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Synthesis and spectral study of phenoxy and active methylene derivatives of 6-Cyano-5-Oxo-7-(methylthio)-5*h*-thiazolo[3,2-*A*]pyrimidine

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Abstract
The 6-Cyano-5-oxo-7-(methylthio)-5*H*-thiazolo[3,2-*a*]pyrimidine (1) is reacted with selected nucleophiles such as substituted phenols and active methylene compounds to afford 7-substituted derivatives of parent thiazolo[3,2-*a*]pyrimidine in N,N-dimethyl formamide (DMF) and anhydrous potassium carbonate under reflux condition. The newly synthesized compounds were analyzed by different spectral analysis techniques like Infrared Spectroscopy and Nuclear Magnetic Resonance Spectroscopy.

Keywords: 6-Cyano-5-oxo-7-(methylthio)-5*H*-thiazolo[3,2-*a*]pyrimidine,Spectroscopy, K_2CO_3, N,N-dimethyl formamide

Introduction

Heterocyclic compounds have attracted the attention of chemist over the decades due to their interesting medicinal properties. Thiazolo pyrimidine compounds contain Sulfur and nitrogen and these heterocycles proven to be significant in the process of drug discovery [1-2]. The synthesis of thiazolo pyrimidine derivatives involves the fusion of pyrimidine and thiazole moieties through various synthetic methodologies. This structural fusion impart diverse chemical and biological properties to the resulting compounds, making them important building blocks for the development of new drugs and bioactive molecules. Based on the reported literature on the importance of thiazolo pyrimidines in medicinal chemistry, chemist have continued the interest of synthesizing thiazolo pyrimidine compounds. The compounds having thiazolo[3,2-*a*]pyrimidine moiety shows interesting a variety of medicinal properties such as anticancer [3], antimicrobial [4], anti-inflammatory [5], antioxidant [6], antitumor [7] and antiviral [8]. Hence the synthesis of various thiazolo[3,2-*a*]pyrimidines derivatives is of great importance. In this paper, we reported synthesis of phenoxy and active methylene derivative of thiazolo[3,2-*a*]pyrimidine by condensing 6-Cyano-5-oxo-7-(methylthio)-5*H*-thiazolo[3,2-*a*]pyrimidine with selected nucleophile like substituted phenols and active methylene compounds in N,N-dimethyl formamide (DMF) and anhydrous potassium carbonate. The synthesized compounds were characterized by IR, ^{1}HNMR and Mass spectroscopy. The present work provides significant method include simple, inexpensive experimental procedure, short reaction time, and good yield.

Experimental

All the chemicals used in present works are from analytical grade and used without additional purification. Melting points of the products were determined in open capillary tubes on an electro thermal melting point apparatus and were uncorrected. The progress of reactions and the purity of the isolated compounds were monitored by thin layer chromatography on Ultra Violet active silica gel plate (Merck). Infrared spectra were recorded on Shimadzu FT-IR spectrophotometer, ^{1}HNMR spectra were obtained on Bruker advance spectrophotometer 500 MHz in DMSO-d_6 using tetramethyl silane (TMS) as an internal standard. Mass spectrums were analyzed on GC-MS spectrometer using the electron spray ionization technique.

General Procedure

7-Substituted derivative of 6-Cyano-5-oxo-5*H*-thiazolo [3,2-*a*] pyrimidine (2a-2d,3a-3d):

A mixture of 6-cyano-5-oxo-7-(methylthio)-5*H*-thiazolo[3,2-*a*]pyrimidine (1) (0.001 mol) and independently with aromatic phenols and active methylene compounds (0.001mol) in 15 mL of N, N'-dimethyl formamide and anhydrous potassium carbonate (10mg) was refluxed for 4 hours. The reaction mixture was cooled to room temperature and poured in to ice cold water. The separated solid product was filtered, washed with cold water and recrystallized from N, N'- dimethyl formamide- ethanol mixture to give pure (2a-2d & 3a-3d) (Scheme 1 and Scheme 2).

