Efficient iodination of structurally varying pyrazoles in heterophase medium*

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A synthesis of 4-iodo-substituted pyrazoles by iodination of pyrazole and its derivatives in the heterophase ($H_2O/CHCl_3$ (CCl_4)) medium with the system KI—KIO_3 in the presence of H_2SO_4 additives was accomplished. The yields of 4-iodo-substituted pyrazoles in the iodination of pyrazole, 3,5-dimethylpyrazole, pyrazole-3(5)-carboxylic acid, 1-methylpyrazole-3-carboxylic acid, 1-methylpyrazole-5-carboxylic acid, 3-nitropyrazole, 1-methyl-3-nitropyrazole, 1-methylpyrazole, 1-ethylpyrazole, and 1-isopropylpyrazole were within 80—97%, whereas in the case of 3-nitropyrazole-5-carboxylic acid it was 32%.

Key words: iodination, KI—KIO_3 system, pyrazole, 3,5-dimethylpyrazole, pyrazole-3(5)-carboxylic acid, 1-methylpyrazole-3-carboxylic acid, 1-methylpyrazole-5-carboxylic acid, 3-nitropyrazole, 1-methyl-3-nitropyrazole, 1-methylpyrazole, 1-ethylpyrazole, 1-isopropylpyrazole, 3-nitropyrazole-5-carboxylic acid.

Iodine is known[1] to be the least reactive in the halogenation reactions of arenes. This stimulates the search for the more efficient methods of iodination of pyrazoles (Pz), since the interest to the preparation of Pz iodo derivatives is caused by their use in the synthesis of biologically active compounds with antitumor, antiviral, antibacterial activity[2—5] or as reagents in organic synthesis.[6—8]

Analysis of the literature data showed that existing methods for the preparation of iodopyrazoles are not without disadvantages, because of the limitations concerning either the structures of starting Pz, or the high cost or toxicity of the iodinating agents, or the environmental problems. Thus, the use of the system[9—12] I_2—NaI—K_2CO_3 in aqueous EtOH gives good results (the yields of 75—90%) only for Pz with electron-donating substituents in the ring. Note that Pz with donor substituents in the ring are also iodinated in high (63—99%) yields in aqueous medium with the mixture[13] of I_2—H_2O_2(30%), however, the reaction is slow enough (24—72 h). When the system[14] I_2—NH_3 (aqueous) was used, the process was nonselective (mono-, di-, and triiodopyrazoles were formed) and could lead to the generation of explosive nitrogen iodide. *N*-Iodosuccinimide[9,15—18] is used for the iodination of Pz with any substituents in the ring in good (70—90%) yield in 50% aqueous H_2SO_4 or other (CF_3SO_3H, CF_3COOH, EtOAc) media, however, the high cost of the reagent limits the scope of its application. Pyrazoles with alkyl or phenyl substituents in the ring can be fairly well iodinated upon the action of ICl (the yields of 4-iodopyrazoles are within 51—92%) in aqueous HCl (see Ref. 14) or organic (AcOH, EtOAc) media,[18,19] as well as upon the action of a mixture of I_2 with diacetoxyiodobenzene[20] in CH_2Cl_2, however, in this case the target products require chromatographic purification. Good results (the yields of the target products of 80—90%) were obtained when I_2—$(NH_4)Ce(NO_3)_6$ in MeCN (see Ref. 21) and I_2—AgOAc in CH_2Cl_2 (see Ref. 22) were used as the iodinating agents, though the use of aprotic medium and expensive enough reagents is required to effect such processes.

Finally, the iodination of pyrazoles of virtually any structure is described upon the action of I_2—HIO_3 in AcOH with CCl_4 additives.[23—25] The reaction is efficient enough and does not produce toxic waste, that makes this process the most attractive. That is why in the present work, in the development of a new approach to the iodination of Pz of various structure, we attempted to modify this process with respect to the aqueous media and have chosen a mixture of KI—KIO_3 in the presence of H_2SO_4 additives as the key system.

Results and Discussion

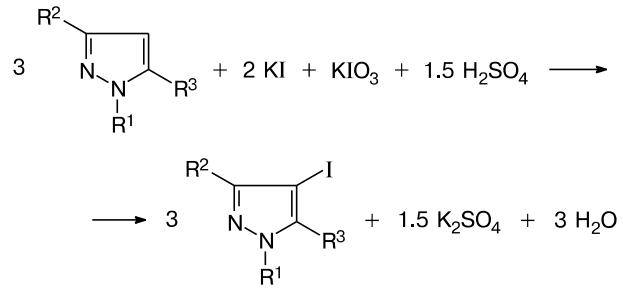
Proceeding from the literature analogies,[26] it could have been expected that the iodination process under study would follow Scheme 1.

Since there are no literature data on the iodination of Pz using the system KI—KIO_3 in aqueous acid (H_2SO_4) medium, in the first stage we have chosen iodination of

* Dedicated to Academician of the Russian Academy of Sciences I. P. Beletskaya on the occasion of her anniversary.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 4, pp. 1043—1050, April, 2013.

Scheme 1



R^1 = H, Me, Et, Pr^i; R^2 = H, Me, NO_2, COOH; R^3 = H, Me, COOH

unsubstituted Pz (**1**) as a model substrate to study both a possibility of its realization and specific features of this process. In the second stage, a wide enough variety of functionally substituted Pz **1**—**11** were studied to discover factors determining efficiency of the iodination system suggested.

Unsubstituted Pz. It is quite obvious that when the process shown in Scheme 1 is effected, the reaction of KI and KIO_3 in aqueous acid medium would lead to the formation of I_2 poorly soluble in aqueous medium (mainly precipitates), which (see below) is an active intermediate of the iodination process. That is why we used a two-phase system $H_2O/CHCl_3$ as the medium in the assumption that I_2 dissolved in the organic phase would be transferred into the aqueous phase as it is consumed.

