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Reactions of 1-Cyanoimidazoles with Phenols

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Abstract—Phenols with p$K_a \geq 7$ react with 1-cyanoimidazole and 1-cyano-2-methylimidazole to give addition products at the cyano group; phenols with p$K_a \leq 1$ give rise to the corresponding quaternary salts, 1-cyanoimidazolium phenolates; phenols with p$K_a \approx 4$ do not react with 1-cyanoimidazoles.

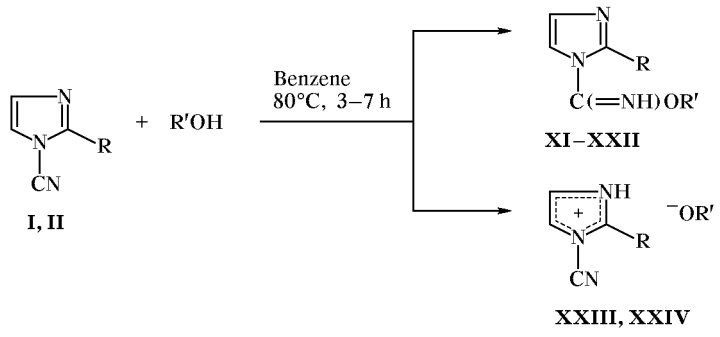
We showed in [1–3] that 1-cyanoazoles are highly reactive compounds which can be used as condensing agents in the synthesis of various carboxylic acid derivatives. There are also data [4–7] on the use of 1-cyanoimidazole for building up phosphorus ester bond in the synthesis of oligonucleotides. Probably, due to high reactivity of the cyano group, 1-cyanoimidazoles can be used not only as condensing agents but also as substrates for synthesis of new azole derivatives.

Acceptor substituents at the cyano group enhance its activity in addition reactions, both electrophilic and nucleophilic [8]. Therefore, the cyano group in 1-cyanoimidazoles is more reactive toward hydroxyl-containing nucleophiles than the cyano group in alkyl or aryl cyanides. The latter react with phenols only in the presence of an acid or base catalyst [8].

We examined reactions of 1-cyanoimidazole (**I**) and 1-cyano-2-methylimidazole (**II**) with phenols **III**–**X** in the absence of a catalyst. The acidity of phenols **III**–**X** varied in the pK_a range from 10 to 0.7: phenol (**III**) 10.0, 1-naphthol (**VII**) 9.85, 8-hydroxyquinoline (**IX**) 9.81, 2-naphthol (**VIII**) 9.63, 4-hydroxybenzaldehyde (**X**) 7.62, 4-nitrophenol (**IV**) 7.15, 2,4-dinitrophenol (**V**) 4.11, 2,4,6-trinitrophenol (**VI**) 0.71. The reactions were carried out in dry benzene on heating. Depending on the reactant nature, two kinds of products were obtained (Scheme 1).

The reactions of cyanoimidazoles **I** and **II** with phenols **IV** and **VII**–**X** gave aryl imidazole-1-carboximidates **XI**–**XX**. By reactions of **I** and **II** with 2,4,6-trinitrophenol (**VI**) the corresponding 1-cyanoimidazolium picrates **XXIII** and **XXIV** were obtained. However, no reactions with phenol (**III**) and 2,4-di-

Scheme 1.



I, II **XI–XXII** **XXIII, XXIV**

I, R = H; **II**, R = CH_3; **III**, R′ = Ph; **IV**, R′ = 4-$NO_2C_6H_4$; **V**, R′ = 2,4-$(NO_2)_2C_6H_3$; **VI**, R′ = 2,4,6-$(NO_2)_3C_6H_2$; **VII**, R′ = 1-naphthyl; **VIII**, R′ = 2-naphthyl; **IX**, R′ = 8-quinolinyl; **X**, R′ = 4-$OHCC_6H_4$; **XI**, R = H, R′ = 4-$NO_2C_6H_4$; **XII**, R = H, R′ = 1-naphthyl; **XIII**, R = H, R′ = 2-naphthyl; **XIV**, R = H, R′ = 8-quinolinyl; **XV**, R = H, R′ = 4-$OHCC_6H_4$; **XVI**, R = Me, R′ = 4-$NO_2C_6H_4$; **XVII**, R = Me, R′ = 1-naphthyl; **XVIII**, R = Me, R′ = 2-naphthyl; **XIX**, R = Me, R′ = 8-quinolinyl; **XX**, R = Me, R′ = 4-$OHCC_6H_4$; **XXI**, R = H, R′ = Ph; **XXII**, R = Me, R′ = Ph; **XXIII**, R = H, R′ = 2,4,6-$(NO_2)_3C_6H_2$; **XXIV**, R = Me, R′ = 2,4,6-$(NO_2)_3C_6H_2$.

