J. Chem. Eng. Data **1987**, *32*, 387–389

Synthesis and Properties of Quaternary Ammonium Salts of Substituted α-Phenylcinnamonitriles

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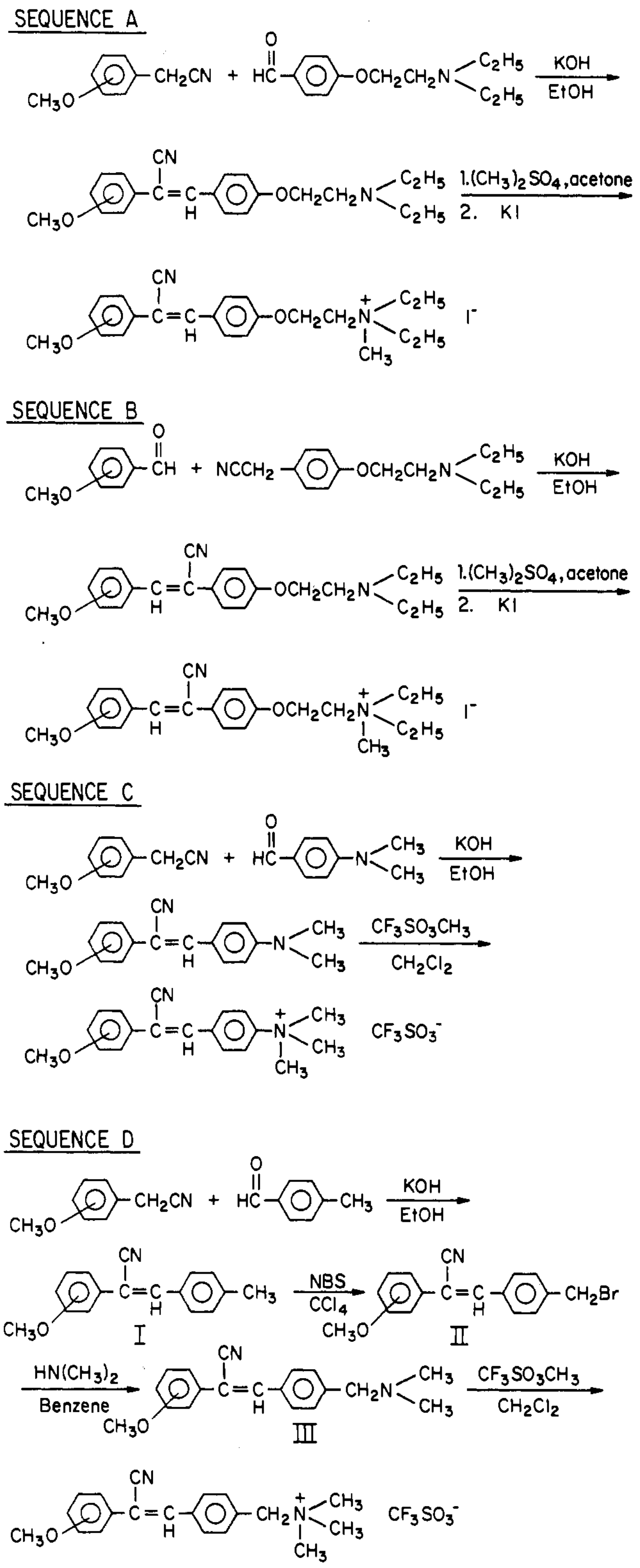
Quaternary ammonium salts of substituted α-phenylcinnamonitriles were synthesized via base-catalyzed condensations of substituted phenylacetonitriles and aldehydes, followed by alkylation of the amino moieties with dimethyl sulfate or methyl trifluoromethanesulfonate. A summary of the physical properties of the new quaternary ammonium salts is presented.

Interest in this laboratory in the use of quaternary ammonium salts of substituted α-phenylcinnamonitriles as potential analytical reagents resulted in the synthesis of some model compounds (Table I). A literature search revealed that little, if any, information was available concerning the synthesis and physical properties of these substances.

