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A FACILE APPROACH TO TRANSFORMATION OF HETERO ARYL AMIDES FROM HETERO ARYL HALIDES

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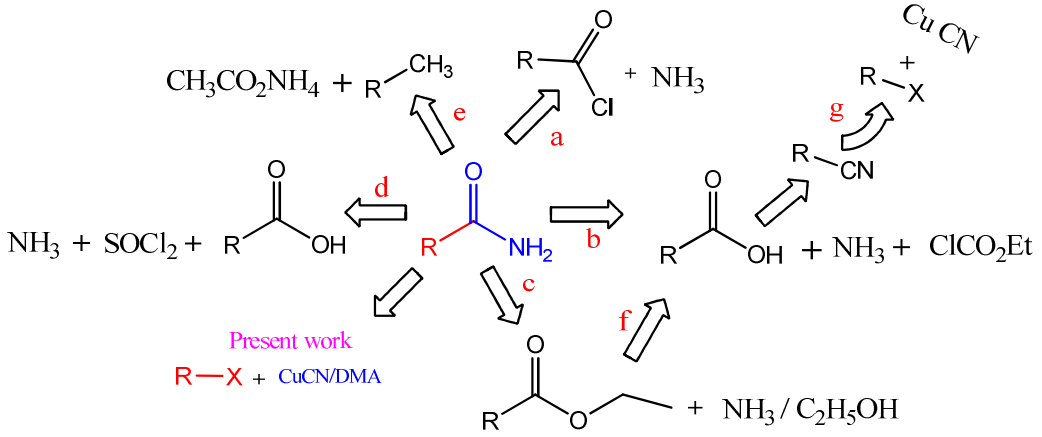
Abstract:
A novel and efficient amidation method for the synthesis of hetero aryl amides has been developed under mild and environment benign conditions, which is a facile one-pot approach to synthesis of heteroaryl amides from heteroaryl bromides/ chlorides by CuCN with DMA under aqueous conditions.

Keywords: Halothiazoles, amides, DMA, CuCN,

Introduction

A primary amide functionality ($CONH_2$) is found in a variety of natural products and pharmaceutically active substances [I] Aromatic amides are important building blocks for the synthesis of fine chemicals such as pharmaceuticals, natural products and functional materials. The preparation of functionalized amides from readily available precursors is therefore of great interest. Among others, the transformations of carboxylic acids derivatives [II], organohalides [III] amides,[IV] alcohols [V] and aldehydes [VI] etc. These reactions are based on the functional group transformations and require pre-activation, pre-functionalization or a strong oxidant, suffering from low atom-economic efficiency. Typically, hetero aryl halides like thiazolyl amides **(path a)** are synthesized by reacting thiazol-4-carboxylchloride with NH_3 in benzene [VII] as solvent. Several additional methods have also been developed, such as thiazol-4-carboxylic acid **(path b)** treated with NH_3 and chloroformate and ethyl ester by Iverson P.O et al [VIII], Thiazole-ester react with NH_3 in ethanol reported by Brookes P et al [IX] **(path c)** and also esters converted into acids which are obtained from corresponding cyanides **(path f)**. Some of thiazol amides [X] are also prepared by reacting thaizol acids with $SOCl_2$ and followed by addition of NH_3 in toluene as solvent **(path d).** Recently, the amides were prepared by reacting methyl thiazole **(path e)** with ammonium acetate, oxygen and copper (I) bromide in dioxane solvent [XI]. Since, Rosenmund-von-Braun and Jones. G [XII] reported the cyanation reaction employing aryl halides with CuCN in DMF solvent **(path g)**. Flipo Morian et al [XIII] reported the synthesis of 2-cyanothiazole from thiazol-2-

carbaldehydeoxime and Nani Ganesh et al [XIV] also reported from 2-formyl thaizole. These methods posses a number of draw backs including in highly toxic substances, low functional group tolerance, more time and less yield. To overcome these problems, we developed the synthesis of hetero aryl amides from hetero aryl halides in one pot synthesis by using CuCN and DMA as a catalyst as well as solvent.

