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ORIGINAL ARTICLE

Synthesis and antimicrobial activities of new mono and bisphenyl linked bispyrazole and bispyrazolone derivatives

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Abstract The entitled bispyrazole and bispyrazolone compounds (**4a–4t**) were synthesized in good yield using a simplified experimental procedure under both conventional and microwave heating from easily available starting materials. The structure of synthesized bispyrazole and bispyrazolone compounds (**4a–4t**) was established with the help of physico-chemical analysis and various spectroscopic techniques like FT-IR, Mass, ^{1}H NMR and ^{13}C NMR. The results of analyses are in good agreement with the proposed structure of all the synthesized compounds. Further, all the synthesized compounds were evaluated for their antimicrobial (antibacterial and antifungal) activities using various species like *Bacillus subtilis*, *Escherichia coli*, *Aspergillous niger* and *Aspergillous flavus* by using the agar cup method. The results of antimicrobial screening showed that compounds have mild to moderate activity. However, compounds **4g** and **4h** have shown good activity among all the tested compounds.

1. Introduction

Pyrazole and pyrazolone derivatives are important synthons and reagents in organic synthesis and have found applications with numerous pharmacological activities, like analgesic, anti-inflammatory, antipyretic, antidiabetic, antibacterial, antiarrhythmic, tranquilizer, muscle relaxant, psychoanaleptic, anticonvulsant, monoamine epoxidase inhibitor, antianxiety etc. (Badawey and Ashmawey, 1998; Geronikaki et al., 2004; Gürsoy et al., 2000; Haddad et al., 2004; Kees et al., 1996; Tanitame et al., 2004). Further, pyrazoles and pyrazolones have been found to be useful in agrochemicals, dyestuffs and with other diversified applications (Elmorsi and Hassanein, 1999; Foulds, 1998; Ito et al., 2001; Kepe et al., 1998; Yang et al., 2000).

To date, there are many reports available describing the synthesis of pyrazole and pyrazolone derivatives (Batten and Robson, 1998; Liu et al., 2004; Majumder et al., 2009; Uzoukwu et al., 1998; Zhang et al., 2010; Zheng et al., 2009, 2010). However, there are only few reports on the synthesis of

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bispyrazole and bispyrazolone derivatives (Deb et al., 2009; Mabkhoot, 2009; Niknam et al., 2010; Tewari et al., 2010; Veettil and Haridas, 2009).

In recent years, the application of microwave assisted reactions in organic synthesis has received considerable attention. Compared to conventional heating, microwave irradiation often gives enhanced reaction rates and decreases the formation of byproducts (Alvarez et al., 2006; Dos Santos et al., 2004; Marquez et al., 2006). Microwave irradiation has been used for many organic reactions such as pericyclic (Srikrishna and Nagaraju, 1992), cyclization (Rama Rao et al., 1992), aromatic substitution (Laurent et al., 1994), oxidation (Gedye et al., 1986), alkylation (Yulin and Yuncheng, 1994), decarboxylation (Jones and Chapman, 1993), radical reactions (Bose et al., 1991), condensation (Sharma et al., 2011), and peptide synthesis (Yu et al., 1992).

Perusal of the above literature survey reveals that among the available reports, there are no reports in which two pyrazole or pyrazolone moieties are linked by mono and bisphenyl linkage in a single molecular framework. Therefore, we have been prompted for the synthesis of new bispyrazole and bispyrazolone derivatives based on aromatic diamines under conventional as well as microwave heating conditions. All the synthesized compounds were checked for their biological (antibacterial and antifungal) activities.

2. Results and discussion

2.1. Chemistry

The simpler and easily available diphenylic diamines [diaminodiphenyl sulphon–DAPSON (**1a**), diaminodiphenyl ether–DDE (**1b**) and diaminodiphenyl methane–DDM (**1c**)] were preferred as precursors, and were first tetra azotized and then coupled with 1,3-diones (acetyl acetone (**2a**)/methyl acetoacetate (**2b**)) to form hydrazono compounds (**3a**–**3f**), which upon cyclization with hydrazine derivatives (hydrazine hydrate and phenyl hydrazine) under conventional and microwave heating condition, produced entitled diphenylic bispyrazole (**4a**–**4f**) and bispyrazolone (**4g**–**4l**) derivatives respectively in quantitative yield, as shown in Scheme 1.

