PREPARATION OF UNSATURATED NITRILES

Miloš PROCHÁZKA and Miroslav ŠIROKÝ

Department of Organic Chemistry, Charles University, 128 40 Prague 2

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The yield and the rate of formation of nitriles X—CH=CH—CN and 3- or 4-substituted nitriles X—C_6H_5CN (X = CH_3; OR; SR; $COOCH_3$) were investigated in the reaction of vinyl and aryl bromides with $CN^{(-)}$, under catalysis with Pd^0 and macrocyclic polyethers, and in the reaction with CuCN in dipolar aprotic solvents. Individual procedures were compared from the point of view of the possibility of a preparative utilization.

Nucleophilic substitution of halogen on a multiple bond takes place sufficiently rapidly only in the presence of electron accepting groups. In their absence energetic reaction conditions are required. In unactivated systems cuprous cyanide was used for the synthesis of nitriles at temperatures of 180–250°C and in the absence of solvent[1–4], while at lower temperatures basic solvents (pyridine[5,6], quinoline[7]) or dipolar solvents (N-methylpyrrolidone[8,9], dimethyl sulfoxide, tetramethylurea[10]) could be used. In some instances substitution took place more rapidly with sodium cuprous dicyanide[1], $NaCu(CN)_2$, or potassium hexacyanodinickelate[12], $K_4Ni_2(CN)_6$. Often hydrogenolytic side reaction[10] and a doubling of radicals[12] was also observed. The reaction with alkaline cyanide deposited on alumina[13] or brought into solution with crown-ether[14] under catalysis with Pd^0 complexes was carried out successfully; the mechanism of the reaction catalysed with Pd^{2+} in hexamethylphosphoric triamide[15,16] was also proposed. In this paper we concentrated on substitution reactions of vinyl and aryl bromides in the presence of electron donating substituents which would proceed with high yields and under mild conditions. The optimum method for the synthesis of nitriles was studied with (*E*) and (*Z*)-1-bromo-2-phenylethene and bromobenzene and applied to the series (*E*; *Z*)—X—CH=CH—Br (X = CH_3; C_2H_5S; C_2H_5O; for comparison also $COOCH_3$) and to derivatives of bromobenzene with analogous substituents in the position 3 and 4. In reactions with cuprous cyanide the mechanism[7] shown in equation (*1*) was proposed, based on the effect of oxidizing substances[1] and the formation of complexes of nitriles with cuprous cyanide[17].

$$ArX + CuCN \rightarrow (ArCN)_2CuX \rightarrow ArCN + CuX \qquad (1)$$

In complex compounds of the elements of the 8th group the coordinatively saturated

complex[18,19] reacts according to scheme (2) (refs[16,20,21]).

$$Pd^0(L)_4 \leftrightarrows Pd(L_2) + 2\,L \rightarrow R{-}Pd(L)_2X \qquad (2)$$

$$R{-}PdX \xrightarrow[\text{aq}]{CN^-} RPdCN \rightarrow Pd^0 + RCN$$

$$L = (C_6H_5)_3P$$

Generally it is an oxidative addition, substitution and insertion of the ligand, with subsequent reductive elimination.

Aliphatic Compounds

The reaction of (*E*) and (*Z*)-1-bromophenylethene with alkali cyanides in aliphatic alcohols or aromatic hydrocarbons does not take place, while in tetrahydrofuran and acetonitrile $E-Z$ isomerization takes place. The equilibrium observed coincides with that obtained under catalysis with iodine (92 ± 1% (*E*) and 8 ± 1% (*Z*)-isomer at 100°C in tetrahydrofuran). In dipolar aprotic solvents, dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and hexamethylphosphoric triamide (HMPT), antiperiplanar elimination of hydrogen bromide from the (*Z*)-isomer takes place in consequence of the increased basicity of the cyanide anion, while the (*E*)-isomer remains unchanged. The phenylethane formed was detected by IR spectra and gas chromatography. Neither an increase in the solubility of potassium cyanide by addition of crown-ethers, nor the use of phase-transfer catalysts (hexadecyltrimethylammonium bromide) led to the formation of nitrile.

