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INVESTIGATIONS ON THE SYNTHESIS OF DL-SERINE FROM α-HALOACRYLIC ACID DERIVATIVES

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Abstract: The alkoxide-catalyzed addition of alcohols 2 to α-chloroacrylonitrile (1) at -35°C gives rise to 3-alkoxy-2-chloropropanenitriles 3; at 0-5°C with excess 2 alkyl 3-alkoxy-2-chloropropanimidates 4 are obtained. The yields of 3 or 4 decrease with increasing pK_a values of the alcohols 2. In the base-catalyzed addition of phenols 5 to 1, a temperature-dependent addition equilibrium is set up in which the position of equilibrium is shifted in favour of the addition products 6 with increasing pK_a values of 5. The 3-alkoxy-2-chloropropanoates 8, which are readily accessible by hydrolysis of 4, react smoothly with sodium azide in the presence of a phase transfer catalyst to furnish the 3-alkoxy-2-azidopropanoates 10. Starting from benzyl 2-azido-3-benzyloxypropanoate (10b), the specific syntheses of DL-serine (14), DL-serine hydrochloride (14·HCl), DL-serine methyl ester hydrochloride (13a·HCl), O-benzyl-DL-serine (12b), and O-benzyl-DL-serine benzyl ester hydrochloride (11b·HCl) are possible by variation of the hydrogenation conditions.

INTRODUCTION

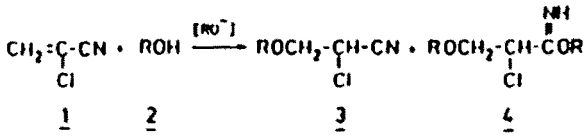
The present demand for L-serine[3] can no longer be fulfilled from protein hydrolysates and it has thus become necessary to develop alternative methods for obtaining L-serine. Fermentation processes for the production of L-serine have not been generally accepted. The usual method for producing L-serine consists of the enzymatic racemate cleavage of DL-serine prepared by chemical routes.[4a] Relevant chemical syntheses of DL-serine have been summarized in two review articles.[4a,b] Only those processes starting from acetaldehyde or acrylic acid derivatives have aroused technical interest to date.

In the present work, we report on new variations of the addition of oxygen nucleophiles to α-haloacrylic acid derivatives which lead to products that are suitable for the production of DL-serine.

ADDITION OF OXYGEN NUCLEOPHILES TO α-CHLOROACRYLONITRILES

Disadvantages of the presently known, technical-scale syntheses of DL-serine starting from acetaldehyde or acrylic acid derivatives are, on the one hand, the necessity to use expensive bromine compounds instead of the cheaper chlorine derivatives in order to achieve good yields and, on the other hand, the problems associated with the cleavage of alkyl ethers on a technical scale when O-methyl- or O-ethylserine are involved as precursors.[5]

The use of bromine compounds as intermediates can be avoided by means of the alkoxide-catalyzed addition of alcohols 2 to α-chloroacrylonitrile (1) to give 3-alkoxy-2-chloropropanenitriles 3 which can also be transformed to DL-serine.[6]



1 2 3 4

Depending on the reaction conditions, the imino ester 4 can be obtained as well as the addition product 3.[6a] The yields of the addition products 3 and/or 4 depend to a major extent on the nature of the alcohol 2 employed. Good yields of the addition products are generally obtained with methanol (2a) whereas, for example, no addition products could be isolated when benzyl alcohol (2b) was used.[6a] However, it are just the O-benzyl compounds that are of particular interest for the production of DL-serine since their cleavage, either by hydrogenolysis or under acid catalysis, is considerably simpler than the cleavage of the O-methyl compounds. For this reason, we have investigated the addition of alcohols 2 to 1 in dependence on the various reaction parameters and initially attempted to synthesize the monoaddition products 3 specifically.

This was indeed possible when equimolar amounts of 2 were added dropwise to 1 in the presence of 5 mol% alkoxide as catalyst at temperatures below 0°C (Method A, Table 1). With excess 2 at somewhat higher temperatures in the presence of 5 mol% alkoxide, the diaddition products 4 are obtained exclusively (Method B, Table 1). Products 4 are also formed by the alkoxide-catalyzed addition of 2 to 3, as demonstrated for the example of the reaction of 3a with 2a in the presence of sodium methoxide to give 4a.

