Study of Synthesis of 2-(2-Alkoxyphenyl)-1*H*-imidazoles. Comparison of Oxidative Aromatization Reactions of Imidazolines.

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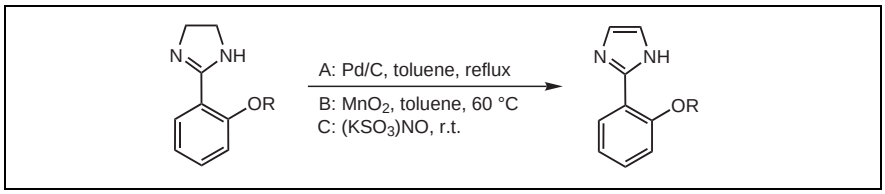

The reaction of methyl salicylate with ethane-1,2-diamine has been used to prepare 2-(2-hydroxyphenyl)-1*H*-imidazoline. This compound was alkylated with alkyl halides to give five new 2-(2-alkoxyphenyl)-1*H*-imidazolines (alkyl = propyl, isopropyl, isobutyl, *sec*-butyl, benzyl). Seven types of transformation reactions of imidazolines into the respective imidazoles were tested. Out of them successful were the dehydrogenation on palladium in toluene (several-day refluxing), oxidation with activated manganese dioxide in toluene (several-hour heating at 60 °C), and the oxidation with potassium nitrosodisulfonate (Fremy's salt) at room temperature. Seven new 2-(2-alkoxyphenyl)-1*H*-imidazoles were synthesized (alkyl = ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, benzyl) *via* mentioned methods. Comparison of individual oxidative aromatization reactions is discussed from the point of view of experimental arrangement, reaction time and conditions, purity of the products obtained, and yields.

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Introduction.

Oxazoline and *bis*oxazoline derivatives are known as ligands for potential catalysts of asymmetric syntheses [1,2]. Replacement of oxygen atom by nitrogen would cause an increase in basic properties and nucleophilicity of such heterocyclic ring, *i.e*. imidazoline and, still more, imidazole. Recently, such derivatives have increasingly been attracting interest, which is documented not only by research activities in the field of synthesis, but also investigation in the area of their catalytic behavior [3-5]. Therefore, we have chosen 2'-substituted 2-phenyl-1*H*-imidazoline as a general model skeleton for potential ligands. 2-(2-Alkoxyphenyl)-1*H*-imidazoles have proved to be good models for the purposes of preparation of a pilot non-chiral series of such derivatives and for testing various synthetic ways leading to 2-phenylimidazole.

2-(2-Hydroxyphenyl)-1*H*-imidazoline can be prepared by syntheses analogous to the synthesis of 2-phenyl-1*H*-imidazoline. They include reactions starting from derivatives of carboxylic acids, *e.g*. 2-hydroxybenzonitrile [6], 2-hydroxybenzamide [7], methyl salicylate [8] or 2-hydroxybenzoic acid [9], which react with ethane-1,2-diamine. The most reliable reaction producing 2-(2-alkoxyphenyl)-1*H*-imidazolines is the alkylation of 2-(2-hydroxyphenyl)-1*H*-imidazoline with the respective alkyl bromides in ethanolic solutions without addition of bases (NaOH, K_2CO_3) [10]. The authors expected formation of *N*-substituted derivatives, but this expectation failed to come true.

The most frequently adopted method for transformation of imidazolines into imidazoles consists in the oxidation of imidazolines. 2-Substituted 1*H*-imidazolines can be dehydrogenated in gas phase in the presence of noble metals at a temperature of *ca* 300 °C or in the presence of aluminium-zinc oxide at a temperature of 300-600 °C [11]. In some cases, this synthesis gives better yields than the Radziszewski reaction (*e.g*. for 2-arylsubstituted 1*H*-imidazoles). Literature [12] describes dehydrogenation of 2-substituted 1*H*-imidazolines using potassium permanganate in dry dioxane as effective and competitive with related procedures. Also dehydrogenations of imidazoline system to imidazole on metal catalysts at various conditions were described [13] (Zn-Al_2O_3, 300-600 °C, [14]; Ni, 300 °C, [15]); however, these methods employ rather harsh conditions and cause some undesirable transformations of functional groups on the imidazoline ring. The dehydrogenation of 1*H*-imidazolines and 2,4-disubstituted 1*H*-imidazolines into 1*H*-imidazoles can also be carried out on the catalyst Pd/C [8,16]. Barium manganate ($BaMnO_4$) is used for oxidations of 2-aryl-1*H*-imidazolines to 2-aryl-1*H*-imidazoles [17]. The preparation of 2-aryl-1*H*-imidazoles is also dealt with in a study that for this purpose recommends the dehydrogenation by heating in dimethyl sulfoxide or by means of 10 % Pd/C [18]. The preparation took 48 h at the temperature of 120 °C. Imidazoles can be prepared by oxidation of imidazolines with selenium [19], active manganese dioxide [20], dibenzoyl peroxide [21], bromine in pyridine/chloroform [21], and Fremy's salt [22]. It would

also be possible to adopt synthetic routes leading to cognate five-membered heterocycles, such as *e.g.* the oxidation with active manganese dioxide giving pyrazoles [23] and oxazoles [24], or the oxidation using nickel peroxide [25] giving pyrazoles. The oxidation using trichloroisocyanuric acid [26] and a similar method using oxalyl chloride [27] have been published in very recent time.

