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Received 00th January 20xx, Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

I₂ – Catalyzed Transformation of o-Aminobenzamide to o-Ureidobenzonitrile Using Isothiocyanates

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Present work describes the unexpected and unique protocol for the iodine catalysed synthesis of o-ureidobenzonitriles using o-aminobenzamides and isothiocyanates via intramolecular rearrangement. The metal free route achieved here is insensitive to moisture and applicable to the synthesis of wide variety of o-ureidobenzonitriles with excellent yields even in scalable fashion.

Introduction

Urea and its derivatives have significant role in drug discovery and medicinal chemistry due to their ability to form stable hydrogen bonds with protein and receptor targets.¹ Urea functionality is incorporating in drug design to enhance the selectivity and potency of the drugs. Some of the urea derivatives are in use as hypnotics, sedatives, anticonvulsants, antibacterial, antiviral, anti-HIV and anticancer agents.^{2,3} The FDA approved drugs Sorafenib, Linifanib and Lenvatinib which contain diphenyl urea as a key moiety are being used in the treatment of carcinoma and thyroid cancer (Fig. 1).^{4,5,6}



Figure 1: Bioactive molecules containing urea moiety

Nitriles, which have extensive applications in organic synthesis and pharmaceuticals are generally synthesized by the dehydration of primary amides and aldoximes. The functional group transformation of amide to nitrile is not an easy task, which requires harsh, acidic dehydrating reagents such as P_2O_5 , $POCl_3$, $TiCl_4$ or $SOCl_2$.⁷ Stephan Enthaler et al developed the Cu and Zn catalyzed dehydration of amides to nitriles using N-methyl-N-(trimethylsilyl)trifluoroacetamides as dehydrating agent.⁸ Again, only few methods have been reported for the synthesis of o-ureidobenzonitriles (Scheme 1). The traditional method involves the reaction between o-aminobenzonitrile and isocyanates in presence of base.^{9a} The method reported by Pedro Molina et al requires three steps, starting with oaminobenzamide (1a).^{9b}

In continuation of our work on the synthesis of heterocyclic compounds via novel methodologies,¹⁰ we initiated to synthesize biologically active quinazolinone¹¹ derivatives but unexpectedly ended up with o-ureidobenzonitriles. Likewise, recently we have reported an unprecedented procedure for the synthesis of N, N'- substituted ureas.¹²



Scheme 1: Methods for the synthesis of o-ureidobenzonitriles

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 Electronic Supplementary Information (ESI) available: General experimental protocols, characterization details, ¹H-NMR, ¹³C-NMR, HRMS spectra of compounds and Crystallographic data [CCDC Number-1974299]. See DOI: 10.1039/x0xx00000x

The most commonly used protocols for the synthesis of nitriles and o-ureidobenzonitriles are expensive, moisture sensitive, time consuming, requires high temperature and large amount of activating reagents, have toxicological issues, narrow substrate scope and mainly suffer from lower yield. Our method is able to synthesize variety of o-ureidobenzonitriles which includes phenyl, benzyl and aliphatic isothiocyanates, at optimum conditions with maximum yields. Moreover, the procured o-ureidobenzonitrile which contain nitrile group at ortho position to urea is a precursor for the synthesis of heterocycles like quinazolines and quinazolinones.^{9a,13}

Results and Discussion

Initially we started the work with o-aminobenzamide **(1a)**, phenyl isothiocyanate **(2a)** using 0.5 eq of I_2 as catalyst in DMF solvent and stirred the contents for 6 hr at room temperature. A new spot observed in TLC was isolated with 80 % yield. The molecular ion peak (m/z = 238.0685) observed in the mass spectra supported the formation of expected product 2- (phenylamino)quinazolin-4(3H)-one (Scheme 2). However, the ambiguity raised when we observed two –NH- protons in the same region (9.402 & 8.747 ppm) of ¹H-NMR spectra. Further investigation of the product with ¹³C-NMR and crystal analysis (Fig. 2) revealed the exact structure of the molecule, which is nothing but 1-(2-cyanophenyl)-3-phenylurea **(3a)**. Surprisingly, the expected and obtained product's molecular masses are same.



3a Obtained Product

Scheme 2: Expected and obtained product.



Figure 2: Single crystal structure of 1-(2-cyanophenyl)-3phenylurea (3a): CCDC Number-1974299.

