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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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, the 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 membered 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. 'H-NMR spectra (500 MHz) were recorded on a Bruker instrument using TMS as internal standard and DMSO-d6 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 (aliph. CH), 2941, 2854 (arom. CH), 1558 (C=N and C=C). 'H NMR (DMSO-d6, δ, ppm): 1.40 (t, J = 7.7 Hz, 3H), 1.91 (q, J = 7.7 Hz, 2H), 2.39 (br, 2H, Haliph.), 2.82 (s, 2H, Haliph.), 3.67 (d, J = 8.05 Hz, 2H, Haliph.), 4.81 (br, 1H, C=H), 4.26 (br, 1H, C=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, SH). 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 (v(carbonyl)), 2931, 2854 (v(arom. CH), 2742 v(SH)), 1523 v(C=N and C=C). 'H NMR (DMSO-d6, δ, ppm): 1.19 (q, J = 12.9 Hz, 2H, Haliph.), 1.53 (d, J = 12.9 Hz, 1H, Haliph.), 1.70 (d, J = 12.6 Hz, 2H, Haliph.), 1.77 (d, J = 11.0 Hz, 2H, Haliph.), 2.00 (br, 2H, Haliph.), 4.26 (br, 1H, CH=N), 7.61 (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, SH). 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: 90%. M.p: 314-316 °C. IR (KBr, cm⁻¹): 3098 (v(carbonyl)), 2941, 2854 (v(arom. CH), 2729 v(SH)), 1558 v(C=N and C=C). 'H NMR (DMSO-d6, δ, ppm): 0.96 (d, J=12.9 Hz, 1H, Haliph.), 1.19 (q, J = 12.0 Hz, 2H, Haliph.), 1.54 (d, J = 12.5 Hz, 1H, Haliph.), 1.72 (d, J = 12.9 Hz, 2H, Haliph.), 1.76 (d, J = 11.7 Hz, 2H, Haliph.), 2.13 (br, 2H,
1,3,4-Thiadiazole was synthesized by a two-step process. The first step involves the condensation of an amine with mercuric acetate in ethanol. The product was then purified by recrystallization from a mixture of acetic acid and 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.

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(=C=N and C=C), 1H NMR (DMSO-d₆, δ, ppm): 1.17-1.36 (m, 5H, H₅), 1.81 (d, J = 10.4 Hz, 2H, H₄), 2.01 (d, J = 9.8 Hz, 2H, H₃), 7.37 (t, 1H, H₋), 7.71 (t, 1H, J = 5.6 Hz, Ar-H), 8.03 (d, J = 5.2 Hz, Ar-H), 8.37 (s, 1H, NH), 8.68 (d, J = 4.1 Hz, 1H, Ar-H). MS (EI, m/z(%)): 260 (M⁺), 241 (base peak), 199, 105, 55.

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(=C=N and C=C), 1H NMR (DMSO-d₆, δ, ppm): 1.19-1.35 (m, 5H, H₅), 1.58 (d, J = 10.8 Hz, 2H, H₄), 1.70 (d, J = 10.0 Hz, 2H, H₃), 2.01 (d, J = 9.2 Hz, 2H, H₂), 3.57 (br, 1H, CH-N), 7.50 (br, 1H, Ar-H), 8.05 (s, 1H, NH, D₂O 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(=C=N and C=C), 1H NMR (DMSO-d₆, δ, ppm): 1.19-1.35 (m, 5H, H₅), 1.57 (d, J = 11.9 Hz, 1H, H₂), 1.71 (d, J = 8.8 Hz, 2H, H₃), 2.01 (d, J = 9.8 Hz, 2H, H₄), 3.58 (br, 1H, CH-N), 7.70 (d, J = 4.6 Hz, 2H, Ar-H), 8.20 (s, 1H, NH, D₂O exchange), 8.64 (d, J = 4.4 Hz, 2H, Ar-H). MS (EI, m/z(%)): 260 (M⁺), 203, 178 (base peak), 119, 105, 55.

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(=C=N and C=C), 1H NMR (DMSO-d₆, δ, ppm): 1.18 (d, J = 4.9 Hz, 1H, H₋), 1.32 (q, J = 5.4 Hz, 2H, H₋), 1.57 (d, J = 11.8 Hz, 1H, H₋), 1.73 (q, J = 4.9 Hz, 2H, H₋), 1.96 (d, J = 1.9 Hz, 2H, H₋), 3.45 (br, 1H, CH-N), 7.76 (d, J = 4.2, 7.8 Hz, 1H, Ar-H), 8.08 (s, 1H, NH, D₂O exchange), 8.36 (d, J = 6.1 Hz, 1H, Ar-H), 8.89 (d, J = 4.9, 1.5 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(=C=N and C=C), 1H NMR (DMSO-d₆, δ, ppm): 1.19-1.35 (m, 5H, H₅), 1.58 (d, J = 10.8 Hz, 2H, H₄), 1.70 (d, J = 10.0 Hz, 2H, H₃), 2.01 (d, J = 9.2 Hz, 2H, H₂), 3.57 (br, 1H, CH-N), 7.50 (br, 1H, Ar-H), 8.05 (s, 1H, NH, D₂O 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-oxadiazol-2-amine (6c):
Yield: 70%. M.p.: 231-232 °C. IR (KBr, cm⁻¹): 3150 ν(NH), 3040 ν(=C=N and C=C), 1H NMR (DMSO-d₆, δ, ppm): 1.18 (d, J = 12.1 Hz, 1H, H₋), 1.32 (q, J = 5.6 Hz, 2H, H₋), 1.57 (d, J = 12.3 Hz, 1H, H₋), 1.74 (q, J = 4.8 Hz, 2H, H₋), 1.97 (d, J = 8.3 Hz, 2H, H₋), 3.43 (br, 1H, CH-N), 7.57 (d, J = 4.8, 7.9 Hz, 1H, Ar-H), 7.88 (d, J = 7.5 Hz, 1H, Ar-H), 8.15 (s, 1H, NH, D₂O exchange), 8.69 (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⁺), 227, 162 (base peak), 119, 78.
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 thiosemicarbazide 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. 1H NMR spectra of compounds 4a-c have shown a singlet signal at 14 ppm due to the resonance of NH 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 1H NMR spectra of the compounds 5a-c and 6a-c showed characteristic absorption (singlet at $\delta=8.0$, D:O 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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References