EXPERIMENTAL

General Data: The purity of imidazolines and imidazoles was checked by elemental analysis using an automatic analyser EA 1108 (Fisons). ^{1}H NMR spectra of the model compounds were measured at 25 °C using their 5% solutions in DMSO-d_6 or $CDCl_3$ on a Bruker AMX 360 apparatus at 360.14 MHz, and on a Bruker Avance 500 apparatus at 500.13 MHz, the chemical shifts were referenced to the solvent signal. Infra-red spectra were measured in KBr or in Nujol (for only one liquid product 2-(2-*sec*-butoxyphenyl)-1*H*-imidazoline) in the range of 4000-350 cm^{-1} on an Infrared Spectrophotometer 684 (Perkin-Elmer) connecting to data station DS 3600 (Perkin-Elmer).

2-(2-Hydroxyphenyl)-1*H*-imidazoline (**1a**) [8].

Mixture of methyl salicylate (0.13 mol, 40 g) and ethane-1,2-diamine (0.8 mol, 48 g) was intensively mixed for 11 h under reflux. The excess of ethane-1,2-diamine was removed by distillation leaving a crude product which was crystallized from water/ethanol (2:1). Yellow crystals were obtained in 50.3 % yield (20.1 g), mp 200-202 °C (200-203 °C [8]).

General Procedure for Synthesis of 2-(2-Alkoxyphenyl)-1*H*-imidazolines **1b** – **1i** [10].

Mixture of 2-(2-hydroxyphenyl)-1*H*-imidazoline, alkyl halide, and absolute ethanol (100 mL) was refluxed. Ethanol was then vacuum evaporated and the residue was treated with 15% aqueous natrium hydroxide and chloroform. Chloroform layer was then washed twice with 15% aqueous natrium hydroxide, dried and chloroform was evaporated. The crude product was crystallized from heptane. Amounts of starting materials, reaction times, and yields are summarized in Table I.

General Procedures for Synthesis of 2-(2-Alkoxyphenyl)-1*H*-imidazoles **2a** – **2i**.

Method A, Dehydrogenation of Imidazolines on Palladium [18].

Mixture of starting 2-(2-alkoxyphenyl)imidazoline (0.004 mol), dry toluene (70 mL), and of Pd/C (5%) (0.7 g) was stirred and refluxed under argon atmosphere. Conversion was monitored by tlc. The precipitate was removed by filtration and toluene evaporated after the reaction termination. The crude product was crystallized from toluene/hexane (1:1).

In the case of synthesis of **2g** after refluxing even for 97 hour the reaction mixture contains about 25% of starting imidazoline **1g**. In spite of this the imidazole **2g** was obtained after crystallization from the same solvent.

Method B, Oxidation of Imidazolines Using Activated Manganese Dioxide [23].

Mixture of starting 2-(2-alkoxyphenyl)imidazoline (0.006 mol), dry toluene (80 mL), and activated manganese dioxide (10 g) was intensively stirred and heated at 60 °C. Conversion was monitored by tlc. The precipitate was removed by filtration and toluene evaporated after the reaction termination. Resulting product was crystallized from hexane/toluene (1:1) if necessary.

Method C, Oxidation of Imidazolines Using Fremy's Salt [22,28].

Ice-cold solution of sodium bisulfite (17.5 g) in water (50 mL) was added during 3 minutes to a stirred mixture of sodium nitrite (17.3 g), water (50 mL), and crushed ice (100 g) at -5 °C followed by addition of glacial acetic acid (10 mL) during 1 minute at 0 °C. After addition of cold concentrated aqueous ammonia (14 mL) during 1 minute at 0 °C, ice cold potassium permanganate solution (6.4 g) in water (200 mL) was added dropwise during 40 minutes with continued cooling in an ice bath. Precipitated manganese dioxide was removed by gravity filtration and purple Fremy's salt solution was allowed to warm up to room temperature.

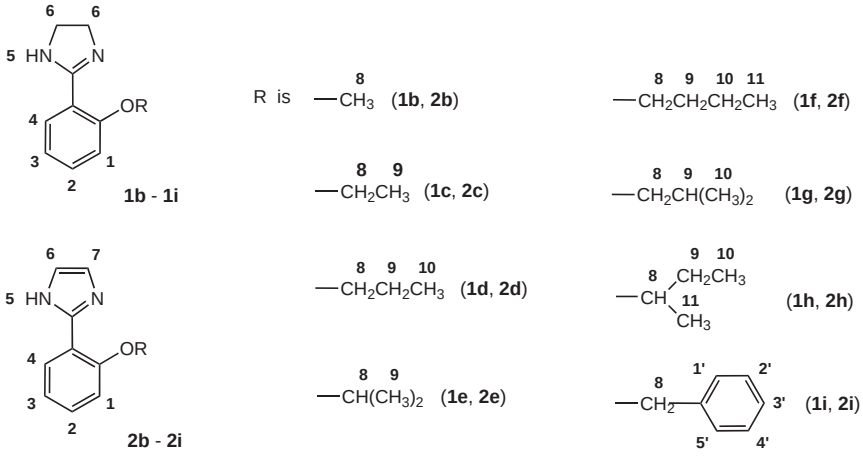
The mixture of starting 2-(2-alkoxyphenyl)imidazoline (0.01 mol), fresh Fremy's salt solution (300 mL), methanol (100 mL), and sodium carbonate (5 g) was stirred overnight at r.t. Precipitated material was collected by filtration. Methanol was evaporated while product doesn't precipitate. Product was crystallized from hexane/toluene (1:1).