The reaction of 1-bromo-2-phenylethene with cuprous cyanide in dipolar aprotic solvents requires an elevated temperature (150°C) and it gives good yields only in dimethylformamide and dimethyl sulfoxide (Table I), while in hexamethylphosphoric triamide it is very slow (20% of nitrile after 20 h). The use of sodium dicyanocuprate increased the specificity of the reaction, but in this case the reaction in dimethylformamide proceeded slowly, while good results were obtained only when hexamethylphosphoric triamide was used (Table II), where substitution is accompanied by thermal ($E-Z$)-isomerization of the nitrile.

The reaction of 1-bromo-2-phenylethene with alkali cyanides in the presence of catalysts was carried out with $K_4Ni_2(CN)_6$ in a number of solvents at 20–100°C, but the yield did not exceed 20%.

Substitution did not take place under catalysis with palladium bis(triphenylphosphine)chloride, $Pd((C_6H_5)_3P)_2Cl_2$; iron pentacarbonyl is a good catalyst of the substitution during the reaction in methanol, but a rapid addition of methanol to the formed nitrile also takes place, which was proved by a separate experiment. In other types of solvents the formation of nitrile was not observed. The most sui-

table synthesis of (*E*)- and (*Z*)-3-phenylpropenonitrile was that carried out by reaction of alkali cyanide transferred into the benzene solution with crown-ether, catalysed with $Pd((C_6H_5)_3P)_4$ at 80°C. The reaction proceeded stereospecifically under retention of configuration and the yields of both isomers were almost quantitative. This procedure and the reaction with cuprous cyanide or sodium dicyanocuprate in aprotic dipolar solvents were studied in substitution reactions of further members of the aliphatic series (X—CH=CH—Br, X = CH_3; C_2H_5O and C_2H_5S; $COOCH_3$).

TABLE I

Yields of nitriles (%) in the reaction of bromo olefins with $Cu_2(CN)_2$ at 150° C

Starting compound	Solvent	(*E*)-	(*Z*)-Nitrile, %
(*E*)-1-Bromo-2-phenylethene	DMF	85	6
	DMSO	71	3
(*Z*)-1-Bromo-2-phenylethene	DMF	59	30
	DMSO	24	55
(*E*)-1-Bromo-1-propene	DMF	62	25
	DMSO	50	39
(*Z*)-1-Bromo-propene	DMF	60	27
	DMSO	65	22

TABLE II

Yields (%) of the reactions of (*E*)- and (*Z*)-1-bromo-2-phenylethene with $NaCu(CN)_2$ in hexamethylphosphoric triamide at 140°C in dependence on time

Product	Reaction time, h				
	1	4	12	24	72
(*E*)-1-Bromo-2-phenylethene					
(*E*)-3-Phenylpropenonitrile	0·1	6	47	61	95
(*Z*)-3-Phenylpropenonitrile	0	0	1	2	4
(*Z*)-1-Bromo-2-phenylethene					
(*E*)-3-Phenylpropenonitrile	0	0	3	8	44
(*Z*)-3-Phenylpropenonitrile	1	18	51	71	55

(*E*)- and (*Z*)-1-bromo-1-propene reacted with cuprous cyanide in dimethylformamide and dimethyl sulfoxide at 150°C under isomerization, in 85–87% yield, while in hexamethylphosphoric triamide the reaction of both isomers was very slow, similarly as with $NaCu(CN)_2$ in dimethylformamide and hexamethylphosphoric triamide. The reaction with cyanide catalysed with $Pd((C_6H_5)_3P)_4$ in the presence of crown-ether proceeded at 80°C stereospecifically with yields about 90% and under retention of configuration. The substitution reaction of 1-bromo-2-ethoxyethene was unsuccessful. The (*Z*)-isomer did not react either with $Cu_2(CN)_2$ or with $NaCu(CN)_2$ in dimethylformamide or hexamethylphosphoric triamide even after 50 h at 180°C, or cyanide under catalysis with $Pd((C_6H_5)_3P)_4$. The substitution reaction of (*E*) and (*Z*)-1-bromo-2-(ethylthio)ethene with cuprous cyanide at 150°C is accompanied by the formation of polymeric products, so that the yields do not exceed 30%; a temperature decrease to 120°C leads to a practically complete stop of the substitution reaction. In the case of the (*E*)-isomer the reaction with cyanide under catalysis with $Pd((C_6H_5)_3P)_4$ takes place non-stereospecifically and with low yield (15%), while the (*Z*)-isomer did not react at all. In contrast to ethoxy derivatives ethylthiobromoethene reacted with sodium cyanide in ethanol (at 100°C the (*E*)-isomer gave 11% of (*Z*) and 43% of (*E*)-ethylthiopropenonitrile, while the (*Z*)-isomer gave only 49% of (*Z*)-ethylthiopropenonitrile). In dimethyl sulfoxide the reaction of the (*E*)-isomer with sodium cyanide at 80°C gave 13% of (*Z*) and 35% of (*E*)-ethylthiopropenonitrile, while the reaction of the (*Z*)-isomer gave 44% of (*Z*)-ethylthiopropenonitrile. Methyl ester of (*E*)- and (*Z*)-3-bromopropenoic acid gave under the reaction conditions given for 1-bromo-2-phenylethene only high-molecular dark products.

