Synthesis of 4-iodopyrazoles: A Brief Review

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Abstract: The selective incorporation of halogen into organic molecules provides a challenge to academic and industrial research. This microreview presents an overview of the available methodologies for the synthesis of 4-iodopyrazoles, valuable precursors for the selective construction of highly functionalized organic molecules of synthetic and biological importance.

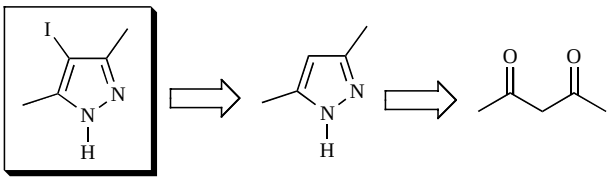
Keywords: Pyrazoles, 4-iodopyrazoles, heterocycles, green chemistry.

I. INTRODUCTION

Pyrazoles exhibit a variety of pharmacological properties, including anti-hyperglycemic, analgesic, antiinflammatory, anti-pyretic, anti-bacterial, hypoglycemic and sedative-hypnotic activities [1]. Recently, several pyrazole derivatives were reported to have non-nucleoside HIV-1 reverse transcriptase inhibitory activity [2]. Extensive studies have been devoted to pyrazole derivatives such as celecoxib, the well-known cyclooxygenase-2 inhibitor [3a]. In particular, 4-iodopyrazoles (Fig. **1**) are key substructures for the synthesis of a large variety of compounds with important biological activities [3b].

Halopyrazoles are capable of undergoing transition-metal-catalyzed cross-coupling reactions, such as the Heck reaction [4], Sonogashira reaction [5], Suzuki reaction [6] and other important reactions [7]. In view of the importance of 4-iodopyrazoles in organic synthesis, the aim of this review is to highlight recent methodologies for the iodination of pyrazoles.

In general, pyrazoles are produced synthetically through the reaction of 1,3-diketones with hydrazine. Quite simply, double condensation of a 1,3-diketone, or synthetic equivalent, with a hydrazine produces the aromatic pyrazole directly (Fig. **1**). Electrophilic substitutions with carbon electrophiles such as in Friedel-Crafts processes, are virtually unknown in azole chemistry. Electrophilic substitution takes place normally at C-4 of the pyrazole nucleus [8]. Under special conditions, reaction of pyrazoles with appropriate reagents leads to iodopyrazoles. In particular, 4-iodopyrazoles have been extensively applied in synthetic organic chemistry [7]. We report here a brief review of the preparation of 4-iodopyrazoles.



4-iodo-3,5-dimetylpyrazole

Fig. (1).

II. CONVENTIONAL SYNTHETIC APPROACHES FOR THE PREPARATION OF 4-IODOPYRAZOLES

In 1988, Ohsawa and co-authors reported the preparation of 4-iodo-1,3,5-trimethyl pyrazole from 1,3,5-trimethylpyrazole using iodine monochloride in methylene chloride [9], (Scheme **1**).

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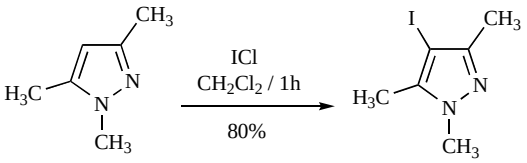
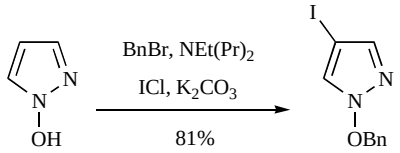


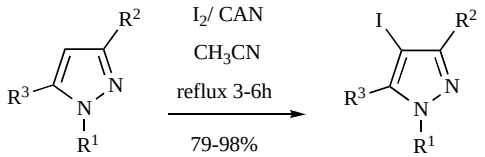
Scheme 1. Iodination of 3,5-dimethylpyrazole using ICl.

Vedsø and co-workers proposed the synthesis of 1-(benzyloxy)-4-iodopyrazole by benzylation of 1-hydroxypyrazole followed by iodination of crude 1-(benzyloxy)pyrazole in 81% yield, using 3 equivalents of iodine monochloride (Scheme **2**) [10].



Scheme 2. Iodination and benzylation of 1-(hydroxy)pyrazole using ICl and benzyl bromide.

