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Highly Regioselective Iodination of *N*-Phenylureas with Iodine/Trichloroisocyanuric Acid

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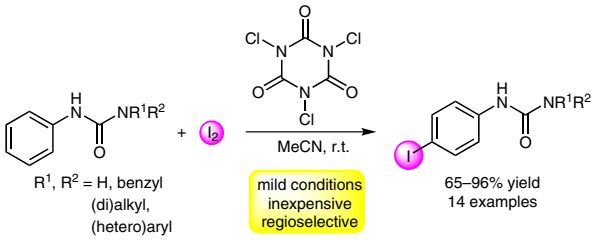
Dedicated to the memory of Prof. José Barluenga



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Abstract An efficient regioselective iodination of *N*-phenylureas was developed using iodine/trichloroisocyanuric acid in acetonitrile at room temperature. This protocol proved to be effective on a broad range of substituted *N*-phenylureas, forming the *p*-iodinated compounds in 65–96% yield under mild and neutral conditions.

Key words iodination, *N*-phenylureas, trichloroisocyanuric acid, iodine, S_EAr

Urea and its derivatives belong to a recognized group of molecules due to their wide applications in agrochemistry,[1] industrial chemistry,[2] material science,[3] organic synthesis,[4] and medicinal chemistry.[5] Some of these compounds display a vast range of biological activities, such as anticonvulsant,[5a] antibacterial, antifungal,[5b–d] antimalarial,[5e] anti-inflammatory,[5f] and others.[5g,h] It has been demonstrated that substituted ureas can act as antiglycating agents,[6] inhibitors of HIV-1 protease-DMP450,[7] and effective drugs for the treatment of different types of cancer.[8]

N-Aryl-*N*′-(2-chloroethyl)ureas (CEUs) are soft alkylating agents with potential anticancer activity.[9] CEUs exhibit cytotoxicity on numerous cancer cell lines and remain active on most chemoresistance cells.[9a,b] Among these compounds, the iodinated derivative *N*-(4-iodophenyl)-*N*′-(2-chloroethyl)urea (ICEU) stands out not only by its improved antiproliferative and anti-angiogenic actions, but also increased antitumor activity and life-span in murine colon carcinoma, establishing that ICEU is more stable to biotransformation than previously studied CEU analogues. Furthermore, the introduction of an iodine atom in these structures increases their *in vivo* stability.[9c] Also, the cyclic derivative of ICEU, *N*-(4-iodophenyl)-4,5-dihydrooxazol-2-amine (IOxa), is three times more active than ICEU and shares the same cytotoxic properties in melanoma cells.[9d]

N-(Iodoaryl)ureas constitute interesting targets due to their promising biological activities.[9c,d] They are also useful synthetic intermediates in metal-catalyzed (Suzuki, Heck, Sonogashira, and related) C–C and C–N cross-coupling reactions that aim to prepare more complex molecules bearing a urea moiety.[10,11] Recently, we reported a green Suzuki–Miyaura cross-coupling reaction of *N*-(4-iodophenyl)ureas using palladium nanoparticles stabilized by cyclodextrins to produce a series of new biphenylureas[11] with potential use in medicinal chemistry.[12]

To the best of our knowledge, there is not a protocol for the direct iodination of *N*-phenylureas described in the literature. Frequently they have been prepared from the reaction of the very expensive iodophenyl isocyanate with amines[13] or isocyanates with iodinated anilines.[9a,b,14]

Interested in the synthesis of symmetrical and unsymmetrical ureas, our group reported an easy and efficient method for the preparation of substituted ureas by oxidation of thioureas with aqueous $KICl_2$ (~2 M, pH 3).[10] Moreover, by simply changing the reaction conditions to reflux, *N*-arylthioureas undergo sequential oxidation and aryl group iodination.[10] This protocol is effective to obtain *N*-(4-iodophenyl)urea and *N*′-substituted *N*-(4-iodophenyl)ureas. However, *N*′,*N*′-disubstituted *N*-(4-iodophenyl)ureas could not be obtained as mostly hydrolyzed products were observed (4-iodoaniline). Therefore, the search for a new methodology employing mild and neutral conditions to circumvent this inconvenience is of great interest.