The reaction temperature has a considerable influence on the yields of 3 obtained from these reactions; yield maxima were found at -30 to -40°C in general. The lower yields at lower temperatures are apparently a result of the insufficient reaction times; the lower yields at higher temperatures may be explained by subsequent reactions of the products 3 with the catalyst such as, for example, elimination of hydrogen chloride or nucleophilic substitution of chloride by alkoxide. These reactions consume the catalyst and thus bring the addition reaction of alcohol to 1 to a standstill. The data given in Table 1 clearly show the extent to which the yields of 3 depend on the nature of the alcohol 2. When the yields of 3 are correlated with the pK_a values of the alcohols 2 employed as addends, a very good relationship is obtained. The more acidic 2a undergoes better addition to 1 than 2e which is less acidic by two pK_a units. The diadducts 4 are obtained exclusively from the alcohol addition to 1 in excess alcohol 2 at 0 to 5°C. In comparison to the alcohol additions to furnish monoadducts 3, the reactions show a somewhat less pronounced dependency on the acidity of the alcohol 2 employed. The optimized reaction conditions for obtaining high yields in the specific preparations of the addition products 3 and 4 are summarized in Table 1.

Table 1. Addition of alcohols 2 to 2-chloropropenenitrile (1) to form
A) 3-alkoxy-2-chloropropanenitriles 3 according to Method A
B) 3-alkoxy-2-chloropropanimidates 4 according to Method B

2	R	pK_a[a]	react. temp. (°C)[b]	products	(yield,%)[c]	
2a	CH_3	15.09	-35	3a	77	(99)
2b	$C_6H_5CH_2$	15.40	-27	3b	60	(85)
2c	$CH_2=CHCH_2$	15.52	-30	3c	53	
2d	C_2H_5	15.93	-35	3d	25	(48)
2e	$(CH_3)_2CH$	17.10	0	3e	3	
2f	$(CH_3)_3C$	19.2	+20	3f	-	
2a			+5	4a	86	
2b			+5	4b	80	
2c			0	4c	79	
2d			+5	4d	76	

[a] In water at 25°C according to Ref.[7]. - [b] Reaction times: after slow dropwise addition at the given temperature in Method A: 45 min at the given temperature and 2 h at room temperature; in Method B: 1 h at the given temperature and 2 h at room temperature. - [c] Values in brackets are the yields determined by ^{1}H-NMR-spectroscopy.

The following reaction mechanism is assumed to be in operation for the alkoxide-catalyzed additions of 2 to 1.

$$CH_2{=}\underset{Cl}{\overset{|}{C}}\text{-}CN \cdot RO^{\ominus} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ROCH_2\text{-}\underset{Cl}{\overset{|}{\overset{\ominus}{C}}}\text{-}CN$$

1

$$ROCH_2\text{-}\underset{Cl}{\overset{|}{\overset{\oplus}{C}}}\text{-}CN \cdot ROH \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} ROCH_2\text{-}\underset{Cl}{\overset{|}{C}}\text{H-}CN \cdot RO^{\ominus}$$

2 3

$$3 \cdot RO^{\ominus} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} ROCH_2\text{-}\underset{Cl}{\overset{|}{C}}\text{H-}\overset{\overset{\|}{NH}^{\ominus}}{\overset{|}{C}}\text{OR}$$

$$ROCH_2\text{-}\underset{Cl}{\overset{|}{C}}\text{H-}\overset{\overset{\|}{NH}^{\ominus}}{\overset{|}{C}}\text{OR} \cdot ROH \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} ROCH_2\text{-}\underset{Cl}{\overset{|}{C}}\text{H-}\overset{\overset{\|}{NH}}{\overset{|}{C}}\text{OR} \cdot RO^{\ominus}$$

2 4

The absence of the formation of 3f in the attempt to add 2f to 1 is probably the result of the comparable acidities of 3f and 2f so that, with catalytic amounts of tert.-butoxide, the addition of 2f to 1 comes to a standstill relatively rapidly. We consider steric hindrance to the addition of 2f to 1 to be less probable. The CH-acidity of the imino ester 4 is apparently somewhat less than that of the nitrile 3 and hence, for example, the formation of 4d is also favoured in 2d, which is less acidic than 2a ($k_4 > k_{-4}$).

The reaction of 1 with phenol (5a) has already been described;[8] in the presence of 19 mol% of sodium phenoxide and excess 5a at 60°C 6a was obtained exclusively in 40% yield and a second addition at the nitrile group was not observed.[8] On repeating the phenoxide-catalyzed addition of 5a to 1 to give 6a, we have found that this addition is in fact an equilibrium and that the equilibrium position is, as expected, strongly dependent on temperature. We have studied the attainment of the equilibrium both in the addition to give 6a and in the phenolate-catalyzed cleavage of 6a and obtained comparable results.

