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Synthesis of some pyridyl and cyclohexyl substituted 1,2,4 triazole, 1,3,4-thiadiazole and 1,3,4-oxadiazole derivatives

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ABSTRACT

New 1,2,4-triazoles (4a-c), 1,3,4-thiadiazoles (5a-c) and 1,3,4-oxadiazoles (6a-c) containing isomeric pyridyl and cyclohexyl were synthesized by intramolecular cyclization of 1,4-disubstituted thiosemicarbazides (3a-c) in alkaline media, acid and neutral condition respectively. The chemical structures of newly synthesized compounds were established with help of FT-IR, ^{1}H-NMR and mass spectral data.

1. Introduction

In the last few decades, the chemistry of five-membered heterocyclic rings has received considerable attention owing to their synthetic and effective biological importance. Derivatives of 1,3,4–oxadiazole, 1,3,4–thiadiazole and 1,2,4-triazole have been found to possess a wide spectrum of biological activity [1-8].

Moreover, the mercapto- and thione-substituted 1,2,4-triazole ring systems have been well studied and a variety of biological activities have been reported for a large number of their derivatives, such as antiproliferative [9], antimicrobial [10], antifungal [11], anticancer [12,13] properties. In addition, mercapto-1,2,4-triazoles are also of great utility to prepare other heterocyclic compounds [14-16].

Prompted by these observations and as a continuation of our research program on the synthesis of 1,2,4-triazole derivatives [17-21], herein we wish to disclose synthesis of some novel five memberd heterocycle derivatives via intramolecular cyclization reactions in good yield.

2. Experimental

2.1. Instrumentation

All melting points are uncorrected. IR spectra (KBr) were recorded on a Galaxy series FT-IR 5000 spectrophotometer. ^{1}H-NMR spectra (500 MHz) were recorded on a Bruker instrument using TMS as internal standard and DMSO-d_6 as solvent. Mass spectra were recorded on a MAT-112-s machine (EI, 70 eV).

2.2. General procedure for the synthesis of 1,2,4-triazoles 4a-c

A solution of thiosemicarbazide **3a-c** (10 mmol) in 2N NaOH (10 mL) was refluxed for 3 h. The resulting solution was cooled to room temperature and acidified (pH = 3) with 2N HCl. The solid was filtered, washed with water. The compound so obtained was dried and crystallized from DMF:EtOH (1:2) to give compound **4a-c** (Scheme 1).

4-cyclohexyl-5-(pyridin-2-yl)-4H-1,2,4-triazole-3-thiol (**4a**): Yield: 87%. M.p.: 238-240 °C. IR (KBr, cm^{-1}): 3098 ν(arom. CH), 2858 ν(aliph. CH), 2777 ν(SH), 1556 ν(C=N and C=C). ^{1}H NMR (DMSO-d_6, δ, ppm): 1.03 (d, *J* = 11.6 Hz, 1H, $H_{aliph.}$), 1.23 (d, 2H, *J* = 11.7 Hz, $H_{aliph.}$), 1.57 (d, *J* = 10.9 Hz, 1H, $H_{aliph.}$), 1.67 (d, *J* = 8.6 Hz, 2H, $H_{aliph.}$), 1.73 (d, *J* = 11.0 Hz, 2H, $H_{aliph.}$), 2.30 (br, 2H, $H_{aliph.}$), 4.81 (br, 1H, C*H*-N), 7.61 (s, 1H, Ar-H), 7.84 (d, *J* = 6.4 Hz, 1H, Ar-*H*), 8.01 (s, 1H, Ar-*H*), 8.77 (s, 1H, Ar-*H*), 14.05 (s, 1H, S*H*). MS (EI, m/z(%)): 260 (M$^+$), 179, 119, 105 (base peak), 77.