After the confirmation of structure, we attempted to optimize the reaction conditions to obtain the compound 32 and better yield (Table 1). In the beginning, o-aminobenzamide (1a) (1 eq) and phenyl isothiocyanate (2a) (1 eq) were allowed to stir for 24 h in DMF (10 vol) solvent without I₂, but no desired product was observed (Table 1, entry 1). Then we tested with 0.6 and 0.7 eq of I₂ and obtained slightly lower yields compared to the yield obtained with 0.5 eq of I_2 (Table 1, entries 2-4). After that, we tried with 0.4, 0.3 and 0.2 eq of I_2 and procured 80, 81 and 50 % yield respectively (Table 1, entries 5-7). With these results, 0.3 eq of I₂ was found to be enough for better yield (Table 1, entry 6). Extending the reaction time with 0.3 eq of I_2 didn't improve the yield (Table 1, entry 8). In addition, we investigated the temperature dependency of the reaction by keeping it at 40 °C, 50 °C and 60 °C but recorded lesser yields compared to room temperature condition (Table 1, entries 9-11). Effect of solvent in terms of yield was also screened (Table 1, entries 12-19). From the Table 1, the best optimized conditions for the reaction are: o-aminobenzamide (1a) (1 mmol), phenyl isothiocyanate (2a) (1 mmol) and I₂ (0.3 mmol) in DMF (1 ml) solvent stirred for 3 h at room temperature to synthesize 1-(2-cyanophenyl)-3-phenylurea (3a) (Table 1, entry 6).

Table 1: Optimization of the reaction conditions (catalyst equivalence, solvent, temp., time) for the synthesis of 1-(2-cyanophenyl)-3-phenylurea(3a).^a



Entry	I ₂	Solvent	Temp.	Time	%
	(equivalence)		°C	h	Yield ^b
1	0.0	DMF	rt	24	
2	0.5	DMF	rt	3	80
3	0.6	DMF	rt	3	78
4	0.7	DMF	rt	3	76
5	0.4	DMF	rt	3	80
6	0.3	DMF	rt	3	81
7	0.2	DMF	rt	3	50
8	0.3	DMF	rt	15	80
9	0.3	DMF	40	3	75
10	0.3	DMF	50	3	71
11	0.3	DMF	60	3	69
12	0.3	DMSO	rt	3	78
13	0.3	EtOAc	rt	3	50
14	0.3	EtOH	rt	3	65

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Published on 17 March 2020. Downloaded by National University of Singapore on 3/18/2020 3:02:47 PM

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15	0.3	CHCl ₃	rt	3	
16	0.3	Toulene	rt	3	
17	0.3	CH ₃ CN	rt	3	63
18	0.3	DCM	rt	3	
19	0.3	H ₂ O	rt	3	

^aReaction conditions: Reactions were performed with 1a (1 mmol) and 2a (1 mmol) using I_2 (0.3 mmol) in DMF solvent (1 ml) at rt for 3 h. ^b Isolated yield.

With the help of above optimized reaction conditions, we further explored the scope and generality of the reaction using various substituted o-aminobenzamides 1 and isothiocyanates 2 and the results are summarized in Scheme 3. Both electron donating and withdrawing groups at different positions on phenyl ring of isothiocyantes gave almost similar yields with oaminobenzamides. The yields obtained with benzyl and alkyl isothiocyanates are also comparable with phenyl isothiocyanates. These examples clearly describe the utility of the protocol for wider applicability. The approach of this reaction is also good even in gram scale synthesis. We synthesized 1a in 2.0 g scale and procured 78 % yield which was 81 % when synthesized in mmol scale. We tried to extend the scope of the reaction by taking o-(methylamino)benzamide and o-hydroxybenzamide in place of o-aminobenzamide, but the starting materials were remained as it is without undergoing any further reactions (Scheme 4).

A possible reaction mechanism for the formation of oureidobenzonitrile has been proposed (Scheme 5). The reaction of o-aminobenzamide **1a** with phenyl isothiocyante **2a** first produces the thiourea intermediate **A**. The Lewis acid-base interaction between molecular iodine and sulfur atom of thiocarbonyl group, followed by the nucleophilic attack of carbonyl oxygen on the thiocarbonyl carbon leads to the formation of cyclized thiol intermediate **B** with the regeneration of iodine. This is the key step which resulted the unexpected chemistry. This unstable intermediate **B** further undergoes intramolecular rearrangement to produce o-ureidobenzonitrile **3a** with the liberation of H₂S. At the end of the reaction, the amide group of o-aminobenzamide **1a** transformed to nitrile and amine group converted to urea.

In order to support the proposed mechanism, we performed a few reactions (Scheme 6). Suppose the dehydration of amide to nitrile and the conversion of thiocarbonyl to carbonyl are two independent reactions, then the reactions (a), (b) and (c) have to be ended with positive results as shown in Scheme 6, but they didn't. Only the corresponding thiourea intermediates have formed without affecting the amide moiety. The yields of thiourea intermediates formed were around 75%. The reaction (d) was performed under nitrogen atmosphere and obtained the product **3a** with almost same yield compared to the yield obtained when the reaction was

performed at ordinary conditions. Also, we vet in the one of the





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On the basis of the experimental results of Scheme 6 and literature reports,^{9b,15} we can conclude that the product is forming through intramolecular rearrangement mechanism and the oxygen atom which is re[placing sulfur is from amide moiety only as depicted in Scheme 5.