Table 2. Addition of phenol (5a) to 1 to form 2-chloro-3-phenoxypropanenitrile (6a) and cleavage of 6a[a]

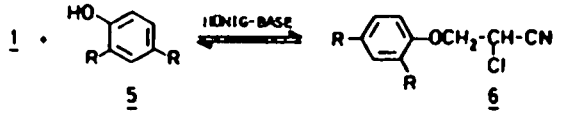
	reaction temperature (°C)							
	100	80	70	60	50	40	30	22
Addition: 6 (yield %)[b]	20	26	34	38	39	45	28	29
after h	6	6	6	6	27	48	166	185
Cleavage: uncleaved 6a (yield %)[b]	19	27	31	38	42	45	48	50
after h	6	6	6	6	27	119	119	139

[a] In the presence of 5 mol% of sodium phenoxide. - [b] Determined by ^{1}H-NMR-spectroscopy.

It can be seen from Table 2 that, at higher temperatures, more substrate 1 and at lower temperatures more addition product 6a is present. We could not achieve an equilibrium concentration of 6a of more than 50% even when the reaction temperature was lowered further and the reaction time extended accordingly.

Earlier studies on the addition of substituted phenols 5 to 1 at higher temperatures have shown that donor-substituted phenols undergo addition readily, chlorophenols less readily, and 4-nitrophenol not at all.[9] We have now investigated the addition of the substituted phenols 5b-f to 1 at 35°C in the presence of 5 mol% of the HÜnig base diisopropyl(ethyl)amine. The reaction times were selected so that the attainment of the equilibrium addition ⇌ elimination - recognizable on the basis of the constant concentrations of the addition products 6 - was certain; as a consequence of the relatively low reaction temperature (35°C), long reaction times were necessary in some cases.

Table 3. Addition of phenols 5 to 1 to form 3-aryloxy-2-chloropropanenitriles 6



5 6

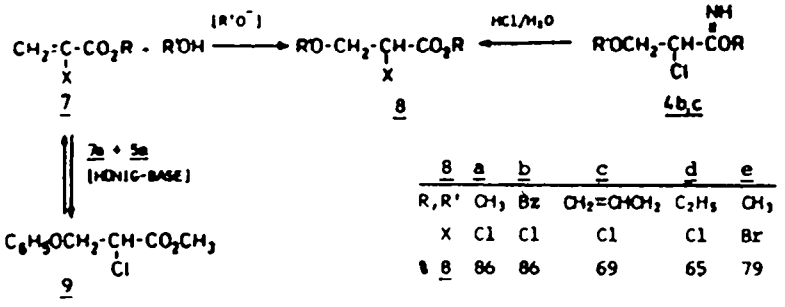
5	R	pK_a (in H_2O)	reaction time (h)	product (yield, %)
5a	H	9.89[b]	95	6a 38 (48)
5b	2,4-Cl_2	7.85[c]	160	6b 5 (11)
5c	4-NO_2	7.15[b]	120	6c 2 (3)
5d	4-Cl	9.18[b]	170	6d 27 (40)
5e	4-CH_3	10.17[b]	101	6e 42 (54)
5f	4-CH_3O	10.20[c]	76	6f 40 (56)

[a] Values in brackets are the yield determined by ^{1}H-NMR spectroscopy. - [b] According to Ref.[10a]. - [c] According to Ref.[10b]

The decrease in the yield of 6 with increasing acidity of the phenol 5 is a result of the better leaving group properties of the more stable phenoxide ions. In contrast to the addition of alcohols 2 to 1, in which the second partial step is decisive for the formation of the addition products 3 and thereby leads to the higher yields of 3 with more acidic alcohols, the first partial step is decisive for product formation in the addition of 5 to 1. That means the higher the acidity of the phenols, the more stable are the corresponding phenoxides and the more strongly is the equilibrium shifted towards the substrate 1.

ADDITION OF OXYGEN NUCLEOPHILES TO α-CHLOROACRYLATES

In analogy to the reactions of α-chloroacrylonitrile (1), we have also studied the dependency of the reactions of α-haloacrylates 7 with alcohols 2 and phenol (5a) on the temperature and catalyst. The addition of 2 to 7 proceeds analogously to that of 2 to 1 in the presence of 5 mol% of alkoxide as catalyst at reaction temperatures of about 0°C to give optimum yields of the 3-alkoxy-2-halopropanoates 8.



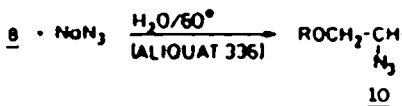
8	a	b	c	d	e
R,R'	CH_3	Bz	CH_2=CHCH$_2$	C_2H_5	CH_3
X	Cl	Cl	Cl	Cl	Br
% 8	86	86	69	65	79

The advantages of the above method in comparison with the previous methods[4a,11] are the facts that monohalo compounds are now employed and that cheaper chloro compounds may also be used. The disadvantage of the alcohol addition to 7 is that the pure addition product 8 is only formed when the alcohol to be added is not different from the alcohol of the ester group. When the alcohol groups are different (R≠R'), transesterification can occur and result in product mixtures that are difficult to separate. We have thus prepared the benzyl (8b) and allyl (8c) derivatives by acidic hydrolysis of the imino esters 4b,c (both accessible in good yields) and not by addition of the corresponding alcohol to 7.