Rodriguez-Franco and co-workers reported an alternative synthesis of 4-iodo alkylpyrazoles via the reaction of alkyl pyrazoles of interest with iodine and CAN [ammonium hexanitratocerium(IV)] in acetonitrile under reflux for 3-6 hours. After extraction, the products were purified on silica gel using flash column chromatography. The isolated 4-iodopyrazoles were obtained in satisfactory yields, 79-98% (Scheme **3,** Table **1**). In the same work, another alternative for the synthesis of 4-iodopyrazoles employing a mixture of I_2/ NaI and CH_3COONa in water was reported [11]. Using the I_2/CAN procedure for iodination of pyrazoles, Casida and co-workers synthesized compounds analogous to Fipronil. Fipronil is the most important example of the phenylpyrazole or fiprole insecticides [12].



Scheme 3. Iodination of pyrazoles via CAN and I_2.

In recent years, solid supports have received special attention due to the enhanced selectivity, milder reaction conditions, and the ease of manipulation typical of these supported reagents. The combined reagent of iodobenzene diacetate plus iodine was used as an alternative iodinating agent for conversion of pyrazoles to the corresponding 4-iodopyrazole derivatives at room temperature [13]. The 4-iodopyrazoles were isolated in good yields (Scheme **4**, Table

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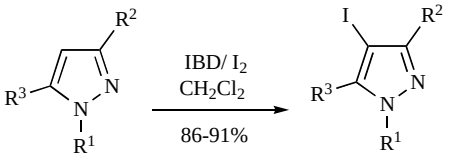
Table 1. Iodination of Pyrazoles via I_2/NaI or I_2/CAN [12]

Entry	R^1	R^2	R^3	Time (t, h)	Yield[a](%)
1[b]	H	OCH_3	CH_3	24	80
2[b]	H	CH_3	CH_3	48	55
3[c]	H	CH_3	CH_3	3	93
4[c]	H	H	H	3	98
5[c]	H	H	CH_3	3	90
6[c]	CH_2Ph	H	H	4	79
7[c]	CH_2Ph	CH_3	CH_3	6	80

[a]Isolated yields of 4-iodopyrazole derivatives
[b] Method: $2I_2$, 6NaI, $2CH_3CO_2Na$, H_2O.
[C] Method: $0.6I_2$, 0.5CAN, CH_3CN.



IBD = iodobenzene diacetate - $PhI(OAc)_2$

Scheme 4. Iodination of pyrazoles via iodobenzene diacetate.

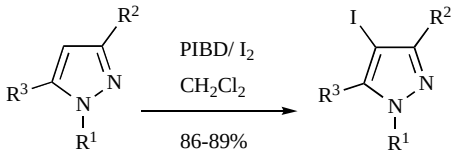
The use of water as solvent in organic synthesis has been extensively studied [14-15], with applications in many organic reactions. Recently, Katzenellenbogen and co-workers [7] prepared 1,3-diaryl-4-iodo-pyrazoles by the reaction of 1,3-diarylpyrazoles with KI/I_2 in sodium acetate (Scheme **6,** Table **3**).

In 1956, Larsen and co-workers first reported the use of potassium dichloroiodate ($KICl_2$) as an iodinating agent [16] for aromatic molecules. More recently, the synthesis was improved and the scope of this reaction extended to hydroxyquinoline, imidazoles and

Table 2. Iodination of Pyrazoles via IBD, PIBD and Recycled Resin [13]

Entry	R^1	R^2	R^3	Time (t, min)	Yield[a] (%)
1[a]	H	CH_3	CH_3	15	90
2[a]	H	CH_3	C_6H_5	20	88
3[a]	H	C_6H_5	C_6H_5	15	91
4[a]	C_6H_5	C_6H_5	C_6H_5	20	86
5[a]	2,4-$(NO_2)_2$ C_6H_3	CH_3	CH_3	30	90
6[a]	*p*-ClC_6H_4	CH_3	C_6H_5	30	91
7[b]	H	CH_3	CH_3	25	87
8[b]	H	CH_3	C_6H_5	30	87
9[b]	H	C_6H_5	C_6H_5	30	89
10[b]	C_6H_5	C_6H_5	C_6H_5	30	86
11[b]	2,4-$(NO_2)_2$ C_6H_3	CH_3	CH_3	40	87
12[b]	*p*-ClC_6H_4	CH_3	C_6H_5	35	89
13[c]	*p*-ClC_6H_4	CH_3	C_6H_5	40	87

