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One Pot Synthesis of Hetero/Aryl-Urea Derivatives: Chlorosulfonyl Isocyanate, *in situ* Hydrolysis Method

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An interesting approach for the direct and general synthesis of primary hetero/aryl urea compounds from corresponding amines. The highly efficient synthesis of mono-substituted hetero-aryl urea compounds by using chlorosulfonyl isocyanate followed by hydrolysis provides the corresponding urea in high yield and purity in reliable reaction conditions. Total 13 derivatives (**4a-4m**) were successfully synthesized by this approach and characterized. These were more interesting as further preparation of more cyclized compounds in use of drug and agro discoveries.

Key Words: Hetero/aryl urea, Chlorosulfonyl isocyanate, Hydrolysis.

INTRODUCTION

The urea functional group is of importance in a wide range of biological compounds such as, enzyme inhibitors[1] and pseudo peptides[2]. Aryl- and hetero-aryl, substituted urea's are found in natural products[3], pharmaceutical and agricultural preparations[4]. These inhibitors are described as effective therapeutic in cytokin mediated diseases, including inflammatory and autoimmune diseases. A key step in the synthesis of these compounds is the formation of the urea bond. Many investigations have been made to search for an efficient and practical method to synthesize urea derivatives.

The typical procedure for the synthesis of urea is treating isocyanate with primary or secondary amines in organic solvents[5]. In the presence of transition metal catalysts, selenium[6] or sulphur[7] compounds, symmetrical, unsymmetrical and even cyclo-urea's can be prepared by reacting primary amine or ammonia with carbon monoxide. On the other hand, with the development of solid phase synthesis, solid phase urea synthesis[8] has attracted considerable attention in urea-containing combinational libraries. It is regretting that a favourite resin is not easy in many times.

As reported in the above references, an aryl and hetero-aryl amine reacted with an aryl and hetero-aryl isocyanate to generate corresponding urea. At first corresponding isocyanate prepared with phosgene or triphosgene and followed by reaction with corresponding amine to provide the urea[9]. Other approaches to forming the urea known in the chemical literature are to form a carbamate, by reaction of an amine with chloroformate derivatives then this will reacted with an amine followed by hydrogenolysis to provide urea[10]. In addition, the synthesis of isocyanates from primary amines and phenylalanine methyl ester using the Mitsunobu chemistry[11] and modified phosphine imide reaction[12] also preparation of urea by catalytic carbonation of amines with carbon monoxide or carbon dioxide has been documented in the literature.

The present approach is the synthesis of hetero/aryl-urea derivatives developed in a very convenient and one pot methodology, also useful for commercial preparation.

EXPERIMENTAL

General procedure: Under nitrogen atmosphere, to a suspension of hetero/aryl amine (**1a-1m**) (1.15 mmol) in dry CH_2Cl_2 (10 mL) was added drop wise chloro sulfonyl isocyanate (1.50 mmol) at 0 ºC. The resulting mixture was stirred for 45 min at room temperature and removed the solvent completely under *vacuo*. The residue was charged with 4 M HCl in 1,4-dioxane (6 mL) and water (2 mL) at 10 ºC and the mixture was stirred 2 h at room temperature. The reaction mixture was concentrated under reduced pressure and solid was charged 10 % $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3 mL × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *via* rota vapour to afford corresponding hetero/aryl urea as a solid.

1-(5-Bromopyridin-3-yl)urea (4a): Yield 90 %. Off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95(s, 1H);

8.42 (d, 1H, *J* = 2.4Hz); 8.30 (d, 1H, *J* = 2.4 Hz); 8.22 (d, 1H, *J* = 2.4 Hz) 6.15 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.17, 142.58, 138.97, 138.40, 126.72, 120.15. IR (KBr, ν_{max}, cm^{-1}, neat): 3397, 3210, 2920, 1680, 1570, 1444, 598. MS (EI, 70 eV): m/z = 218.0 [M^{2+}].

1-(4-Bromopyridin-3-yl)urea (4b): Yield 87 %. Off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (s, 1H); 8.03 (d, 1H, *J* = 5.2 Hz); 8.02 (s, 1H); 7.65 (dd, 1H, *J* = 5.2 Hz); 6.47 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.75, 144.12, 143.79, 135.66, 127.82, 122.81; MS (EI, 70 eV): m/z = 216.0, 217 [M^{2+}].

1-(3-Bromopyridin-4-yl)urea (4c): Yield 89 %. Off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.55 (s, 1H); 8.28 (d, 1H, *J* = 5.6 Hz); 8.24 (s, 1H); 8.21(d, 1H, *J* = 5.6 Hz); 6.78 (br s, 2H); IR (KBr, ν_{max}, cm^{-1}, neat): 3368, 3241, 2918, 1657, 1461, 569; MS (EI, 70 eV): m/z = 216.2[M^{2+}].

