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Synthesis of novel 2-amino thiazole derivatives

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ABSTRACT

Structurally diverse thiazoles were conveniently synthesised by one pot procedure by the reaction of α-haloketones and thioamides substituted with electron-donating and electron-withdrawing groups. The desired 2-aminothiazoles with alkyl or aryl or halo substitutions can be obtained in good yields. The effect of substitution was investigated. Their chemical structures were established by IR, ^{1}H NMR, mass spectral studies and elemental analyses.

Keywords: α-haloketones, Wienreb amides, 2-aminothiazoles

INTRODUCTION

Thiazoles are important class of natural and synthetic compounds. Thiazole derivatives display a wide range of biological activities such as cardiotonic[1], fungicidal[2], sedative[3], anaesthetic[4], bactericidal[5] and anti-inflammatory[6]. The synthesis of thiazole derivatives is important for their wide range of pharmaceutical and biological properties. One classical and widely used method is the condensation of *α*-haloketones with thioamides, known as the Hantzsch reaction [7-9]. Another efficient method is the introduction of substitution onto a thiazole core structure through Stille coupling [10], which involves the use of organostannane intermediates. A new and frequently encountered method for thiazole synthesis is the conversion of thiazoline derivatives by using dehydrogenating reagents such as sulphur[11], $KMnO_4$[12], Cu(I)/Cu(II)/peroxide oxidation[13], MnO_2, etc.

In course of the studies on the synthesis of thiazoles, recently, a particular interest has been aimed at the Hantzsch method for the synthesis of 2-aminothiazole derivatives which have been found to be active local anaesthetics[14-15]. The versatility of Wienreb amides in the synthesis of 2-amino thiazoles is well documented [16-19]. Wienreb amides with a wide range of applications are further converted to 2-amino thiazole derivatives[20-22].

In view of the above reports, we herein report the synthesis of novel 2-aminothiazole derivatives by Hantzsch method. Their structures were established by IR, ^{1}H-NMR and mass spectral data.

MATERIALS AND METHODS

Melting points were determined in an open capillary tube on Mel-temp apparatus, Tempo instruments, India and were uncorrected. Sigma-Aldrich, Merck and Lancaster Chemicals were used as such. Solvents used for spectroscopic and other physical studies were reagent grade and were further purified by standard procedures and techniques. The IR spectra were recorded (in KBr pellets) on SCHIMADZU spectrophotometer. ^{1}H NMR spectra were recorded (in DMSO/$CDCl_3$) on a JEOL AL300 FTNMR Spectrometer using TMS as internal standard. Mass spectra were recorded on LCMS-2010A, SHIMADZU spectrometer. Elemental analyses were performed on a Perkins-Elmer CHN Elemental analyzer.

Scheme-1

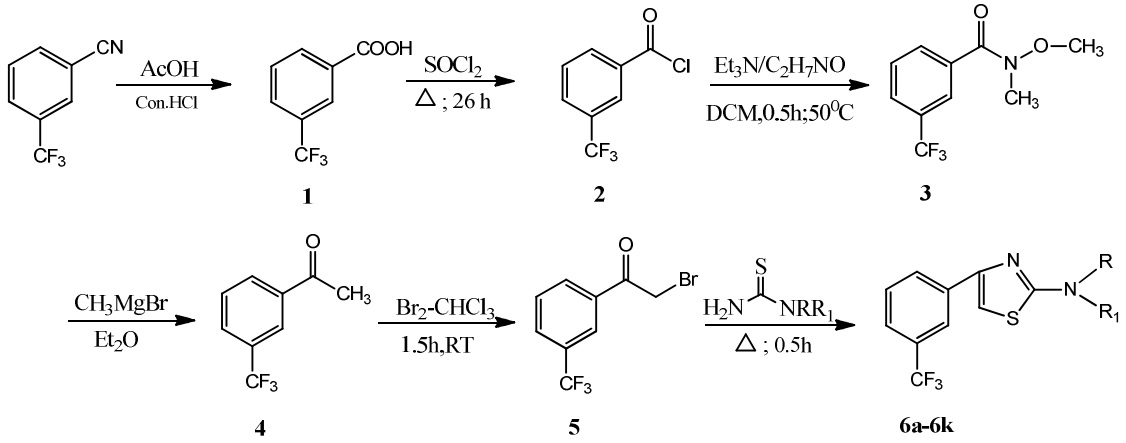
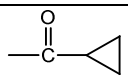
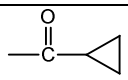
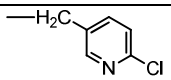
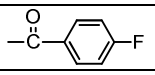
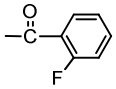
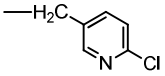
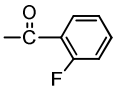
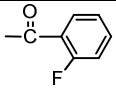
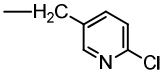
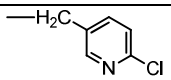
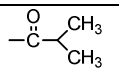
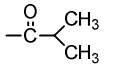
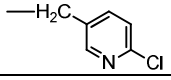
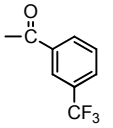