STUDIES ON THE PREPARATION OF DL-SERINE FROM THE 3-ALKOXY-2-CHLOROPROPANOIC ACID DERIVATIVES 3, 4 AND 8

In order to convert the above-mentioned compounds 3, 4, and 8 to DL-serine, exchange of chlorine for a suitable nitrogen function and cleavage of the O-alkyl substituent at the 3-position are necessary.

As a consequence of the ready elimination (see above), we have only attempted the halogen exchange with strongly nucleophilic but weakly basic compounds. Even potassium cyanate, which reacts with 2-halocarboxylates to give substitution products in good yields[12], effects exclusive elimination of hydrogen chloride from 10a in 2a. In contrast, reactions of 3-alkoxy-2-chloropropanoates 8 with sodium azide under phase transfer conditions[11b,c] are successful and give good yields of the substitution products 10; products of elimination were not detected.

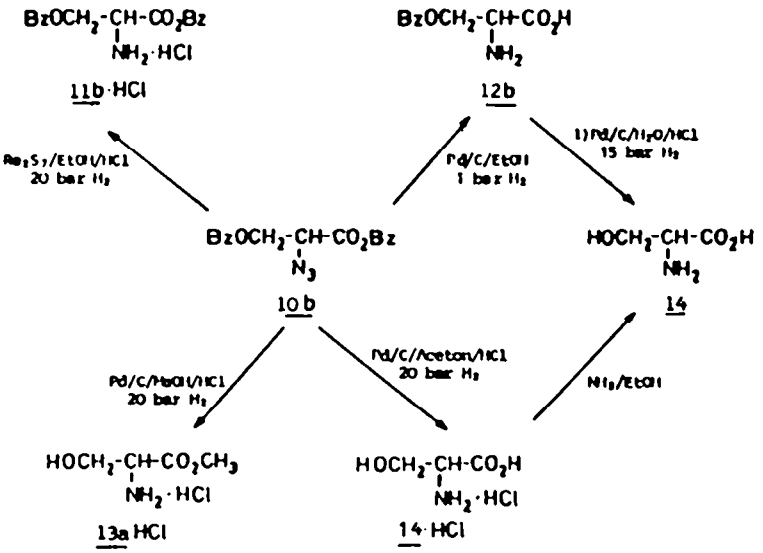


10

10	a	b	c	d
R	CH_3	Bz	CH_2=CHCH$_2$	C_2H_5
%	96 (79)	92 (82)	78 (27)	83 (67)

( ) = % after purification by CC

2-Chloropropanenitriles 3 only react to give poor yields and the imino esters 4 do not react with sodium azide under these conditions. Now that the 2-chloropropanoates 8 are also accessible from 1 in high yields by means of a "one-pot" process involving the addition products 3 and 4 and hydrolysis of 4, we have investigated the preparation of DL-serine via compounds 8 in more detail. The benzyl derivative 10b was of special interest as a result of the easily possible ether cleavage. By variation of the hydrogenation conditions, we have prepared DL-serine (14) and the derivatives listed in Table 4 specifically and in good yields.



From these results, it can be seen that use of Re_2S_7 as catalyst in 2d and in the presence of HCl results only in hydrogenation of the 2-azido group whereas use of Pd/C as catalyst in 2d without HCl leads to additional ester cleavage to give O-benzyl-DL-serine (12b).

Hydrogenation with Pd/C in 2a in the presence of HCl effects, in addition to hydrogenation of the azido group, ether cleavage and transesterification, resulting in the formation of DL-serine methyl ester hydrochloride (13a·HCl). The transesterification can be avoided by performing the reaction in acetone, allowing the isolation of DL-serine hydrochloride (14·HCl) or, after neutralisation with ammonia, of DL-serine (14). On hydrogenation with Pd/C without HCl, the benzyl ester group is hydrogenolytically cleaved twice as rapidly as the benzyl ether group; thus, selective hydrogenation of 10b offers the advantage of obtaining specifically protected DL-serine derivatives directly from the synthesis.

In summary, DL-serine (14) can be synthesized in an overall yield of about 70% in a few steps starting from 1. In comparison to the previously known processes, the high yields, the cheaper starting materials, and the low formation of salts are decisive advantages of this new method.