A series of experiments performed confirmed the possibility of the iodination of Pz with the system KI—KIO_3 in the heterophase medium. However, for the stoichiometric (see Scheme 1) ratio of the starting Pz, KI, and H_2SO_4, the yield of the target product (Table 1, entry *1*) turned out to be low (13%). We further attempted to optimize this process and determine the nature of the key iodinating agent, since no efforts were undertaken to clarify the nature of such an agent in the works cited above[24,26].

The yield of the target product **1′** turned out to increase with the increase in the concentration of Pz **1** (see Table 1, *cf.* entries *2*, *4*, and *5*), as well as with the increase of the reaction temperature from 30 to 50 °C. Simultaneously, the reaction time became shorter, which was 2 h at 50 °C instead of 4 h at 30 °C (*cf.* entries *5* and *6*). The iodination process was considered to reach completion when the solution lost its color because of the consuming of the intermediately formed I_2. However, note that a possibility to increase the temperature is limited to 50 °C, since the boiling point of the azeotrope $CHCl_3/H_2O$ is[27] 56 °C.

The increase in the v/v ratio of aqueous and organic phases from 2.5 : 1 to 5 : 1 promoted the process even to a greater extent, that led to a sharp decrease in the time

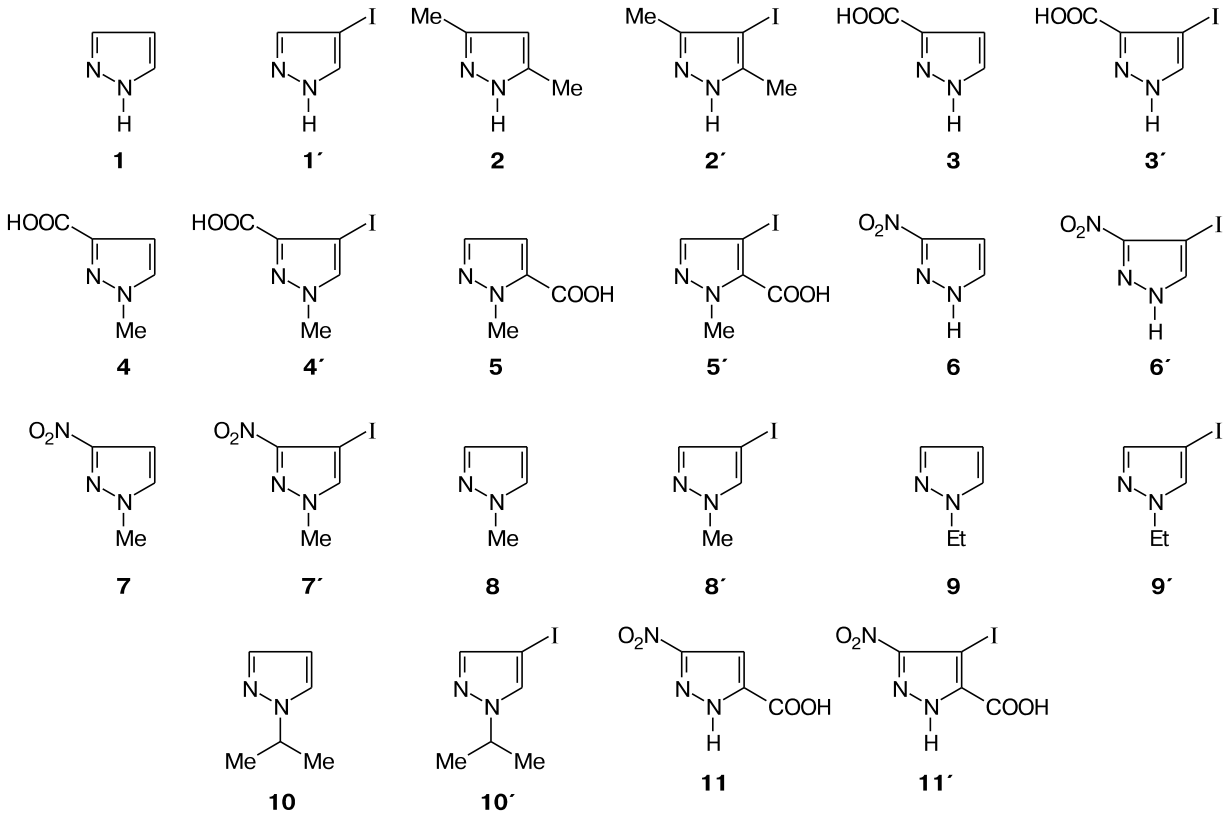


Table 1. Influence of the experimental conditions on the yield of 4-iodopyrazole (**1´**) in the chemical iodination of Pz (**1**) in $H_2O/CHCl_3$ by the system KIO_3—KI—H_2SO_4 (the molar ratio **1** : KIO_3 : KI = 3 : 1 : 2)

Entry	Loading/mol		Aqueous solution : $CHCl_3$ (vol.)	*T*/°C	τ/h	Conversion[a] of KIO_3	Yield[b] of **1´**
	1	H_2SO_4				%	
1	0.015	0.0075	2.5 : 1	30	4.0	43.2	13.0
2	0.015	0.0150	2.5 : 1	30	4.0	56.0	19.9
3	0.015	0.0300	2.5 : 1	30	4.0	75.3	58.3
4	0.030	0.0300	2.5 : 1	30	4.0	66.3	30.2
5	0.090	0.0900	2.5 : 1	30	4.0	89.1	68.0
6	0.090	0.0900	2.5 : 1	50	2.0	98.7	98.6
7	0.090	0.0900	5 : 1	50	0.5	93.1	88.8

[a] Conversion of KIO_3 was determined by iodometric analysis.
[b] Yield of 4-iodopyrazole was calculated based on the ^{1}H NMR spectroscopic data for the isolated mixture of products.

necessary for the reaction to reach completion: 0.5 h instead of 2 h (*cf.* entries *6* and *7*).

