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Mild Regioselective Iodination of Pyrazoles Using *n*-Butyltriphenylphosphonium Peroxodisulfate[1]

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Abstract—A practical, efficient and inexpensive method of synthesis of iodopyrazoles by the reaction of pyrazoles with iodine using *n*-butyltriphenylphosphonium peroxodisulfate as an oxidant at room temperature is reported. The use of *n*-butyltriphenylphosphonium peroxodisulfate is feasible due to its easy preparation and handling, high stability and activity.

Keywords: pyrazoles, iodopyrazoles, butyltriphenylphosphonium peroxydisulfate, iodination

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In view of the current interest in synthetic applications of peroxodisulfate ion [1–3], we have been exploring its potential use in carbon–heteroatom bond formation. Recently we have reported [4] a very efficient peroxodisulfate ion mediated addition of iodine to aromatic compounds leading to the formation of monoiodo aromatic compounds. Subsequently we encountered a novel procedure for the synthesis of 4-iodopyrazoles directly from pyrazoles using iodine mediated by *n*-butyltriphenylphosphonium peroxodisulfate [$(n\text{-BuPPh}_3)_2S_2O_8$].

RESULTS AND DISCUSSION

The initial experiment involved the reaction of pyrazole with iodine using [$(n\text{-BuPPh}_3)_2S_2O_8$] in acetonitrile under reflux that led to a mixture of 4-iodopyrazole (**2**) and 3,4-diiodopyrazole (**3**) in 4 : 1 ratio.

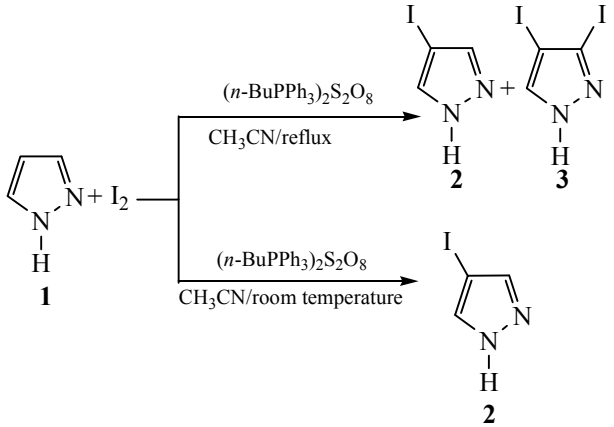
The reaction of **1** with [$(n\text{-BuPPh}_3)_2S_2O_8$] (0.5 mmol) and iodine (0.6 mmol) was conducted at room temperature to give 4-iodopyrazole (89%) with no diiodopyrazole detected (Scheme 1).

Various substituted pyrazoles under similar experimental conditions gave corresponding 4-iodopyrazoles (Scheme 2, table). In all cases [$(n\text{-BuPPh}_3)_2S_2O_8$] was added in portions to a solution containing a heterocyclic substrate and iodine. With the increase of oxidant/pyrazole ratio to 1 : 1 time of oxidation shortened, but only the compound (**2a**) was formed without further oxidation. A mixture of CH_3CN/H_2O (10 : 2) was determined to be the best solvent. The reaction of (**1a**) in dry acetonitrile did not complete in 4 h.

At room temperature the monoiodinated product at the position 4 was formed as the only isolated product, except for the reaction of 3-ethoxy-5-methyl-pyrazole (see table, entry 5) which gave the low yield of diiodopyrazole.

