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Original article

Synthesis and antimicrobial activity of (1,4-phenylene) bis(arylsulfonylpyrazoles and isoxazoles)

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ABSTRACT

A new class of (1,4-phenylene)bis(arylsufonylpyrazoles and isoxazoles) were synthesized by 1,3-dipolar cycloaddition of nitrile imines and nitrile oxides to the 1,4-bis((*E*)-2-(arylsulfonyl)vinyl)benzenes in the presence of chloramine-T. Compound **7f** exhibited pronounced antimicrobial activity.

1. Introduction

A vast number of bioactive natural products and pharmaceutical drugs are based on pyrazole and isoxazole ring systems [1–3] such as celecoxib, valdecoxib, leflunomide, cloxacillin, *etc.*, As such these azole derivatives have become attractive targets in the areas of different research fields [4–6]. Pyrazoles display various biological activities such as antimicrobial [7], antifungal [8], antidepressant [9], immunosuppressive [10], anticonvulsant [11], antitumor [12], antiamoebic [13], antibacterial [14] and anti-inflammatory [15]. Isoxazole derivatives also possess antibacterial, antiviral [16–18], anticancer [19] and antithrombotic activities [20]. Exploitation of simple molecules for the development of heterocycles is the one of the major targets in organic synthesis. In fact, we have utilized a variety of activated olefins to develop pyrazole and isoxazole compounds and studied their bioassay [21–24]. The increasing resistance of microorganisms to currently available antimicrobial drugs indeed demands the development 3 of novel microbial drugs. In this perspective, we have planned to design and synthesize a new class of bis(pyrazoles) and bis(isoxazoles) and studied their antimicrobial activity.

2. Chemistry

The compounds 1,4-bis(3-aryl-(1-phenyl)-4-(arylsulfonyl)-1*H*-pyrazol-5-yl)benzene (**6**) and 1,4-bis(3-aryl-4-(arylsulfonyl)-isoxazol-5-yl)benzene (**7**) were prepared from the Michael acceptor 1,4-bis-((*E*)-2-(arylsulfonyl)vinyl)benzene (**3**) adopting 1,3-dipolar cycloaddition methodology. The synthetic intermediate, **3** was prepared by the Knoevenagel reaction of 2-arylsulfonylacetic acid (**1**) with terephthaldehyde (**2**) in the presence of benzylamine and glacial acetic acid (Scheme 1). The ^{1}H NMR spectrum of compound **3a** showed two doublets at 7.19 and 7.63 ppm due to olefin protons, H_A, H_B. The downfield signal was assigned to H_A. The coupling constant value $J_{AB} = 15.3$ Hz indicated that they possess *trans* geometry. The 1,3-dipolar cycloaddition of an ylide to an alkene involving 3 + 2 principle, is a facile route to prepare five membered heterocycles. Thus, 1,3-dipolar cycloaddition of nitrile imine generated from araldehyde phenylhydrazone in the presence of chloramine-T to compound **3** produced 1,4-bis(3-aryl-(1-phenyl)-4-(arylsulfonyl)-4,5-dihydropyrazol-5-yl)benzene (**4**). In a similar way, cycloaddition of nitrile oxide generated from araldoxime in the presence of chloramine-T to compound **3** afforded 1,4-bis(3-aryl-4-(arylsulfonyl)-4,5-dihydroisoxazol-5-yl)benzene (**5**) (Scheme 2). The ^{1}H NMR spectra of **4a** and **5a** displayed two doublets at 3.72, 3.62 and 3.97, 4.52 ppm due to C_4–H and C_5–H of pyrazoline and isoxazoline rings respectively. The coupling constant value, $J \approx 7.0$ Hz indicated that they possess *cis* geometry. Compounds **4** and **5** on oxidation with chloranil in xylene furnished