Concerning specific features of realization of this process, based on the analogy with iodination of arenes[28] upon the action of I_2/IO_3^- in sulfuric acid it could have been suggested that in our case the triiodide cation I_3^+ (formed by oxidation of I_2) could also serve as the iodinating agent. But it turned out that the rate of the iodination reaction and, therefore, the yield of 4-iodopyrazole (**1´**), as well as the conversion of KIO_3, increased with the increase in the concentration of H_2SO_4 (*cf.* entries *1—3* in Table 1). This fact is difficult to explain in the suggestion that the cation I_3^+ is the iodinating agent. At the same time, the direct dependence of the process efficiency from the concentration of the acid is characteristic[29] of the halogenation reactions involving hypohalic acids (HOHal). Therefore, it can be considered that the iodination process under conditions studied also proceeds through the intermediate formation of HOI, especially as the fact of the formation of HOI by the reaction of I_2 with KIO_3 in an acidified aqueous solution is confirmed by the literature data.[30]

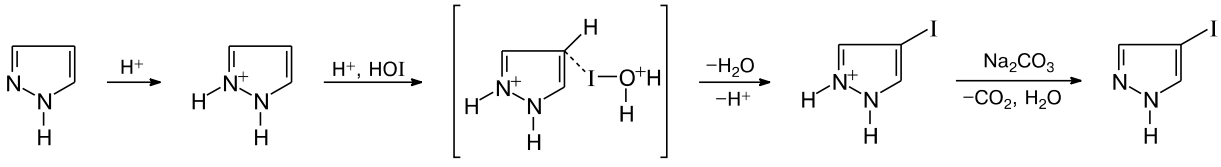
Based on the stated above, the process of iodination of Pz in the system KI—KIO_3 in aqueous acid medium was described by Scheme 2 (eqs (1)—(4)). According to Scheme 2, HIO_3 (formed from KIO_3 in acidic medium) reacts with KI generating I_2 (the fast step), whose reaction with HIO_3 is accompanied by the formation of HOI serving as a key iodinating agent with respect to Pz (the slow step). It is known[31] that pK_{BH^+} of the starting Pz is equal

Scheme 2

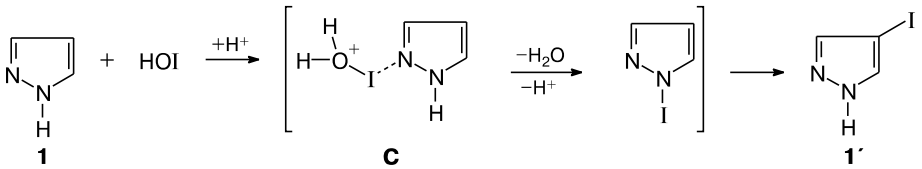
$$2\,KI + H_2SO_4 \longrightarrow 2\,HIO_3 + K_2SO_4 \quad (1)$$

$$HIO_3 + 5\,KI + 2.5\,H_2SO_4 \longrightarrow 3\,I_2 + 2.5\,K_2SO_4 + 3\,H_2O \quad (2)$$

$$2\,I_2 + HIO_3 + 2\,H_2O \rightleftharpoons 5\,HCl \quad (3)$$



1 **C** **1´** (4)



1 **C** **1´** (5)

C is the σ-complex.

to 2.52, therefore, under the experimental conditions (~10% aqueous H_2SO_4), a protonated form would undergo the iodination. This process (see eq. (4)) most likely proceeds through the generation of a σ-complex, where the electrophilic agent (HOI) is coordinated at C(4) atom of the pyrazole ring (which possesses the highest electron density[32]) and is catalyzed by H_2SO_4, which provides the electrophilic assistance in the elimination of the OH group from HOI. The neutralization (addition of Na_2CO_3 to pH 7—8) of the reaction mixture containing protonated 4-iodopyrazole leads to the target product.

To sum up this part of our studies, note that under the optimal conditions (the medium: H_2O—$CHCl_3$ (5 : 1); loadings of Pz **1**, KI, KIO_3, and H_2SO_4 are equal to 0.09, 0.06, 0.03, and 0.09 mol, respectively, T = 50 °C, the reaction time of 0.5 h) the iodination of Pz leads to the preparation of the target 4-iodopyrazole in high (88.8%) yield calculated from the starting pyrazole.

Substituted Pz. As compared to the unsubstituted Pz, its alkyl derivatives possess even higher basicity, and the mechanism of their iodination is also described by Eqs (1)—(4) (see Scheme 2), whereas the Pz nitro derivatives (**6**, **7**, and **11**) are weakly basic (for example, pK_{BH^+}(**6**) is equal to[31] –4.66) and under the experimental conditions they mainly are present in the unprotonated form. The mechanism of iodination of this-type of compounds should be described by Eq. (5) (see Scheme 2). As in the iodination of the strongly basic Pz, the process, according to the data in the work,[33] proceeds through the generation of a σ-complex, however in this case the electrophilic agent (HOI) is coordinated already at N(2) nitrogen atom of the heterocycle, with the acid (H_2SO_4) still playing the role of a catalyst with the electrophilic assistance to the elimination of the OH group from HOI (leaves as H_2O). The thus formed *N*-iodopyrazole undergoes rearrangement to generate the target 4-iodopyrazole.