The compounds were synthesized via base-catalyzed condensations of substituted phenylacetonitriles and aldehydes (*1*, *2*) followed by alkylation of the amino substituents as shown by the reaction sequences A, B, and C (Scheme I). In sequence D, the *p*-methyl-substituted phenylcinnamonitrile (I) was brominated to compound II followed by conversion to the tertiary amine compound III prior to alkylation of the amino moiety (*3*, *4*). The alkylation reactions involved the use of either dimethyl sulfate or methyl trifluoromethanesulfonate. The use of the latter substance as an alkylating reagent for tertiary amines was especially attractive because it results in a near-quantitative yield of quaternary salts at room temperature conditions (*5*). The quaternary salts synthesized in this paper crystallized readily from ethanol or ethanol–water mixtures.

Table II presents a summary of the physical properties of the quaternary salts. There was special interest in the fluorescence of these compounds since previous experience with other types of α-phenylcinnamonitriles had shown that such substances possessed good fluorescent intensity in the solid state and in solution (*6*, *7*). Fluorescent measurements were performed by visual examination of the dry powders using long wavelength ultraviolet light (Ultra-violet Products, Inc., San Gabriel, CA) and by determination of the excitation and emission maxima of the compounds in ethanol solution. All except compounds **4** and **6** possessed varied fluorescent intensities in the solid state. Comparison of the fluorescent intensity of the compounds in solution to quinine sulfate via the quinine reference unit (QRU) was performed (*8*). It was concluded that compounds **1–6** possessed very weak fluorescence in solution compared to quinine sulfate. Compounds **7**, **8**, and **10** were the most fluorescent of the quaternary salts synthesized in that they showed QRU values of 1, 1.8, and 2.2, respectively. Compound **9** possessed only moderate fluorescence intensity in solution. Visual examinaion of solution fluorescence also indicated that the compounds displayed more intense fluorescence in ethanol than water.

Scheme I



Experimental Section

Melting points were determined in open capillary tubes with a Thomas-Hoover apparatus; they are uncorrected. UV spectra were determined in 95% ethanol with a Beckman Du-7 spectrophotometer. IR spectra were recorded as KBr disks on a Perkin-Elmer Model 684 spectrophotometer. Fluorescence spectra were determined in 95% ethanol with a Perkin-Elmer MPF-4 spectrophotofluorometer equipped with a corrected

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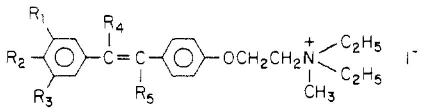
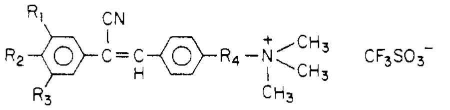
Table I. Quaternary Ammonium Salts of Substituted α-Phenylcinnamonitriles[a]



compd	R_1	R_2	R_3	R_4	R_5	mp, °C
1	OCH_3	OCH_3	OCH_3	CN	H	191–193
2	H	OCH_3	OCH_3	CN	H	171–174
3	H	OCH_3	H	CN	H	190.5–192
4	H	H	H	CN	H	188.5–192
5	OCH_3	OCH_3	OCH_3	H	CN	189–191
6	H	OCH_3	OCH_3	H	CN	204–205



compd	R_1	R_2	R_3	R_4	mp, °C
7	OCH_3	OCH_3	OCH_3		191–194
8	H	OCH_3	OCH_3		172–173
9	H	OCH_3	H		225–228
10	H	OCH_3	OCH_3	CH_2	197–198.5

[a] No attempt was made to optimize yields of intermediates or final products. All of the compounds were analyzed for C, H, N content and were found to be within calculated percentages ±0.4%.

spectra accessory. Proton NMR spectra were obtained in Me_2SO-d_6 with a Jeol FX-90Q spectrometer. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA.