Table 4. Catalytic hydrogenation of benzyl 2-azido-3-benzyloxypropanoate (10b) with Pd/C at 25°C

solvent	HCl_{gas}	bar H_2	time (h)	product	m.p.(°C)	[Lit.]	yield (%)
2d[a]	+	20	20	11b·HCl	144-145	[147.5-148][15]	48[b]
2d	-	1	8	12b	202-206	[218][5c]	79
2a	+	20	25	13a·HCl	131-133	[133-134][16]	96
acetone	+	20	20	14·HCl[c]	140-145	[140-142][17]	81
2d	+	20	20	14[d]	224-226	[228-236][18]	90
2d	-	40 +50	25[e] +24[f]	14	229-231		97

[a]With Re_2S_7. - [b]Yield of crude product: 88%. - [c,d]Work up: [c]Filtration, extraction of the filter residue with hot water, concentration, and crystallisation of the remaining oil with diethyl ether; [d]as before but with neutralization of the remaining oil with ammonia and precipitation of 14 with 2d at 0°C. - [e]At 50°C. - [f]At 70°C after addition of water and further Pd/C.

EXPERIMENTAL SECTION

Preparative column chromatography was performed on silica gel (Merck, particle size 0.040-0.063 mm) in glass columns of varying dimensions. ^{1}H-NMR-spectra were recorded on Varian A-60, T-60, EM 360, and Bruker HX 90 spectrometers.

REACTIONS OF 2-CHLOROPROPENENITRILE (1) WITH ALCOHOLS (see Table 1):

General: Method A: At the temperature given in Table 1, sodium (0.115 g, 5.0 mmol) dissolved in the respective alcohol 2 (0.110 mol) is added dropwise with stirring to 1 (8.75g, 0.10 mol); the colour of the solution changes to green, dark blue, or black initially. Stirring is continued at the same temperature for 45 min and room temperature for 2 h. The reaction mixture is then neutralized by passage of CO_2, filtered, and distilled.
Method B: At the temperature given in Table 1, 1 (8.75 g) is added dropwise with stirring to sodium (0.115 g) dissolved in the respective alcohol 2 (0.4 mol); the colour of the solution changes to green or blue initially. Stirring is continued at the same temperature for 1 h and at room temperature for 2 h. The mixture is worked up as described under Method A.

By Method A: 2-Chloro-3-methoxypropanenitrile (3a): using methanol (2a; 3.52 g); yield: 9.23 g; b.p. 64-65°C/12-13 torr (Ref.[6a], b.p. 69-71°C/12 torr).
3-Benzyloxy-2-chloropropanenitrile (3b): using benzyl alcohol (2b; 12.0 g); yield: 11.74 g; b.p. 81-83°C/5·10-3 torr. Calcd. for $C_{10}H_{10}ClNO$: C, 61.39; H 5.15; N, 7.16; Cl, 18.12. Found: C, 61.23; H, 5.41; N, 7.45; Cl, 18.20.
3-Allyloxy-2-chloropropanenitrile (3c): using allyl alcohol (2c; 5.81 g); yield: 7.75 g; b.p. 86°C/11 torr (Ref.[6c], b.p. 52°C/3 torr).
2-Chloro-3-ethoxypropanenitrile (3d): using ethanol (2d; 5.07 g); yield: 3.4 g; b.p. 67-68°C/12-13 torr (Ref.[6a], b.p. 75-76°C/14 torr).
2-Chloro-3-isopropoxypropanenitrile (3e): using isopropyl alcohol (2e; 16.85 g, 0.28 mol) and 1 (17.15 g, 0.2 mol), addition temperature 0°C; yield: 0.97 g; addition temperature +20°C; yield: 0.59 g; b.p. 74°C/13 torr. Calcd. for $C_6H_{10}ClNO$: C, 48.82; H, 6.83; N, 9.49; Cl, 24.02. Found: C, 48.98; H, 7.03; N, 9.62; Cl, 23.94.

By Method B: Methyl 2-Chloro-3-methoxypropanimidate (4a): using 2a (12.82 g); yield: 13.01 g; b.p. 73°C/13 torr. Calcd. for $C_5H_{10}ClNO_2$: C, 39.62; H, 6.65; N, 9.24; Cl, 23.39. Found: C, 39.36; H, 6.79; N, 9.48; Cl, 23.23.
Benzyl 3-Benzyloxy-2-chloropropanimidate (4b): using 2b (43.26 g); yield: 24.3 g; b.p. 150-154°C/5·10-3 torr. Calcd. for $C_{17}H_{18}ClNO_2$: C, 67.21; H, 5.97; N, 4.61; Cl, 11.67. Found: C, 67.47; H, 6.04; N, 4.81; Cl, 11.44.
Allyl 3-Allyloxy-2-chloropropanimidate (4c): using 2c (29.04 g); yield: 16.11 g; b.p. 112°C/10 torr. Calcd. for $C_9H_{14}ClNO_2$: C, 53.08; H, 6.93; N, 6.88; Cl, 17.41. Found: C, 53.14; H, 7.17; N, 6.76; Cl, 17.32.
Ethyl 2-Chloro-3-ethoxypropanimidate (4d): using 2d (23.04 g, 0.5 mol); yield: 13.7 g; b.p. 87-89°C/12-13 torr (Ref.[6a], b.p. 94-96°C/14 torr).