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nitrophenol (**V**) occurred. When the reactions with phenol were carried out in the presence of sodium hydride as base catalyst, we isolated phenyl imidazole-1-carboximidates **XXI** and **XXII**. Compounds **I** and **II** failed to react with 2,4-dinitrophenol even in the presence of a base catalyst.

The yields, melting points, spectral data, and elemental analyses of the products are given in table. The ^{1}H NMR spectra of compounds **XI**–**XXIV** contain signals from protons of the imidazole and benzene rings and NH group.

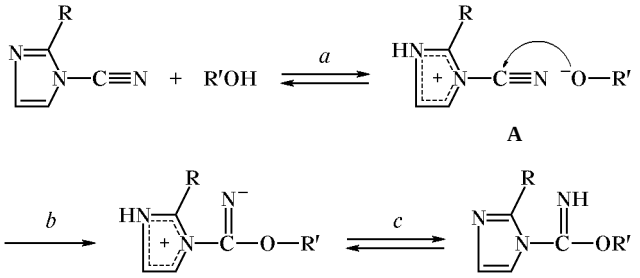
All aryl imidizole-1-carboximidates **XI**–**XXII** characteristically show in the IR spectra medium and strong absorption bands in the region 3330–3240 and 1710–1690 cm^{-1}, which correspond to stretching vibrations of the N–H and C=N bonds in the newly formed imino group.

The IR spectra of 1-cyanoimidazolium picrates **XXIII** and **XXIV** contain absorption bands of the cyano group (2295 cm^{-1}) but lack bands typical of carboximidate moiety. The CN stretching frequencies in the spectra of **XXIII** and **XXIV** are similar to those observed for initial 1-cyanoimidazoles, whereas absorption bands of C–H bonds in the imidazole ring displaced to the higher-frequency region and changed their multiplicity. The IR spectrum of 1-cyanoimidazole (**I**) contains two bands at 3165 and 3190 cm^{-1}, and the corresponding picrate **XXIII**, three bands at 3170, 3200, and 3210 cm^{-1}; 1-cyano-2-methylimidazole shows three absorption bands at 3105, 3120, and 3160 cm^{-1}; the corresponding bands in the spectrum of picrate **XXIV** are located at 3140, 3165, and 3180 cm^{-1}. These data indicate that protonation of molecules **I** and **II** occurs at the N^1 or N^3 atom rather than at the cyano group.

The IR spectra of **XXIII** and **XXIV** are consistent with the results of MNDO quantum-chemical calculations of compounds **I** and **II**. The calculated negative charges on the imidazole nitrogen atoms are greater (N^1, –0.182, –0.168; N^3, –0.214, –0.207) than on the nitrogen atom of the cyano group (–0.067).

Scheme 2 shows a probable mechanism of the reactions of 1-cyanoimidazoles **I** and **II** with phenols **III**–**X**. Presumably, addition of phenol at the cyano group (steps *b* and *c* in Scheme 2) is preceded by acid dissociation of phenol with formation of ion pair **A** (step *a*). Step *b* is nucleophilic addition of phenoxide ion at the cyano group, which yields the final aryl imidazole-1-carboximidate. The proposed mechanism explains formation of different products in the reactions of **I** and **II** with phenols **III**–**X**. In the case of weakly acid phenols (p$K_a \geq 10$) equilibrium *a* is

Scheme 2.



displaced toward the initial reactants (ionization of phenol does not occur). Phenols with pK_a in the range from 10 to 7.15 favor formation of ion pair **A**, leading to final aryl imidazole-1-carboximidates.

Decrease in pK_a from 7.15 to 4.11 leads to even stronger shift of the equilibrium toward formation of ion pair **A**, but the nucleophilicity of phenoxide ion is insufficient for the reaction to proceed further. This is also confirmed by the fact that 2,4-dinitrophenol (**V**) with compounds **I** and **II** does not form addition products in the presence of 2,4-dinitrophenoxide ion generated by the action of a base. The reaction stops at the stage of reversible formation of quaternary salt which can be neither converted into aryl imidazole-carboximidate nor isolated. Further decrease of pK_a from 4.11 to 0.71 leads to complete dosplacement of equilibrium *a* to the right, and the cooresponding picrates (**XXIII** and **XXIV**) can be isolated.