4-cyclohexyl-5-(pyridin-3-yl)-4H-1,2,4-triazole-3-thiol (**4b**): Yield: 85%. M.p.: 230-232 °C. IR (KBr, cm^{-1}): 3055 ν(arom. CH), 2931, 2854 ν(aliph. CH), 2742 ν(SH), 1523 ν(C=N and C=C). ^{1}H NMR (DMSO-d_6, δ, ppm): 0.91 (d, *J* = 7.7 Hz, 1H, $H_{aliph.}$), 1.19 (q, *J* = 12.9 Hz, 2H, $H_{aliph.}$), 1.53 (d, *J* = 12.6 Hz, 1H, $H_{aliph.}$), 1.70 (d, *J* = 12.8 Hz, 2H, $H_{aliph.}$), 1.77 (d, *J* = 11.0 Hz, 2H, $H_{aliph.}$), 2.00 (br, 2H, $H_{aliph.}$), 4.26 (br, 1H, C*H*-N), 7.61 (d, d, *J* = 7.2, 5.3 Hz, 1H, Ar-*H*), 8.05 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 8.77 (s, 1H, Ar-*H*), 8.80 (d, *J* = 4.5 Hz, 1H, Ar-*H*), 14.04 (s, 1H, S*H*). MS (EI, m/z(%)): 260 (M$^+$), 179 (base peak), 105, 77.

4-cyclohexyl-5-(pyridin-4-yl)-4H-1,2,4-triazole-3-thiol (**4c**): Yield: 86%. M.p.: 314-316 °C. IR (KBr, cm^{-1}): 3098 ν(arom. CH), 2941, 2854 ν(aliph. C-H), 2729 ν(SH), 1558 ν(C=N and C=C). ^{1}H NMR (DMSO-d_6, δ, ppm): 0.96 (d, *J*=12.9 Hz, 1H, $H_{aliph.}$), 1.19 (q, *J* = 12.0 Hz, 2H, $H_{aliph.}$), 1.54 (d, *J* = 12.5 Hz, 1H, $H_{aliph.}$), 1.72 (d, *J* = 12.9 Hz, 2H, $H_{aliph.}$), 1.76 (d, *J* = 11.7 Hz, 2H, $H_{aliph.}$), 2.13 (br, 2H,

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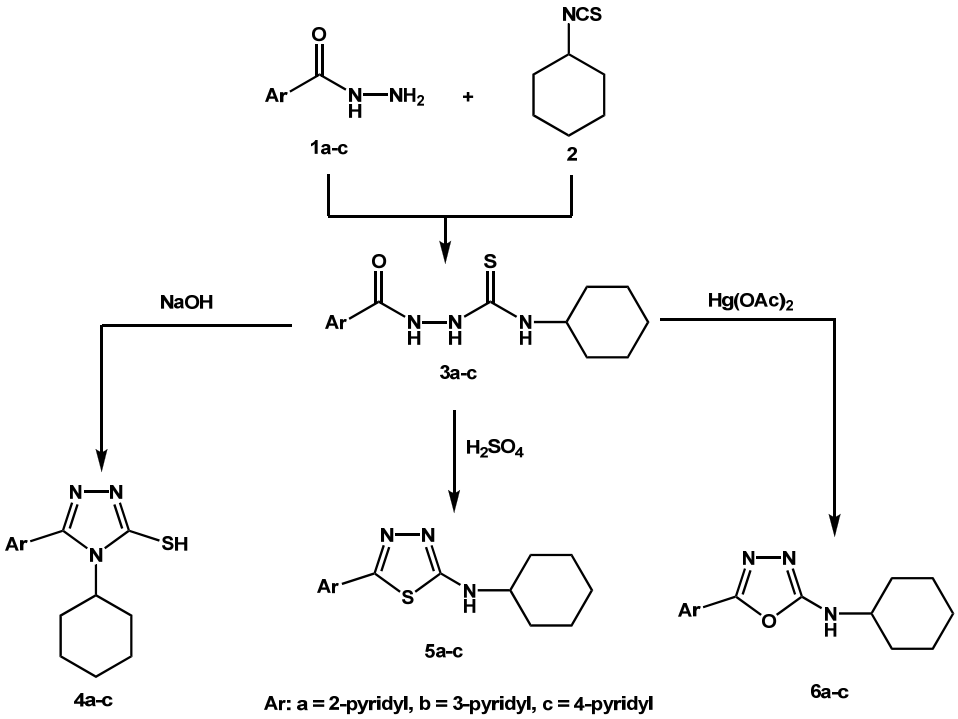

