CONVENIENT SYNTHESIS OF NEW 7-METHYLTETRAZOLO[1,5-a]QUINOLINE-4-CARBADEHYDE DERIVATIVES

Ibrahim Ali M. Radini[a]

Keywords: Tetrazolo[1,5-a]quinoline-4-carbaldehyde, hydrazonoyl chlorides, thiazole, chromene.

7-Methyltetrazolo[1,5-a]quinoline-4-carbaldehyde (1) was reacted with thiosemicarbazide to give the appropriate thiosemicarbazone (2). Compound (2) was reacted with different α-halocarbonyl compounds such as phenacyl bromide, hydrazonoyl chlorides and α-chloroaecetic acid to afford thiazoles (4), aryldiazynylthiazoles (6), and thiazolidin-4-one (8), respectively. A series of 7-methyltetrazolo[1,5-a]quinoline derivatives, such as 2-imino-2H-chromene (11), arylacrylohydrazides (13), (15) and (17) (and heteroaryl-ethylidene) acrylhydroazides (19), (21) and (23) has been synthesized. The structures of the newly synthesized compounds have been confirmed by spectral and elemental analyses.

Synthesis of 2-(7-Methyltetrazolo[1,5-a]quinolin-4-yl)methylcarboxylic acids (2).

To a solution of 2-cyanoacetohydrazide (0.91 g, 10 mmol) in absolute ethanol (30 mL) containing two drops of glacial acetic acid, 7-methyltetrazolo[1,5-a]quinoline-4-carbaldehyde (1) (2.12 g, 10 mmol) was added. The reaction mixture was heated under reflux for 2 h then left to cool. The solid product obtained was collected by filtration and recrystallized from EtOH-DMF as green powder, m.p. >300 °C, Yield, 83 %; IR (KBr, cm⁻¹): ν = 3412 (NH₂), 3251, 3161(NH), 1598 (C=O) cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆): δ = 2.68 (s, 3H, CH₃), 7.43 (d, 1H, J = 8, quinoline-H), 7.56 (d, 1H, J = 8, quinoline-H), 7.62 (s, 1H, quinoline-H), 7.75 (d, 1H, J = 8, quinoline-H), 7.88 (s, D₂O exchangeable, 2H, NH₂), 8.24 (s, 1H, CH=N), 8.48 (s, 1H, quinoline-H), 10.92 (s, D₂O exchangeable, 1H, NH), 13C NMR (125 MHz, DMSO-d₆): δ = 19.78 (CH₃), 121.85, 126.64, 128.12, 128.62, 131.12, 134.15, 136.38, 143.56, 147.17, 149.14, 175.11 (C=S). EI-Ms: m/z (%): 285 [M⁺, 85]; Anal. Calcd. for C₁₀H₈N₇O₃S: (285.32): C, 50.51; H, 3.89; N, 34.36 %; Found: C, 50.34; H, 3.90; N, 34.17 %.

Experimental

Melting points were determined on digital Gallen-Kamp MFB-595 instrument using open capillary tubes and are uncorrected. IR spectra were recorded on Schimadzu FTIR 440 spectrometer using KBr pellets. Mass spectra were performed at 70 eV on an MS-50 Kratos (A.E.I.) spectrometer provided with a data system. ¹H NMR (500 MHz or 400 MHz) and ¹³C NMR (125 MHz or 100 MHz) spectra were recorded on a Bruker model Ultra Shield NMR spectrometer in DMSO-d₆ using tetramethylsilane (TMS) as an internal standard, chemical shifts are reported as δ ppm units. The elemental analyses (% C, H, N) were done at the Microanalytical Center, Cairo University, Cairo, Egypt. Solvents were dried by standard techniques. The monitoring of the progress of all reactions and homogeneity of the synthesized compounds was carried out by TLC using aluminum sheets silica gel 60 F₂₅₄ (Merck).

General procedure for the preparation of compound (4).

To a suspension of thiosemicarbazone (0.285g, 1 mmol) in EtOH (20 mL), the appropriate 1-aryl-2-bromoethanones (3a or 3b) (0.01 mol) was added and heated under reflux for 4 h (TLC), then left to cool, the formed solid product was filtered off, washed with ethanol, dried, and crystallized from EtOH-DMF to afford (4a) or (4b).

