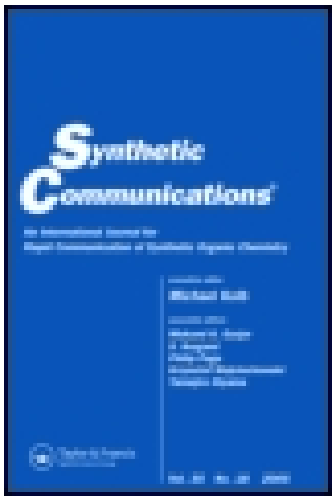

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Synthesis of some 2-(3-alkyl/aryl-5-trifluoromethylpyrazol-1-yl)-4-(coumarin-3-yl)thiazoles as novel antibacterial agents

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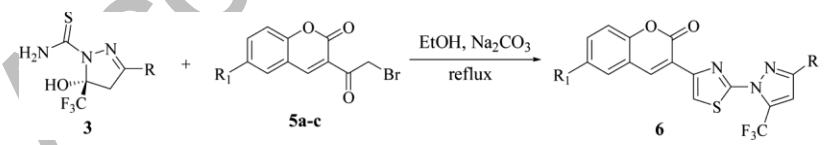
Abstract

Herein, we describe a one-pot synthesis of some novel 2-(3-alkyl/aryl-5-trifluoromethylpyrazol-1-yl)-4-(coumarin-3-yl)thiazoles **(6)** involving the reaction of 3-alkyl/aryl-5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazole-1-thiocarboxamides **(3)** with 3-bromoacetylcoumarins **(5)** in presence of sodium carbonate in ethanol. Reaction of **3** with **5** in the absence of sodium carbonate, however, resulted in the formation of 2-(3-alkyl/aryl-5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazol-1-yl)-4-(coumarin-3-yl)thiazoles which were subsequently dehydrated to **6** by refluxing in ethanol in presence of sodium carbonate. The structure of the synthesized compounds (**6**) was confirmed by IR, mass, ^{1}H, and ^{13}C NMR spectra and elemental analyses data. Newly synthesized compounds (**6**) showed moderate to good activity against Gram-positive bacteria.



KEYWORDS: 3-(2-Bromoacetyl)coumarins; 3-alkyl/aryl-5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazole-1-thiocarboxamides; 2-(3-alkyl/aryl-5-trifluoromethylpyrazol-1-yl)-4-(coumarin-3-yl)thiazoles; Sodium carbonate; antibacterial

INTRODUCTION

Heterocyclic rings containing nitrogen and sulphur have been under investigation for a long time because of their important medicinal properties. Thiazole and its derivative are found to be associated with various biological activities, such as antibacterial, antifungal, anthelmintic, cytotoxic, algicidal, and antithrombotic activities[1-10] and recently, found in many applications in drug development for the treatment of schizophrenia,[11] inflammation,[12] HIV infections,[13] and hypertension[14].

Much attention has been addressed to trifluoromethylated heterocyclic compounds because they often show unique biological and physiological activities associated with them. In particular, trifluoromethyl substituted pyrazoles and other five-membered heterocycles have interesting biological activities viz. anti-inflammatory, antimicrobial, antihypertensive etc.[15-20] The search for a simple and efficient access to such compounds with a CF_3 group at a specific position is one of the important goals in this area. However, there are a limited number of regioselective syntheses of trifluoromethyl containing heteroaromatic compounds in good yield.

Coumarin and its derivative represent one of the most active class of compounds possessing a wide spectrum of biological activity. Many of these compounds have proved to be active as, antibacterial,[21–24] antitumor,[25] anticoagulant,[26] antiviral,[27] and anti-inflammatory[28-29] agents. In addition, these compounds are used as additives to food and cosmetics.[30] Coumarin derivatives are commonly used as optical whiteners, luminescence dyes,[31-32] active media for lasers[33] and solar collector[34]. Thus, the

synthesis of coumarin derivatives is still a popular research topic in organic chemistry. Recently, we have reported the synthesis of 2-(3-alkyl/aryl-5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazol-1-yl)-4-(coumarin-3-yl)thiazole (**5**) which exhibited excellent level of antibacterial and anti-inflammatory activity.[35]

Prompted by these reports and in continuation of our search for biological active molecules comprising of 2,4-disubstituted thiazole ring,[17-20, 35-37] we have synthesized some novel thiazoles having trifluoromethyl substituted pyrazole as well as coumarin ring in order to investigate their biological activity.

