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Coumarins. IV. The Acid-catalyzed Reaction of Phenols with Allyl Cyanide[1]

Takeshi AMAKASU[2]

Chemical Laboratory, Seimi Chemical Co., Ltd., Chigasaki, Chigasaki-shi, Kanagawa

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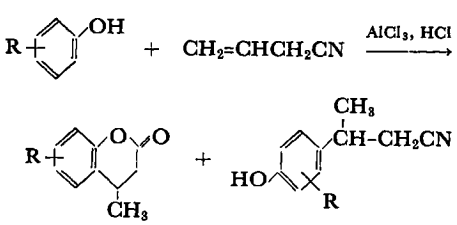
A new route to the syntheses of 4-methyldihydrocoumarins has been developed by means of the aluminum chloride-catalyzed reaction of phenols with allyl cyanide. The reaction of excess phenol with allyl cyanide in the presence of 2 equivalents of anhydrous aluminum chloride and an excess of hydrogen chloride yielded β-(*p*-hydroxyphenyl)-butyronitrile in a 16% yield. In contrast, the corresponding 4-methyldihydrocoumarins were obtained, together with β-arylbutyronitriles, from *o*- and *m*-cresols. *p*-Cresol gave rise to 4, 6-dimethyldihydrocoumarin as the sole product in a 8% yield. In diisopropyl ether, resorcinol underwent a similar reaction with allyl cyanide and afforded 4-methyldihydroumbelliferone in a 50% yield.

In the first paper of this series[3] dealing with the direct synthesis of dihydrocoumarins, it was established that anhydrous aluminum chloride, accompanied by dry hydrogen chloride, was an effective catalyst for the reaction of phenols with α, β-unsaturated nitriles. These studies have now been extended to 3-butenenitrile, *i. e.*, allyl cyanide. Although the aluminum chloride-catalyzed addition reaction of benzene to allyl cyanide has previously been shown[4] to give an excellent yield of β-phenylbutyronitrile, the present author could find no report concerning the acid-catalyzed reaction of phenols with allyl cyanide.

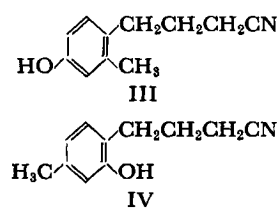
In the present study the author has examined the acid-catalyzed reaction of phenols with allyl cyanide, using anhydrous aluminum chloride and dry hydrogen chloride (Scheme 1).



Ia, R=6-CH₃ IIa, R=H
b, R=7-CH₃ b, R=2-CH₃
c, R=8-CH₃ c, R=3-CH₃
d, R=7-OH

Scheme 1

When 5 equivalents of *m*-cresol were treated with allyl cyanide in the presence of 2 equivalents of anhydrous aluminum chloride and an excess of hydrogen chloride, the corresponding dihydrocoumarin, Ib, and white crystals (mp 100—100.5°C) were obtained in 13 and 14% yields respectively. The structure of the former follows from the infrared spectrum (Table 2), which clearly shows a lactone C=O band at 1770 cm^{-1}. The analytical data of the latter agreed with the formula $C_{11}H_{13}NO$, which is in accord with the structures of the addition products, IIb, III, and IV. The infrared spectrum exhibited hydroxyl and cyano absorptions respectively at 3370 and 2230 cm^{-1}, in addition to an out-of-plane deformation of aromatic C–H at 810 cm^{-1}. This eliminates the possibility of such a structure as carbon-oxygen addition products, but not such as III and IV.



Finally, a NMR spectrum was obtained which was in complete accord with the β-aryl-butyronitrile structure. The characteristic doublets at 8.62 (J= 7 cps) and 7.51 (J=7 cps) τ were assigned to the terminal methyl and the methylene protons, while the two singlets at 7.73 and 5.25 τ were due to ortho-methyl and hydroxyl protons respectively. The aromatic multiplet appeared between 2.77—3.82 τ, along with that of the methine proton at

1) This investigation was presented at the 20th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1967; and was supported mainly by Asahi Glass Co., for which the author is grateful. Part III of this series: T. Amakasu and K. Sato, This Bulletin, **40**, 1428 (1967).

2) Present address: Department of Applied Chemistry, Faculty of Engineering, Yokohama National University, Ohka-machi, Minami-ku, Yokohama.

3) K. Sato, T. Amakasu and S. Abe, *J. Org. Chem.*, **29**, 2971 (1964).

4) I. P. Tsukervanik and A. D. Grebenyuk, *Dokl. Akad. Nauk SSSR*, **76**, 223 (1951).

