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Efficient Direct Halogenation of Unsymmetrical *N*-Benzyl- and *N*-Phenylureas with Trihaloisocyanuric Acids

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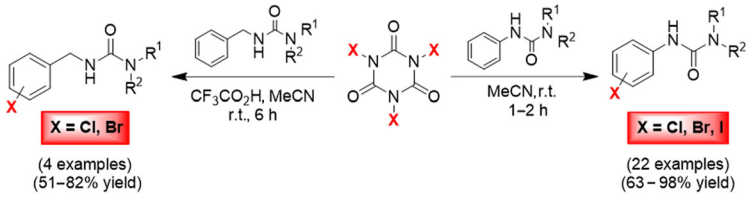

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Abstract A simple and efficient methodology for the direct halogenation of *N*-phenylureas was developed using trihaloisocyanuric acids in acetonitrile at room temperature. This protocol proved to be effective for the construction of *N*-phenylureas with different patterns of substitution. Additionally, less reactive *N*-benzylureas were halogenated in the presence of a mixture of trifluoroacetic acid and acetonitrile at room temperature.

Key words ureas, trihaloisocyanuric acids, halogenation, electrophilic aromatic substitution, arenes, chemoselectivity, regioselectivity

Substituted ureas have attracted great interest over the last years due to their diverse properties in several fields of chemistry. Their structural properties are exploited in supramolecular chemistry,[1] for preparation of nanosheets,[2] as chiral resolving agents,[3] and as organocatalysts,[4] to name a few.

N-(Halophenyl)ureas are useful building blocks in the synthesis of more complex molecules.[5] Besides, diverse halogenated *N*-phenylureas exhibit biological activity (Figure 1). In medicinal chemistry, they play an important role as anticancer agents due to the wide range of activities against various leukemias and solid tumors.[6] For example, Sorafenib[7] (Nexavar®) is a chlorinated biarylurea used as kinase inhibitor drug for the treatment of renal and hepatocellular carcinoma, while ICEU[8] has antitumor activity in murine colon carcinoma, and both were shown to block tumor proliferation and angiogenesis. As agrochemicals, halogenated derivatives of *N*-phenylurea are recognized by their herbicidal activity (Diuron[9] and Metobromuron[10]) and as a plant growth regulator (Forchlorfenuron[11]).

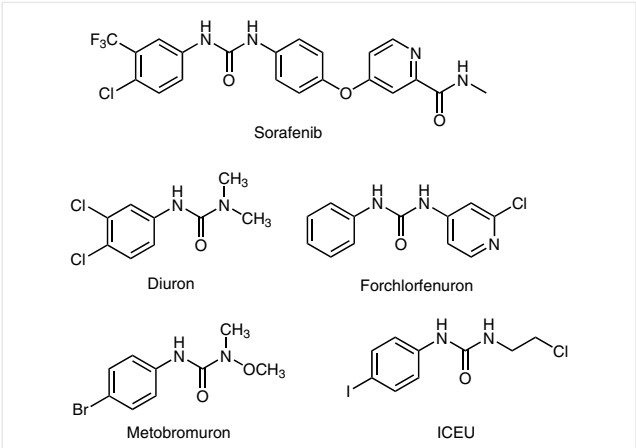


Figure 1 Halogenated *N*-phenylurea derivatives with biological activity

There are only a few methodologies for the direct halogenation of *N*-arylureas.[12–14] More commonly, they have been prepared by the reaction of expensive haloaryl-isocyanates with amines[5c,15] or isocyanates with halogenated anilines.[1a,8a,16]

Being interested in the synthesis of iodinated substituted *N*-phenylureas, we have already established that upon treatment of thioureas with acidic aqueous potassium dichloroiodate ($KICl_2$),[13] they undergo sequential oxidation and iodination reactions giving iodoaryl ureas (mono- and disubstituted). More recently, our group reported another efficient protocol for direct iodination of *N*-phenylurea derivatives using iodine and trichloroisocyanuric acid[14] under mild and neutral conditions. This method proved to be efficient for a broad range of substituted *N*-phenylureas, even with trisubstituted derivatives, forming the *p*-iodinated compound regioselectively in high yields.

Trihaloisocyanuric acids (TXCA, Figure 2) are analogue reagents to the traditional *N*-halosuccinimides. Among the trihaloisocyanuric acids, the most widely used is the inexpensive and commercially available trichloroisocyanuric acid (TCCA).[17] Although not readily commercially available, tribromoisocyanuric acid (TBCA)[18] can be prepared by a green methodology using cyanuric acid, KBr and Oxone®,[19] while triiodoisocyanuric acid (TICA)[20] can be prepared by reaction of iodine with TCCA. These trihaloisocyanuric acids are efficient halogenating reagents of activated aromatic compounds, due to their high capacity to provide halenium ions ('X^+').[17–22]

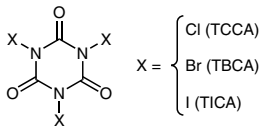
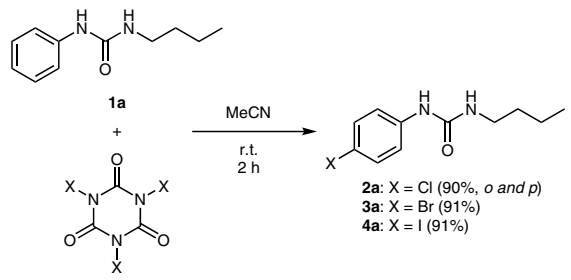


Figure 2 Trihaloisocyanuric acids (TXCA)

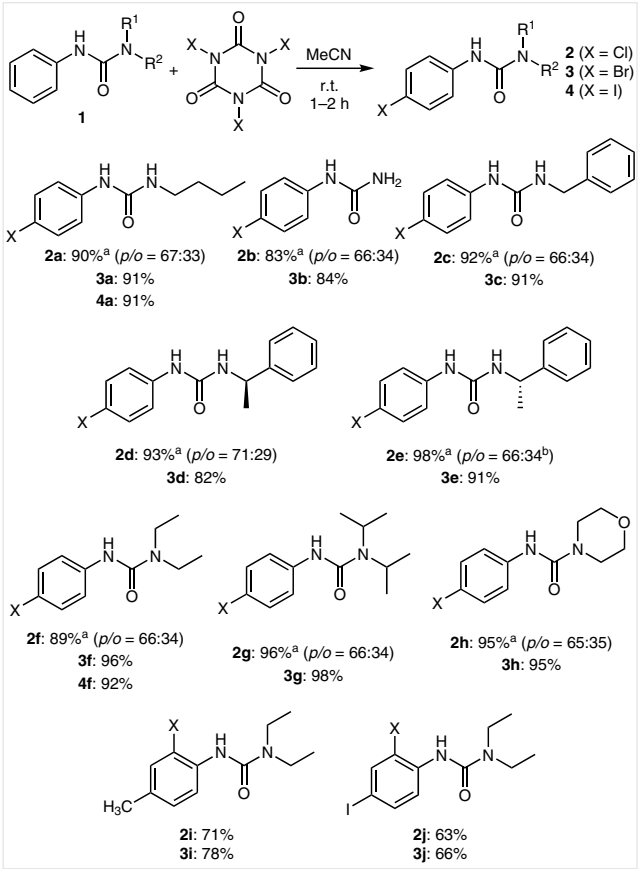
Continuing our interest on the preparation of halogenated ureas, we decided to investigate the reaction of arylureas with trihaloisocyanuric acids.