Table I

Type of alkyl halide, amount of starting materials, reaction times, and yields of syntheses of 2-(2-alkoxyphenyl)-1*H*-imidazolines **1b** – **1i** (R is alkyl).

product	RX	n (**1a**) / mol	n (RX) / mol	time / h	yield / %
1b	MeI	0.123	0.240	26	51
1c	EtI	0.031	0.037	22	29
1d	PrBr	0.068	0.134	25	50
1e	isoPrBr	0.100	0.200	23	75
1f	BuBr	0.050	0.050	20	20
1g	isoBuBr	0.100	0.150	24	14
1h	*sec*-BuBr	0.100	0.100	20	30
1i	BnBr	0.100	0.100	24	40

Scheme 1



Proton numbering for assignment of 1H NMR shifts.

Tlc was succesfully used for conversion monitoring in the case of synthesis of 2-(2-alkoxyphenyl)-1*H*-imidazolines and of 2-(2-alkoxyphenyl)-1*H*-imidazoles by methods A and B. Chromatography was accomplished using Silikagel 60 F254 (Merck) with methanol as mobile phase: for 2-(2-hydroxyphenyl)-1*H*-imidazoline, 2-(2-alkoxyphenyl)-1*H*-imidazolines, and 2-(2-alkoxyfenyl)-1*H*-imidazoles are R_f 0.25 – 0.35, 0, and 0.55 – 0.65, respectively.

Yields, melting points, ^{1}H NMR shifts, IR bands, and results of elemental analyses of imidazolines **1a** – **1i** are given in the text below.

2-(2-Hydroxyphenyl)-1*H*-imidazoline (**1a**).

Colourless crystals. Yield: 50%, m.p. 200-202 °C (water/ethanol 2:1) (200-203 °C [8]). ^{1}H NMR (DMSO-d_6): δ = 3.74 s, 4 H (H-6); 6.72 m, 1 H (H-3); 6.81 dd, 1 H (H-1); 7.30 m, 1 H (H-2); 7.63 dd, 1 H (H-4); 11.01 br s, 2 H (H-5, OH).

Anal. Calcd. for $C_9H_{10}N_2O$ (162.2): C, 66.65; H, 6.21; N,17.27. Found: C, 66.89; H, 6.46; N, 17.38.

2-(2-Methoxyphenyl)-1*H*-imidazoline (**1b**).

Colourless crystals. Yield: 39%, m.p. 60-64 °C (heptane) (60 °C [10]). IR (KBr): ν 3441, 3224 (NH), 1600 (C=N), δ_s 1440 (CH_3), ν_{as} 1245 (C-O-C), γ 768 cm^{-1} (CH arom); ^{1}H NMR (DMSO-d_6): δ = 3.59 s, 4 H (H-6); 3.88 s, 3 H (H-8); 7.02 m, 1 H (H-3); 7.14 d, 1 H (H-1); 7.46 m, 1 H (H-2); 7.91 dd, 1 H (H-4).

Anal. Calcd. for $C_{10}H_{12}N_2O$ (176.2): C, 68.16; H, 6.86; N, 15.90. Found: C, 68.55; H, 7.08; N, 16.07.

2-(2-Ethoxyphenyl)-1*H*-imidazoline (**1c**).

Colourless crystals. Yield: 29%, m.p. 72-76 °C (heptane) (76 °C [10]). IR (KBr): ν 3436, 3194 (NH), 1600 (C=N), δ_s 1391 (CH_3), ν_{as} 1243 (C-O-C), γ 743 cm^{-1} (CH arom); ^{1}H NMR ($CDCl_3$): δ = 1.45 t, 3 H (H-9); 3.71 s, 4 H (H-6); 4.11 q, 2 H (H-8); 6.90 d, 1 H (H-1); 6.97 t, 1 H (H-3); 7.34 m, 1 H (H-2); 8.09 m, 1 H (H-4).

Anal. Calcd. for $C_{11}H_{14}N_2O$ (190.2): C, 69.45; H, 7.42; N, 14.72. Found: C, 69.72; H, 7.30; N, 14.75.

2-(2-Propoxyphenyl)-1*H*-imidazoline (**1d**).

Colourless crystals. Yield: 50%, m.p. 61-65 °C (heptane). IR (KBr): ν 3442, 3206 (NH), 1600 (C=N), δ_s 1392 (CH_3), ν_{as} 1242 (C-O-C), γ 755 cm^{-1} (CH arom); ^{1}H NMR (DMSO-d_6): δ = 1.03 t, 3 H (H-10); 1.83 m, 2 H (H-9); 3.60 s, 4 H (H-6); 4.06 t, 2 H (H-8); 7.00 m, 1 H (H-3); 7.14 d, 1 H (H-1); 7.43 m, 1 H (H-2); 7.90 dd, 1 H (H-4).