Scheme 1

$H_{aliph.}$), 4.25 (br, 1H, C*H*-N), 7.62 (d, 2H, *J* = 4.6 Hz, Ar-*H*), 8.80 (d, *J* = 4.5 Hz, 2H, Ar-*H*), 14.08 (s, 1H, S*H*). MS (EI, m/z(%)): 260 (M^+), 179 (base peak), 119, 105, 77.

2.3. General procedure for the synthesis of 1,3,4-thiadizoles **5a-c**

Each thiosemicarbazide **3a-c** (5 mmol,) was added portion wise to 10 mL of conc. sulfuric acid with continuous stirring. The reaction mixture was stirred further for 3 h at room temperature. The reaction mixture was slowly poured into crashed ice with stirring and neutralized with ammonia. The mixture was allowed to stand overnight and the solid separated out was filtered and washed with cold water. The solid was dried and crystallized from a mixture of acetic acid and water (1:2) to furnish di-substituted 1,3,4-thiadiazole **5a-c** (Scheme 1).

N-cyclohexyl-5-(pyridin-2-yl)-1,3,4-thiadiazol-2-amine (**5a**): Yield: 70%. M.p.: 168-169 °C. IR (KBr, cm^{-1}): 3277 ν(NH), 3013 ν(arom. CH), 2930, 2858 ν(aliph. C-H), 1548 ν(C=N and C=C). ^{1}H NMR (DMSO-d_6, δ, ppm): 1.17-1.36 (m, 5H, $H_{aliph.}$), 1.57 (d, 1H, *J* = 12.2 Hz, $H_{aliph.}$), 1.71 (d, 2H, *J* = 10.1 Hz, $H_{aliph.}$), 2.00 (d, 2H, *J* = 10.8 Hz, $H_{aliph.}$), 3.57 (br, 1H, C*H*-N), 7.41 (t, 1H, *J* = 5.6 Hz, Ar-*H*), 7.91 (t, 1H, *J* = 7.6 Hz, Ar-*H*), 8.03 (d, 1H, *J* = 5.2 Hz, Ar-*H*), 8.05 (s, 1H, N*H*, D_2O exchange), 8.57 (d, *J* = 4.1 Hz, 1H, Ar-*H*). MS (EI, m/z(%)): 260 (M^+), 178 (base peak), 119, 105, 78, 55, 41.

N-cyclohexyl-5-(pyridin-3-yl)-1,3,4-thiadiazol-2-amine (**5b**): Yield: 60%. M.p.: 144-145 °C. IR (KBr, cm^{-1}): 3205 ν(NH), 3011 ν(arom. CH), 2937, 2852 ν(aliph. C-H), 1550 ν(C=N and C=C). ^{1}H NMR (DMSO-d_6, δ, ppm): 1.19-1.35 (m, 5H, $H_{aliph.}$), 1.58 (d, *J* = 10.8 Hz, 1H, $H_{aliph.}$), 1.70 (d, *J* = 10.0 Hz, 2H, $H_{aliph.}$), 2.01 (d, *J* = 9.2 Hz, 2H, $H_{aliph.}$), 3.57 (br, 1H, C*H*-N), 7.50 (br, 1H, Ar-*H*), 8.05 (s, 1H, N*H*, D_2O exchange), 8.13 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 8.61 (s, 1H, Ar-*H*), 8.94 (s, 1H, Ar-*H*). MS (EI, m/z(%)): 260 (M^+), 203, 178 (base peak), 156, 119, 105, 77.