1-(6-Chloropyridin-3-yl)urea (4d): Yield 90 %. White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.87 (s, 1H); 8.39 (s, 1H); 7.97 (dd, 1H, *J* = 2.8 Hz); 7.37 (d, 1H, *J* = 8.4 Hz) 6.08 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.18, 141.90, 139.45, 137.34, 128.76, 124.30. IR (KBr, ν_{max}, cm^{-1}, neat): 3390, 3254, 2919, 1664, 1580, 1136, 749. MS (EI, 70 eV): m/z = 172.2 [M^{1+}].

1-(5-Fluoropyridin-2-yl)urea (4e): Yield 91 %. White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.12 (s, 1H); 8.17 (d, 1H, *J* = 2.8 Hz); 7.66 (d, 1H, *J* = 2.8 Hz); 7.58 (s, 1H) 6.69 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.78, 150.54, 134.43, 126.08, 113.07. IR (KBr, ν_{max}, cm^{-1}, neat): MS (EI, 70 eV): m/z = 156.2 [M^{1+}].

1-(2,6-Dichloropyridin-3-yl)urea (4f): Yield 89 %. White solid, ^{1}H NMR (400 MHz, DMSO-d_6): δ: 8.60 (d, 1H, *J* = 8.8 Hz); 8.32 (s, 1H); 7.47 (d, 1H, *J* = 8.8 Hz); 6.59 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.74, 139.86, 137.09, 134.18, 131.69, 124.09. IR (KBr, ν_{max}, cm^{-1}, neat): 3405, 3300, 1667, 1574, 1142, 703. MS (EI, 70 eV): m/z = 206.8 [M^{1+}].

1-(2-Nitropyridin-3-yl)urea (4g): Yield 84 %. Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.11 (s, 1H); 8.74 (d, 1H, *J* = 1.6 Hz); 8.17 (d, 1H, *J* = 1.6 Hz); 7.73 (dd, 1H, *J* = 4Hz, 4.4 Hz); 6.76 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.46, 146.43, 140.97, 132.73, 131.64, 129.87. IR (KBr, ν_{max}, cm^{-1}, neat): MS (EI, 70 eV): m/z = 182.2 [M^{1+}].

1-(4,6-Dimethylpyridin-2-yl)urea (4h): Yield 86 %. White solid, ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.99 (s, 1H); 6.97 (s, 1H); 6.63 (s, 1H); 6.02 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.09, 155.35, 153.50, 149.36, 117.53, 109.10, 24.01, 21.15. IR (KBr, ν_{max}, cm^{-1}, neat): 3329, 3233, 2922, 1682, 1566, 1401, 1083; MS (EI, 70 eV): m/z = 166.2 [M^{1+}].

1-(2,6-Dichloropyrimidin-4-yl)urea (4i): Yield 90 %. White solid, ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.19 (s, 1H); 7.85 (s, 1H); 7.06 (br s, 1H); 6.40 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.12, 160.85, 158.65, 154.43, 105.94, IR (KBr, ν_{max}, cm^{-1}, neat): MS (EI, 70 eV): m/z = 205.2, 207.2 [M^{1+}].

1-(4,6-Dimethylpyrimidin-2-yl)urea (4j): Yield 88 %, white solid. White solid, ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.26 (s, 1H); 8.63 (br s, 1H); 6.98 (br s, 1H); 6.81 (s, 1H); 2.34 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.74, 158.39, 155.29, 113.62, 23.83, MS (EI, 70 eV): m/z = 167.2 [M^{1+}].

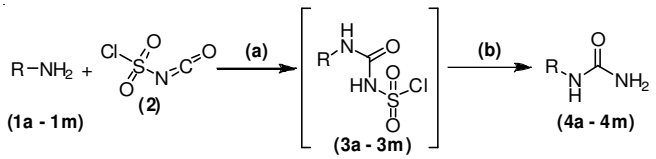
1-(2-Bromopyrimidin-5-yl)urea (4k): Yield 92 %. Off white solid, ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.81 (s, 1H); 8.71 (s, 2H); 8.09 (br s, 1H); 7.08 (br s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 158.78, 157.25, 154.69, 110.68. IR (KBr, ν_{max}, cm^{-1}, neat): 3441, 3142, 2954, 1683, 1561, 1442, 1124, 558. MS (EI, 70 eV): m/z = 217.0, 219.0 [M^{2+}].

1-(5-Nitropyrimidin-2-yl)urea (4l): Yield 86 %. Yellow crystaline solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H); 9.32 (s, 2H); 8.27 (br s, 1H); 7.43 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.53, 158.28, 153.97, 137.30. IR (KBr, ν_{max}, cm^{-1}, neat): MS (EI, 70 eV): m/z = 184.0 [M^{1+}].