Anal. Calcd. for $C_{12}H_{16}N_2O$ (204.3): C, 70.56; H, 7.89; N, 13.71. Found: C, 70.41; H, 7.99; N, 13.73.

2-(2-isoPropoxyphenyl)-1*H*-imidazoline (**1e**).

Colourless liquid. Yield: 23.5%, n_D^{20} 1.5531. IR (KBr): ν 3442, 3205 (NH), 1605 (C=N), δ_s 1387, 1374 (CH_3), ν_{as} 1237 (C-O-C), γ 752 cm^{-1} (CH arom); ^{1}H NMR (DMSO-d_6): δ = 1.36 d, 6 H (H-9); 3.60 s, 4 H (H-6); 4.74 m, 1 H (H-8); 6.99 t, 1 H (H-3); 7.15 d, 1 H (H-1); 7.42 m, 1 H (H-2); 7.93 dd, 1 H (H-4).

Anal. Calcd. for $C_{12}H_{16}N_2O$ (204.3): C, 70.56; H, 7.89; N, 13.71. Found: C, 70.81; H, 7.66; N, 13.80.

2-(2-Butoxyphenyl)-1*H*-imidazoline (**1f**).

Colourless crystals. Yield: 20%, m.p. 47-52 °C (heptane) (55 °C [10]). IR (KBr): ν 3435, 3280 (NH), 1602 (C=N), δ_s 1395 (CH_3), ν_{as} 1243 (C-O-C), γ 750 cm^{-1} (CH arom); ^{1}H NMR (DMSO-d_6): δ = 0.98 t, 3 H (H-11); 1.47 m, 2 H (H-10); 1.80 p, 2 H (H-9); 3.60 s, 4 H (H-6); 4.09 t, 2 H (H-8); 7.00 t, 1 H (H-3); 7.13 d, 1 H (H-1); 7.43 m, 1 H (H-2); 7.91 dd, 1 H (H-4).

Anal. Calcd. for $C_{13}H_{18}N_2O$ (218.3): C, 71.53; H, 8.31; N, 12.83. Found: C, 71.52; H, 8.20; N, 12.65.

2-(2-isoButoxyphenyl)-1*H*-imidazoline (**1g**).

Colourless crystals. Yield: 14%, m.p. 70-75 °C (heptane). IR (KBr): ν 3442, 3249 (NH), 1600 (C=N), δ_s 1390, 1360 (CH_3), ν_{as} 1239 (C-O-C), γ 770 cm^{-1} (CH arom); ^{1}H NMR ($CDCl_3$): δ = 1.03 d, 6 H (H-10); 2.15 m, 1 H (H-9); 3.60 s, 4 H (H-6); 3.89 d, 2 H (H-8); 7.01 m, 1 H (H-3); 7.13 d, 1 H (H-1); 7.44 m, 1 H (H-2); 7.87 dd, 1 H (H-4).

Anal. Calcd. for $C_{13}H_{18}N_2O$ (218.3): C, 71.53; H, 8.31; N, 12.83. Found: C, 71.35; H, 8.19; N, 12.83.

2-(2-sec-Butoxyphenyl)-1*H*-imidazoline (**1h**).

Orange liquid. Yield: 30%, n_D^{20} 1.5312. IR (nujol): ν 3442 (NH), 1604 (C=N), ν_{as} 1235 (C-O-C), γ 749 cm^{-1} (CH arom); ^1H NMR ($CDCl_3$): δ = 0.98 t, 3 H (H-10); 1.31 d, 3 H (H-11); 1.67 m, 1 H (H-9); 1.77 m, 1 H (H-9); 3.62 s, 4 H (H-6); 4.52 m, 1 H (H-8); 7.00 t, 1 H (H-3); 7.13 d, 1 H (H-1); 7.42, 1 H (H-2), 7.98 dd, 1 H (H-4).

Anal. Calcd. for $C_{13}H_{18}N_2O.HCl$ (254.8): C, 61.31; H, 7.47; N, 11.00; Cl, 13.93. Found: C, 62.15; H, 7.33; N, 11.53; Cl, 13.90.

2-(2-Benzyloxyphenyl)-1*H*-imidazoline (**1i**).

Colourless crystals. Yield: 40%, m.p. 37-43 °C (heptane). IR (KBr): ν 3438 (NH), 1605 (C=N), ν_{as} 1232 (C-O-C), γ 749 cm^{-1} (CH arom); ^1H NMR (DMSO-d_6): δ = 3.59 s, 4 H (H-6); 5.00 s, 2 H (H-8); 6.85-6.97 m, 2 H (H-1,3); 7.24-7.33 m, 6 H (H-2, H-1', H-2', H-3', H-4', H-5'); 8.10 dd, 1 H (H-4).

Anal. Calcd. for $C_{16}H_{16}N_2O$ (252.3): C, 76.17; H, 6.39; N, 11.10. Found: C, 75.88; H, 6.66; N, 11.34.

Melting points, ^1H NMR shifts, IR bands, and results of elemental analyses of imidazoles **2a** – **2i** are given in the following text. Analyses of products obtained by all three methods (A, B, and C) are comparable.