Preparation of Intermediate Tertiary Amines. Reaction Sequence A, B, and C. To a solution of 0.02 mol of the appropriate phenylacetonitrile and 0.02 mol of the substituted benzaldehyde in 50 mL of absolute ethanol stirred at 50 °C, 5 mL of a 50% aqueous potassium hydroxide solution was added slowly. The mixture was then heated for an additional 5 min at 50 °C and cooled to room temperature, and the precipitate was filtered and dried. Compounds were recrystallized from ethanol–water mixtures.

Reaction Sequence D. 2-(3,4-Dimethoxyphenyl)-3-(p-methylphenyl)acrylonitrile (I) was prepared by the same method indicated above for sequences A, B, and C.

2-(3,4-Dimethoxyphenyl)-3-(p-bromomethylphenyl)-acrylonitrile (II). 0.02 mol of compound I, 0.02 mol of *N*-bromosuccinimide, and a catalytic amount (20 mg) of benzoyl peroxide were dissolved in 100 mL of carbon tetrachloride and refluxed for 1.5 h with stirring at 100 °C. The mixture was cooled to room temperature and the succinimide was filtered off. The solvent was evaporated to dryness on a rotary evaporator and the residue was collected and dried. The compound was recrystallized from absolute methanol.

2-(3,4-Dimethoxyphenyl)-3-((p-(dimethylamino)-methyl)phenyl)acrylonitrile (III). A round-bottom flask fitted

Table II. Summary of Physical Properties of Quaternary Ammonium Salts of α-Phenylcinnamonitriles

compd	UV (EtOH) λ_{max}, nm	IR γ_{max}, cm^{-1}	NMR δ	fluorescence			rel fluor QRU[c]
					solution[b]		
				solid[a]	ex	em	
1	344 (25 600)[d] 214 (36 700)	2205 (CN) 1605 (arom) 1513 (arom) 1250 (OCH_3)	3.87 (6 H, s, *m*-OCH_3) 3.71 (3 H, s, *p*-OCH_3) 3.07 (3 H, s N^+–CH_3) 1.28 (6 H, t, –CH_3)	*e*	398	459	2.43×10^{-4}
2	351 (23 500) 209 (30 700)	2205 (CN) 1605 (arom) 1520 (arom) 1250 (OCH_3)	3.86 (3 H, s, *m*-OCH_3) 3.81 (3 H, s, *p*-OCH_3) 3.08 (3 H, s, N^+–CH_3) 1.29 (6 H, t, –CH_3)	blue	403	450	3.71×10^{-4}
3	343 (29 500) 220 (24 000) 206 (18 000)	2210 (CN) 1609 (arom) 1518 (arom) 1250 (OCH_3)	3.82 (3 H, s, *p*-OCH_3) 3.08 (3 H, s, N^+–CH_3) 1.28 (6 H, t, –CH_3)	white	395	430	1.57×10^{-4}
4	332 (27 500) 222 (21 600)	2205 (CN) 760 (mono-Ar) 695 (sub Ar)	3.08 (3 H, s, N^+–CH_3) 1.29 (6 H, t, –CH_3)	*e*	390	440	0.50×10^{-4}
5	348 (28 500) 217 (28 700)	2205 (CN) 1603 (arom) 1512 (arom) 1250 (OCH_3)	3.84 (6 H, s, *m*-OCH_3) 3.75 (3 H, s, *p*-OCH_3) 3.08 (3 H, s, N^+–CH_3) 1.29 (6 H, t, –CH_3)	blue	396	432	1.29×10^{-4}
6	355 (27 300) 220 (26 400) 207 (23 400)	2205 (CN) 1610 (arom) 1520 (arom) 1275 (OCH_3)	3.84 (3 H, s, *m*-OCH_3) 3.82 (3 H, s, *p*-OCH_3) 3.08 (3 H, s, N^+–CH_3) 1.29 (6 H, t, –CH_3)	*e*	402	430	0.79×10^{-4}
7	340 (17 500) 260 (12 600) 205 (45 400)	2210 (CN) 1590 (arom) 1515 (arom) 1260 (OCH_3)	3.88 (6 H, s, *m*-OCH_3) 3.73 (3 H, s, *p*-OCH_3) 3.66 (9 H, s, N^+–$(CH_3)_3$)	blue	351	500	1.04
8	353 (16 700) 268 (11 300) 207 (22 600)	2210 (CN) 1595 (arom) 1525 (arom) 1270 (OCH_3)	3.87 (3 H, s, *m*-OCH_3) 3.83 (3 H, s, *p*-OCH_3) 3.66 (9 H, s, N^+–$(CH_3)_3$)	yellow	355	496	1.82
9	341 (20 800) 246 (11 800) 206 (16 200)	2210 (CN) 1610 (arom) 1515 (arom) 1255 (OCH_3)	3.84 (3 H, s, *p*-OCH_3) 3.64 (9 H, s, N^+–$(CH_3)_3$)	pale purple	350	430	0.31
10	353 (20 500) 273 (12 300) 208 (24 200)	2210 (CN) 1600 (arom) 1520 (arom) 1265 (OCH_3)	4.58 (2 H, s, Ar–CH_2–N) 3.87 (3 H, s, *m*-OCH_3) 3.83 (3 H, s, *p*-OCH_3) 3.07 (9 H, s, N^+–$(CH_3)_3$)	green	357	476	2.15

