Research Article

Synthesis of New Imidazolidine and Tetrahydropyrimidine Derivatives

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Synthesis of new imidazolidine and tetrahydropyrimidine derivatives **3a**, **b** and **4a–c** as cyclic 1,3-diamines under two reaction conditions (A and B) is described. Under reaction conditions-A, a suspension of (*E*)-2-cyano-2-(oxazolidin-2-ylidene)ethanethioamide **1** (1 eq.) and diaminoalkanes **2a–e** (2 eq.) in absolute ethanol is heated under reflux for 16–22 h to afford **3a**, **b** and **4a–c**. Alternatively, under reaction conditions-B, a solution of thioamide **1** (1 eq.) in diaminoalkanes **2a–e** (3 eq.) is stirred under solvent-free conditions at room temperature for 3 days to give desired products. Reaction conditions-A for having higher yields, shorter reaction times, and required less diamines is more effective than reaction conditions-B. Oxazolidine ring opening is observed by reacting compound **1** with all of the diamines **2a–e**, but the thioamide group only reacts with nonbulky diamines **2a**, **b**. The chemical structures of novel compounds were confirmed by ^1H NMR, ^{13}C NMR, elemental analysis, and FT-IR spectrometry.

1. Introduction

Imidazolidines (tetrahydroimidazoles) are important building blocks in biologically active compounds [1] and carriers of pharmacologically active carbonyl compounds [2]. They have been reported to have important biological activities including, for example, 2-[(arylmethoxy) imino]imidazolidines as potential α -adrenergic receptor agonist [3], bis-imidazolidines and 1,3-disubstituted imidazolidines as antimicrobial [4], 5-(4-chloro or fluoro-benzylidene-3-(4-nitrobenzyl)-4-thioxo-imidazolidin-2-one as antiparasitic [5], sulfonyliminoimidazolidines as oral hypoglycaemic [6], imidazolidin-2,4-diones, 2-thioxoimidazolidin-4-ones, 5-cycloalkylidene-hydantoin, and 5-cycloalkylidene-thiohydantoin as antiarrhythmic and anticonvulsant [7, 8], 1,3-dibenzyl-2-arylimidazolidine as anti-inflammatory [9], *N,N'*-di-aryl-methyl-2-(4-diethylamino phenyl) tetrahydroimidazoles and *N,N'*-di-4-diethylamino benzyl-2-(aryl) tetrahydroimidazoles as analgesic [10]. They have also been utilized as a versatile template for the synthesis of compounds with potential cyclooxygenase-2 inhibition activity [11] and termed as a promising group of NSAIDs with potential anti-inflammatory activities [9].

The pyrimidine fragment is present in various biologically active compounds, many of which have been found to be used in medical practice [12, 13]. Recently, much attention has been paid to derivatives of pyrimidine, including their hydrogenation products. This class of compounds displays wide ranges of biological and pharmacological properties such as anti-inflammatory [14], analgesic [15], antitumor [16], antidepressant [17], antibacterial, antifungal, and antitubercular effects [18–20].

The application of these compounds in pharmaceutical field prompted us to synthesize some new imidazolidines and tetrahydropyrimidines under two reaction conditions. These synthesized compounds are characterized by NMR, IR spectral data, and elemental analysis.

2. Results and Discussion

Cyclic 1,3-diamines **3a**, **b** and **4a–c** were prepared under two reaction conditions. Under reaction conditions-A, a mixture of (*E*)-2-cyano-2-(oxazolidin-2-ylidene)ethanethioamide **1** (1 eq.) and appropriate diaminoalkanes **2a–e** (2 eq.) in absolute ethanol are refluxed for 16–22 h to afford the solid products **3a**, **b** and **4a–c** (Scheme 1). Under reaction conditions-B,

SCHEME 1: Total synthesis of cyclic 1,3-diamines **3a, b** and **4a-c**. SCHEME 2: The proposed mechanism of formation **3a, b** and **4a-c**.

similar treatment of the thioamide **1** (1 eq.) with appropriate diaminoalkanes **2a-e** (3 eq.) under solvent-free conditions at room temperature for 3 days afforded the desired products. The yields of the products obtained are depicted in Table 1.

A comparison between the results obtained from both reaction conditions leads us to the conclusion that reaction conditions-A is from 65% to 77% as efficient as reaction conditions-B, also the former has shorter reaction times and required less diamines but requires a supply of heat. It is worth noting that oxazolidine ring opening is observed by reacting compound **1** with all of the diamines **2a-e**, but the thioamide group only reacts with nonbulky diamines **2a, b**. This is probably due to the rigid structure of compound **1** that prevents the effective interaction with bulky diamines **2c-e**.

A plausible mechanism is depicted for the formation of these compounds (Scheme 2). As depicted in Scheme 2, intermediates **3'a, b** and **4a-c** probably were produced from two successive Michael substitution reaction thioamide **1** and diaminoalkanes **2a-e**. It predicts that during adding amine

to oxazolidine ring, the C–O bond breaks faster than the C–N bond because alkoxy is a better leaving group than amine. Note that in this multistep synthesis, the likely key intermediates **3'a, b** were not isolated except for intermediates **4a-c** which were isolated and their structures identified by spectral analysis. When intermediates **3'a, b** were treated with diaminoalkanes **2a, b**, amidines **4'a, b** that are produced as intermediates followed by a ring closure to **3a, b**.

