Synthesis of pyrazole, 1,3-dithiolan and thiophene derivatives pendant to thiazolo[2,3-c]-1,2,4-triazole moiety

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1. Introduction

Heterocycles are widely used in the development of modern pharmaceuticals; this is being one of the reasons why continuous efforts are placed towards the design of amenable synthetic approaches for the synthesis of new heterocyclic systems. Thiazole ring systems are known to possess various pharmacological properties such as anti-tubercular, antifungal, analgesic and anticancer activities [1-4]. 1,2,4-Triazole and their derivatives are found to be associated with various biological activities such as anticonvulsant [5-7], antifungal [8-10], anticancer [11-14], anti-inflammatory [15-17] and antibacterial properties [18-21]. In addition, compounds incorporating 1,2,4-triazole and 1,3-thiazole have been attracting widespread attention due to their diverse pharmaceutical such as antimicrobial, anti-inflammatory and antitumor activities [22,23].

Also, pyrazoles have emerged as a group of compounds possessing a broad spectrum of useful medicinal such as herbicide, fungicide and analgesic activities [24-26]. On the other hand many thiophene containing compounds including annulated compounds, exhibit biological activities [27-29].

Based on the above observations, we expected that incorporation of the above various nuclei will yield compounds with enhanced biological activities and as a part of our research program aimed at developing simple and efficient synthetic approaches for fused ring systems with bridgehead nitrogen atom, utilizing the inexpensive and readily obtainable starting materials like 5-acetyl-2-amino-4-methylthiazole [30-35], we report here on the utility of the highly versatile, multifunctional intermediates 6 and 7 as building blocks for the synthesis of the title compounds.

2. Experimental

2.1. Instrumentation

Melting points were determined on a Gallenkamp apparatus and are uncorrected. The IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The 1H and 13C NMR spectra were determined in DMSO-d6 at 300 and 75 MHz, respectively, on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

2.2. Synthesis

2.2.1. Synthesis of N’-(5-acetyl-4-methylthiazol-2-yl)-2-oxo propanehydrazonoyl chloride (3)
5-Acetyl-2-amino-4-methylthiazole salt (1) was prepared according to the reported literature [36]. The freshly diazonium salt 1 (10 mmol) was added portionwise with stirring to a cold solution (0-5 °C) of 3-chloropentane-2,4-dione (2) (10 mmol) in ethanol (50 mL) in the presence of AcONa.3H2O (2 g) over period of 30 min. The reaction mixture was stirred for further 2 h, at 0-10 °C then kept in an ice box for 24 h. The precipitate product was filtered off, washed with water, dried and finally recrystallized from dioxane to afford of the hydrazone [Scheme 1]. Yield: 55%. M.p.: 205-207 °C. FT-IR (KBr, ν, cm⁻¹): 2340, 3150 (NH), 1693, 1686 (C=O).1H NMR (300 MHz, DMSO-d₆, δ, ppm): 2.32 (s, 3H, CH₃), 2.63 (s, 3H, CH₂), 2.74 (s, 3H, CH₃), 9.88 (s, 1H, NH). MS (EL, m/z (%)): 259 [M⁺], 261 [M⁺+2]. Anal. calcd. for C₉H₇N₃O₂SBr₂: C, 28.37; H, 1.85; S, 14.32%. Found: C, 28.4; H, 2.0; S, 14.32%.

2.2.2. Synthesis of 3,6-diacetyl-5-methylthiazolo[2,3-c]-1,2,4-triazole (5)

A solution of the hydrazone 3 (10 mmol) in pyridine (20 mL) was heated under reflux for 4 h, then left to cool, then diluted with ice water containing few drops of acetic acid. The separated solid was collected by filtration, washed with water, dried and finally recrystallized from dioxane to afford of compound 5 [Scheme 1]. Yield: 46%. M.p.: 207-209 °C. FT-IR (KBr, ν, cm⁻¹): 1698, 1687 (C=O).1H NMR (300 MHz, DMSO-d₆, δ, ppm): 2.31 (s, 3H, CH₃), 2.62 (s, 3H, CH₂), 2.71 (s, 3H, CH₂).13C NMR (75 MHz, DMSO-d₆, δ, ppm): 192.3, 190.9 (CDO), 167.3 (C-3), 159.8 (C-7a), 126.7 (C-5), 124.8 (C-6), 25.5, 25.3, 16.4 (3CH₂). MS (EL, m/z (%)): 223 [M⁺]. Anal. calcd. for C₉H₉N₃O₂S: C, 48.42; H, 4.06; N, 18.82; S, 14.36. Found: C, 48.38; H, 4.10; N, 18.86; S, 14.32%.

