ISSN 1070-3632, Russian Journal of General Chemistry, 2018, Vol. 88, No. 5, pp. 874–878. © Pleiades Publishing, Ltd., 2018.
Original Russian Text © M.A. Brusina, Yu.A. Gubina, D.N. Nikolaev, S.M. Ramsh, L.B. Piotrovskii, 2018, published in Zhurnal Obshchei Khimii, 2018, Vol. 88, No. 5, pp. 729–733.

Influence of Oxidation Conditions on the Yield of 2-Substituted Imidazole-4,5-dicarboxylic Acids

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Received January 25, 2018

Abstract—Conditions were found which allow 2-alkyl-substituted imidazole-4,5-dicarboxylic acids to be synthesized in preparative quantities by the oxidation of 2-alkylbenzimidazoles with hydrogen peroxide. It was shown that optimal results can be obtained at the concentration of 2-alkylimidazole in sulfuric acid of 1 M and the hydrogen peroxide : 2-alkylbenzimidazole molar ratio of 11 : 1. Oxidation under these conditions results in higher yields of the target 2-alkylimidazole-4,5-dicarboxylic acids, including those with a branched alkyl group.

Keywords: imidazole-4,5-dicarboxylic acid, oxidation, hydrogen peroxide, 2-alkylbenzimidazoles

DOI: 10.1134/S1070363218050055

The considerable interest of researchers in the synthesis of 2-alkyl derivatives of imidazole-4,5-dicarboxylic acid is explained by the fact that 2-propylimidazole-4,5-dicarboxylic acid is an intermediate compound in the synthesis of olmesartan medoxomil, an active ingredient of the antihypertensive drug produced under the trademarks Cardosal and Benicar [1]. 2-Alkyl derivatives of imidazole-4,5-dicarboxylic acid are interesting for medicinal chemistry and experimental pharmacology [1–3]. In particular, it was shown that they are ligands of the NDMA receptor recognition site, and 2-propyl- and 2-phenylimidazole-4,5-dicarboxylic acids show a pronounced anticonvulsant effect [3].

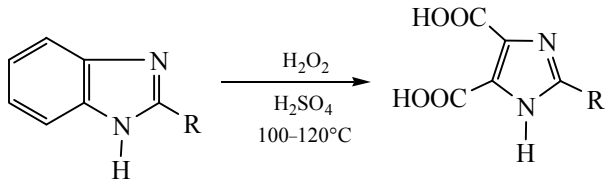
However, the synthesis of these compounds is still associated with considerable difficulties. In principle, the synthesis can be performed in two ways: assembly of the imidazole ring [1, 4, 5] or oxidation of a more complicated bicyclic structure which already contains the imidazole ring [6–10]. The imidazole ring can be assembled on the basis of diaminomaleonitrile [1], tartaric acid [4], or reaction of glyoxal with aldehydes [5]. The second synthetic approach to 2-alkyl-substituted imidazole-4,5-dicarboxylic acids involves the oxidation of 2-alkylbenzimidazoles with potassium bichromate [6], hydrogen peroxide [7–10], or ozone [11].

The most common method of synthesis is the oxidation of benzimidazoles with hydrogen peroxide, which is likely to be explained by the simplicity of this method and the availability and stability of the starting compounds [7–10]. However, this method has a considerable limitation: the yield of the target 2-alkylimidazole-4,5-dicarboxylic acids sharply decreases with increasing length of the 2-alkyl substituent [7], because of the 2-alkyl substituent in the resulting acid tends to undergo oxidative degradation. As a result, a mixture of products is formed: the target 2-alkyl-substituted imidazole-4,5-dicarboxylic acid and by-product unsubstituted imidazole-4,5-dicarboxylic acid [10].

In this connection, in the present work we set ourselves the goal to adapt the oxidative method for the preparation of 2-alkylimidazole-4,5-dicarboxylic acids with long and branched 2-alkyl substituents. To this end, we optimized the oxidation conditions of 2-alkyl-substituted benzimidazoles with 33% hydrogen peroxide in conc. H_2SO_4 in terms of yield and product composition, i.e. we strived to maximize the yield of the target 2-alkylimidazole-4,5-dicarboxylic acid and minimize the yield of the by-product imidazole-4,5-dicarboxylic acid.