Scheme 4: Extended reactions



Scheme 5: Proposed mechanism for the synthesis of oureidobenzonitrile.







Experimental

Materials and methods

All the reagents, chemicals and solvents used were from Sigma Aldrich and Sd-fine chemicals and were used without additional purification. The instrumental techniques employed for the characterization of the newly synthesized compounds include ¹H and ¹³C NMR and HRMS. ¹H and ¹³C NMR spectra were recorded on Agilent 400 MHz spectrometer in DMSO-d₆ solution using tetramethylsilane (TMS) as internal standard. Chemical shifts were recorded in ppm relative to TMS. High resolution mass spectra were obtained via electrospray (ESI). Column chromatography was performed on silica gel 60 (60–120 mesh) and thin layer chromatography was performed on TLC plates (Merck, silica gel 60 F254). The mobile phases employed for column chromatography and TLC were hexane and ethyl acetate in 9:1 ratio.

Synthetic procedures

General procedure for synthesis of o-ureidobenzonitriles (3a-3x)

The mixture of o-aminobenzamide (1) (1 mmol) and isothiocyanates (2) (1 mmol) were allowed to stir in DMF solvent (2 ml) in presence of molecular iodine (0.3 mmol) at room temperature for 3 h. After that, the contents were poured to 30 ml, 10 % aqueous solution of sodium thiosulfate and extracted with 30 ml ethyl acetate. The ethyl acetate extract was separated and dried over anhydrous sodium sulfate then the solvent was removed under reduced pressure to afford corresponding o-ureidobenzonitrile. The crude residue thus obtained was purified by column chromatography over silica gel using ethyl acetate in hexane as eluent to get pure o-ureidobenzonitrile.

1-(2-cyanophenyl)-3-phenylurea (3a)

Yield: 192 mg, 81 %; MP. 178 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm : 6.971-7.008 (t, 1H, Ar, J=7.6 Hz), 7.139-7.176 (t, 1H, Ar, J=7.6 Hz), 7.269-7.307 (t, 2H, Ar, J=8 Hz), 7.450-7.470 (d, 2H, Ar, J=8 Hz), 7.602-7.641 (t, 1H, Ar, J=7.6 Hz), 7.718-7.738 (d, 1H, Ar, J=8 Hz), 8.059-8.080 (d, 1H, Ar, J=8.4 Hz), 8.747 (s, 1H, -NH-), 9.402 (s, 1H, -NH-); ¹³C- NMR (400 MHz, DMSO-d6): δ ppm: 102.452, 117.395, 118.826, 121.725, 122.795, 123.447, 129.343, 133.565, 134.421, 139.665, 142.389, 152.459; HRMS: m/z calculated for [C₁₄H₁₁N₃O+H⁺] = 238.0975: found = 238.0974.

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1-(2-cyanophenyl)-3-(4-methoxyphenyl)urea (3b)

Yield: 222 mg, 83 %; MP. 188 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm : 3.687 (s, 3H, -OCH₃), 6.846- 6.868 (d, 2H, Ar, J=8.8 Hz), 7.103-7.141 (t, 1H, Ar, J=7.6 Hz), 7.332-7.354 (d, 2H, Ar, J=8.8 Hz), 7.572- 7.610 (t, 1H, Ar, J=7.6 Hz), 7.688-7.707 (d, 1H, Ar, J=7.6 Hz), 8.047-8.068 (d, 1H, Ar, J=8.4 Hz), 8.617 (s, 1H, -NH-), 9.183 (s, 1H, -NH-); ¹³C- NMR (400 MHz, DMSO-d₆): δ ppm : 55.626, 102.121, 114.535, 117.405, 120.606, 121.491, 123.194, 132.612, 133.507, 134.373, 142.594, 152.527, 155.251; HRMS: m/z calculated for [C₁₅H₁₃N₃O₂+H⁺] = 268.1081: found = 268.1084.

