STABLE ISOMERIC BENZONITRILE OXIDES DERIVED FROM 6-CHLORO-2,4-DIMETHOXYANILINE

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The Rieche formylation of N-acyl-6-chloro-2,4-dimethoxyanilines proceeds at C^5, while metallation occurs at C^3. As a result, isomeric aldehydes were obtained, which were converted into stable nitrile oxides.

In the present work, we developed rather simple approaches to the synthesis of functionally substituted benzonitrile oxides, which may hold interest as polymer modifiers and intermediates in the synthesis of physiologically active compounds.

6-Chloro-2,4-dimethoxyaniline(I), which is readily obtained in a one-step synthesis from p-benzoquinone monooxime by treatment with methanol and HCl [1], served as the starting compound. Vilsmeier formylation led only to the formation of dimethylformamidine (II). Further formylation was not observed, apparently due to the strong basicity of (II) and deactivation as the result of salt formation.

N-Acetyl derivative (IIIa) does not undergo the Vilsmeier reaction with DMF and $POCl_3$ even at 120°C. However, the Rieche formylation of (IIIa) using $MeOCHCl_2$ or n-$BuOCHCl_2$ and $TiCl_4$ gave an aldehyde identified as 6-chloro-5-acetylamino-2,4-dimethoxybenzaldehyde (IVa) since the electrophilic substitution of the dimethyl ether of 5-chlororesorcin occurs at C^4, i.e., between the chlorine atom and methoxy group [1]. The presence of an acylamino group in the meta position to the leaving group should not apparently alter the direction of the substitution.

N-Pivaloyl-6-chloro-2,4-dimethoxyaniline (IIIb) analogously forms aldehyde (IVb) in the Rieche reaction in good yield.

The metallation of (IIIb) by butyllithium, in contrast to the formylation, proceeds at the position between the two methoxy groups. The action of DMF on the lithium derivative gave aldehyde (V) in 43% yield. Carboxylation gave the corresponding acid (VI) in 63% yield. Polymetallation products in the case of excess metallating agent were not observed.

The structures of aldehydes (IVb) and (V) and acid (VI) (Table 1) were also supported by spectral data. The PMR spectral data are given in Table 2, which also contains literature data for compounds with established structure for comparison. The chemical shifts (CS) of the protons between the methoxy group and chlorine atom are located ≥0.1 ppm downfield relative to the protons between the two methoxy groups, independently of the nature of the meta-substituent. Such chemical shift differences were also observed in the ^{13}C NMR spectra (Table 3, see underlined values) for carbon atoms bearing hydrogen atoms. The downfield chemical shifts (by about 10 ppm) are assigned to the carbon atom between the chlorine atom and methoxy group. When both possible isomers are present, assignment to one or the other series is readily accomplished.

Both isomeric aldehydes are converted to oximes (VII) and (VIII), which were oxidized by the action of NaOCl to the corresponding benzonitrile oxides (IX) and (X). These oxides give the ordinary 1,3-dipolar cycloaddition adducts with styrene (XI) and (XII). The period of 50% conversion of (IX) is 0.5 year. The major reason for the relative instability of (IX) apparently lies in its isomerization to the isocyanate, as indicated by the disappearance of the IR band at 2300 cm^{-1} and appearance of a band at 2280 cm^{-1}. The period for 50% conversion of (X) is greater than one year.