N-Butyl-*N*′-phenylurea (**1a**) was chosen as a model substrate for the halogenation reaction (Scheme 1). After testing different urea/TCCA ratios, it was established that with a 1:0.34 (urea/TCCA) ratio in a 0.25 mmol scale, chlorination of **1a** proceeded smoothly at room temperature (25 °C) giving the regioisomeric mixture of *p*- and *o*-*N*-(chlorophenyl)ureas **2a** and **2a′** in excellent combined yield (90%) with 2:1 selectivity in favor of the *para*-isomer **2a**, after separation by thin-layer chromatography. On the other hand, when the same substrate **1a** reacted with tribromoisocyanuric acid (TBCA) and triiodoisocyanuric acid (TICA), the reactions did not reach completion and it was necessary to increase the amount of the halogenation reagent. Therefore, using 1:0.5 (urea/TXCA) ratio, both bromination and iodination of **1a** were highly regioselective in the *para*-position, forming *N*-butyl-*N*′-(4-halophenyl)ureas **3a** and **4a** as the major isolated products (91%).



Scheme 1 Reaction of *N*-butyl-*N*′-phenylurea with trihaloisocyanuric acids

Based on the above results, we extended our methodology to diverse *N*-phenylureas **1** with different patterns of substitution (Scheme 2) performing the reactions in a 0.25 mmol scale. It was observed that mono-halogenation reactions take place in good to excellent yields (83–98%), independently of the *N*-phenylurea **1** and trihaloisocyanuric acid employed. Moreover, increasing the reaction scale to 5.0 mmol, the *N*-(halophenyl)ureas **2f** and **3a** were obtained in 96% (crude) and 93% (pure) yield, respectively.

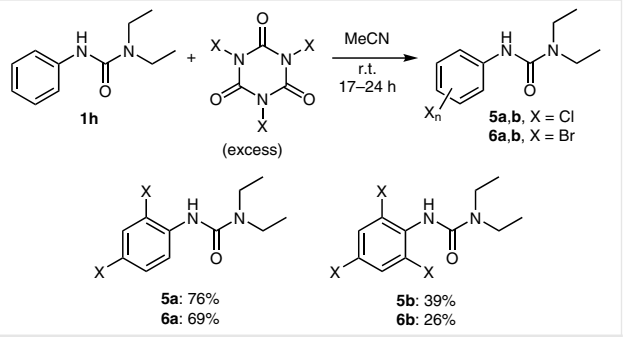


Scheme 2 Halogenation of *N*-phenylureas with trihaloisocyanuric acids (isolated yields of pure products). [a] Combined yield. [b] Determined by NMR spectroscopy.

Once more, the reactions with TCCA led to a regioisomeric mixture of *o*- and *p*-chlorinated products with nearly 1:2 ratio in favor of the *para*-isomer, while reactions with TBCA and TICA led to the halogenated products with a high *para*-regioselectivity. The regioisomeric chlorinated products were separated by using a silica gel thin-layer chromatography plate with hexanes/ethyl acetate as eluent. On the other hand, NMR analyses of the crude bromination and iodination reactions indicated, in some cases, the formation of trace amounts of the *o*-isomers, which were lost during the workup process (simple vacuum filtration). Interestingly, iodination reactions of **1a** and **1f** with TICA gave similar results to those obtained with the more convenient

iodination system I_2/TCCA.[14] Furthermore, when the *para*-position of a *N*-phenylurea was blocked with a substituent, as in **1i** (-Me) and **1j** (-I), the halogenation reactions still occurred, but with a small decrease in the yields (63–78%).

In addition, it was observed that by doubling the amount of trihaloisocyanuric acids and increasing the reaction time, the dihalogenated *N*-phenylureas **5a** (76%) and **6a** (69%) were produced. However, even with a large excess of the halogenating reagents, the introduction of a third halogen atom was difficult and the trihalogenated products **5b** (39%) and **6b** (26%) were obtained in low yields (Scheme 3).

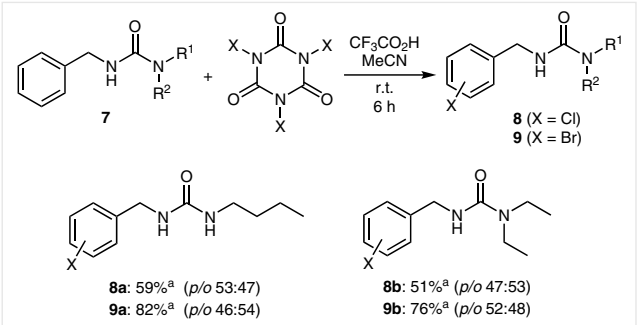


Scheme 3 Polyhalogenation of *N*,*N*-diethyl-*N*-phenylurea with trihaloisocyanuric acids (isolated yields of pure products)

Interestingly the halogenation reactions of *N*-benzyl-*N*′-phenylureas (**1c–e**) were highly chemoselective, affording only halogenated *N*-phenylureas (**2c–e** and **3c–e**), with no halogenation on the benzylic ring being detected. Several attempts to chlorinate or brominate *N*-benzylureas using trihaloisocyanuric acids in acetonitrile were unsuccessful and unreacted substrates were recovered, even using excess of the halogenating reagents, higher temperatures or long reaction times.

As the reactivity of trihaloisocyanuric acids with arenes is highly affected by the acid strength of the reaction media,[23] we investigated the halogenation reaction on the benzene moiety of some *N*-benzylureas **7** using trifluoroacetic acid or a mixture of it with acetonitrile (1:1) as the reaction solvent. Under these acidic media, the reaction took place giving the corresponding halogenated products **8** and **9** in moderate to good yields (51–82%), as shown in the Scheme 4. However, with regard to the halogenation of the *N*-phenylureas, the regioselectivity was lost and ca. 1:1 mixtures of *o*- and *p*-halobenzylureas were obtained. Unfortunately, the reactions with TICA under these conditions led to a mixture of several unidentified products.