1-(2-cyanophenyl)-3-(p-tolyl)urea (3c)

Yield: 201 mg, 80 %; MP. 196 °C; White solid; ¹H-NMR (400MHz, DMSO-d₆): δ ppm: 2.219 (s, 3H, -CH₃), 7.067-7.088 (d, 2H, Ar, J=8.4 Hz), 7.116-7.155 (t, 1H, Ar, J=7.6 Hz), 7.310-7.331 (d, 2H, Ar, J=8.4 Hz), 7.577-7.621 (m, 1H, Ar), 7.694-7.716 (m, 1H, Ar), 8.042-8.063 (d, 1H, Ar, J=8.4 Hz), 8.658 (s, 1H, -NH-), 9.260 (s, 1H, -NH-); ¹³C- NMR (400 MHz, DMSO-d₆): δ ppm: 102.257, 117.395, 118.903, 121.598, 123.311, 129.712, 131.678, 133.536, 134.392, 137.048, 142.477, 152.430; HRMS: m/z calculated for [C₁₅H₁₃N₃O+H⁺] = 252.1137: found = 252.1142.

1-(4-chlorophenyl)-3-(2-cyanophenyl)urea (3d)

Yield: 223 mg, 82 %; MP. 198 °C; White solid; ¹H-NMR (400 MHz, DMSO-d6): δ ppm : 7.137-7.174 (t, 1H, Ar, J=7.2 Hz), 7.305-7.327 (d, 2H, Ar, J=8.8 Hz), 7.458-7.480 (d, 2H, Ar, J=8.8 Hz), 7.587-7.629 (m, 1H, Ar), 7.704-7.726 (m, 1H, Ar), 8.016-8.036 (d, 1H, Ar, J=8 Hz), 8.725 (s, 1H, -NH-), 9.470 (s, 1H, -NH-); ¹³C- NMR (400 MHz, DMSO-d₆): δ ppm : 102.724, 117.337, 120.353, 121.861, 123.641, 126.356, 129.177, 133.555, 134.421, 138.644, 142.166, 152.401; HRMS: m/z calculated for [C₁₄H₁₀ClN₃O+H⁺] = 272.0591: found = 272.0595.

1-(2-cyanophenyl)-3-(4-fluorophenyl)urea (3e)

Yield: 200 mg, 78 %; MP. 205 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm : 7.105-7.180 (m, 3H, Ar), 7.445- 7.478 (m, 2H, Ar), 7.601-7.639 (t, 1H, Ar, J=7.6 Hz), 7.718-7.737 (d, 1H, Ar, J=7.6 Hz), 8.034-8.055 (d, 1H, Ar, J=8.4 Hz), 8.702 (s, 1H, -NH-), 9.388 (s, 1H, -NH-); ¹³C- NMR (400 MHz, DMSO-d₆): δ ppm : 102.57, 115.74, 115.96, 117.36, 120.59, 120.66, 121.77, 123.50, 133.54, 134.41, 135.96, 142.32, 152.53, 156.86, 159.24; HRMS: m/z calculated for [C₁₄H₁₀FN₃O+H⁺] = 256.0881: found = 256.0886.

1-(2-cyanophenyl)-3-(4-(trifluoromethyl)phenyl)urea (3f)

Yield: 247 mg, 81 %; MP. 185 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm: 7.158-7.196 (t, 1H, Ar, J=7.6 Hz), 7.303-7.321 (d, 1H, Ar, J=7.2 Hz), 7.484-7.523 (t, 1H, Ar, J=8 Hz), 7.552-7.573 (d, 1H, Ar, J=8.4 Hz), 7.599-7.641 (m, 1H, Ar), 7.719-7.742 (t, 1H, Ar, J=8.4 Hz), 7.987-8.039 (t, 2H, Ar, J=12.4 Hz), 8.807 (s, 1H, -NH-), 9.704 (s, 1H, -NH-); ¹³C- NMR (400 MHz, DMSO-d₆): δ ppm: 103.094, 114.720, 117.308, 119.040, 122.386, 123.885, 130.471, 133.555, 134.431, 140.541, 141.961, 152.556; HRMS: m/z calculated for [C₁₅H₁₀F₃N₃O+H⁺] = 306.0854 : found = 306.0859.

1-(2-cyanophenyl)-3-(4-nitrophenyl)urea (3g)

Yield: 226 mg, 80 %; MP. >250 °C; White solid; ¹H-NMR (400 MHz-DMSO-d₆): δ ppm: 7.200-7.238 (t, 1H, Ar, J=7.6 Hz), 7.630-7.692 (m, 3H, Ar), 7.752-7.772 (d, 1H, Ar, J=8 Hz), 7.981-8.002 (d, 1H, Ar, J=8.4 Hz), 8.176- 8.198 (d, 2H, Ar, J=8.8 Hz), 8.934 (s, 1H, -NH-), 10.016 (s, 1H, -NH-); ¹³C- NMR (400 MHz, DMSO-d₆): δ ppm : 103.639, 117.220, 118.252, 122.464, 124.332, 125.607, 133.643, 134.643, 141.572, 141.913,

 146.252, 152.206; HRMS: m/z calculated for $[C_{14}H_{140}M_{A}O_{de}+H_{n}^+]$

 281.0826: found = 281.0830.