2-(2-Hydroxyphenyl)-1*H*-imidazole (**2a**).

Colourless crystals, m.p. 117-125 °C (133-134 °C [8]). IR (KBr): ν 3239 (NH), 1605, 1595 (C=N), ν_{as} 1266 (C-O-C), γ 765, 743 (CH arom), 700 cm^{-1} (CH imidazole); ^1H NMR (DMSO-d_6): δ = 6.95-7.00 m, 2 H (H-1,3); 7.25-7.30 m, 3 H (H-2,6,7); 7.92 dd, 1 H, (H-4); 12.96 br s, 2 H (H-5, OH).

Anal. Calcd. for $C_9H_8N_2O$ (160.2): C, 67.49; H, 5.03; N, 17.49. Found: C, 67.42; H, 5.05; N, 17.50.

2-(2-Methoxyphenyl)-1*H*-imidazole (**2b**).

Colourless crystals, m.p. 126-133 °C (hexane/toluene 1:1) (129-131 °C [29]). IR (KBr): ν 3434 (NH), 1607, 1588 (C=N), ν_{as} 1242, 1268 (C-O-C), γ 763, 749 (CH arom), 712 cm^{-1} (CH imidazole); ^1H NMR (DMSO-d_6): δ = 3.93 s, 3 H (H-8); 7.05-7.09 m, 2 H, (H-3,6 [7]); 7.17-7.20 m, 2 H (H-1,6[7]); 7.35-7.39 m, 1 H (H-2); 8.14 dd, 1 H (H-4); 11.82 s, 1 H (H-5).

Anal. Calcd. for $C_{10}H_{10}N_2O$ (174.2): C, 68.95; H, 5.79; N, 16.08. Found: C, 68.73; H, 5.96; N, 16.11.

2-(2-Ethoxyphenyl)-1*H*-imidazole (**2c**).

Colourless crystals, m.p. 130-133 °C. IR (KBr): ν 3454 (NH), 1604, 1583 (C=N), ν_{as} 1244, 1269 (C-O-C), γ 749 (CH arom), 712 cm^{-1} (CH imidazole); ^1H NMR (DMSO-d_6): δ = 1.46 t, 3 H (H-9); 4.29 q, 2 H (H-8); 7.04-7.08 m, 2 H (H-3,6[7]); 7.18 d, 1 H (H-1); 7.23 s, 1 H (H-6 [7]); 7.33-7.38 m, 1 H (H-2); 8.11 dd, 1 H (H-4); 11.53 s, 1 H (H-5).

Anal. Calcd. for $C_{11}H_{12}N_2O$ (188.2): C, 70.19; H, 6.43; N, 14.88. Found: C, 70.18; H 6.57; N, 14.66.

2-(2-Propoxyphenyl)-1*H*-imidazole (**2d**).

Colourless crystals, m.p. 101-102 °C. IR (KBr): ν 3438 (NH), 1604, 1582 (C=N), ν_{as} 1239, 1268 (C-O-C), γ 769, 740 (CH arom), 712 cm^{-1} (CH imidazole); ^1H NMR (DMSO-d_6): δ = 1.42 d, 6 H (H-9); 4.81 m, 1 H (H-8); 7.04-7.08 m, 2 H (H-3,6[7]); 7.18 d, 1 H (H-1); 7.24 s, 1 H (H-6 [7]); 7.33-7.38 m, 1 H (H-2); 8.08 dd, 1 H (H-4); 11.49 s, 1 H (H-5).

Anal. Calcd. for $C_{12}H_{14}N_2O$ (202.3): C, 71.26; H, 6.98; N, 13.85. Found: C, 71.18; H, 7.22; N, 13.59.

2-(2-isoPropoxyphenyl)-1*H*-imidazole (**2e**).

Colourless crystals, m.p. 96.5-101 °C (hexane/toluene 1:1). IR (KBr): ν 3439 (NH), 1602, 1583 (C=N), ν_{as} 1232, 1263 (C-O-C), γ 765, 749 (CH arom), 710 cm^{-1} (CH imidazole); ^1H NMR (DMSO-d_6): δ = 1.42 d, 6 H (H-9); 4.81 m, 1 H (H-8); 7.02-7.06 m, 2 H (H-3,6[7]); 7.20 d, 1 H (H-1); 7.23 s, 1 H (H-6 [7]); 7.32-7.37 m, 1 H (H-2); 8.09 dd, 1 H, (H-4); 11.31 s, 1 H (H-5).

Anal. Calcd. for $C_{12}H_{14}N_2O$ (202.3): C, 71.26; H, 6.98; N, 13.85. Found: C, 71.16; H, 7.22; N, 13.84.

2-(2-Butoxyphenyl)-1*H*-imidazole (**2f**).

Colourless crystals, m.p. 88-96 °C (hexane/toluene 1:1). IR (KBr): ν 3439 (NH), 1607, 1586 (C=N), ν_{as} 1244, 1269 (C-O-C), γ 746 (CH arom), 715 cm^{-1} (CH imidazole); ^1H NMR (DMSO-d_6): δ = 0.97 t, 3 H (H-11); 1.45 m, 2 H (H-10); 1.86 m, 2 H (H-9); 4.22 t, 2 H (H-8); 7.04-7.07 m, 2 H (H-3,6 [7]); 7.18 d, 1 H (H-1); 7.23 s, 1 H (H-6 [7]); 7.33-7.37 m, 1 H (H-2); 8.08 dd, 1 H (H-4); 11.49 s, 1 H (H-5).