RESULTS AND DISCUSSION

5-Hydroxy-5-trifluoromethylpyrazole-1-thiocarboxamides (**3**), prepared by the condensation of thiosemicarbazide (**1**) with trifluoromethyl-β-diketones (**2**),[38-39] was refluxed with 3-(2-bromoacetyl)coumarins **(5)** in ethanol in presence of small amount of sodium carbonate to obtain 2-(3-alkyl/aryl-5-trifluoromethylpyrazol-1-yl)-4-(coumarin-3-yl)thiazole (**6**). 3-(2-bromoacetyl)coumarins **(5a-c)** were prepared by the bromination of 3-acetylcoumarins **(4a-c)** with liquid bromine in chloroform. The synthetic reactions are outlined in Scheme 1.

Recently, we have reported the synthesis of some fluorinated pyrazolylthiazoles where the reaction of 5-hydroxy-5-trifluoromethylpyrazole-1-thiocarboxamides (**3**) with α-bromomethyl ketones led to the formation of 4-aryl-2-(3-phenyl-5-trifluoromethylpyrazol-1-yl)thiazole in refluxing ethanol, accompanied by simultaneous

dehydration of 4-aryl-2-(3-phenyl-5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazol-1-yl)thiazole.[19] It was suggested that acid (HBr) generated during the synthesis of thiazole ring facilitated the simultaneous dehydration of 4-aryl-2-(3-phenyl-5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazol-1-yl)thiazole to 4-aryl-2-(3-phenyl-5-trifluoromethylpyrazol-1-yl)thiazole . However, in the present work presence of a strong electron withdrawing coumarin ring instead of an aryl ring in α-bromomethyl ketones makes 2-(3-alkyl/aryl-5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazol-1-yl)-4-(coumarin-3-yl)thiazole **(7)** resistant to undergo dehydration under the conditions of Hantzsch thiazole synthesis and formation of 2-(3-alkyl/aryl-5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazol-1-yl)-4-(coumarin-3-yl)thiazole **(7)** takes place, which further may dehydrated to corresponding pyrazoles (**6**) on refluxing in acetic anhydride. In this article we are describing a single step pathway to synthesize the targeted compounds i.e. 2-(3-alkyl/aryl-5-trifluoromethylpyrazol-1-yl)-4-(coumarin-3-yl)thiazole (**6**), by refluxing 5-hydroxy-5-trifluoromethylpyrazol-1-thiocarboxamides (**3)** with 3-(2-bromoacetyl)coumarins **(5)** in ethanol in the presence of small amount of sodium carbonate (1.0 mole equivalent). In another experiment **6** was obtained when **7** (prepared by refluxing equimolar mixture of **3** and **5** in ethanol) was refluxed in ethanol in the presence of small amount of sodium carbonate. Generally acidic media e.g. HCl in ethanol, acetic anhydride, $SOCl_2$-pyridine, P_2O_5 in chloroform, EtOH-H_2SO_4 etc. have been reported for the dehydration of hydroxypyrazoline.[18, 40-43] This report shows that hydroxypyrazoline may be dehydrated in the presence of a weak base e.g. sodium carbonate. Larock *et al* have reported dehydration of *N*-acyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles to corresponding pyrazoles using Li_2CO_3 (2 equiv.) and ICl (3 equiv.).[44] To

the best of our knowledge this is the first report describing the dehydration of hydroxyl pyrazoline with such a mild base like sodium carbonate (0.5 equiv.) in absolute EtOH with excellent yields, thus providing a greener and efficient protocol with reduced number of steps for such type of reactions. Structure of all the newly synthesized compounds was established by spectral data such as IR, mass, NMR (^{1}H and ^{13}C) and elemental analyses.

In ^{1}H NMR spectra of **6** two singlets, of one proton intensity each, appeared at δ 7.15-7.30 and 8.38-8.48 ppm corresponding to position-4 of pyrazole ring and position-5 of thiazole ring, respectively. A singlet appeared at δ 8.5-8.6 ppm is characteristic signal for an olefinic proton present at position-4 of coumarin ring. In ^{13}C NMR spectra of **6**, signals at δ 109-110, 130-133 and 131-134 ppm were assigned to C_4, C_3 and C_5 carbon of aromatic pyrazole ring, respectively. These values are in close agreement with the reported values for pyrazole carbons 4, 3 and 5.[18-19, 45]

ANTIBACTERIAL ACTIVITY

The *in vitro* antibacterial activity of five chemical compounds was evaluated by the agar well diffusion method.[46] On the basis of maximum inhibitory activity shown against Gram-positive bacteria, compounds namely **6a**, **6b** and **6f** were found to be the most effective against *B. subtilis* and *S. aureus* with zone of inhibition of 19.6, 20.4, 18.3 mm, and 22.3, 19.2, 20.6 mm, respectively, whereas other tested compounds displayed moderate activity (Table 1). In the whole series, the MIC of various tested chemical compounds ranged between 32 and 256 µg/ml against Gram-positive bacteria. Compound

6a, **6b** and **6f** were found to be best as they exhibit the lowest MIC of 32, 32, 64 µg/ml against *S. aureus* and MIC of 32, 64, 32 µg/ml against *B. subtilis* (Table 2)**.** One compound could not be tested for antibacterial activity due to poor solubility in DMSO.