The search for optimal conditions was performed using 2-propyl-1*H*-benzimidazole **1c** as a model compound

Scheme 1.



1a–**1i** **2a**–**2i**

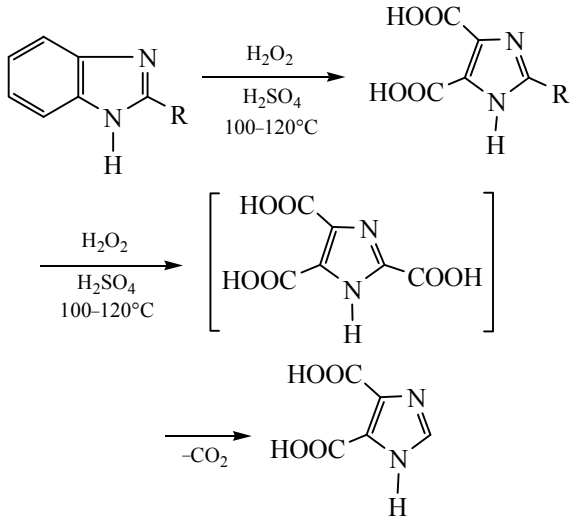
R = Me (**a**), Et (**b**), Pr (**c**), *i*-Pr (**d**), Bu (**e**), *i*-Bu (**f**), *t*-Bu (**g**), Pent (**h**), Ph (**i**).

(Scheme 1). The choice of this specific model compound was motivated, on the one hand, by the fact that its oxidation product is used in chemical pharmaceutical industry [1] and, on the other, by the nature of the substituent, because the presence of the middle methylene group makes it similar to longer alkyl substituents. Moreover, as we have shown earlier [10], oxidative degradation sharply decreased the yield of the target acid **2c** even in the case of such a short 2-alkyl substituent as propyl.

We studied the effect of the substrate and oxidant (benzimidazole **1c** and H_2O_2) molar ratio starting with the proposed in [7] initial concentration of benzimidazole **1c** in conc. H_2SO_4 0.7 M, the effect of the initial concentration of benzimidazole **1c** in conc. H_2SO_4 starting with the defined optimal molar ratio and the solvent effect on the composition of the oxidation products.

The table lists the results of analysis of the precipitates isolated from the reaction mixtures obtained

Scheme 2.



R = Alk, Ar.

Effect of the starting reagent ratio of the composition of the reaction products[a]

H_2O_2 : **1c** (mol)	Yield of **2c**, %	Yield[b] of imidazole-4,5-dicarboxylic acid, %
15 : 1	<1	31
11 : 1	61±2	~0
8 : 1	47±2	~0
4 : 1	Traces	~0

[a] The initial concentration of benzimidazole **1c** in conc. H_2SO_4 is 0.7 M.

[b] The yields of compound **2c** and imidazole-4,5-dicarboxylic acid are averages of three runs.

at 15 : 1 [10], 11 : 1, 8 : 1, and 4 : 1 molar ratios of H_2O_2 (33%) and benzimidazole **1c**. At a 15 : 1 oxidant : substrate ratio the yield of the target product was negligibly low (< 1%), and the main product was imidazole-4,5-dicarboxylic acid (31%) [10]. At a 4 : 1 ratio, almost no oxidation took place. At 11 : 1 and 8 : 1 ratios, the ^{1}H NMR spectra of the precipitates isolated from the reaction mixtures showed no other signals than those of compound **2c**, whereas the CH proton singlet of the unsubstituted imidazole-4,5-dicarboxylic acid was absent. This finding revealed the absence of the by-product in the precipitates. Evidence for the absence of the unsubstituted imidazole-4,5-dicarboxylic acid in the reaction mixtures obtained with reduced amount of oxidant was also provided by TLC. These data are consistent with the suggestion of consecutive oxidative degradation of the benzene ring and 2-substituent: the latter starts to degrade only after the starting 2-alkylbenzimidazole has completely oxidized to 2-alkylimidazole-4,5-dicarboxylic acid [10] (Scheme 2).

