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ARTICLE

Synthesis and Characterization of 2-(3-Substituted thioamidoformamidino-4-isobutoxyphenyl)-4-methyl-5-carboxy-1,3-thiazoles

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ABSTRACT

A simple, novel and suitable method has been developed for the synthesis of 2-(3-substituted thioamidoformamidino-4-isobutoxyphenyl)-4-methyl-5-carboxy-1,3-thiazoles by the reaction of 2-(3-cyano-4-isobutoxyphenyl)-4-methyl-5-carboxy-1,3-thiazole, HCl and thiourea derivatives in 60 % ethanol-acetone. The method provides rapid and easy access to compounds in good yields by using 60 % ethanol-acetone medium.

KEYWORDS

2-(3-Cyano-4-isobutoxyphenyl)-4-methyl-5-carboxy-1,3-thiazole, Thioureas, Acetone-ethanol medium.

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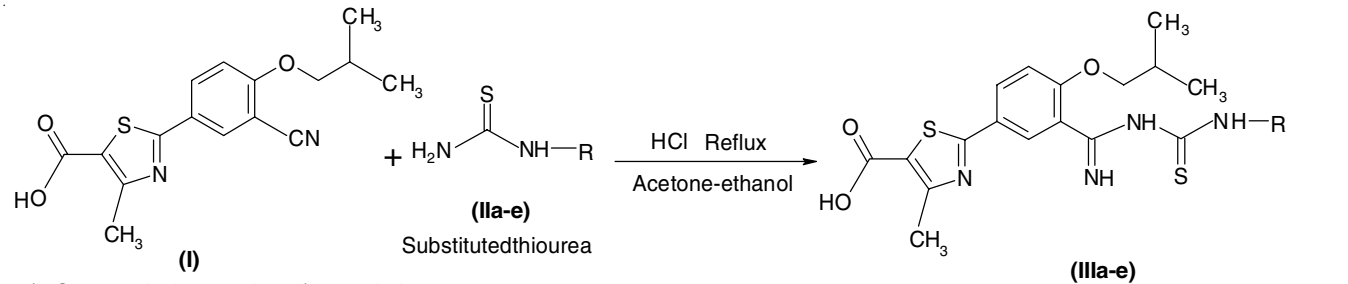
INTRODUCTION

Heterocyclic compounds are one of the most complex and intriguing part of organic transformation and its compounds constitute the largest and most varied family in organic chemistry [1-4]. Heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly and economically useful as therapeutic agents [5]. Thiocarbamido nucleus containing heterocyclic compounds show antitubercular, antibacterial, antifungal, antiviral and anti-inflammatory activities [6-10].

Thiocarbamide, dithiazines, triazines, compound have their own identity, importance and applications in medicinal, biological, agricultural, industrial and biochemical sciences [11-22].

EXPERIMENTAL

All reagents were purchased from commercial suppliers and used without further purification. All reactions were run in oven-dried round bottom flask or vial containing a teflon-coated stir bar and sealed with septum. Analytical thin layer chromatography was carried out on silica pre-coated glass plates (silica gel 60 F_{254}, 0.25 mm thickness) and visualized with UV light at 254 nm. ^{1}H NMR spectra were recorded on Bruker 400-MHz Ultrashield Advance II 400 model (400 and 100 MHz, respectively) at ambient temperature with $CDCl_3$ or DMSO-d_6 as solvents. Spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm), DMSO-d_6 (δ 2.50 ppm) or with tetramethylsilane (TMS, δ ppm) as the internal standard. Chemical shifts (δ) were reported as part per million (ppm).



Scheme-I

Synthesis of 2-(3-substituted thioamidoformamidino-4-isobutoxyphenyl)-4-methyl -5-carboxy-1,3-thiazoles (3a-e): A reaction mixture of 2-(3-cyano-4-isobutoxyphenyl)-4-methyl-5-carboxy -1,3-thiazole (**1**) and substituted thioureas (**2a-e**) was refluxed in 60 % ethanol-acetone medium (60 mL) on water bath for 3 h. The reaction mixture was concentrated under reduced pressure to remove medium and the residue was triturated in diethyl ether at 0 ºC to afford solids which was collected by filtration and washed with ice cooled diethyl ether to afford the pure product (**3a-e**) and finally recrystallized from ethanol (**Scheme-I**).

2-(3-Thioamidoformamidino-4-isobutoxyphenyl)-4-methyl-5-carboxy-1,3-thiazole (3a): (Yield: 333 mg, 85 %) white solid; m.p. 166 ºC; ^{1}H NMR (400 MHz,DMSO-d_6): 11.146 (1H, s), 8.1244-8 (1H, s, *J* =14.8 Hz), 8.3935 (1H, s, *J* = 14.8 Hz), 8.203 (1H, s), 4.918 (2H, s), 4.927 (1H, s), 3.511 (2H, d, *J* = 12 Hz), 1.011 (1H, m, *J* = 12 Hz), 1.028 (6H, d), 1.213 (1H, s). ^{13}C NMR:195, 192.2,164.3 162.5, 154.3, 148.5, 146.3, 143.1, 142, 138.5, 134.2, 130.2, 42.1, 35.2, 29.2, 25.8. IR (KBr, ν_{max}, cm^{-1}): 3349.0 s, 1682.1 s, 1605 s, 1427.0 s, 1297.0 s, 1200 s.

