CATRINA (2013), 8 (1): 1- 4

Synthesis and Reactions of Some Thiazole Derivatives

Sahar S. A. El-Sakka*, Mohamed H. A. Soliman and Rokaia S. A. Abdullah
Chemistry Department, Faculty of Science, Suez University, Suez, Egypt

ABSTRACT

A series of novel 2-aminothiazole derivatives (3a-e) has been synthesized by the reaction of 4-[4-methoxy-3-methylphenyl]-4-oxobutenoic acid (1) with thiourea derivatives (2a-e). The thiazolopyridazine derivatives (4a-c) and (5) were obtained from the reaction of 4-hydroxy-1,3-thiazole (3a-e) with hydrazine and phenylhydrazine, respectively. The behavior of the 4-hydroxy-1,3-thiazole (3a-e) toward acetic anhydride and bromine was also studied. The proposed structures of the products were based on microanalytical and spectroscopic data.

Key words: β-Aroylacrylic Acid, Thiazole, Thiazolopyridazine, Thiourea.

INTRODUCTION

Thiazole derivatives are a diverse and biologically significant class of compounds in which there has been considerable interest. They have considerable chemical and pharmacological importance. Particularly, they are useful as anticonvulsant activity(Uluosy*et al*., 1996), antimicrobial (Vicini*et al*., 2008; Shah *et al*., 2007), anticancer(Baselt*et al*., 2008) and anti-inflammatory (Vazzana*et al*., 2004). Because their broad spectrum of biological activity, there has been intense development of methodology to construct such moieties (Wipf, 1995; Jagodzi, 2003; Wipf*et al*., 1996; Lee *et al*., 2005; Narender*et al*., 2005; Potewar*et al*., 2007).In this regard, the present work deals with the synthesis and reactivity of novel thiazole derivatives towards some nucleophilic and electrophilic reagents.

MATERIALS AND METHODS

Study Subjects

All melting points reported are uncorrected and determined by the open capillary tube method on a Gallen Kamp melting point apparatus:1H NMR spectra were measured on Bruker (200 MHz) with DMSO-d6 as the solvent and TMS was used as internal standard (chemical shifts are expressed as δ, ppm).IR spectra were recorded on a Perking Elmer 1430 ratio recording infrared spectrophotometer with CDS data station using KBr Wafer technique and Mass spectra were measured on a GC-MSQP 1000EX Schimadzu at microanalytical laboratory, Cairo University, Cairo, Egypt.

General procedure for the synthesis of 2-substitutedamino-4-hydroxy-5-[2-(4-methoxy-3-methylphenyl)-2-oxoethyl]-1,3-thiazoles (3a-d)

A mixture of the acid (0.01mol),appropriate thioureas (0.01mol), namely thiourea, phenyl thiourea,p-tolylthiourea and/or 4-chlorophenyl thiourea and ethanol (20 ml) in the presence of few drops of glacial acetic acid, was refluxed for 4 hrs., the solid product that obtained after cooling was filtered, washed by ethanol and crystallized from the suitable solvent to give (3a-d).

2-amino-4-hydroxy-5-[2-(4-methoxy-3-methylphenyl)-2-oxoethyl]-1,3-thiazole (3a)

Frombutanol, m.p. 240°C. IR spectrum (KBr, ν, cm^{-1}): 3219 (NH), 2964 (CH aliph.), 1665 (C=O). 1H NMR spectrum (DMSO-d6, δ ppm): 2.14 (3H, s, CH_3), 3.29-3.45 (2H, m, CH_2CH), 3.80 (3H, s, OCH_3), 4.34-4.39 (1H, m, CH-CH_2), 7.03-7.80 (3H, m, Ar-H), 8.76, 9.00 (1H, 2s, NH). MS: m/z: 278 (20 %) (M^+); Anal. calcd. C: 56.10%, H: 5.07%, N: 10.06%, for: $C_{13}H_{14}N_2O_3S$ (278.32); found: C: 56.00%, H: 5.00%, N: 10.12%.

2-anilino-4-hydroxy-5-[2-(4-methoxy-3-methylphenyl)-2-oxoethyl]-1,3-thiazole (3b)

From butanol, m.p. 210°C. IR spectrum (KBr, ν, cm^{-1}): 3260 (NH), 1664 (C=O). 1H NMR spectrum (DMSO-d6, δ ppm): 2.11 (3H, s, CH_3), 3.29- 3.64 (2H, m, CH_2CH), 3.86 (3H, s, OCH_3), 4.40 - 4.50 (H, m, CH-CH_2), 6.96 - 7.89 (8H, m, Ar-H), 11.15 (H, s, NH). MS: m/z: 354 (42 %) (M^+); Anal. calcd. C: 64.39%, H: 5.12%, N: 7.90%, for: $C_{19}H_{18}N_2O_3S$ (354.42); found: C: 64.40%, H: 5.00%, N: 8.03%.