Thus, as seen from the data in the table, the optimal molar ratio of H_2O_2 to benzimidazole **1c** is 11 : 1.

The oxidation reaction in [7] was carried out at the substrate **1c** concentration in conc. H_2SO_4 of 0.7 M and the H_2O_2 : **1c** ratio of 15 : 1. The yield of acid **2c** under such conditions was 39%. At the same substrate concentration but the optimal H_2O_2 : **1c** ratio of 11 : 1, we isolated acid **2c**, as already mentioned (see table), with a much higher yield (61±2%). The yield of acid **2c** could be further increased to 72±2%[1], when the substrate concentration was increased to 1 M. However, ata higher concentration of benzimidazole **1c** (2 M), the yield of 2-propylimidazole-4,5-dicarboxylic acid

[1] The yield of compound **2c** is an average of three runs.

2c fell down to 66±4%. Therewith, the reaction product contained no admixture of the unsubstituted imidazole-4,5-dicarboxylic acid in all the above-described experiments. Thus, the optimal concentra-tion of the starting benzimidazole **1c** in conc. H_2SO_4 is 1 M.

The reaction product was usually isolated by adding water to the reaction mixture [7–10]. Dilution decreased the acidity of the medium, and the reaction product partially precipitated. However, even being diluted with water the reaction mixture still remain strongly acidic, and part of 2-alkylimidazol-4,5-dicarboxylic acid was present in the soluble cationic form. Therefore, for a more complete isolation we had to increase the pH of the medium to a value close to the isoelectric point of the target product. The protonation constants of 2-alkylimidazole-4,5-dicarboxylic acids are unknown, but they can be tentatively estimated from the pK_a values for *N,N'*-disubstituted 2-alkylimidazole-4,5-dicarboxamides, which span the range from –1 to 1 [12]. The deprotonation constant of 2-methylimidazole-4,5-dicarboxylic acid is 4.2 [13]. Thus, the tentative estimates for the isoelectric points of 2-alkylimidazole-4,5-dicarboxylic acids are between 1.6 and 2.6. In view of the aforesaid, the reaction mixture was neutralized to pH ~2.

The oxidation medium should meet a number of requirements: it should readily dissolve the starting 2-alkylbenzimidazole and sparingly dissolve the target 2-alkylimidazole-4,5-dicarboxylic acid, and, therewith, it should allow the process to be performed at a sufficiently high temperature and favor oxidation of the benzimidazole benzene ring. Sulfuric acid is traditionally used as such a solvent [7–10]. Under the oxidation reaction conditions, the addition of H_2O_2 to conc. H_2SO_4 leads to the formation of peroxymonosulfuric acid (Caro's acid), which is likely to act as an oxidant in the oxidation of benzimidazole to imidazole-4,5-dicarboxylic acid [14]. Analysis of published data showed that glacial acetic acid which, too, form peroxy acid with H_2O_2 could be used as an alternative reaction medium [14, 15]. Moreover, peroxyacetic acid is used to oxidize the fused benzene ring of phenanthrene into diphenic acid, and, therewith, the isolable yield of the product is quite high (90%) [15]. Therefore, we undertook an attempt to oxidize 2-propyl- (**1c**) and 2-phenylbenzimidazoles (**1i**) in glacial acetic acid in the presence of 1–10% of conc. H_2SO_4 as a catalyst. The reaction temperature was the same as in the reaction in sulfuric acid. The molar ratio of H_2O_2 and benzimidazoles **1c** and **1i** was 15 : 1, and the concentration of benzimidazoles **1c** and **1i** in glacial acetic acid was 0.7 M. However, no oxidation took place under these conditions: no other compounds than the starting 2-substituted benzimidazoles were detected in the reaction mixture. The result did not change, when the H_2O_2 amount was doubled. The possible explanation is that peroxyacetic acid is an insufficiently stong oxidant to oxidize benzimidazoles into imidazole-4,5-dicarboxylic acids.

