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Selective Nitrations of 2-(1′-Phenylpyrazol-4′-yl) Benzimidazoles

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Abstract. Nitration of 2-(1′-phenylpyrazol-4′-yl) benzimidazole ring system was found to be temperature dependent. Room temperature nitration occurred at the phenyl ring of pyrazole, while at 100 °C, a dinitrated product is obtained where the second nitro group is introduced at the 5-position of the benzimidazole ring. Nitration at 100 °C leads directly to the expected dinitration product. Mass spectral fragmentations for both the compounds is described.

Keywords: pyrazoles, benzimidazoles, nitration, mass spectra

Introduction

Benzimidazole is an important heterocyclic system. It is present in many natural products of animal and plant origin and plays a vital role in many biochemical processes. The chemistry of benzimidazole has been extensively reviewed and documented (Grimmett, 1997; Hofmann, 1953; Wright, 1951). Some of its 2-aryl and hetaryl derivatives are endowed with manifold biological activities. For example 2-(thiazole-4′-yl) benzimidazole commonly known as thiabendazole is an effective anthelminitic and fungicidal compound (Tocco *et al.,* 1964) and many derivatives of 2-pyridylbenzimidazole are shown to be allosteric glucose activators (Takahashi *et al.,* 2009). Various other 2-furyl-, and 2-thienyl-benzimidazoles have also been reported in the literature (Achkasova *et al.,* 2005).

In the earlier work on heteroaromatic compounds, the synthesis of 2-(pyrazol-4′-yl) benzimidazole was reported (Rashid *et al.,* 2002; 1999). In the present work, nitration studies on 2-(3′,5′-dimethyl-1′-phenylpyrazol-4′-yl) benzimidazole (**I**) are described. Mass spectral fragmentation patterns of the compound and its nitro products are also suggested.

Materials and Methods

The proton magnetic resonance (PMR) spectra were obtained on a Brucker AM-500 spectrometer with tetramethylsilane as an internal standard. The infrared absorption spectra (IR) were taken by the Hitachi-270-30 spectrometer and were measured as potassium bromide disks. Mass spectra were obtained on a Finnigan MAT-112 spectrometer.

Melting points were taken on Gallenkamp apparatus and are uncorrected. 2-(3′,5′-dimethyl-1′-phenylpyrazol-4′-yl) benzimidazole (**I**) used in the nitrations was prepared earlier from the reaction of 3,5-dimethyl-1-phenylpyrazol-4-carboxaldehyde with *o*-phenylene diamine (Rashid *et al.,* 2002).

Nitration of 2-(3′, 5′-dimethyl-1′-phenylpyrazol-4′-yl) benzimidazole: ***At room temperature.*** Compound (**I**)1g was added to a nitrating mixture of 3 ml conc. nitric acid and 3 ml conc. sulphuric acid at room temperature and allowed to stand for 4 h at room temperature. Afterwards, the reaction mixture was poured over crushed ice, filtered and washed with water. The precipitate was dried and crystallized from aqueous ethanol to give the product 2-(3′,5′-dimethyl-1′-*p*-nitrophenylpyrazol-4′-yl) benzimidazole (**II**): m.p. 218-220 °C, yield 80%.

Compound (**II**) was identical (mixed m.p., IR, PMR spectra) with the product obtained from the reaction of 3,5-dimethyl-1-*p*-nitrophenylpyrazol-4-carboxaldehyde and *o*-phenylenediamine (Rashid *et al.,* 2002). Mass spectra m/z (%): 333(100); 332(90); 302(04); 287(14); 286(35); 285(07); 245(07); 244(17); 243(05); 219(04); 218(03); 217(02); 190(02); 179(02); 138(10).

At 100 °C. Nitration of compound (**I**) was carried out as above. The reaction mixture was heated on a water bath for 3 h, allowed to cool and poured over crushed ice. After filtration the precipitate was washed, dried and crystallized from ethanol to get compound (**III**): m.p. 196-198 °C, yield 75%.

Compound (**III**) was identical with the product of reaction of 3,5-dimethyl-1-*p*-nitrophenylpyrazole-4-carboxaldehyde and 5-nitro-*o*-phenylenediamine as well as the product obtained from further nitration of compound (**II**) at 100 °C. Mass spectra m/z (%): 378(100); 377(73); 347(05); 346(03); 332(09); 331(26); 302(02); 301(02); 286(07); 285(08); 273(02); 244(02); 232(01); 217(01); 216(01); 190(01); 170(01); 129(03); 88(02).