 DOI: 10.1039/D00B00118J

 1-(2-cyanophenyl)-3-(3-methoxyphenyl)urea (3h)

Yield: 214 mg, 80 %; MP. 188 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm: 3.718 (s, 3H, -OCH₃,), 6.564- 6.583 (d, 1H, Ar, J=7.6 Hz), 6.936-6.955 (d, 1H, Ar, J=7.6 Hz), 7.163-7.206 (t, 3H, Ar, J=8.8 Hz), 7.604- 7.643 (t, 1H, Ar, J=8.0 Hz), 7.722-7.740 (d, 1H, Ar, J=7.2 Hz), 8.055-8.076 (d, 1H, Ar, J=8.4 Hz), 8.702 (s, 1H, -NH-), 9.379 (s, 1H, -NH-); ¹³C- NMR (400 MHz, DMSO-d₆): δ ppm : 55.392, 102.384, 104.573, 108.270, 111.091, 117.376, 121.686, 123.466, 130.121, 133.555, 134.431, 140.862, 142.331, 152.381, 160.164; HRMS: m/z calculated for [C₁₅H₁₃N₃O₂+H⁺] = 268.1081: found = 268.1085.

1-(2-cyanophenyl)-3-(m-tolyl)urea (3i)

Yield: 214 mg, 85 %; MP. 189 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm : 2.287 (s, 3H, -CH₃), 6.823-6.841 (d, 1H, Ar, J=7.2 Hz), 7.162-7.200 (t, 2H, Ar, J=7.6 Hz), 7.237-7.257 (d, 1H, Ar, J=8.0 Hz), 7.316 (s, 1H, Ar), 7.638 (s, 1H, Ar), 7.738-7.757 (d, 1H, Ar, J=7.6 Hz), 8.080-8.101 (d, 1H, Ar, J=8.4 Hz), 8.713 (s, 1H, -NH-), 9.316 (s, 1H, -NH-); ¹³C- NMR (400 MHz, DMSO-d₆): δ ppm : 21.651, 102.306, 116.024, 117.396, 119.361, 121.628, 123.379, 123.544, 129.168, 133.546, 134.402, 138.527, 139.568, 142.429, 152.411; HRMS: m/z calculated for [C₁₅H₁₃N₃O+H⁺] = 252.1137; found = 252.1142.

1-(3-bromophenyl)-3-(2-cyanophenyl)urea (3j)

Yield: 258 mg, 82 %; MP. 191 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm : 7.158-7.295 (m, 4H, Ar), 7.605- 7.643 (t, 1H, Ar, J=7.6 Hz), 7.724-7.743 (d, 1H, Ar, J=7.6 Hz), 7.839 (s, 1H, Ar), 7.994-8.015 (d, 1H, Ar, J=8.4 Hz), 8.767 (s, 1H, -NH-), 9.519 (s, 1H, -NH-); ¹³C- NMR (400 MHz, DMSO-d₆): δ ppm : 103.016, 117.328, 117.658, 121.083, 122.056, 122.221, 123.846, 125.344, 131.269, 133.585, 134.451, 141.339, 142.020, 152.401; HRMS: m/z calculated for [C₁₄H₁₀BrN₃O+H⁺] = 316:0080: found = 316.0085.

1-(3-chlorophenyl)-3-(2-cyanophenyl)urea (3k)

Yield: 228 mg, 84 %; MP. 186 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm : 7.022-7.041 (d, 1H, Ar, J=7.6 Hz), 7.179-7.198 (d, 1H, Ar, J=7.6 Hz), 7.232-7.252 (d, 1H, Ar, J=8 Hz), 7.281-7.301 (d, 1H, Ar, J=8 Hz), 7.694 (s, 1H, Ar), 7.724-7.744 (d, 1H, Ar, J=8 Hz), 7.996-8.018 (d, 1H, Ar, J=8.8 Hz), 8.771 (s, 1H, -NH-), 9.531 (s, 1H, -NH-); ¹³C- NMR (400 MHz, DMSO-d₆): δ ppm : 102.996, 117.240, 117.337, 118.174, 122.046, 122.426, 123.836, 130.968, 133.595, 133.702, 134.461, 141.203, 142.010, 152.411; HRMS: m/z calculated for [C₁₄H₁₀ClN₃O+H⁺] = 272.0591: found = 272.0595.