2.2.3. Synthesis of 1,1′-(5-methylthiazolo[2,3-c]-1,2,4-triazole-3,6-diyli)bis(2-bromoethaneone) (6)

A solution of the 3,6-diacetyl-5-methylthiazolo[2,3-c]-1,2,4-triazole 5 (20 mmol) in AcOH (50 mL) was heated at 90-100 °C with stirring. To the hot solution, bromine (40 mmol) in AcOH (20 mL) was added dropwise over a period of 30 min with stirring, maintaining the temperature at 90-100 °C. After complete addition, the mixture was stirred vigorously at room temperature for further 1 h, until evolution of hydrogen bromide ceased. The reaction mixture was allowed to cool and the precipitated solid was filtered off, washed with water, dried and finally recrystallized from ethanol to afford of compound 6 [Scheme 2]. Yield: 52%. M.p.: 213-215 °C. FT-IR (KBr, ν, cm⁻¹): 1684, 1692 (C=O).1H NMR (300 MHz, DMSO-d₆, δ, ppm): 2.32 (s, 3H, CH₃), 4.29 (s, 2H, CH₂).438 (s, 2H, CH₂). MS (EL, m/z (%)): 381 [M⁺]. Anal. calcd. for C₄H₈N₂O₂SBr₂: C, 28.37; H, 1.85; N, 11.03; S, 8.42. Found: C, 28.4; H, 1.89; N, 11.10; S, 8.38%.

2.2.4. Synthesis of 3,3′-(5-methylthiazolo[2,3-c]-1,2,4-triazole-3,6-diyli)bis(3-oxopropanenitrile) (7)

To a solution of compound 6 (15 mmol) in absolute ethanol (50 mL) was added a solution of KCN (30 mmol in 15 mL H₂O) with stirring. The reaction mixture was heated on a boiling water bath. The reaction mixture was left at room temperature for 24 h, with stirring, then diluted with H₂O. The solid that precipitated was filtered off, washed with water, dried and finally recrystallized from EtOH to afford of compound 7 [Scheme 3]. Yield: 48%. M.p.: 229-230 °C. FT-IR (KBr, ν, cm⁻¹): 1685, 1695 (C=O), 2213, 2223 (2CN).1H NMR (300 MHz, DMSO-d₆, δ, ppm): 2.32 (s, 3H, CH₃), 4.50 (s, 2H, CH₂), 4.59 (s, 2H, CH₂).13C NMR (75 MHz, DMSO-d₆, δ, ppm): 196.1, 197.3 (C=O), 166.5 (C-3), 1582 (C-7a), 126.4 (C-5), 123.7 (C-6), 116.4 (2CN), 26.1, 23.5 (2CH₃), 168 (CH₃). MS (EL, m/z (%)): 273 [M⁺]. Anal. calcd. for C₈H₁₀N₂O₅: C, 48.35; H, 2.58; N, 25.63; S, 11.73. Found: C, 48.42; H, 2.60; N, 25.61; S, 11.68%.

2.2.5. Synthesis of 3,3′-(5-methylthiazolo[2,3-c]-1,2,4-triazole-3,6-diyli)bis[(bis(methylthio)methylene)-3-oxopropanenitrile] (8)