6-Cyano-5-oxo-7-phenoxy-5*H*-thiazolo[3,2-*a*]pyrimidine (2a)

Brown powder, Yield 88 %, M.P.204°C (dec.).IR (KBr/cm^{-1}) 1730.24 (C=O stretch), 2214.23 (CN stretch), ^{1}H NMR spectrum: (DMSO-d_6, δ ppm) 5.2-6.3 (dd, 2H,-CH=CH-), 6.1-7.6 (m, 5H, Ar-H), Mass spectrum: m/z 269.03 [M^+].

6-Cyano-5-oxo-7-(4-methyl phenoxy)-5*H*-thiazolo[3,2-*a*]pyrimidine (2b)

Brown powder, Yield 83 %, M.P.202°C (dec.).IR (KBr/cm^{-1}) 1740.30 (C=O stretch), 2218.12 (CN stretch), ^{1}H NMR spectrum: (DMSO-d_6, δ ppm) 2.5 (s, 3H, Ar-CH_3), 5.4-6.7 (dd, 2H,-CH=CH-), 6.1-7.6 (m, 4H, Ar-H), Mass spectrum: m/z 283.04 [M^+].

6-Cyano-5-oxo-7-(4-methoxyphenoxy)-5*H*-thiazolo[3,2-*a*]pyrimidine (2c)

Brown powder, Yield 80 %, M.P.205°C (dec.).IR (KBr/cm^{-1}) 1735.10 (C=O stretch), 2214.24 (CN stretch), ^{1}H NMR spectrum: (DMSO-d_6, δ ppm) 3.6 (s, 3H, Ar-OCH_3), 5.1-6.5 (dd, 2H,-CH=CH-), 6.2-7.1 (m, 4H, Ar-H), Mass spectrum: m/z 299.04 [M^+].

6-Cyano-5-oxo-7-(4-chloro phenoxy)-5*H*-thiazolo[3,2-*a*]pyrimidine (2d)

Brown powder, Yield 84 %, M.P.207°C (dec.).IR (KBr/cm^{-1}) 1720.30 (C=O stretch), 2217.30 (CN stretch), ^{1}H NMR spectrum: (DMSO-d_6, δ ppm) 5.3-6.4 (dd, 2H,-CH=CH-), 6.5-7.6 (m, 4H, Ar-H), Mass spectrum: m/z 302.99 [M^+].

6-Cyano-5-oxo-7-malonyl-5*H*-thiazolo[3,2-*a*]pyrimidine (3a)

Brown powder, Yield 83%, M.P.197°C (dec.).IR (KBr/cm^{-1}) 1715.24 (C=O stretch), 2208.23 (CN stretch), ^{1}H NMR spectrum: (DMSO-d$_6$, δ ppm) 4.1 (s, 1H, -CH-), 5.1-6.0 (dd, 2H,-CH=CH-), Mass spectrum: m/z 241.01 [M$^+$].

6-Cyano-5-oxo-7-ethyl acetoacetyl-5*H*-thiazolo[3,2 *a*]pyrimidine (3b)

Brown powder, Yield 90 %, M.P.214°C (dec.).IR (KBr/cm^{-1}) 1730.24 (C=O stretch), 2214.23 (CN stretch), ^{1}H NMR spectrum: (DMSO-d$_6$, δ ppm) 1.5(t, 3H,-CH$_3$), 2.8 (s, 3H,-COCH$_3$), 3.9 (s, 1H,-CH-), 4.3 (q, 2H, -CH$_2$-), 5.2-6.2 (dd, 2H,-CH=CH-), Mass spectrum: m/z 305.05 [M$^+$].