Trihaloisocyanuric acids (TXCA) (Figure 1) are efficient halogenating reagents of activated aromatic compounds, due to their ability to transfer halenium ions ('X^+').[15] We have shown that TCCA/NaCl or TBCA/NaBr are effective systems for the vicinal dihalogenation of alkenes through the

in situ generation of molecular halogens.[16] Furthermore, reaction of styrene with both TCCA/NaBr or TBCA/NaCl led to 2-bromo-1-chloro-1-phenylethane, indicating the possible in situ formation of BrCl.[16] Akhlaghinia and Rahmani reported the iodination of activated arenes and phenols by I_2/TCCA/wet silica gel under heterogeneous conditions (CH_2Cl_2).[17] More recently, we have shown that activated aromatic compounds can be readily iodinated by just I_2/TCCA in MeCN.[18]

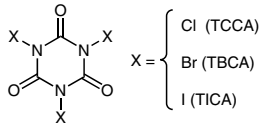
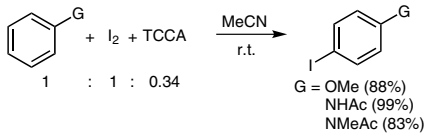


Figure 1 Trihaloisocyanuric acids (TXCA)

Continuing our interest in the chemistry of trihaloisocyanuric acids[19] and the preparation of new urea derivatives,[10,11,20] we decided to investigate the iodination reaction of substituted *N*-phenylureas using iodine/TCCA.

Previous results showed that the best molar ratio for iodination of electron-rich substrates was using 1:1:0.34 (arene/I_2/TCCA).[18] Hence, applying this proportion for anisole, acetanilide, and *N*-methylacetanilide in acetonitrile at room temperature, the corresponding 4-iodinated products were obtained in high yields (Scheme 1). The choice of employing both acetanilide and *N*-methylacetanilide as substrates was based on their chemical similarity to *N*-phenylureas.



Scheme 1 Iodination of activated arenes with iodine/trichloroisocyanuric acid

The direct iodination of arenes with I_2 is quite difficult due to its low reactivity in S_EAr reactions; usually it is only effective in the presence of oxidizing agents.[21] On the other hand, activated aromatic compounds are easily chlorinated under mild conditions by trichloroisocyanuric acid in acetonitrile to produce *o*- and *p*-chloroarenes.[15d] Therefore, as I_2/TCCA is an effective system for the iodination of activated arenes, these results clearly suggest the former reaction of I_2 with TCCA to produce a different electrophilic iodination reagent. Besides, the high *para* regioselectivity obtained in our reactions is similar to that observed when different electrophilic iodinating reagents are used.[21] Although the reaction pathway is not clear, we can imagine the possible formation of ICl as the iodinating reagent, but the in situ generation of triiodoisocyanuric acid (TICA) or the highly reactive dichloroiodoisocyanuric acid[15g] cannot be discarded.

Based on the above results, we extended our methodology to diverse *N*-phenylureas **1** with different patterns of substitution and the results are summarized in Table 1.

The reactions were performed in acetonitrile at room temperature on a 0.25-mmol scale and 1:1:0.34 (urea/I_2/TCCA) ratio. The iodinated products were isolated after workup by simple vacuum filtration, and they were characterized by traditional analytical techniques. Albeit the ureido group is an *ortho*/*para* director in aromatic electrophilic substitution reactions, under our conditions the iodination of all *N*-phenylureas **1** was highly selective in the *para* position, forming *N*-(4-iodophenyl)ureas **2** as major products. Nonetheless with some *N*′,*N*′-disubstituted *N*-phenylureas, **1e** and **1f**, diiodination products were detected (5% or less). The characteristic pattern of *para*-substituted products, i.e. two doublets between δ = 7.15–7.65 in ^{1}H NMR, as well as a signal at ca. δ = 85 in ^{13}C NMR spectra (C–I) support the regioselective iodination.