4-hydroxy-5-[2-(4-methoxy-3-methylphenyl)-2-oxoethyl]-2-(4-toludino)-1,3-thiazole (3c)

From butanol, m.p. 225°C. IR spectrum (KBr, ν, cm^{-1}): 3181(NH), 1684 (C=O). 1H NMR spectrum (DMSO-d6, δ ppm): 2.11, 2.26 (6H, 2s, $2CH_3$-Ar.), 3.28-3.55 (2H, m, CH_2-CH), 3.86 (3H, s, OCH_3), 4.44-4.48 (H, m, CH-CH_2), 6.88-7.89 (7H, m, Ar-H). MS: m/z: 368 (98 %) (M^+); Anal. calcd. C: 65.20%, H: 5.47%, N: 7.60%, for: $C_{20}H_{20}N_2O_3S$ (368.45); found: C: 65.51%, H: 5.63%, N: 7.91%.

2-(4-chloroanilino)-4-hydroxy-5-[2-(4-methoxy-3-methylphenyl)-2-oxoethyl]-1,3-thiazole (3d)

Fromacetic acid, m.p. 228°C. IR spectrum (KBr, ν, cm^{-1}): 3173 (NH), 1667 (C=O). 1H NMR spectrum (DMSO-d6, δ ppm): 2.17 (3H, s, CH_3), 3.28 - 3.67(2H, m, CH_2-CH), 3.86 (3H, s, OCH_3), 4.40-4.60 (H, m, CH-CH_2), 6.91-7.98 (7H, m, Ar-H), 11.32 (H, s, NH). MS: m/z: 388 (62 %), (M^+),

* *Corresponding Author: saharelsakka@hotmail.com*

390 (27%) (M^++2); Anal. calcd. C: 58.69%, H: 4.41%, N: 7.20%, for: $C_{19}H_{17}C_lN_2O_3S$ (368.45); found: C: 59.06%, H: 4.92%, N: 6.97%.

General procedure for the synthesis of 6-arylamino-1,4-dihydro-3-[4-methoxy-3-methylphenyl]-1,3-thiazolo[4,5-c]pyridazines (4a-c)

To a solution of the thiazoles (3b-d) (0.01 mol) in ethanol (20 ml); hydrazine hydrate 80% (0.015 mol) was added and the reaction mixture was refluxed for 6 hrs.,The solid that separated after cooling was crystallized from suitable solvent to give the corresponding thiazolopyridazine (4a-c).

6-anilino-1,4-dihydro-3-[4-methoxy-3-methylphenyl]-1,3-thiazolo[4,5-c]pyridazine (4a)

From ethanol, m.p. 290°C. IR spectrum (KBr, ν, cm^{-1}): 3349 (NH), 1601 (C=N) or (C=C). 1H NMR spectrum (DMSO-d6, δ ppm): 2.19 (3H, s, CH_3), 3.24 (2H, s, CH_2), 3.89 (3H, s, OCH_3), 6.75-7.85 (7H, m, Ar-H). MS: m/z: 350 (1.3 %) (M^+); Anal. calcd. C: 65.12%, H: 5.18%, N: 15.99%, for: $C_{19}H_{18}N_4OS$ (350.43); found: C: 65.33%, H: 5.16%, N: 16.11%.

1,4-dihydro-3-[4-methoxy-3-methylphenyl]-6-(4-toludino)-1,3-thiazolo[4,5-c]pyridazine (4b)

From ethanol, m.p. 240-242°C. IR spectrum (KBr, ν, cm^{-1}): 3342 (NH), 1603 (C=N) or (C=C). 1H NMR spectrum (DMSO-d6, δ ppm): 2.16, 2.19 (6H, 2s, $2CH_3$-Ar), 3.33 (2H, s, CH_2), 3.80 (3H, s, OCH_3), 6.93-7.89 (7H, m, Ar-H), 8.96 (H, s, NH), 13.1 (H, s, NH). MS: m/z: 363 (14.7 %) (M^+- H); Anal. calcd. C: 65.91%, H: 5.53%, N: 15.37%, for: $C_{20}H_{20}N_4OS$ (364.46); found: C: 66.05%, H: 5.76%, N: 15.29%.