N-cyclohexyl-5-(pyridin-4-yl)-1,3,4-thiadiazol-2-amine (**5c**): Yield: 66%. M.p.: 230-231 °C. IR (KBr, cm^{-1}): 3190 ν(NH), 3010 ν(arom. CH), 2930, 2850 ν(aliph. C-H), 1580 ν(C=N and C=C). ^{1}H NMR (DMSO-d_6, δ, ppm): 1.19-1.35 (m, 5H, $H_{aliph.}$), 1.57 (d, *J* = 11.9 Hz, 1H, $H_{aliph.}$), 1.71 (d, *J* = 8.8 Hz, 2H, $H_{aliph.}$), 2.01 (d, *J* = 9.8 Hz, 2H, $H_{aliph.}$), 3.58 (br, 1H, C*H*-N), 7.70 (d, *J* = 4.6 Hz, 2H, Ar-*H*), 8.20 (s, 1H, N*H*, D_2O exchange), 8.64 (d, *J* = 4.4 Hz, 2H, Ar-*H*). MS (EI, m/z(%)): 260 (M^+), 203, 178 (base peak), 119, 105, 55, 41.

2.4. General procedure for the synthesis of 1,3,4-oxadizoles **6a-c**

A mixture of thiosemicarbazide **3a-c** (10 mmol) and mercuric acetate (10 mmol) in ethanol (30 mL) was refluxed for 3 h. The mixture was cooled at room temperature, the solid was filtered and solvent was evaporated. The crude product was crystallized from a mixture of tetrahydrofuran and petroleum ether (1:2) to furnish di-substituted 1,3,4-oxadiazole **6a-c** (Scheme 1).

N-cyclohexyl-5-(pyridin-2-yl)-1,3,4-oxadiazol-2-amine (**6a**): Yield: 85%. M.p.: 210-211 °C. IR (KBr, cm^{-1}): 3244 ν(NH), 3010 ν(arom. CH), 2931, 2851 ν(aliph. C-H), 1562 ν(C=N and C=C). ^{1}H NMR (DMSO-d_6, δ, ppm): 1.18 (d, *J* = 4.9 Hz, 1H, H_{aliph}), 1.32 (q, *J* = 5.4 Hz, 4H, H_{aliph}), 1.57 (d, *J* = 11.8 Hz, 1H, $H_{aliph.}$), 1.73 (q, *J*= 4.9 Hz, 2H, $H_{aliph.}$), 1.96 (d, *J* = 1.9 Hz, 2H, $H_{aliph.}$), 3.45 (br, 1H, C*H*-N), 7.76 (d, d, *J* = 4.2, 7.8 Hz, 1H, Ar-*H*), 8.08 (s, 1H, N*H*, D_2O exchange), 8.36 (d, d, *J* = 6.1, 1.4 Hz, 1H, Ar-*H*), 8.89 (d, d, *J* = 4.9, 1.5 Hz, 1H, Ar-*H*), 9.18 (d, d, *J* = 4.8, 0.9 Hz, 1H, Ar-*H*). MS (EI, m/z(%)): 244 (M^+), 227, 162 (base peak), 119, 78.

N-cyclohexyl-5-(pyridin-3-yl)-1,3,4-oxadiazol-2-amine (**6b**)**:** Yield: 65%. M.p.: 160-161 °C. IR (KBr, cm^{-1}): 3200 ν(NH), 3010 ν(arom. CH), 2930, 2858 ν(aliph. C-H), 1565 ν(C=N and C=C). ^{1}H NMR (DMSO-d_6, δ, ppm): 1.12 (d, *J* = 12.2 Hz, 1H, H_{aliph}), 1.31 (q, *J* = 9.4 Hz, 4H, H_{aliph}), 1.58 (d, *J* = 12.3 Hz, 1H, $H_{aliph.}$), 1.74 (q, *J* = 4.8 Hz, 2H, $H_{aliph.}$), 1.97 (d, *J* = 8.3 Hz, 2H, $H_{aliph.}$), 3.43 (br, 1H, C***H***-N), 7.57 (d, d, *J* = 4.8, 7.9 Hz, 1H, Ar-*H*), 7.88 (d, *J* = 7.5 Hz,1H, Ar-*H*), 8.15 (s, 1H, N*H*, D_2O exchange), 8.69 (d, d, *J* = 4.9, 1.1 Hz, 1H, Ar-*H*), 8.98 (d, *J* = 1.5 Hz, 1H, Ar-*H*). MS (EI, m/z(%)): 244 (M^+), 162 (base peak), 119, 78, 55.