Anal. Calcd. for $C_{13}H_{16}N_2O$ (216.3): C, 72.19; H, 7.46; N, 12.95. Found: C, 72.04; H, 7.31; N, 13.11.

2-(2-isoButoxyphenyl)-1*H*-imidazole (**2g**).

Colourless crystals, m.p. 114-123 °C (hexane/toluene 1:1). IR (KBr): ν 3417 (NH), 1605, 1583 (C=N), ν_{as} 1244, 1269 (C-O-C), γ 761, 749 (CH arom), 710 cm^{-1} (CH imidazole); ^1H NMR (DMSO-d_6): δ = 1.00 d, 6 H (H-10); 2.30 m, 1 H (H-9); 3.99 d, 2 H (H-8); 7.04-7.08 m, 2 H (H-3,6 [7]); 7.18 d, 1 H (H-1); 7.25 s, 1 H (H-6 [7]); 7.33-7.38 m, 1 H (H-2); 8.06 dd, 1 H (H-4); 11.45 s, 1 H (H-5).

Anal. Calcd. for $C_{13}H_{16}N_2O$ (216.3): C, 72.19; H, 7.46; N, 12.95. Found: C, 72.16; H, 7.69; N, 12.70.

2-(2-sec-Butoxyphenyl)-1*H*-imidazole (**2h**).

Colourless crystals, m.p. 78-81 °C (hexane/toluene 1:1). IR (KBr): ν 3438 (NH), 1604, 1580 (C=N), ν_{as} 1239, 1266 (C-O-C), γ 761, 747 (CH arom), 721 cm^{-1} (CH imidazole); ^1H NMR (DMSO-d_6): δ = 0.95 t, 3 H (H-10); 1.37 d, 3 H (H-11); 1.71 m, 1 H (H-9); 1.93 m, 1 H (H-9); 4.59 m, 1 H (H-8); 7.02-7.06 m, 2 H (H-3,6 [7]); 7.19 d, 1 H (H-1); 7.24 s, 1 H (H-6 [7]); 7.32-7.36 m, 1 H (H-2); 8.11 dd, 1 H (H-4); 11.28 s, 1 H (H-5).

Anal. Calcd. For $C_{13}H_{16}N_2O$ (216.3): C, 72.19; H, 7.46; N, 12.95. Found: C, 71.91; H, 7.63; N, 12.86.

2-(2-Benzyloxyphenyl)-1*H*-imidazole (**2i**).

Colourless crystals, m.p. 113-115 °C (hexane/toluene 1:1). IR (KBr): ν 3435 (NH), 1602, 1583 (C=N), ν_{as} 1223, 1273 (C-O-C), γ 771, 740 (CH arom), 697 cm^{-1} (CH imidazole); ^1H NMR (DMSO-d_6): δ = 5.46 s, 2 H (H-8); 7.01-7.05 m, 1 H (H-3); 7.09 s, 1 H (H-6 [7]); 7.16 d, 1 H (H-1); 7.25-7.30 m, 2 H (H-2,6 [7]); 7.31-7.35 m, 1 H (H-3'); 7.38-7.43 m, 2 H (H-2',4'); 7.51-7.53 m, 2 H (H-1',5'); 8.11 dd, 1 H (H-4); 11.87 s, 1 H (H-5).

Anal. Calcd. for $C_{16}H_{14}N_2O$ (250.3): C, 76.78; H, 5.64; N, 11.19. Found: C, 76.72; H, 5.92; N, 11.01.

Results and Discussion.

Imidazolines.

The most reliable synthesis of 2-(2-alkoxyphenyl)-1*H*-imidazolines was the alkylation of 2-(2-hydroxyphenyl)-1*H*-

imidazolines. Hence, the 2-(2-alkoxyphenyl)-1*H*-imidazolines were prepared by a two-step synthesis starting from methyl salicylate. In the first step, methyl salicylate reacted with ethane-1,2-diamine to give 2-(2-hydroxyphenyl)-1*H*-imidazoline, which was subsequently submitted the alkylation with alkyl halides to give the respective 2-(2-alkoxyphenyl)-1*H*-imidazoline. Beger & Wagner [10] used the starting substances for the alkylation in the molar ratio of 1:1 and obtained the required 2-(2-alkoxyphenyl)-1*H*-imidazolines in the yields ranging about 40 %. In our alkylation reactions, an approximately double amount of alkyl halide was adopted, because the application of equimolar ratio of the reactants led to alkoxyimidazolines that were contaminated with unreacted 2-(2-hydroxyphenyl)-1*H*-imidazoline that was difficult to remove. In this way, eight 2-(2-alkoxyphenyl)-1*H*-imidazolines were prepared with the substituents alkyl = Me, Et, Pr, isoPr, Bu, isoBu, *sec*-Bu, Bn, in the yields about 30 %. The propyl, isopropyl, isobutyl, *sec*-butyl, and benzyl derivatives have not been described in literature yet. No formation of *N*-alkylated products was observed. The measured melting points as well as the ^{1}H NMR chemical shifts of the known imidazolines **1a**, **1b**, **1c**, **1f** agree with the literature data [8,10].