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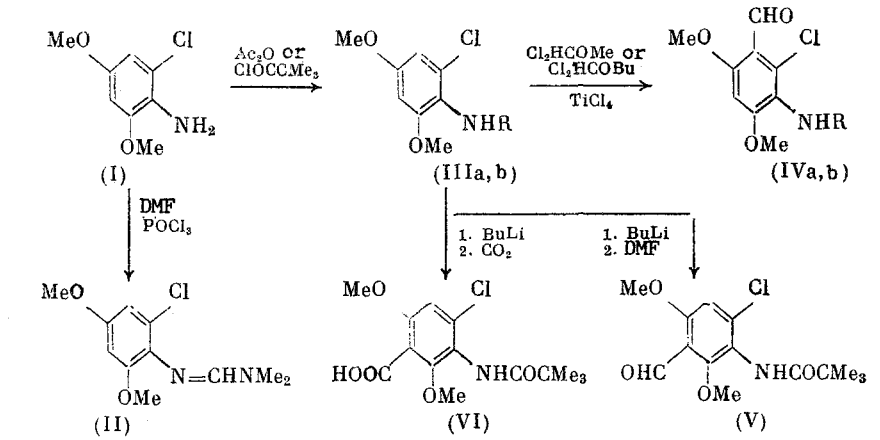
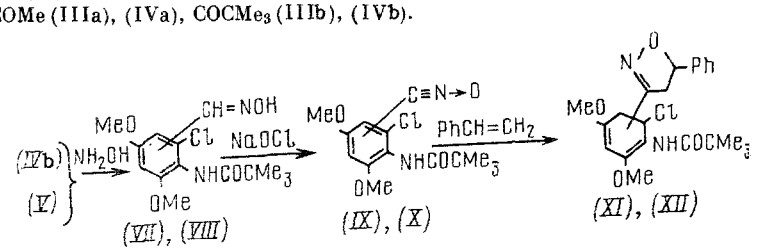


R = COMe (IIIa), (IVa), $COCMe_3$ (IIIb), (IVb).



EXPERIMENTAL

The melting points were determined on a Boetius block. The mass spectra were taken on a Varian MAT CH-6 mass spectrometer at 70 eV. The temperature of the ionization chamber was 50-150°C. The PMR spectra were taken on a Bruker WM-250 spectrometer at 250 MHz. The ^{13}C and ^{14}N NMR spectra were taken on a Bruker AM-300 spectrometer at 75.47 MHz for the ^{13}C NMR spectra and 21.688 MHz for the ^{14}N NMR spectra. The IR spectra were taken on a Perkin–Elmer 577 spectrometer at 400-4000 cm^{-1}.

The physical constants, yields, and elemental analysis data for the compounds synthesized are given in Table 1. The PMR spectral data are given in Table 2. The ^{13}C NMR spectral data are given in Table 3.

N,N′-Dimethyl-N-(6-chloro-2,4-dimethoxyphenyl)formamidine (II). A sample of 9.15 ml (100 mmoles) $POCl_3$ was added with rapid stirring over 2 h to a solution of 9.38 g (50 mmoles) (I) in 30 ml DMF at 0°C, stirred for an additional 30 min at 0°C, and left for 12 h at ~20°C. The mixture was then neutralized with cooling by the addition of 20% aq. NaOH. The precipitate formed was extracted with ether. The extract was dried over $MgSO_4$. The solvent was evaporated and the residue was recrystallized from CCl_4.

N-Acetyl-6-chloro-2,4-dimethoxyaniline (IIIa) was obtained by the action of acetic anhydride on (I) at 120°C for 3 h.

N-Pivaloyl-6-chloro-2,4-dimethoxyaniline (IIIb) was obtained from (I) and pivaloyl chloride according to Suffert [2].

6-Chloro-5-acetylamino-2,4-dimethoxybenzaldehyde (IVa). A solution of 1 ml (11 mmoles) $MeOCHCl_2$ at 0°C was added with stirring to a solution of 1.34 g (5.8 mmoles) (IIIa) in 13 ml CH_2Cl_2 and, after 10 min, a solution of 2.5 ml (23 mmoles) $TiCl_4$ in 2 ml CH_2Cl_2 was added. Stirring was continued for 2.5 h at 0-5°C. The reaction mixture was poured onto a mixture of equal parts of ice and concentrated hydrochloric acid. The precipitate was filtered off, washed with water, and dried. Product (IVa) was purified through its bisulfite derivative., IR spectrum (ν, cm^{-1}): 1690 (C=O).

6-Chloro-5-pivaloylamino-2,4-dimethoxybenzaldehyde (IVb) was obtained analogously to (IIIb) with n-$BuOCHCl_2$ as the formylating agent. Product (IVb) was purified by crystallization from acetone. IR spectrum (ν, cm^{-1}): 1690 (C=O). Oxime (VII) (Table 1). PMR spectrum in C_5D_5N (δ, ppm): 1.50 s (Me_3C), 3.62 s (MeO), 3.75 s (MeO), 6.54 s (H^3), 8.78 s (CH), 9.48 s (NH), 13.38 s (OH).