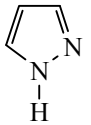
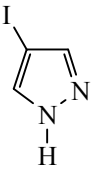
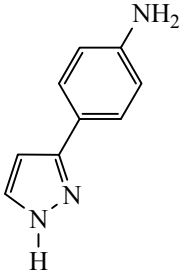
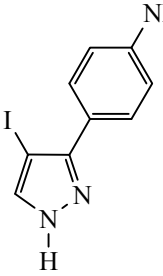
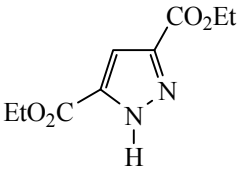
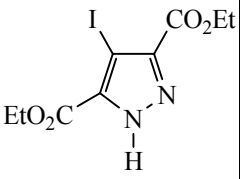
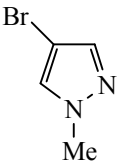
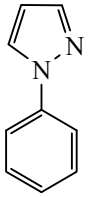
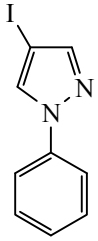
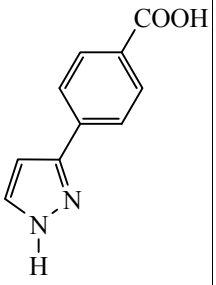
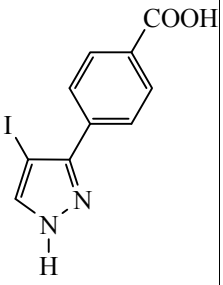
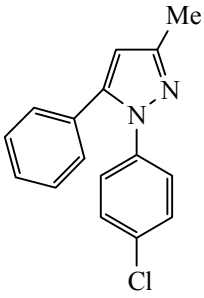
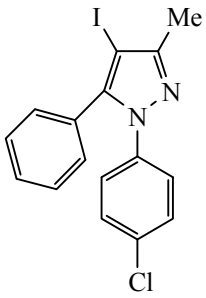
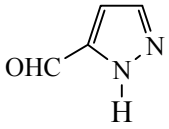
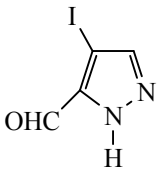
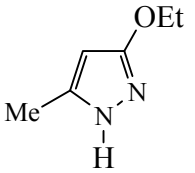
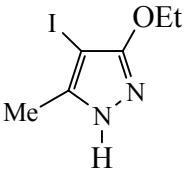
Efficiency and applicability of the current protocol were tested in several competitive reactions (Scheme 3) that demonstrated streoselectivity. Unsubstituted in the

Scheme 1. Synthetic approach to iodopyrazoles.



[1] The text was submitted by the authors in English.

Table 1. Iodination of pyrazoles in the presence of $[(n\text{-BuPPh}_3)_2S_2O_8]$

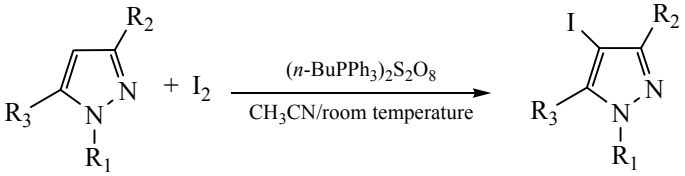
Comp. no.	Substrate	Product[a]	Time, h	Yield[b], %	Comp. no.	Substrate	Product[a]	Time, h	Yield[b], %
1			2.0	89	**6**			1.0	90
2			3.5	87	**7**		–	3.0	–
3			2.0	91	**8**			2.5	85
4			2.0	88	**9**			3.0	88
5			1.0	92					

[a] All products were identified by comparison with authentic samples [5–6]. [b] Isolated yields.