In conclusion, it was established that trihaloisocyanuric acids are efficient reagents for the direct halogenation of a variety of *N*-phenylureas, even when the *para*-position is blocked. This process takes place in high yields under mild and neutral reaction conditions. The bromination of *N*-phenylureas stands out due to its higher *para*-selectivity. Although



Scheme 4 Halogenation of *N*-benzylureas with trihaloisocyanuric acids (isolated yields of pure products). [a] Combined yield.

N-benzylureas are less reactive than their phenyl analogues, they can also be halogenated in the presence of trifluoroacetic acid. Furthermore, by increasing the amount of TXCA, polyhalogenated *N*-phenylureas can be obtained.

TCCA was purchased from Aldrich and used as received. Commercially available reagents and solvents were used without further purification. TBCA,[19] TICA[20] and *N*,*N*-diethyl-*N*′-(4-iodophenyl)urea[14] **1j** were prepared as described. Substituted *N*-phenylureas **1** were prepared by reaction of *p*-toluyl or phenyl isocyanate with the corresponding amine in CH_2Cl_2 or hexanes while substituted *N*-benzylureas **7** were prepared via treatment of the corresponding thioureas with $KICl_2$[13] (see the Supporting Information). The reactions were monitored by TLC and the crude products were purified by thin-layer chromatography (silica gel, 35 mesh) or column chromatography (silica gel, 230–400 mesh) using hexanes/EtOAc as eluent. ^1H and ^{13}C NMR spectra were recorded with Bruker Avance 300 and 500 MHz spectrometers using $CDCl_3$ or DMSO-d_6 as solvents and TMS as internal standard. IR spectra were recorded with a Nicolet 6700FT-IR spectrophotometer as neat films on KBr plates. HRMS were obtained with a Brukermicro-TOF II mass spectrometer using ESI.

Monohalogenation of *N*-Arylureas 1; General Procedure for the Preparation of *N*-(Haloaryl)ureas 2–4

TCCA (0.083 mmol) was added to a stirred solution of the substituted *N*-phenylurea (0.25 mmol) in MeCN (5–10 mL) at r.t. (25 °C) and the mixture was stirred until completion of the reaction (TLC). The reaction was quenched with 15% $NaHSO_3$ (10 mL). The final mixture was extracted with EtOAc and washed with brine and water. The organic layer was separated, dried over anhydrous sodium sulfate followed by removal of solvent under reduced pressure. The crude products were separated on silica gel thin-layer chromatography plates using EtOAc/hexanes as eluent.

For the bromination and iodination reactions, the above procedure was performed using 0.125 mmol of TBCA or TICA. After quenching the reaction with $NaHSO_3$ solution, the crude products precipitated and were filtered off. They did not require further purification.

N-Butyl-*N*′-(4-chlorophenyl)urea (2a)[24]

Yield: 34.0 mg (60%); white powder; mp 161–162 °C (Lit.[24] 173–174 °C); R_f = 0.47 (EtOAc/hexanes, 1:1).

IR (KBr): 3328, 3299, 2959, 2936, 2866, 1630, 1589, 1561, 1519, 1489, 1233, 1091, 832, 687 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.54 (s, 1 H), 7.41 (d, J = 8.8 Hz, 2 H), 7.24 (d, J = 8.8 Hz, 2 H), 6.16 (t, J = 5.5 Hz, 1 H), 3.07 (dd, J = 12.6, 6.5 Hz, 2 H), 1.45–1.20 (m, 4 H), 0.88 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 155.0, 139.6, 128.4, 124.3, 119.0, 38.7, 31.8, 19.5, 13.6.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{11}H_{16}ClN_2O$: 227.094567; found: 227.094371.

***N*-Butyl-*N*′-(2-chlorophenyl)urea (2a′)**[12]

Yield: 17.0 mg (30%); white powder; mp 110–111 °C; R_f = 0.62 (EtOAc/hexanes, 1:1).

IR (KBr): 3346, 3283, 2961, 2934, 2871, 1635, 1587, 1553, 1473, 1440, 1298, 1231, 1056, 1031, 746 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.16 (dd, J = 8.3, 1.4 Hz, 1 H), 7.97 (s, 1 H), 7.37 (dd, J = 8.0, 1.4 Hz, 1 H), 7.25–7.18 (m, 1 H), 6.99 (t, J = 5.4 Hz, 1 H), 6.92 (ddd, J = 8.0, 7.4, 1.6 Hz, 1 H), 3.09 (dd, J = 12.3, 6.6 Hz, 2 H), 1.46–1.24 (m, 4 H), 0.89 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 154.7, 136.8, 129.0, 127.4, 122.2, 121.0, 120.6, 38.7, 31.6, 19.5, 13.6.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{11}H_{16}ClN_2O$: 227.094567; found: 227.093817.

***N*-(4-Chlorophenyl)urea (2b)**[25]

Yield: 23.5 mg (55%); white powder; mp 210 °C (dec.) (Lit.[26] 212 °C, dec.); R_f = 0.08 (EtOAc/hexanes, 1:1).

IR (KBr): 3427, 3314, 3214, 1655, 1612, 1587, 1550, 1491, 1401, 1357, 1251, 1091, 821 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.78 (s, 1 H), 7.42 (d, J = 8.7 Hz, 2 H), 7.24 (d, J = 8.7 Hz, 2 H), 5.94 (s, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 156.0, 139.6, 128.4, 124.5, 119.2.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_7H_7ClN_2NaO$: 193.013911; found: 193.014674.

***N*-(2-Chlorophenyl)urea (2b′)**[25]

Yield: 12.0 mg (28%); white powder; mp 177 °C (dec.) (Lit.[27] 175 °C, dec.); R_f = 0.19 (EtOAc/hexanes, 1:1).

IR (KBr): 3423, 3294, 3204, 1653, 1603, 1580, 1519, 1480, 1442, 1357, 1062, 771, 757, 734, 691, 604 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.13 (d, J = 8.3 Hz, 1 H), 8.08 (s, 1 H), 7.38 (d, J = 8.0 Hz, 1 H), 7.22 (t, J = 7.8 Hz, 1 H), 6.94 (t, J = 7.6 Hz, 1 H), 6.42 (s, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 155.6, 136.8, 129.0, 127.3, 122.5, 121.4, 121.2.