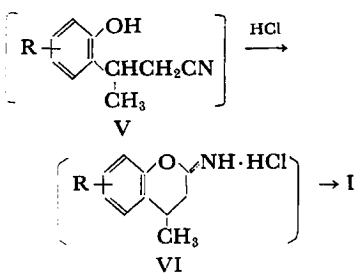
TABLE 1. THE ACID-CATALYZED REACTION OF PHENOLS WITH ALLYL CYANIDE

Phenol R	Procedure[a]	Reaction Temp. °C	Reaction hr	Product yield, % I	Product yield, % II
H	A	100—105	3	—	16
2-CH_3	A	105—110	5	8	16
3-CH_3	A	100—105	5	13	14
4-CH_3	A	105—110	5	8	—
3-OH	B	50— 55	4	50	—

a) See experimental section.

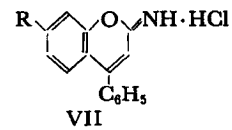
6.68 τ. Thus, it may be concluded that the β-substituted butyronitrile structure, II, must be assigned to the latter product from *m*-cresol.

o-Cresol behaved analogously when treated with allyl cyanide, giving the corresponding dihydrocoumarin, IC, as well as the butyronitrile, IIc. In contrast, only 4, 6-dimethyldihydrocoumarin (Ia) was obtained from *p*-cresol, while phenol, upon similar treatment with allyl cyanide, underwent nuclear-addition reaction leading to β-(*p*-hydroxyphenyl)butyronitrile (IIa). The results, summarized in Table 1, indicate that phenols predominantly undergo the nuclear addition reaction to allyl cyanide, while the resulting *o*-addition intermediates V, β-(*o*-hydroxyphenyl)butyronitriles, afford the corresponding dihydrocoumarins, I, through subsequent intramolecular cyclization, followed by acid hydrolysis (see Scheme 2).

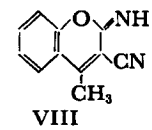


Scheme 2

Neither V nor VI could be isolated in any case, whereas the acid-catalyzed reaction of phenols with benzoylacetonitrile has been demonstrated[5] to furnsih 4-phenyl-2-iminocoumarins, VII, corresponding to VI, and 3-cyano-4-methyliminocoumarin (VIII) may be obtained by the base-catalyzed condensation of 2-hydroxyacetophenone with malononitrile.[6] This is presumably due to the difference in resonance stability between the intermediates VI and either VII or VIII.



VII



VIII

R=OH, OCH_3, CH_3

On the other hand, 4-methyldihydroumbelliferone (Id) was obtained, in a 50% yield, on a similar treatment of resorcinol with allyl cyanide in a diisopropyl ether solution at 50—55°C for 4 hr. Under the same conditions, however, no reaction occurred between the less reactive phenols, such as crescls, and allyl cyanide. Moreover, the use of such other inert solvents as tetrachloroethane for the reaction of the monohydride phenols resulted in the recovery of the starting phenols.

Tables 2 and 3 summarize the analytical characteristics of compounds I and II respectively. The most significant feature in Table 3 is the definite difference between the physical properties of IIb and those of either IIa or IIc. This might be related, to a certain degree, to the steric strain and the conformational rigidity involved only in IIb.

It is interesting to note whether the Friedel-Crafts reaction of phenols, particularly *o*- and *m*-cresols,

TABLE 2. ANALYTICAL CHARACTERISTICS OF 4-METHYLDIHYDROCOUMARINS (I)

Compd	Bp, °C/mmHg	n_D^{20}	Retention times, min[e]	IR, cm^{-1} C=O	C, % Found	C, % Calcd	H, % Found	H, % Calcd
Ia	74—77/1.5[a]	1.5061	6.0	1765				
Ib	109—114/0.5[b]	1.5395[b]	20.6	1770	74.98	74.97	6.67	6.86
Ic	85—90/1[c]	1.5061[c]	5.0	1765	75.25	74.97	7.06	6.86
Id	164—169/1[d]	d)		1740				

a) Ref. 3 (lit.[3] bp 100—105°C/5 mmHg).
b) K. Fries and G. Fickewirth [*Ann.*, **362**, 44 (1908)] have not reported the boiling point for Ib (lit. n_D^{20} 1.5321).
c) This is a new compound.
d) Mp 110—110.5°C (lit.[12] mp 109—110°C): (lit.[12] bp 190—193°C/7 mmHg).
e) Their retention times were determined under the conditions for gas chromatography described as follows; a 150 cm column packed with PEG (10%) on Diasolid; column temperature, 173°C, carrier gas, helium, 30 ml/min.