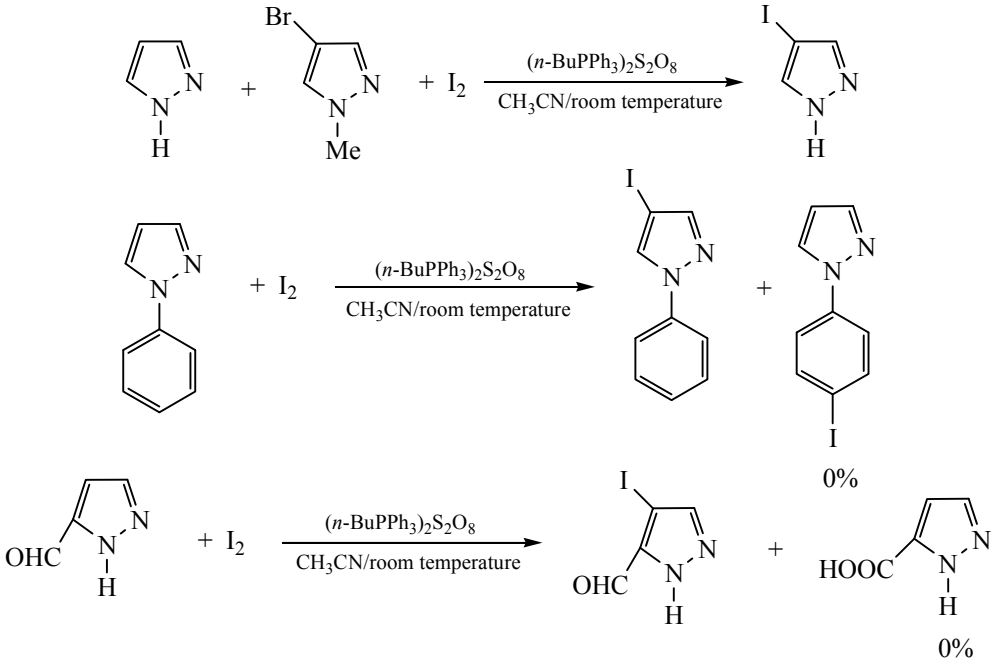
position 4 derivatives were iodinated in the presence of 4-substituted pyrazoles with high selectivity. Iodination of pyrazoles dominated over that of phenyl groups. Stereoselective iodination of pyrazoles in the presence of other oxidizable functional groups, such as aldehyde and methyl, was achieved using the same reaction system.

Oxidative effect of $[(n\text{-BuPPh}_3)_2S_2O_8]$ was tested in the reaction of 1-phenylpyrazole (1 mmol) with iodine

Scheme 2. 4-Iodination of pyrazoles.



Scheme 3. Stereoselective iodination of pyrazoles.



(0.6 mmol) in the absence of an oxidant at room temperature. Only 5% of 4-iodo-1-phenylpyrazole was formed after 4 h of the process.

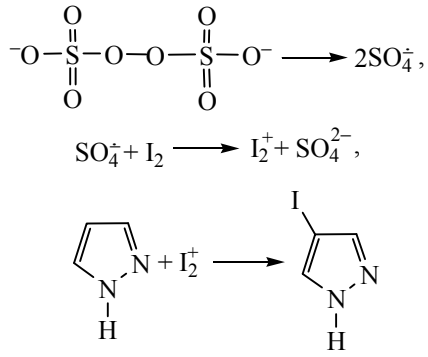
The reaction probably occured (Scheme 4) via the one-electron transfer process with the formation of the iodonium radical cation which could act as a highly reactive electrophile, leading to iodination within short reaction time.

EXPERIMENTAL

n-Butyltriphenylphosphonium peroxodisulfate was prepared as described earlier [7]. Other chemicals were purchased from Merck Chemical Company, Darmstadt, Germany. Elemental analyses were performed on an ECS4010 instrument. Melting points were measured by KSPIN apparatus. NMR spectra were measured on a 400 MHz Brucker Spectrometer (100 MHz for ^{13}C). Purity tests of the products and reaction monitoring were carried out by TLC on polygram SILG/UV 254 plates.

General procedure for iodination of pyrazoles. *n*-Butyltriphenylphosphonium peroxodisulfate (0.5 mmol) was added in small portions to a solution of pyrazole (1 mmol) and iodine (0.6 mmol) in CH_3CN/H_2O (10 : 2 mL) in a 50 mL round-bottome flask equipped with a magnetic stirrer. The reaction mixture was stirred at ambient temperature for the appropriate time (see table). Upon completion of the reaction, as

Scheme 4. Mechanistic outline for the formation of iodinated pyrazole.



indicated by TLC, the reaction mixture was poured into an aqueous sodium thiosulfate solution (1 M) and extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried over $MgSO_4$. The solvent was concentrated in vacuo, the resulting product was purified on silica gel using column chromatography (diethyl ether : *n*-hexane = 1 : 4) to afford the pure compound.