It has been earlier shown that the oxidation of 2-substituted benzimidazoles with hydrogen peroxide allows synthesis exclusively of the lower representatives of 2-alkylimidazole-4,5-dicarboxylic acids which contain no more than 3 carbon atoms in an unbranched alkyl substituent [7, 10]. The optimal conditions of the process, found in the present work, allowed us not only to avoid the oxidative degradation of the 2-substituent and thus increase the yield of 2-alkyl(phenyl)imidazole-4,5-dicarboxylic acids **2a–2c**, **2i**, but also to use this reaction to synthesize 2-alkylimidazole-4,5-dicarxylic acids with a branched (**2d**, **2f, 2g**) and longer alkyl chain (**2e**, **2h**). It should be noted that 2-*n*-butylimidazole-4,5-dicarboxylic acid **2e** and its isomers **2f** and **2g** have never been prepared by this method, while the yield of 2-*n*-pentylimidazole-4,5-dicarboxylic acid **2h** prepared by the optimized procedure is more than 3 times higher than that reported in [7] (46% against 15%).

Thus, we developed a method of synthesis of 2-substituted imidazole-4,5-dicarboxylic acids with alkyl substituents, including branched and aromatic ones, by the oxidation of 2-substituted benzimidazoles with 33% H_2O_2 in conc. H_2SO_4, leading to individual reaction products in satisfactory yields. Optimal reaction conditions were found, specifically, the concentration of 2-substituted benzimidazole in sulfuric acid is 1 M and oxidant:substrate molar ratio is 11 : 1. Evidence was obtained to show that the process involves a number of consecutive stages: the first stage involves oxidation of the benzene ring to form the target product and then, provided a considerable excess of the oxidant is present, the 2-substituent undergoes oxidative degradation to form by-product imidazole-4,5-dicarboxylic acid.

EXPERIMENTAL

The ^{1}H NMR spectra were run on a Bruker Avance III-400 instrument at 400 MHz in DMSO-d_6. The melting points were measured on a Franz Kustner

Nacht HMK instrument. Thin-layer chromatography was performed on Sorbfil PTSKh-PA-UV plates; eluent ethanol–25% ammonia, 7 : 3; detection in UV light.

Sulfuric acid (Vekton, State Standard 14262-78, OSCh 11-5, weight fraction of the main substance 98.3%, *d* 1.84 g/cm^3) and hydrogen peroxide (Vekton, State Standard 177-88, Extra, weight fraction of the main substance 33%, *d* 1.13 g/cm^3) were used.

2-Alkyl(phenyl)benzimidazoles 1a–1i were prepared by the procedures in [16, 17].

Synthesis of 2-alkylimidazole-4,5-dicarboxylic acids 2a–2i *(general procedure)*. To a stirred solution of 10.0 mmol of compound **1a–1i** in 10 mL of conc. H_2SO_4 we added dropwise 10 mL (0.11 mmol) of 33% aqueous hydrogen peroxide at 100–105°C. The mixture was stirred for 0.5 h at 120°C, let to cool down, and poured in water. The pH of the solution was adjusted to ~2 with sodium carbonate, and the precipitate of 2-alkylimidazole-4,5-dicarboxylic acid **2a–2i** was filtered off and recrystallized from water.

2-Methylimidazole-4,5-dicarboxylic acid (2a). Yield 82%, mp 271–272°C (mp 272–273°C [9]). ^{1}H NMR spectrum, δ, ppm: 2.51 s (3H, CH_3), 4.58 br.s (2H, COOH, NH).

