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One pot synthesis of 2-hydroxy pyrrolidine derivatives

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Abstract: One pot reaction of various 2-amino-thiadiazoles or thiazoles and 2,3-dihydrofuran under mild condition in presence of $CeCl_3.7H_2O$ as catalyst transformed the amino group of 2-amino-thiadiazoles or thiazoles into a medicinally important 2-hydroxy pyrrolidine ring system in good to excellent yields. The generality of the reaction was sufficiently investigated and demonstrated. The new reaction path way for this conversion was established by spectroscopic and analytical methods.

Keywords: 2-Hydroxypyrrolidine; cerium(III)chloride heptahydrate; 2,3-dihydrofuran

1. Introduction

The synthetic utility of domino reaction between aryl amines, in particularly with various anilines and cyclic enol ethers such as 2,3-dihydrofuran and 3,4-dihydro-*2H*-pyran in the straight forward synthesis of tricyclic furo/pyrano tetrahydroquinolines has continued to attract considerable synthetic interest in developing new methods for their synthesis.[1-2]

Literature survey revealed that the hydroxy pyrrolidine ring system is present in many biologically active alkaloids[3] and these type of compounds were also exploited as catalyst in asymmetric synthesis, i.e., stereoselective reduction of ketones and Diels-Alder reaction, respectively.

It is also reported that the cyclic enamines are versatile intermediates for the synthesis of alkaloids and nitrogen heterocycles[4-5] and were obtained by dehydration of 2-hydroxy pyrrolidines which in turn obtained by the reduction of lactams with sodium borohydrides.[6] Apart from these

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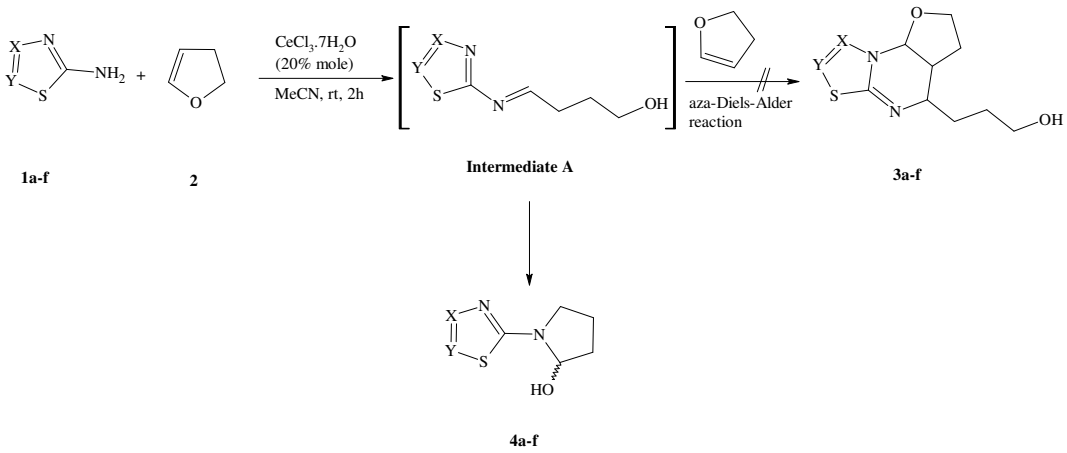
applications, the 2-hydroxy pyrrolidines were also used as intermediates for the synthesis of various substituted pyrrolidines.[7-8]

Our earlier reports on aza Diels-Alder reactions[9-12] prompted us to investigate this new reaction with various heterocyclic amines and cyclic enol ethers such as 2,3-dihydrofuran. We herein report our new findings.

