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Short Communication

A Facile Synthesis of 5-(2-Bromo-4-Methylthiazol-5-yl)-3-(Methylthio)-1*H*-Pyrazole

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ABSTRACT

Ethyl-2-bromo-4-methylthiazole-5-carboxylate (2) was obtained by bromination of 2-Amino-4-methyl thiazole-5-ethylcarboxylate (1) using hydrogen bromide in presence of sodium nitrite. This compound undergoes hydrolysis with sodium hydroxide in THF to form 2-bromo-4-methylthiazole-5-carboxylic acid (3). Then acid 3 is transformed to 2-bromo-N-methoxy-N,4-dimethylthiazole-5-carbaxamide using N, O-dimethyl hydroxylamine hydrochloride in presence of EDC.HCl (4) which on treating with Grignard reagent gave 1-(2-bromo-4-methylthiazol-5-yl)ethanone (5). The ethanone gave compound 6 on reaction with carbon disulphide in presence of sodium hydride and methyl iodide which is cyclised to form 5-(2-bromo-4-methylthiazol-5-yl)- 3-(methylthio)-1H-pyrazole (7) in presence of hydrazine hydride and ethanol.

Keywords: Thiazoles, Cyclocondensation, Heterocycles, 5-(2-bromo-4-methylthiazol-5-yl)-3-(methylthio) -1H-pyrazole.

INTRODUCTION

Pyrazole and thiazole derivatives are a class of heterocyclic compounds that have drawn much attention, due to their biological and pharmaceutical activities [1]. A brief survey on the biological activities of these derivatives showed anti-microbial [2-4], analgesic [5, 6], anti-inflammatory [7-9], anti-cancer [10, 11], anti-tubercular [12], anthelmintic [13] and diuretic [14] properties. In addition to these effects, pyrazole derivatives are well known because of their as anti hypertensive [15] and anti-depressant [16] activity. Moreover, thiazole derivatives play an important role in anti-microbial activity and anti bacterial activity [17, 18] screening due to presence of toxophorric unit (S-C=N). Thiazoles are non-carcinogenic in nature [19] having enhanced lipid solubility and are easily metabolized by routine biochemical reactions. Therefore, compounds possess both pyrazole and thiazole moieties are worthy and imperative bioactivities, which render them useful substances in organic synthesis. However, bis-heterocyclic compounds which contain pyrazole and thiazole have rarely been reported. Thus it is necessary to find simple and convenient procedures for the synthesis of pyrazole and thiazole based heterocyclic compounds with different substituent with potentially enhanced properties is of great importance to both synthetic and medicinal

chemists. The aim of the present paper is to develop an efficient synthetic route for the preparation of novel 3-heteroaryl-pyrazoles, which have not been reported hitherto.

In this paper, we report our novel synthetic protocol for the synthesis of 5-(2-bromo-4-methylthiazol-5-yl) -3-(methylthio)-1H-pyrazole (7) from 2-Amino-4-methylthiazole-5-ethylcarboxylate (1). The biological activity results of synthesized compounds will be reported in due course.

MATERIALS AND METHODS

All chemicals and solvents of reagent grade were purchased and used without further purification. The ^{1}H NMR spectra was recorded in $CDCl_3$-d_1 and DMSO-d_6 solvent on a Varian 400 MHz spectrometer and the chemical shifts (δ) downfield from tetramethylsilane (TMS) as internal standard. The mass spectra were recorded on a Jeol JMS D-300 spectrometer. The homogeneity of the compounds was checked using precoated TLC plates (E. Merk Kieselgel 60 F_{254}).

Ethyl 2-bromo-4-methylthiazole-5-carboxylate (2)
To the cold solution (20 mL) of compound **1** (20g 0.107 mol) in HBr taken in a 100 ml flask, pre cooled aqueous solution of $NaNO_2$ (10 mL) was added in drop wise for 1 h. Then cold solution of Zinc bromide in 50% HBr was added to the reaction mixture in 30 minutes duration and the reaction mixture was stirred at room temperature for 20h. The reaction progress was monitored by TLC until the starting material completely disappeared. After the reaction mixture was diluted with water and extracted desired compound using dichloromethane. The organic layer was collected and washed with Na_2CO_3 solution, dried over Na_2SO_4. The organic fraction was concentrated by evaporating solvent under reduced pressure to obtain pure compound **2** as off-white solid.
Yield: 13.12 g, 49.24%.
^{1}H NMR ($CDCl_3$): δ 1.28 (t, 3H), 2.78 (s, 3H), 4.25 (q, 2H).
MS: *m/z* 251.9 (M+2).

