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Facile synthesis of [1,2,4]triazino[4,3-b][1,2,4,5]tetrazepin derivatives by a one-pot reactions using 4-amino-3-hydrazinyl-6-methyl-1,2,4-triazin-5(4*H*)-one

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Abstract

4-Amino-3-mercapto-6-methyl-1,2,4-triazin-5(4*H*)-one **1** converted to 4-amino-6-methy-3-(methylthio)-1,2,4-triazin-5(4*H*)-one by methylation with methyl iodide. Controlled hydrazination of the resulting compound afforded 4-amino-3-hydrazinyl-6-methyl-1,2,4-triazin-5(4*H*)-one **2** as a building block, to the synthesis of some novel derivatives of [1,2,4]triazino [4,3,*b*][1,2,4,5]tetrazepine **3–6**, by the reaction with 3-chloropentane-2,4-dione, chloro acetonitrile, 1,3-dichloroacetone, and methyl bromoacetate. This general synthetic procedure can be extended to the preparation of wide variety of tetrazepines using 1,2-bielectrophiles derivatives.

Keywords: 4-Amino-3-hydrazinyl-6-methyl-1,2,4-triazin-5(4H)-one; [1,2,4]Triazino [4,3,b][1,2,4,5]tetrazepine; 3-Chloropentane-2,4-dione; Chloro acetonitrile; 1,3-Dichloroacetone; Methyl bromoacetate

Tetrazepinones are a novel class of antiproliferative agents that are more potent than their clinical counterparts in tumour cells expressing the DNA repair enzyme O6-alkylguanine transferase (AGT) [1–3]. The multistep synthesis of tetrazepiones derivatives has been reported [4,5]. These compounds have antiproliferative and apoptotic effects against K562, K562-R (imatinib mesilate resistant) [4]. Literature provides only a few examples of tetrazepinone ring fused to a heterocyclic nucleus [6,7] and therefore it was decided to synthesize new derivatives of this class of heterocycles.

In the present work we have performed a one-pot synthesis of some novel derivatives of [1,2,4]triazino [4,3,*b*][1,2,4,5]tetrazepine **3–6** by the reaction of 4-amino-3-hydrazinyl-6-methyl-1,2,4-triazin-5(4*H*)-one **2** serving as a starting material. The reason for using **2** as a building block is that it is excellent binucleophilic reagent which can react with a wide variety of 1,2-bielectrophiles.

The mercaptan **1** was methylated on sulfur by methyl iodide before reacting with hydrazine hydrate to give the compound **2** which was characterized by ^{1}H NMR, IR and mass spectroscopy. In the ^{1}H NMR spectrum it exhibits

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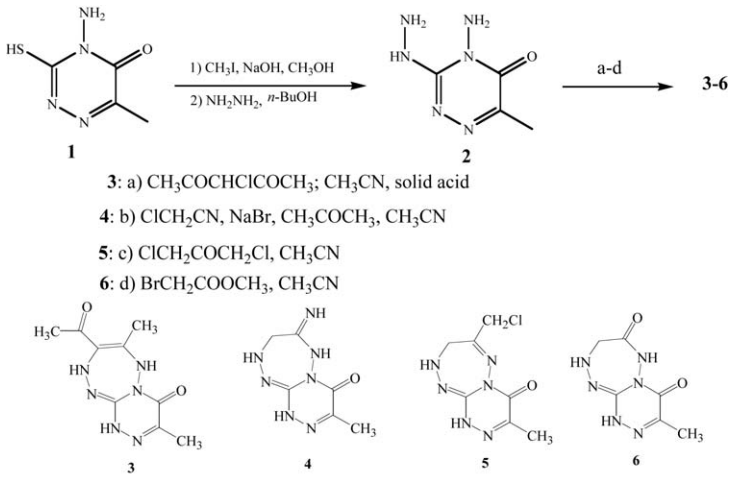

Scheme 1.

singlets at δ 11.59 (NH), 6.19 (N–NH_2), 5.71 (NH_2 of hydrazine) and a singlet at δ 1.98 indicating the methyl group. IR spectrum showed absorption bands in the regions of 3254 cm^{-1} and 3321 cm^{-1} (NH_2), 3346 cm^{-1} (NH), and 1684 cm^{-1} (C=O), respectively.