However, experimentation with monophenylic diamines (1,3- or 1,4- phenylene diamine), results in complex reaction mass upon tetra azotization and the results were not reproducible in our hands. Therefore, we have attempted another path to synthesize monophenylic derivatives (**4m**–**4t**); for that, the nitro derivatives of aniline [*m*-nitroaniline (**1d**) and *p*-nitroaniline (**1e**)] were first diazotized and coupled with **2a** and **2b** to produce hydrazono compounds (**3m**, **3n** and **3q**, **3r**), which were further cyclized likewise to form mono phenylic linked pyrazole (**5m**–**5p**) and pyrazolone (**5q**–**5t**) derivatives. The nitro functionality in **5m**–**5t** was reduced using sodium polysulphide to produce corresponding amines (**6m**–**6p** and **6q**–**6t**), which were again diazotized and coupled with **2a** and **2b,** and further cyclized under both conventional and microwave heating yielding entitled mono phenylic linked bispyrazole or bispyrazolone compounds (**4m**–**4p** and **4q**–**4t**). The synthetic path is given in Scheme 2.

All the hydrazono derivatives (**3a**–**3f**, **3m**, **3n**, **3q**, **3r** and **7m**–**7t**) were also cyclized using microwave heating to obtain pyrazole and pyrazolone derivatives. Comparison of both conventional and microwave synthetic methods has been included in Table 1, which indicates an increase in yields and lowering of reaction time by following microwave heating.

The decomposition temperatures of all the synthesized compounds **4a**–**4t**, **5m**–**5t**, **6m**–**6t** and **7m**–**7t** are ranging from 180–235, 210–280, 195–235, 190–290 °C respectively, were checked with the help of a digital melting point apparatus and were uncorrected. All the compounds have characteristic color from yellow to reddish brown shade. The structure of the synthesized compounds was confirmed by using various characterization techniques like elemental analysis, infrared (FT-IR), mass and nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectroscopy. The elemental and mass spectroscopic analysis for all the synthesized compounds showed that, calculated and observed values are in good agreement with each other.

FT-IR spectra for all the synthesized compounds showed the important IR bands at appropriate frequencies as expected (Pavia et al., 2008). The IR spectra of all nitro pyrazole/pyrazolone (**5m**–**5t**), amino pyrazole/pyrazolone (**6m**–**6t**), hydrazones (**3a**–**3f**, **3m**, **3n**, **3q**, **3r**, **7m**–**7t**) and bispyrazole or bispyrazolone compounds (**4a**–**4t**) showed that they resemble each other in their general shape, though certain characteristic differences have been observed. In case of nitro compounds (**5m**–**5t**) it showed characteristic band ranging from 1520 to 1550 cm^{-1} due to the presence of the NO_2 group that disappears after reduction (**6m**–**6t**). One of the significant differences to be expected between the IR spectrum of the hydrazono and bispyrazole compounds (**4a**–**4f, 4m**–**4p**) is that in case of hydrazono compound there is presence of more bands in the region of 1706–1788 cm^{-1} due to the presence of the C═O group that disappears after formation of the pyrazole ring. However, in case of bispyrazolone these bands persist even after formation of the pyrazolone ring but in decreased amount. This is also explained by the fact that the band of C═N stretching vibration of pyrazole and pyrazolone rings appeared at lower frequency around 1450 cm^{-1} in the IR spectrum of hydrazono compounds. Further, weak bands at 980, 780 and 660 cm^{-1} are corresponding to the presence of the phenyl ring. Thus, all of these characteristic features of the FT-IR studies supported the formation of pyrazole and pyrazolone ring containing compounds. In the, ^{1}H NMR spectra of intermediates (**5m**–**5t**), (**6m**–**6t**) and (**7m**–**7t**), signals for aliphatic protons of the methyl (CH_3) group in pyrazole or pyrazolone ring system appeared as singlets between δ 2.21 and 4.20 ppm. In case of hydrogens of primary amines (**6m**–**6t**), they signalled from δ 6.12 to 6.42 ppm as a singlet. Protons of hydrazono group(s) of compounds **5m**, **5o**, **5q**–**5t**, **6m**, **6o**, **6q**–**6t** and **7m**–**7t** appeared as singlets in down field region from δ 9.62 to 10.68 ppm; but in pyrazolone compounds proton attached to the nitrogen of the pyrazolone ring appeared as broad singlet in most down field range from δ 11.69 to 11.86 ppm. Whereas in entitled compounds **4a**–**4t**, three protons of the methyl (CH_3) group of pyrazole or pyrazolone ring system gave signals between δ 2.24 and 2.70 ppm and appeared as a singlet. In addition the signal appeared at little lower field attributed to two protons of methylene (Ar–CH_2–Ar) group present in **4e**, **4f**, **4k** and **4l,** and appeared at around δ 3.80 ppm. Aromatic protons of all the compounds resonated in the region of δ 6.73–7.98 ppm. Further, comparison of signals of equivalent aromatic protons in compounds containing sulphone and ether linkage (**4a, 4b, 4g, 4h** and **4c, 4d, 4i, 4j**) appeared at higher δ values to those of methylene linkage (**4e**, **4f**, **4k** and **4l**). Signals due to protons

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