Brown powder, m.p. 288 °C, Yield, 83 %; IR (KBr, cm⁻¹): ν = 3248 (NH), 1612, 1581 (C=N) cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆): δ = 2.67 (s, 3H, CH₃), 7.538 (s, 1H, thiazole-H), 7.618-7.635 (dd, 4H, J = 7, J = 2, Ar-H), 7.803-7.848 (m, 3H, quinoline-H), 8.159 (s, D₂O exchangeable, H, NH), 8.476 (s, 1H, CH=N), 8.589 (s, 1H, quinoline-H). ¹³C NMR (125 MHz, DMSO-d₆): δ = 20.87 (CH₃), 105.56, 116.29, 119.72, 120.62, 123.89, 127.54, 127.82, 129.32, 131.65, 132.76, 134.15, 134.85, 145.86, 144.45, 148.14, 168.32. El-Ms: m/z (%): 463 [M⁺, 100], 465 [(M⁺ + 2), 98]. Anal. Calcd for C₂₀H₁₄BrN₇S (464.34): C, 51.73; H, 3.04; N, 13.28; Br, 21.12 %. Found: C, 51.36; H, 2.89; N, 20.91 %.

NMR (100 MHz, DMSO-d₆): δ = 15.40, 21.70, 106.36, 121.49, 123.45, 124.77, 127.80, 128.43, 129.55, 131.30, 131.68, 133.38, 145.23, 145.49, 146.06, 149.11, 150.33, 154.43, 164.42. El-Ms: m/z (%): 325 [M⁺, 73]. Anal. Calcd for C₂₁H₂₁N₉S (427.48): C, 51.68; H, 3.41; N, 30.14 %. Found: C, 51.36; H, 3.21; N, 29.85 %.

Synthesis of 2-(7-methyltetrazolo[1,5-a]quinolin-4-yl)methylene)hydrazolidin-4-one (8)

A mixture of thiosemicarbazone (2) (0.285g, 1 mmol) and chloroacetic acid (7) (0.1 g, 1 mmol) in glacial acetic acid (30 mL) containing anhydrous sodium acetate (0.33 g, 4 mmol) was heated under reflux for 6 h (TLC). The reaction mixture was cooled; the formed solid product was filtered off, washed with ethanol, dried, and recrystallized from AcOH to afford (8). Brown, m.p. 290 °C (charing), yield, 89 %; IR (KBr, cm⁻¹): ν = 3222 (NH), 1648 (C=O) cm⁻¹; 1H NMR (500 MHz, DMSO-d₆): δ = 2.65 (s, 3H, CH₃), 3.97 (s, 1H, CH=NH), 8.16 (s, 1H, quinoline-H), 8.53 (d, 1H, J = 8.5, quinoline-H), 8.89 (s, 1H, CH=NH), 8.84 (s, 1H, quinoline-H), 11.20 (s, D₂O exchangeable, H, NH). ¹³C NMR (125 MHz, DMSO-d₆): δ = 21.70 (CH₃), 111.30, 112.31, 115.86, 118.96, 120.19, 124.93, 128.33, 128.41, 129.55, 129.61, 131.53, 131.65, 132.40, 138.07, 143.59, 145.37, 145.53, 146.07, 146.29, 152.20, 158.44, 163.54. El-Ms: m/z (%): 453 [M⁺, 5].

Synthesis of 2-cyano-N'-(7-methyltetrazolo[1,5-a]quinolin-4-yl)methylene)acetohydrazide (9)

To a solution of 2-cyanoacetohydrazide (0.99 g, 10 mmol) in absolute ethanol (30 mL) in the presence of few drops of triethylamine as a catalyst was heated under reflux for 3 h (TLC), then left to cool. The solid formed was isolated by filtration, washed with ethanol, dried, and recrystallized from EtOH-DMF (2:1) to afford (6a) or (6b).