***N*-Benzyl-*N*′-(4-chlorophenyl)urea (2c)**[25]

Yield: 39.8 mg (61%); white powder; mp 160 °C (dec.); R_f = 0.47 (EtOAc/hexanes, 1:1).

IR (KBr): 3422, 3313, 3062, 1636, 1594, 1566, 1489, 1398, 1237, 1088, 747, 698, 655 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.10 (s, 1 H), 7.45 (d, J = 8.1 Hz, 2 H), 7.34–7.24 (m, 5 H), 7.25 (d, J = 8.2 Hz, 2 H), 7.02 (s, 1 H), 4.29 (d, J = 5.0 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 155.2, 140.3, 139.7, 128.4, 128.3, 127.1, 126.7, 124.4, 119.1, 42.7.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{14}H_{13}ClN_2NaO$: 283.060861; found: 283.060099.

***N*-Benzyl-*N*′-(2-chlorophenyl)urea (2c′)**[25]

Yield: 20.2 mg (31%); white powder; R_f = 0.62 (EtOAc/hexanes, 1:1).

IR (KBr): 3440, 3307, 3024, 1689, 1637, 1589, 1549, 1469, 1440, 1384, 1301, 1233, 743, 700 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.21 (s, 1 H), 8.15 (d, J = 8.3 Hz, 1 H), 7.61 (s, 1 H), 7.39 (d, J = 8.0 Hz, 1 H), 7.37–7.30 (m, 4 H), 7.29–7.20 (m, 2 H), 6.95 (t, J = 7.7 Hz, 1 H), 4.31 (d, J = 5.4 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 154.9, 139.9, 136.7, 129.1, 128.4, 127.4, 127.3, 126.9, 122.5, 121.3, 120.9, 42.8.

***N*-(4-Chlorophenyl)-*N*′-[(1*R*)-phenylethyl]urea (2d)**[28]

Yield: 45.3 mg (66%); white powder; mp 162–163 °C; R_f = 0.65 (EtOAc/hexanes, 1:1).

IR (KBr): 3301, 3090, 3034, 2970, 1632, 1591, 1565, 1490, 1450, 1397, 1235, 1090, 1023, 834, 803, 744, 693 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.75 (s, 1 H), 7.38 (d, J = 8.8 Hz, 2 H), 7.32–7.29 (m, 4 H), 7.21 (d, J = 8.8 Hz, 2 H), 7.18–7.15 (m, 1 H), 6.86 (d, J = 7.8 Hz, 1 H), 4.79 (quint, J = 7.0 Hz, 1 H), 1.35 (d, J = 7.0 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 154.3, 145.2, 139.5, 128.4, 128.4, 128.3, 126.6, 125.8, 124.4, 119.0, 48.6, 23.0.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{16}ClN_2O$: 275.094567; found: 275.093955.

***N*-(2-Chlorophenyl)-*N*′-[(1*R*)-phenylethyl]urea (2d′)**[28]

Yield: 18.5 mg (27%); white powder; R_f = 0.74 (EtOAc/hexanes, 1:1).

IR (KBr): 3300, 3031, 2976, 2932, 1633, 1588, 1558, 1493, 1472, 1441, 1248, 1233, 1052, 744, 696 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.13–8.10 (m, 1 H), 8.09 (s, 1 H), 7.59 (d, J = 7.6 Hz, 1 H), 7.38–7.34 (m, 1 H), 7.32 (d, J = 4.3 Hz, 4 H), 7.24–7.15 (m, 2 H), 6.92–6.89 (m, 1 H), 4.80 (quint, J = 6.9 Hz, 1 H), 1.37 (d, J = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 153.9, 145.0, 136.7, 129.0, 128.3, 127.4, 126.7, 125.8, 122.3, 120.9, 120.4, 48.8, 23.1.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{16}ClN_2O$: 275.094567; found: 275.093953.

***N*,*N*-Diethyl-*N*′-(4-chlorophenyl)urea (2f)**[29]

Yield: 33.3 mg (59%); white powder; mp 108–110 °C; R_f = 0.43 (EtOAc/hexanes, 1:1).

IR (KBr): 3328, 3254, 3107, 2983, 2936, 2874, 1634, 1589, 1519, 1494, 1418, 1304, 1086, 1011, 818 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (d, J = 8.9 Hz, 2 H), 7.21 (d, J = 8.8 Hz, 2 H), 6.34 (s, 1 H), 3.35 (q, J = 7.1 Hz, 4 H), 1.21 (t, J = 7.2 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.5, 138.0, 128.8, 127.8, 121.2, 41.8, 14.0.

***N*,*N*-Diethyl-*N*′-(2-chlorophenyl)urea (2f′)**[30]

Yield: 16.9 mg (30%); yellow oil; R_f = 0.57 (EtOAc/hexanes, 1:1).

IR (KBr): 3443, 3335, 3070, 2973, 2932, 2874, 1678, 1594, 1518, 1489, 1440, 1301, 1263, 1234, 1159, 1097, 1034, 974, 936, 751 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.25 (dd, J = 8.3, 1.5 Hz, 1 H), 7.32 (dd, J = 8.0, 1.5 Hz, 1 H), 7.25–7.21 (m, 1 H), 7.00 (s, 1 H), 6.93 (td, J = 7.9, 1.5 Hz, 1 H), 3.41 (q, J = 7.2 Hz, 4 H), 1.26 (t, J = 7.2 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.0, 136.2, 128.8, 127.8, 122.8, 122.1, 120.8, 42.0, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{16}ClN_2O$: 227.094567; found: 227.094860.

***N*,*N*-Diisopropyl-*N*′-(4-chlorophenyl)urea (2g)**[30]

Yield: 40.1 mg (63%); white powder; mp 137–138 °C; R_f = 0.62 (EtOAc/hexanes, 1:1).

IR (KBr): 3319, 2968, 2933, 2759, 1636, 1591, 1525, 1494, 1431, 1395, 1375, 1334, 1261, 1242, 824, 608 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.8 Hz, 2 H), 7.21 (d, *J* = 8.9 Hz, 2 H), 6.20 (s, 1 H), 3.97 (hept, *J* = 6.8 Hz, 2 H), 1.32 (d, *J* = 6.9 Hz, 12 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.6, 138.0, 129.0, 128.9, 127.8, 121.2, 45.8, 21.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{20}ClN_2O$: 255.125867; found: 255.124831.

***N*,*N*-Diisopropyl-*N*′-(2-chlorophenyl)urea (2g′)**[30]

Yield: 21.0 mg (33%); white powder; mp 63–64 °C; R_f = 0.68 (EtOAc/hexanes, 1:1).

