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Short communication

Synthesis and antibacterial activity of some new 1-heteroaryl-5-amino-4-phenyl-3-trifluoromethylpyrazoles

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Abstract

Treatment of 1,1,1-trifluoromethyl-3-cyano-3-phenylpropanone (**1**) with several heteroarylhydrazines (**2a**–**e**) in refluxing ethanol affords 1-heteroaryl-5-amino-4-phenyl-3-trifluoromethylpyrazoles (**4**) in a regioselective manner. The location of trifluoromethyl group at position-3 was established by a combined use of ^{13}C and ^{19}F NMR spectroscopy. The reaction proceeds through the intermediacy of the hydrazone which was isolated and characterized in one case (**3e**) by performing the reaction at room temperature. The compounds **3e** and **4** were tested for their antibacterial property against six Gram-positive and three Gram-negative bacteria. Two compounds, namely 1-(benzothiazol-2′-yl)-5-amino-4-phenyl-3-trifluoromethylpyrazole (**4a**) and 1-(6′-methylbenzothiazol-2′-yl)-5-amino-4-phenyl-3-trifluoromethylpyrazole (**4b**) have displayed antibacterial activity comparable to the commercial antibiotics.
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Keywords: Trifluoromethylpyrazoles; NMR spectroscopy; Antibacterial activity

1. Introduction

Pyrazoles and their derivatives are widely used as agrochemicals [1] and pharmaceuticals [2], the earliest example being antipyrine dating back 1884. Since then the chemistry of pyrazoles has received much attention and many methods for their synthesis have been developed to obtain substituted pyrazole derivatives. There has been particular interest in the synthesis of 5-aminopyrazoles and 3-trifluoromethylpyrazoles with a wide array of groups at N-1 and C-4, as these were reported to be selective inhibitor of cyclooxygenase [3] and have antidiabetic [4], herbicidal [5] and antibacterial properties [6]. In view of these observations, it was envisaged in the present investigation to undertake the synthesis of a number of pyrazoles, having both the pharmacophores i.e. CF_3 and NH_2 at positions 3 and 5 of the pyrazole moiety, respectively, with an aim to find new and more potent antibacterial agents.

2. Chemistry

Synthesis of 1-heteroaryl-5-amino-4-phenyl-3-trifluoromethylpyrazoles (**4**) is summarized in Scheme 1. The starting compound 1,1,1-trifluoromethyl-3-cyano-3-phenylpropanone (α-phenyltrifluoroacetylacetonitrile, **1**), was readily prepared by the condensation of phenyl acetonitrile with ethyl trifluoroacetate under the influence of sodium ethoxide [7]. Reaction of **1** with heteroarylhydrazines (**2a**–**e**) in refluxing ethanol gave regioselectively, 1-heteroaryl-5-amino-4-phenyl-3-trifluoromethylpyrazoles **4a**–**e** in high yield. The compounds were characterized by a combined application of ^{13}C and ^{19}F NMR spectroscopy. The pyrazole 3 carbon resonated at δ 141–142 ppm in all these compounds, which is a characteristic signal for the location of trifluoromethyl group at that carbon. Had the trifluoromethyl group been located at position 5 of the pyrazole, there would have been signal at δ 133 ppm [8].

In conformity with the earlier reports, carbon 5 of the pyrazole ring in **4** resonated at 146–147 ppm, which is a charac-

Abbreviations: ATCC, American type culture collection; EtOH, ethanol; MHA, Muller Hinton agar; MIC, minimum inhibitory concentration; MTCC, microbial type culture collection and gene bank; SCDA, soybean casein digest agar.

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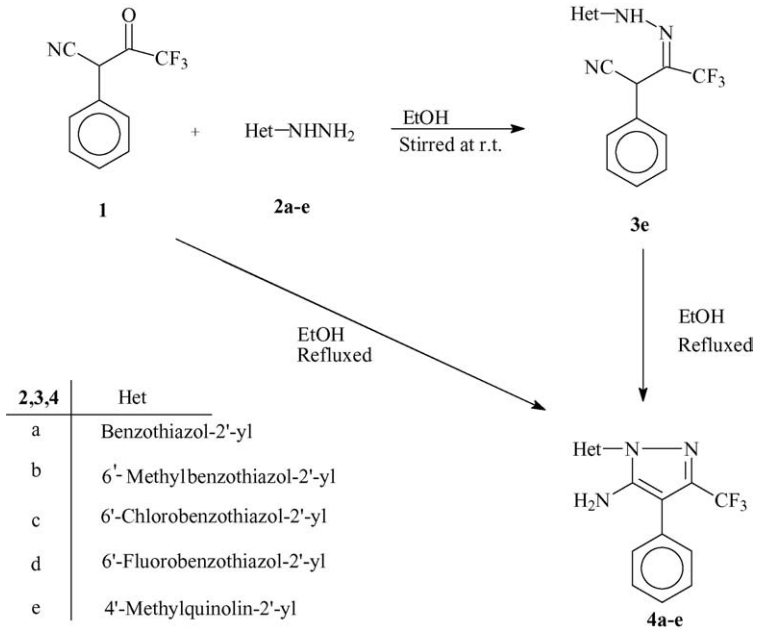