4-Methyl-2-2-(7-methyltetrazolo[1,5-a]quinolin-4-yl)methylene-5-(phenylidazeny)thiazole (6a)

Red crystals, m.p. >300 °C, Yield, 85 %; IR (KBr, cm⁻¹): ν = 3251 (NH), 1707 (C=O), 1558, 1539 (C=N) cm⁻¹; 1H NMR (500 MHz, DMSO-d₆): δ = 2.67 (s, 3H, CH₃), 7.52-7.930 (m, 7H, coumarin-H and quinoline-H), 8.663 (s, 1H, thiazole-H), 8.013 (s, 1H, coumarin-H), 8.159 (s, D₂O exchangeable, H, NH), 8.526 (s, 1H, CH=N), 8.689 (s, 1H, quinoline-H). ¹³C NMR (125 MHz, DMSO-d₆): δ = 21.70 (CH₃), 111.30, 112.31, 115.86, 118.96, 120.19, 124.93, 128.33, 128.41, 129.55, 129.61, 131.53, 131.65, 132.40, 138.07, 143.59, 145.37, 145.53, 146.07, 146.29, 152.20, 158.44, 163.54. El-Ms: m/z (%): 453 [M⁺, 5].

Synthesis of Compounds (11), (13), (15) and (17)

Equimolecular mixture of 9 (0.293 g, 1 mmol) and appropriate aldehyde (1 mmol), [2,4-dihydroxy benzaldehyde (10) in case of (11), 4-(dimethylamino) benzaldehyde (12) in case of (13), 2-chloroquinoline-3-car-
Synthesis of 7-Me-tetrazolo[1,5-a]quinoline-4-carbaldehyde derivatives

Section A-Research paper

Synthesis of compounds (19) and (21)

Equimolecular mixture of (1) (0.221 g, 1 mmol) and appropriate hydrazones (18) and (20) (1 mmol) in anhydrous methanol (20 mL) containing piperidine (0.5 mL) was heated under reflux for 3.5 h (TLC). The formed solid was collected by filtration and recrystallized from methanol to give compound (19) and (21).

2-Cyano-3-(7-methyltetrazolo[1,5-a]quinolin-4-yl)-N’-(1-(thien-2-yl)ethyldiene)acrylohydrazide (19)

Brown powder, m.p. >300 °C; Yield, 81 %; IR (KBr, cm−1): ν = 3197 (NH), 2205 (CN), 1619 (C=O) cm−1; 1H NMR (500 MHz, DMSO-d6): δ = 2.29 (s, 3H, CH3), 2.89 (s, 3H, CH3), 6.49-7.15 (m, 3H, furan-H), 7.65-8.60, (m, 4H, quinoline-H), 8.76 (s, 1H, CH=C), 11.60 (s, 1H, NH, D2O exchangeable); EI-Ms: m/z (%): 401 [M+], 43. Anal. Calcd. for C25H15N11O (401.44): C, 62.03; H, 3.61; N, 25.16 %; Found: C, 61.60; H, 3.52; N, 23.72 %.

Results and Discussion

The synthetic procedures adopted to obtain the target compounds are depicted in Schemes 1-3. The starting material (1) was prepared according the literature procedures.14

Reaction of (1) with molar amount of thiosemicarbazide in boiling absolute ethanol containing few drops of acetic acid for 2 h, afforded 2-(7-methyltetrazolo[1,5-a]quinolin-4-yl)methylene hydrazinecarbothioamide (2) in a good yield.

The reaction of compound (2) with equivalent amount of α-haloketones, for example, 4-bromophenacyl bromide (3a) and 3-bromoacetyloumarin (3b), was performed in refluxing ethanol to yield (4a) and (b) in good yields. Also, (2) was reacted with hydrazonoyl chlorides, e.g. (5a) and (5b), in boiling ethanol in the presence of catalytic amount of triethyl amine to give thiazoles (6a) and (6b) in good yields.

Yellow crystals, m.p. 266-267 °C, Yield, 85 %; IR (KBr, cm−1): ν = 3237 (NH), 2214 (CN), 1667 (C=O) cm−1; 1H NMR (500 MHz, DMSO-d6): δ = 2.83 (s, 6H, 2CH3), 6.99-8.28 (m, 8H, Ar-H), 8.51 (s, 1H, CH=C), 8.72 (s, 1H, CH=NH), 12.05 (s, 1H, NH, D2O exchangeable); EI-Ms: m/z (%): 401 [M+], 43. Anal. Calcd. for C25H15N11O (401.44): C, 62.03; H, 3.61; N, 25.16 %.