CONCLUSION

In conclusion, we have described a one-pot synthesis of some novel 2-(3-alkyl/aryl-5-trifluoromethylpyrazol-1-yl)-4-(coumarin-3-yl)thiazoles **(6)** involving the reaction of 3-alkyl/aryl-5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazole-1-thiocarboxamides **(3)** with 3-bromoacetylcoumarins **(5)** in presence of sodium carbonate in ethanol. Compounds **6a**, **6b** and **6f** have shown good antibacterial activity against Gram-positive bacteria when compared with Ciprofloxacin.

EXPERIMENTAL

Fluorinated trifluoromethyl-β-diketones (**2a-d**) were prepared according to the literature procedure.[47-48] 5-Hydroxy-5-trifluoromethyl-3-aryl-4,5-dihydropyrazole-1-thiocarboxamides **(3a-d)** and 6-substituted-3-bromoacetylcoumarins (**5a-c**) were also synthesized according to literature procedure.[35, 38]

General procedure for the preparation of 2-(3'-alkyl/aryl-5'-trifluoromethylpyrazol-1'-yl)-4-(coumarin-3'''-yl)thiazoles **(6a-g)**

An ethanolic solution (30 ml) of 3-(2-bromoacetyl)coumarin (**5a**) (0.53g, 2 mmol) and 5-hydroxy-3,5-bis(trifluoromethyl)-4,5-dihydropyrazol-1-thiocarboxamide (**3**)

(0.56g, 2 mmol) was refluxed in the presence of sodium carbonate (0.11g, 1 mmol) on water bath for 6 hr. On completion of the reaction (observed by TLC), solvent was evaporated. The solid thus obtained was dissolved in chloroform (25 ml) and washed with hot water (50 ml, to dissolve sodium carbonate). Separated the organic layer and distilled off the excess solvent. It was crystallized with aqueous ethanol to afford the targeted compound **6a**.

Similarly, the other compounds **6b-g** were prepared by following the same procedure.

6a: *2-(3',5'-Bis-trifluoromethylpyrazol-1'-yl)-4-(coumarin-3'''-yl)thiazole* mp 190-191 ^{o}C; Yield: 79%; IR (KBr, cm^{-1}): 1720, 1528, 1296, 1180, 1142, 1095, 957, 756; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 8.65 (s, 1H, 4'''-H), 8.46 (s, 1H, 5-H), 7.69 (d, 1H, *J*=7.5 Hz, 5'''-H), 7.62 (m, 1H, 7'''-H), 7.43 (m, 2H, 8''', 6'''-H), 7.19 (s, 1H, 4'-H); ^{19}F NMR ($CDCl_3$, δ ppm): -80.34 (5-CF_3), -66.98 (3-CF_3); HRMS (m/z): 431.0160 $[M]^+$, requires 431.0163; Anal. Calcd. for $C_{17}H_7F_6N_3O_2S$: C, 47.34; H, 1.64; N, 9.74. Found C, 47.32; H, 1.61; N, 9.69.

6f*: 2-(3'-(p-Bromophenyl)-5'-trifluoromethylpyrazol-1'-yl)-4-(6'''-bromocoumarin-3'''-yl)thiazole* mp 305-306 ^{o}C; Yield: 69%; IR (KBr, cm^{-1}): 1713, 1543, 1288, 1227, 1149, 1011, 949, 818, 787; ^{1}H NMR (300 MHz, δ ppm): 8.58 (s, 1H, 4'''-H), 8.39 (s, 1H, 5-H), 7.82 (ds, 1H, *J*=2.1 Hz, 5'''-H), 7.80 (d, 2H, *J*=8.7 Hz, 2", 6"-H), 7.67 (ds, 1H, *J*=2.1 Hz, 7'''-H), 7.64 (d, 2H, *J*=8.7 Hz, 3", 5"-H), 7.31 (d, 1H, *J*=8.7 Hz, 8'''-H), 7.22 (s, 1H, 4'-H);

^{19}F NMR ($CDCl_3$, δ ppm): -80.50 (5-CF_3); Anal. Calcd. for $C_{22}H_{10}Br_2F_3N_3O_2S$: C, 44.25; H, 1.69; N, 7.04. Found C, 44.24; H, 1.65; N, 6.95.