Aromatic Compounds

In the aromatic series bromobenzene was selected as the basic substance. No solvent could be found in which the reaction with alkali cyanides would take place at 50 to 150°C, and the formation of nitrile was not observed even under catalysis with $Fe(CO)_5$; $K_4Ni_2(CN)_6$ or $Pd((C_6H_5)_3P)_2Cl_2$ either. Neither the use of phase-transfer catalysts or crown-ethers gave any nitrile. The reaction with potassium cyanide catalysed with $Pd((C_6H_5)_3P)_4$ in the presence of crown-ether in benzene gave benzonitrile in 93% yield after 65 h reaction time at 100°C.

In the reaction with cuprous cyanide and related compounds among a number of solvents dimethylformamide and dimethyl sulfoxide were found suitable, while in hexamethylphosphoric triamide the reaction proceeds much slower (at 150°C with $Cu_2(CN)_2$ in dimethylformamide 86% and in dimethyl sulfoxide 80% yield). $NaCu.(CN)_2$ reacts much slower and $Ni(CN)_2$ did not react in any of these solvents up to 180°C.

The reactions with $Cu_2(CN)_2$ (Table III) and with KCN + $Pd((C_6H_5)_3P)_4$ +

+ crown-ether (Table IV) were investigated in the series of substituted bromobenzenes and good yields were obtained by both procedures with all substituents used.

Kinetic Study

In addition to the measurements of yields kinetic measurements were also carried out in the aliphatic and the aromatic series for both the reactions with cuprous

TABLE III

Yields of nitriles (%) in the reaction of substituted bromobenzenes with $Cu_2(CN)_2$ in various solvents at 150°C

Substituent	DMF	DMSO	HMPT
3-CH_3	85	82	35[a]
4-CH_3	89	90	36[a]
3-OCH_3	78	82	51[b]
4-OCH_3	65	68	45[b]
3-SCH_3	95	87	—
4-SCH_3	96	92	—
3-$COOCH_3$	66	57	—
4-$COOCH_3$	80	73	—

[a] After 40 h; [b] 70 h.

TABLE IV

Yields of nitriles (%) in the reaction of vinyl bromides, X—CH=CH—Br, and X-substituted aryl bromides with KCN in benzene at 80°C, under catalysis with $Pd((C_6H_5)_3P)_4$ and 18-crown-6-ether

X in vinyl bromide	Nitrile, %	X in aryl bromide	Nitrile, %
(*E*)-CH_3	89(*E*)	3-CH_3	87
(*Z*)-CH_3	92(*Z*)	4-CH_3	85
(*Z*)-OC_2H_5	0	3-OCH_3	81[a]
(*E*)-SC_2H_5	15(*E*)	4-OCH_3	85[a]
(*Z*)-SC_2H_5	0	3-SCH_3	92
		4-SCH_3	97
(*E*)-$COOCH_3$	polymerizes	3-$COOCH_3$	87
(*Z*)-$COOCH_3$	polymerizes	4-$COOCH_3$	95

[a] 70°C.

cyanide and the reactions with potassium cyanide, catalysed with $Pd((C_6H_5)_3P)_4$ and in the presence of crown-ethers. The reaction mixture was analysed by gas chromatography and mass spectrometry.