2-Cyano-3-(7-methyltetrazolo[1,5-a]quinolin-4-yl)-N’-(1-(fur-2-yl)ethyldiene)-3-(7-methyltetrazolo[1,5-a]quinolin-4-yl)methyleneacrylohydrazide (13)

Orange crystals, m.p. 290-291 °C, Yield, 87 %; IR (KBr, cm−1): ν = 3205 (NH), 2202 (CN), 1660 (C=O); 1H NMR (500 MHz, DMSO-d6): δ = 3.67 (s, 3H, CH3), 3.87 (s, 3H, 2CH3), 6.83-8.63 (m, 8H, Ar-H), 8.47 (s, 1H, CH=C), 8.68 (s, 1H, CH=NH), 12.08 (s, 1H, NH, D2O exchangeable) ppm; EI-Ms: m/z (%): 424 [M+], 33. Anal. Calcd. for C23H16N5O (424.17): C, 65.08; H, 4.75; N, 26.40; Found C, 64.87; H, 4.59; N, 26.05.

2-Cyano-3-(7-methyltetrazolo[1,5-a]quinolin-4-yl)methyleneacrylohydrazide (11)

Brown powder, m.p. >300 °C, Yield, 85 %; IR (KBr, cm−1): ν = 3396.6 (OH), 3284 (NH), 1678 (C=O) cm−1; 1H NMR (500 MHz, DMSO-d6): δ = 2.68 (s, 3H, CH3), 6.96-8.22 (m, 9H, Ar-H), 8.47 (s, 1H, CH=C), 8.68 (s, 1H, CH=NH), 12.08 (s, 1H, NH, D2O exchangeable) ppm; EI-Ms: m/z (%): 401 [M+], 43. Anal. Calcd. for C20H15N7OS (401.44): C, 62.33; H, 3.92; N, 25.44 %; Found: C, 62.03; H, 3.61; N, 25.16 %.

7-Hydroxy-2-imino-N’-(7-methyltetrazolo[1,5-a]quinolin-4-yl)methylene)-2H-chromene-3-carbohydrazide (11)

2-Cyano-3-(4-(dimethylamino)phenyl)-N’-(7-methyltetrazolo[1,5-a]quinolin-4-yl)methyleneacrylohydrazide (15)

Yellow crystals, m.p. 296 °C, Yield 79 %; IR (KBr, cm−1): ν = 3124 (NH), 2214 (CN), 1619 (C=O) cm−1; 1H NMR (500 MHz, DMSO-d6): δ = 2.33 (s, 3H, CH3), 2.89 (s, 3H, CH3), 6.49-7.15 (m, 3H, furan-H), 7.65-8.60, (m, 4H, quinoline-H), 8.76 (s, 1H, CH=C), 11.60 (s, 1H, NH, D2O exchangeable); EI-Ms: m/z (%): 401 [M+], 33. Anal. Calcd. for C25H15N11O (401.44): C, 62.03; H, 3.61; N, 25.16 %.

3-(2-Chloroquinolin-3-yl)-2-cyano-N’-(7-methyltetrazolo[1,5-a]quinolin-4-yl)methyleneacrylohydrazide (15)

Yellow crystals, m.p. 290-292 °C, Yield, 89 %; IR (KBr, cm−1): ν = 3234 (NH), 2205 (CN), 1660 (C=O); 1H NMR (500 MHz, DMSO-d6): δ = 3.67 (s, 3H, CH3), 3.87 (s, 3H, 2CH3), 6.96-8.22 (m, 9H, Ar-H), 8.47 (s, 1H, CH=C), 8.68 (s, 1H, CH=NH), 12.08 (s, 1H, NH, D2O exchangeable) ppm; EI-Ms: m/z (%): 466 [M+], 33. Anal. Calcd. for C25H15N11O (466.88): C, 61.74; H, 3.24; N, 24.00; Found C, 61.11; H, 2.99; N, 23.78.

2-Cyano-3-(7-methyltetrazolo[1,5-a]quinolin-4-yl)-N’-(7-methyltetrazolo[1,5-a]quinolin-4-yl)methyleneacrylohydrazide (17)

2-Cyano-3-(7-methyltetrazolo[1,5-a]quinolin-4-yl)-N’-(7-methyltetrazolo[1,5-a]quinolin-4-yl)methyleneacrylohydrazide (17)
Scheme 1. Synthesis of compounds (4), (6) and (8).