[a] Ascertained by visual observation of dry powder when exposed to UV light from a long-wavelength UV lamp. [b] Measurements were recorded on a Perkin-Elmer MPF-4 spectrophotofluorometer using ethanol as solvent. [c] Quinine reference unit, see ref 8. [d] Molar absorptivity. [e] Denotes that no fluorescence was visually observed in the solid state.

with a stirrer and a drying tube was immersed in an ice bath and a solution of 0.03 mol of anhydrous dimethylamine in 100 mL of dry benzene was added. Then 0.01 mol of compound II was added very slowly to the vigorously stirred solution in the flask. The mixture was then stirred at room temperature overnight. Water (150 mL) was added, the layers were separated, and the aqueous phase was extracted with two 100-mL portions of diethyl ether. The ether extracts were washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was evaporated on a rotary evaporator and an oily liquid was collected but not purified.

Preparation of Quaternary Ammonium Salts. Compounds 1-6. A solution of 0.01 mol of the tertiary amine, 0.03 mol of dimethyl sulfate, and 5 g of potassium carbonate in 60 mL of acetone was refluxed for 2 h. The hot mixture was filtered and the filtrate evaporated to dryness on a rotary evaporator. The crude methosulfate salt was collected and redissolved in a minimum amount of water. Solid potassium iodide was added to the aqueous solution of the crude methosulfate salt followed by stirring with a glass rod. The iodide salt was immediately formed and filtered. The residue was dried and recrystallized from ethanol-water mixtures.

Compounds 7-10. The tertiary amine (0.01 mol) was dissolved in a minimal amount of methylene chloride. Addition of 0.01 mol of methyl trifluoromethanesulfonate to the stirred solution of the amine formed the trifluoromethanesulfonate salt immediately. The salt was filtered, dried, and recrystallized from 95% ethanol.

Registry No. **1**, 108472-52-2; **1** (amine), 108472-66-8; **2**, 108472-53-3; **2** (amine), 108472-67-9; **3**, 108472-54-4; **3** (amine), 47502-97-6; **4**, 108472-55-5; **4** (amine), 108472-68-0; **5**, 108472-56-6; **5** (amine), 108472-69-1; **6**, 108472-57-7; **6** (amine), 108472-70-4; **7**, 108472-59-9; **7** (amine), 21132-48-9; **8**, 108472-61-3; **8** (amine), 21132-46-7; **9**, 108472-63-5; **9** (amine), 6582-06-5; **10**, 108472-65-7; I, 108472-71-5; II, 108472-72-6; III, 108472-73-7; 3,4,5-$(CH_3O)_3C_6H_2CH_2CN$, 13338-63-1; 3,4-$(CH_3O)_2C_6H_3CH_2CN$, 93-17-4; 4-$CH_3OC_6H_4CH_2CN$, 104-47-2; $C_6H_5CH_2CN$, 140-29-4; 4-$OHCC_6H_4O(CH_2)_2N(C_2H_5)_2$, 15182-94-2; 3,4,5-$(CH_3O)_2C_6H_3CHO$, 86-81-7; 3,4-$(CH_3O)_2C_6H_3CHO$, 120-14-9; 4-$NCCH_2C_6H_4O(CH_2)_2N(C_2H_5)_2$, 92373-69-8; 4-$OHCC_6H_4N(CH_3)_2$, 100-10-7; 4-$OHCC_6H_4CH_3$, 104-87-0; $(CH_3)_2NH$, 124-40-3.