The treatment of **2** with 3-chloropentane-2,4-dione in refluxing with acetonitrile in the presence of a catalytic amount of solid acid, prepared by boiling silica gel and sulphuric acid in acetone as reported [9], afforded 8-acetyl-3,7-dimethyl-[1,2,4]triazino[4,3-b][1,2,4,5]tetrazepin-4(1*H*,6*H*,9*H*)-one **3** (Scheme 1). IR spectrum of compound **3** showed absorption bands at 1384 cm^{-1} (CH_3), 3203 cm^{-1} (NH) and 1680 cm^{-1}(C=O). ^{1}H NMR spectrum of compound **3** confirmed singlet signals at δ 2.1, 2.2 and 2.3 for methyl groups and signals at δ 7.6, 8.1 and 8.6 for three different type of NH which was exchanged for deuterium in D_2O. When compound **2** was allowed to react with chloro acetonitrile in the presence of sodium bromide it gave 7-imino-3-methyl-6,7,8,9-tetrahydro-[1,2,4]triazino[4,3-b][1,2,4,5]tetrazepin-4(1*H*)-one **4** (Scheme 1). The structure of compound **4** was elucidated by its spectral data. IR spectrum showed absorption bands in the regions of 1689 cm^{-1} (CO), 3205 cm^{-1} (NH), 1431 cm^{-1} (CH_2), 1379 cm^{-1} (CH_3), and 1618 cm^{-1}(C=N). ^{1}H NMR spectrum appeared signals at δ 2.1 and 2.2 for methyl and methylene, respectively and signals at δ 5.9, 7.3, 8.3 and 12.5 for NH groups which disappeared on exchanging with D_2O. Moreover, when compound **2** was allowed to react with 1,3-dichloroacetone in refluxing with acetonitrile, it yielded 7-(chloromethyl)-3-methyl-8,9-dihydro-[1,2,4]triazino[4,3-b][1,2,4,5]tetrazepin-4(1*H*)-one **5** (Scheme 1). The structure of compound **5** was confirmed by spectral data. IR spectrum confirmed absorption bands at 1691 cm^{-1} (CO), 1625 cm^{-1} (C=N), 1429 cm^{-1} (CH2), 3149 cm^{-1} (NH) and 746 cm^{-1} (C–Cl). ^{1}H NMR spectrum verified signals at δ 2.1, 2.3 for the methyl and methylene, respectively and signals at δ 7.8 and 12.2 for two different types of NH groups which proton–deuterium exchange occurred when D_2O was used.

Finally, the reaction of **2** with methyl bromoacetate in the presence of triethylamine yielded 3-methyl-8,9-dihydro-[1,2,4]triazino[4,3-b][1,2,4,5]tetrazepine-4,7(1*H*,6*H*)-dione **6**. IR spectrum of compound **6** showed absorption bands at 1629 cm^{-1} and 1706 cm^{-1} (C=O), 1442 cm^{-1} (CH_2) and 1382 cm^{-1} (CH_3). ^{1}H NMR confirmed signals at δ 2.1 and 2.3 for methyl and methylene, respectively and signals at δ 5.7, 7.3 and 11.3 for three type of NH groups which disappeared on exchanging with D_2O.

All melting points were measured in a BUCHI 530 melting point apparatus. The IR spectra were recorded on an FT-IR-8400 Shimadzu spectrometer. The NMR spectra were recorded on a Brucker AC-100 spectrometer using tetramethylsilane as an internal standard. High resolution Mass Spectra were recorded on a Shimadzu GT-17A spectrometer. 4-Amino-3-mercapto-6-methyl-1,2,4-triazin-5(4*H*)-one was synthesized according to a procedure reported in the literature [8].

4-Amino-3-hydrazinyl-6-methyl-1,2,4-triazin-5(4H)-one ***2***: 4-Amino-3-mercapto-6-methyl-1,2,4-triazin-5(4*H*)-one (5.8 g, 0.03 mol) was added to a solution of sodium hydroxide (1.57 g, 0.3 mol) in methanol (40 mL), stirred

for 5 min before adding excess amount of methyl iodide (6.8 mL). The mixture was stirred for 4 h at room temperature. The precipitate was filtered off and crystallized in water to give colourless crystals of 4-amino-6-methyl-3-methylthio-1,2,4-triazin-5(4*H*)-one (86%). mp 165 °C. To a solution of 4-amino-6-methyl-3-methylthio-1,2,4-triazin-5(4*H*)-one (2.0 g, 0.032) in *n*-butanol (30 mL) was added hydrazine hydrate (3.2 mL, 80%) during two steps. The mixture was refluxed for 8 h, cooled to room temperature to give crystals which was filtered off and recrystallized in *n*-butanol (47%), mp 263 °C; ^{1}H NMR (DMSO-d_6): δ 1.98 (s, 3H, CH_3), 5.71 (s, 2H, NH_2), 6.19 (s, 2H, NH_2), 11.59 (1H, NH); FT-IR(KBr disc) ν (cm^{-1}): 1684 (C=O), 3254 (NH_2), 3321 (NH_2), 3346 (NH); *m/z*: 158 (10, M+2), 156(27, M^+), 140 (34), 124 (6), 114 (18), 105 (100), 98 (3), 89 (27), 72 (28), 56 (52), 41 (62), 27 (96), 17 (90).