Scheme 2. Synthesis of compounds (11), (13), (15) and (17).
The structures suggested for compounds (9), (11), (13), (15), and (17) are in a good agreement with their analytical and spectroscopic data. The $^1$H-NMR spectrum of (9) indicated the presence of a singlet signal at δ = 3.98 ppm, assignable for the active methylene group (–COCH$_2$–CN). The IR spectrum of (11) revealed the absence of the nitrile group this confirmed the cyclization process. Also, mass spectrum of (11) contains a molecular ion peak at m/z 413, which supports the structure of compound (11).

On the other hand, Knoevenagel condensation reaction of (1) with 2-cyano-N’-(1-(thien-2-yl)ethylidene)aceto-hydrazide (18) and 2-cyano-N’-(1-(fur-2-yl)ethylidene)acetohydrazide (20) in refluxed methanol containing few drops of piperidine afforded 2-cyano-3-(7-methyltetrazolo[1,5-a]quinolin-4-yl)-N’-(1-(heteroaryl)ethylidene)acrylohydrazide (19) and (21), respectively. The structures of compounds (19) and (21) are in a good agreement with their analytical and spectroscopic data (c.f. experimental section).

Similarly, 2-((7-methyltetrazolo[1,5-a]quinolin-4-yl)methylene)hydrazono) thiazolidin-4-one (8) was obtained from the reaction of (2) with chloroacetic acid in acetic acid in the presence of sodium acetate at reflux temperature.

Spectroscopic data (IR, $^1$H NMR, and MS) and elemental analysis of compounds (4), (6), and (8) confirmed their structures. The IR spectra of compounds (4), (6), and (8) revealed the absence of absorption bands of NH$_2$ and C=S functions. In addition $^1$H NMR of these compounds indicates the disappearance of NH$_2$ signal. Also, C=S signals was disappeared in $^{13}$C NMR spectrum. Thus clearly indicating the carbothioamide moiety was involved in cyclization reaction to afford thiazole ring. The mass spectra of compounds (4), (6), and (8) showed the molecular ion peaks which were in agreement with the calculated masses (c.f. experimental section).

Reaction of compound (1), with molar amount of 2-cyanoacetoxyhydrazide in boiling absolute ethanol containing few drops of acetic acid for 2 h, afforded 2-cyano-N’-(7-methyltetrazolo[1,5-a]quinolin-4-yl) methylene)acetohydrazide (9) in a good yield. Condensation of (9) with equimolar amounts of different aldehydes, namely 2,4-dihydroxybenzaldehyde (10), 4-(dimethylamino) benzaldehyde (12), 2-chloroquinoline-3-carbaldehyde (14), and 7-methyltetrazolo[1,5-a]quinoline-4-carbaldehyde (16) in methanol in the presence of few drops of piperidine at reflux temperature gave 7-hydroxy-2-imino-N’-(7-methyltetrazolo[1,5-a]quinolin-4-yl)methylene)acrylohydrazide (11), 2-cyano-3-(4-(dimethylamino) phenyl)-N’-(7-methyltetrazolo[1,5-a]quinolin-4-yl)methylene)acrylohydrazide (13), 3-(2-chloroquinolin-3-yl)-2-cyano-N’-(7-methyltetrazolo[1,5-a]quinolin-4-yl)methylene)acrylohydrazide (15), 2-cyano-3-(7-methyltetrazolo[1,5-a]quinolin-4-yl)-N’-(7-methyltetrazolo[1,5-a]quinolin-4-yl)methylene)acrylohydrazide, respectively (Scheme 2). The formation of (11) probably takes place through condensation of the aldehydic group with the active methylene function followed by nucleophilic attack of the hydroxyl group on the neighboring nitrile residue eventually giving the target compound.

The structures of compounds (18) and (20) are in a good agreement with their analytical and spectroscopic data (c.f. experimental section).

Scheme 3. Synthesis of compounds (19), and (21).

References
Synthesis of 7-Me-tetrazolo[1,5-a]quinoline-4-carbaldehyde derivatives

Section A-Research paper


Received: 16.07.2016  
Accepted: 07.08.2016.