To a stirred solution of sodium hydride (40 mmol) in DMSO (20 mL), compound 7 (10 mmol) was added. The resulting mixture was stirred for 1 h, and then CS₂ (20 mmol) was added and the stirring was continued for additional 6 h, and then CH₂C≡C≡C (20 mmol) was added dropwise. Stirring continued for additional 6 h. The resulting reaction mixture was then poured onto crushed ice and the solid product was filtered off, washed with water, dried and finally recrystallized from EtOH to afford of compound 8 [Scheme 3]. Yield: 62%. M.p.: 206-208 °C. FT-IR (KBr, ν, cm⁻¹): 1683, 1692 (C=O); 2216, 2220 (2CN).1H NMR (300 MHz, DMSO-d₆, δ, ppm): 2.35 (s, 3H, CH₃), 2.63 (s, 6H, SCH₃), 2.79 (s, 6H, SCH₃).13C NMR (75 MHz, DMSO-d₆, δ, ppm): 187.9, 186.7 (C=O), 187.9, 186.1 (=CCS), 165.3 (C-3), 157.2 (C-7a), 127.2 (C-5), 137.6 (C-6), 115.9 (CN), 107.2, 92.4 (=CCS), 17.5 (SCH₃), 17.1 (CH₃). MS (EL, m/z (%)): 483 [M⁺+2]. Anal. calcd. for C₈H₁₀N₂O₂S₂: C, 42.39; H, 3.14; N, 14.54; S, 33.29. Found: C, 42.34; H, 3.18; N, 14.58; S, 33.36%.

2.2.6. Synthesis of [5-methylthiazolo[2,3-c]-1,2,4-triazole-3,6-diyli]bis[(3-amino-5-methylthio)-1H-pyrazol-4-yl)methanone] (10)

To a solution of compound 8 (10 mmol) in EtOH (25 mL), hydrazine hydrate (80%, 20 mmol) was added and the reaction mixture was refluxed for 4 h, and then left to cool. The solid product so formed was filtered off, washed with EtOH, dried and finally recrystallized from DMF:H₂O (1:1, v/v) to afford of compound 10 [Scheme 3]. Yield: 52%. M.p.: 312-314 °C.
2.2.7. Synthesis of 3,3'-([5-methylthiazolo][2,3-c]1,2,4-triazole-3,6-diyl)bis(2-(4-oxo-1,3-dithiolan-2-ylidene)-3-oxopropanenitrile) (11)

To a stirred solution of KOH (10 mmol) in DMF (30 mL), compound 7 (5 mmol) was added, after stirring for 1 h, CS₂ (10 mmol) was added to the resulting mixture. Stirring was continued for 12 h, and then chloroacetyl chloride (10 mmol) was added dropwise. Stirring was continued for an additional 8 h, then the reaction mixture was poured onto ice water. The solid product that formed was filtered off, dried and finally recrystallized from EtOH afford of compound 11 (Scheme 4). Yield: 64%. M.p.: 295-297 °C. FT-IR (KBr, ν cm⁻¹): 3417, 3356, 3291, 3228 (NH and NH₂). 1H NMR (300 MHz, DMSO-d₆, δ ppm): 2.35 (s, 3H, CH₃), 2.61 (s, 3H, SCH₃), 2.72 (s, 3H, SCH₃) 5.93 (brs, 4H, NH₂). MS (EI, m/z (%)): 505 (M⁺). Anal. calcd. for C₂₉H₁₅N₉O₄S₇: C, 40.38; H, 1.40; N, 13.85; S, 31.71. Found: C, 40.45; H, 1.48; N, 13.81; S, 31.76%.

2.2.8. Synthesis of 3,3'-(5-methylthiazolo[2,3-c]1,2,4-triazole-3,6-diyl)bis(2-(4-oxo-(5-phenylhydrazono)-1,3-dithiolan-2-ylidene)-3-oxopropanenitrile) (12)

To a solution of 11 (5 mmol) in pyridine (20 mL), an ice-cooled solution of the aniline diazonium salt (15 mmol) was added dropwise with stirring for 30 min, after which water was added and the precipitate product was filtered off, washed with water several times, dried and finally recrystallized from DMF: H₂O (1:1, v/v) to give of compound 12 (Scheme 4). Yield: 53%. M.p.: 264-266 °C. FT-IR (KBr, ν cm⁻¹): 3317, 3237 (NH), 2221, 2201, 1716, 1704, 1675, 1672 (C=O). 1H NMR (300 MHz, DMSO-d₆, δ ppm): 2.34 (s, 3H, CH₃), 7.23-7.86 (m, 10H, Ar), 11.91 (brs, 2H, NH, D₂O-exchangeable). Anal. calcd. for C₇₉H₇N₉O₅S₅: C, 48.80; H, 2.12; N, 17.66; S, 22.46. Found: C, 48.86; H, 2.15; N, 17.61; S, 22.49%.