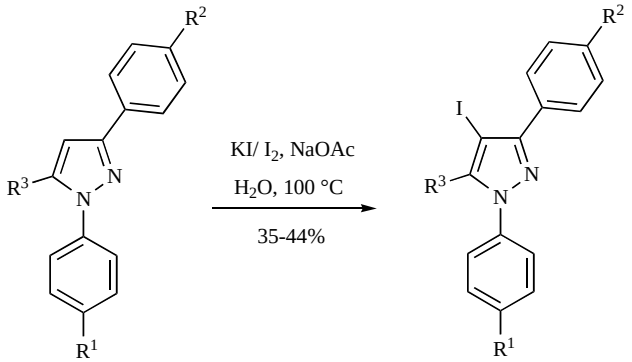
[a] Isolated yields of 4-iodo pyrazole derivatives, employing iodobenzene diacetate
[b] Isolated yields of 4-iodo pyrazole derivatives, employing polymer-supported iodobenzene diacetate
[c] Isolated yields of 4-iodo pyrazole derivatives, employing recycled resin



PIBD = polymer-supported iodobenzene diacetate

Scheme 5. Iodination of pyrazoles via polymer-supported iodobenzene diacetate (PIBD) and I_2.

2). These same authors [13] also described the preparation of 4-iodopyrazoles using polymer-supported iodobenzene diacetate (PIBD) with short reaction times and good yields (Scheme **5**, Table **2**). The regenerated resin was used to repeat the reaction with no loss of activity. After removal of the solvent, the products were recrystallized from ethanol or water.



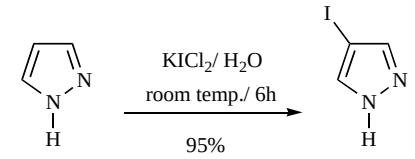
Scheme 6. Iodination of aryl pyrazoles via KI/I_2 and NaOAc.

1-*H*-pyrazole [17]. The conversion of 1-*H*-pyrazole to 4-iodo-1-*H*-pyrazole required 6 hours of reaction (Scheme **7**).

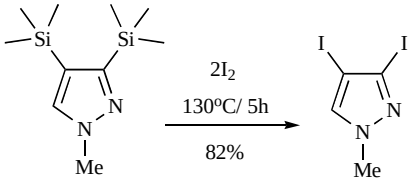
Table 3. Iodination of 1,3-via KI/I_2 and NaOAc in Water [7]

Entry	R^1	R^2	R^3	Time (t, h)	Yield[a] (%)
1	OMe	OMe	Et	3	87
2	OMe	H	Pr	3	85
3	OMe	H	Et	3	83
4	H	H	Et	3	74

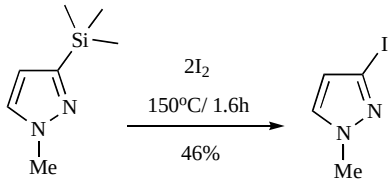
[a]Isolated yields based on iodo-pyrazole derivatives



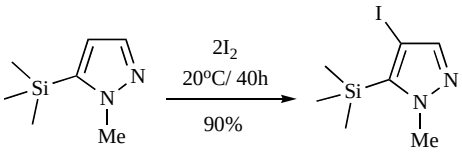
Scheme 7. Iodination of pyrazole via $KICl_2$ in water.



Scheme 8. Reaction of 3,4-Bis(trimethylsilyl)-1-methylpyrazole with I_2.



Scheme 9. Reaction of 3-(trimethylsilyl)-1-methylpyrazole with I_2.



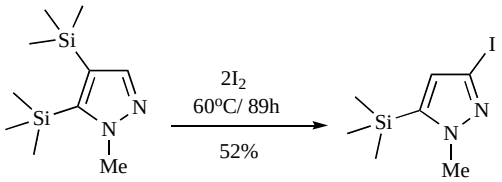
Scheme 10. Reaction of 5-(trimethylsilyl)-1-methylpyrazole with I_2.