IR (KBr): 3455, 3202, 2964, 2928, 1628, 1584, 1525, 1481, 1442, 1338, 1260, 1100, 1056, 1033, 803, 609 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.25 (dd, *J* = 8.4, 1.3 Hz, 1 H), 7.31 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.22 (t, *J* = 7.9 Hz, 1 H), 6.93 (s, 1 H), 6.93–6.87 (m, 1 H), 4.06 (hept, *J* = 6.9 Hz, 2 H), 1.35 (d, *J* = 6.9 Hz, 12 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.2, 136.5, 128.8, 127.8, 122.6, 121.9, 121.0, 45.7, 21.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{20}ClN_2O$: 255.125867; found: 255.125135.

***N*-(4-Chlorophenyl)morpholine-4-carboxamide (2h)**[31]

Yield: 39.1 mg (65%); white powder; mp 198–199 °C (Lit.[32] 199–202 °C); R_f = 0.17 (EtOAc/hexanes, 1:1).

IR (KBr): 3296, 2953, 2889, 2849, 1634, 1591, 1510, 1498, 1422, 1305, 1276, 1248, 1115, 833, 822, 812 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.65 (s, 1 H), 7.49 (dd, *J* = 8.9, 2.5 Hz, 2 H), 7.27 (dd, *J* = 8.9, 2.5 Hz, 2 H), 3.60 (s, 4 H), 3.41 (s, 4 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 155.0, 139.5, 128.2, 125.5, 121.1, 66.0, 44.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}ClN_2O_2$: 241.073832; found: 241.072879.

***N*-(2-Chlorophenyl)morpholine-4-carboxamide (2h′)**[33]

Yield: 18.0 mg (30%); white powder; mp 124–126 °C (Lit.[34] 125 °C); R_f = 0.32 (EtOAc/hexanes, 1:1).

IR (KBr): 3323, 2964, 2911, 2888, 2853, 1632, 1512, 1453, 1290, 1251, 1119, 1071, 1001, 752 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.23 (s, 1 H), 7.51 (d, *J* = 8.0 Hz, 1 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 7.28 (t, *J* = 7.7 Hz, 1 H), 7.14 (t, *J* = 7.7 Hz, 1 H), 3.61 (s, 4 H), 3.42 (s, 4 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 155.2, 136.5, 129.2, 128.2, 127.2, 127.0, 125.6, 66.0, 44.2.

***N*,*N*-Diethyl-*N*′-(2-chloro-4-methylphenyl)urea (2i)**

Yield: 42.5 mg (71%); yellow oil; R_f = 0.52 (EtOAc/hexanes, 1:1).

IR (KBr): 3446, 3336, 2973, 2931, 2873, 1674, 1612, 1583, 1520, 1486, 1403, 1300, 1264, 1159, 1097, 819 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.4 Hz, 1 H), 7.13 (s, 1 H), 7.03 (d, *J* = 8.4 Hz, 1 H), 6.88 (s, 1 H), 3.39 (q, *J* = 7.2 Hz, 4 H), 2.26 (s, 3 H), 1.24 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.2, 133.7, 132.7, 129.0, 128.4, 122.0, 120.9, 41.9, 20.5, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}ClN_2O$: 241.110217; found: 241.109766.

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

Yield: 55.6 mg (63%); yellow-redish oil; R_f = 0.54 (EtOAc/hexanes, 1:1).

IR (KBr): 3442, 2969, 2927, 2871, 1673, 1574, 1510, 1402, 1377, 1299, 1269, 1259, 1234, 1160, 1082, 833, 818, 749, 725 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.8 Hz, 1 H), 7.63 (d, *J* = 2.0 Hz, 1 H), 7.51 (dd, *J* = 8.8, 2.0 Hz, 1 H), 6.96 (s, 1 H), 3.39 (q, *J* = 7.2 Hz, 4 H), 1.25 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.7, 136.7, 136.7, 136.3, 122.8, 122.2, 83.8, 42.0, 13.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{14}ClIN_2NaO$: 374.973159; found: 374.971995.

***N*-Butyl-*N*′-(4-bromophenyl)urea (3a)**[12]

Yield: 61.5 mg (91%); white powder; mp 184–185 °C (Lit.[35] 185 °C); R_f = 0.47 (EtOAc/hexanes, 1:1).

IR (KBr): 3350, 3277, 2959, 2929, 2857, 1745, 1636, 1582, 1553, 1467, 1296, 1045, 1025, 744, 642 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.92 (s, 1 H), 7.36 (s, 4 H), 6.46 (t, *J* = 5.4 Hz, 1 H), 3.05 (dd, *J* = 12.5, 6.4 Hz, 2 H), 1.43–1.21 (m, 4 H), 0.87 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 155.2, 140.2, 131.2, 119.4, 111.9, 62.8, 38.5, 31.8, 19.5, 13.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{16}BrN_2O$: 271.044052; found: 271.043038.

***N*-(4-Bromophenyl)urea (3b)**[25]

Yield: 45.4 mg (84%); white powder; mp 270 °C (dec.) (Lit.[36] 265–268 °C, dec.); R_f = 0.06 (EtOAc/hexanes, 1:1).

IR (KBr): 3427, 3310, 3214, 1654, 1610, 1584, 1549, 1487, 1399, 1356, 1249, 1072, 817, 721 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.98 (s, 1 H), 7.55–7.21 (m, 4 H), 6.01 (s, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 156.0, 140.1, 131.2, 119.6, 112.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_7H_7BrN_2NaO$: 236.963396; found: 236.964329.

***N*-Benzyl-*N*′-(4-bromophenyl)urea (3c)**[25]

Yield: 69.2 mg (91%); white powder; mp 208–210 °C; R_f = 0.47 (EtOAc/hexanes, 1:1).

IR (KBr): 3315, 3289, 3030, 2932, 2884, 1634, 1590, 1561, 1484, 1474, 1238, 1009, 745, 701 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.72 (s, 1 H), 7.37 (s, 4 H), 7.34–7.22 (m, 5 H), 6.67 (t, *J* = 5.9 Hz, 1 H), 4.30 (d, *J* = 5.9 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 155.0, 140.2, 139.9, 131.3, 128.3, 127.1, 126.7, 119.6, 112.4, 42.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{13}BrN_2NaO$: 327.010346; found: 327.008886.

***N*-(4-Bromophenyl)-*N*′-[(1*R*)-phenylethyl]urea (3d)**[28]

Yield: 65.2 mg (82%); white powder; mp 190–191 °C; R_f = 0.52 (EtOAc/hexanes, 1:1).

