

Hypervalent iodine oxidation of 1-phenyl-3-arylpyrazole-4-carboxaldehyde oximes: a facile and efficient synthesis of new 3,4-bis(1-phenyl-3-arylpyrazolyl)-1,2,5-oxadiazole-*N*-oxides

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Abstract

Oxidation of pyrazole-4-carboxaldehyde oximes **2** with iodobenzene diacetate leads to dimerization of initially formed nitrile oxides, thereby offering an easy and efficient method for the synthesis of new 3,4-bis(1-phenyl-3-arylpyrazolyl)-1,2,5-oxadiazole-*N*-oxides (**4**).

Keywords: IBD, 3,4-bis(1-phenyl-3-arylpyrazolyl)-1,2,5-oxadiazole-*N*-oxide, pyrazole-4-carboxaldehyde oxime, oxidation, hypervalent iodine reagents

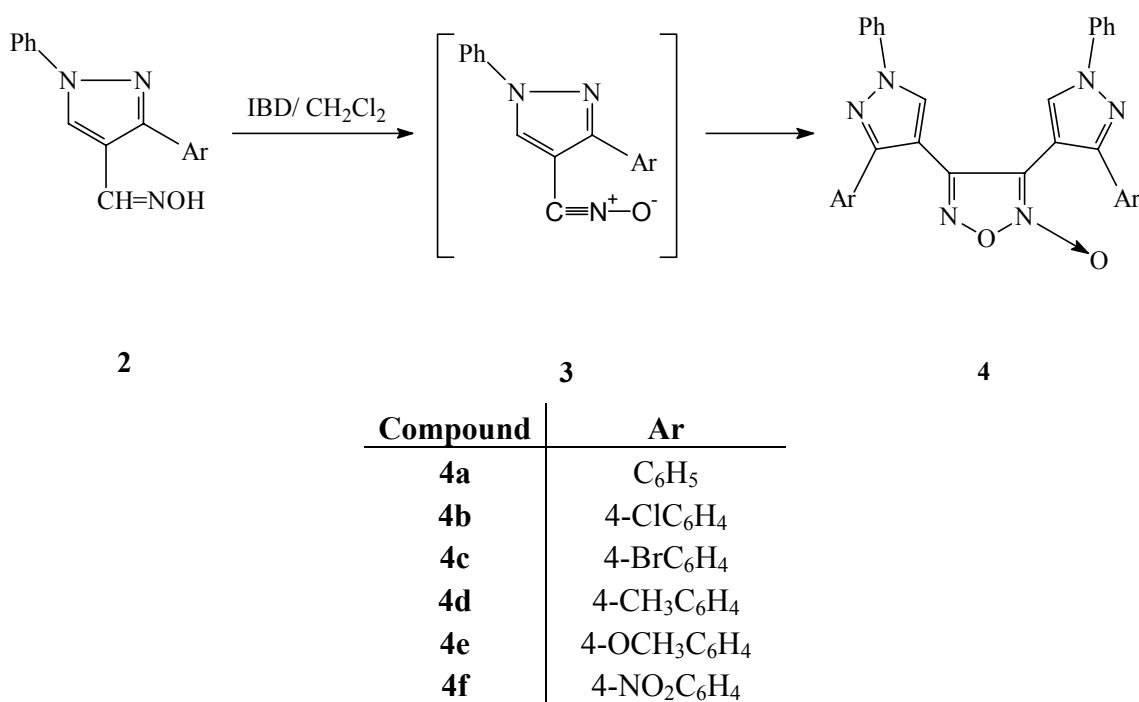
Introduction

Hypervalent iodine reagents¹ such as iodobenzene diacetate (IBD),² [hydroxy(tosyloxy)iodo]benzene (HTIB)³ and iodobenzene (IOB)⁴ have been extensively used in organic synthesis because of their low toxicity, ready availability and easy handling. Among the various applications of these reagents, one area of recent interest is the oxidative studies of 'N' containing compounds such as oximes, hydrazones and acid hydrazides, etc. While ketoximes,⁵ hydrazones⁶ and acid hydrazides⁷ undergo efficient oxidative cleavage to the parent ketone and acids/esters, I(III) mediated reactions of aldoximes offer an easy method for the formation of aromatic nitrile oxides which are valuable intermediates in organic synthesis.⁸

As part of our ongoing programme on the synthetic utility of organoiodine(III) reagents, we now undertook the reaction of some 4-pyrazolylaldoximes with IBD. The study is particularly aimed to: (i) determine whether aldoximes containing pyrazole moiety behave like aromatic aldoximes or differently with I(III) reagents and (ii) synthesise new pyrazole derivatives of potential biological interest.

