Pergamon

Tetrahedron Letters 42 (2001) 863–865

TETRAHEDRON LETTERS

A mild and efficient method for the regioselective iodination of pyrazoles

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Received 17 July 2000; accepted 10 November 2000

Abstract—The iodination of *N*-H or *N*-benzylpyrazoles using elemental iodine in the presence of CAN as the in situ oxidant is a mild and efficient method to prepare 4-iodopyrazoles containing even electron-withdrawing substituents. The reaction is regioselective since the iodine atom preferred pyrazole instead of the benzyl group, and the 4-pyrazolic position instead of other possible positions in the heterocycle.

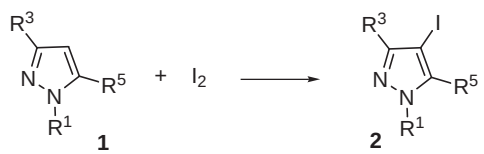
1. Introduction

Since Sugiyama demonstrated in 1981 that ceric ammonium nitrate [ammonium hexanitratocerate (IV): CAN] and iodine can iodinate benzenoid aromatics,[1] this method has been used for the iodination of some aromatic and heteroaromatic compounds (e.g. uracil nucleosides[2]). However, to our knowledge, there is no published work about CAN-mediated iodination of pyrazoles.

4-Iodopyrazoles are valuable starting products in the synthesis of biologically active compounds.[3,4] They have been used in cross-coupling reactions with terminal acetylenes,[4,5] organotin aryl derivatives,[6] or aryl boronic acids.[7] In addition, halogen-metal exchange is an attractive route to enter electrophiles in the position 4 of the pyrazolic nucleus, not always accessible by direct metalation.[8,9]

Although there are reports on the iodination of pyrazoles, it presents rather complicated problems.[10] The iodine–iodide method (I_2, KI)[11–13] and the more reactive iodine monochloride (ICl)[8,14] have been applied to pyrazoles with alkyl- or electron-donating groups, but have as a disadvantage the use of large quantities of reactants. The iodine–ammonium hydroxide combination has been used in *N*-alkylated pyrazoles, but it gave mixtures of 3,4-diiodo- and 3,4,5-triiodopyrazoles.[15] The oxidative iodination using I_2–HIO_3 has been applied to 1-methylpyrazoles with electron-withdrawing substituents, also yielding diiodinate derivatives.[16]

Continuing with our work on biologically active pyrazoles that showed muscarinic properties[17,18] or selective complexation of neurotransmitters,[19,20] we are now interested in the regioselective iodination of the 4-pyrazolic position as a way to obtain 4-functionalized derivatives. In this work, we report our findings concerning the oxidative iodination of *N*-H or *N*-substituted pyrazoles using elemental iodine in the presence of CAN as the in situ oxidant. This constitutes a mild and efficient method to prepare 4-iodopyrazoles containing even electron-withdrawing substituents.



a, R^1 = H; R^3 = OMe; R^5 = Me
b, R^1 = H; R^3 = R^5 = Me
c, R^1 = H; R^3 = R^5 = CO_2Et
d, R^1 = R^3 = R^5 = H
e, R^1 = R^5 = H; R^3 = Me
f, R^1 = CH_2Ph; R^3 = R^5 = H
g, R^1 = CH_2Ph; R^3 = R^5 = Me

Scheme 1.

Keywords: pyrazole; iodination; ceric ammonium nitrate; regioselectivity.

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† This paper comprises a part of Isabel Dorronsoro's PhD Thesis.

0040-4039/01/$ - see front matter
PII: S0040-4039(00)02136-5

Table 1. Reactions of pyrazoles **1(a–g)** with iodine

Starting pyrazole	Method	Reaction conditions	Product (% yield)
1a	A	Reflux, 24 h	**2a** (80)
1b	A	Reflux, 48 h	**2b** (55)
1c	A	Reflux, 72 h	**2c** (0)
1b	B	Rt, 3 h	**2b** (93)
1c	B	Reflux, 6 h	**2c** (80)
1d	B	Rt, 3 h	**2d** (98)
1e	B	Rt, 3 h	**2e** (90)
1f	B	Rt, 4 h	**2f** (79)
1g	B	Rt, 6 h	**2g** (80)

Method A: $2I_2$, 6NaI, $2CH_3CO_2Na$, H_2O.
Method B: $0.6I_2$, 0.5CAN, CH_3CN.

2. Results and discussion

Preliminary experiments have been carried out using the classical iodine–iodide method, using 2 equiv. of iodine, 6 equiv. of sodium iodide and 2 equiv. of sodium acetate in water to reflux for 24–48 h (Scheme 1). Under these conditions (Table 1, method A), the iodination reaction afforded good yields only with activated pyrazoles (e.g. 4-iodo-3-methoxy-5-methylpyrazole **2a**, 80% yield), but it provided poor yields with pyrazoles bearing alkyl groups (e.g. 3,5-dimethyl-4-iodopyrazole **2b**, 55%), and it failed completely with pyrazoles with electron-withdrawing substituents [e.g. 3,5-bis(ethoxycarbonyl)-4-iodopyrazole **2c**, 0% yield].