2,3,4	Het
a	Benzothiazol-2'-yl
b	6'-Methylbenzothiazol-2'-yl
c	6'-Chlorobenzothiazol-2'-yl
d	6'-Fluorobenzothiazol-2'-yl
e	4'-Methylquinolin-2'-yl

Scheme 1.

teristic signal for the carbon 5 bearing an amino group [9]. The complete assignment of the signals in ^{13}C NMR spectra of these compounds is given in Table 1.

Finally, the location of trifluoromethyl group at position-3 of the pyrazole ring was firmly established by ^{19}F NMR spectra of compounds **4**. It has already been reported by us that fluorine of trifluoromethyl group resonates at about δ –62 ppm when the trifluoromethyl group is located at position 3, and at about δ –58 ppm when the same group is located at position 5 [10]. ^{19}F NMR spectra of all these compounds (**4a–e**) display a signal between δ –61 and –62 ppm in conformity with our earlier observations. The exact values are given in Table 2.

The reaction apparently proceeds through the intermediacy of hydrazone, which was isolated in one case by performing the reaction in ethanol by stirring **1** and **2e** at room temperature. The formation of **3e** indicates that the unsubstituted nitrogen of heteroarylhydrazines preferentially, reacts with the carbonyl carbon of compound **1**. The hydrazone **3e** was characterized by IR and NMR spectroscopy. The IR spectrum of **3e** showed a characteristic band due to CN str. at 2179 cm^{-1}. The ^{19}F spectrum of compound **3e** showed fluorine signal at δ –65 ppm as expected. Refluxing of **3e** in ethanol afforded compound **4e** in quantitative yield.

3. Biological results and discussion

Six chemically synthesized compounds were tested in vitro for their antibacterial activity against *Staphylococcus aureus* (MTCC 3160), *S. aureus* (ATCC 25923), methicillin-resistant *S. aureus* (MRSA) (ATCC 700698), *Bacillus pumilus* (MTCC 1456), *Bacillus megaterium* (MTCC 428) (Gram-positive) and *Staphylococcus epidermidis* (MTCC 2639) *Salmonella typhi* (MTCC 733), *Escherichia coli* (MTCC 51) and *Pseudomonas aeruginosa* (MTCC 3541) (Gram-negative) bacteria (Tables 3 and 4). Many of these compounds possess excellent antibacterial activity against both Gram-positive and Gram-negative bacteria. All of the compounds showed MIC 2–8 μg ml^{-1} against Gram-positive bacteria namely *S. aureus* (MTCC 3160) and *S. aureus* (ATCC 25923). All the compounds except **4a** showed MIC 16–32 μg ml^{-1} against MRSA (Gram-positive) whereas compound **4a**, showed MIC of 4 μg ml^{-1} against the same organism. Compound **4a–e** exhibited less antibacterial activity against *B. pumilus* and *B. megaterium* (Gram-positive) except compound **3e**, which showed noticeable activity i.e. MIC 8 μg ml^{-1} against these organisms (Table 4).

Among the Gram-negative bacteria, namely *S. typhi*, *E. coli*, *P. aeruginosa* and *S. epidermidis*, which were used for antibacterial activity, all the compounds of the series showed MIC ranging from 2 to 32 μg ml^{-1}, except against *S. epidermidis* having MIC 64 μg ml^{-1}. Compound **4a–d** were more effective in inhibiting *E. coli* and *P. aeruginosa* as compared to compound **4e** and **3e**. The antibacterial activity of these compounds was also compared with three commercial antibiotics namely Linezolid, Cefaclor and Cefuroxime axetial, as Linezolid is an active drug against resistant staphylococci as well as MRSA and other two against Gram-positive and Gram-negative bacteria, respectively. Many of these compounds showed comparable activity as displayed in Table 4 and Fig. 1.

Kane et al. [6] reported seventeen ureas of 5-aminopyrazoles only having antibacterial activity against MRSA. The MIC of many of these compounds was ranging from 0.7 to 22.9 μg ml^{-1}. Of these four were found to be inactive and some of them having MIC 12–22.9 μg ml^{-1}. In comparison to these findings, the results obtained of the synthesized

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