1-(6-Chlorobenzo[d]thiazol-2-yl)urea (4m): Yield 91 %. white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.76 (s, 1H); 7.99 (s, 1H); 7.61 (d, 1H, *J* = 8.4 Hz); 7.38 (d, 1H, *J* = 2.4); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.20, 155.01, 148.52, 133.77, 127.03, 126.42, 121.46, 121.30. IR (KBr, ν_{max}, cm^{-1}, neat): 3343, 3186, 2978, 1693, 1498, 1124, 792. MS (EI, 70 eV): m/z = 228.0 [M^{1+}].

RESULTS AND DISCUSSION

Hetero/aryl urea derivative were synthesized from corresponding hetero/aryl amine (**1a-1m**) in presence of the chlorosulfonyl isocyanate and further *in situ* hydrolysis using hydrochloric acid according to **Scheme-I** to afford (**4a-4m**) (calcd. yield: 84-94 %) as solid.



Reagents and Conditions: (a) CH_2Cl_2, 0ºC, 45 min; **(b)** 4M HCl in 1,4-dioxane- H_2O (3:1), 2 h.
Scheme-I: Synthesis of hetero/aryl urea derivatives

The amines (**1a-1m**) were used and afforded products with corresponding yield mentioned in Table-1.

Conclusion

The reaction coupled with chlorosulfonyl isocyanate and further successfully carried hydrolysis to afford urea derivatives with good yield in single pot reaction. The yields are compared the difference having electron with drawing group moieties afforded slight high yield rather than electron donating group having moieties. In depth exploration the scope of the reaction for the possible application in organic synthesis, a study of functional group tolerance was considered. Various substituted hetero/aryl mine treated with CSI. At first the effect of halogen substituents was evaluated. The yield of urea (**4d**) from mono chloro substituted amine (**1d**) 90 % and di chloro substituted amines (**4f**), bromo-substituted amines (**1a**, **1b**, **1c**) afforded their respective urea in nearly identical yields. In contrast to the halogen substituted amines, substituted with the +I effective methyl group (**1h**) also resulted significant yield of urea (**4h**). The electron-poor nitro substituted pyridyl urea also isolated in 86 % yields (Table-1).

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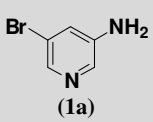
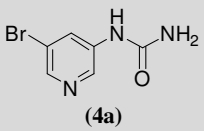
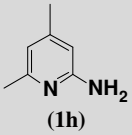
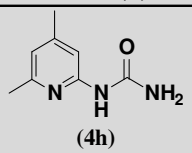
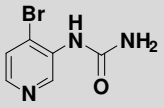
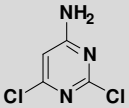
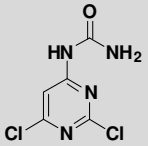
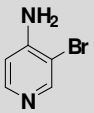
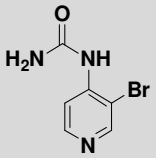
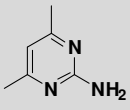
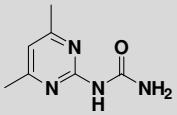
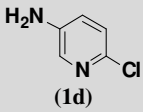
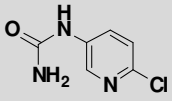
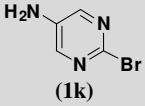
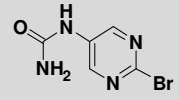
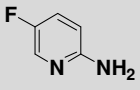
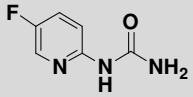
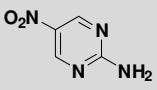
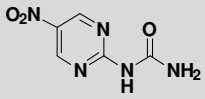
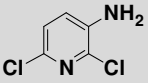
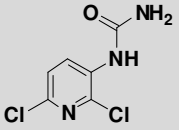
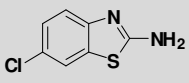
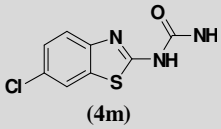
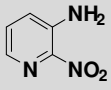
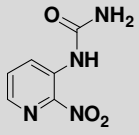
TABLE-1
AMINE (**1a-1m**) AND AFFORDED PRODUCTS (**4a-4m**) WITH YIELD

S. No.	Amine (R)	Product (R)	Yield (%)	S. No.	Amine (R)	Product (R)	Yield (%)
1	 (1a)	 (4a)	90	8	 (1h)	 (4h)	86
2	 (1b)	 (4b)	87	9	 (1i)	 (4i)	90
3	 (1c)	 (4c)	89	10	 (1j)	 (4j)	88
4	 (1d)	 (4d)	90	11	 (1k)	 (4k)	92
5	 (1e)	 (4e)	91	12	 (1l)	 (4l)	86
6	 (1f)	 (4f)	89	13	 (1m)	 (4m)	91
7	 (1g)	 (4g)	84	–	–	–	–

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