As it was shown earlier,[21,34] the efficiency of iodination of Pz strongly depends on the nature of the substituent and its position in the pyrazole ring. For example, the high yield (80%) of 4-iodopyrazole was obtained[21] by the iodination with the system I_2—NaI—NaOAc in aqueous medium (boiling with a reflux condenser for 24—48 h) for Pz with the strong donor substituents in the ring (3-methoxy-4-methylpyrazole), the moderate yield (55%) was obtained for 3,5-dimethylpyrazole, whereas 3,5-bis(ethoxycarbonyl)pyrazole with two acceptor groups in the ring did not give the iodination reaction at all. This prompted us to study iodination of Pz with substituents of different nature: electron-donating (3,5-dimethylpyrazole (**2**)) and electron-withdrawing (pyrazole-3-carboxylic acid (**3**) and 3-nitropyrazole (**6**)), as well as *N*-alkylated Pz (1-methylpyrazolecarboxylic acids (**4**, **5**), 1-methyl-3-nitropyrazole (**7**), and 1-alkylpyrazoles (**8**—**10**)). The results obtained are summarized in Table 2.

Table 2. Influence of the experimental conditions on the yield of 4-iodo-substituted pyrazoles in the chemical iodination of pyrazoles (Pz) with KIO_3—KI—H_2SO_4 (loadings of Pz of 0.09 mol, the molar ratio Pz : KIO_3 : KI : H_2SO_4 = 3 : 1 : 2 : 3) in the system H_2O/$CHCl_3$ (CCl_4) with the v/v ratio of phases of 5 : 1

Entry	Starting Pz	T/°C	Organic phase	τ/min	Conversion of (%)		Product of iodination	Yield[a] of product (%)	
					KIO_3[b]	Pz[a]		I	II
1	**2**	50	$CHCl_3$	7	99.0	96.7	**2´**	96.7	100.0
2	**3**	50	$CHCl_3$	10	95.5	97.4	**3´**	92.1	94.6
3	**4**	50	$CHCl_3$	25	92.0	99.7	**4´**	92.6	92.9
4	**5**	50	$CHCl_3$	10	61.1	59.4	**5´**	49.4	83.2
5	**5**	50	$CHCl_3$	60	71.1	63.4	**5´**	60.0	94.6
6[c]	**5**	66	CCl_4	60	93.6	98.0	**5´**	86.8	88.5
7[c,d]	**6**	66	CCl_4	180	85.3	93.0	**6´**	83.5	89.9
8[c,d]	**7**	66	CCl_4	180	63.5	70.6	**7´**	58.7	92.4
9	**8**	50	$CHCl_3$	30	90.5	95.0	**8´**	84.0	88.8
10	**9**	50	$CHCl_3$	30	89.5	90.1	**9´**	80.2	89.0
11	**10**	50	$CHCl_3$	30	89.9	90.3	**10´**	82.0	90.8
12[c,d]	**11**	66	CCl_4	180	36.2	51.5	**11´**	32.2[e]	62.5[e]

[a] Conversion of the starting Pz and yields of products were calculated based on the ^{1}H NMR spectroscopic data for the isolated mixture of products: I calculated based on the starting Pz, II calculated based on the reacted Pz.

[b] Conversion of KIO_3 was determined by iodometric analysis.

[c] CCl_4 was used as the organic phase instead of $CHCl_3$, since the boiling point of the CCl_4/H_2O azeotrope is higher than that in the case of $CHCl_3$ and is equal[27] to 66 °C.

[d] Loading of Pz was 0.0045 mol, the molar ratio Pz : KIO_3 : KI : H_2SO_4 = 3 : 1 : 2 : 6.

[e] Since product **11´** does not give characteristic signals in the ^{1}H NMR spectrum, to determine the molar ratio of the reaction products, the obtained mixture of acids **11´**—**11** was converted to a mixture of their methyl esters and then analyzed by ^{1}H NMR. The yield of acid **11´** is given in calculation on its methyl ester.

A comparison of the data on the iodination of unsubstituted Pz **1** and substituted Pz **2**, **3**, and **4** (*cf.* entry *7* in Table 1 and entries *1—3* in Table 2) showed that the presence in the pyrazole ring of two methyl groups (Pz **2**), the COOH group at the carbon atom (Pz **3**), or the methyl group at the nitrogen atom and the COOH group at the carbon atom (Pz **4**) has low influence on the yield of 4-iodo derivative, which remained around 90%. It is obvious, that this is due to the high reactivity of HOI as the iodinating agent, that essentially levels the negative influence of the moderately strong electron-withdrawing substituents in the pyrazole ring on the iodination process.

The data on the iodination of *N*-alkylated Pz deserved special attention; on the whole it proceeded less efficiently as compared to the iodination of Pz unsubstituted at position 1. This effect is especially pronounced for Pz having a strong acceptor substituent in the ring. Thus, as compared to 3-nitropyrazole **6**, the iodination of *N*-methyl derivative (**7**) proceeded with the decrease in the yield of the target product and the conversion of the starting pyrazole by ~25% (see Table 2, *cf.* entries *7* and *8*). In the iodination of pyrazole-3-carboxylic acid (**3**), this effect is less pronounced than in the case of 1-methylpyrazole-3-carboxylic acid (**4**). Nevertheless, to obtain the same yield of the target product of iodination of Pz **4**, the twice as long reaction time is required (see Table 2, *cf.* entries *2* and *3*). Even iodination of 1-methylpyrazole (**8**) proceeds with the yield lower than in the case of unsubstituted Pz **1** by 10% (*cf.* entry *7* in Table 1 and entry *9* in Table 2), in this case the nature of the *N*-alkyl (Me, Et, Pr^i) substituent virtually does not influence the efficiency of the process (see Table 2, *cf.* entries *9—11*).