8-Acetyl-3,7-dimethyl-[1,2,4]triazino[4,3-b][1,2,4,5]tetrazepin-4(1H,6H,9H)-one ***3***: 4-Amino-3-hydrazinyl-6-methyl-1,2,4-triazin-5(4*H*)-one (0.7 g, 4.5 mmol) and 3-chloropentane-2,4-dione (0,7 mL, 5.2 mmol) was dissolved in acetonitrile followed by adding solid acid (0.07 g). The mixture was refluxed for 6 h, cooled to room temperature to give a precipitate which was filtered off and recrystalized from ethanol to yield brown crystals (57%), mp 237 °C; ^{1}H NMR (DMSO-d_6): δ 2.1 (s, 3H, CH_3), 2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 7.6 (1H, NH), 8.1 (1H, NH), 8.6 (1H, NH); FT-IR (KBr disc) ν (cm^{-1}): 1650 (C=O), 1584 (C=O), 3203(NH), 1384 (CH_3); *m/z*: 236 (3, M^+), 225 (4), 211 (5), 197 (5), 183 (7), 169 (8), 155 (10), 141 (13), 127 (18), 113 (23), 99 (30), 85 (93), 71 (100), 57 (100).

7-Imino-3-methyl-6,7,8,9-tetrahydro-[1,2,4]triazino[4,3-b][1,2,4,5]tetrazepin-4(1H)-one ***4***: 4-Amino-3-hydrazinyl-6-methyl-1,2,4-triazin-5(4*H*)-one (0.34 g, 2.16 mmol) was dissolved in acetonitrile (5 mL) and a few drops of acetone. Chloro acetonitrile (0.4 mL, 6.35 mmol) and sodium bromide (0.22 g, 2.12 mmol) was added and the mixture was refluxed for 8 h. After concentrating of the mixture by evaporating some of the solvents the product was precipitated out which was filtered off and recrystalized from *n*-butanol to give a yellow crystals (53%), mp (200–202 °C); ^{1}H NMR (DMSO-d_6): δ 2.1 (s, 3H, CH_3), 2.2 (s, 2H, CH_2), 5.9 (1H, NH), 7.3 (1H, NH), 8.3 (1H, NH), 12.5 (broad, 1H, NH); FT-IR(KBr disc) ν (cm^{-1}): 1689.5 (C=O), 3205.5 (NH), 1431 (CH_3), 1379 (CH_2), 1618 cm^{-1} (C=N); *m/z*: 195 (6, M^+), 181 (7), 167 (6), 156 (3), 141 (11), 127 (7), 113 (13), 96 (14), 85 (39), 71 (57), 57 (100).

7-(Chloromethyl)-3-methyl-8,9-dihydro-[1,2,4]triazino[4,3-b][1,2,4,5]tetrazepin-4(1H)-one ***5****:* 4-Amino-3-hydrazinyl-6-methyl-1,2,4-triazin-5(4*H*)-one (0.5 g, 3.2 mmol) and 1,3-dichloroacetone (0.42 g, 3.35 mmol) in acetonitrile (10 mL) and solid acid (0.05 g) was refluxed for 5 h, cooled to room temperature, filtered off the precipitate and recrystalized in ethanol to give brown crystals (48%), mp (250–252 °C); ^{1}H NMR (DMSO-d_6): δ 2.1 (s, 3H, CH_3), 2.3 (s, 2H, CH_2NH), 4.0 (s, 2H, CH_2Cl), 7.8 (1H, NH), 12.2 (1H, NH); FT-IR (KBr disc) ν (cm^{-1}): 1691 (C=O), 1625 (C=N), 3149(NH), 1380 (CH_3), 1429 (CH_2), 746.1 (C–Cl); *m/z*: 228 (6, M^+), 211 (5), 196 (7), 181 (7), 169 (25), 156 (66), 140 (86), 127 (18), 112 (48), 97 (36), 82 (100), 69 (95), 57 (100).

3-Methyl-8,9-dihydro-[1,2,4]triazino[4,3-b][1,2,4,5]tetrazepine-4,7(1H,6H)-dione ***6****:* 4-Amino-3-hydrazinyl-6-methyl-1,2,4-triazin-5(4*H*)-one (0.7 g, 4.5 mmol) and methyl bromoacetate (0,55 mL, 3.85 mmol) in acetonitrile (20 mL) and containing 5 drops of triethylamine was refluxed for 7 h. After cooling the mixture of the reaction to room temperature the product was precipitated out which was crystallized in methanol to give a yellow crystals (37%), mp 260–262 °C; ^{1}H NMR (DMSO-d_6): δ 2.1 (s, 3H, CH_3), 2.3 (s, 2H, CH_2), 5.7 (1H, NH), 7.3 (1H, NH), 11.3 (1H, NH); FT-IR(KBr disc) ν (cm^{-1}):1629 (C=O), 1706 (C=O), 3217 (NH), 1442 (CH_2), 1382 (CH_3); *m/z*: 196 (7, M^+), 181 (9), 167 (5), 152 (6), 141 (33), 127 (11), 112 (13), 98 (7), 82 (40), 69 (49), 57 (100).

In summery facile synthesis of [1,2,4]triazino[4,3-b][1,2,4,5]tetrazepin derivatives by a one-pot reactions was investigated. This general synthesis can be extended to the preparation of wide variety of tetrazepines using 1,2-bielectrophiles derivatives.

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