2.2.9. Synthesis of 4,4'-([5-methylthiazolo][2,3-c]1,2,4-triazole-3,6-diyl)bis(3-benzoyl-2-(phenyl-amino)thiophene-3-carbonitrile) (15)
To a stirred solution of KOH (10 mmol) in DMF (30 mL), compound 7 (10 mmol) was added, after stirring for 1 h, phenyl isothiocyanate (20 mmol) was added to the resulting mixture. The reaction was stirred for additional 6 h, during which the 2-bromo-1-phenylethanone went into solution and a yellow product precipitated. The solid product was filtered off, washed with water, dried and finally recrystallized from DMF: EtOH (1:2, v:v) to afford compound 15 (Scheme 4). Yield: 59%. M.p.: > 330 °C FT-IR (KBr, v, cm⁻¹): 3298, 3218 (NH), 2218, 2224 (CN), 1665, 1669 (C=O). ¹H NMR (300 MHz, DMSO-­d₆, δ, ppm): 2.35 (s, 3H, CH₃), 7.21-7.83 (m, 20H, ArH), 10.93 (brs, 2H, NH, D₂O-exchangeable). Anal. calcd. for C₁₆H₁₇N₇O₂S: C, 55.61; H, 3.87; N, 28.59; S, 5.99%. Found: C, 55.61; H, 3.87; N, 28.59; S, 5.99%.

2.2.10. Synthesis of 2,2′-(5-methylthiazolo[2,3-c][1,2,4]triazole-3,6-dicarboxylic acid(3-phenyl amino)acrylonitrile) (16)

To a stirred solution of KOH (20 mmol) in DMF (30 mL) was added compound 7 (10 mmol). After stirring for 1 h, phenyl isothiocyanate (20 mmol) was added to the resulting mixture. Stirring continued for additional 6 h and then CH₂Cl₂ (20 mmol) was added, stirring continued for additional 1 h. Then, the reaction mixture was poured onto ice water. The solid product that formed was filtered off, washed with ethanol, dried and finally recrystallized from DMF: EtOH (1:1, v:v) to afford compound 16 (Scheme 5). Yield: 63%. M.p.: 312-314 °C FT-IR (KBr, v, cm⁻¹): 3392, 3268 (NH), 2223, 2198 (CN), 1698, 1694 (C=O). ¹H NMR (300 MHz, DMSO-­d₆, δ, ppm): 2.34 (s, 3H, CH₃), 2.83 (s, 3H, SCH₃), 2.89 (s, 3H, SCH₃), 7.23-7.96 (m, 10H, ArH), 9.87 (brs, 2H, NH, D₂O-exchangeable). MS (EI, m/z (%)): 572 (M+1). Anal. calcd. for C₂₁H₂₂N₅O₅S: C, 56.72; H, 3.70; N, 17.15; S, 16.83. Found: C, 56.66; H, 3.74; N, 17.09; S, 16.80%.

2.2.11. Synthesis of 2,2′-(5-methylthiazolo[2,3-c][1,2,4-triazole-3,6-diyli)dibis(3-amino-5-(phenylamino)-1H-pyrazol-4-yl) methanone) (17)

A mixture of 16 (10 mmol) and hydrazine hydrate 80%, (25 mmol) was heated on boiling water bath for 4h, then left to cool. The reaction mixture was triturated with ethanol and the resulting solid was filtered off, washed with EtOH, dried and finally recrystallized from DMF: EtOH (1:2, v:v) to afford compound 17 (Scheme 5). Yield: 62%. M.p.: 262-264 °C FT-IR (KBr, v, cm⁻¹): 3473, 3376 (NH₂), 3285, 3258, 3225 (NH), 1686, 1663, 1569 (C=O). ¹H NMR (300 MHz, DMSO-­d₆, δ, ppm): 2.35 (s, 3H, CH₃), 7.28-7.79 (m, 10H, Ar), 6.12 (brs, 4H, NH, D₂O-exchangeable); 8.74 (brs, 2H, NH, D₂O-exchangeable). MS (EI, m/z (%)): 1309, 1247 (M+1). Anal. calcd. for C₂₅H₂₁N₁₁O₂S: C, 55.65; H, 3.92; N, 28.55; S, 5.94. Found: C, 55.61; H, 3.87; N, 28.59; S, 5.99%.

