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Synthesis of Some New 2-(3-Aryl-1-phenyl-4-pyrazolyl)-benzoxazoles Using Hypervalent Iodine Mediated Oxidative Cyclization of Schiff's Bases

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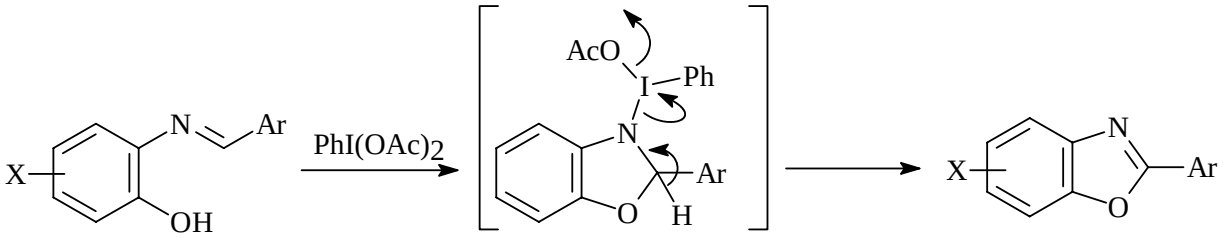
Abstract: Ten new 2-(3-aryl-1-phenyl-4-pyrazolyl)benzoxazoles have been synthesized by oxidative intramolecular cyclization of the corresponding Schiff's bases using iodobenzene diacetate in methanol as an oxidant.

Keywords: Hypervalent iodine; Iodobenzene diacetate; Schiff's base; Oxidation; Benzoxazoles.

Introduction

In connection with our ongoing programme directed towards the use of organoiodine(III) compounds as unique reagents in organic synthesis [1-2], we have recently reported that oxidation of phenolic Schiff's bases (SBs) with iodobenzene diacetate (IBD) leads to facile intramolecular cyclization, thus providing an efficient synthesis of 2-substituted benzoxazoles (Scheme 1) [3]. This observation, coupled with the fact that benzoxazoles [4] and pyrazoles [5] are often associated with important biological properties, prompted us to extend the scope of this iodine(III) mediated approach to the synthesis of some new 2-(3-aryl-1-phenyl-4-pyrazolyl)benzoxazoles **4aa-4be**.