The structural assignments of compounds **3a, b** and **4a-c** were based on their analytical and spectral data. The ^1H NMR spectra of compounds **3a-e** showed broad signals due to $-\text{NH}-$ groups within $\delta = 7.70\text{--}9.51$ ppm region. The ^{13}C NMR spectra of the products exhibited signals within $\delta = 27\text{--}65$, $117\text{--}119$, $157\text{--}166$ ppm regions attributed to the $\text{N}\equiv\text{C}-\text{C}=\text{C}-$, $-\text{C}\equiv\text{N}$, $\text{N}=\text{C}-\text{C}=\text{C}-$ carbons, respectively. The FT-IR spectra of **3a, b** and **4a-c** in KBr disk showed the absorption bands within $\nu = 3273\text{--}3311\text{ cm}^{-1}$ corresponding to $-\text{NH}-$ groups, within $\nu = 2170\text{--}2187\text{ cm}^{-1}$ belonging to nitrile groups and within $\nu = 1589\text{--}1688\text{ cm}^{-1}$ attributed to the $-\text{C}=\text{C}-$ exocyclic

TABLE 1: Comparing yields of compounds **3a**, **b** and **4a–c** obtained under two reaction conditions A and B.

Entry	Products	Diaminoalkane	Time (h) ^a	Yield (%)	
				A	B
1	3a	Ethylenediamine	16	75	47
2	3b	1,3-Diaminopropane	16	60	46
3	4a	2,2-Dimethyl-1,3-propanediamine	20	77	50
4	4b	1,2-Diaminopropane	18	56	44
5	4c	1,2-Diaminocyclohexan	22	54	42

^a Only for reaction conditions-A.

bonds. All this evidence plus microanalytical data strongly supports the formation of all products.

3. Materials and Methods

3.1. Materials. Melting points were recorded on a Kruss type KSPIN melting point meter and are uncorrected. The IR spectra of products **3a**, **b** and **4a–c** were determined using KBr disks with Bruker Tensor-27 FT-IR spectrometer and only major absorptions are listed. The ¹H and ¹³C NMR spectra of DMSO-d₆ solutions were recorded on a Bruker FT-NMR Ultra Shield-400 spectrometer (400 and 100 MHz, resp.) with residual protons of the solvent as internal standard (2.50 ppm for ¹H and 39.48 ppm for ¹³C). Elemental analyses were performed on a Thermo Finnigan Flash EA micro-analyzer. Monitoring of the progress of reactions and the purity of the products were effected by TLC on alufoil plates precoated with silica gel (60, Merck); eluent was CHCl₃-CH₃OH, 9:1, visualization with I₂ vapor. Compound **1** was obtained according to the published method [21].

3.2. Methods

3.2.1. General Procedure for the Synthesis of Cyclic 1,3-diamines (3a, b and 4a–c). Reaction conditions-A. A suspension of (*E*)-2-cyano-2-(oxazolidin-2-ylidene)ethanethioamide **1** (0.845 g, 5 mmol) and diaminoalkanes **2a–e** (10 mmol) in absolute ethanol (10 mL) is heated under reflux for 16–22 h. The reaction mixture is treated with 2-propanol (10 mL), refrigerated overnight, filtered, and washed with 2-propanol; the residual products are recrystallized from methanol to give **3a**, **b** and **4a–c**.

Reaction conditions-B. A solution of (*E*)-2-cyano-2-(oxazolidin-2-ylidene)ethanethioamide **1** (0.845 g, 5 mmol) in diaminoalkanes **2a–e** (15 mmol) is stirred at room temperature for 3 days. Excess diamines are then evaporated in vacuo and the residual products are recrystallized from methanol.

4. Data for Compounds

2-(4,5-Dihydro-1H-imidazol-2-yl)-2-(imidazolidin-2-ylidene)acetonitrile 3a. White needles, mp 218–219°C; FT-IR, ν , cm⁻¹: 3280 (broad, medium, -NH-), 2170 (strong, sharp, -C≡N), and 1688 (strong, sharp, -C=C-); ¹H NMR, δ , ppm: 3.55 (s, 8H, -CH₂-); 8.21 (b, 3H, -NH-, D₂O exchangeable); ¹³C NMR, δ , ppm: 27.8 (N≡C-C=C-), 43.7

(-CH₂-), 117.8 (-C≡N), and 166.5 (N≡C-C=C-). Anal. Calcd. for C₈H₁₁N₅ (177) C 54.22; H 6.26; N 39.52%, Found: C 54.11; H 6.34; N 39.55.