In order to increase the yields, we carried out the alkylation reactions in several modifications. The synthesis of 2-(2-propoxyphenyl)-1*H*-imidazoline was realized with addition of an equimolar amount of sodium hydrogencarbonate. However, the resulting reaction mixture contained besides the required product also the starting substance and two other compounds. Apart from this, the alkylation of 2-(2-hydroxyphenyl)-1*H*-imidazoline was carried out in the presence of potassium carbonate in *N*,*N*-dimethylformamide as the solvent. This reaction failed to give the required product. Finally, we also tested the methylation of 2-(2-hydroxyphenyl)-1*H*-imidazoline with dimethyl sulfate in aqueous sodium hydroxide, which did not give the expected 2-(2-methoxyphenyl)-1*H*-imidazoline either. Hence, none of the modifications used resulted in optimization of the alkylation reaction.

The preparation of 2-(2-alkoxyphenyl)-1*H*-imidazolines by the reaction of methyl 2-alkoxybenzoates with ethane-1,2-diamine (starting from the analogy with the reaction of methyl salicylate and ethane-1,2-diamine giving 2-(2-hydroxyphenyl)-1*H*-imidazoline) turned out to be entirely unsuitable. The reactions tested by us were carried out with methyl 2-methoxybenzoate, methyl 2-ethoxybenzoate and methyl 2-propoxybenzoate [30] as the starting substances, our aim being to synthesize 2-(2-methoxyphenyl)-1*H*-imidazoline, 2-(2-ethoxyphenyl)-1*H*-imidazoline, and 2-(2-propoxyphenyl)-1*H*-imidazoline, respectively. If the final reaction mixture was rid of ethane-1,2-diamine by atmospheric distillation, then the isolated product of all the three preparations was 2-(2-hydroxyphenyl)-1*H*-imidazoline. If the ethane-1,2-diamine was removed by distillation under reduced pressure, then the resulting mixture could not be separated and identified. The decomposition of 2-(2-alkoxyphenyl)-1*H*-imidazolines by dealkylation, giving 2-(2-hydroxyphenyl)-1*H*-imidazoline, could be caused by thermal instability of the alkoxy derivatives at the high temperature of removal of ethane-1,2-diamine by distillation at atmospheric pressure. A similar problem is discussed in literature [31], describing a decomposition of 2-methoxybenzoic acid giving salicylic acid on heating at atmospheric pressure. Also the heating of methyl salicylate at atmospheric pressure results in its decomposition, whereas the compound is relatively stable during heating in vacuum.

Imidazoles.

Our first successful transformation of imidazoline ring into imidazole was achieved by dehydrogenation of 2-(2-propoxyphenyl)-1*H*-imidazoline by means of Pd/C (5 %) with refluxing in dry toluene under the inert atmosphere of argon. The reaction was also successful in the cases of the hydroxy derivative and the other alkoxy derivatives, except for the synthesis of 2-(2-benzyloxyphenyl)-1*H*-imidazole, in which case the reaction mixture contained the non-reacted imidazoline and the dealkylation product (2-(2-hydroxyphenyl)-1*H*-imidazoline) besides the desired product even after 146 h refluxing; the resulting mixture could be separated neither chromatographically nor in any other way.

In the case of method A, 5% Pd/C was safely replaced by 10% Pd/C. In the case of some alkoxyphenylimidazoles synthesized, it even was not necessary to carry out further purification of the product obtained.

Imidazolines can also be oxidized by activated MnO_2 in toluene [20]. In the case of oxidation of the 2-(2-propoxyphenyl)-1*H*-imidazoline, the reaction mixture was stirred at room temperature for 24 h (in accordance with [23]), but no product was formed. Therefore, the reaction temperature was increased to 60 °C, and the reaction mixture was stirred at this temperature for another 24 h to give 2-(2-propoxyphenyl)-1*H*-imidazole in the yield of 65 %. For that reason the oxidation reactions of another imidazolines were carried out at the temperature of 60 °C; the degree of conversion during the reaction course was monitored by means of tlc, and the reaction was finished always after the starting imidazoline had disappeared. The individual reaction times are given in Table II. Moreover, we tested a modification of this reaction, in which dry toluene was mixed with activated MnO_2, and the water present in the reagent was removed by azeotropic distillation [24]. Then the starting 2-(2-propoxyphenyl)-1*H*-imidazoline was introduced and the reaction was carried out by refluxing and concomitant removal of the reaction water. After 1 h, the starting imidazoline disappeared (tlc), and the product was formed in the yield of 78 %. Hence, removing the reaction water by azeotropic distillation can increase the reaction yields. For successful results of this oxidation method to be achieved, it is necessary to adopt the activated MnO_2 (<5 micron, activated, 85%, Aldrich). The reaction was unsuccessfully tested with the use of MnO_2 (99+%, Aldrich).