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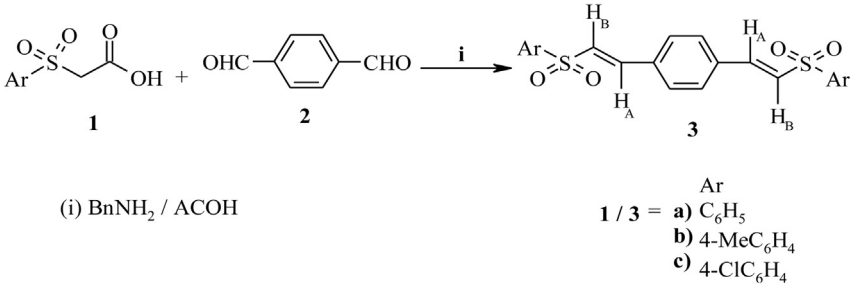
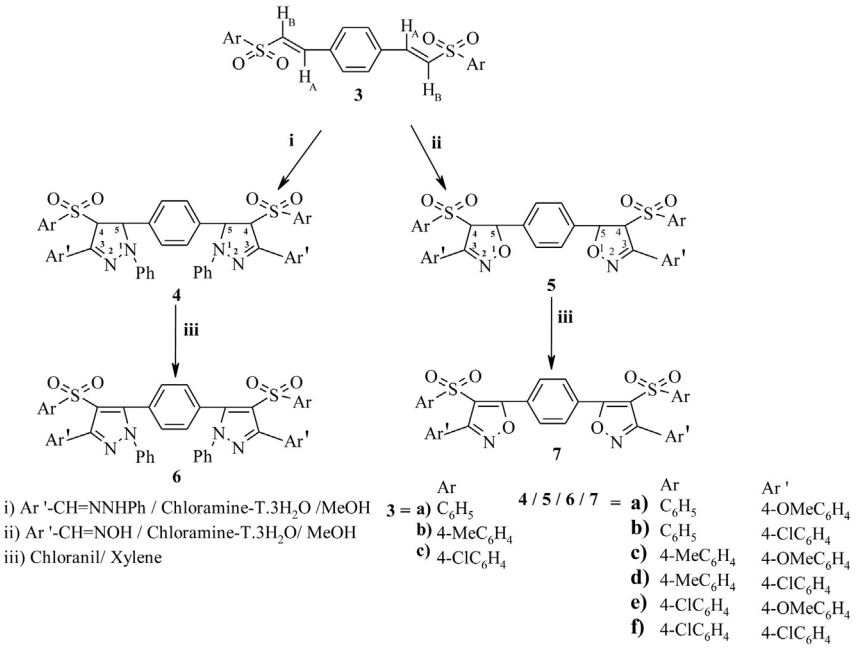


Scheme 1. Synthesis of 1,4-bis((*E*)-2-(arylsulfonyl)vinyl)benzenes **3**.



Scheme 2. Synthesis of (1,4-phenylene)bis(arylsulfonylpyrazoles and isoxazoles).

the respective pyrazole and isoxazole, 1,4-bis(3-aryl-(1-phenyl)-4-(arylsulfonyl)-1*H*-pyrazol-5-yl)benzene (**6**) and 1,4-bis(3-aryl-4-(arylsulfonyl)-isoxazol-5-yl)benzene (**7**) (Scheme 2). The absence of doublets corresponding to pyrazoline/isoxazoline ring protons in the ^{1}H NMR spectra of **6** and **7** confirmed their formation. The structures of all the new compounds were further established by IR and ^{13}C NMR spectral parameters.

3. Biology

3.1. Antimicrobial activity

Compounds **4**–**7** were tested for antimicrobial activity at two different concentrations 50 and 100 μg/ml.

4. Result and discussion

4.1. Antimicrobial activity

The results of antibacterial activity presented in Table 1 and Fig. 1 showed that Gram-positive bacteria were more susceptible towards the tested compounds than Gram-negative bacteria. Amongst bis heterocyclic compounds, the aromatized bis heterocycles **6** and **7** displayed greater activity than the respective non-aromatized compounds **4** and **5**. In fact, bis(isoxazole) compound **7f** exhibited excellent antibacterial activity (38 mm at 100 μg/ml) particularly on *Bacillus subtilis* than bis(pyrazole) compound **6f** (34 mm at 100 μg/ml), when compared with the standard drug Chloramphenicol (38 mm at 100 μg/ml). It was also observed that the chloro substituted compounds **6f**, **7b**, **7d** and **7f** displayed higher activity than those having methyl and methoxy substituents (Fig. 1).

All the compounds inhibited the spore germination against tested fungi. In general, all the compounds displayed slightly higher antifungal activity towards *Penicillium chrysogenum* than *Aspergillus niger*. Compounds **7b** and **7f** showed comparable activity particularly against *P. chrysogenum* almost equivalent to the standard drug Ketoconazole (Table 2 and Fig. 2). This may be due to the presence of more eletronegative atom *viz.*, chlorine in the aromatic ring which may enhance the biological potency, bioavailability, metabolic stability and lipophilicity. Enhanced lipophilicity may lead to easier absorption and transportation of molecules within the biological systems.

The MIC, MBC and MFC values of the compounds assayed are presented in Table 3. Compound **7f** exhibited low MIC values when compared with **6f**, **7b** and **7d**. In addition MBC value is 2 × MIC in