TABLE 1. Parameters of Products Synthesized

Compound	Yield, %	Mp, °C	Chemical formula*	Found / Calculated, %			
				C	H	Cl	N
(II)	95	78,5–79	$C_{11}H_{15}ClN_2O_2$	54,19 / 54,43	6,50 / 6,23	14,49 / 14,61	11,55 / 11,54
(IIIa)	91	157–158	$C_{10}H_{12}ClNO_3$	52,77 / 52,29	5,56 / 5,27	15,26 / 15,44	6,02 / 6,10
(IIIb)	83	98,5–99,5	$C_{13}H_{18}ClNO_3$	57,89 / 57,45	6,54 / 6,67	13,08 / 13,04	5,28 / 5,15
(IVa)	20	193–194	$C_{11}H_{12}ClNO_4$	51,31 / 51,27	4,71 / 4,69	13,55 / 13,76	5,48 / 5,45
(IVb)	80	178–181	$C_{14}H_{18}ClNO_4$	55,80 / 56,09	5,95 / 6,05	11,98 / 11,82	5,26 / 4,67
(V)	43	130–132	$C_{14}H_{18}ClNO_4$	56,04 / 56,09	6,23 / 6,05	11,69 / 11,82	4,55 / 4,67
(VI)	63	225–227	$C_{14}H_{18}ClNO_5$	53,06 / 53,25	5,89 / 5,75	11,22 / 11,23	4,39 / 4,44
Methyl ester (VI)	--	175–177	$C_{15}H_{20}ClNO_5$	54,60 / 54,62	6,18 / 6,11	11,10 / 10,75	4,27 / 4,25
(VII)	87	272–273	$C_{14}H_{19}ClN_2O_4$	53,39 / 53,42	5,98 / 6,08	11,07 / 11,26	9,09 / 8,90
(VIII)	83	236–238	$C_{14}H_{19}ClN_2O_4$	53,41 / 53,42	6,53 / 6,09	11,59 / 11,26	8,95 / 8,90
(IX)	83,6	173–175	$C_{14}H_{17}ClN_2O_3$	53,65 / 53,76	5,66 / 5,48	11,19 / 11,34	8,84 / 8,96
(X)	57	140–142	$C_{17}H_{17}ClN_2O_4$	53,57 / 53,76	5,55 / 5,48	11,10 / 11,34	9,13 / 8,96
(XI)	71	232–234	$C_{22}H_{25}ClN_2O_4$	63,56 / 63,38	6,28 / 6,04	8,89 / 8,51	6,66 / 6,72
(XII)	75	193–195	$C_{22}H_{25}ClN_2O_4$	63,05 / 63,38	6,11 / 6,04	8,68 / 8,51	6,51 / 6,72

*(M^+) for all the compounds corresponds to the calculated molecular masses.

4-Chloro-3-pivaloylamino-2,6-dimethoxybenzaldehyde (V). A sample of 29 ml (47.5 mmoles) ethereal BuLi was added over 10 min with rapid stirring to a solution of 1.5 g (5.5 mmoles) (IIIb) in 35 ml abs. ether in a dry argon atmosphere at from -62 to -72°C, stirred for 1.5 h at -72°C and for 2 h at 20°C, heated at reflux for 2 h, cooled to -50°C, and 4.26 ml (5.5 mmoles) DMF was added rapidly. The mixture was brought to 20°C and then heated at reflux for 1 h, cooled, and poured onto a mixture of 26 ml ice and 16 ml concentrated hydrochloric acid. The mixture was extracted with ethyl acetate, dried over $MgSO_4$, and evaporated. Aldehyde (V) was purified through its bisulfite derivative. IR spectrum (ν, cm^{-1}): 1700 (C=O). Oxime (VIII) (Table 1). PMR spectrum in $(CD_3)_2CO$ (δ, ppm): 1.38 s (Me_3C), 3.70 s (MeO), 3.88 s (MeO), 6.91 s (H^5), 8.16 br.s (NH), 8.20 s (CH), 10.38 s (OH).