An alternative procedure for the preparation of 2-(3'-alkyl/aryl-5'-trifluoromethylpyrazol-1'-yl)-4-(coumarin-3'''-yl)thiazoles **(6)** *from 2-(3'-alkyl/aryl-5'-hydroxy-5'-trifluoromethyl-4',5'-dihydropyrazol-1'-yl)-4-(coumarin-3'''-yl)thiazoles* (**7**)

An ethanolic solution of 2-(3′-alkyl/aryl-5′-hydroxy-5′-trifluoromethyl-4′,5′-dihydropyrazol-1′-yl)-4-(coumarin-3″-yl)thiazole (**7a**, 0.898 g, 2 mmol) and Na_2CO_3 (0.106 g, 1 mmol) was refluxed in ethanol (20 ml) for 5 hrs. Excess of ethanol was distilled off from the reaction mixture and added chloroform. The organic layer was washed thoroughly (2×25 ml) with water. The organic layer thus separated was dried over anhyd. Na_2SO_4. The reaction mixture was concentrated and cooled to room temperature. Filtered and washed the solid with aqueous ethanol. On drying dehydrated product **6a** was obtained, which was confirmed by comparing its mp and ^{1}H NMR.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

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Table 1. *In vitro* antibacterial activity of chemical compounds through agar well diffusion method

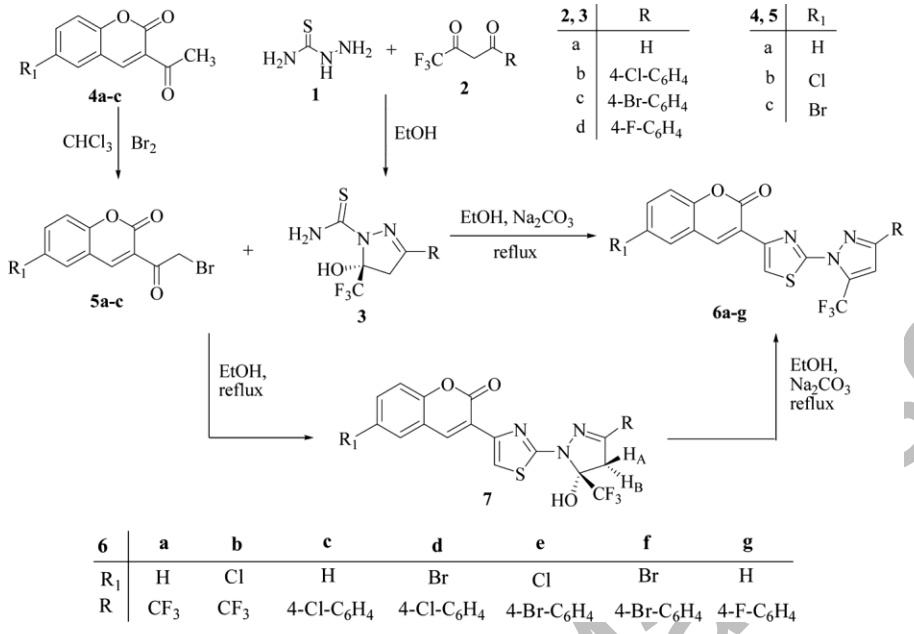
Compound	Diameter of growth of inhibition zone (mm)			
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*
6a	19.6	22.3	-	-
6b	20.4	19.0	-	-
6c	14.3	16.6	-	-
6d	15.0	16.3	-	-
6f	18.3	20.6	-	-
6g	15.6	16.3	-	-
Ciprofloxacin	24.6	23.0	24.0	21.0

No activity; [a]Values, including diameter of the well (8mm), are means of three replicates

Table 2. Minimum inhibitory concentration (MIC) (in µg/ml) of compounds (**6**)

Compound	*S. aureus*	*B. subtilis*
6a	32	32
6b	32	64
6c	128	64
6d	128	128
6f	64	32
6g	128	64
Ciprofloxacin	6.25	6.25

Scheme 1. Synthesis of 2-(3'-alkyl/aryl-5'-trifluoromethylpyrazol-1'-yl)-4-(coumarin-3'''-yl)thiazoles **(6a-g)**



2, 3	R
a	H
b	4-Cl-C_6H_4
c	4-Br-C_6H_4
d	4-F-C_6H_4

4, 5	R_1
a	H
b	Cl
c	Br

6	a	b	c	d	e	f	g
R_1	H	Cl	H	Br	Cl	Br	H
R	CF_3	CF_3	4-Cl-C_6H_4	4-Cl-C_6H_4	4-Br-C_6H_4	4-Br-C_6H_4	4-F-C_6H_4