2-Bromo-4-methylthiazole-5-carboxylic acid (3)
To the solution of compound **2** (4g 0.016 mol) in THF (20mL) and 5N NaOH (15 mL) was stirred at room temperature for 14 hours and the progress of the reaction was monitored by TLC. The reaction mixture was cooled and neutralized with concentrated HCl. After that organic layer was extracted with ethyl acetate and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to obtain crude product. The crude product was purified by column chromatography using silica gel (100-200 mesh) by varying 0-10% ethyl acetate in pet-ether as eluent gave compound **3** as off-white solid.
Yield: 2.5 g, 70.82%.
^{1}H NMR (DMSO-d_6): δ 2.56 (s, 3H), 13.55 (br, 1H).
MS: *m/z* 223.86 (M+2).

2-Bromo-N-methoxy-N, 4-dimethylthiazole-5-carboxamide (4)
To the solution of compound **3** (2.5g 0.011 mol), N, O-dimethyl hydroxylamine.HCl (0.011 mol), EDC.HCl (0.011 mol), DIPEA (0.011 mol) and dichloromethane (15 mL) was added at room temperature and stirred for 1 h. The completion of the reaction was confirmed by TLC. Then reaction mass was diluted with dichloromethane, washed the organic layer with water. The organic layer was dried over anhydrous Na_2SO_4, and concentrated to get crude product. The crude product was purified by silica gel (100-200 mesh) column chromatography using 0-10% ethyl acetate in pet-ether as the eluent gave compound **4** as off-white solid.
Yield: 2.72 g, 93.47%.
^{1}H NMR ($CDCl_3$): δ 2.68 (s, 3H), 3.26 (s, 3H), 3.74 (s, 3H).
MS: *m/z* 266.92 (M+2).

1-(2-Bromo-4-methylthiazol-5-yl)ethanone (5)
To the solution of compound **4** (2.72g 0.01 mol), in THF (20 mL) at 0 ^{0}C was added methyl magnesium bromide and stirred for 2 h. Then the reaction mixture was poured in aqueous NH_4Cl and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and evaporated the solvent under reduced pressure to give crude product. The crude product was purified by silica gel (100-200 mesh) column chromatography using 0-10% ethyl acetate in pet-ether as the eluent gave compound **5** as off-white color solid.
Yield: 1.8 g, 81.81%.
^{1}H NMR ($CDCl_3$): δ 2.49 (s, 3H), 2.76 (s, 3H).
MS: *m/z* 219.87 (M+2).

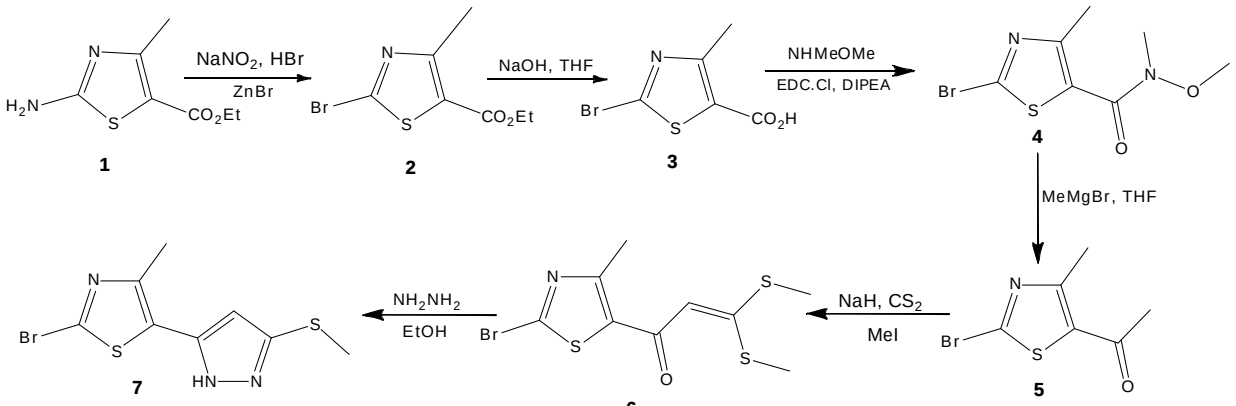
1-(2-Bromo-4-methylthiazol-5-yl)-3, 3-bis (methylthio)prop-2-en-1-one (6)
To the solution of compound **5** (2.2g 0.01 mol) in THF (20 mL) at 0^{o}C was added NaH (0.02 mol) and stirred for 1 h and followed by carbon disulfide (0.033 mol) was added and continued stirring for another 1 h. Then methyl Iodide (0.033 mol) was added to the reaction mixture and stirred at room temperature for 18h. The reaction mixture was poured in cold water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and evaporated the solvent under reduced pressure to offer crude product. The crude product was purified by silica gel (100-200 mesh) column chromatography using 0-20% ethyl acetate in pet-ether as the eluent gave compound **6** as off-white color solid.
Yield: 2.82 g, 86.76%.
^{1}H NMR ($CDCl_3$): δ 2.45 (s, 6H), 2.75 (s, 3H), 6.24 (s, 1H).