5) T. Amakasu and K. Sato, to be published; presented at the 19th Annual Meeting of the Chemical Society of Japan, Yokohama, April, 1966.
6) H. Junek, *Monatsh.*, **95**, 234 (1964).

TABLE 3. IDENTIFICATION OF β-ARYLBUTYRONITRILES (I)[a]

Compd	Bp, °C/mmHg	n_D^{20}	Retention times min[c]	IR, cm^{-1}			C, %		H, %	
				O-H	CN	C-H (aromatic)	Found	Calcd	Found	Calcd
IIa	135—141/1	1.5398	26.7	3400	2250	830	74.35	74.51	7.19	6.88
IIb	168—171/0.5	b)	22.3	3370	2230	810	75.20	75.40	7.60	7.48
IIc	115—118/1	1.5398	26.5	3400	2250	820	75.59	75.40	7.75	7.48

a) They are the hitherto unknown compounds.
b) Mp 100—100.5°C; recrystallized from benzene.
c) Their retention times were taken under the conditions for vapor phase chromatography shown as follows; a 150 cm column packed with PEG (10%) on Diasolid; column temperature, 200°C; carrier gas, helium, 60 ml/min.

takes place at the position ortho or para to the hydroxyl group. The results presented in Table 1 appear to contrast with those of a number of previous studies on the acid-catalyzed C-alkylation of them, indicating that attacks by electrophiles, in general, occur at both positions,[7] ortho and para to the hydroxyl group, except in some cases which lead to the predominant formation of an *o*-[8] or *p*-substituted product.[9] In addition, it is noteworthy that 4-methyldihydrocoumarin (I, R=H) can not be obtained from the reaction of phenol with allyl cyanide, while the reaction with crotononitrile may favor its formation.[3]

Experimental[10]

Materials. The allyl cyanide was prepared from allyl chloride and cuprous cyanide.[11] The other materials were obtained from commercial sources.

The Acid-catalyzed Reaction of Phenols with Allyl Cyanide. *General Procedure A.* Finely-powdered anhydrous aluminum chloride (0.4 mol) was added slowly to a mixture of allyl cyanide (0.2 mol) and the phenol (1 mol), after which stirring was vigorously continued at 30—40°C. Dry hydrogen chloride was passed into a viscous slurry; then the mixture, into which dry gas had been continuously passed, was gradually heated in an oil bath and kept under the conditions shown in Table 1. Thereafter the resulting mixture was chilled and poured over water containing crushed ice and concentrated hydrochloric acid. The organic layer was separated from the aqueous layer, which was then shaken with ether. The extract was combined with the separated organic material, and then washed with water. After the extract had been dried over anhydrous magnesium sulfate and the solvent had been removed, the residue was distilled under reduced pressure to give the crude products, I and/or II (containing phenol and unidentified by-products as contaminants). The analytical sample was prepared by vapor-phase chromatographic fractionation. The results with individual compounds are shown in Table 1. The infrared spectrum of 4, 6-dimethyldihydrocoumarin (Ia) was identical with that reported previously.[8] The analytical data for Compounds I and II are presented in Tables 2 and 3 respectively.

4-Methyldihydroumbelliferone (Id). *Procedure B.* To a stirred solution of resorcinol (22 g, 0.2 mol) and

7) D. R. Stevens and R. S. Bowman, U. S. Pat. 2560666 (1951); Ng. Ph. Buu-Hoi, H. Le Bihan and F. Binon, *J. Org. Chem.*, **17**, 243 (1952); J. F. Miquel, Ng. Ph. Buu-Hoi and R. Royer, *J. Chem. Soc.*, **1955**, 3417; V. L. Valser and A. M. Polikarpova, *Dokl. Akad. Nauk SSSR*, 108, 469 (1956); E. A. Viktorova, N. I. Shulkin and G. V. Popova, *Vestn. Mosk. Univ., Ser. II, Khim.*, **15**, No. 6, 62 (1960); E. A. Viktorova, N. I. Shulkin and P. N. Komarov, *ibid.*, **16**, No. 2, 53 (1961); N. I. Sulkin, E. A. Viktorova and I. E. Pokrovskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1961**, 1094, 2192; E. A. Viktorova, N. I. Shulkin and E. A. Karakhanov, *ibid.*, **1962**, 1080; N. I. Shulkin and E. A. Viktorova, *Novye Metody Ratsional. Ispol'z Mestnykh. Topliv, Trudy Soveshchaniya Riga*, **1958**, 265; E. A. Viktorova, N. I. Shulkin, I. E. Pokrovskaya and S. L. Aleksandrova, *Neftekhimiya*, **1**, 648 (1961); V. I. Isagulyants and V. P. Evstaf'ev, *Dokl. Akad. Nauk Arm. SSSR*, **38**, 235 (1964); *Mosk. Inst. Neftekhim. i Gaz. Prom.* No. **51**, 105 (1964); D. E. Mishiev, M. M. Guseinov and A. A. Mekhraliev, *Azerb. Khim. Zh.*, **1964**, 23; R. A. Babakhanov, D. E. Mishiev, E. E. Gaidarova and T. Samedova, *ibid*, **1965**, 42; A. I. Kakhniashvili and D. Ya. Bugianishvili, *Zh. Organ. Khim.*, **1**, 1043 (1965).