4-Chloro-3-pivaloylamino-2,4-dimethoxybenzoic Acid (VI). A sample of 30 ml (60 mmoles) ethereal BuLi was added over 10 min in portions to a solution of 2.03 g (7.5 mmoles) (IIIb) in 50 ml abs. ether in a dry argon atmosphere at -69°C, stirred for 1.5 h at -72°C, heated at reflux for 1 h, cooled, and poured into a mixture of CO_2 and ether. The precipitate of the lithium salt was filtered off, washed with dry ether, and converted to the acid by the action of dilute sulfuric acid. The acid was purified by crystallization from acetonitrile. The methyl ester was obtained by the action of CH_2N_2.

TABLE 2. PMR Spectra of Products Synthesized in $CDCl_3$ (δ, ppm)

Compound	CS of aromatic protons (J, Hz)		MeO	CS of other protons (J, Hz)
	H^3	H^5		
6-Chloro-2,4-dimethoxybenzaldehyde*	6,38 d	6,50d (2,1)	3,86 s, 3,88 s	10,36 s (CHO)
Methyl 6-chloro-2,4-dimethoxybenzoate*	6,35 d	6,49 d (2,1)	3,78 s	3,90 s (MeOCO)
(I) *	6,36 d	6,45 d (2,4)	3,70 s, 3,80 s	3,76 s (NH_2)
(II)	6,38 d	6,53 d (3,03)	3,76 s	3,01 s (Me), 7,43 s (CH=)
(IIIa)	6,40 d	6,58d (3,03)	3,80 s	2,20 s (Me), 6,81 br.s (NH)
(IIIb)	6,40 d	6,58d (3,03)	3,78 s	1,33 s (Me_3C), 6,81 br.s (NH)
(IVa)	6,38 s	–	3,91 s	7,20 s (NH), 10,33 s (CHO)
(IVb)	6,29 s	–	3,78 s, 3,82 s	1,27 s (Me_3C), 7,06 br.s (NH), 10,24 s (CHO)
(V)	–	6,61 s	3,59 s, 3,75 s	1,27 s (Me_3C), 7,49 br.s (NH), 10,13 s (CHO)
Methyl ester (VI)	–	6,79 s	3,78 s, 3,88 s	1,37 s (Me_3C), 3,92 s (MeOCO), 6,92 s (NH)
(IX)	6,39 s	–	3,87s, 3,92 s	1,33 s (Me_3C), 6,89 br.s (NH)
(X)	–	6,85 s	3,88s, 3,92 s	1,34 s (Me_3C), 6,91 br.s (NH)
(XI)	6.44 s	–	3,83 s, 3,86 s	1,36 s (Me_3C), 3,21 d.d (J=8,0; 17,0), 3,67 d.d (CH_2, J=11,6; 17,0), 5.73 d.d (isoxazoline ring CH, J = 8.0; 11.0) 7,90 s (NH), 7,30–7,50 m (C_6H_5)
(XII)	–	6,79 s	3,70 s, 3,82 s	1,36 s (Me_3C), 3,27 d.d (J=8,8; 17,5), 3,69 d.d (CH_2, J=11.4; 17.5), 5,73 d.d (CH isoxazoline ring, J=8,8; 11.4), 7,03 s (NH), 7,32–7,42 m (C_6H_5)

*Data taken from Sargent [1].

6-Chloro-5-pivaloylamino-2,4-dimethoxybenzonitrile Oxide (IX). A sample of 2.58 g (8 mmoles) oxime (VII) was added with rapid stirring to a mixture of 12.5 ml aq. NaOCl (24 mmoles, 0.15 g/ml active chlorine), and 39.5 ml CH_2Cl_2 at 0°C and stirred for 8 h at 0°C. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with cold water and dried over $MgSO_4$. The solvent was evaporated without heating. Product (IX) was purified by precipitation from a solution in CH_2Cl_2 by the addition of hexane. IR spectrum (ν, cm^{-1}): 2307 C≡N), 1350 N=O). ^{14}N NMR spectrum in $CDCl_3$ (δ, ppm): 172.65 ppm (CNO).

4-Chloro-3-pivaloylamino-2,6-dimethoxybenzonitrile oxide (X) was obtained analogously to (IX). IR spectrum (ν, cm^{-1}): 2307 (C≡N), 1350 (N=O). ^{14}N NMR spectrum in $CDCl_3$ (δ, ppm): 170.67 ppm (CNO).