1-(4-chloro-2-cyanophenyl)-3-phenylurea (3l)

Yield: 217 mg, 80 %; MP. 204 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm : 6.968-7.004 (t, 1H, Ar, J=7.2 Hz), 7.257-7.297 (t, 2H, Ar, J=8.4 Hz), 7.423-7.442 (d, 1H, Ar, J=7.6 Hz), 7.660-7.690 (m, 1H, Ar), 7.897-7.903 (d, 1H, Ar, J=2.4 Hz), 8.085-8.108 (d, 1H, Ar, J=9.2 Hz), 8.798 (s, 1H, -NH-), 9.406 (s, 1H, -NH-); ¹³C-NMR (400 MHz, DMSO-d₆): δ ppm : 103.726, 116.121, 118.903, 122.951, 123.126, 126.716, 129.343, 132.602, 134.470, 139.461, 141.562, 152.274; HRMS: m/z calculated for [C₁₄H₁₀ClN₃O+H⁺] = 272.0591: found = 272.0593. **1-(4-chloro-2-cyanophenyl)-3-(p-tolyl)urea (3m)**

Yield: 222 mg, 78 %; MP. 195 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm : 2.220 (s, 3H, -CH₃-), 7.070-7.091 (d, 2H, Ar, J=8.4 Hz), 7.302-7.322 (d, 2H, Ar, J=8 Hz), 7.646-7.674 (m, 1H, Ar), 7.873-7.879 (d, 1H, Ar, J=2.4 Hz), 8.081-8.104 (d, 1H, Ar, J=9.2 Hz), 8.727 (s, 1H, -NH-), 9.283 (s, 1H, -NH-); ¹³C-NMR (400 MHz, DMSO-d₆): δ ppm : 103.580, 116.131, 119.010, 123.048, 126.589, 129.722, 131.872, 132.563, 134.441,

136.863, 141.660, 152.264; HRMS: m/z calculated for $[C_{15}H_{12}CIN_3O+H^+]$ = 286.0742: found = 286.0743.

1-(4-chloro-2-cyanophenyl)-3-(4-fluorophenyl)urea (3n)

Yield: 225 mg, 78 %; MP. 196 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm : 7.094-7.139 (t, 2H, Ar, J=9.2 Hz), 7.425-7.460 (m, 2H, Ar), 7.659-7.688 (m, 1H, Ar), 7.890-7.896 (d, 1H, Ar, J=2.4 Hz), 8.057-8.079 (d, 1H, Ar, J=8.8 Hz), 8.763 (s, 1H, -NH-), 9.405 (s, 1H, -NH-); ¹³C- NMR (400 MHz, DMSO-d₆): δ ppm : 103.862, 115.771, 115.995, 116.121, 120.674, 120.752, 123.184, 126.794, 132.602, 134.461, 135.784, 141.524, 152.372, 156.945, 159.319; HRMS: m/z calculated for [C₁₄H₉ClFN₃O+H⁺] = 290.0496: found = 290.0507.

1-(2-cyano-4-fluorophenyl)-3-phenylurea (30)

Yield: 199 mg, 78 %; MP. 191 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm : 6.963-6.999 (t, 2H, ar, J=7.2 Hz), 7.259-7.297 (t, 2H, Ar, J=7.6 Hz), 7.445-7.465 (d, 2H, Ar, J=8.0 Hz), 7.518-7.560 (m, 1H, Ar), 7.735-7.755 (t, 1H, Ar, J=2.4 Hz), 7.944-7.979 (m, 1H, Ar), 8.932 (s, 1H, -NH-), 9.452 (s, 1H, -NH-); ¹³C- NMR (400 MHz, DMSO-d₆): δ ppm : 104.242, 104.339, 116.287, 118.874, 119.468, 119.731, 121.832, 122.056, 122.805, 124.478, 124.566, 129.314, 139.170, 139.637; HRMS: m/z calculated for [C₁₄H₁₀FN₃O+H⁺] = 256.0881: found= 256.0885.

1-(2-cyano-4-fluorophenyl)-3-(4-fluorophenyl)urea (3p)

Yield: 207 mg, 76 %; MP. 208 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm : 7.124-7.168 (t, 2H, Ar, J=8.8 Hz), 7.459-7.494 (m, 2H, Ar), 7.534-7.585 (m, 1H, Ar), 7.761-7.789 (m, 1H, Ar), 7.977-8.013 (m, 1H, Ar), 8.742 (s, 1H, -NH-), 9.345 (s, 1H, -NH-); ¹³C- NMR (400 MHz, DMSO-d₆): δ ppm : 104.602, 104.699, 115.703, 115.917, 116.287, 119.458, 119.721, 120.538, 120.616, 121.774, 121.998, 124.683, 124.761, 136.017, 139.092, 139.072, 152.751, 156.127, 156.847, 158.531, 159.221; HRMS: m/z calculated for [C₁₄H₉F₂N₃O+H⁺] = 274.0786: found = 274.0786.