C-Silyl azoles undergo substitution of the *C*-silyl groups with electrophilic reagents making silylazoles synthetic equivalents of organometallic derivatives [18]. Effenberger and Krebs published extensive studies of halo- and carbodesilylation of (trimethylsilyl)-1-methylpyrazoles [19]. The authors showed the synthesis of 4,5-diiodo-1-methylpyrazole via the reaction of 3,4-Bis(trimethylsilyl)-1-methylpyrazole with iodine (Scheme **8**) [19].

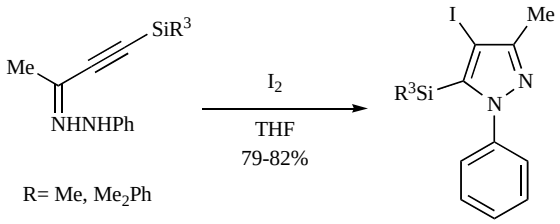
Although 3-(trimethylsilyl)-1-methylpyrazole reacts with iodine to give 3-iodo-1-methylpyrazole in moderate yield (46%) (Scheme **9**), the reaction of 5-(trimethylsilyl)-1-methylpyrazole with iodine results in 4-methyl-5-(trimethylsilyl)-1-methylpyrazole in good yield (90%) (Scheme **10**) [19].

The reaction of 4,5-bis(trimethylsilyl)-1-methylpyrazole with iodine results in iododesilylation, furnishing 3-iodo-5-(trimethylsilyl)-1-methylpyrazole. After a reaction time of 89 hours (Scheme **11**) [19].

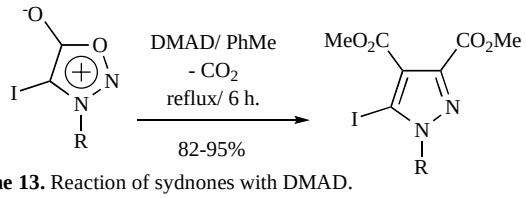
Cuadrado and co-workers described important studies utilizing silyl azoles. These authors reported the one-pot synthesis of 4-iodo-5-silylpyrazoles in good yield (79-82%) [20], based on the reaction of silyl hydrazones with I_2 in THF (Scheme **12**).



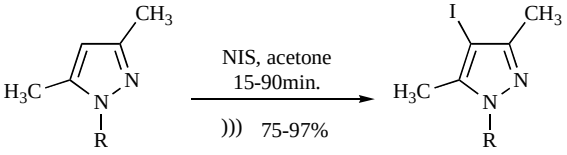
Scheme 11. Reaction of 4,5-Bis(trimethylsilyl)-1-methylpyrazole with I_2.



Scheme 12. One-pot synthesis of 4-iodo-5-silylpyrazoles.



Scheme 13. Reaction of sydnones with DMAD.



Scheme 14. Iodination of 3,5-dimethylpyrazole by sonochemistry using NIS.

The transformation of sydnones into pyrazoles by 1,3-dipolar cycloaddition reactions with acetylenic esters has been studied by Huisgen and co-workers [21]. The synthesis of 5-iodopyrazoles by direct iodination of sydnones with ICl [22] and posterior treatment with dimethyl acetylenedicarboxylate (DMAD) has also been reported (Scheme **13**).

III. ULTRASOUND- AND MICROWAVE-ASSISTED SYNTHESIS OF 4-IODOPYRAZOLES

Recently, we described the synthesis of a variety of compounds under non-traditional conditions employing microwaves [23-25] and sonochemistry [26-29]. The beneficial effects of ultrasonic irradiation are playing an increasing role in process chemistry [30-31], especially in cases where classical methods require drastic conditions or prolonged reaction times. When the process involves sensitive reagents or there is the possibility of decomposition under prolonged reaction conditions, ultrasound also has advantages. The potential of ultrasonic irradiation to decrease reaction times and

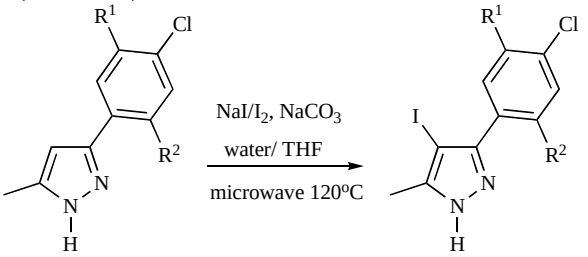
Table 4. Iodination of Pyrazoles via NIS and Sonochemistry