6-(4-chloroanilino)-1,4-dihydro-3-[4-methoxy-3-methylphenyl]-1,3-thiazolo[4,5-c]pyridazine (4c)

From butanol, m.p. 256-258°C. IR spectrum (KBr, ν, cm^{-1}): 3331 (NH), 1601 (C=N) or (C=C). 1H NMR spectrum (DMSO-d6, δ ppm): 2.16 (3H, s, CH_3), 3.30 (2H, s, CH_2), 3.80 (3H, s, OCH_3), 6.93-7.55 (7H, m, Ar-H), 9.2 (H, s, NH), 13.2 (H, s, NH). MS: m/z: 384 (4.5 %) (M^+); Anal. calcd. C: 59.29%, H: 4.45%, N: 14.56%, for: $C_{19}H_{17}C_lN_4OS$ (384.88); found: C: 59.00%, H: 4.56%, N: 14.48%.

Synthesis of 1,4 –dihydro-3-[4-methoxy-3 methylphenyl]-1-phenyl-6-(4-toludino)-1,3-thiazolo[4,5-c]pyridazine (5)

A mixture of 4-hydroxy-5-[2-(4-methoxy-3-methyl-phenyl)-2-oxoethyl]-2-(4-toludino)-1,3-thiazole (3b) (0.005 mol) and phenyl hydrazine hydrochloride (0.006 mol) in pyridine (5 ml) was heated under reflux for 6 hrs., the solid separated after evaporation of the most of the solvent and cooling, was washed by benzene and crystallized from the proper solvent to give (5) with m.p. 316°C. 3018 (CH-Ar), 2839-2918 (CH aliph.), 1620 (C=C). 1H NMR spectrum (DMSO-d6, δ ppm): 2.23 and 2.25 (6H, 2s, $2CH_3$-Ar), 2.36 (2H, s, CH_2), 3.89 (3H, s, OCH_3), 7.20-8.03 (12H, m, Ar- H) 9.23 (H, s, NH). MS: m/z: 440 (10 %) (M^+); Anal. calcd. C: 70.88%, H: 5.49%, N: 12.72%, for: $C_{26}H_{24}N_4OS$ (440.56); found: C: 71.32%, H: 5.42%, N: 12.66%.

Synthesis of acetyl derivatives of thiazoles (6a-d)

A solution of thiazoles (3a-d) (1gm) in acetic anhydride (5 ml) was refluxed for 4 hrs., the solid product obtained, after evaporation of most of the solvent and cooling, was filtrerd off, washed with ethanol and crystallized from the proper solvent to give (6a-d).

4-acetoxy-2-amino-5-[2-(4-methoxy-3-methylphenyl)-2-oxoethyl]-1,3-thiazole (6a)

From butanol, m.p 205°C. IR spectrum (KBr, ν, cm^{-1}): 3439 (OH), 3237 (NH), 1779 (CO-CH_3), 1672 (CO-Ar). 1H NMR spectrum (DMSO-d6, δ ppm): 2.05-2.14 (2H, m, CH_2-CH), 2.17 (3H, s, CH_3Ar), 2.48-2.50 (H, m, CH-CH_2), 3.80 (3H, s, OCH_3), 6.81-7.42 (3H, m, Ar-H), 12.34 (H, s, NH). MS: m/z: 320 (100 %) (M^+); Anal. calcd. C: 56.24%, H: 5.03%, N: 8.74%, for: $C_{15}H_{16}N_2O_4S$ (320.36); found: C: 56.47%, H: 4.88%, N: 8.91%.

4-acetoxy-2-anilino-5-[2-(4-methoxy-3-methylphenyl)-2-oxoethyl]-1,3-thiazole (6b)

From chloroform, m.p 275°C. IR spectrum (KBr, ν, cm^{-1}): 1781 (CO-CH_3), 1679 (CO-Ar). 1H NMR spectrum (DMSO-d6, δ ppm): 2.15-2.17 (2H, m, CH_2-CH), 2.27 (3H, s, CH_3Ar), 2.51 (3H, s, CH_3-CO), 3.87 (3H, s, OCH_3), 7.05-7.88 (8H, m, Ar-H). MS: m/z: 396 (4.4 %) (M^+); Anal. calcd. C: 63.62%, H: 5.08%, N: 7.07%, for: $C_{21}H_{20}N_2O_4S$ (396.46); found: C: 63.90%, H: 5.21%, N: 6.66%.