In the case of Pz **5**, the yield of the iodination product (**5´**), as well as the conversion of KIO_3 and the starting Pz, are significantly lower than in the iodination of pyrazole **4** (*cf.* entries *3*, *4*, and *5* in Table 2). The obvious explanation for this is the poor solubility of Pz **5** in aqueous solution and, as a consequence, the low rate of chemical reaction because of the low effective concentration of Pz **5**. In fact, the increase in the yield of the target product to the acceptable level (86.8%, entry *6*) was accomplished (see Table 2, entries *4—6*) only by the increase of the reaction time to 60 min, as well as by the increase of its temperature to 66 °C.

It should be emphasized that the replacement of the COOH group in the pyrazole ring (Pz **3**) with the more electron-withdrawing NO_2 group (Pz **6**) decreases the efficiency of iodination. As a consequence, for the preparation of iodo derivative **6´** with a high enough yield (83.5% calculated on the loaded Pz **6**) more vigorous conditions are required than for the preparation of 4-iodopyrazole-3(5)-carboxylic acid (**3´**): 66 °C instead of 50 °C, with the reaction time of 3 h instead of 10 min (see Table 2, *cf.* entries *2* and *7*).

However, note for the comparison that in the iodination of 3-nitropyrazole (**6**) by the system[34] $KIO_3—I_2—H_2SO_4$ in AcOH (with H_2O and CCl_4 additives), 21 h at 80—85 °C are required for the yield of the target product **6´** to reach 86% calculated on the loaded Pz **6**, whereas in our experiment, the iodination of Pz **6** (see Table 2, entry *7*) proceeds at lower temperature and decreases the reaction time by the factor of 7 with the yield of the target product **6´** being comparable.

As it was expected, the introduction into the molecule of Pz **6** of the second (besides the NO_2 group) electron-withdrawing substituent (the COOH group), Pz **11**, led to the decrease (by 50%) in the yield of the corresponding 4-iodo derivative (see Table 2, *cf.* entries *7* and *12*). At the same time, from the data of entry *12* (see Table 2) it is seen that the conversion of both the starting Pz **11** and KIO_3 was only ~50%. From this it follows that the efficiency of iodination of Pz with two electron-withdrawing substituents can be principally increased through the increase of the experimental time.

In conclusion, we studied and suggested a new approach to the efficient performing of chemical iodination of pyrazoles, which under the optimal conditions (the $H_2O—CHCl_3$ (CCl_4) (5 : 1) medium; the loadings of Pz, KIO_3, KI, and H_2SO_4 equal to 0.045—0.09, 0.015—0.03, 0.03—0.06, and 0.09 mol, respectively; the reaction time of 0.5—3.0 h, 50—66 °C) allows one to obtain the target products in good yields (59—93% calculated on the loaded or 92—93% calculated on the reacted Pz).

In general, the method of iodination of pyrazoles described in the present work is not inferior to the best of the known methods in its yield of the target products and is favorably distinguished by the use of available, inexpensive, and nontoxic reagents, the rapidness of the overall process carried out in aqueous medium and can be applied for the efficient iodination of pyrazoles of various structures.

Experimental

Pyrazole (**1**) and 3,5-dimethylpyrazole (**2**) were commercially available products (Acros) and were used without additional purification. Pyrazole-3(5)-carboxylic (**3**), 1-methylpyrazole-3-carboxylic (**4**), and 1-methylpyrazole-5-carboxylic (**5**) acids,[35] 3-nitropyrazole (**6**),[36] 1-methyl-3-nitropyrazole (**7**),[24] 1-methylpyrazole (**8**),[37] 1-ethylpyrazole (**9**),[38] 1-isopropylpyrazole (**10**),[39] 3-nitropyrazole-5-carboxylic acid (**11**)[40] were synthesized according to the procedures described earlier.

Compounds obtained by iodination were identified by ^{1}H NMR spectroscopy by the comparison with the spectra of standard samples described in the literature: 4-iodopyrazole (**1´**),[41] 4-iodo-3,5-dimethylpyrazole (**2´**),[18] 4-iodo-3-nitropyrazole (**6´**),[34] 4-iodo-1-methyl-3-nitropyrazole (**7´**),[24] 4-iodo-1-methylpyrazole (**8´**),[42] 1-ethyl-4-iodopyrazole (**9´**);[43] and those synthesized according to the known procedures: 4-iodopyrazole-3(5)-carboxylic (**3´**),[41] 4-iodo-1-methylpyrazole-3-carboxylic (**4´**)

and 4-iodo-1-methylpyrazole-5-carboxylic (**5´**) acid[24], 4-iodo-1-isopropylpyrazole (**10´**);[43] 4-iodo-3-nitropyrazole-5-carboxylic acid (**11´**) was identified (see below) as its methyl ester.[44]

^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer (300 MHz), DMSO-d_6 was used as the solvent. Chemical shifts are given relative to $SiMe_4$.

***A*. Chemical iodination of pyrazole (1)** (taking entry *7* in Table 1 as an example). *Carrying out the reaction*. Pyrazole **1** (6.12 g, 0.09 mol), KIO_3 (6.42 g, 0.03 mol), KI (9.96 g, 0.06 mol), H_2O (100 mL), and $CHCl_3$ (20 mL) were placed in a three-neck flask equipped with a dropping funnel, thermometer, mechanical stirrer, and refluxed condenser and placed in a bath with controlled temperature. The reaction mixture was vigorously stirred, followed by a dropwise addition (cooling, $T \leq 40$ °C) of conc. H_2SO_4 (5.2 mL, 0.09 mol). Then, the temperature was increased to 50 °C, the solution was stirred for 30 min (until the violet color of I_2 emerged after addition of H_2SO_4 disappeared) and cooled to ~20 °C.