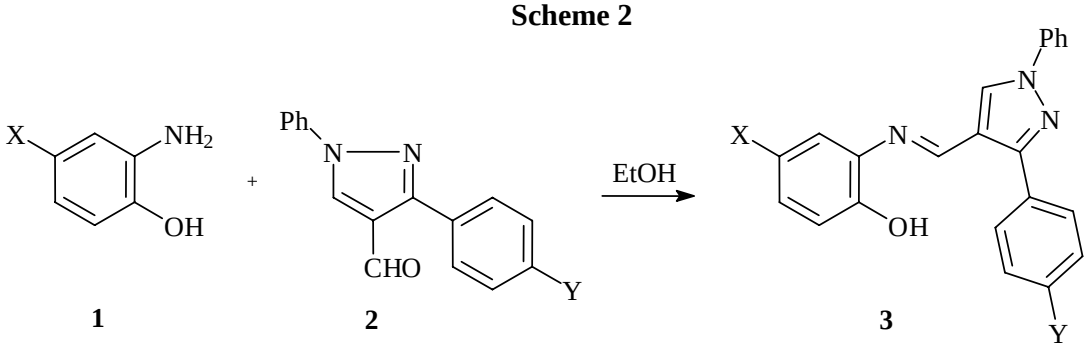
Scheme 1

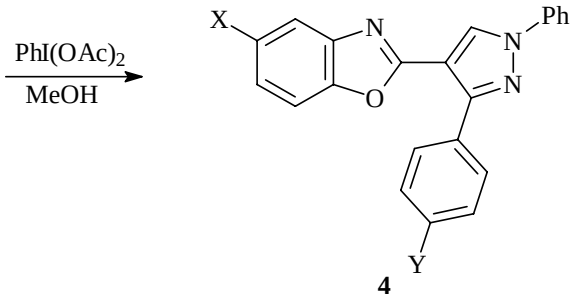


Results and Discussion

First we prepared Schiff's base **3aa** by the condensation of *o*-aminophenol (**1a**) with 4-formyl-1,3-diphenylpyrazole (**2a**). Then, oxidation of **3aa** was tried using our previously reported procedure involving 1.1 equivalents of IBD in dichloromethane. The reaction occurred readily, but the yield of the expected product **4aa** was not good (only 24%). Interestingly, using methanol as a solvent in this reaction, compound **4aa** was obtained in noticeably improved yield (60%). In order to study the scope of this approach, other Schiff's bases **3aa-3be**, available by the condensation of **1a** or **1b** with different formylpyrazoles **2a-e**, were subjected to oxidative cyclization using 1.1 equivalents of IBD in methanol. The reaction, indeed, afforded the desired benzoxazole derivatives **4aa-4be** in yields ranging from 55% to 88% (Scheme 2, Table 1).

Scheme 2



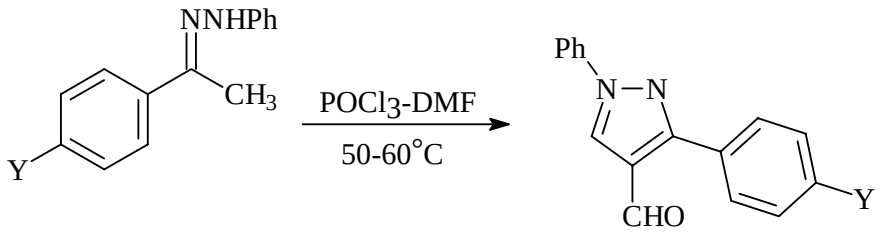


1	X	2	Y	3, 4	X	Y
a	H	**a**	H	**aa**	H	H
b	Cl	**b**	Cl	**ab**	H	Cl
		c	OMe	**ac**	H	OMe
		d	Me	**ad**	H	Me
		e	NO_2	**ae**	H	NO_2
				ba	Cl	H
				bb	Cl	Cl
				bc	Cl	OMe
				bd	Cl	Me
				be	Cl	NO_2

The formylpyrazoles **2a-e** needed in this study were prepared by Vilsmeier-Haack reaction of acetophenone phenylhydrazones (Scheme 3) [6]. The formylpyrazoles **2a** and **2e** are known compounds [6] and were identified by comparison of their melting points with those reported in the literature. The products **2b**-**2d** are new compounds and were characterized by their spectral data.

The products **3aa**-**3be** and **4aa**-**4be** are also all new compounds and their structures were established by spectral and elemental analysis data. Schiff's bases **3aa**-**3be** were characterized by the absence of the 1674 cm^{-1}(C=O stretch) signal and presence of a broad weak signal at 3360 cm^{-1}(O-H stretch) in their IR spectra. A distinctive feature of their ^{1}H-NMR spectra was presence of two singlets between 8.3 δ- 8.8 δ corresponding to the C_5-**H** and C**H**=N protons (Table 2). The intramolecular cyclization of Schiff's bases to 2-(3-aryl-1-phenyl-4-pyrazolyl)benzoxazoles **4aa**-**4be** was characterized by the disapperance of the 3360 cm^{-1} (O-H stretch) signal in the IR spectra, a downfield shift of the C_5-**H** proton as a result of the cyclization and the disappearance of the C**H**=N proton signal in the corresponding ^{1}H-NMR spectra (Table 2).

Scheme 3



2

Conclusions

In summary, the synthesis of new pyrazolylbenzoxazoles reported in this study provides a novel example of an attractive and effective iodine(III) mediated heterocyclic synthesis. The organoiodine (III) mediated approach described is preferred over the existing methods because of the less toxic nature of these reagents compared to other oxidants previously used in this type of transformation, namely, lead tetraacetate [7], nickel peroxide [8], copper (I) chloride in the presence of dioxygen [9], which are highly toxic.