3-(6-Chloro-5-pivaloylamino-2,4-dimethoxyphenyl)-5-phenyl-2-isoxazoline (XI). A sample of 0.5 ml styrene was added to a solution of 0.65 g (2 mmoles) nitrile oxide (IX) in 20 ml CH_2Cl_2 and stirred for 1.5 h. Product (XI) was isolated from CH_2Cl_2 solution by the addition of hexane or crystallization from acetone.

TABLE 3. ^{13}C NMR Spectral Data in $CDCl_3$ (δ, ppm)

Compound	Me	$\underline{C}Me_3$	2-MeO	4-MeO	CS of aromatic C atoms						C=O	CHO
					C^1 *	C^2	C^3	C^4	C^5	C^6		
(IIIb)	27,44	39,02	55,44	55,91	116,98	156,51	97,86	158,91	105,41	133,39	176,99	–
(IVb)	27,45	39,15	58,22	58,22	– **	160,73	93,98	162,65	114,89	136,33	177,32	187,74
(V)	27,54	39,31	56,42	62,80	122,56	159,39	117,82	160,29	108,67	140,55	177,65	188,03 168,70
(VI) ***	23,15	40,60	57,26	63,01	120,18	156,77	–	157,34	109,63	137,32	181,25	(COOH)
(IX)	27,48	39,17	56,13	56,35	– **	158,72	94,02	162,03	– **	117,95	177,21	–
(X)	27,42	39,23	56,48	61,79	121,73	160,05	– **	160,42	107,82	137,48	177,70	–

*Numbering of carbon atom given analogously to (IIIb).
*Signals not detected.
***In CD_3OD.

3-(4-Chloro-3-pivaloylamino-2,6-dimethoxyphenyl)-5-phenyl-2-isoxazoline (XII) was obtained analogously to (XI).

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2. J. Suffert, J. Org. Chem., 54, No. 2, 509 (1989).

ELECTROPHILIC ISOMERIZATION OF FLUOROALIPHATIC OXYGEN-CONTAINING COMPOUNDS

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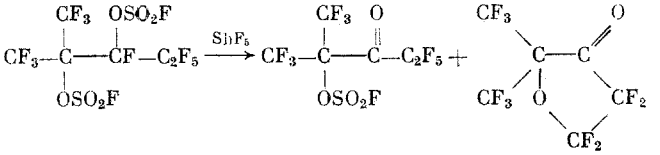
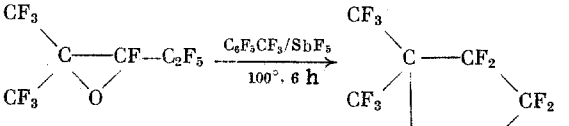
An unusual electrophilic cyclization of fluorine-containing carbonyl compounds and α-oxides was discovered. Upon the action of SbF_5, perfluorinated ketones, diketones, and α-oxides isomerize to oxolanes. This reaction proceeds with the obligatory participation of the terminal CF_3 group.

In previous work [1], we have shown that heating 2,3-bis(fluorosulfato)perfluoro-(2-methylpentane) (I) in the presence of SbF_5 gives 2-fluorosulfatoperfluoro-(2-methyl-3-pentanone) (II) as well as an unusual cyclization product, namely, perfluoro-2,2- dimethoxy-3-oxolanone (III), which is formally the cyclocondensation product of (II).*



(I) (II) (III), 18%

An analogy for this reaction is found in the isomerization of perfluoro(2-methyl-2-pentene) oxide (IV) upon its heating with a mixture of perfluorotoluene and SbF_5, leading to perfluoro(2,2-dimethyloxolane) (V) [2].†



(IV) (V), 83%

Such reactions accompanied by the cleavage of a C–F bond in an unactivated CF_3 group far removed from any functional group, double bond, or aromatic system, do not find analogy in the chemistry of organofluorine compounds.

*In the present work, we found that heating (I) in the presence of SbF_5 in an autoclave at 150°C for 12 h leads to the formation of (III) in 87% yield.

†Oxide (IV) does not react with SbF_5 in the absence of perfluorotoluene upon heating to 300°C [3].

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