a. Isolation of the main portion of the target product. Chloroform was evaporated at the atmospheric pressure, the aqueous solution left was neutralized by the addition of Na_2CO_3 (to pH 7—8). A precipitate formed was filtered off, washed with water, and dried to obtain 4-iodopyrazole (**1´**) (15.2 g), which was identified by the melting point of 109 °C (*cf.* Ref. 45: m.p. 108.5 °C) and the ^{1}H NMR spectral characteristics. After the isolation of the main portion of the target product, an aliquot was collected from the mother liquor, and the amount of the unreacted KIO_3 (6.9%) was determined by iodometric analysis.[46]

b. Additional isolation. For the salting out the residual amount of the target product, NaCl (~30 g) was added to the mother liquor. A precipitate formed was extracted with $CHCl_3$ (2×30 mL), the extracts were combined and dried with $CaCl_2$. The evaporation of $CHCl_3$ gave a white powder (0.52 g), which according to the ^{1}H NMR spectroscopic data was a mixture of the target product **1´** and the starting Pz **1**. Their molar ratio of 1 : 1 was determined from the integral intensities of the signals for **1´** at δ 7.75 (s, 2 H, H(3(5))) and **1** at δ 7.60 (s, 2 H, H(3(5))). Taking these data into account, the total yield of product **1´** was 88.8%, with the conversion of the starting Pz **1** being 93.1%.

B*. Iodination of 3,5-dimethylpyrazole (2)** (taking entry *1* in Table 2 as an example). The reaction was carried out similarly to example ***A with the following composition of the reaction mixture: Pz **2** (8.64 g, 0.09 mol), KIO_3 (6.42 g, 0.03 mol), KI (9.96 g, 0.06 mol), H_2O (100 mL), $CHCl_3$ (20 mL), and conc. H_2SO_4 (5.2 mL, 0.09 mol). After the reaction reached completion (disappearance of the reaction mixture color, the reaction time of 7 min), the products were isolated and analyzed as described above (see example ***A***, ***a***) to obtain 4-iodo-3,5-dimethylpyrazole (**2´**) (18.85 g, 94.3%), which was identified by its melting point 137 °C (*cf.* Ref. 47: m.p. 137—138 °C) and ^{1}H NMR spectral characteristics. The conversion of KIO_3 was 94.0%. An additional amount (0.67 g) of the product was isolated from the mother liquor as described above (see example ***A***, ***b***), which (^{1}H NMR spectroscopic data) was a mixture of the target product **2´** and the starting **2**. The molar ratio of these compounds in the reaction mixture of 0.58 : 1.0 was determined from the integral intensities of the signal for Pz **2** at δ 5.70 (s, 1 H, H(4)) and the overlapped signal for Pz **2** and **2´** at δ 2.15 (s, 6 H, CH_3). Taking these data into account, the total yield of product **2´** was 96.7%, with the conversion of Pz being **2** 96.7%.

C*. Iodination of pyrazole-3-carboxylic acid (3)** (taking entry *2* in Table 2 as an example). The reaction was carried out similarly to example ***A with the following composition of the reaction mixture: acid **3** (10.08 g, 0.09 mol), KIO_3 (6.42 g, 0.03 mol), KI (9.96 g, 0.06 mol), H_2O (100 mL), $CHCl_3$ (20 mL), and conc. H_2SO_4 (5.2 mL, 0.09 mol). After carrying out the reaction (see example ***A***) for 10 min, $CHCl_3$ was evaporated, the aqueous solution left was neutralized to pH 1 by the addition of NaOH. A precipitate formed was filtered off, washed with water, and dried to obtain a residue (19.35 g) containing (^{1}H NMR spectroscopic data) a mixture of 4-iodopyrazole-3(5)-carboxylic acid (**3´**) and the starting compound **3**. Their molar ratio of 35.1 : 1.0 was determined from the integral intensities of the signals for compounds **3´** at δ 7.90 (s, 1 H, H(5)) and **3** at δ 7.70 (s, 1 H, H(5)). After the precipitate was isolated, the amount of the unreacted KIO_3 (4.5%) in the mother liquor was determined (see example ***A***), then water was evaporated under reduced pressure. The residue was extracted with Me_2CO (2×25 mL) and EtOH (2×25 mL), the extracts were combined and after evaporation of the solvents, an additional amount (0.65 g) of the mixture containing (see ^{1}H NMR spectroscopic data given above) compounds **3´** and **3** in the molar ratio of 70 : 1.0 was isolated.

The mixtures of compounds **3´** and **3** (19.35 and 0.65 g) were combined, mixed with hot H_2O (80 mL), and cooled to ~20 °C in order to isolate product **3´**. A precipitate formed was filtered off and dried to obtain the purified product **3´** (16 g, 73.7%), which was identified by the melting point of 240 °C (*cf.* Ref. 34: m.p. 240 °C) and ^{1}H NMR spectral characteristics. According to the ^{1}H NMR spectroscopic data, the yield of product **3´** containing in the mixture with **3** was 92.1%, with the conversion of compound **3** being 97.6%.