N-cyclohexyl-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine (**6c**): Yield: 70%. M.p.: 231-232 °C. IR (KBr, cm^{-1}): 3150 ν(NH), 3040 ν(arom. CH), 2930, 2855 ν(aliph. C-H), 1600 ν(C=N and C=C). ^{1}H NMR (DMSO-d_6, δ, ppm): 1.18 (d, *J* = 12.1 Hz, 1H, H_{aliph}), 1.32

(q, *J* = 8.7 Hz, 4H, H_{aliph}), 1.58 (d, *J* = 12.2 Hz, 1H, $H_{aliph.}$), 1.73 (q, *J*= 4.7 Hz, 2H, Ar-*H*), 1.96 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 3.46 (br, 1H, C*H*-N), 7.72 (d, *J* = 5.4 Hz, 2H, Ar-*H*), 8.01 (s, 1H, N*H*, D_2O exchange), 8.73 (d, *J* = 5.4 Hz, 2H, Ar-*H*). MS (EI, m/z(%)): 244 (M^+), 277, 162 (base peak), 119, 78, 55, 41.

3. Results and discussion

The synthesis of all the intermediate and target compounds were accomplished by the reaction sequence illustrated in Scheme 1. The synthesis of new 1,3,4-thiadiazole, 1,3,4-oxadiazole and 1,2,4-triazole compounds was performed in several steps. The required isomeric pyridine carboxylic acid hydrazides **1a-c** were prepared by treatment of the corresponding pyridine carboxylic acid with hydrazine hydrate according the reported procedure [22]. The thiosemicarbazides **3a-c** were prepared by the reaction of pyridine carboxylic acid hydrazides **1a-c** and cyclohexyl isothiocyanate **2**. Then 4-cyclohexyl-5-(pyridyl)-4H-1,2,4-triazole-3-thiol **4a-c** were prepared by the reaction of the appropriate thiosemicarbazides **3a-c** and sodium hydroxide in ethanol for 3 hours under reflux, followed by acidification with hydrochloric acid. The substituted thiosemicarbazides **3a-c** in conc. sulfuric acid underwent intramolecular dehydration to form substituted 1,3,4-thiadiazoles **5a-c**. 1,3,4-oxadiazole **6a-c** was synthesized from corresponding thiosemacarbazide in presence of mercuric acetate as an oxidizing agent.

The IR, NMR and Mass spectra data were used to establish the structures of synthesized compounds. ^{1}H NMR spectra of compounds **4a-c** have shown a singlet signal at 14 ppm due to the resonance of SH proton. In the IR spectra of compounds **4a-c** the absence of absorptions due to NH and carbonyl groups and the appearance of the absorption at 2750 cm^{-1} (SH), established their structures. Similarly the ^{1}H NMR spectra of the compounds **5a-c** and **6a-c** showed characteristic absorption (singlet at δ=8.0, D_2O exchange) that was attributed to the NH group, is a good evidence of the expected reactions.

4. Conclusion

A series of new 1,2,4-triazoles **4a-c,** 1,3,4-thiadiazoles **5a-c**, and 1,3,4-oxadiazoles **6a-c**, were synthesized by intramolecular cyclization of 1,4-disubstituted thiosemicarbazides in alkaline, acid and neutral condition, respectively. In addition to the efficiency and simplicity provided, this protocol describes good yields of cyclization and simple purification for these products.

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