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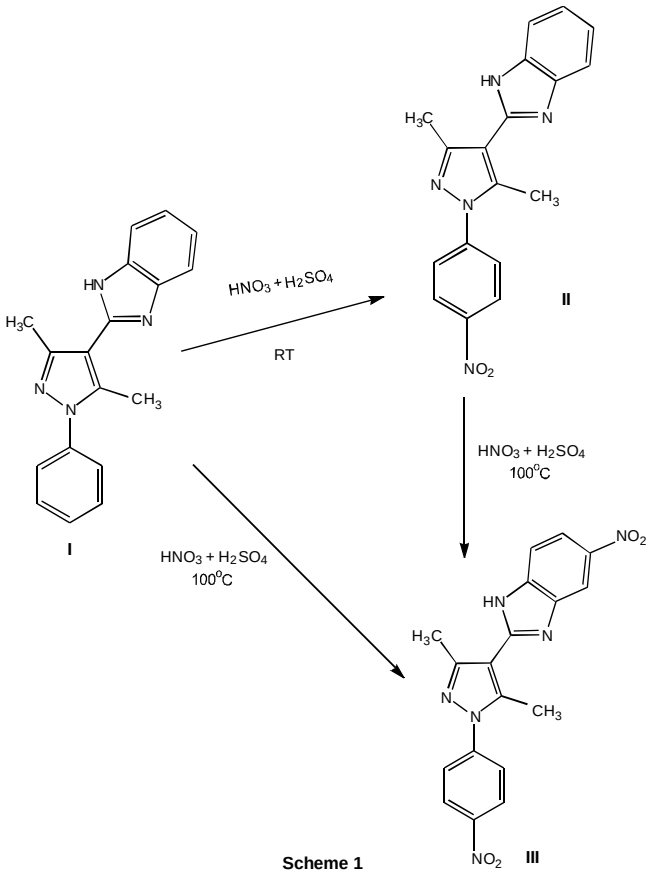
Results and Discussion

Nitration of compound (**I**) with mixed acids at room temperature gives a mononitro product, which was identified as compound (**II**), where the nitro group has entered at the *para* position of the phenyl ring of the phenylpyrazole moiety. The nitration reaction at 100 °C leads to a dinitro product (**III**), where one nitro group enters at the phenyl ring of the phenylpyrazole while the second nitro group is found at the 5-position of the benzimidazole part of the molecule (Scheme 1). No evidence for a trinitro product was found under the reaction conditions. The identity of these compounds, **(II**) and (**III**), was established through their melting points, IR and PMR spectra which were compared with those of the compounds obtained by unambiguous synthesis are reported elsewhere (Rashid *et al*., 2002).

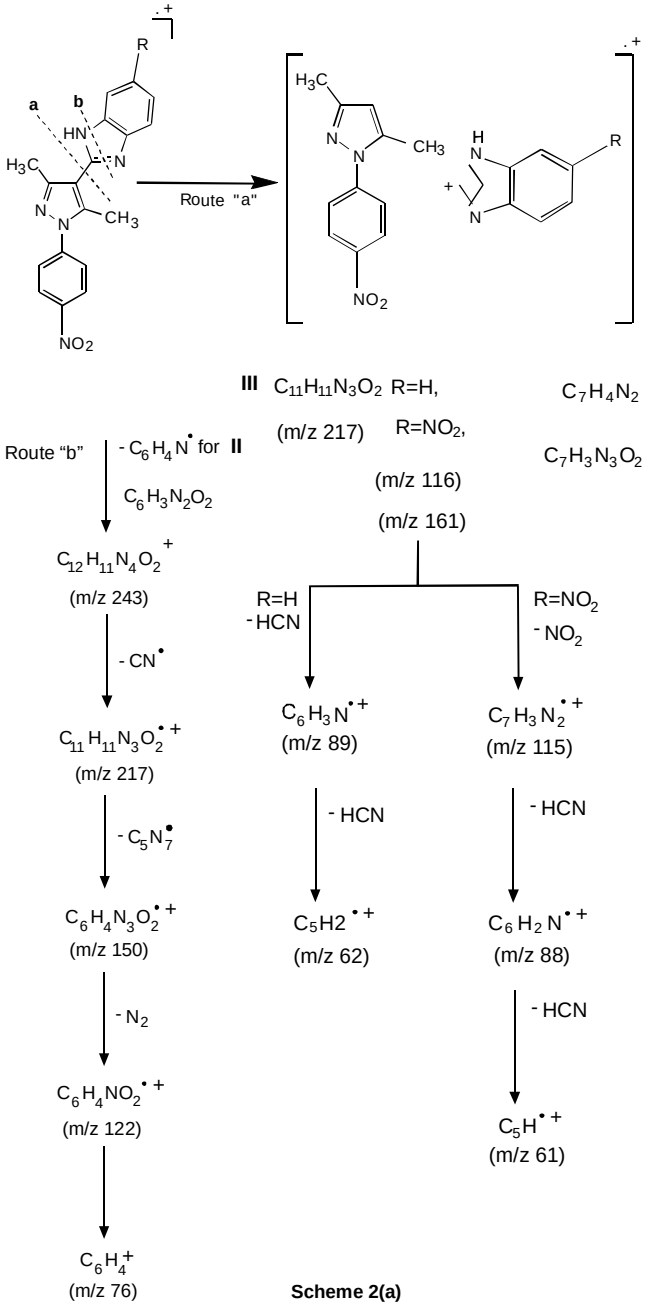
The nitration behaviour is reminiscent of the mixed acid nitration pattern earlier observed in the 1-phenylpyrazole series. The *para*-position of 1-phenylpyrazole part seems to be relatively more reactive than the 5-position of benzimidazole. However, there is an indication of the deactivating effect of benzimidazole on the reactivity of the phenyl ring of the pyrazoles, which is reported to undergo dinitration of the phenyl ring at 100 °C (Finar and Hurlock, 1957).