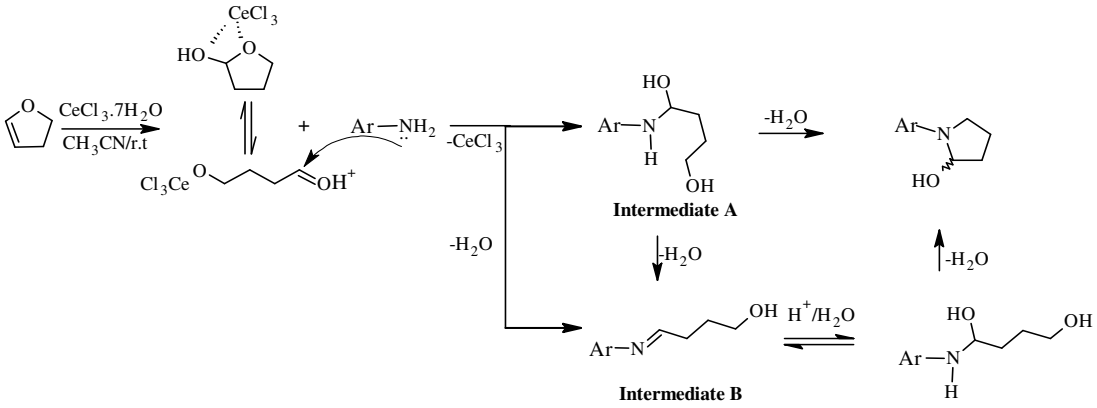
2. Results and discussion

Initially we attempted the domino reactions of 2,3-dihydrofuran (**2**) with aromatic heterocyclic amines (**1a-f**). At first, 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine **(1a)** was reacted with 2,3-dihydrofuran (**2**) in the presence of $CeCl_3.7H_2O$. In this reaction, we obtained 2-hydroxy pyrrolidine derivative **4a** instead of **3a**. The studies of the reaction in the other heterocyclic amines are also resulted in the similar 2-hydroxypyrrolidine compounds (**4b-f**).



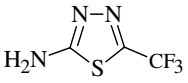
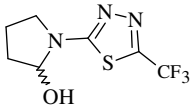
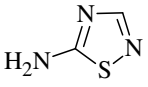
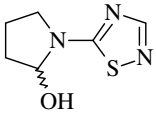
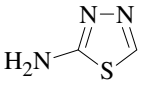
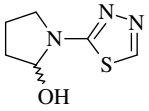
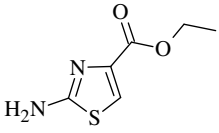
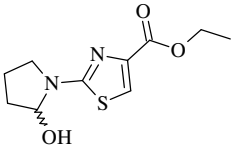
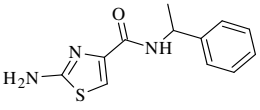
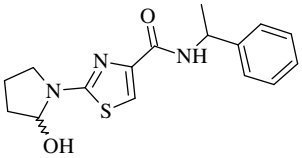
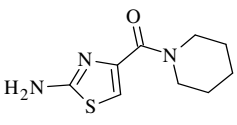
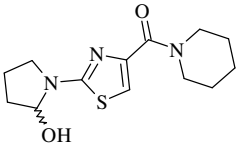
Scheme 1. Synthesis of *N*-heteroaryl substituted 2-hydroxy pyrrolidine derivatives (**4a-f**).

The progress of the reactions was checked through GC-MS analysis. The molecular mass of compound (**4a**) was found to be *m/z* = 240 (M+1), the peak corresponding to the molecular formula of **4a**. Although the molecular weight of Schiff base, intermediate A, and compound **4a** having the same formula weight, we distinguish these two compounds by ^{1}H NMR technique. The OH signals attached to secondary carbons have appeared at δ = 9.20 as doublets which were disappeared when ^{1}H NMR was recorded in D_2O. Furthermore, ^{1}H NMR did not give the signal corresponds to *imine* (-CH=N-) proton present in the intermediate A. Therefore all these data are sufficient to justify the structure assigned to the products. Furthermore splitting pattern of the methylene protons in the ^{1}H NMR spectra is clearly different from methylene protons in the intermediate A. After establishing the structures of the products we presume that the mechanism of the reaction was found to occur is as shown in Scheme 2.



Scheme 2. A proposed mechanism for the reaction of 2,3-dihydrofuran and heterocyclic amines in presence of $CeCl_3.7H_2O$.