Reaction of 3a with 2a to give 4a: Sodium (0.115 g, 5.0 mmol) in 2a (3.32 g, 0.1 mol) is added dropwise with stirring at 5°C to 3a (11.95 g, 0.1 mol) and 2a (3.32 g, 0.1 mol), stirring is continued at 5°C for 1.5 h and at room temperature for 1 h. The reaction mixture is worked up as described above; yield: 12.29 g (81%).

Temperature-Dependent Addition of 2 to 1 to give 3 (see Tab. 1): A solution of 5 mol% of sodium alkoxide in an equimolar amount of the respective alcohol 2 is slowly added dropwise to a stirred solution of 1 in mesitylene at the temperature given, stirring is continued at that temperature for 45 min, and at room temperature for 2 h. After neutralization by passage of CO_2, the yield of 3 in the reaction mixture is determined by ^{1}H-NMR spectroscopy on the basis of the signals for the proton at C-2 (triplet) and the two protons at C-3 (doublet) using mesitylene as standard.

Reaction of 1 with Phenol (5a): (a) To a stirred solution of sodium (0.115 g, 5.0 mmol) in 5a (11.29 g, 0.12 mol) at 35°C is added dropwise 1 (8.75 g, 0.10 mol) and stirring is continued at 35°C for 95 h. The reaction mixture is then cooled, taken up in diethyl ether, washed with 5% NaOH solution until free of phenol, neutralized with dilute HCl, washed with water, and dried with magnesium sulfate. The diethyl ether is distilled off and the residue is distilled under vacuum to give 2-chloro-3-phenoxypropanenitrile (6a); yield: 6.7 g (37%); b.p. 103°C/0.1 torr (Ref.[8], b.p. 105-110°C/0.3 torr).
(b) For determination of the position of the equilibrium (see Table 2) 5a (0.56 g, 6.00 mmol), 1 (0.44 g, 5.0 mmol), and sodium phenoxide (5 mol%) are used for the addition and 6a (0.76 g, 5.00 mol) and sodium phenoxide (5 mol%) are used for the cleavage, both reactions with stirring at the given temperatures for the given times. The yields are finally determined by ^{1}H-NMR spectroscopy.
(c) As described under (a) above but with triethylamine (5 mol%) as catalyst in place of sodium phenoxide, reaction time: 26 h, temperature: 40°C; yield of 6a (by ^{1}H-NMR spectroscopy): 37%.

Reactions of 1 with Substituted Phenols 5 (see Tables 3 and 5):
General: As described under (a) above but with the Hünig base (diisopropyl(ethyl)amine; 5 mol%) and the reaction times given in Table 3. After distillation of diethyl ether, the crude products are purified either by distillation or by column chromatography on silica gel.

PREPARATION OF 3-ALKOXY-2-HALOPROPANOATES 8:

Methyl 2-Chloro-3-methoxypropanoate (8a):A solution of sodium (0.115 g) in 2a (3.2 g, 0.1 mol) is added dropwise to a stirred solution of methyl 2-chloropropenoate (7a; 12.05 g, 0.1 mol) in 2a (6.41 g, 0.2 mol) at 0°C. The colour of the solution changes through yellow to green. Stirring is continued at 0°C for 1 h and at room temperature for 2 h. The reaction mixture is neutralized by passage of CO_2, filtered, and distilled; yield: 13.06 g (86%); b.p. 67-68°C/13-14 torr (Ref.[13], b.p. 77°C/19 torr).

Benzyl 3-Benzyloxy-2-chloropropanoate (8b):(a) To a solution of 4b (15.19 g, 0.05 mol) in diethyl ether (40 ml) at room temperature is added dropwise 10% HCl (30 ml). The reaction mixture is stirred at room temperature for 1 h, extracted with diethyl ether, the ether phase is neutralized with sodium hydrogen carbonate solution, dried with magnesium sulfate, and concentrated; yield: 13.14 g (86%).
(b) "One-Pot" Procedure: Compound 1 (17.7 g, 0.2 mol) is added dropwise to a solution of sodium (0.23 g, 0.01 mol) in 2b (108.15 g, 1.0 mol), the reaction mixture is stirred at 0°C for 1 h, and at room temperature for 2 h. Diethyl ether (60 ml) is added, followed by slow addition of 10% HCl (60 ml), and the mixture is worked up as described above; yield: 52.80 g; after distillation at 165-166°C/0.02 torr: 44.06 g (72%). Calcd. for $C_{17}H_{17}ClO_3$: C, 67.00; H, 5.62; Cl, 11.63. Found: C, 67.13; H, 5.67; Cl, 11.37.