1-(3-bromophenyl)-3-(4-chloro-2-cyanophenyl)urea (3q)

Yield: 279 mg, 80 %; MP. 183 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm : 7.165-7.180 (d, 1H, Ar, J=6.0 Hz), 7.224-7.262 (t, 1H, Ar, J=7.6 Hz), 7.313 (s, 1H, Ar), 7.685-7.705 (d, 1H, Ar, J=8.0 Hz), 7.844 (s, 1H, Ar), 7.919 (s, 1H, Ar), 7.987-8.008 (d, 1H, Ar, J=8.4 Hz), 9.160 (s, 1H, -NH-), 9.808 (s, 1H, -NH-); ¹³C- NMR (400 MHz, DMSO-d₆): δ ppm : 104.320, 116.063, 117.736, 121.180, 122.212, 123.486, 125.490, 127.154, 131.269, 132.641, 134.470, 141.174, 141.213, 152.236; HRMS: m/z calculated for [C₁₄H₉BrClN₃O+H⁺] = 349.9690: found = 349.9681.

1-(3-bromophenyl)-3-(2-cyano-4-fluorophenyl)urea (3r)

Yield: 256mg, 77 %; MP. 182 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm : 7.157-7.175 (d, 1H, Ar, J=7.2 Hz), 7.220-7.307 (m, 2H, Ar), 7.525-7.562 (t, 1H, Ar, J=8.0 Hz), 7.756-7.770 (d, 1H, Ar, J=5.6 Hz), 7.840 (s, 1H, Ar), 7.935-7.969 (m, 1H, Ar), 8.797 (s, 1H, -NH-), 9.475 (s, 1H, -NH-); ¹³C- NMR (400 MHz, DMSO-d₆): δ ppm : 104.971, 105.069, 116.248, 117.688, 119.565, 119.828, 121.122, 121.842, 122.066, 122.202, 124.926, 125.004, 125.344, 131.250, 138.780, 141.359, 152.576, 156.312, 158.725; HRMS: m/z calculated for [C₁₄H₉BrFN₃O+H⁺] = 333.9991: found = 333.9997.

1-(3-chlorophenyl)-3-(2-cyano-4-fluorophenyl)urea (3s)

Yield: 234 mg, 81 %; MP. 198 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm : 7.050-7.069 (d, 1H, Ar, J=7.6 Hz), 7.257-7.349 (m, 2H, Ar), 7.547-7.589 (m, 1H, Ar), 7.710 (s, 1H, Ar), 7.759-7.780 (d, 1H, Ar, J=8.4 Hz), 7.962-7.997 (m, 1H, Ar), 8.785 (s, 1H, -NH-), 9.474 (s, 1H, -NH-); ¹³C- NMR (400 MHz,

DMSO-d₆): δ ppm : 104.95, 105.05, 116.23, 117,67,47,119,55, 119.81, 121.10, 121.82, 122.04, 122,18; 10,24:99,00,224:99,125.32, 131.22, 138.76, 141.33, 152.55, 156.29, 158.71; HRMS: m/z calculated for [C₁₄H₉ClFN₃O + H+] = 290.0496: found = 290.0502.

1-(2-cyanophenyl)-3-(2,4-dichlorophenyl)urea (3t)

Yield: 279 mg, 75 %; MP. 184 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm: 7.212 (s, 1H, Ar), 7.383-7.400 (d, 1H, Ar, J = 6.8 Hz), 7.631 (s, 2H, Ar), 7.759 (s, 1H, Ar), 7.986-8.002 (d, 1H, Ar, J = 6.0 Hz), 8.097-8.116 (d, 1H, Ar, J = 7.6 Hz), 9.039 (s, 1H, -NH-), 9.518 (s, 1H, -NH-); ¹³C- NMR (400 MHz, DMSO-d₆): δ ppm:103.321, 117.554, 122.798, 123.771, 124.112, 124.229, 127.498, 128.218, 129.278, 133.880, 134.561, 135.378, 141.926, 152.541; HRMS: m/z calculated for [C₁₄H₉Cl₂N₃O + H⁺] = 306.0201: found = 306.0208.

1-benzyl-3-(2-cyanophenyl)urea (3u)

Yield: 188 mg, 75 %; MP. 208 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm : 4.304-4.317 (d, 2H, -CH₂-, J=5.6 Hz), 7.074-7.111 (t, 1H, Ar, J=7.2 Hz), 7.111-7.360 (m, 5H, Ar), 7.412-7.426 (d, 1H, Ar, J=5.6 Hz), 7.553-7.590 (t, 1H, Ar, J=7.6 Hz), 7.666-7.683 (d, 1H, Ar, J=6.8 Hz), 8.055-8.077 (d, 1H, -NH-, J=8.8 Hz), 8.569 (s, 1H, -NH-); ¹³C- NMR (400 MHz, DMSO-d₆): δ ppm : 43.286, 101.537, 117.464, 121.190, 122.717, 127.349, 127.728, 128.827, 133.429, 134.305, 140.084, 143.139, 154.979; HRMS: m/z calculated for [C₁₅H₁₃N₃O+H⁺] = 252.1136: found = 252.1139.