Table 1. The structure of products, reactants and some experimental data

Entry	Reactant (1a-f)	Product (4a-f)	Time / h	Yield (%)[a]
4a			2.0	98
4b			2.0	88
4c			2.0	98
4d			2.0	95
4e			2.0	95
4f			2.0	92

[a]Isolated yield

3. Conclusion

From the literature survey, we realized that this unexpected result can be a very useful to get pyrrolidine heterocyclic ring system **(4a-f)** through one pot straight forward approach and may also serve as a potential key intermediate for cyclic enamine synthesis bearing heterocyclic ring systems as well as for easy construction of 2-hydroxy pyrrolidine ring system into the amino group of a heterocyclic compounds.

4. Experimental

Commercially available chemicals were used directly as received. ^{1}H NMR was recorded at 300 or 400 MHz in $CDCl_3$ or DMSO-d_6. ^{13}C NMR was recorded at 100 MHz in $CDCl_3$ or DMSO-d_6. Mass spectra were recorded on Finnigan Mat 1020 C spectrometer using ionization energy of 70 eV. Elemental analysis was recorded on varioMICRO CHNS.

General Procedure

To the solution of 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine (200 mg, 1.18 mmol) in acetonitrile (5 ml), the 2,3-dihydrofuran (80 mg, 1.18 mmol) was added. Then the cerium(III) chloride heptahydrate ($CeCl_3.7H_2O$) (88 mg, 20 mole %) was added to the reaction mixture as a catalyst. The reaction mixture was stirred at room temperature for about 2 h. After complete conversion of the starting material as indicated by TLC, the reaction mixture was diluted with water, and the product was extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated by vacuum. The crude mass was purified by column chromatography, packed with silica gel 60-120 and eluted with petroleum ether/EtOAc (8:2 v/v) to give 1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]pyrrolidin-2-ol.

1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl] pyrrolidin-2-ol (4a). White crystalline solid; mp.130-132 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.93-2.15 (m, 4H), 3.73-3.82 (m, 2H), 5.42-5.45 (m, 1H), 9.20 (d, J = 5.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.09, 120.79, 118.09, 87.15, 67.41, 32.04, 23.81 ppm; MS: m/z = 240 (M+1). Anal. Calcd. for $C_7H_8F_3N_3OS$: C, 35.15, H, 3.37, N, 17.57. Found: C, 35.49, H, 3.36, N, 17.68.

1-(1,2,4-thiadiazol-5-yl)pyrrolidin-2-ol (4b). White crystalline solid; mp.135-138 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.90-2.00 (m, 3H), 2.07-2.14 (m, 1H), 3.71-3.78 (m, 2H), 5.33-5.37 (m, 1H), 8.01(s, 1H), 9.08 (d, J = 7.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.99, 32.27, 67.49, 86.53, 158.78, 183.48 ppm; MS: m/z = 172.0. (M+1) ppm; Anal. Calcd. for $C_6H_9N_3OS$: C, 42.09, H, 5.30, N, 24.54. Found: C, 42.06, H, 5.10, N, 25.10.

1-(1,3,4-thiadiazol-2-yl)pyrrolidin-2-ol (4c). White crystalline solid; mp.150 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.82-1.99 (m, 3H), 2.09- 2.14 (m, 1H), 3.71-3.80 (m, 2H), 5.37-5.33 (m, 1H), 8.01 (s, 1H), 9.06 (d, J = 7.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.0, 32.36, 67.46, 86.51, 159.13, 183.44 ppm; MS: m/z = 172.2; Anal. Calcd. for $C_6H_9N_3OS$: C, 42.09, H, 5.30, N, 24.54. Found: C, 42.06, H, 5.10, N, 25.10.