In the substitution reaction with cuprous cyanide a dependence of the reaction rate after a time period appeared, corresponding to the complex binding of the nitrile formed and the change of reagent. In Table V the comparison of the effect of substituents on the reaction rate is shown, in the aliphatic series the comparison is limited by the extent of polymerization. The total differences in rates are small and hardly interpretable; in both series the reaction rate decreases in the following order: dimethylformamide $\geqslant$ dimethyl sulfoxide > hexamethylphosphoric triamide. In the case of the reaction with potassium cyanide in benzene with crown-ether and under catalysis with $Pd((C_6H_5)_3P)_4$ a coinciding graph of the reaction course was found for all the members of the investigated series of compounds, in which the curves follow a linear dependence on time up to a high percentage of conversion, which may be interpreted by the formation of complexes, for example crown-ether + KCN

TABLE V

Relative substitution rate of vinyl and aryl bromides with cuprous cyanide in various media

Starting compound[a]	Relative reaction rate		
	DMF	DMSO	HMPT
Brombenzene	29	21	1
1-Bromo-3-methylbenzene	9	10	4
1-Bromo-4-methylbenzene	9	12	5
1-Bromo-3-methoxybenzene	12	13	3
1-Bromo-4-methoxybenzene	7	8	2
1-Bromo-3-methylthiobenzene	40	37	—[b]
1-Bromo-4-methylthiobenzene	31	22	—[b]
Methyl-3-bromobenzoate	19	18	—[b]
Methyl-4-bromobenzoate	35	26	—[b]
(*E*)-1-Bromo-2-phenylethene	41	23	11
(*Z*)-	41	24	12
(*E*)-1-Bromo-1-propene	88	84	54
(*Z*)-	100	84	72
(*Z*)-1-Bromo-2-ethoxyethene	0	0	0

[a] Owing to strong polymerization the reaction rate for (*E*; *Z*)-1-bromo-2-ethylthioethene and methyl-3-bromopropenoate could not be determined; [b] the value could not be determined owing to overlapping of chromatographic peaks.

and RBr + $Pd((C_6H_5)_3P)_4$ which react together at constant concentrations. In this phase of the reaction the conversion will correspond to the zero order until the concentration approaches that of the crown-ether with cyanide or $Pd((C_6H_5)_3P)_4$ with bromide when the concentration of the complexes begins to decrease. The comparison of the rates is presented in Table VI.

In this case too, the effect of substitution cannot be assigned to one decisive reaction step. When benzene is used as solvent benzonitrile is also formed in addition to the substituted benzonitrile in less than 5% yield (except for the case of X = = $COOCH_3$). The amount of benzonitrile increases with temperature which indicates the hydrogen transfer from the solvent, with an intermediate of radicalic or carbocationic character.

EXPERIMENTAL

The bromo derivatives and nitriles used were prepared according to literature. The purity and identity of the substances was checked by spectral methods, gas chromatography, thin-layer chromatography, elemental analyses and melting point determinations. The infrared spectra

TABLE VI

Reaction rate of the substitution of vinyl and aryl bromides with potassium cyanide catalysed with 18-crown-6-ether and $Pd((C_6H_5)_3P)_4$ in benzene at 80°C

Starting compound, X	Relative reaction rate	
X—CH=CH—Br[a]	(*E*)-isomer	(*Z*)-isomer
C_6H_5	9·8	3·8
CH_3	1·3	0·9
C_2H_5O	—	0
X—C_6H_5—Br	3-isomer	4-isomer
H	0·4	0·4
Br	0·4	0·5
C_2H_5O	0·7	0·4
CH_3S	17·5	5·3
$COOCH_3$	1·5	2·2

[a] Owing to extensive polymerization reactions the reaction rate for X = C_2H_5S— and —$COOCH_3$ was not determined.

were measured on a UR-20 (GDR) spectrophotometer, the mass spectra on a Jeol K 100 (Japan) instrument at 70 eV. Gas chromatographic analyses were also carried out for the kinetic study of exchange reactions, using a Chrom 3 (Czechoslovakia) chromatograph with flame ionization detection and nitrogen as carrier gas. Column length was 2·4 m and its diameter 6 mm. Apiezon K (10% on Chromaton NAW-DMCS, 0·25–0·30 mm) and elastomer XE 60 (10% on Chromaton NAW-DMCS, 0·25–0·30 mm) were used as supports. Preparative gas chromatography was carried out on a metallic column (5 m, and 6 mm diameter) packed with 10% of silicone elastomer SE 30 and E 301 (1 : 1) on Chromaton NAW-DMCS, 0·2–0·25 mm particle size. Thin-layer chromatography was carried out on Silufol UV 254 (Kavalier) and detection under an ultraviolet lamp or with a 1% potassium permanganate solution. The melting points were measured on a micromelting point apparatus Boetius (GDR). The reactions were carried out in sealed glass ampules under argon in a heated aluminium block with a tyristor regulation of temperature. Kinetic measurements and the determination of yields were carried out directly in the reaction mixture by gas chromatography. The content of nitriles was determined by peak height determination and reading from a calibration curve.