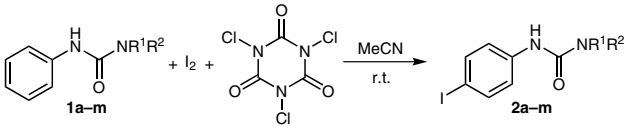
The iodination of *N*-benzyl-*N*′-phenylurea (**1c**) was highly chemoselective affording *N*-benzyl-*N*′-(4-iodophenyl)urea (**2c**) as a unique product. However, in order to test the iodination of a benzyl group, we carried on the reaction of *N*-benzyl-*N*′-butylurea using I_2/TCCA (1:0.34 mol equiv) at room temperature, but it was not successful, even when doubling the amounts of I_2 and TCCA under reflux (2 h). Nevertheless, these results were quite expected, since halogenation reactions of less reactive aromatic rings, such as benzyl groups, using trihaloisocyanuric acids demand more drastic reaction conditions (strong acid media).[22]

To our satisfaction, trisubstituted ureas **1d–f** were iodinated in high yields (85–94%) and cleavage of the urea moiety was not observed as occurred when we reacted the same substrates with $KICl_2$ under reflux. Moreover, in a scaled-up reaction (2.0 mmol), *N*-phenylureas **1e** and **1f** gave the corresponding iodinated products **2e** and **2f** without any significant change in the yields.

In contrast to the complete iodination observed for *N*-phenyl-*N*′-alkylureas **1a–f**, the reaction of some *N*′-aryl-substituted *N*-phenylureas **1g–k** with I_2/TCCA at room temperature was not complete under the same conditions; even using an excess of both I_2 and TCCA under reflux, *N*,*N*′-bis(4-iodophenyl)urea (**2g**) was obtained in higher conversion, but a small quantity of the substrate still remains unchanged.

Interestingly, for all substrates studied, the iodination reaction occurred in the unsubstituted phenyl ring, even for electron-rich arenes **1j** and **1k** which are more reactive in electrophilic aromatic substitution reactions.

Table 1 Iodination of *N*-Phenylureas with Molecular Iodine and Trichloroisocyanuric Acid[a]



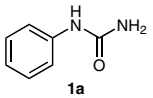
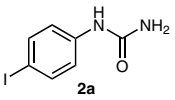
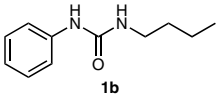
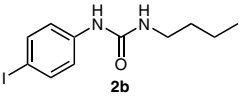
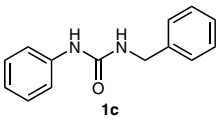
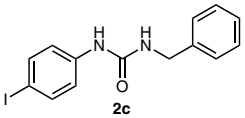
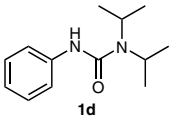
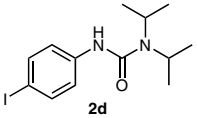
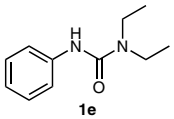
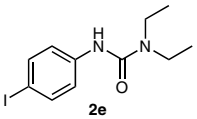
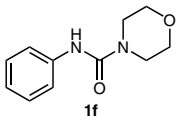
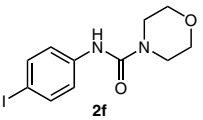
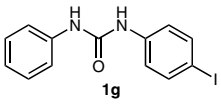
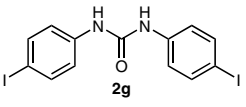
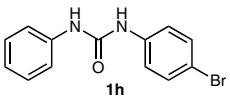
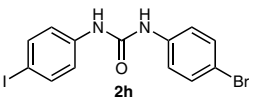
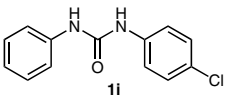
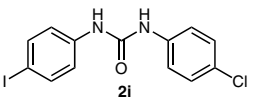
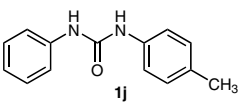
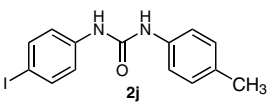
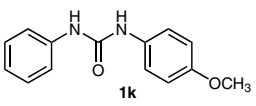
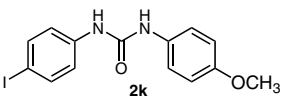
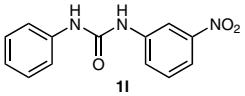
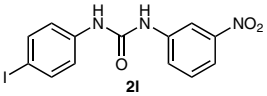
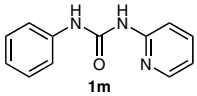
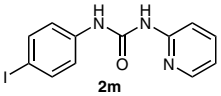
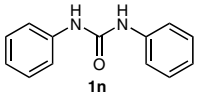
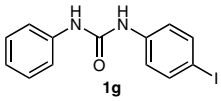
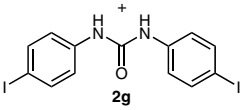
Substrate **1**	Product **2**	Time (h)	Yield[b] (%)
 **1a**	 **2a**	0.25	87
 **1b**	 **2b**	0.25	92
 **1c**	 **2c**	0.25	96
 **1d**	 **2d**	0.25	93
 **1e**	 **2e**	0.5	85[c]
 **1f**	 **2f**	0.5	93 (94[c])
 **1g**	 **2g**	8 2[d,f]	65[e] 90[e]
 **1h**	 **2h**	8	78[e]
 **1i**	 **2i**	2	80[e]
 **1j**	 **2j**	3	88[e]
 **1k**	 **2k**	3	66[e]