1-benzyl-3-(2-cyano-4-fluorophenyl)urea (3v)

Yield: 204 mg, 76 %; MP. 210 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm : 4.315-4.329 (d, 2H, -CH₂-, J=5.6 Hz), 7.244-7.404 (m, 6H, Ar), 7.473-7.525 (m, 1H, Ar), 7.681-7.708 (m, 1H, Ar), 7.997-8.034 (m, 1H, -NH-), 8.609 (s, 1H, -NH-); ¹³C-NMR (400 MHz, DMSO-d₆): δ ppm : 48.024, 107.830, 120.993, 123.815, 124.077, 126.344, 126.568, 128.514, 128.582, 131.939, 132.308, 133.418, 144.557, 144.713, 159.745, 160.212, 162.615; HRMS: m/z calculated for [C₁₅H₁₂FN₃O+H⁺] = 270.1037: found = 270.1039.

1-(2-cyanophenyl)-3-propylurea (3w)

Yield: 154 mg, 76 %; MP. 199 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm : 0.853-0.888 (t, 3H, -CH₃, J=7.2 Hz), 1.412-1.462 (m, 2H, -CH₂-), 3.037-3.051 (d, 2H, -CH₂-, J=5.6 Hz), 6.968 (s, 1H, Ar), 7.041-7.076 (t, 1H, Ar, J=6.8 Hz), 7.525-7.562 (t, 1H, Ar, J=7.6 Hz), 7.637-7.655 (d, 1H, Ar, J=7.2 Hz), 8.039-8.059 (d, 1H, - NH-, J=8.0 Hz), 8.412 (s, 1H, -NH-); ¹³C- NMR (400 MHz, DMSO-d₆): δ ppm : 11.805, 23.149, 41.401, 101.216, 117.503, 121.005, 122.474, 133.390, 134.266, 143.324, 154.911; HRMS: m/z calculated for [C₁₁H₁₃N₃O+H⁺] = 204.1131: found = 204.1136.

1-(2-cyano-4-fluorophenyl)-3-propylurea (3x)

Yield: 164 mg, 74 %; MP. 204 °C; White solid; ¹H-NMR (400 MHz, DMSO-d₆): δ ppm : 0.863-0.900 (t, 3H, -CH₃, J = 7.6 Hz), 1.423-1.476 (m, 2H, -CH₂-), 3.032-3.079 (m, 2H, -CH₂-), 6.913 (s, 1H, Ar), 7.478-7.499 (t, 1H, Ar, J=2.4 Hz), 7.665-7.692 (m, 1H, Ar), 7.987-8.022 (m, 1H, -NH-), 8.465 (s, 1H, -NH-); ¹³C-NMR (400 MHz, DMSO-d₆): δ ppm : 16.395, 27.787, 46.059, 107.392, 121.042, 123.776, 124.029, 126.354, 126.578, 128.271, 144.762, 159.628, 160.046, 162.430; HRMS: m/z calculated for [C₁₁H₁₂FN₃O+H⁺] = 222.1042: found = 222.1047.

Journal Name

Conclusion

Herein, we are reporting a straight forward protocol for the synthesis of o-ureidobenzonitrile derivatives at ambient conditions using inexpensive and readily available starting materials. The substrate scope for this method is very broad and yields are excellent. The synthesized products can serve as precursors for many cyclized products like quinazolines and quinazolinones. Utilization of the above unique reaction path to explore some new kinds of reaction and further extension of the substrate scope to synthesize derivatives of biological interest and their biological studies are under progress.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The author S.S thank the UGC, New Delhi for the financial support in the form of UGC-JRF/SRF fellowship. Financial support from the Minor Research Project, University of Mysore (grant No. DV6/ 375/ MRP/ 2017-18, dated: 12–02-2018) and VGST Project (Grant No. Ksteps/ VGST/ GRD-681/ KFIST(L1)/ 2018, dated: 27-08-2018) is gratefully acknowledged.

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I₂ – Catalysed Transformation of o-Aminobenzamide to o-Ureidobenzonitrile Using **Isothiocyanates**

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> of o-ureidobenzonitriles. ŇΗ S || C || N .c_0 ċ H₂N. R₂ N NH₂ R₂ č I₂, DMF, rt, 3 h R₂ C || 0 24 examples with 75-85 % yield.

Organic & Biomolecular Chemistry Accepted Manuscript

DOI: 10.1039/D0OB00118J