D*. Iodination of 1-methylpyrazole-3-carboxylic acid (4)** (taking entry *3* in Table 2 as an example). The reaction was carried out similarly to example ***A with the following composition of the reaction mixture: acid **4** (11.34 g, 0.09 mol), KIO_3 (6.42 g, 0.03 mol), KI (9.96 g, 0.06 mol), H_2O (100 mL), $CHCl_3$ (20 mL), and conc. H_2SO_4 (5.2 mL, 0.09 mol). After carrying out the reaction (see example ***A***) for 25 min, the products were isolated as described in example ***C*** to obtained 4-iodo-1-methylpyrazole-3-carboxylic acid (**4´**) (19.5 g, 86.6%) as the main product, which was identified by the melting point 182 °C (*cf.* Ref. 24: m.p. 180—181.5 °C) and ^{1}H NMR spectral characteristics. The conversion of KIO_3 was 92.0%. After isolation of the main portion of the product, an additional amount (1.53 g) of a precipitate was isolated from the mother liquor left (as described in example ***C***), which was (^{1}H NMR spectroscopic data) a mixture of compounds **4´** and **4**. The molar ratio of these compounds in reaction mixture of 25.9 : 1.0 was determined from the integral intensities of the signals for **4´** at δ 8.0 (s, 1 H, H(5)) and **4** at δ 7.75 (c, 1 H, H(5)). Because of the difficulty of isolation of product **4´** from the reaction mixture, the obtained target product **4´** (19.5 g) and the mixture of compounds **4´** and **4** (1.53 g) were combined to determine the total yield (92.6%) of product **4´** based on the ^{1}H NMR spectroscopic data, with the conversion of compound **4** being 99.7%.

E*. Iodination of 1-methylpyrazole-5-carboxylic acid (5)** (taking entry *6* in Table 2 as an example). The reaction was carried out similarly to example ***A, but at $T = 66$ °C and the following composition of the reaction mixture: acid **5** (11.34 g, 0.09 mol), KIO_3 (6.42 g, 0.03 mol), KI (9.96 g, 0.06 mol), H_2O (100 mL), CCl_4 (20 mL), and conc. H_2SO_4 (5.2 mL, 0.09 mol). After carry-

ing out the reaction (see example ***A***) for 60 min, the products were isolated as described in example ***C***. The conversion of KIO_3 was 93.6%. The residue (19.05 g) obtained was (^{1}H NMR spectroscopic data) a mixture of 4-iodo-1-methylpyrazole-3-carboxylic acid (**5′**) and compound **5**. The molar ratio of these compound in the reaction mixture of 45 : 1.0 was determined from the integral intensities of the signals for compounds **5′** at δ 7.60 (s, 1 H, H(3)) and **5** at δ 7.50 (s, 1 H, H(3)). Then, the mother liquor was treated as described in example ***C*** to additionally isolate some product (0.86 g), which was (^{1}H NMR spectroscopic data) a mixture of compounds **5′** and **5** in the molar ratio of 31 : 1.0. The thus obtained mixtures of compounds (19.05 and 0.86 g) were combined to determine the total yield (86.8%) of product **5′** based on the ^{1}H NMR spectroscopic data, with the conversion of compound **5** being 98.0%.

F. **Iodination of 3-nitropyrazole (6)** (taking entry *7* in Table 2 as an example). The reaction was carried out similarly to example ***A***, but at T = 66 °C and the following composition of the reaction mixture: pyrazole **6** (5.09 g, 0.045 mol), KIO_3 (3.21 g, 0.015 mol), KI (4.98 g, 0.03 mol), H_2O (100 mL), CCl_4 (20 mL), and conc. H_2SO_4 (5.2 mL, 0.09 mol)). After the reaction mixture was kept at T = 66 °C for 180 min, the products were isolated as indicated in example ***E***. the conversion of KIO_3 was 85.3%. The thus isolated residue (8.54 g) was (^{1}H NMR spectroscopic data) a mixture of 4-iodo-3-nitropyrazole (**6′**) and pyrazole **6**. The molar ratio of these compound in the reaction mixture of 30.3 : 1.0 was determined from the integral intensities of the signals for compounds **6′** at δ 8.25 (s, 1 H, H(5)) and **6** at δ 8.0 (s, 1 H, H(5)). Solid Na_2SO_3 was added to the mother liquor left after isolation of the precipitate to destroy the large amount of unreacted KIO_3 until the solution became colorless (disappearance of the color from I_2, formed by the reaction of KIO_3 and Na_2SO_3). Then, the mother liquor was treated as in example ***E*** to additionally isolate 0.79 g of the product, which was (^{1}H NMR spectroscopic data) a mixture of product **6′** and the starting compound **6** in the molar ratio of 1.2 : 1.0. The thus obtained mixtures of the target product **6′** and the starting compound **6** (8.54 and 0.79 g) were combined to determine the total yield of product **6′** (83.5%) based on the ^{1}H NMR spectroscopic data, with the conversion of compound **6** being 93.0%.

G. **Iodination of 1-methyl-3-nitropyrazole (7)** (taking entry *8* in Table 2 as an example). The reaction was carried out similarly to example ***A***, but at T = 66 °C and the following composition of the reaction mixture: pyrazole **7** (5.71 g, 0.045 mol), KIO_3 (3.21 g, 0.015 mol), KI (4.98 g, 0.03 mol), H_2O (100 mL), CCl_4 (20 mL), and conc. H_2SO_4 (5.2 mL, 0.09 mol). After the reaction mixture was kept at T = 66 °C for 180 min, the products were isolated as indicated in example ***F***. The conversion of KIO_3 was 63.5%. The thus isolated residue (7.92 g) was (^{1}H NMR spectroscopic data) a mixture of 4-iodo-1-methyl-3-nitropyrazole (**7′**) and the starting compound **7**. The molar ratio of these compounds in the reaction mixture of 2.4 : 1.0 was determined from the integral intensities of the signals for compounds **7′** at δ 8.25 (s, 1 H, H(5)) and **7** at δ 8.0 (s, 1 H, H(5)). The mother liquor left after isolation of the precipitate was treated as in example ***F*** to additionally isolate 0.44 g of the product, which was (^{1}H NMR spectroscopic data) a mixture of the target product **7′** and the starting compound **7** in the molar ratio of 0.24 : 1.0. The thus obtained mixtures of the target product **7′** and the starting compound **7** (7.92 and 0.44 g) were combined to determine the total yield of product **7′** (58.7%) based on the ^{1}H NMR spectroscopic data was, with the conversion of compound **7** being 70.6%.