Potassium nitrosodisulphonate $(KSO_3)NO$ (Fremy's salt) is used most frequently for oxidation of phenols and aromatic amines to the corresponding quinones; it is also used in oxidative aromatization [32]. We prepared Fremy's salt according to [28] and used it in the form of a solution, because it is somewhat unstable in solid form. The reagent was successfully used in the transformations of all the 2-(2-alkoxyphenyl)-1*H*-imidazolines to the respective imidazoles. Only in the case of synthesis of 2-(2-hydroxyphenyl)-1*H*-imidazole the reaction failed both when carrying it at room temperature overnight and after subsequent heating of the reaction mixture to 65 °C for 5 h.

The methods A, B and C were used to synthesize all the 2-(2-alkoxyphenyl)-1*H*-imidazoles **2b** – **2i** (except for **2i**, where method A failed). In this way, seven 2-(2-alkoxyphenyl)-

1*H*-imidazoles were prepared (alkyl = Et, Pr, isoPr, Bu, isoBu, *sec*-Bu, Bn), which have not been described in literature so far. Both the melting points and ^{1}H NMR chemical shifts of the known imidazoles **2a** and **2b** agree with the literature data [8,29].

Table II

Reaction times and yields of syntheses of imidazoles **2a** – **2i** by methods A, B, and C.

	method A		method B		method C
product	time / h	yield / %	time / h	yield / %	yield / %
2a	23	66 [a]	48	-	-
2b	73	95	18	50.5	52.5
2c	49	67	30	26.5	16
2d	45	62 [a]	43	67	61
2e	46.5	60	4	25	14
2f	50	81	21	11.5	58
2g	97	38	14	38.5	15
2h	117	60	5	46	18.5
2i	146	-	8	29	25

[a] yield of product without crystallization.

We also tested other oxidation reactions usually adopted for aromatization of imidazolines and cognate derivatives using selected 2-(2-alkoxyphenyl)-1*H*-imidazolines. An unsuccessful attempt at transformation of imidazoline to imidazole was the oxidation of 2-(2-methoxyphenyl)-1*H*-imidazoline performed by its reaction with bromine in a mixture of chloroform and pyridine [21]. The introduced synthesis did not provide the expected 2-(2-methoxyphenyl)-1*H*-imidazole, the non-reacted starting imidazoline being isolated instead. 2-(2-Methoxyphenyl)-1*H*-imidazoline was also oxidized with dibenzoyl peroxide in toluene [21]. Also this reaction gave only the non-reacted imidazoline. Moreover, 2-(2-hydroxyphenyl)-1*H*-imidazoline was oxidized with potassium permanganate in dioxane in the presence of 18-crown-6-ether [12]; the reaction gave a mixture of substances that could be neither separated nor identified. The oxidation process of heating of 2-(2-hydroxyphenyl)-1*H*-imidazoline in dimethyl sulfoxide [18] failed, too.

On the basis of analogy with the synthesis [33] leading to 2-(imidazol-2-yl)benzoic acid, we carried out a reaction of 2-methoxybenzaldehyde with aqueous glyoxal and ammonium acetate with the aim of direct building of imidazole ring. The required 2-(2-methoxyphenyl)-1*H*-imidazole was not obtained, and the identification of product showed that it represents a mixture of substances, mainly the starting non-reacted 2-methoxybenzaldehyde. On the other hand, the realization of analogy of another synthesis [34] was successful: it consisted in the reaction of 2-hydroxybenzaldehyde with glyoxal trimer dihydrate and ammonium acetate in acetic acid, giving 2-(2-hydroxyphenyl)-1*H*-imidazole.

We can compare methods A, B, and C, which have been used for oxidative aromatization of imidazolines to imidazoles. Advantages of all the three methods lie in simple experimental arrangement, simple separation of products, absence of by-products, and no need of purification of the product in some cases. The yields of all the three methods are roughly comparable, or higher in the case of method A, and they are good or satisfactory, in some cases very low: 66 %, 37 % and 33 % are average yields calculated from individual yields obtained from methods A, B, and C, respectively. Methods A and B are convenient in that easy monitoring of reaction process using tlc is possible.

The long lasting refluxing during dehydrogenation (method A) can be taken as a handicap. The application of method B or C is more favorable from this point of view. The reaction time is shorter and reaction temperature lower in the case of method B. The oxidation reactions using Fremy's salt (method C) were even performed overnight only at room temperature. Furthermore, mild conditions of method C can be safe for various functional groups. A certain disadvantage of method B can be seen in the necessity of using large excess of the reagent. The highest yields were reached using method A.

Nevertheless, very recently it was reported [26,27] that 2-imidazoles can be oxidized by another way. So far, we have not tested these syntheses.

Conclusions.

2-(2-Alkoxyphenyl)-1*H*-imidazolines have been prepared by alkylation of 2-(2-hydroxyphenyl)-1*H*-imidazoline using the corresponding alkyl halides in ethanol without any addition of bases. The yields were rather low, about 30 %. *N*-Alkylation was not observed.

Several oxidative aromatization reactions were tested and three successful methods were used for oxidation of imidazolines to imidazoles, namely dehydrogenation on Pd/C, oxidation by activated manganese dioxide, and oxidation by potassium nitrosodisulphonate. The general results of the methods used were comparable from the point of view of experimental arrangement, purity and yields of the products, so we can recommend all of them.

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