4-acetoxy-2-(4-toludino)-5-[2-(4-methoxy-3-methylphenyl)-2-oxoethyl]-1,3-thiazole(6c)

From ethanol, m.p 215°C. IR spectrum (KBr, ν, cm^{-1}): 1768 (CO-CH_3), 1672 (CO-Ar). 1H NMR spectrum (DMSO-d6, δ ppm): 1.90-2.00 (2H, m, CH_2-CH), 2.18, 2.28 (6H, 2s, $2CH_3$-Ar), 2.389 (3H, s, CH_3-C=O), 2.50 - 2.51 (H, m, CH-CH_2), 3.81 (3H, s, OCH_3), 6.72-7.41(7H, m, Ar- H). MS: m/z: 410 (16.7 %) (M^+); Anal. Calcd. C: 64.37%, H: 5.40%, N: 6.82%, for: $C_{22}H_{22}N_2O_4S$ (410.48); found: C: 64.20%, H: 5.02%, N: 6.77%.

4-acetoxy-2-(4-chloroanilino)-5-[2-(4-methoxy-3-methylphenyl)-2-oxoethyl]-1,3-thiazole (6d)

From butanol, m.p. 208°C. IR spectrum (KBr, ν, cm^{-1}): 1768 (CO-CH_3), 1672 (CO-Ar). 1H NMR spectrum (DMSO-d6, δ ppm): 1.98 (3H, s, CH_3-Ar), 2.17- 2.20 (2H, m, CH_2-CH), 2.28 (3H, s, CH_3-CO), 2.49-2.51 (H, m, CH- CH_2), 3.81 (3H, s, OCH_3), 6.73-7.64 (7H, m, Ar- H). MS: m/z: 430 (60.6 %) (M^+); Anal. calcd. C: 58.54%, H: 4.44%, N: 6.50%, for: $C_{21}H_{19}C_lN_2O_4S$ (430.90); found: C: 58.55%, H:4.44%, N: 6.38%.

Synthesis of 2-substitutedamino-4-hydroxy-5-[2-(4-methoxy-3-methylphenyl)-1-bromo-2-oxoethyl]-1,3-thiazoles (7a-b)

To a solution of thiazoles (3b) or (3d) (0.005 mol) in acetic acid (40 ml), a bromine solution (0.005 mol) inacetic acid (10 ml) was added slowly with stirring. After addition was complete, the mixture was gently warmed until HBr gas evolution ceased. The precipitated solid was filtered off, washed with ethanol, air dried and crystallized from the proper solvent to give (7a-b).

2-anilino-4-hydroxy-5-[2-(4-methoxy-3-methyl-phenyl)-1-bromo-2-oxoethyl]-1,3-thiazole (7a)

From ethanol, m.p. 250-252°C. IR spectrum (KBr, ν, cm^{-1}): 3254 (NH), 1696 (CO-Ar). 1H NMR spectrum (DMSO-d6, δ ppm): 2.19 (3H, s, CH_3-Ar), 3.32-3.45 (2H, m, CH-CH), 3.89 (3H, s, OCH_3), 7.04-8.10 (8H, m, Ar- H), 11.76 (H, s, NH). MS: m/z: 433 (1.0 %) (M^+); Anal. calcd. C: 52.67%, H: 3.95%, N: 6.46%, for: $C_{19}H_{17}BrN_2O_3S$ (433.31); found: C: 52.49%, H: 3.88%, N: 6.52%.

2-(4-chloroanilino)-4-hydroxy-5-[2-(4-methoxy-3-methylphenyl)-1-bromo-2-oxoethyl]-1,3-thiazole (7b)

From ethanol, m.p. 278-280°C. IR spectrum (KBr, ν, cm^{-1}): 3253 (NH), 1682 (CO-Ar). 1H NMR spectrum (DMSO-d6, δ ppm): 2.18 (3H, s, CH_3-Ar), 3.53-3.56 (2H, m, CH-CH), 3.89 (3H, s, OCH_3), 7.39-8.10 (7H, m, Ar- H), 11.87 (H, s, NH). MS: m/z: 386 (18.3 %) (M^+-HBr); Anal. calcd. C: 48.79%, H: 3.45%, N: 5.99%, for: $C_{19}H_{16}BrC_lN_2O_3S$ (467.76); found C: 49.20%, H: 3.55%, N: 6.10%.