EXPERIMENTAL

The IR spectra were recorded in KBr on an IKS-29 spectrometer. The ^{1}H NMR spectra were obtained on a Bruker WP-200SJ instrument (200.13 MHz) using CD_3CN as solvent and TMS as internal reference. Quantum-chemical calculations of compounds **I** and **II** were performed by the MNDO method [9] using HyperChem software. Flash chromatography on dry columns was carried out according to [10]; silica gel for TLC was used as sorbent, column length 25 mm, diameter 15 mm, overall eluent (ethyl acetate) volume 50 ml. The pK_a values of phenols were taken from reference literature [11, 12].

4-Nitrophenyl imidazole-1-carboximidate (XI). To a solution of 0.143 g (1.03 mmol) of 4-nitrophenol in 20 ml of dry benzene we added 0.096 g (1.031 mmol) of freshly sublimed 1-cyanoimidazole. The mixture was refluxed for 3 h, and the solvent was removed under reduced pressure (water-jet pump). The crystalline residue was washed with dry diethyl ether (3×5 ml) and dried.

Compounds **XIV**–**XVI** and **XIX** were synthesized in a similar way.

1-Naphthyl imidazole-1-carboximidate (XII). To a solution of 0.055 g (0.381 mmol) of 1-naphthol in 11 ml of dry benzene we added 0.036 g (0.381 mmol) of 1-cyanoimidazole, and the mixture was heated for 5 h. Removal of the solvent left an oily substance which was purified by flash chromatography.

Compounds **XIII**, **XVII**, **XVIII**, and **XX** were synthesized in a similar way.

Phenyl imidazole-1-carboximidate (XXI). To a solution of 0.032 g (0.034 mmol) of freshly distilled phenol in 3 ml of dry benzene we added 0.0004 g (0.017 mmol) of sodium hydride. When evolution of hydrogen ceased, we added to the resulting suspension 0.03 g (0.32 mmol) of 1-cyanoimidazole, and the mixture was refluxed for 5 h. It was then cooled to 18–20°C and filtered, the filtrate was evaporated under reduced pressure, the residue was dissolved in 2 ml of dry diethyl ether, 3 ml of petroleum ether was

Yields, melting points or R_f values, spectral parameters, and elemental analyses of compounds **XI**–**XXIV**

Comp. no.	Yield, %	mp, °C (R_f)[a]	IR spectrum, ν, cm^{-1}			^{1}H NMR spectrum, δ, ppm
			N–H	C=N	C≡N	
XI	80	112–112.5	3325	1700	–	3.30 br.s (1H, NH), 6.72 d (2H, C_6H_4, J = 9.2 Hz), 6.97 s, 7.72 (2H, CH, imidazole), 7.90 d (2H, C_6H_4, J = 9.2 Hz), 8.32 s (1H, CH, imidazole)
XII	27	[b] (0.60)	3300	1690	–	4.95 br.s (1H, NH), 6.88–6.91 m (2H, $C_{10}H_7$), 7.24–7.34 m (2H, $C_{10}H_7$), 7.38–7.47 m (3H, $C_{10}H_7$), 7.09 s, 7.76 s (2H, CH, imidazole), 8.22 s (1H, CH, imidazole)
XIII	30	[b] (0.65)	3340	1710	–	5.4 br.s (1H, NH), 7.12–7.19 m (3H, $C_{10}H_7$), 7.26–7.43 m (4H, $C_{10}H_7$), 7.10 s, 7.75 s (2H, CH, imidazole), 8.20 s (1H, CH, imidazole)
XIV	42	127–128	3315	1710	–	–
XV	44	128.5–129	3290	1710	–	3.38 br.s (1H, NH), 7.07 s, 7.64 s (2H, CH, imidazole), 7.45 d (2H, C_6H_4, J = 8.2 Hz), 8.05 d (2H, C_6H_4, J = 8.2 Hz), 8.24 s (1H, CH, imidazole), 10.02 s (1H, CHO)
XVI	65	100–101	3300	1710	–	2.52 s (3H, CH_3), 3.03 br.s (1H, NH), 6.94 d (2H, C_6H_4, J = 9.2 Hz), 7.52 s, 8.33 s (2H, CH, imidazole), 8.12 d (2H, C_6H_4, J 9.2 Hz)
XVII	6	[b] (0.55)	3315	1690	–	2.35 s (3H, CH_3), 3.04 br.s (1H, NH), 6.86–6.92 m (2H, $C_{10}H_7$), 7.26–7.36 m (2H, $C_{10}H_7$), 7.40–7.50 m (3H, $C_{10}H_7$), 7.82 d, 8.14 d (2H, CH, imidazole, J = 1.7 Hz)
XVIII	12	[b] (0.62)	3330	1695	–	2.36 s (3H, CH_3), 3.37 br.s (1H, NH), 7.07–7.15 m (3H, $C_{10}H_7$), 7.24–7.43 m (4H, $C_{10}H_7$), 7.73 d, 7.77 d (2H, CH, imidazole, J = 1.7 Hz)
XIX	15	110–112	3240	1700	–	–
XX	22	(0.26)	3330	1690	–	2.37 s (3H, CH_3), 3.41 br.s (1H, NH), 6.92 d, 7.77 d (2H, CH, imidazole, J = 1.8 Hz), 6.97 m, 7.72 m (4H, C_6H_4), 9.79 s (1H, CHO)
XXI	54	69.5–70.5	3240	1710	–	4.0 br.s (1H, NH), 7.15–7.29 m (5H, C_6H_5), 7.37 s, 7.68 s (2H, CH, imidazole), 8.27 s (1H, CH, imidazole)
XXII	55	[b] (0.40)	3330	1700	–	2.36 s (3H, CH_3), 3.93 br.s (1H, NH), 6.74–6.87 m (5H, C_6H_5), 7.15 d, 7.23 d (2H, CH, imidazole, J = 1.6 Hz)
XXIII	91	115–116	–	–	2295	7.20 s, 8.00 s (2H, CH, imidazole), 8.50 s (1H, CH, imidazole), 8.59 s (2H, C_6H_2), 9.04 br.s (1H, NH)[c]
XXIV	94	109.5–110.5	–	–	2295	2.55 s (3H, CH_3), 7.15 d, 7.90 d (2H, CH, imidazole, J = 1.7 Hz), 8.59 s (2H, C_6H_2), 9.38 br.s (1H, NH)[c]