Table 1 (continued)

Substrate **1**	Product **2**	Time (h)	Yield[b] (%)
 **1l**	 **2l**	8	88
 **1m**	 **2m**	6[d,f]	81
 **1n**	 **1g** +  **2g**	2 4[d]	63[e] (**1g**) + 28[e] (**2g**) 27[e] (**1g**) + 73[e] (**2g**)

[a] Reactions conditions: *N*-phenylurea (0.25 mmol), I_2 (0.25 mmol), TCCA (0.083 mmol) unless otherwise stated.
[b] Isolated yield unless otherwise stated.
[c] Using *N*-phenylurea (2.0 mmol), I_2 (2.0 mmol), TCCA (0.68 mmol).
[d] Using substrate (0.25 mmol), I_2 (0.50 mmol), TCCA (0.17 mmol).
[e] Yield of crude product.
[f] At reflux.

When the *N*′-aryl group of the *N*′-aryl-substituted *N*-phenylureas was changed to a *N*′-(pyridin-2-yl) group **1m**, once again, a decrease in the reactivity between the urea and the I_2/TCCA system was observed; consequently, stronger reaction conditions were employed [I_2 (2 equiv), TCCA (0.68 equiv), reflux].

Subjecting carbanilide (*N*,*N*′-diphenylurea, **1n**) to the reaction gave a mixture of *N*-(4-iodophenyl)-*N*′-phenylurea (**1g**) along with *N*,*N*′-bis(4-iodophenyl)urea (**2g**). This crude mixture was analyzed by ^{1}H NMR spectroscopy and this indicated a ca. 2.2:1 ratio of **1g**/**2g**. In order to obtain the diiodinated product **2g**, the amounts of I_2/TCCA were doubled, as well as the reaction time. Hence, the amount of the diiodinated product increased, but the reaction was still incomplete and, once more, **1g** and **2g** were obtained (ca. 1:2.6 ratio, by ^{1}H NMR spectroscopy).

In conclusion, we have developed an efficient and simple methodology for regioselective iodination of a variety of *N*-phenylureas. As advantages of our protocol we could highlight the high *para* selectivity of the reaction, the use of safe, inexpensive, and readily available reagents; mild and neutral reaction conditions; clean chemical transformation; and easy workup. The iodination process appears to be invariant with respect to the electron-deficient or electron-rich aryl system, affording the desired iodinated product in good to excellent yields. The reaction mechanism is still under investigation in our laboratory and will be presented in due course.