RESULTS

In the present investigation the reaction of 4-methoxy-3-methylbenzoyl acrylic acid (1) with thiourea derivatives (2a-e) namely thiourea, phenyl thiourea, 4-methylphenyl thiourea, 4-chlorophenyl thiourea in ethanol in the presence of glacial acetic acid gave the corresponding 2-amino-4-hydroxy-thiazoles (3a-e) in good yields (Scheme 1).

The formation of thiazoles were assumed to proceed via nucleophilic addition of the sulfur atom to the α-. The acetylation of the thiazoles (3a-c) was carried out carbon in the acid (1) followed by amidation of the carboxylic group. In 1H NMR spectra of these compounds, the signals characteristic for methylene and methine groups of the thiazole ring appeared as two multiplets at 3.28-3.67 ppm and 4.34-4.60 ppm, respectively.

The 2-aminothiazole derivatives (3a-c) were considered as key starting material in which they reacted with various reagents (Scheme 1).

Thus, the treatment of (3a-c) with hydrazine hydrate in refluxing ethanol or phenylhydrazine hydrochloride in pyridine afforded the corresponding thiazolo-pyridazine derivatives (4a-c) and (5), respectively. The structures of these compounds were confirmed by the absence of the characteristic absorption bands corresponding to the carbonyl group in their IR spectra.

The acetylation of the thiazoles (3a-c) was carried out by boiling them with acetic anhydride giving the 5-acetoxy-2-substitutedamino-thiazoles (6a-c). The IRspectra of these compounds showed the appearance of new bands in the region 1768-1781 cm^{-1}corresponding to the acetate group which confirmed that the acetylation occurred at the hydroxyl groups and the appearance of new singlets in the aliphatic regions corresponding to the acetate groups (δ= 2.28-2.51) in their 1H NMR spectra.

The 2-aminothiazolone derive-atives (3b-c) underwent bromination upon treatment with bromine in acetic acid affording the 2-substituted amino-4-hydroxy-5-[2-(4-methoxy-3-methylphenyl)-1-bromo-2-oxoethyl]-1,3-thiazoles (7a-b).

REFERENCES

BASELT, T. AND K.REHSE. 2008." New 2-amino-thiazole-4-acetamides with antiplatelet activity. Archived der pharmazie.**24:** 645-654.

JAGODZI´NSKI, T. S.2003.Thioamides as useful synthons in the synthesis of heterocycles. Chem. Rev., 103, 197.

LEE, I. Y., J. Y.LEE,H. J. LEE, ANDY. D. GONG. 2005. Traceless Solid-Phase Synthesis of 2,4,5-Trisubstituted Thiazoles. Synlett, 2483.

NARENDER, M., M.S.REDDY,R. SRIDHAR,Y.V.D. NAGESWAR, ANDK.R. RAO. 2005. Aqueous phase synthesis of thiazoles and aminothiazoles in the presence of β-cyclodextrin.' Tetrahedron Lett., 46, 5953.

POTEWAR, T. M., S.A. INGALE, ANDK.V. SRINIVASAN. 2007. Tetrahedron, 63, 11066.

SHAH, T. J. AND V.A. DESAI. 2007. Synthesis of some novel fluorinated 4- thiazolidinones containing amide linkages and their antimicrobial screening." ARKIVOC (xiv): 218-228.

ULUSOY, N., N. ERGEN, A .C. EKINCI AND H. OZER. 1996. Synthesis and anticonvulsant activity of some new arylidenehydrazides and 4- thiazolidinones. Mon-atshefte fur Chemie**127**:1197-1202.

VAZZANA, I. E. TERRANOVA, F. MATTIOLI AND F. SPARATORE. 2004. Aromatic Schiff bases and 2,3-disubstituted-1,3-thiazolidin-4-one derivatives as antiinflammatoryagentsArkivoc**(v)**:364-374.

VICINI, P.,A. GERONIKAKI, M. INCERTI, F.ZANI, J. DEARDENCAND M. AYE HEWITT. 2008. Heteroar-ylimino-5-benzylidene-4-thiazolidinones analogues of 2-thiazolylimino-5-benzylidene-4-thiazolidinoes with antimicrobial activity: Synthesis and structureativity relationship. BioorgMedChem **16**: 3714 - 3724.

WIPF, P. 1995. Synthetic Studies of Biologically Active Marine Cyclopeptides. Chem. Rev., 95, 2115.

WIPF, P., ANDS. VENKATRAMAN. 1996. A New Thiazole Synthesis by cyclocondensation of Thioamides and Alkynyl(Aryl)Iodonium Reagents. J. Org. Chem., 61, 8004.

Received February 27, 2013
Accepted March 5, 2013