2.2.12. Synthesis of (5-methylthiazolo[2,3-c][1,2,4-triazole-3,6-diyli)dibis(3-amino-5-(phenylamino)-isoxazol-4-yl) methanone) (18)

A solution of 15 (10 mmol) in ethanol (30 mL) was treated with hydroxylamine hydrochloride (20 mmol) and sodium carbonate. The reaction mixture was heated under reflux 6 h, then left to cool. The reaction solid product was collected by filtration, washed with water several times, dried and finally recrystallized from DMF:H₂O (1:1; v:v) to afford compound 18 (Scheme 5). Yield: 59%. M.p.: 308-309 °C FT-IR (KBr, v, cm⁻¹): 3445, 3351 (NH₂), 3331, 3241 (NH), 1689, 1682 (C=O). ¹H NMR (300 MHz, DMSO-­d₆, δ, ppm): 2.35 (s, 3H, CH₃), 7.25-7.76 (m, 10H, Ar); 5.71 (brs, 4H, NH, D₂O-exchangeable), 9.29 (brs, 2H, NH, D₂O-exchangeable). MS (EI, m/z (%)): 541 (M+). Anal. calcd. for C₂₅H₂₃N₁₁O₂S: C, 55.45; H, 3.54; N, 23.28; S, 5.92. Found: C, 55.40; H, 3.57; N, 23.22; S, 5.87%.

2.2.13. Synthesis of (5-methylthiazolo[2,3-c][1,2,4-triazole-3,6-diyl)dibis(1-(4-amino-1,2-dihydro-6-(phenylamino)-2-thioxopyrimidin-5-yl)methanone) (19)

A solution of compound 15 (10 mmol) in EtOH (30 mL) containing Et₃N (1 mL) was treated with solution of thiourea (20 mmol) in ethanol (15 mL). The reaction mixture was heated under reflux 16 h, then the reaction was poured onto ice water. The solid product that for was filtered off, dried and finally recrystallized from DMF to afford of compound 19 (Scheme 5). Yield: 61%. M.p.: > 332 °C FT-IR (KBr, v, cm⁻¹): 3336, 3320 (NH₂), 3261, 3158, 3117 (NH), 1678 (C=O).
to the corresponding 3,6-diacetyl-5-methylthiazolo[2,3-] revealed absorption bands at 1687 and 1698 cm−1 assignable to Its IR spectra showed the disappearance of NH absorption and analytical and spectral data consist with its assigned structure.

hydrogen chloride [37,38] (Scheme 1). The product 3 gave analytical and spectral data consist with its assigned structure. Its IR spectra showed the disappearance of NH absorption and revealed absorption bands at 1687 and 1698 cm−1 assignable to two carbonyl groups. Its 1H NMR spectrum revealed two singlet signals at δ 9.88 ppm assignable to hydrazone NH proton. The absence of any other CH signal in the 1H NMR spectrum of compound 3 excludes the presence of the azo tautomer [4].

Compound 3 undergoes a facile intramolecular cyclisation to the corresponding 3,6-diacetyl-5-methylthiazolo[2,3-]1,2,4-triazole (5) upon refluxing in pyridine via loss of hydrogen chloride [37,38] (Scheme 1). The product 5 gave analytical and spectral data consist with its assigned structure. Its IR spectra showed the disappearance of NH absorption and revealed absorption bands at 1687 and 1698 cm−1 assignable to two carbonyl groups. Its 1H NMR spectrum revealed two singlet signals at δ 2.62 and 2.71 ppm assignable to two acetyl protons, respectively.