Commercially available reagents and solvents were used without further purification. Carbanilide was purchased from Sigma; other substituted *N*-phenylureas **1** were prepared by reaction of phenyl isocyanate with the corresponding amine in CH_2Cl_2 or hexane (see Supporting Information). ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300 and 500 MHz spectrometers using $CDCl_3$ and DMSO-d_6 as solvents. IR spectra were recorded on a Nicolet 6700FT-IR spectrophotometer as neat films on KBr plates. HRMS were obtained on a Bruker microTOF II mass spectrometer using ESI. Melting points were determined on a Fisatom 431 apparatus and are uncorrected.

Substituted *N*-(4-Iodophenyl)ureas 2a–m; General Procedure

TCCA (0.083 mmol) was added to a stirred solution of I_2 (0.25 mmol) in MeCN (5–10 mL) at r.t. The appropriate substituted *N*-phenylurea (0.25 mmol) was added and the mixture was stirred until completion of the reaction (TLC). The reaction was quenched with 15% aq $NaHSO_3$ solution (10 mL) and the precipitated product was filtered, not needing further purification. When the product did not precipitate, the aqueous mixture was extracted with EtOAc (3 × 10 mL), dried (anhyd Na_2SO_4), and filtered, and the solvent evaporated under reduced pressure to give the desired product.

N-(4-Iodophenyl)urea (2a)[10]

Pale rose powder; yield: 57 mg (87%); mp 200 °C (dec.); R_f = 0.06 (EtOAc/hexane, 1:1).

IR (KBr): 3427, 3306, 3216, 1654, 1611, 1588, 1578, 1545, 1482, 1355, 812, 498 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.63 (s, 1 H), 7.52 (d, *J* = 8.6 Hz, 2 H), 7.25 (d, *J* = 8.5 Hz, 2 H), 5.90 (s, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 155.7, 140.4, 137.1, 120.0, 83.6.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_7H_6N_2OI$: 260.9519; found: 260.9541.

***N*-Butyl-*N*′-(4-iodophenyl)urea (2b)**[10]

White powder; yield: 73 mg (92%); mp 187–188 °C; R_f = 0.51 (EtOAc/hexane, 1:1).

IR (KBr): 3329, 2954, 2930, 2862, 1633, 1588, 1561, 1483, 1300, 1236, 829, 629, 502 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.50 (s, 1 H), 7.51 (d, *J* = 8.8 Hz, 2 H), 7.23 (d, *J* = 8.8 Hz, 2 H), 6.14 (t, *J* = 5.4 Hz, 1 H), 3.06 (dd, *J* = 12.7, 6.8 Hz, 2 H), 1.43–1.36 (m, 2 H), 1.29 (dq, *J* = 14.2, 7.1 Hz, 2 H), 0.88 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 155.0, 140.5, 137.1, 119.9, 83.4, 38.7, 31.8, 19.5, 13.7.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{11}H_{14}N_2OI$: 317.0145; found: 317.0151.

***N*-Benzyl-*N*′-(4-iodophenyl)urea (2c)**[10]

Pale rose powder; yield: 85 mg (96%); mp 209–210 °C; R_f = 0.49 (EtOAc/hexane, 1:1).

IR (KBr): 3296, 3163, 3084, 1635, 1584, 1561, 1484, 1390, 1308, 1237, 814, 693, 501 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.69 (s, 1 H), 7.54 (d, *J* = 8.7 Hz, 2 H), 7.39–7.16 (m, 5 H), 7.27 (d, *J* = 8.7 Hz, 2 H), 6.66 (t, *J* = 5.9 Hz, 1 H), 4.29 (d, *J* = 5.9 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 155.0, 140.4, 140.2, 137.1, 128.3, 127.1, 126.7, 120.0, 83.6, 42.7.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{14}H_{12}N_2OI$: 350.9989; found: 351.0002.

***N*,*N*-Diisopropyl-*N*′-(4-iodophenyl)urea (2d)**

Pale yellow powder; yield: 80 mg (93%); mp 169–170 °C; R_f = 0.68 (EtOAc/hexane, 1:1).