Table. (Contd.)

Compound no.	Found, %			Formula	Calculated, %		
	C	H	N		C	H	N
XI	51.70	3.53	24.00	$C_{10}H_8N_4O_3$	51.72	3.48	24.13
XII	70.82	4.70	17.90	$C_{14}H_{11}N_3O$	70.86	4.68	17.71
XIII	70.83	4.73	17.30	$C_{14}H_{11}N_3O$	70.86	4.68	17.71
XIV	69.57	4.58	18.70	$C_{13}H_{10}N_3O$	69.62	4.50	18.74
XV	61.33	4.29	19.63	$C_{11}H_9N_3O_2$	61.38	4.22	19.52
XVI	53.60	4.15	22.70	$C_{11}H_{10}N_4O_3$	53.65	4.10	22.75
XVII	71.62	5.30	16.50	$C_{15}H_{13}N_3O$	71.69	5.22	16.72
XVIII	71.60	5.26	16.92	$C_{15}H_{13}N_3O$	71.69	5.22	16.72
XIX	66.64	4.83	22.40	$C_{14}H_{12}N_4O$	66.65	4.80	22.21
XX	62.84	4.90	18.10	$C_{12}H_{11}N_3O_2$	62.87	4.85	18.33
XXI	64.08	5.00	22.10	$C_{10}H_9N_3O$	64.15	4.86	22.44
XXII	65.60	5.60	20.96	$C_{11}H_{11}N_3O$	65.65	5.52	20.88
XXIII	37.31	1.95	25.93	$C_{10}H_6N_6O_7$	37.28	1.88	26.08
XXIV	39.26	2.43	24.70	$C_{11}H_8N_6O_7$	39.29	2.40	24.99

[a] Values of R_f for oily products were determined on silica gel with ethyl acetate as eluent.
[b] Undergoes oxidation with atmospheric oxygen on prolonged storage.
[c] The spectrum was recorded on a Bruker WM-250 instrument (250 MHz) in DMSO-d_6.

added to the solution, and the mixture was left to stand for 12 h at –5°C.

Phenyl 2-methylimidazole-1-carboximidate (XXII) was synthesized as described above for compound **XXI**. After removal of solvent from the filtrate, the oily residue was purified by flash chromatography.

1-Cyanoimidazolium picrate (XXIII). To a solution of 0.073 g (0.32 mmol) of 2,4,6-trinitrophenol in 10 ml of dry benzene we added 0.03 g (0.32 mmol) of 1-cyanoimidazole. The mixture was refluxed for 10 min, the solvent was distilled off, and the residue was recrystallized from dry toluene. Yield 91%. The same procedure was used to synthesize 2-methyl-1-cyanoimidazolium picrate (**XXIV**).

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