Allyl 3-Allyloxy-2-chloropropanoate (8c):"One-Pot" Procedure: From sodium (0.23 g, 0.01 mol), 2c (58.08 g, 1.0 mol), and 1 (17.7 g) as described above under (b) and subsequent treatment with 10% HCl (60 ml) and diethyl ether (60 ml); yield of crude product after work up: 34.90 g (85%); after distillation: 28.24 g (69%); b.p. 130-131°C/22 torr. Calcd. for $C_9H_{13}ClO_3$: C, 52.82; H, 6.40; Cl, 17.32. Found: C, 53.07; H, 6.57; Cl, 17.55.

Ethyl 2-Chloro-3-ethoxypropanoate (8d):Analogous to 8a but with ethyl 2-chloropropenoate (7d; 17.81 g, 0.132 mol) in 2d (12.2 g, 0.265 mol) and sodium (0.152 g; 5 mol%) in 2d (6.1 g, 0.132 mol); yield: 15.53 g (65%); b.p. 93°C/22 torr(Ref.[6a], b.p. 81-83°C/14 torr).

Methyl 2-Bromo-3-methoxypropanoate (8a'):Analogous to 8a but with methyl 2-bromo-3-propenoate (16.50 g; 0.10 mol) in 2a (6.41 g, 0.20 mol) and sodium (0.115 g; 5 mol%) in 2a (3.20 g, 0.10 mol); yield: 15.63 g (79%); b.p. 69°C/11 torr (Ref.[14], b.p. 87-88°C/13 torr).

Methyl 2-Chloro-3-phenoxypropanoate (9):Compounds 5a (5.65 g, 60.0 mmol) 7a (6.03 g, 50.0 mmol) and the Hünig base (0.32 g, 2.5 mmol) are stirred at 35°C for 165 h. The yield at this stage as determined by ^{1}H-NMR spectroscopy is 10%. The reaction mixture is dissolved in diethyl ether , washed with dilute sodium hydroxide solution until free of phenol, neutralized with dilute HCl, washed with water, dried with magnesium sulfate, and distilled; yield: 0.36 g (3%); b.p. 95°C/0.06 torr.

Table 5. 3-Aryloxy-2-chloropropanenitriles 6 from 2-chloropropenenitrile (1), phenol (5a) or substituted phenols 5b-f in the presence of Hünig base (5 mol%) (reaction temperature: 35°C, for reaction times and yields (%) see Table 3).

1 g (mol)	5	g (mol)	Hünig base(g)	pro-duct	yield (g)	b.p.(°C/torr) [m.p.(°C)]	analysis	calcd. (found) C	H	Cl	N
21.88 (0.25)	5a	28.23 (0.30)	1.62	6a	17.21[a]	77/0.02 [54-55]	C_9H_8ClNO	59.52 (59.35)	4.44 (4.45)	19.52 (19.75)	7.71 (7.53)
2.19 (0.025)	5b	4.89 (0.03)	0.16	6b	0.33[b]	120-121/0.01	$C_9H_6Cl_3NO$	43.15 (43.11)	2.41 (2.55)	42.46 (42.72)	5.59 (5.40)
8.75 (0.1)	5c	16.69 (0.12)	0.65	6c	0.53[c]	[88-88.5]	$C_9H_7ClN_2O_3$	47.70 (47.53)	3.11 (3.25)	15.64 (15.82)	12.36 (12.13)
4.38 (0.05)	5d	7.72 (0.06)	0.32	6d	2.97[b]	130/0.15 [37-38]	$C_9H_7Cl_2NO$	50.03 (50.07)	3.27 (3.32)	32.82 (32.61)	6.48 (6.24)
2.19	5e	3.24 (0.03)	0.16	6e	2.07[b]	86-87/$5\cdot10^{-3}$ [22-23]	$C_{10}H_{10}ClNO$	61.39 (61.26)	5.15 (5.25)	18.12 (18.27)	7.16 (7.16)
4.38	5f	7.45 (0.06)	0.32	6f	4.19[b]	128-129/0.1 [41-42]	$C_{10}H_{10}ClNO_2$	56.75 (56.77)	4.76 (4.59)	16.75 (16.82)	6.62 (6.81)

[a] After purification by distillation. - [b] After purification by column chromatography with petroleum ether/ethyl acetate (15/1). - [c] After purification by column chromatography with petroleum ether/ethyl acetate /7/3).

Transformation of Alkyl 3-Alkoxy-2-chloropropanoates 8 to Alkoxy-2-azidopropanoates 10 (see Table 6)

General: The respective compound 8 is stirred with sodium azide in the presence of Aliquat 336 (5 mol%) and water at 60°C. The reaction mixture is then cooled, extracted with dichloromethane, the extract is dried with magnesium sulfate, and concentrated. The crude products are purified by column chromatography over silica gel with petroleum ether/ethyl acetate (15/1) as eluent.