6-Cyano-5-oxo-7-ethyl cyanoacetyl-5*H*-thiazolo[3,2-*a*]pyrimidine (3c)

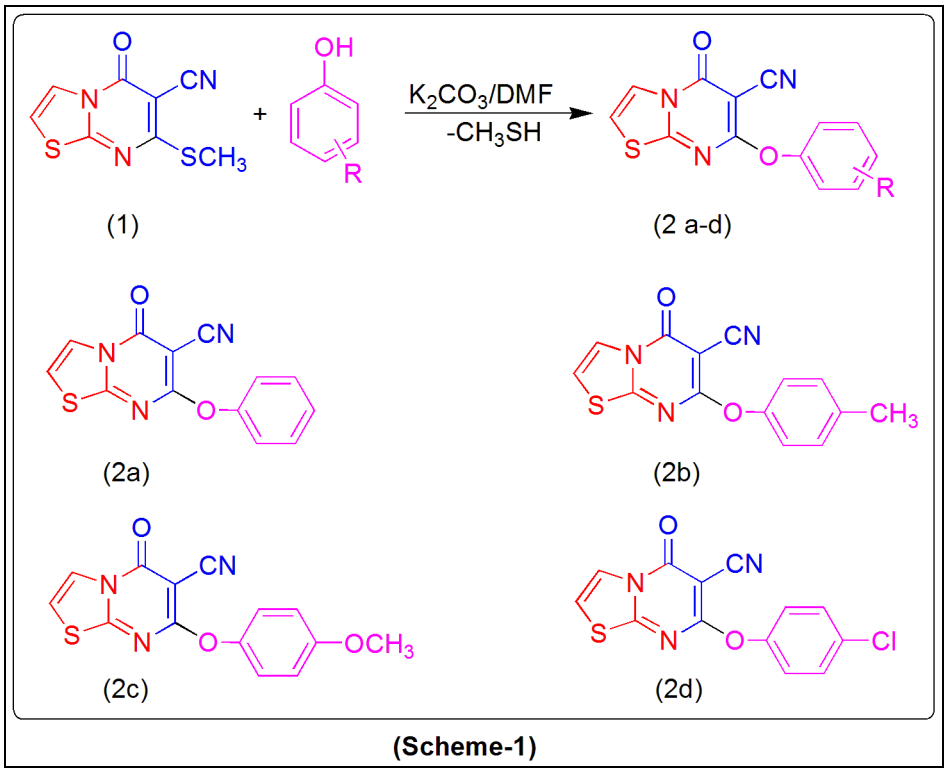
Brown powder, Yield 82 %, M.P.216°C (dec.).IR (KBr/cm^{-1}) 1710.45 (C=O stretch), 2218.05 (CN stretch), ^{1}H NMR spectrum: (DMSO-d$_6$, δ ppm) 1.2 (t, 3H,-CH$_3$), 4.1 (s,1H,-CH-), 4.4 (q, 2H, -CH$_2$-), δ 5.1-6.4 (dd, 2H,-CH=CH-), Mass spectrum: m/z 288.03 [M$^+$].

6-Cyano-5-oxo-7-acetyl acetonyl-5*H*-thiazolo[3,2-*a*]pyrimidine (3d)