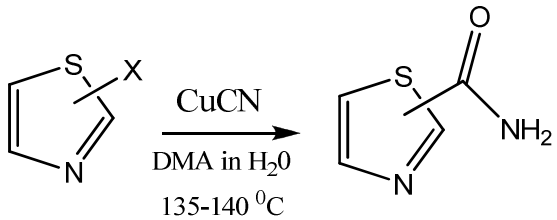


Scheme 1: Synthetic methods for hetero aryl amides

Results and discussion:

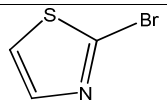
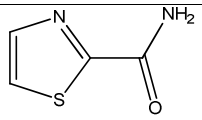
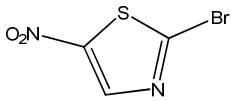
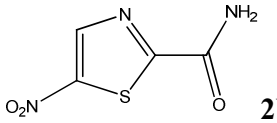
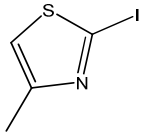
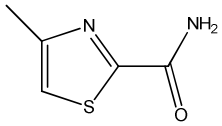
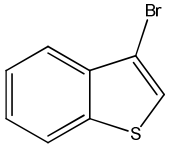
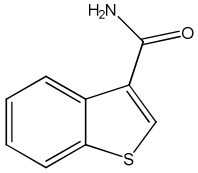
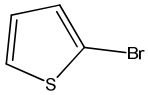
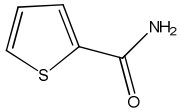
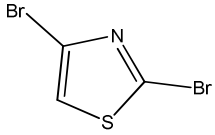
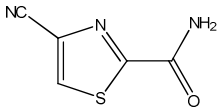
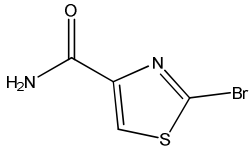
Initially, we examined the reaction of 2-bromothiazole **1a** with CuCN in the presence of DMA **(Table 1, entry 1a)** to yield 63% of the corresponding compound thiazol-2-acetamide **(2a)**. After identification of product and reaction conditions, we conduct next set of reactions to exploring the scope and limitations of the protocol using various hetero halides **(Scheme-1)**. In general, 4-methyl-2-iodothiazole **(1c)** afford 76 % yield of the corresponding 4-methylthiazol-2-carboxamide **(2c).** As exemplified by 2, 5 and 2, 4-dibromothiazoles **(entry 1f & 1g)** two amido groups could be generated in one pot to produce the corresponding mixture of amides in good yields **(2f & 2g)**. For 2-chloro benzothiazole **(1h)** the desired product 2-amido benzothiazole was not obtained but got the unexpectedly N, N-dimethyl benzo[d]thiazole-2-amine **(2j)** with 58 % of yield. All the newly synthesized compounds were characterized by spectroscopic data.

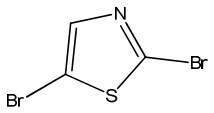
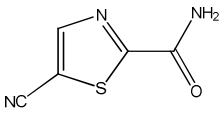
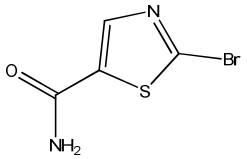
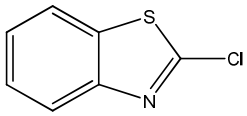
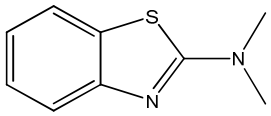
Scheme-1:



1(a-h) **2(a-j)**

Table 1: Reaction of hetero aryl halides with CuCN/DMA in H_2O leading to hetero aryl amides
(2a-j):

Entry	Reactant	Products	Time (h)	% Yield
1a		 **2a**	4.6	63
1b		 **2b**	4.2	69
1c		 **2c**	4.5	76
1d		 **2d**	8.0	70
1e		 **2e**	6.0	70
1f		 **2f**	6.5	38
		 **2g**		25

1g		 **2h**	6.3	36
		 **2i**		20
1h		 **2j**	8.0	58

Experimental:

General Procedure: Melting points were uncorrected. Infra Red spectra were obtained by using a Bruker WM-4(X) spectrometer (577 model). ^{1}H NMR (400MHz) and ^{13}C NMR (100MHz) spectra were recorded on a Bruker WM-400 spectrophotometer in $CDCl_3$ with Tetra Methyl Silane as reference. Mass spectra (ESI) were carried out on a JEOL SX-102 spectrophotometer. Elemental analysis was done by the Carlo Erba EA 1108 automatic elemental analyzer. The chemicals and solvents were used for the synthesis of commercial grade which were used without further purification unless otherwise stated. Purification of the synthesized compounds by column chromatography and thin-layer chromatography (TLC) was carried out by using aluminium sheets purchased from Merck.