IR (KBr): 3301, 3086, 2981, 1627, 1587, 1556, 1486, 1450, 1394, 1234, 1131, 1022, 832, 697 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.52 (s, 1 H), 7.35 (d, *J* = 4.0 Hz, 4 H), 7.33 (d, *J* = 4.3 Hz, 4 H), 7.23 (dq, *J* = 8.6, 4.2 Hz, 1 H), 6.66 (d, *J* = 7.8 Hz, 1 H), 4.81 (quint, *J* = 7.0 Hz, 1 H), 1.38 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 154.2, 145.0, 139.8, 131.4, 128.3, 126.7, 125.8, 119.5, 112.3, 48.6, 23.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}BrN_2O$: 319.044052; found: 319.043238.

***N*-(4-Bromophenyl)-*N*′-[(1*S*)-phenylethyl]urea (3e)**[28]

Yield: 72.3 mg (91%); white powder; mp 190–191 °C; R_f = 0.52 (EtOAc/hexanes, 1:1).

IR (KBr): 3301, 3086, 2981, 1627, 1587, 1556, 1486, 1450, 1394, 1234, 1131, 1022, 832, 697 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.52 (s, 1 H), 7.36 (d, *J* = 4.0 Hz, 4 H), 7.33 (d, *J* = 4.3 Hz, 4 H), 7.23 (dt, *J* = 8.6, 4.4 Hz, 1 H), 6.66 (d, *J* = 7.8 Hz, 1 H), 4.81 (quint, *J* = 7.0 Hz, 1 H), 1.38 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 154.2, 145.0, 139.8, 131.3, 128.3, 126.7, 125.8, 119.5, 112.3, 48.6, 23.0.

***N*,*N*-Diethyl-*N*′-(4-bromophenyl)urea (3f)**[33]

Yield: 64.8 mg (96%); white powder; mp 114–116 °C; R_f = 0.43 (EtOAc/hexanes, 1:1).

IR (KBr): 3330, 3259, 2982, 2935, 1635, 1584, 1529, 1518, 1490, 1418, 1303, 1284, 1078, 817 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.36 (d, *J* = 8.9 Hz, 2 H), 7.27 (d, *J* = 8.9 Hz, 2 H), 6.32 (s, 1 H), 3.35 (q, *J* = 7.2 Hz, 4 H), 1.21 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 154.4, 138.6, 131.8, 121.5, 115.3, 41.8, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{16}BrN_2O$: 271.044052; found: 271.043975.

***N*,*N*-Diisopropyl-*N*′-(4-bromophenyl)urea (3g)**[37]

Yield: 73.2 mg (98%); yellow powder; mp 155–157 °C (Lit.[37] 160–162 °C); R_f = 0.62 (EtOAc/hexanes, 1:1).

IR (KBr): 3319, 2999, 2969, 2933, 1636, 1588, 1525, 1490, 1430, 1391, 1375, 1334, 1241, 1145, 1054, 822, 607 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.8 Hz, 2 H), 7.27 (d, *J* = 8.8 Hz, 2 H), 6.18 (s, 1 H), 3.96 (hept, *J* = 6.8 Hz, 2 H), 1.32 (d, *J* = 6.9 Hz, 12 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.4, 138.6, 131.8, 121.3, 115.1, 45.7, 21.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{20}BrN_2O$: 299.075352; found: 299.074008.

***N*-(4-Bromophenyl)morpholine-4-carboxamide (3h)**[33]

Yield: 67.2 mg (95%); white powder; mp 160 °C (dec.); R_f = 0.17 (EtOAc/hexanes, 1:1).

IR (KBr): 3295, 3096, 3068, 2970, 2908, 2846, 1639, 1586, 1510, 1419, 1284, 1246, 1113, 1080, 828 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.64 (s, 1 H), 7.47–7.42 (m, 2 H), 7.41–7.37 (m, 2 H), 3.62–3.56 (m, 4 H), 3.43–3.39 (m, 4 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 154.9, 139.9, 131.3, 121.4, 113.3, 66.0, 44.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}BrN_2O_2$: 285.023316; found: 285.022839.

***N*,*N*-Diethyl-*N*′-(2-bromo-4-methylphenyl)urea (3i)**

Yield: 55.4 mg (78%); yellow oil; R_f = 0.48 (EtOAc/hexanes, 1:1).

IR (KBr): 3432, 3336, 2973, 2930, 2872, 1674, 1609, 1577, 1519, 1487, 1401, 1298, 1275, 1159, 1802, 820, 749 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.4 Hz, 1 H), 7.30 (d, *J* = 1.8 Hz, 1 H), 7.10–7.03 (m, 1 H), 6.89 (s, 1 H), 3.40 (q, *J* = 7.2 Hz, 4 H), 2.27 (s, 3 H), 1.26 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.2, 134.8, 133.3, 132.3, 129.1, 121.1, 113.0, 42.0, 20.5, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}BrN_2O$: 285.059702; found: 285.059040.

***N*,*N*-Diethyl-*N*′-(2-bromo-4-iodophenyl)urea (3j)**

Yield: 65.5 mg (66%); yellow-reddish oil; R_f = 0.59 (EtOAc/hexanes, 1:1).

IR (KBr): 3428, 3339, 2972, 2930, 2872, 1674, 1578, 1567, 1509, 1488, 1463, 1400, 1296, 1268, 1232, 1159, 1029, 829, 748 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.8 Hz, 1 H), 7.79 (d, *J* = 2.0 Hz, 1 H), 7.54 (dd, *J* = 8.8, 2.0 Hz, 1 H), 6.98 (s, 1 H), 3.40 (q, *J* = 7.2 Hz, 4 H), 1.26 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.7, 139.6, 137.3, 137.3, 122.4, 113.4, 84.3, 42.0, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{15}BrIN_2O$: 396.940700; found: 396.938756.

***N*-Butyl-*N*′-(4-iodophenyl)urea (4a)**[14]

Yield: 72.3 mg (91%); white powder; mp 187–188 °C; R_f = 0.51 (EtOAc/hexanes, 1:1).

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

^{1}H 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*,*N*-Diethyl-*N*′-(4-iodophenyl)urea (4f)**[14]

Yield: 73.1 mg (92%); pale-yellow powder; mp 104–106 °C; R_f = 0.47 (EtOAc/hexanes, 1:1).

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

^{1}H NMR (500 MHz, DMSO-d_6): 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, DMSO-d_6): 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.

