am. Chem. Soc.*, **68**, 1322 (1946).
- (4) German Patent, 547,082 (1930): *Chem. Abstr.*, **26**, 3624 (1932).
- (5) H. L. Wehrmeister, *J. Org. Chem.*, **26**, 3821 (1961).
- (6) H. L. Wehrmeister, U.S. Patent, 3,876,770 (1975).
- (7) F. Effenberger and W. Hartmann, *Chem. Ber.*, **102**, 3260 (1969).
- (8) C. E. Kaslow and B. Buchner, *J. Org. Chem.*, **23**, 271 (1958).