4-Iodo-1*H*-pyrazole (1). Yield 89%, mp 109–110°C. ^{13}C NMR spectrum, δ_C, ppm: 57.6, 138.8. Found, %: C 18.6, H 1.57, N 14.40. $C_3H_3IN_2$. Calculated, %. C 18.57, H 1.56, N 14.43.

3,5-Bis(ethoxycarbonyl)-4-iodo-1*H*-pyrazole (2). Yield 87%, mp 165–166°C. ^{13}C NMR spectrum, δ_C, ppm: 13.1, 59.3, 62.8, 142.5, 160.8. Found, %: C 31.89, H 3.25, N 8.27. $C_9H_{11}IN_2O_4$. Calculated, %. C 31.97, H 3.29, N 8.28.

4-Iodo-1-phenylpyrazole (3). Light yellow oil, yield 91%. ^{13}C NMR spectrum, δ_C, ppm: 61.6, 123.9, 126.9, 128.9, 131.8, 138.2, 146.2 Found, %: C 39.91, H 2.60, N 10.33. $C_9H_7IN_2$. Calculated, %. C 40.02, H 2.62, N 10.37.

1-(*p*-Chlorophenyl)-4-iodo-3-methyl-5-phenyl pyrazole (4). Yield 88%, mp 138–139°C. ^{13}C NMR spectrum, δ_C, ppm: 14.1, 63.2, 115.9, 121.6, 123.9, 127.4, 128.4, 129.0, 131.8, 137.6, 143.9, 148.4. Found, %: C 48.72, H 3.1, N 7.03. $C_{16}H_{12}IN_2Cl$. Calculated, %. C 48.69, H 3.07, N 7.09.

3-Ethoxy-4-iodo-5-methyl-1*H*-pyrazole (5). Yield 92%, mp 105–107°C. ^{13}C NMR spectrum, δ_C, ppm: 13.5, 14.5, 55.4, 63.7, 145.2, 164.2. Found, %: C 28.48, H 3.51, N 11.05. $C_6H_9IN_2O$. Calculated, %. C 28.59, H 3.60, N 11.11.

3-(4-Amino phenyl)-4-iodo-1*H*-pyrazole (6). Yellow oil, yield 90%. ^{13}C NMR spectrum, δ_C, ppm: 58.2, 113.8, 125.6, 126.7, 140.3, 142.4, 148.8. Found, %: C 38.12, H 2.87, N 14.68. $C_9H_8IN_3$. Calculated, %. C 37.92, H 2.83, N 14.73.

3-(4-Carboxy phenyl)-4-iodo-1*H*-pyrazole (8). Yield 85%, mp 190–192°C. ^{13}C NMR spectrum, δ_C, ppm: 58.3, 130.5, 131.7, 135.1, 135.9, 141.0, 149.9, 161.5. Found, %: C 38.51, H 2.21, N 8.64. $C_{10}H_7IN_2O_2$. Calculated, %: C 38.24, H 2.25, N 8.92.

5-Carbaldehyde-4-iodo-1*H*-pyrazole (9). Yield 88%, mp 134–1365°C. ^{13}C NMR spectrum, δ_C, ppm: 57.3, 143.5, 154.0, 169.1. Found, %: C 21.46, H 1.33, N 12.58. $C_4H_3IN_2O$. Calculated, %: C 21.64, H 1.37, N 12.61.

CONCLUSIONS

We have developed a facile process of synthesis of iodopyrazole by the reaction of pyrazoles with iodine using *n*-butyltriphenylphosphonium peroxodisulfate as an oxidant at room temperature.

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