Di- and Trihalogenation of *N*,*N*-Diethyl-*N*′-phenylurea (1f); General Procedure for Preparation of *N*′-(Polyhalophenyl)ureas 5 and 6

TXCA (0.17–1.0 mmol) was added to a stirred solution of *N*,*N*-diethyl-*N*′-phenylurea (**1f**; 0.25 mmol) in MeCN (5–10 mL) at r.t. (25 °C) and the mixture was stirred for 17–24 h. The reaction was quenched with 15% $NaHSO_3$ solution (10 mL). The final mixture was extracted with EtOAc and washed with brine water. The organic layer was separated, dried over anhydrous sodium sulfate followed by removal of solvent under reduced pressure. The crude products were separated by silica gel column chromatography using EtOAc/hexanes as eluent.

N,*N*-Diethyl-*N*′-(2,4-dichlorophenyl)urea (5a)[33]

Reaction using TCCA (0.17 mmol) for 17 h.

Yield: 49.4 mg (76%); yellow oil; R_f = 0.68 (EtOAc/hexanes, 1:1).

IR (KBr): 3444, 3336, 3115, 3077, 2974, 2932, 2874, 1674, 1578, 1514, 1402, 1382, 12991261, 1159, 1098, 862, 843, 792, 751 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 9.0 Hz, 1 H), 7.33 (d, *J* = 2.4 Hz, 1 H), 7.21 (dd, *J* = 9.0, 2.4 Hz, 1 H), 6.94 (s, 1 H), 3.40 (q, *J* = 7.2 Hz, 4 H), 1.26 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.8, 135.1, 128.4, 127.9, 127.2, 122.5, 121.6, 42.0, 13.9.

HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{14}Cl_2N_2NaO$: 283.037539; found: 283.037884.

N,*N*-Diethyl-*N*′-(2,4,6-trichlorophenyl)urea (5b)

Reaction using TCCA (0.34 mmol) for 24 h.

Yield: 28.6 mg (39%); white powder; mp 141–142 °C; R_f = 0.61 (EtOAc/hexanes, 1:1).

IR (KBr): 3247, 2979, 2931, 2872, 1640, 1579, 1555, 1505, 1488, 1278, 1173, 1084, 858, 846, 815, 800, 755, 704 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 (s, 2 H), 6.05 (s, 1 H), 3.40 (q, *J* = 7.1 Hz, 4 H), 1.25 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.0, 133.5, 133.2, 131.7, 128.3, 41.9, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}Cl_3N_2O$: 295.016623; found: 295.016609.

N,*N*-Diethyl-*N*′-(2,4-dibromophenyl)urea (6a)

Reaction using TBCA (0.5 mmol) for 17 h.

Yield: 60.0 mg (69%); red oil; R_f = 0.55 (EtOAc/hexanes, 1:1).

IR (KBr): 3429, 2973, 2931, 2872, 1676, 1583, 1571, 1513, 1041, 1378, 1297, 1268, 1257, 1231, 1159, 1079, 1032, 832, 749 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 8.9 Hz, 1 H), 7.62 (d, *J* = 2.3 Hz, 1 H), 7.38 (dd, *J* = 8.9, 2.2 Hz, 1 H), 6.97 (s, 1 H), 3.40 (q, *J* = 7.2 Hz, 4 H), 1.26 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.8, 136.7, 134.0, 131.4, 122.0, 114.5, 113.2, 42.0, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{14}Br_2N_2NaO$: 370.936508; found: 370.936685.

N,*N*-Diethyl-*N*′-(2,4,6-tribromophenyl)urea (6b)

Reaction using TBCA (1.0 mmol) for 24 h.

Yield: 27.7 mg (26%); white powder; mp 152–153 °C; R_f = 0.48 (EtOAc/hexanes, 1:1).

IR (KBr): 3244, 2976, 2927, 1638, 1565, 1541, 1505, 1485, 1454, 1401, 1276, 1173, 1096, 856, 754, 739 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (s, 2 H), 6.07 (s, 1 H), 3.40 (d, *J* = 7.2 Hz, 4 H), 1.26 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.8, 136.1, 134.6, 123.7, 119.7, 41.9, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{13}Br_3N_2NaO$: 448.847020; found: 448.846456.

Halogenation of *N*-Benzylureas 7; General Procedure for Preparation of *N*-(Halobenzyl)ureas 8 and 9

TXCA (0.125 mmol) was added to a stirred solution of the appropriate substituted *N*-benzylurea **7** (0.25 mmol) in MeCN–CF_3CO_2H 1:1 (3 mL) (or CF_3CO_2H (3 mL) for **8a**/**a′**) at r.t. (25 °C) and the mixture was stirred until completion of the reaction (TLC). The reaction was quenched with 15% $NaHSO_3$ solution (10 mL) and carefully neutralized with $NaHCO_3$. The final mixture was extracted with EtOAc and washed with brine water. The organic layer was separated, dried over anhydrous sodium sulfate followed by removal of solvent under reduced pressure. The crude products were separated by silica gel column chromatography using EtOAc/hexanes as eluent.

N-Butyl-*N*′-(4-chlorobenzyl)urea (8a)[38]

Yield: 18.8 mg (31%); white powder; mp 83–85 °C; R_f = 0.21 (EtOAc/hexanes, 1:1).

IR (KBr): 3329, 2954, 2928, 2870, 1620, 1588, 1523, 1491, 1467, 1257, 1092, 1033, 1013, 816, 650 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.4 Hz, 2 H), 7.13 (d, *J* = 8.4 Hz, 2 H), 5.37 (s, 1 H), 4.99 (s, 1 H), 4.21 (d, *J* = 5.9 Hz, 2 H), 3.13–3.01 (m, 2 H), 1.42–1.35 (m, 2 H), 1.31–1.23 (m, 2 H), 0.87 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.7, 138.2, 133.0, 128.8, 128.7, 43.7, 40.3, 32.4, 20.1, 13.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{17}ClN_2NaO$: 263.092162; found: 263.091920.

N-Butyl-*N*′-(2-chlorobenzyl)urea (8a′)

Yield: 16.7 mg (27%); white powder; mp 108–110 °C; R_f = 0.32 (EtOAc/hexanes, 1:1).

IR (KBr): 3335, 2956, 2929, 2871, 1625, 1589, 1468, 1442, 1412, 1290, 1251, 1047, 1037, 756 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.32 (m, 1 H), 7.31–7.28 (m, 1 H), 7.20–7.13 (m, 2 H), 5.34 (t, *J* = 5.8 Hz, 1 H), 4.93 (s, 1 H), 4.37 (d, *J* = 6.2 Hz, 2 H), 3.18–2.97 (m, 2 H), 1.46–1.33 (m, 2 H), 1.28 (dq, *J* = 14.3, 7.2 Hz, 2 H), 0.87 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.6, 137.0, 133.3, 129.4, 128.6, 127.1, 42.2, 40.4, 32.4, 20.1, 13.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{17}ClN_2NaO$: 263.092162; found: 263.091923.