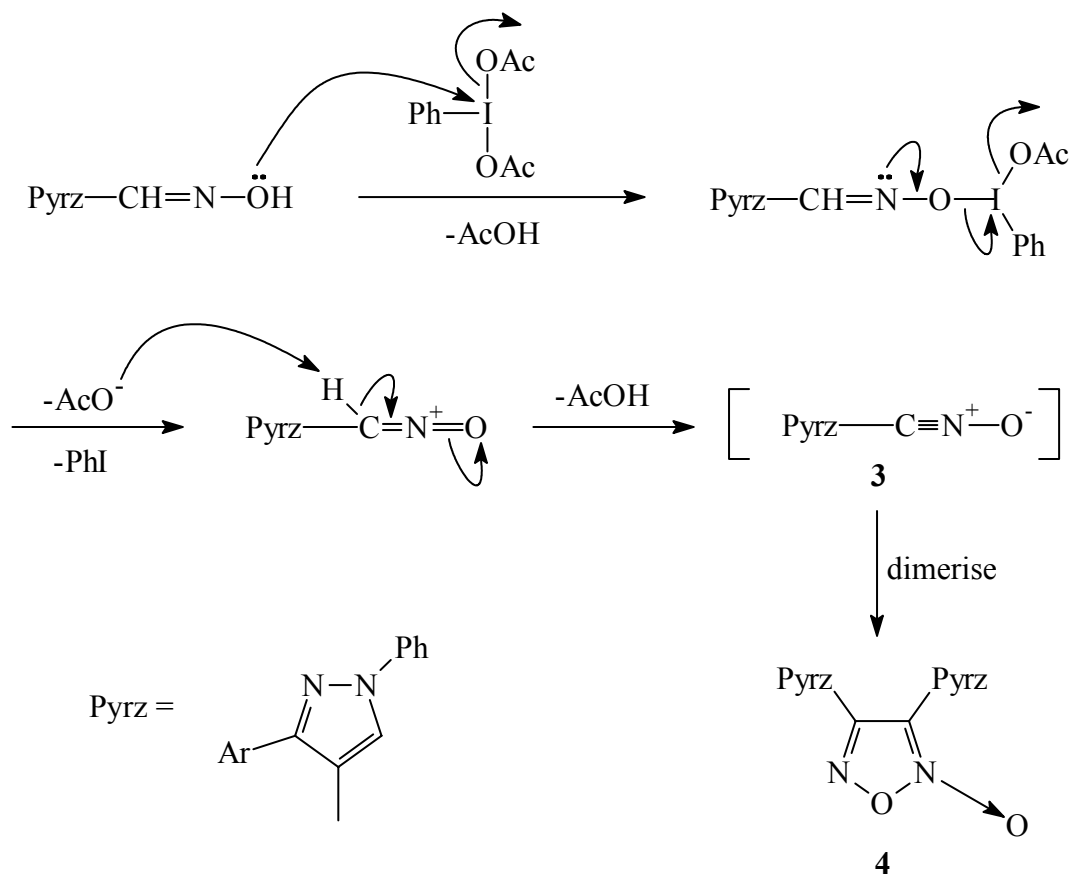
On the basis of literature reports concerning the reaction of aromatic aldoximes with oxidizing agents, namely lead tetraacetate,⁹ alkali hypohalite,⁸ *N*-bromosuccinimide in DMF,¹⁰ etc,¹¹⁻¹³ it was anticipated that oxidation of the pyrazolyl aldoximes **2** might afford either nitrile oxides **3** or their dimer oxadiazole-*N*-oxides **4**. Thus, 1,3-diphenylpyrazole-4-carboxaldehyde

oxime (**2a**) was treated with IBD (1.1 equivalents) in dichloromethane at room temperature. A rapid reaction occurred and a yellow solid product was separated out of the clear solution within 5 minutes (**Scheme 1**). There was no characteristic peak of $C\equiv N$ in IR spectrum and 1H NMR data was also not in accordance with structure **3**. Further analysis of the spectral and elemental analytical data concluded that the product obtained from this reaction was 3,4-bis(1,3-diphenylpyrazolyl)-1,2,5-oxadiazole-N-oxide (**4a**). The 1H NMR signals at δ 9.1 and δ 9.3 correspond to C5'-H of two pyrazole rings attached at C-3 and C-4 of oxadiazole ring system, in oxime **2** the C5'-H proton appeared at δ 8.9, the downfield shift of protons can be attributed to cyclization of $HC=NOH$ at C-4' to give oxadiazole **4**. In carbon spectrum (^{13}C NMR) peaks are observed at 111.6 (C-3) and 153.4 (C-4) ppm, which are characteristic of 1,2,5-oxadiazole ring.¹⁴ This observation clearly indicated that the initially formed N-oxides of the type **3** undergo dimerisation to give **4** and rule out the possibility of any other isomeric structure.