		Sonochemistry [32]		Conventional Method [Lit.]	
Entry	**R**	**Time (min)**	**Yield**	**Time (h)**	**Yield**
1	H	20	85	48	55 [11]
2	Me	15	75	1	80 [9]
3	Ph	60	92	48	[33][a]
4[b]	*p*-$NO_2C_6H_4$	20	76	-	-
5[b]	C_6F_5	90	97	-	-

[a] The yield was not reported
[b] Literature [32]

improve yields has been demonstrated [30-31]. As part of our work in this area, we reported the convenient C-4 iodination of 3,5-dimethylpyrazoles using *N*-iodosuccinimide under ultrasonic irradiation in good yields (75-97%) with short reaction times (15-90 minutes) in the absence of catalyst or without using toxic reagents like ICl (Scheme **14,** Table **4**) [32]. In addition, halogenation of 3,5-dimethylpyrazole on a larger scale (20 mmol) furnished the corresponding product in good yield (70-82%) under the same reaction conditions. The important aspect of this reaction procedure is the work-up, in which treatment with aqueous $Na_2S_2O_3$ was found to give the 4-iodopyrazole products without the necessity of further purification [32].

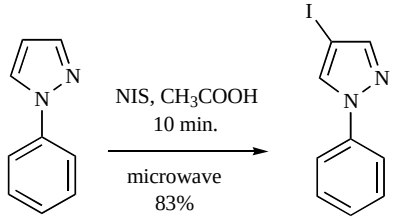
Microwave irradiation offers a considerable advantage over conventional heating because it results in substantial rate enchancements for a wide range of organic reactions. Cleaner reactions are also commonly achieved, together with improvements in yield and selectivity. The increasing demand for clean and "green" chemical syntheses has resulted in increased use of microwave irradiation [34,35]. Cheung and co-workers reported the preparation of 3-aryl-4-iodopyrazoles [36] via the microwave-promoted reaction with sodium iodide, sodium carbonate and iodine in aqueous THF (Scheme **15**).



R^1= OH, R^2= H
R^1= H , R^2= OH

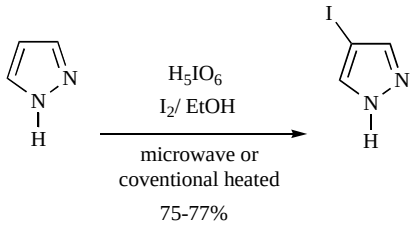
Scheme 15. Microwave-assisted iodination of 4-arylpyrazoles via NaI/I_2.

In a very recent publication, Li and co-workers demonstrated the use of microwave irradiation for the iodination of 1-phenylpyrazole by reaction with *N*-iodosuccinimide (NIS) in acid medium [37]. The product, 4-iodo-1-phenylpyrazole, was isolated in 83% yield after 10 minutes of reaction (Scheme **16**).



Scheme 16. Iodination of 1-phenylpyrazole with NIS in CH_3COOH under microwave irradiation.

Sosnowsk and Slulski reported a comparison of the microwave-accelerated and conventionally heated iodination reactions of several arenes and heterocycles with *ortho*-periodic acid (Scheme **17**). With conventional heating, 4-iodo-1-*H*-pyrazole was isolated after 30 minutes in 75 % yield. Under microwaves, the product was isolated after 7 minutes of irradiation in 77% yield [38].



Scheme 17. Iodination of 1-*H*-pyrazole via *ortho*-periodic acid and I_2.

IV. CONCLUSIONS

4-Iodopyrazoles are valuable precursors for the selective construction of highly functionalized organic molecules of high synthetic and biological importance. Currently available methodologies permit the synthesis of a wide variety of 4-iodopyrazoles using conventional iodination reagents such as ICl and polymer-supported iodobenzene diacetate. Of particular interest are recent studies reporting "green chemical" approaches to the synthesis of 4-iodopyrazoles that also furnish these compounds in good yield and purity with short reaction times, minimal work-up and the potential of rather simple scale-up.

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