IR (KBr): 3308, 3000, 2967, 2932, 1636, 1583, 1523, 1487, 1428, 1387, 1241, 1503, 821, 506 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.8 Hz, 2 H), 7.16 (d, *J* = 8.8 Hz, 2 H), 6.18 (s, 1 H), 3.96 (hept, *J* = 6.8 Hz, 2 H), 1.31 (d, *J* = 6.9 Hz, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.4, 139.3, 137.8, 121.6, 85.3, 45.7, 21.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{20}N_2OI$: 347.0615; found: 347.0618.

***N*,*N*-Diethyl-*N*′-(4-iodophenyl)urea (2e)**

Pale yellow powder; yield: 68 mg (85%); mp 104–106 °C; R_f = 0.47 (EtOAc/hexane, 1:1).

IR (KBr): 3333, 3259, 3093, 2977, 1635, 1580, 1487, 1415, 1382, 1304, 1241, 816, 501 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.8 Hz, 2 H), 7.18 (d, *J* = 8.8 Hz, 2 H), 6.30 (s, 1 H), 3.35 (q, *J* = 7.0 Hz, 4 H), 1.21 (t, *J* = 7.0 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.3, 139.3, 137.7, 121.8, 85.6, 41.8, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{16}N_2OI$: 319.0302; found: 319.0298.

***N*-(4-Iodophenyl)morpholine-4-carboxamide (2f)**

Pale orange powder; yield: 78 mg (94%); mp 199–200 °C (dec.); R_f = 0.15 (EtOAc/hexane, 1:1).

IR (KBr): 3259, 3085, 2956, 2846, 1634, 1578, 1519, 1273, 1245, 1107, 803, 502 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.61 (s, 1 H), 7.55 (d, *J* = 8.4 Hz, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 3.61–3.57 (m, 4 H), 3.43–3.39 (m, 4 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 154.8, 140.4, 136.9, 121.8, 84.8, 66.0, 44.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}N_2O_2I$: 333.0095; found: 333.0105.

***N*,*N*′-Bis(4-iodophenyl)urea (2g)**[23]

Pale rose powder; yield: 75 mg (65% crude); mp 270 °C (dec.); R_f = 0.47 (EtOAc/hexane, 1:1).

IR (KBr): 3302, 1637, 1590, 1552, 1483, 1387, 1301, 1236, 1006, 816, 771, 636, 503 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.82 (s, 2 H), 7.59 (d, *J* = 8.8 Hz, 4 H), 7.29 (d, *J* = 8.8 Hz, 4 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 152.2, 139.4, 137.3, 120.6, 84.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}N_2OI_2$: 464.895535; found: 464.896671.

***N*-(4-Bromophenyl)-*N*′-(4-iodophenyl)urea (2h)**[23]

Pale yellow powder; yield: 81 mg (78% crude); mp 220 °C (dec.); R_f = 0.47 (EtOAc/hexane, 1:1).

IR(KBr): 3298, 1636, 1586, 1555, 1485, 1443, 1389, 1299, 1281, 1236, 818, 502 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.87 (s, 1 H), 8.85 (s, 1 H), 7.59 (d, *J* = 8.8 Hz, 2 H), 7.30 (d, *J* = 8.8 Hz, 2 H), 7.48–7.37 (m, 4 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 152.2, 139.4, 139.0, 137.3, 131.5, 120.6, 120.2, 113.4, 84.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}N_2OBrI$: 416.9094; found: 416.9092.

***N*-(4-Chlorophenyl)-*N*′-(4-iodophenyl)urea (2i)**[23]

White powder; yield: 74 mg (80% crude); mp 285 °C (dec.); R_f = 0.43 (EtOAc/hexane, 1:1).

IR (KBr): 3299, 3167, 3074, 1635, 1590, 1556, 1489, 1389, 1300, 1237, 1089, 820, 640, 507 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.85 (s, 1 H), 8.83 (s, 1 H), 7.59 (d, *J* = 8.7 Hz, 2 H), 7.47 (d, *J* = 8.9 Hz, 2 H), 7.34–7.28 (m, 4 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 152.3, 139.5, 138.5, 137.3, 128.6, 125.5, 120.6, 119.8, 84.9.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}N_2OClI$: 372.9605; found: 372.9637.