Scheme 1

The mechanistic pathway for the formation of **4** involves an electrophilic attack of IBD on lone pair of oxygen of aldoxime **2** to give intermediate **5**, which then undergoes reductive elimination of iodobenzene along with loss of a molecule of acetic acid to give **3**. Subsequent dimerisation of **3** results in the formation of product **4** (**Scheme 2**).



Scheme 2

The pyrazole-4-carboxaldehyde oximes **2a-f** needed in this study were prepared by using one-pot procedure involving Vilsmeier-Haack reaction of acetophenonephenylhydrazones followed by treatment with hydroxylamine hydrochloride and sodium bicarbonate (**Scheme 3**).¹⁵



Scheme 3

In conclusion, a new series of 3,4-bis(1-phenyl-3-arylpyrazolyl)-1,2,5-oxadiazole-*N*-oxide derivatives of potential biological interest has been synthesized by a simple and efficient method employing readily available, non-toxic hypervalent iodine(III) reagent IBD. The experimental procedure involves mild reaction conditions, easy work-up, short reaction time and high to excellent yields.

Experimental Section

General Procedures. All reagents were purchased from commercial sources and were used without further purification. Melting points were taken in open capillaries and are uncorrected. ¹H 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. Pyrazole-4-carboxaldehyde oximes were prepared using literature procedure¹⁵ and were confirmed by comparison of their melting points with those reported in literature.

Preparation of 3,4-bis(1-phenyl-3-arylpyrazolyl)-1,2,5-oxadiazole-*N*-oxides (4a-4f) from 2a-2f. To a solution of appropriate pyrazole-4-carboxaldehyde oxime **2a-2f** (10 mmol) in dichloromethane (10 ml) was added IBD (11 mmol) and the mixture was stirred for 5 minutes at room temperature. The solid separated was filtered off and washed with dichloromethane. The crude product, thus obtained, was recrystallised from dimethylformamide.

3,4-Bis(1,3-diphenylpyrazolyl)-1,2,5-oxadiazole-*N*-oxide (4a). M.p. 166 °C. Yield: 75 % ¹H NMR (DMSO, 300 MHz, δ): 7.11-8.01 (m, 20 H, ArH), 9.10 (s, 1 H, C-5 H), 9.30 (s, 1H, C-5 H). ¹³C NMR¹⁶ (DMSO, 300 MHz, δ): 111.6 (C-3), 153.4 (C-4)

Elemental analysis: Calculated for C 73.56, H 4.21, N 16.09; Found C 73.46, H 4.18, N 16.04

3,4-Bis[1-phenyl-3(4-chlorophenyl)pyrazolyl]-1,2,5-oxadiazole-*N*-oxides (4b). M.p. 187-188 °C. Yield: 78 %, ¹H NMR (DMSO, 300 MHz, δ): 7.22-8.25 (m, 18 H, ArH), 9.13(s, 1 H, C-5 H), 9.30 (s, 1H, C-5 H). Elemental analysis: Calculated for C 65.08, H 3.39, N 14.24; Found C 65.24, H 3.32, N 14.17. Mass (m/z): 295, 297.

3,4-Bis[1-phenyl-3(4-bromophenyl)pyrazolyl]-1,2,5-oxadiazole-*N*-oxide (4c). M.p. 178-179 °C. Yield: 72 %. ¹H NMR (DMSO, 300 MHz, δ): 7.35-8.42(m, 18 H, ArH), 9.04(s, 1 H, C-5 H), 9.32 (s, 1H, C-5 H). Elemental analysis: Calculated for C 56.64, H 2.95, N 12.39; Found C 56.58, H 2.92, N 12.17. Mass (m/z): 323, 325.

3,4-Bis[1-phenyl-3(4-methylphenyl)pyrazolyl]-1,2,5-oxadiazole-*N*-oxide (4d). M.p. 170-173 °C. Yield: 68 %. ¹H NMR (DMSO, 300 MHz, δ): 2.43 (s, 6 H, CH₃), 7.36-8.20 (m, 18 H, ArH), 8.99 (s, 1 H, C-5 H), 9.25(s, 1H, C-5 H). Elemental analysis: Calculated for C 74.18, H 4.73, N 15.27; Found C 74.04, H 4.62, N 15.02.