***N,N*-Diethyl-*N*′-(4-chlorobenzyl)urea (8b)**

Yield: 16.2 mg (27%); pale-yellow oil; R_f = 0.26 (EtOAc/hexanes, 1:1).

IR (KBr): 3322, 2970, 2930, 2870, 1623, 1537, 1490, 1451, 1425, 1403, 1310, 1283, 1016, 833, 767, 654, 581 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.4 Hz, 2 H), 7.22 (d, *J* = 8.5 Hz, 2 H), 4.71 (s, 1 H), 4.38 (d, *J* = 5.7 Hz, 2 H), 3.26 (q, *J* = 7.1 Hz, 4 H), 1.13 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.2, 138.7, 132.9, 129.0, 128.7, 44.3, 41.4, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$calcd for $C_{12}H_{17}ClN_2NaO$: 263.092162; found: 263.092251.

***N,N*-Diethyl-*N*′-(2-chlorobenzyl)urea (8b′)**

Yield: 14.4 mg (24%); white powder; mp 82–83 °C; R_f = 0.34 (EtOAc/hexanes, 1:1).

IR (KBr): 3355, 3065, 2968, 2929, 1627, 1534, 1443, 1412, 1363, 1290, 1263, 1100, 1047, 1038, 798, 739, 557 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.41 (dd, *J* = 7.3, 1.9 Hz, 1 H), 7.33 (dd, *J* = 7.5, 1.6 Hz, 1 H), 7.24–7.17 (m, 2 H), 4.90 (s, 1 H), 4.49 (d, *J* = 5.9 Hz, 2 H), 3.25 (q, *J* = 7.1 Hz, 4 H), 1.13 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.2, 137.3, 133.6, 130.4, 129.5, 128.6, 127.1, 43.0, 41.4, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$calcd for $C_{12}H_{17}ClN_2NaO$: 263.092162; found: 263.092107.

***N*-Butyl-*N*′-(4-bromobenzyl)urea (9a)**

Yield: 27.0 mg (38%); white powder; mp 110–111 °C; R_f = 0.26 (EtOAc/hexanes, 1:1).

IR (KBr): 3325, 3133, 2960, 2927, 2860, 1621, 1581, 1487, 1472, 1403, 1261, 1099, 1069, 1028, 1012, 809, 645 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 8.4 Hz, 2 H), 7.09 (d, *J* = 8.3 Hz, 2 H), 5.27 (s, 1 H), 4.90 (s, 1 H), 4.21 (d, *J* = 5.9 Hz, 2 H), 3.08 (q, *J* = 7.0 Hz, 2 H), 1.39 (quint, *J* = 7.2 Hz, 2 H), 1.28 (dq, *J* = 14.3, 7.2 Hz, 2 H), 0.88 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.6, 138.8, 131.7, 129.1, 121.1, 43.8, 40.4, 32.4, 20.1, 13.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$calcd for $C_{12}H_{17}BrN_2NaO$: 307.041646; found: 307.041137.

***N*-Butyl-*N*′-(2-bromobenzyl)urea (9a′)**

Yield: 31.2 mg (44%); white powder; mp 133–134 °C; R_f = 0.35 (EtOAc/hexanes, 1:1).

IR (KBr): 3335, 3140, 3058, 2957, 2928, 2860, 1624, 1589, 1462, 1439, 1411, 1289, 1261, 1107, 1026, 802, 753 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.47 (dd, *J* = 7.9, 0.9 Hz, 1 H), 7.32 (dd, *J* = 7.7, 1.2 Hz, 1 H), 7.20 (td, *J* = 7.5, 0.9 Hz, 1 H), 7.07 (td, *J* = 7.8, 1.6 Hz, 1 H), 5.49 (s, 1 H), 5.07 (s, 1 H), 4.33 (d, *J* = 6.2 Hz, 2 H), 3.08 (q, *J* = 7.0 Hz, 2 H), 1.38 (quint, *J* = 7.7, 7.2 Hz, 2 H), 1.27 (dq, *J* = 14.3, 7.2 Hz, 2 H), 0.86 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.7, 138.6, 132.7, 129.5, 128.8, 127.7, 123.4, 44.6, 40.4, 32.4, 20.2, 13.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$calcd for $C_{12}H_{17}BrN_2NaO$: 307.041646; found: 307.041679.

***N,N*-Diethyl-*N*′-(4-bromobenzyl)urea (9b)**

Yield: 28.1 mg (39%); pale-yellow oil; R_f = 0.24 (EtOAc/hexanes, 1:1).

IR (KBr): 3336, 2970, 2929, 1626, 1535, 1487, 1401, 1282, 1040, 1011, 789 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 8.4 Hz, 2 H), 7.16 (d, *J* = 8.3 Hz, 2 H), 4.73 (s, 1 H), 4.36 (d, *J* = 5.7 Hz, 2 H), 3.26 (q, *J* = 7.1 Hz, 4 H), 1.12 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.2, 139.2, 131.6, 129.4, 120.9, 44.3, 41.3, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$calcd for $C_{12}H_{17}BrN_2NaO$: 307.041646; found: 307.042468.

***N,N*-Diethyl-*N*′-(2-bromobenzyl)urea (9b′)**

Yield: 25.9 mg (36%); white powder; mp 100–101 °C; R_f = 0.32 (EtOAc/hexanes, 1:1).

IR (KBr): 3350, 3066, 2976, 2930, 1627, 1541, 1494, 1461, 1441, 1410, 1377, 1266, 1209, 1027, 739 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.53 (dd, *J* = 7.9, 0.8 Hz, 1 H), 7.43 (dd, *J* = 7.6, 1.4 Hz, 1 H), 7.29–7.25 (m, 1 H), 7.12 (td, *J* = 7.7, 1.6 Hz, 1 H), 4.93 (s, 1 H), 4.48 (d, *J* = 6.0 Hz, 2 H), 3.26 (q, *J* = 7.2 Hz, 4 H), 1.14 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.1, 138.9, 132.6, 130.7, 129.0, 127.8, 123.8, 45.3, 41.4, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$calcd for $C_{12}H_{17}BrN_2NaO$: 307.041646; found: 307.043161.

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Supporting Information

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