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Received for review November 20, 1986. Accepted April 1, 1987.

2-Aryl-4(3*H*)-quinazolinone-5-carboxylic Acids

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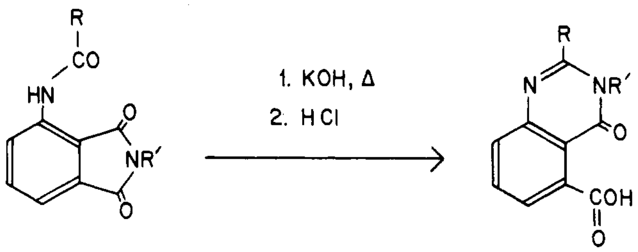
Twelve 2-aryl-4(3*H*)-quinazolinone-5-carboxylic acids have been prepared by the base-catalyzed rearrangement of 3-(aroylamino)phthalimides. This rearrangement reaction is inhibited by an ortho substituent on the aroyl group.

Bogert and Jouard (*1*) in 1909 reported that 3-acetamidophthalimide (I, R = CH_3, R′ = H) undergoes isomerization to form 2-methyl-4(3*H*)-quinazolinone-5-carboxylic acid (II, R = CH_3, R′ = H) when dissolved in hot, aqueous base and then acidified. This reaction was rediscovered in 1961 by Arcoria (*2*, *3*), who showed (*4*, *5*) that it is also applicable to cases in which R is aryl and R′ is methyl or phenyl (Scheme I).

Recently we reported (*6*) the results of our studies of the spectral properties of some 3-benzamidophthalimide (I, R = aryl, R′ = H). The isomerization of a few of these compounds to 2-aryl-4(3*H*)-quinazolinone-5-carboxylic acids (II, R = aryl, R′ = H) had been described by Arcoria, together with the ultraviolet absorption spectra of basic aqueous solutions of the products (*4*, *5*). Acoria's work included no examples of cases in which R possessed an ortho substituent. Since the necessary starting materials were at hand, further studies of this rearrangement reaction were possible.

Table I summarizes the results of these syntheses. The products were white powders with high melting points and low solubilities in all solvents except aqueous bases. The attempted rearrangement of 3-benzamidophthalimdes with ortho substituents on the benzamide moiety yielded the expected product only in the case in which R was 2-methoxyphenyl, and then in only 34% yield. For the cases in which R was 2-nitrophenyl or 2-chlorophenyl, the original 3-benzamidophthalimide was recovered unchanged upon acidification of the reaction mixture.

Scheme I



I

II

Table I. 2-Aryl-4(3*H*)-quinazolinone-5-carboxylic Acids (II, R′ = H)

compound II, R =	yield, %	melting point, °C found	melting point, °C reported[a]
phenyl	72	305–307	299
4-methoxyphenyl	21	308–311	310
2-methoxyphenyl	34	255–258	
4-methylphenyl	85	308–309	310
3-methylphenyl	52	266–267	272–273
4-chlorophenyl	60	*b*	>280[c]
3-chlorophenyl	89	329–330	
4-fluorophenyl	51	340–341	
3-fluorophenyl	67	315–316	
3-nitrophenyl	71	335–336	334–335
3,5-dinitrophenyl	65	283–285	
2-furyl	70	299–300	

[a] Reference *5*. [b] Sublimes >335 °C. [c] Reference *9*.

In the case where R was 2-fluorophenyl an analytically pure product could not be obtained. When R was 2-methylphenyl, the final acidification failed to precipitate a product.