Reaction with alkali cyanides: The following solvents were used: heptane, benzene, tetrahydrofuran, acetone, acetonitrile, 2-methyl-2-propanol, methanol, dimethylformamide, dimethyl sufoxide, hexamethylphosphoric triamide and water. In all instaces 25 mg (0·5 mmol) of sodium cyanide or potassium cyanide and 0·5 mmol of bromo derivative in 0·5 ml of solvent were used for the reaction. The reaction mixture was heated at 50–150°C for 50 h.

Reactions with alkali cyanides in the presence of crown-ethers were carried out in tetrahydrofuran in the presence of dibenzo-18-crown-6-; dicyclohexyl-18-crown-6-; 18-crown-6-ethers. The results were identical for all three macrocyclic polyethers and therefore only 18-crown-6-ether was used for further experiments. 20 mg of it (0·08 mmol) were mixed with 33 mg (0·5 mmol) of potassium cyanide and 0·5 mmol of bromo derivative. The reaction was carried out at 50–150°C for 50 h. In the attempt at the catalysis of the exchange reaction with the phase transfer catalyst, hexadecyltrimethylammonium bromide, the aqueous phase contained a saturated potassium cyanide solution, while the organic phase (benzene) contained a 10% solution of the catalyst and a 1% halogen derivative solution. The mixture was stirred and heated at 50–150°C for 50 h.

Reaction with cuprous cyanide: This was carried out in benzene, tetrahydrofuran, acetonitrile, acetone, ethanol, water, dimethylformamide, dimethyl sulfoxide and hexamethylphosphoric triamide. For the reaction 9 mg (0·1 mmol) of cuprous cyanide and 0·1 mmol of bromo derivative in 0·5 ml of solvent were used, at 150°C. In some experiments cuprous cyanide was replaced by sodium dicyanocuprate, formed by dissolution of 18 mg (0·2 mmol) of cuprous cyanide and 10 mg (0·2 mmol) of sodium cyanide in 0·5 ml of dimethylformamide, hexamethylphosphoric cyanide at 100°C. The reaction in hexamethylphosphoric triamide at 140°C went best. The reaction in dimethyl sulfoxide was accompanied by a decomposition of the solvent and therefore it was not studied.

Reaction with alkali cyanides in the presence of catalysts: Potassium hexacyanodinickelate[22] (107 mg; 0·25 mmol) was used for catalysis of the reaction of 33 mg (0·5 mmol) of potassium cyanide and 0·5 mmol of bromo derivative. Methanol, ethanol, acetone, benzene, dimethylformamide, dimethyl sulfoxide, hexamethylphosphoric triamide, acetone–water (1 : 1) and methanol–water (2 : 1) mixtures at 20–100°C were used as solvents. Palladium bis(triphenylphosphine)chloride did not display catalytic effects in the reaction of 10 mg (0·014 mmol) of Pd.$((C_6H_5)_3P)_2Cl_2$, 0·2 mmol of bromo derivative and 13 mg (0·2 mmol) of potassium cyanide in 0·5 ml of benzene. toluene, acetone, methanol, dimethylformamide, and water at 40 and 100°C for 50 h. The reaction could not be influenced by bringing potassium cyanide into solution with the addition of 10 mg (0·04 mmol) of 18-crown-6-ether, either. Palladium tetrakis(triphenyl-

phosphine)[23] was used for the catalysis by mixing 23 mg (0·02 mmol) of it with 0·1 mmol of bromo derivative in benzene, and addition of 6·5 mg (0·1 mmol) of potassium cyanide at 80°C. The latter component was brought into solution by addition of 10 mg (0·04 mmol) of 18-crown-ether.

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