2-(3-Phenylthioamidoformamidino-4-isobutoxyphenyl)-4-methyl-5-carboxy-1,3-thiazole (3b): (Yield: 383 mg, 82 %), yellow solid; m.p. 190 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): 11.404 (1H, s), 7.1244 (1H, s, *J* = 14.8 Hz), 7.435 (1H, s, *J* = 14.8 Hz), 7.203 (1H, s), 6.756 (5H, s), 5.131 (2H, s), 5.140 (1H, s), 2.504 (2H, d, *J* = 12 Hz), 1.612 (1H, m, *J* = 12 Hz), 1.483 (6 H d), 1.411 (1H, s). ^{13}C NMR: 196.3, 190.2, 163.3 162.5, 155.3, 147.5, 144.3, 142.1, 141.2, 137.5, 132.4, 131.5, 128.0, 41.1, 34.2, 28.2, 24.8. IR (KBr, ν_{max}, cm^{-1}): 3095.45 s, 1636.45 s, 1594.50 s, 1373.51 s, 1280.54 s, 1059.34 s.

2-(3-Methylthioamidoformamidino-4-isobutoxyphenyl)-4-methyl-5-carboxy-1,3-thiazole (3c): (Yield 383 mg, 82 %), brown solid; m.p. 162 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): 11.321 (1H, s), 7.104 (1H, s, *J* = 12.8 Hz), 7.345 (1H, s, *J* = 12.8 Hz), 7.203 (1H, s), 5.032 (2H, s), 5.440 (1H, s), 2.642 (2H, d, *J* = 12 Hz), 1.673 (1H, m, *J* = 12Hz), 1.483 (6H, d), 1.043 (1H, s); ^{13}C NMR: 193.6,191.2,164.3 162.5, 155.3, 147.5, 145.3, 142.5, 140.5, 136.5, 134.2, 129.2, 41.1, 37.2, 28.2, 24.8, 20.2; IR (KBr, ν_{max}, cm^{-1}): 3340.1 s, 1680.12 s, 1617.21 s, 1420.2 s, 1207.2 s,1145.2 s.

2-(3-Ethylthioamidoformamidino-4-isobutoxyphenyl)-4-methyl-5-carboxy-1,3-thiazole (3d): (Yield 385 mg, 80 %), ivory solid; m.p. 168 ºC; ^{1}H NMR (400 MHz,DMSO-d_6): 11.421 (1H, s), 7.274 (1H, s, *J* = 14 Hz), 7.234 (1H, s, *J* = 14 Hz), 7.103 (1H, s), 5.131 (2H, s), 5.021 (1H, s), 2.304 (2H, d, *J* = 12 Hz), 1.763 (1H, m, *J* = 12Hz), 1.632 (6H, d), 1.043 (1H, s); ^{13}C NMR: 196, 192.2,164.3, 162.5, 155.3, 149.5, 145.3, 142.1, 141.7, 139.5, 135.2, 131.2, 41.1, 36.2, 31.2, 26.8, 24.5, 20.2; IR (KBr, ν_{max}, cm^{-1}): 3294.54 s, 1762.32 s, 1654.2 s, 1502.0 s, 1280.53 s, 1124.58 s.

2-(3-Allylthioamidoformamidino-4-isobutoxyphenyl)-4-methyl-5-carboxy-1,3-thiazole (3e): (Yield 385 mg, 80 %), pale yellow solid; m.p. 188 ºC; ^{1}H NMR (400 MHz,DMSO-d_6): 12.652 (1H, s), 7.654 (1H, s, *J* = 14 Hz), 7. (1 H, s, *J* = 14 Hz), 7.432 (1H, s), 5.234 (2H, s), 5.643 (1H, s), 2.642 (2H, d, *J* = 12 Hz), 1.654 (1H, m, *J* = 12Hz), 1.212 (6H, d), 1.456 (1H, s); ^{13}C NMR: 195.5, 188.2, 165.3, 162.5, 152.3, 148.5, 142.3, 141.1, 140, 139.5, 132.2, 130.2, 78, 54.2, 41.2, 36.9, 28.4, 24.8.19.9; IR (KBr, ν_{max}, cm^{-1}): 3813.10 s, 1715.19 s, 1620.2 s, 1490.3 s, 1197.2 s, 1112.55 s.

RESULTS AND DISCUSSION

During designing the present reaction scheme, it was planned to develop a new route for the synthesis of 2-(3-substituted thioamidoformamidino-4-isobutoxyphenyl)-4-methyl-5-carboxy-1,3-thiazole by the interactions of 2-(3-cyano-4-isobutoxyphenyl)-4-methyl-5-carboxy-1,3-thiazole, HCl and substituted thioureas in acetone, ethanol, ethanol-acetone medium at various percentage compositions and ratio. The main objective of this work is to synthesize a novel series of 2-(3-substituted thioamidoformamidino-4-isobutoxyphenyl)-4-methyl-5-carboxy-1,3-thiazoles and also to investigate a new reaction medium for such types of reactions and also to set up new reaction condition to reduce the time span of such type of reactions and at the same time, it was also thought to increase the yield of product. During the study, it was observed that the 60 % ethanol-acetone medium was the best solvent which shorten the time span.

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