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Experimental

General

All reagents were purchased from commercial sources and were used without further purification. Melting points were taken in open capillaries and are uncorrected. ^{1}H-NMR spectra were recorded on a

Bruker 300 MHz instrument using TMS as an internal standard. IR spectra were recorded on a Buck Scientific IR M-500 spectrophotometer. Yields, physical properties (m.p.) and spectroscopic data of the prepared compounds are summarized in Tables 1 and 2.

General Method for the Preparation of 3-Aryl-4-formyl-1-phenylpyrazoles **2a-e**:

The appropriate acetophenone phenylhydrazone (15 mmol) was added to a cold solution of dimethylformamide (25 mL) and phosphorus oxychloride (5 mL), and the resulting mixture was stirred at 50-60 °C for 5-6 hrs, then cooled to room temperature and poured into ice-cold water. A saturated solution of sodium bicarbonate was added to neutralize the mixture and thus give formylpyrazoles **2a-e**, which were isolated by filtration, followed by washing with water. **2a:** M.p. 137-138 °C, (Lit. [6] m.p. 140 °C); **2b:** M.p. 110-113 °C, ^{1}H-NMR ($CDCl_3$) δ: 6.9- 7.2 (m, 9 H, aromatic protons), 8.5 (s, 1H, C_5-H), 9.96 (s, 1H, CHO). IR (ν_{max}, KBr): 1674 cm^{-1} (C=O); **2c:** M.p. 100-102 °C, ^{1}H-NMR ($CDCl_3$) δ: 3.83 (s, 3 H, OCH_3), 6.7-7.1 (m, 9 H, aromatic protons), 8.46 (s, 1 H, C_5-H), 9.98 (s, 1 H, CHO). IR (ν_{max}, KBr): 1678 cm^{-1} (C=O); **2d:** M.p. 120-122 °C, ^{1}H-NMR ($CDCl_3$) δ: 1.5 (s, 3 H, CH_3), 6.8-7.6 (m, 9 H, aromatic protons), 8.57 (s, 1 H, C_5-H), 9.87 (s, 1 H, CHO). IR (ν_{max}, KBr): 1680 cm^{-1} (C=O); **2e:** 163-164 °C, (Lit. [6] m.p. 165 °C).

General Method for the Synthesis of Schiff's bases (SBs) **3aa-3be**:

SBs were prepared by refluxing a solution of the appropriate formylpyrazole **2a-e** (20 mmol) and *o*-aminophenol/*p*-chloro-*o*-aminophenol (**1a-b**, 30 mmol) in ethanol (100 mL) for 45-60 minutes. The solid product thus obtained was filtered off and recrystallised from ethanol. The physical and spectral data of the products are listed in Table 2.

General Method for the Synthesis of 2-(3-aryl-1-phenyl-4-pyrazolyl)benzoxazoles **4aa-4be** *from* **3aa-3be**:

To a solution of the appropriate Schiff's base **3aa-be** (10 mmol) in methanol (10 mL) was added IBD (11 mmol) and the mixture was stirred for 45-50 minutes at room temperature. The solid separated was filtered off and washed with methanol. The crude product thus obtained was recrystallized from ethanol. The physical and spectral data of the pure products are listed in Table 1.

Table 1. Physical and ^{1}H-NMR data of 2-(3-aryl-1-phenyl-4-pyrazolyl)benzoxazoles **4aa-4be**

Comp.[a]	m.p. (°C)	Yield[b] (%)	^{1}H-NMR (δ)
4aa	141-142	60	6.84-7.84 (m, 14 H, aromatic protons), 8.65 (s, 1 H, C_5-H)
4ab	186-187	81	7.34-8.05 (m, 13 H, aromatic protons), 8.74 (s, 1 H, C_5-H)
4ac	166-168	64	3.89 (s, 3 H, OCH_3), 7.02-7.99 (m, 13 H, aromatic protons), 8.71 (s, 1 H, C_5-H)
4ad	142-145	58	1.5 (s, 3 H, CH_3), 7.18-7.94 (m, 13 H, aromatic protons), 8.53 (s, 1 H, C_5-H)

Table 1. Cont.