5-(2-Bromo-4-methylthiazol-5-yl)-3-(methylthio)-1H-pyrazole (7)
To the solution of compound **6** (3.25g 0.01 mol) in ethanol (10 mL) was added hydrazine hydrate (0.02 mol) and subjected for reflux at 40 ^{0}C for 14 h. The unwanted solid was filtered and filtrate was concentrated to get crude compound. The crude product was purified by silica gel (100-200 mesh) column chromatography using 0-20% ethyl acetate in pet-ether as the eluent gave the title compound **7** as off-white color solid.
Yield: 1.91 g, 65.86%.
^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H), 2.58 (s, 3H) 6.41 (s, 1H).
MS: *m/z* 290.01 (M^+)

RESULTS AND DISCUSSION

The synthesis of target molecule 5-(2-bromo-4-methylthiazol-5-yl) - 3-(methylthio)-1H-pyrazole **(7)** was achieved by sequences of reactions depicted in the following Scheme. Herein, we report our novel synthetic protocol for the synthesis of 5-(2-bromo-4-methylthiazol-5-yl) - 3-(methylthio)-1H-pyrazole (7) from 2-Amino-4-methylthiazole-5-ethylcarboxylate **(1).**

Ethyl-2-bromo-4-methylthiazole-5-carboxylate **2** was obtained by bromination of 2-Amino-4-methylthiazole-5-ethylcarboxylate **1** using hydrogen bromide in presence of sodium nitrite. Treatment of **2** with sodium hydroxide in refluxing THF afforded isolable acid product **3** that was identified and confirmed on the basis of Mass and ^{1}H NMR spectra. The ^{1}HNMR (CDCl3) spectra of compound **3** showed the characteristic signal at 13.55 as singlet (broad peak) corresponding to the acidic proton. Treatment of compound **3** with N, O-dimethyl hydroxylamine hydrochloride in dichloromethane under reflux conditions yielded compound **4**. The formation of compound **5** was resulted by treating compound **4** with Grignard reagent methyl magnesium bromide in THF solvent under reflux. The structure of compound **4** and **5** was confirmed by their spectral (MS, ^{1}HNMR) data. Reactions of **5** with sodium hydride and methyl iodide in refluxing carbon disulphide afforded compound **6** which showed two characteristic signals at δ 2.45 (s, 6H), 2.75 (s, 3H) in its ^{1}HNMR spectra.



Scheme-1 [6]

The cyclocondensation of compound **6** with hydrazine [20] was performed by refluxing in ethanol to obtain target molecule 5-(2-Bromo-4-methylthiazol-5-yl)-3-(methylthio)-1H-pyrazole in 90 % yield. The ^{1}HNMR Spectra of synthesized compound **7** showed NH proton signal of pyrazole moiety at 6.41 (s, 1H) and the signal of CH_3 protons in compound was observed between 2.45-2.58 ppm.

APPLICATIONS

To the best of our knowledge, this new procedure provides the first example of an efficient approach for the synthesis of 5-(2-Bromo-4-methylthiazol-5-yl)-3-(methylthio)-1H-pyrazoles. This method is the most simple and convenient and would be applicable for the synthesis of different types of nitrogen-containing heterocyclic compounds. The biological activity results of synthesized compounds will be reported in due course.

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