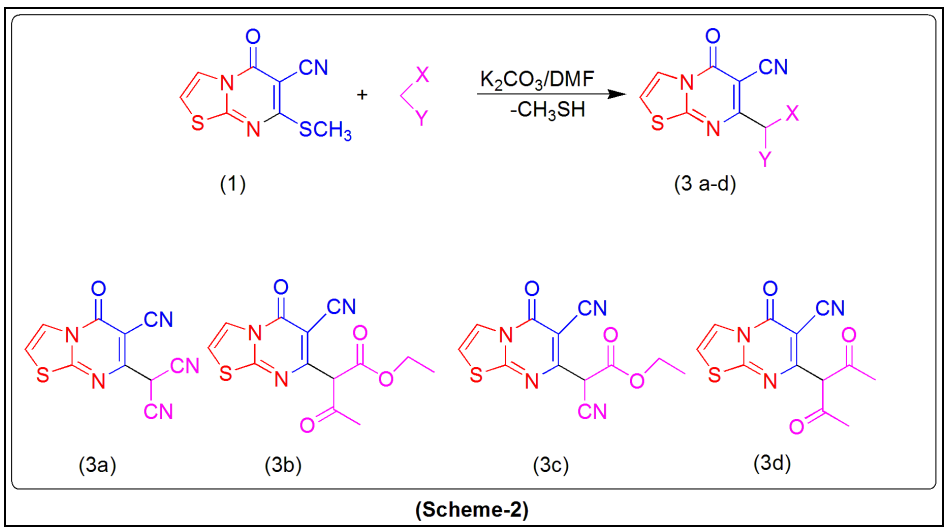
Brown solid, yield-87%, M.P. 205°C, IR spectrum: (KBr / cm^{-1}) 1724.31 (C=O stretch), 2214.15 (CN stretch), ^{1}H NMR spectrum: (DMSO-d$_6$, δ ppm) 2.6 (s, 6H,-COCH$_3$), 4.3 (s,1H,-CH-), 5.1-6.4 (dd, 2H,-CH=CH-), 6.4-7.6 (m, 5H, Ar-H), Mass spectrum: m/z 275.05 [M$^+$].

Result and Discussion

In present work, we reported the synthesis 7-substituted phenoxy(2a-d) and active methylene (3a-d) derivatives of 6-Cyano-5-oxo-7-(methylthio)-5*H*-thiazolo[3,2-*a*]pyrimidine (1). The reaction start with -Cyano-5-oxo-7-(methylthio)-5*H*-thiazolo[3,2-*a*]pyrimidine with substituted phenols and active methylene compounds in DMF and anhydrous K_2CO_3 to afford compound (2a-d) (Scheme 1) and (3a-d)(Scheme 2) respectively.



(Scheme-1)



(Scheme-2)

The structure of the newly synthesized compound (2a-d) was assigned on the basis of analytic and spectral data. IR spectrum of compound (1) shows absorption bands at 1735.42 cm^{-1} and 2206.41 cm^{-1} which can be assigned to >C=O (carbonyl), -CN stretching respectively. The ^1H NMR spectrum of the compound was recorded in DMSO-d_6, shows singlet peak at δ2.65 ppm assignable to -SCH_3 group, singlet at δ7.4- δ7.8 ppm due to thiazole ring proton. Mass spectrum exhibits molecular ion peak at m/z 223 (M^+) which corresponds to its molecular weight. Since parent compound (1) possess best leaving active thiomethyl group at 7-position which is hence, its reaction towards nucleophilic substitution with different nucleophilic regents like substituted phenols and active methylene compounds has been investigated.

Phenoxy derivatives of (1) show All these newly synthesized compounds show strong absorption bands in IR spectrum in the range 2221-2214 cm^{-1} and 1740-1720 cm^{-1} which can be assigned to -CN and >C=O stretching respectively ^1H NMR spectra showed absence of singlet at δ2.65 which shows that substitution of active thiomethyl group takes place.

All active methylene derivatives of (1) shows absorption bands in the range 2218-2208 cm^{-1} and 1730- 1710 cm^{-1} due to -CN and =NH stretching respectively in IR spectrum. Mass spectra showed peaks which show their respective molecular weight of compound, ^1H NMR spectrum show absorption signals in the range δ3.9 to δ 4.1 ppm for -CH- and absence of absorption signal δ2.60 ppm for -SCH_3, indicating substitute of -SCH_3 group by active methylene compounds.

Conclusion

In conclusion we have reported a convenient and efficient method for the synthesis of 7-substituted phenoxy and active methylene derivatives of 6-Cyano-5-oxo-7-(methylthio)-5*H*-thiazolo[3,2-*a*]pyrimidine compound through K_2CO_3 catalyzed reaction. This method provides diverse advantages, including the use of a reusable catalyst, affording high yields, employing a simple reaction procedure, and provides the simple isolation procedure. The synthesized compounds were confirmed on the basis of IR, 1HNMR and Mass Spectroscopic analysis.

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