Comp.[a]	m.p. (°C)	Yield[b] (%)	^{1}H-NMR (δ)
4ae	122-124	61	7.19-8.21 (m, 13 H, aromatic protons), 8.65 (s, 1 H, C_5-H)
4ba	137-139	73	7.22-7.92 (m, 13 H, aromatic protons), 8.65 (s, 1 H, C_5-H)
4bb	160-161	78	7.20-7.93 (m, 12H, aromatic protons), 8.63 (s, 1H, C_5-H)
4bc	128-129	72	3.83 (s, 3 H, OCH_3), 6.94-7.9 (m, 12 H, aromatic protons) 8.63 (s, 1 H, C_5-H)
4bd	148-150	55	1.5 (s, 3 H, CH_3), 6.81-7.93 (m, 12 H, aromatic protons), 8.65 (s, 1 H, C_5-H)
4be	240-242	76	*c*

[a] These are new products and their obtained elemental analyses (C, H, N) were satisfactory.

[b] Yields of isolated pure product based on the amount of Schiff's base employed.

[c] ^{1}H-NMR could not be recorded because of solubility problems.

Table 2. Physical and spectral data of Schiff's bases **3aa**-**3be**

Comp.[a]	m.p. (°C)	Yield[b] (%)	IR (O-H str cm^{-1})	^{1}H-NMR (δ)
3aa	143-144	76	3351	6.84-7.84 (m, 14 H, aromatic protons), 8.60 (s, 1 H, C_5-H), 8.73 (s, 1 H, HC=N)
3ab	142-143	72	3390	6.98-7.84 (m, 13 H, aromatic protons), 8.58 (s, 1 H, C_5-H), 8.69 (s, 1 H, HC=N)
3ac	146-147	81	3375	3.89 (s, 3 H, OCH_3), 7.02-7.99 (m, 13 H, aromatic protons), 8.58 (s, 1 H, C_5-H), 8.71 (s, 1 H, HC=N)
3ad	126-128	58	3348	1.5 (s, 3 H, CH_3), 7.18-7.94 (m, 13 H, aromatic protons), 8.42 (s, 1 H, C_5-H), 8.65 (s, 1 H, HC=N)
3ae	100-101	61	3345	7.19-8.21 (m, 13 H, aromatic protons), 8.52 (s, 1 H, C_5-H), 8.64 (s, 1 H, HC=N)
3ba	182-183	78	3360	6.89-7.77 (m, 13 H, aromatic protons), 8.52 (s, 1 H, C_5-H), 8.59 (s, 1 H, HC=N)
3bb	240-242	79	3359	7.20-7.93 (m, 12 H, aromatic protons), 8.54 (s, 1 H, C_5-H), 8.66 (s, 1 H, HC=N)
3bc	128-129	72	3372	3.83 (s, 3 H, OCH_3), 6.94-7.9 (m, 12 H, aromatic protons), 8.47 (s, 1 H, C_5-H), 8.59 (s, 1 H, HC=N)
3bd	160-162	55	3358	1.5 (s, 3 H, CH_3), 6.81-7.93 (m, 12 H, aromatic protons), 8.53 (s, 1 H, C_5-H), 8.62 (s, 1 H, HC=N)
3be	252-254	86	3414	*c*

[a] These are new products and their obtained elemental analyses (C, H, N) were satisfactory.

[b] Yields of Schiff's bases based on the amount of formylpyrazole used.

[c] ^{1}H-NMR could not be recorded due to poor solubility.

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Sample Availability: Samples available from the authors.