8) V. M. Dixit and A. M. Kanakudati, *J. Indian Chem. Soc.*, **28**, 323 (1951); I. Miyagawa, K. Sakurayama and K. Sawai, *Research Rept. Nagoya Ind. Sci. Research Inst.*, No. 8, 31 (1955); N. I. Shulkin, E. A. Viktorova and V. P. Litvinov, *Vestn. Mosk. Univ., Ser. Mat., Astron., Fiz. i Khim.*, **12**, No. 5, 121 (1957); B. Arventiev, H. Wexler and M. Strul, *Acad. rep. Polulalare Romine Filiala Iasi, Studic cercetări stünt., Chim.*, **11**, 63 (1960); E. A. Viktorova, N. I. Shulkin and G. S. Korostelera, *Vestn. Mosk. Univ., Ser. II, Khim.*, **16**, No. 2, 56 (1961); L. S. Kharchenko and S. V. Zavgorodnii, *Ukr. Khim. Zh.*, **30**, 261 (1964).

9) J. E. Driver and J. B. Sousa, *J. Chem. Soc.*, **1954**, 985; R. Maki, Y. Ishida, K. Satake and R. Oda, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Ind. Chem. Sect.)*, **57**, 42 (1954); I. Romadane and R. Slitke, *Uch. Zap. Rizksk. Politekhn. Inst. Khim. Fak.*, **6**, 123 (1962); L. S. Kharchenko and S. V. Zavgorodnii, *Zh. Prikl. Khim.*, **37**, 165 (1964); I. Romadane and E. A. Kochetkova, *Latvijas PSR Zinatnu Akad. Vestis. Khim. Ser.*, **1964**, 77: A. I. Kakhniaskvili and D. Ya. Bugianishvili, *Soobshch. Akad. Nauk Gruz. SSSR*, **37**, 53 (1965); A. I. Topchiev, B. M. Tumerman and E. M. Buslova, Tr., *Mosk. Inst. Neftekhim. i Gaz. Prom.*, No. **51**, 9 (1964).

10) All melting points and boiling points are uncorrected. Infrared spectra were recorded on a Hitachi Model EPI-S2, and gas chromatographic analyses were carried out on a Shimadzu Model GC-1b chromatograph. NMR spectra were taken in D-chloroform on a JEOL Model INM 4H-100 instrument with tetramethylsilane as an internal standard.

11) E. Rietz, "Organic Syntheses," Coll. Vol. III, p. 852 (1955).

allyl cyanide (13.4 g, 0.2 mol) in 200 m*l* of a solvent such as diisopropyl ether, anhydrous aluminum chloride (53.4 g, 0.4 mol) was added, portion by portion. The mixture, into which dry hydrogen chloride had been passed, was heated on a steam bath and kept for 4 hr at 50—55°C. The subsequent procedure followed Procedure A, already described. After the removal of the solvents, the residual oil was fractionated to give 17.6 g (50%) of a viscous oil: bp 164—169°C/1 mmHg (Lit.[12] bp 190—193°C/7 mmHg): ν_{max}^{film} 3280 (O-H), 1740 (lactone C=O), and 850, 810 cm^{-1} (aromatic C-H). It solidified after standing for a long time and melted at 108—110°C.

The recrystallization from benzene afforded Id; mp 110—110.5°C (lit.[12] mp 109—110°C). Compound Id showed a positive ferric chloride test.

On the other hand, the alternative procedure of adding a solution of resorcinol and allyl cyanide in ether to a stirred suspension of aluminum chloride in ether provided the same results as have been presented above.

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12) T. Kawai, T. Shimizu and M. Suzuki, *Yakugaku Zasshi*, **72**, 553 (1952).