Table-1

Compound	R	R_1
6a	-H	$-CH_3$
6b		$-CH_3$
6c		
6d	$-CH_3$	
6e		
6f	$-CH_3$	
6g		
6h	-H	
6i		$-CH_3$
6j		
6k		$-CH_3$

Chemistry:

The 2-aminothiazole derivatives were synthesised *via* the routes shown in scheme-1. Benzonitriles on hydrolyses with a mixture of acids gave corresponding benzoic acid. Treatment of the acid with thionyl chloride yielded the acid chloride which on further reaction with hydroxylamine hydrochloride and triethylamine gave Wienreb amide. Amide was treated with Grignard reagent followed by cyclo-condensation with thioamides to give corresponding 2-aminothiazole derivatives.

General procedure for the preparation of title compounds 6a-k:

3-(Tri-fluoromethyl)benzoic acid **(1)** (1 g, 5.2mmole) was treated with $SOCl_2$ (1.33g, 11mmole) to give 3-(tri-fluoromethyl)benzoyl chloride **(2)** (1.48g, 0.71m mole) in the presence of triethylamine(TEA) (1.58g) in N,O-

dimethylhydroxylamine and DCM under N_2 atmosphere, stirred at 50^0C for 30mins to give N-methoxy-N-methyl-3-trifluromethyl benzamide **(3)**.The progress of the reaction was monitored by TLC analysis. This on further reaction with Grignard reagent (0.80 mole) in ammonium chloride at room temperature gave ketone **(4)** which on further bromination with Br_2 in $CHCl_3$ yielded 2-bromo-1-(3-trifluromethyl) phenylethanone (**5**). Compound **5** undergoes cyclo-condensation with substituted thiourea to give corresponding 2-amino thiazole derivatives **(6)**. Stoichiometric proportions of 2-bromo-(3-trifluromethyl) phenyl ethanone (**5**) was dissolved in ethanol and appropriate amounts of thioamide / substituted thioamides were slowly added. The reaction mixture was refluxed for 30 mins, and then poured into ice cold water (50ml). It is then extracted with ethyl acetate (100 ml) and the extract is washed with water, dried over $MgSO_4$ and evaporated in vacuo. The resulting solid was recrystallised from ethanol. The titled compounds (**6a-6k**) were prepared from appropriate ketones and thioamides by following the same procedure shown in Table 1.

Analytical data

Synthesis of N-methyl-4-(3-trifluoromethyl) phenyl) thiazole-2-amine (6a):
Yield: 61.62%, M.P: 232^0 C. ^{1}H NMR Spectrum ($CDCl_3$): δ7.60- 8.18 (m, 5H, Ar-H), 2.90 (s, N-H), 2.50 (d,–CH_3). Mass Spectrum, m/z: 259 $(M+H)^+$.

Synthesis of N-methyl-N-(4-(3-(trifluoromethyl) phenyl) thiazol-2-yl) cyclopropane carboxamide (6b):
Yield: 69%, M.P: 275-277^0 C. ^{1}H NMR Spectrum ($CDCl_3$): δ 7.47- 8.18 (m, 4H, Ar-H), 5.30 (s, 1H, –CH_3), 2.12 (m, –CH), 1.16 (d, –CH_2). Mass Spectrum, m/z: 327 $(M+H)^+$.

Synthesis of N-(6-chloropyridin-3-yl) methyl)-N-(4-(3-(trifluoromethyl) phenyl) thiazol-2-yl) cyclopropanecarboxamide (6c):
Yield: 68%, M.P:290^0 C. ^{1}H NMR Spectrum ($CDCl_3$): δ 7.22-8.50 (m, 7H, Ar-H), 5.68 (s, -CH_2), 1.9 (m, -CH of cyclopropane), 0.88-1.00 (m, –CH_2 of cyclopropane). Mass Spectrum, m/z: 438 $(M+H)^+$.

Synthesis of 4-fluoro-N-methyl-N-(4-(3-(trifluoro methyl) phenyl) thiazol-2-yl) benzamide (6d):
Yield: 77%, B.P: 309^0 C. ^{1}H NMR Spectrum ($CDCl_3$): δ 7.47-8.36 (m, 9H, Ar-H), 3.60 (s, -CH_3). Mass Spectrum, m/z: 381 $(M+H)^+$.