H. **Iodination of 1-methylpyrazole (8)** (taking entry *9* in Table 2 as an example). The reaction was carried out similarly to example ***A*** with the following composition of the reaction mixture: pyrazole **8** (7.38 g, 0.09 mol), KIO_3, 9.96 g (6.42 g, 0.03 mol), KI (0.06 mol), H_2O (100 mL), $CHCl_3$ (20 mL), and conc. H_2SO_4 (5.2 mL, 0.09 mol). After carrying out the reaction for 30 min, the products were isolated as described in example ***A***. The conversion of KIO_3 was 90.5%. The oil (16.6 g) obtained was (^{1}H NMR spectroscopic data) a mixture of 4-iodo-1-methylpyrazole (**8′**) and the starting compound **8**. The molar ratio of these compound in the reaction mixture of 15 : 1.0 was determined from the integral intensities of the signals for compounds **8′** at δ 7.50 (s, 1 H, H (3), H (5)) and **8** at δ 7.38 (s, 1 H, H(3), H(5)). The yield of product **8′** (84.0%) in the mixture was determined based on the ^{1}H NMR spectroscopic data, with the conversion of compound **8** being 95.0%.

I. **Iodination of 1-ethylpyrazole (9)** (taking entry *10* in Table 2 as an example). The reaction was carried out similarly to example ***A*** with the following composition of the reaction mixture: pyrazole **9** (8.64 g, 0.09 mol), KIO_3 (6.42 g, 0.03 mol), KI (9.96 g, 0.06 mol), H_2O (100 mL), $CHCl_3$ (20 mL), and conc. H_2SO_4 (5.2 mL, 0.09 mol). After carrying out the reaction for 30 min, the products were isolated as described in example ***A***. The conversion of KIO_3 was 89.5%. The oil obtained (17.8 g) was (^{1}H NMR spectroscopic data) a mixture of 1-ethyl-4-iodopyrazole (**9′**), the starting compound **9**, and $CHCl_3$. The molar ratio of these compound in the reaction mixture of 19.0 : 3.5 : 1.0 was determined from the integral intensities of the signals for product **9′** at δ 7.50 (s, 1 H, H(3), H(5)), the starting compound **9** at δ 7.40 (s, 1 H, H(3), H(5)), and $CHCl_3$ at δ 8.30 (s, 1 H). The yield of product **9′** (80.2%) in the mixture was determined based on the ^{1}H NMR spectroscopic data, with the conversion of compound **9** being 90.1%.

J. **Iodination of 1-isopropylpyrazole (10)** (taking entry *11* in Table 2 as an example). The reaction and the isolation of products were carried out similarly to example ***A*** with the following composition of the reaction mixture: pyrazole **10** (9.90 g, 0.09 mol), KIO_3 (6.42 g, 0.03 mol), KI (9.96 g, 0.06 mol), H_2O (100 mL), $CHCl_3$ (20 mL), and conc. H_2SO_4 (5.2 mL, 0.09 mol). The conversion of KIO_3 was 89.9%. The oil (19.0 g) obtained was (^{1}H NMR spectroscopic data) a mixture of 4-iodo-1-isopropylpyrazole (**10′**), the starting compound **10**, and $CHCl_3$. The molar ratio of these compound in the reaction mixture of 8.5 : 1.0 : 0.6 was determined from the integral intensities of the signals for product **10′** at δ 7.50 (s, 1 H, H (3), H(5)), the starting compound **10** at δ 7.40 (s, 1 H, H(3), H(5)), and $CHCl_3$ at δ 8.30 (s, 1 H). The yield of product **10′** (82.0% in the mixture was determined based on the ^{1}H NMR spectroscopic data, with the conversion of compound **10** being 90.3%.

K. **Iodination of 3-nitropyrazole-5-carboxylic acid (11)** (taking entry *12* in Table 2 as an example). The synthesis and the isolation of products were carried out as indicated in example ***E***, with the following composition of the reaction mixture: acid **11** (7.07 g, 0.045 mol), KIO_3 (3.21 g, 0.015 mol), KI (4.98 g, 0.03 mol), CCl_4 (20 mL), H_2O (100 mL), and conc. H_2SO_4 (5.2 mL, 0.09 mol). The conversion of KIO_3 was 36.5%. A solid compound (1.03 g) was obtained. The mother liquor left after isolation of the precipitate was treated as in example ***E*** to additionally isolate 6.5 g of the compound. The products were combined,

dissolved in MeOH (50 mL), followed by the addition of $SOCl_2$ (6.7 mL, 0.09 mol) and reflux of the reaction mixture with water condenser for 14 h. After cooling of the solution, MeOH was evaporated (at reduced pressure), the residue was dissolved in EtOAc (50 mL), sequentially washed with saturated aqueous $NaHCO_3$ (3×15 mL) and NaCl (1×10 mL), and dried with Na_2SO_4. The evaporation of the organic solvent gave a residue (7.03 g), which (^{1}H NMR spectroscopic data) was a mixture of methyl esters of 4-iodo-3-nitropyrazole-5-carboxylic (**11´**) and 3-nitropyrazole-5-carboxylic (**11**) acids. The molar ratio of these compound in the reaction mixture of 1.0 : 1.5 was determined from the integral intensities of the signals for ester **11** at δ 7.30 (s, 1 H, H(4)) and the overlapped signal for esters of product **11´** and the starting compound **11** at δ 3.90 (s, 3 H, OCH_3). The yield of methyl ester **11´** (32.0%) in the mixture was determined based on the ^{1}H NMR spectroscopic data (calculated based on the loaded acid **11** with its conversion of 51.5%).

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Received December 14, 2012;
in revised form February 22, 2013