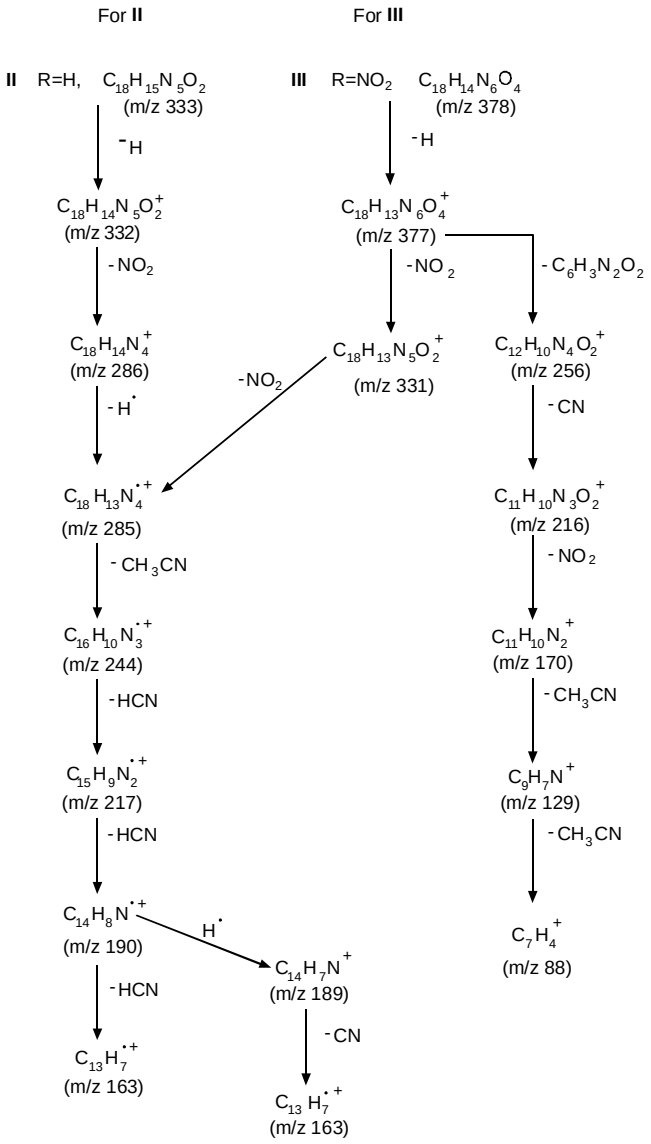
Scheme 1

IR and PMR spectra (Rashid *et al.*, 2002) fully support the structures of the nitration products (**II**) and (**III**). The mass spectra displayed molecular ion peaks at m/z 333 and 378 for the compounds (**II**) and (**III**), respectively, thus confirming mono and dinitration at room temperature and at 100 °C, respectively.