3,4-Bis[1-phenyl-3(4-methoxyphenyl)pyrazolyl]-1,2,5-oxadiazole-*N*-oxide (4e). M.p. 180 °C. Yield: 79 %. ¹H NMR (DMSO, 300 MHz, δ): 3.86 (s, 6 H, OCH₃), 6.98-7.99 (m, 18 H, ArH),

9.10 (s, 1 H, C-5 H), 9.32 (s, 1H, C-5 H). Elemental analysis: Calculated for C 70.10, H 4.47, N 14.43; Found C 69.94, H 4.32, N 14.26.

3,4-Bis[1-phenyl-3(4-nitrophenyl)pyrazolyl]-1,2,5-oxadiazole-N-oxide (4f). M.p. (°C). 173-175 °C. Yield : 65 %. ¹H NMR (DMSO, 300 MHz, δ): 7.32-8.21 (m, 18 H, ArH), 9.04 (s, 1 H, C-5 H), 9.26 (s, 1H, C-5 H). Elemental analysis: Calculated for C 62.74, H 3.26, N 18.30; Found C 62.84, H 3.32, N 18.16.

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References

1. Recent reviews on hypervalent iodine reagents: (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (b) Ladzita, U.; Zhdankin, V. V. *Arkivoc* **2006**, *9*, 26. (c) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (d) Wirth, T. *Top. Curr. Chem.* **2003**, 224.
2. (a) Moriarty, R. M.; Chany II, C. J.; Kosmeder II, J. W. In *Encyclopedia of Reagents in Organic Synthesis* Paquette, L. A., Ed., Wiley: Chichester, 1995, Vol 2, pp1479. (b) Prakash, O.; Singh, S. P. *Aldrichimica Acta* **1994**, *27*, 15. (c) Varvoglis, A. *Chem. Soc. Rev.* **1981**, *10*, 377.
3. (a) Koser, G. F. *Aldrichimica Acta* **2001**, *34*, 89. (b) Prakash, O.; Saini, N.; Sharma, P. K. *Heterocycles* **1994**, *38*, 409. (c) Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett* **1990**, 365.
4. (a) Magnus, P.; Lacour, J.; Weber, W. *J. Am. Chem. Soc.* **1993**, *115*, 9347. (b) Ochiai, M.; Utika, T.; Iwaki, S.; Nagao, Y.; Fujita, E. *J. Org. Chem.* **1989**, *54*, 4832. (c) Zhdankin, V. V.; Mullikin, M.; Tykwinski, R.; Berglund, B.; Caple, R.; Zefirov, N. S.; Kozmin, A. S. *J. Org. Chem.* **1989**, *54*, 2605.
5. (a) Moriarty, R. M.; Prakash, O.; Vavilikolanu, P. R. *Synth. Commun.* **1986**, *16*, 1247. (b) Prakash, O.; Pahuja, S.; Sawhney, S. N. *Indian J. Chem.* **1989**, 26B, 73.
6. (a) Barton, D. H. R.; Jasberenyi, J. Cs.; Liu, W.; Shinada, T. *Tetrahedron* **1996**, *52* (47); (b) Prakash, O.; Gujral, H. K.; Rani, N.; Singh, S. P. *Synth. Commun.* **2000**, *30*, 417. (c) Pundeer, R.; Chaudhri, V.; Kingler, M.; Prakash, O. *Indian J Chem, Sect. B* (In press).
7. (a) Prakash O.; Sharma, V.; Sadana, A. *J Chem Res (S)* **1996**, 100. (b) Wutz, P. G. M.; Goble, M. P. *Org. Lett.* **2000**, *2*, 2139.
8. Grundman, C.; Dean, J. M. *J. Org. Chem.* **1965**, *30*, 2809.
9. Just, G.; Dahl, K. *Tetrahedron Lett.* **1968**, *24*, 5251.

10. Grundman, C.; Richter, R. *J. Org. Chem.* **1968**, *33*, 476.
11. Hassner, A.; Lokanatha R. K. M. *Synthesis* **1989**, 57.
12. Kim, J. N.; Ryu, K. R. *Synth. Commun.* **1990**, *20*, 1373.
13. Radhakrishnan, A. S.; Sivaprakash, K.; Singh, B. B. *Synth. Commun.* **1991**, *21*, 1625.
14. (a) Paton, R. M. *Comprehensive Heterocyclic Chemistry II*; **1996**, Vol. 4, 229. (b) Baker, K. W. J.; Gibb, A.; March, A. R.; Paton, R. M. *Tetrahedron Lett.* **2001**, *42*, 4065.
15. Prakash, O.; Pannu, K.; Kaur, H; Naithani, R. *Synth. Commun.* **2006**, *23*, 5479.
16. ¹³C NMR could be obtained only for representative example **4a** because of insolubility problem of products **4b-f**.