Bormination of compound 5 afforded 1,1′-[5-methyl thiazolo[2,3-]1,2,4-triazole-3,6-diyl]bis[2-bromo]ethane) (6). The structure of compound 6 was established on the basis of elemental and spectral data. Its IR showed absorption bands at 1684 and 1692 cm−1 for two carbonyl groups. The 1H NMR spectrum revealed absorption bands at δ 4.29 and 4.38 ppm assignable to methylene protons.

Treatment of compound 6 with ethanolic potassium cyanide solution furnished 3,3′-[5-methylthiazolo[2,3-c]-1,2,4-

triazole-3,6-diyl]bis[3-oxopropanenitrile] (7). Its IR spectrum revealed absorption bands at 2213 and 2223 cm−1 for two cyano functions and absorption bands at 1689 and 1696 cm−1 for two carbonyl groups. Its 1H NMR spectrum revealed two singlet signals at δ 4.50 and 4.59 ppm assignable to methylene protons (Scheme 2).

The ketene SS-dithioacetals (8) was prepared by the reaction of 3,3′-[5-methylthiazolo[2,3-c]-1,2,4-triazole-3,6-diyl] bis[3-oxopropanenitrile] 7 with sodium hydride and carbon disulfide followed by alkylation with methyl iodide afforded 3,3′-[(5-methylthiazolo[2,3-c]-1,2,4-triazole-3,6-diyl]bis[2-(bis (methylthio)methylene)-3-oxopropanenitrile], 8.

The structure of compound 8 was elucidated on the basis of its elemental analysis and spectral data. The IR spectrum showed the appearance of absorption bands at 2216, 2220 cm−1 and 1692, 1683 cm−1 for cyano and carbonyl functions, respectively. Its 1H NMR spectrum revealed two singlet signals at δ 2.63 and 2.79 ppm assignable to methyl protons while the singlet signal for the methane protons of compound 7 was disappeared.

Reaction of compound 8 with hydrazine hydrate gave (5-methyl-thiazolo[2,3-c]-1,2,4-triazole-3,6-diyl]bis[3-amino-5-(methylthio)-1H-pyrazol-4-yl]methane, (10). The structure of compound 10 was elucidated on the basis of the elemental analysis and spectral data. The IR spectrum displayed stretching absorption bands at 3421 and 3356 cm−1 due to the two formed NH2 and two NH functions at 3291 and 3228 cm−1, while carbonyl absorption band appeared at 1685 and 1692 cm−1. Its 1H NMR spectrum revealed two signals at δ 2.61 and 2.72 ppm assigned for SCH2 protons, in addition to D2O-exchangeable signals at δ 5.93 and 8.36 ppm due to NH2 and NH protons, respectively (Scheme 5).

Reaction of compound 7 with carbon disulfide in DMF containing potassium hydroxide followed by addition of chloroacetyl chloride afforded 3,3′-[5-methylthiazolo[2,3-c]-1,2,4-triazole-3,6-diyl]bis[2-(4-oxo-1,3-dithiolan-2-ylidene)-3-

oxopropanenitrile], (11). The IR spectrum of compound 11 displayed absorption bands for CN at 2196, 2202 cm−1 and at 1716, 1698, 1668 cm−1 for carbonyl functions. Its 1H NMR
The active methylene group in 3-((5-methylthiazolo[2,3-c]-1,2,4-triazole-3,6-diyi)bis[2-(4-oxo-1,3-dithiolan-2-ylidene)-3-oxopropanenitrile] (11) coupled smoothly with benzenediazonium salt yielded 3,3"-(5-methylthiazolo[2,3-c]-1,2,4-triazole-3,6-diyi)bis[2-(4-oxo-[5-phenylhydrazono]-1,3-dithio-1,2-ylidene)-3-oxopropanenitrile], (12). The structure of compound 12 was elucidated on the basis of the elemental analysis and spectral data. Its IR NMR spectrum exhibited appearance of a broad signal at 5.37 ppm assignable for two newly formed amino protons, a broad signal at 8.89 ppm and 9.74 ppm for NH and NH protons, respectively, in addition to an aromatic multiplet in the region 7.28-7.75 ppm (Scheme 5).

4. Conclusion
A series of novel thiazolo[2,3-c]-1,2,4-triazole were prepared with good to moderate yields could be considered as good candidates for future research to develop high potency anti-inflammatory agents.

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References