***N*-(4-Iodophenyl)-*N*′-(4-methylphenyl)urea (2j)**[23]

Pale rose powder; yield: 77 mg (88% crude); mp 270 °C (dec.); R_f = 0.55 (EtOAc/hexane, 1:1).

IR (KBr): 3304, 2911, 1640, 1593, 1555, 1512, 1484, 1405, 1388, 1307, 1237, 1147, 815, 515 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.73 (s, 1 H), 8.58 (s, 1 H), 7.58 (d, *J* = 8.7 Hz, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 7.30 (d, *J* = 8.8 Hz, 2 H), 7.08 (d, *J* = 8.3 Hz, 2 H), 2.24 (s, 3 H).

^{13}C NMR(125 MHz, DMSO-d_6): δ = 152.4, 139.7, 137.3, 136.9, 130.8, 129.2, 120.4, 118.4, 84.4, 20.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}N_2OI$: 353.014537; found: 353.014554.

***N*-(4-Iodophenyl)-*N*′-(4-methoxyphenyl)urea (2k)**[23]

Pale brown powder; yield: 61 mg (66% crude); mp 230 °C (dec.); R_f = 0.42 (EtOAc/hexane, 1:1).

IR (KBr): 3302, 2830, 1638, 1597, 1558, 1484, 1463, 1388, 1303, 1243, 849, 635, 500 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.76 (s, 1 H), 8.56 (s, 1 H), 7.57 (d, *J* = 8.6 Hz, 2 H), 7.35 (d, *J* = 8.9 Hz, 2 H), 7.30 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.9 Hz, 2 H), 3.71 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 154.5, 152.6, 139.9, 137.2, 132.5, 120.4, 120.1, 114.0, 84.3, 55.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}N_2O_2I$: 369.0095; found: 369.0107.

***N*-(4-Iodophenyl)-*N*′-(3-nitrophenyl)urea (2l)**[23]

Yellow powder; yield: 84 mg (88%); mp 230 °C (dec.); R_f = 0.32 (EtOAc/hexane, 1:1).

IR (KBr): 3326, 3093, 1673, 1651, 1589, 1556, 1520, 1483, 1434, 1391, 1347, 1237, 809, 629, 503 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.23 (s, 1 H), 8.95 (s, 1 H), 8.51 (t, *J* = 2.2 Hz, 1 H), 7.79 (ddd, *J* = 8.1, 2.5, 1.0 Hz, 1 H), 7.68 (ddd, *J* = 8.5, 2.0, 1.0 Hz, 1 H), 7.62 (d, *J* = 8.8 Hz, 2 H), 7.53 (t, *J* = 8.0 Hz, 1 H), 7.33 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 152.3, 148.1, 140.9, 139.2, 137.4, 130.1, 124.4, 120.8, 116.4, 112.2, 85.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}N_3O_3I$: 383.9840; found: 383.9843.

***N*-(4-Iodophenyl)-*N*′-(pyridin-2-yl)urea (2m)**

Brown powder; yield: 69 mg (81%); mp 200 (dec.); R_f = 0.38 (EtOAc/hexane, 1:1).

IR (KBr): 3368, 3214, 3112, 3083, 3055, 2977, 2916, 1697, 1600, 1581, 1550, 1509, 1478, 1418, 1395, 1319, 1151, 999, 849, 817, 775, 731, 521, 503 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.62 (s, 1 H), 9.49 (s, 1 H), 8.29–8.26 (m, 1 H), 7.77–7.72 (m, 1 H), 7.63 (d, *J* = 8.7 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 1 H), 7.38 (d, *J* = 8.7 Hz, 2 H), 7.03–6.99 (m, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 152.7, 152.0, 146.9, 138.9, 138.6, 137.4, 121.0, 117.6, 111.9, 85.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}N_3OI$: 339.9941; found: 339.9945.

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