Synthesis of N-(6-chloropyridin-3-yl) methyl)-4-fluoro-N-(4-(3-(trifluoromethyl) phenyl) thiazol-2-yl) benzamide (6e):
Yield: 66%, B.P:211^0 C. ^{1}H NMR Spectrum (DMSO): δ 7.34-8.30 (m, 11H, Ar-H), 5.40 (s, –CH_2 of py). Mass Spectrum, m/z: 492 $(M+H)^+$.

Synthesis of 2-fluoro-N-methyl-N-(4-(3-trifluoro methyl) phenyl) thiazol-2-yl) benzamide (6f):
Yield: 69%, M.P:196^0 C. ^{1}H NMR Spectrum (DMSO): δ 7.38-8.22 (m, 9H, Ar-H), 3.60 (s, –CH_3). Mass Spectrum, m/z: 381 $(M+H)^+$.

Synthesis of N-[{6-chloropyridin-3yl) methyl}-2-fluoro-N-(4-(3-trifluoromethyl) phenyl) thiazol-2-yl) benzamide (6g):
Yield: 60%, B.P:201^0 C. ^{1}H NMR Spectrum ($CDCl_3$): δ 7.22-8.20 (m, 11H, Ar-H), 5.34 (s, –CH_2 of py). Mass Spectrum, m/z: 492 $(M+H)^+$.

Synthesis of N-(6-chloropyridin-3-yl) methyl)-4-(3-(trifluoromethyl) phenyl) thiazol-2-amine (6h):
Yield: 75%, M.P:176^0 C. ^{1}H NMR Spectrum (DMSO): δ 7.30-8.50 (m, 8H, Ar-H), 4.60 (d, -CH_2), 5.50 (s, N-H). Mass Spectrum, m/z: 370 $(M+H)^+$.

Synthesis of N-methyl-N-(4-(3-(trifluromethyl) phenyl) thiazol-2-yl) isobutyramide (6i):
Yield: 67%, B.P:243^0 C. ^{1}H NMR Spectrum ($CDCl_3$): δ 7.47-8.20 (m, Ar-H), 3.84 (s, N-CH_3), 3.10 (sep, –CH), 1.22 (dd, 2x–CH_3). Mass Spectrum, m/z: 329 $(M+H)^+$.

Synthesis of N-{(6-chloropyridin-3-yl)methyl)-N-(4-(3-(trifluoro methyl) phenyl) thiazol-2-yl) isobutyramide (6j):
Yield: 63%, B.P:256^0C. ^{1}H NMR Spectrum (DMSO): δ 7.47-8.20 (m, Ar-H), 7.32-8.40 (m, pyridine), 5.60 (s, –-CH_2), 3.0 (sep, –CH), 1.20 (d, –CH_3). Mass Spectrum, m/z: 440 $(M+H)^+$.

Synthesis of N-methyl-3-(trifluoromethyl)-N-(4-(3-(trifluoromethyl) phenyl) thiazol-2-yl) benzamide (6k):
Yield: 72%, B.P: 1720C. ^{1}H NMR Spectrum (DMSO): δ 7.42-8.18 (m, 2xAr-H), 3.78 (s,–CH_3) . Mass Spectrum, m/z: 431 $(M+H)^+$.

RESULTS AND DISCUSSION

The 2-aminothiazole derivatives were synthesised *via* the routes shown in scheme 1. Benzonitriles on hydrolyses with a mixture of acids gave corresponding benzoic acid. Treatment of the acid with thionyl chloride yielded the acid chloride which on further reaction with hydroxylamine hydrochloride and triethylamine gave Wienreb amide. Amide was treated with Grignard reagent followed by cyclo-condensation with thioamides to give corresponding 2-aminothiazole derivatives. The progress of the reaction was monitored by thin layer chromatography (TLC) analysis and the products were purified by column chromatography. The structures of the titled compounds **6a-k** were established by their spectroscopic data.

The aromatic protons of the titled compounds **6a-k** resonated as a multiplet at δ 7.33-8.20 for (3-trifluoro methyl) phenyl moiety and two doublets at δ 7.34-8.71 for (6-chloropyridyl) moiety. The remaining protons of the titled compounds appeared in expected region.

CONCLUSION

We have successfully synthesised a series of new 2-aminothiazole derivatives in higher yields by Hantzsch reaction by adopting a simple and straight forward procedure. The advantages are shorter reaction times, low cost of the starting chemicals and simple experimental procedures.

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