A tentative fragmentation pattern of compounds (**II**) and (**III**) observed in their mass spectra are presented in Schemes 2(a) and 2(b). The fragmentation takes place in the manner as already has been reported for the benzimidazoles and pyrazoles, separately i.e., loss of successive two HCN from



Scheme 2(a)



Scheme 2(b)

the benzimidazole moiety (Khmel'nitskii *et al.*, 1968; Lawsson *et al.*, 1968; Nishiwaki 1968;) and the loss of CH_3CN from the pyrazole part of the molecule, characteristic of a methyl substituent adjacent to the nitrogen atom (Khmel'nitskii *et al.*, 1967; Nishiwaki, 1967). The intense M^+ ion for both the compounds (**II**) and (**III**) was also observed as the base peak. One of the fragmentation routes observed was a prior fission of a C-C bond linking the two rings (Route 'a'), where the benzimidazole and pyrazole portions fragment as expected. For benzimidazoles, it is presented in the Scheme 2(a) while the pyrazloes behaviour would be identical with that of Route 'a' in the fragmentation mode while in Route 'b', a "pyrazole nitrile" ion is produced which further fragments with successive elimination of a nitrile (C_5H_7, N_2) and NO_2 to give the m/z 76 fragments (Scheme 2(a)).

Loss of a hydrogen atom followed by the loss of a nitro group (for compound **II**) and successive loss of two nitro groups (for compound **III**) followed by other expected fragmentations was also observed and is presented in the Scheme 2(b).

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References

Achkasova, A.A., Elchaninov, M.M., Milov, A.A., Lukyanov, B.S. 2005. Chemistry of 2-hetarylbenzimidazloes. 10. Synthesis and properties of 2-(3¢furyl)-1-methyl-1H-benzimidazoles. *Chemistry of Heterocyclic Compounds* **41:** 1494-1498.

Finar, I.L., Hurlock, R.J. 1957. The preparation of some trinitrophenylpyrazoles. *Journal of the Chemical Society* 3024-3027.

Grimmett, M.R. 1997. *Imidazole and Benzimidazole Synthesis*, Academic Press, Boston, USA.

Hofmann, K. 1953. *Imidazole and its Derivatives*, Interscience, New York, USA.

Khmel'Nitskii, R.A., Kost, A.N., Kondal Reddi, K., Vysockij, V.I. 1968. Mass spectra of benzimidazoles and some methylbenzimidazoles. *Zhurnal Organicheskoi Khimii* **5:** 1153.

Khmel'nitskii, R.A., Krasmoshchek, A.P., Polyakove, A.A., Grandberg I.I. 1967. Mass spectra and structure of organic compounds. XX. Mass spectra of pyrazoles and methylpyrazoles. *Zhurnal Organicheskoi Khimii* **3:** 1540-1545.

Lawesson, S-O., Schroll, G., Bowie. J.H., Cooks, R.G. 1968. Electron Impact Studies. XXII. Mass spectra of substituted benzimidazoles. *Tetrahedron* **24:** 1875.

Nishiwaki, T. 1968. Mass spectrometric studies on 2-alkylbenzimidazoles. Some evidence for fragmentation *via* quinoxalinium ions. *Journal of the Chemical Society, Section C*, 428-430.

Nishiwaki, T. 1967. Electron impact induced fragmentation of pyrazoles. *Journal of the Chemical Society, Section B* 885-888.

Rashid, S., Khan, M.A., Moazzam, M. 2002. Synthesis of some novel 2-(1′-arylpyrazol-4′-yl) Benzimidazoles. *Journal of Pure and Applied Sciences* **21:** 109.

Rashid, S., Khan, M.A., Moazzam M. 1999. Hetarylpyrazoles. VII. Some derivatives of 3,4′-bipyrazolyls. *Journal of*

Pure and Applied Sciences **18:** 93-98.

Takahashi, K., Hashimoto, N, Nakama, C., Kamata, K., Sasaki, K., Yoshimoto, R., Ohyama, S., Hosaka, H., Maruki, H., Nagata, Y., Eiki, J-i., Nishimura, T. 2009. The design and optimization of a series of 2-(pyridine-2-yl)-1H-benzimidazole compounds as allosteric glucokinase activators. *Bioorganic and Medicinal Chemistry* **17:** 7042-7051.

Tocco, D.J., Buhs, R.P., Bro'ltun, H.D., Matzuk, A.R., Mertel, H.E., Trenner, N.R. 1964. The metabolism of thiabendazole in sheep. *Journal of Medicinal Chemistry* **7:** 399-405

Wright, J.B. 1951. The chemistry of benzimidazoles. *Chemical Reviews* **48:** 397-541.