2-(Tetrahydropyrimidin-2(1H)-ylidene)-2-(1,4,5,6-tetrahydropyrimidin-2-yl)acetonitrile 3b. White needles, mp 209–210°C; FT-IR, ν , cm⁻¹: 3286 (broad, medium, -NH-), 2171 (strong, sharp, -C≡N), and 1688 (strong, sharp, -C=C-); ¹H NMR, δ , ppm (J, Hz): 1.77 (q, 4H, J = 5.5, -NHCH₂CH₂-), 3.18 (t, 8H, J = 5.5, -NHCH₂-), and 7.70 (b, 3H, -NH-, D₂O exchangeable); ¹³C NMR, δ , ppm: 19.6 (-NHCH₂CH₂-), 29.2 (N≡C-C=C-), 38.6 (-NHCH₂), and 118.7 (-C≡N); 159.3 (N≡C-C=C-). Anal. Calcd. for C₁₀H₁₅N₅ (205) C 58.51; H 7.37; N 34.12%, Found: C 58.53; H 7.27; N 34.20.

2-Cyano-2-(5,5-dimethyltetrahydropyrimidin-2(1H)-ylidene)ethanethioamide 4a. White needles, mp 216–218°C; FT-IR, ν , cm⁻¹: 3416 (broad, medium, -NH₂), 3311 (broad, medium, -NH-), 2175 (strong, sharp, -C≡N), and 1615 (strong, sharp, -C=C-); ¹H NMR, δ , ppm (J, Hz): 0.95 (s, 6H, -CH₃), 3.00 (d, 4H, J = 2.2, -CH₂-), 7.27 (b, 2H, -NH₂, D₂O exchangeable), and 9.51 (b, 2H, -NH-, D₂O exchangeable); ¹³C NMR, δ , ppm: 23.5 (-CH₃), 25.0 (-C(CH₃)₂-), 49.2 (-CH₂-), 65.0 (N≡C-C=C-), 119.4 (-C≡N), 157.1 (N≡C-C=C-), and 186.7 (-C=S). Anal. Calcd. for C₉H₁₄N₄S (210) C 51.40; H 6.71; N 26.64; S 15.24%, Found: C 51.35; H 6.78; N 26.72; S 15.15.

(Z,E)-2-Cyano-2-(4-methylimidazolidin-2-ylidene)ethanethioamide 4b. Yellow needles, mp 189–190°C; FT-IR, ν , cm⁻¹: 3422 (broad, medium, -NH₂), 3282 (broad, medium, -NH-), 2182 (strong, sharp, -C≡N), and 1626 (strong, sharp, -C=C-); ¹H NMR, δ , ppm (J, Hz): 1.21 (d, 3H, J = 6.2, -CH₃), 3.18, 3.74 (dd, 1H, J = 2.3, J = 7.5, t, 1H, J = 9.7, -CH₂-); 4.05 (m, 1H, -CHCH₃), 7.29 (b, 2H, -NH₂, D₂O exchangeable), and 9.13 (b, 2H, -NH-, D₂O exchangeable). ¹³C NMR, δ , ppm: 20.4 (-CH₃), 50.2 (-CH₂-), 51.2 (-CHCH₃), 63.0 (N≡C-C=C-), 118.9 (-C≡N), 164.3 (N≡C-C=C-), and 188.7 (-C=S). Anal. Calcd. for C₇H₁₀N₄S (182) C 46.13; H 5.53; N 30.74; S 17.59%, Found: C 46.08; H 5.61; N 30.81; S 17.50.

2-Cyano-2-(octahydro-2H-benzo[d]imidazol-2-ylidene)ethanethioamide 4c. Brown needles, mp 238–240°C; FT-IR, ν , cm⁻¹: 3418 (broad, medium, -NH₂), 3273 (broad, medium, -NH-), 2187 (strong, sharp, -C≡N), and 1589 (strong, sharp, -C=C); ¹H NMR, δ , ppm (J, Hz): 1.28–1.56 (m,

4H, $-\text{CHCH}_2\text{CH}_2-$), 1.64–1.74, 2.12 (m, 2H, d, 2H, $J = 11.0$, $-\text{CHCH}_2\text{CH}_2-$), 3.07, 3.82 (m, 1H, m, 1H, $-\text{NHCH}-$), 7.63 (b, 2H, $-\text{NH}_2$, D_2O exchangeable, 54.0 (NHCH), 62.5 ($\text{N}\equiv\text{C}-\text{C}=\text{C}-$), 118.5 ($-\text{C}\equiv\text{N}$), 165.2 ($\text{N}\equiv\text{C}-\text{C}=\text{C}-$), and 189.0 ($-\text{C}=\text{S}$). Anal. Calcd. for $\text{C}_{10}\text{H}_{14}\text{N}_4\text{S}$ (222) C 54.03; H 6.35; N 25.20; S 14.42%, Found: C 54.10; H 6.44; N 25.12; S 14.34.

5. Conclusion

In summary, several new imidazolidines and tetrahydropyrimidines have been synthesized from the reaction of a single thioamide with several various diaminoalkanes. On the basis of our previously reported work [21], the thioamide itself was synthesized in a regioselective manner from functionalized oxazolidine with phosphorus pentasulfide.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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