2-Ethylimidazole-4,5-dicarboxylic acid (2b). Yield 78%, mp 260–261°C (mp 259–260°C [9]). ^{1}H NMR spectrum, δ, ppm: 1.29 t (3H, $CH_2C\underline{H}_3$, $^3J_{HH}$ = 7.6 Hz), 2.88 q (2H, $C\underline{H}_2CH_3$, $^3J_{HH}$ = 7.6 Hz), 5.93 br.s (2H, COOH, NH).

2-Propylimidazole-4,5-dicarboxylic acid (2c). Yield 72%, mp 256–257°C (mp 255–256°C [9]). ^{1}H NMR spectrum, δ, ppm: 0.91 t (3H, $CH_2CH_2C\underline{H}_3$, $^3J_{HH}$ = 7.6 Hz), 1.75 m (2H, $CH_2C\underline{H}_2CH_3$), 2.84 t (2H, $C\underline{H}_2CH_2CH_3$, $^3J_{HH}$ = 7.6 Hz), 5.20 br.s (2H, COOH, NH).

2-Isopropylimidazole-4,5-dicarboxylic acid (2d). Yield 57%, mp 262–263°C (mp 269°C [4]). ^{1}H NMR spectrum, δ, ppm: 1.36 d (6H, CH_3, $^3J_{HH}$ = 6.8 Hz), 3.32 m (1H, CH), 4.40 br.s (2H, COOH, NH).

2-*n*-Butylimidazole-4,5-dicarboxylic acid (2e). Yield 53%, mp 259–261°C (mp 261–263°C [18]). ^{1}H NMR spectrum, δ, ppm: 0.92 t (3H, $CH_2CH_2CH_2C\underline{H}_3$, $^3J_{HH}$ = 7.6 Hz), 1.31 m (2H, $CH_2CH_2C\underline{H}_2CH_3$), 1.71 m (2H, $CH_2C\underline{H}_2CH_2CH_3$), 2.86 t (2H, $C\underline{H}_2CH_2CH_2CH_3$, $^3J_{HH}$ = 7.6 Hz), 4.56 br.s (2H, COOH, NH).

2-Isobutylimidazole-4,5-dicarboxylic acid (2f). Yield 57%, mp 256–257°C (mp 257°C [4]). ^{1}H NMR spectrum, δ, ppm: 0.88 d [6H, $CH_2CH(C\underline{H}_3)_2$, $^3J_{HH}$ = 6.8 Hz], 2.13 m [1H, $CH_2C\underline{H}(CH_3)_2$], 2.72 d [2H, $C\underline{H}_2CH(CH_3)_2$, $^3J_{HH}$ = 7.2 Hz], 4.48 br.s (2H, COOH, NH).

2-*tert*-Butylimidazole-4,5-dicarboxylic acid (2g). Yield 52%, mp 263–264°C (mp 263–264°C [19]). ^{1}H NMR spectrum, δ, ppm: 1.45 s (9H, $3CH_3$), 4.04 br.s (2H, COOH, NH).

2-*n*-Pentylimidazole-4,5-dicarboxylic acid (2h). Yield 46%, mp 258–259°C (mp 260°C [20]). ^{1}H NMR spectrum, δ, ppm: 0.90 t (3H, $CH_2CH_2CH_2CH_2C\underline{H}_3$, $^3J_{HH}$ = 7.2 Hz), 1.26 m (2H, $CH_2CH_2CH_2C\underline{H}_2CH_3$), 1.32 m (2H, $CH_2CH_2C\underline{H}_2CH_2CH_3$), 1.73 m (2H, $CH_2C\underline{H}_2CH_2CH_2CH_3$), 2.84 t (2H, $C\underline{H}_2CH_2CH_2CH_2CH_3$, $^3J_{HH}$ = 7.6 Hz), 4.56 br.s (2H, COOH, NH).

2-Phenylimidazole-4,5-dicarboxylic acid (2i). Yield 47%, mp 269–270°C (mp 265°C [4]). ^{1}H NMR spectrum, δ, ppm: 5.07 br.s (2H, COOH, NH), 7.57 m ($3H_{Ar}$), 8.18 d ($2H_{Ar}$, $^3J_{HH}$ = 6.8 Hz).

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