In contrast, the treatment of the starting pyrazoles **1b**,**c** with 0.6 molar equivalents of iodine in the presence of 0.5 molar equivalents of CAN in acetonitrile for 3 h at room temperature (**1b**) or at reflux (**1c**) afforded the corresponding 4-iodopyrazoles in excellent yields (Table 1, method B), even with electron-withdrawing substituents in the pyrazolic nucleus. This iodination method (I_2–CAN) proceeded with better yields, in shorter time, and under milder conditions than the iodine–iodide mixture. It is worth mentioning that in the I_2–CAN method 0.6 mol of iodine per mol of substrate is enough to complete the reaction, in contrast to the iodine–iodide procedure, where one-half of part of the iodine is discarded.

In order to explore the scope of the I_2–CAN iodination method, other *N*-H and *N*-benzylpyrazoles (**1d–g**) were subjected to this procedure, obtaining the corresponding 4-iodopyrazole (**2d–g**) in good yields (see Table 1). There are some remarkable features in the CAN-mediated iodination of pyrazoles. In every case, only a monoiodinated product was obtained, in contrast to other reported methods.[15,16] In addition, the iodination was found to be regioselective since the iodine atom preferred pyrazole instead of the benzyl group, and the 4-pyrazolic position instead of other possible positions in the heterocycle. This iodination method only failed when 3-nitro-4-ethoxycarbonylpyrazole was used as starting material, due to the presence of a substituent in the 4-position of the pyrazolic nucleus.

In the final products (**2a–g**) the position of iodination was established by comparison of their ^{13}C NMR signals with those of the starting pyrazoles (Table 2), since it is known that the iodine atom causes a large upfield shift of the carbon directly bounded to it.[21,22] In all cases, only the signal of pyrazolic C-4 suffered an upfield shift of 42–49 ppm, confirming that the iodine atom only went to position 4 of the pyrazole system.

Typical experimental procedure for method B: A mixture of pyrazole (1 mmol), iodine (0.6 mmol) and CAN (0.6 mmol) in 10 mL of anhydrous acetonitriline was stirred at room temperature until a TLC control showed that the starting pyrazole had disappeared (1–3 h). The diester **1c** needed more drastic conditions: reflux, 3 h. Then, the solvent was evaporated under reduced pressure and the resulting residue was dissolved in 25 mL of ethyl acetate. The organic solution was washed with 25 mL of an ice-cold aqueous solution of $NaHSO_3$ (5%), then with 25 mL of saturated solution of NaCl, and finally dried over Na_2SO_4 and evaporated to dryness. Products were purified on silica gel using flash column chromatography and their microanalytical data are summarized in Table 3.

Table 2. ^{13}C NMR chemical shifts ($CDCl_3$, δ, ppm) of starting pyrazoles (**1**) and their 4-iodinated derivatives (**2**)

No.	C3	C4	C5	Other carbon atoms	Compare Ref.
1a	164.3	88.5	141.0	56.2; 11.2	–
2a	163.4	45.3	142.9	56.4; 11.9	–
1b	145.3	104.8	145.3	12.8	21
2b	146.1	62.6	146.1	13.5	–
1c	140.0	111.3	140.0	160.5; 61.6; 14.2	23
2c	141.9	66.3	141.9	161.4; 60.9; 15.0	–
1d	133.5	104.7	133.5		21
2d	138.8	56.6	138.8		–
1e	142.8	104.1	134.5	11.7	21
2e	146.0	60.4	140.2	13.2	–
1f	139.0	105.5	128.8	136.4; 128.3; 127.5; 127.2; 55.4	22
2f	144.5	56.3	133.5	135.8; 128.8; 128.2; 127.8; 56.4	22
1g	147.5	105.5	139.1	137.3; 128.6; 127.3; 126.5; 52.5; 13.5; 11.0	–
2g	149.3	63.2	140.6	136.6; 128.7; 127.6; 126.6; 54.0; 14.0; 12.0	–

Table 3. Microanalytical data of prepared 4-iodopyrazoles

No.	Formula (MW)	Calcd			Found		
		C (%)	H (%)	N (%)	C (%)	H (%)	N (%)
2a	$C_5H_7IN_2O$ (238.03)	25.23	2.96	11.77	25.42	3.10	11.63
2b	$C_5H_7IN_2$ (222.03)	27.05	3.18	12.62	26.85	3.01	12.45
2c	$C_9H_{11}IN_2O_4$ (338.10)	31.97	3.28	8.29	31.67	3.09	7.97
2d	$C_3H_3IN_2$ (193.97)	18.58	1.56	14.44	18.22	1.28	14.39
2e	$C_4H_5IN_2$ (208.00)	23.10	2.42	13.47	23.01	2.14	13.29
2f	$C_{10}H_9IN_2$ (284.10)	42.28	3.19	9.86	42.34	3.08	9.54
2g	$C_{12}H_{13}IN_2$ (312.15)	46.17	4.20	8.97	46.30	4.15	8.61

Acknowledgements

The authors gratefully acknowledge the financial supports of C.I.C.Y.T. (SAF 99-098) and Comunidad de Madrid (08.5/0045.1/99) and the fellowship to one of us (I.D.) from the Fundación Ramón Areces. We also thank Mr. E. Barbero for technical assistance by the microanalysis.

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