Table 6. 3-Alkoxy-2-azidopropanoates 10 from 3-alkoxy-2-chloropropanoates 8, sodium azide, and water in the presence of Aliquat 336 at 60°C

8	g (mmol)	NaN_3	Aliquat 336 (g)	H_2O (ml)	time (h)	crude [pure] product	yield(g)	analysis	calcd. (found) C	H	N
8a	4.55 (30)	2.93 (45)	0.62	12	8.5	10a	4.58 [3.75]	$C_5H_9N_3O_3$	37.74 (37.85)	5.70 (5.80)	26.40 (26.40)
8b	4.56 (15)	1.46 (22.5)	0.31	6	9	10b	4.30 [3.83]	$C_{17}H_{17}N_3O_3$	65.58 (65.39)	5.50 (5.60)	13.50 (13.60)
8c	10.18 (50)	4.88 (75)	1.03	25	10	10c	8.26 [2.81][b]	$C_9H_{13}N_3O_3$	51.18 (51.12)	6.20 (6.15)	19.88 (19.92)
8d	4.50 (25)	2.44 (37.5)	0.51	10	8	10d	3.88 [3.14]	$C_7H_{13}N_3O_3$	44.91 (45.07)	7.00 (7.21)	22.45 (22.60)

[a] Yield (%) see scheme 6. - [b] Partial decomposition during purification.

Catalytic Hydrogenation of Benzyl 2-Azido-3-benzyloxypropanoate (10b) (see Table 4):
a) Dry hydrogen chloride (1.5 g, 0.041 mol) is passed into a solution of 10b (1.56 g, 5.0 mmol) in absolute 2d (10 ml), Re_2S_7 (0.03 g, 0.05 mmol) is added, and the mixture is hydrogenated at 25°C in an autoclave under 20 bar H_2 pressure for 20 h. The catalyst is filtered off, the filtrate is concentrated, and the resultant oil (1.42 g; 88% yield of crude O-benzyl-DL-serine benzyl ester hydrochloride; 11b·HCl) is dissolved in chloroform. Diethyl ether is added to precipitate the product which is recrystallized three times from ethanol/diethyl ether; yield of 11b·HCl: 0.78 g.
b) A solution of 10b (1.56 g) in absolute 2d (10 ml) is treated with 10% Pd/C (0.2 g), and hydrogen is passed through a glass frit into the vigorously stirred suspension for 8 h. The mixture is filtered, the filtrate is discarded, and the residue on the filter is extracted with hot water. After evaporation of the extract in a rotary evaporator, the residue is dried at 50°C in vacuum for 24 h; yield of O-benzyl-DL-serine (12b): 0.77 g.
c) Dry hydrogen chloride (0.7 g, 0.019 mol) is passed into a solution of 10b (1.56 g) in absolute 2a (10 ml), 10% Pd/C (0.2 g Pd) is added, and the mixture is hydrogenated at 25°C in an autoclave under 20 bar H_2 pressure for 25 h. The catalyst is then filtered off, the filtrate is concentrated in a rotary evaporator, and the residue recrystallized from methanol/diethyl ether (1/1); yield of DL-serine methyl ester hydrochloride (13a·HCl): 0.75 g.

d) As in c) but in absolute acetone (10 ml) and a hydrogenation time of 20 h. After filtration of the catalyst, the residue on the filter is extracted with hot water, and the extract concentrated in a rotary evaporator. The residual oil is induced to crystallize by treatment with diethyl ether and the crystals are dried in vacuum at 50°C for 24 h; yield of DL-serine hydrochloride (14·HCl): 0.57 g.
e) As in c) with the exception that the oil remaining after concentration of the extract is neutralized with ammonia, the precipitated product is suctioned, filtered, and dried under vacuum at 50°C for 24 h; yield of DL-serine (14): 0.47 g.
f) As in b) with the exception that the initial hydrogenation is carried out in an autoclave at 50°C under 40 bar H_2 pressure for 25 h. After addition of water (5 ml) and further Pd/C (0.1 g), the mixture is hydrogenated again in an autoclave at 70°C under 50 bar H_2 pressure for 24 h. After filtration of the catalyst, the filtrate is evaporated to dryness in a rotary evaporator, and the solid residue is dried at 50°C under vacuum for 24 h; yield of 14: 0.51 g.
Reaction of 12b to 14: 12b (0.976 mg, 5.0 mmol) is treated with Pd/C (0.2 g), 1N HCl (8 ml) and H_2O (15 ml) for 15 h at 50°C under 15 bar H_2 pressure to yield 14 (0.51 g).

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