General procedure for the synthesis of hetero aryl amides 2(a-j):

To a stirred solution of hetero aryl halides (1 mmol) in N,N-Dimethylacetamide (2 mL) in water (1 mL), was added CuCN (2.2 mmol) and stirred at 135-140°C for 4 to 8 h. Then the reaction mixture was cooled to room temperature, filtered through celite pad and portioned between ethyl acetate and water. The organic layer was washed with saturated aqueous NH_4Cl solution than followed by brine solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under *vaccum*. The crude compound was purified by column chromatography on silica gel to afford desired amides.

Thiazole-2-Carboxamide (2a): M. p. 118-119 ^{0}C [XV]; NMR ^{1}H (400 MHz, $CDCl_3$): δ 7.82 (br, s, 1H, -NH_2), 7.98-7.99 (dd, 1H, thiazole-H, 8.01-8.02 (dd, 1H, thiazole-H, 8.13 (br, s, 1H, -NH_2); NMR ^{13}C (100 MHz, $CDCl_3$): δ 134.4, 144.52, 165.22, 166.43; IR (ν max, cm-1): 3412, 3199, 1660; MS (m/z): 128.18, 129.0 (M+), 131.0 (M+2). CHN analysis calc. for $C_8H_4N_2OS$: C, 37.49; H, 3.15; N, 21.86; Found: C, 37.44; H, 3.10; N, 21.82.

5-Nitrothiazole-2-Carboxamide (2b): M. p. 168-169 ^{0}C [XVI]; NMR 1H (400 MHz, $CDCl_3$): δ 8.28 (br, s, 1H, -NH_2), 8.56 (br, s, 1H, -NH_2), 8.93 (s, 1H, thiazole-H); NMR 13C (100 MHz, $CDCl_3$): δ 145.09, 152.72, 160.02, 169.04; IR (ν max, cm-1): 3412, 3184, 1660, 1214, 1216; MS (m/z): 173.15, 174.0 (M+), 175.0 (M+2). CHN analysis calc. for $C_4H_3N_3O_2S$: C, 27.75; H, 1.75; N, 24.27; Found: C, 27.72; H, 1.72; N, 24.23.

4-Methylthiazole-2-Carboxamide (2c): M. p. 180-181 ^{0}C; NMR 1H (400 MHz, $CDCl_3$): δ 2.50(s, 3H, -CH_3), 7.57 (s, 1H, thiazol-H), 7.75 (br, s, 1H, -NH_2), 8.04 (s, 1H, thiazol-H); NMR 13C (100 MHz, $CDCl_3$): δ 18.22, 116.42, 150.29, 1662.72, 168.04; IR (ν max, cm-1): 3410, 3184, 1657, 1216; MS (m/z): 143.1 (M+), 145.1 (M+2). CHN analysis calc. for $C_5H_6N_2OS$: C, 42.24; H, 4.25; N, 19.25; Found: C, 42.20; H, 4.21; N, 19.23.

Benzo[b]lthiophene-3-Carboxamide (2d): M. p. 203-205 ^{0}C; NMR 1H (400 MHz, $CDCl_3$): δ 7.30(br, s, 1H, -NH_2), 7.38-7.46 (m, 2H, thiazol-H), 7.90 (br, s, 1H, -NH_2), 7.99-8.06 (dd, 1H, thiazol-H), 8.38 (s, 1H, thiazol-H), 8.50-8,54 (dd, 1H, thiazol-H); NMR 13C (100 MHz, $CDCl_3$): δ 123. 11, 125.19, 131.26, 131.66, 137.78, 139.93, 165.39; IR (ν max, cm-1): 3390, 3182, 1662; MS (m/z): 177.22, 178.0 (M+), 179.0 (M+2). CHN analysis calc. for C_9H_7NOS: C, 60.99; H, 3.98; N, 7.90; Found: C, 60.87; H, 3.95; N, 7.85.

Thiophene-2-Carboxamide (2e): M. p. 139-141 ^{0}C; NMR 1H (400 MHz, $CDCl_3$): δ 7.11-7.13 (m, 1H, thiazol-H), 7.31-7.40 (br, s, 1H, -NH_2), 7.72-7.74 (t, 2H, thiazole-H), 7.82-7.94(br,s, 1H, -NH_2); NMR 13C (100 MHz, $CDCl_3$): δ 128.32, 129.12, 131.4, 140.74, 163.36; IR (ν max, cm-1): 3410, 3187, 1658; MS (m/z): 127.16, 128.0 (M+), 129.0 (M+2). CHN analysis calc. for C_5H_5NOS: C, 47.23; H, 3.96; N, 11.01; Found: C, 47.19; H, 3.95; N, 10.99.