Ethyl 2-(2-hydroxypyrrolidin-1-yl)-1,3-thiazol e-4-carboxylate (4d). White crystalline solid; mp.78-80 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.24-1.27 (m, 3H), 1.76-1.85 (m, 2H), 1.91-1.98 (m, 1H), 2.07-2.14 (m, 1H), 3.71-3.74 (m, 2H), 4.21 (q, J = 7.0 Hz, 2H), 5.41-5.37 (m, 1H), 7.61 (s, 1H), 8.50 (d, J = 8.0 Hz, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.26, 24.29, 32.26, 61.05, 66.93, 86.37, 117.61, 142.88, 161.50, 167.82 ppm; MS: m/z = 243.0 (M+1) Anal. Calcd. for $C_{10}H_{14}N_2O_3S$: C, 49.57, H, 5.82, N, 11.56. Found: C, 48.87, H, 5.58, N, 11.66.

[2-(2-hydroxypyrrolidin-1-yl)-1,3-thiazol-4-yl] (piperidin-1-yl)methanone (4e). Semi solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.47 (s, 4H), 1.57-1.59 (m, 2H), 1.76-1.85 (m, 2H), 1.92-1.96 (m, 1H), 2.07-2.11 (m, 1H), 3.54 (s, 4H), 3.72 (t, J = 7.0 Hz, 2H), 5.36-5.41 (m, 1H), 7.03 (s, 1H), 8.30 (d, J = 8.0 Hz, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.42. 24.50, 25.59, 26.56, 32.27, 43.60, 48.13, 67.08, 86.50, 111.97, 146.38, 163.45, 167.26 ppm; MS: *m/z* = 282.2 (M+1); Anal. Calcd. for $C_{13}H_{19}N_3O_2S$; C, 55.49, H, 6.81, N, 14.93. Found: C, 54.62, H, 6.66, N, 13.39.

Ethyl-2(2-hydroxypiperidin-1-yl)-1,3-thiazole-4-carboxylate (4f). Semi solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.26 (t, J = 7.1 Hz, 3H), 1.41-1.58 (m, 4H), 1.75-1.82(m, 2H), 3.42-3.48 (m, 1H), 3.81-3.90 (m, 1H), 4.20 (q, J = 7.0 Hz, 2H), 4.74-4.78 (m, 1H), 7.61 (s, 1H), 8.58 (d, J = 7.8 Hz, 1H, OH). MS: *m/z* = 257 (M+1);

D$_2$O Exchanged (–OH) ^{1}H NMR spectra

1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]pyrrolidin-2-ol (4a).^{1}H NMR (400 MHz, DMSO-d_6 in D_2O): δ = 1.90-2.15 (m, 4H), 3.71-3.81 (m, 2H), 5.41-5.44 (m, 1H) ppm.

1-(1,3,4-thiadiazol-2-yl)pyrrolidin-2-ol (4c).^{1}H NMR (400 MHz, DMSO-d_6 in D_2O): δ = 8.01(s, 1H), 5.34 (dd, J = 6.2, 2.7 Hz, 1H), 3.70-3.79 (m, 2H), 2.09-2.13 (m, 1H), 1.88-1.99 (m, 3H) ppm.

Ethyl 2-(2-hydroxypyrrolidin-1-yl)-1,3-thiazole-4-carboxylate (4d).^{1}H NMR (400 MHz, DMSO-d_6 in D_2O): δ = 1.23 (t, J = 7.1 Hz, 3H), 2.12-1.73 (m, 4H), 3.72-3.69 (m, 2H), 4.20 (dd, J = 14.2, 7.1 Hz, 2H), 5.37-5.40 (m, 1H), 7.60 (d, J = 7.6 Hz, 1H) ppm.

[2-(2-hydroxypyrrolidin-1-yl)-1,3-thiazol-4-yl](piperidin-1-yl)methanone (4e).^{1}H NMR (400 MHz, DMSO-d_6 in D_2O): δ = 1.46-2.11 (s, 4H), 1.57-1.58 (m. 2H), 1.74-1.83 (m, 2H), 1.89-2.11 (m, 2H), 3.50-3.72 (m, 6H), 5.37-5.39 (m, 1H), 7.00 (s, 1H) ppm.

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Supporting Information

Supporting Information accompanies this paper on http://www.acgpubs.org/OC

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