4-Cyanothiazole-2-Carboxamide (2f): M. p. 165-167 ^{0}C; NMR ^{1}H (400 MHz, $CDCl_3$): δ 8.21 (br, s, 1H, -NH_2), 8.50 (br, s, 1H, -NH_2), 8.80 (s, 1H, thiazol-H); NMR ^{13}C (100 MHz, $CDCl_3$): δ 114.34, 126.11, 138.76, 160.07, 167.08; IR (ν max, cm-1): 3383, 3177, 2245, 1690, 1674; MS (m/z): 153.16 (M+), CHN analysis calc. for $C_5H_3N_3OS$: C, 39.21; H, 1.97; N, 27.44; Found: C, 39.17; H, 1.93; N, 27.38.

2-Bromothiazole-4-Carboxamide (2g): M. p. 199-201 ^{0}C; NMR ^{1}H (400 MHz, $CDCl_3$): δ 7.96 (br, s, 1H, -NH_2), 8.09 (s, 1H, thiazol-H), 8.32 (br, s, 1H, -NH_2); NMR 13C (100 MHz, $CDCl_3$): δ 124.86, 125.15, 160.22, 165.45; IR (ν max, cm-1): 3359, 3145, 1683, 1659; MS (m/z): 205.98 (M+), 207.87 (M+2). CHN analysis calc. for $C_4H_3BrN_2OS$: C, 23.20; H, 1.46; N, 13.53; Found: C, 23.17; H, 1.43; N, 13.51.

5-Cyanothiazole-2-Carboxamide (2h): M. p. 198-200 ^{0}C; NMR ^{1}H (400 MHz, $CDCl_3$): δ 8.08 (br, s, 1H, -NH_2), 8.48 (br, s, 1H, -NH_2), 9.06 (s, 1H, thiazol-H); NMR ^{13}C (100 MHz, $CDCl_3$): δ 116.42, 127.14, 138.79, 160.25,167.18; IR (ν max, cm-1): 3413, 3164, 2230, 1697; MS (m/z): 205.91 (M+), 207.82 (M+2). CHN analysis calc. for $C_4H_3BrN_2OS$: C, 23.20; H, 1.46; N, 13.53; Found: C, 23.19; H, 1.46; N, 13.50.

2-Bromothiazole-4-Carboxamide (2i): M. p. 227-229 ^{0}C; NMR ^{1}H (400 MHz, $CDCl_3$): δ 7.95 (br, s, 1H, -NH_2), 8.15 (s, 1H, thiazol-H), 8.30 (br, s, 1H, -NH_2); NMR ^{13}C (100 MHz, $CDCl_3$): δ 124.81, 126.12, 160.22, 166.42; IR (ν max, cm-1): 3434, 3168, 1692, 1651; MS (m/z): 205.98 (M+), 207.87 (M+2). CHN analysis calc. for $C_4H_3BrN_2OS$: C, 23.20; H, 1.46; N, 13.53; Found: C, 23.17; H, 1.43; N, 13.51.

N, N-Dimethylbenzo[*d*]thiazol-2-amine (2j): M. p. 188--189 ^{0}C; NMR 1H (400 MHz, $CDCl_3$): δ 3.14 (s, 6H, 2xCH_3) 7.01 (m, 1H, thiazol-H), 7.26(m, 1H, thiazol-H), 7.42 (dd, 1H, thiazol-H), 7.78 (dd,, 1H, thiazol-H); NMR 13C (100 MHz, $CDCl_3$): δ 40.20, 118.64, 121.06, 121.46, 131.24, 153.49, 168.48; MS (m/z): 179.06 (M+). CHN analysis calc. for $C_9H_{10}N_2S$: C, 60.64; H, 5.65; N, 15.72; Found: C, 60.62; H, 5.63; N, 15.70.

Conclusions: In this paper, we have developed a new and efficient method for the preparation of hetero aryl amides from the corresponding hetero aryl halides. This method is suitable for a one-pot preparation of functionalized heterocyclic compounds like substituted thiazoles, benzo[b] thiazole and thiophenyl amides. Further extensions of this method are currently underway in our laboratories.

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