A simple and efficient synthesis of diaryl ureas with reduction of the intermediate isocyanate by triethylamine

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Thirty symmetrical diaryl urea derivatives were synthesised in moderate to excellent yields from arylamine and triphosgene with triethylamine as a reducing agent for the intermediate, isocyanate. It was significant that part of the products could be collected in almost quantitative yield without column chromatography. The procedure under mild reaction conditions was tolerant of a wide range of functional groups. The structures of the compounds were determined by NMR, MS and X-ray crystallographic analyses.

Keywords: diaryl ureas, triphosgene, triethylamine

The urea group plays an important role in agricultural, supramolecular, and medicinal chemistry.[1–6] For example, recent reports have cited examples of ureas as antimalarial agents,[7,8] cardiac-specific myosin activators,[9] anaplastic lymphoma kinase inhibitors,[10] tyrosine and Raf kinase inhibitors,[11] soluble epoxide hydrolase inhibitors for the treatment of diabetes, hypertension, stroke, and inflammatory diseases.[12,13] Moreover, urea derivatives also impart important function in organic synthesis as intermediates and bifunctional organocatalysts.[14–17]

Typically, efficient synthesis of the urea functional group is achieved through the condensation of an amine with an isocyanate, or the coupling of amines with phosgene or a phosgene equivalent.[18,19] Unfortunately, phosgene poses handling issues due to its toxicity, so developing a less hazardous synthetic route to ureas has attracted considerable interest over the years.[20–24] Bis(trichloromethyl) carbonate (BTC) or triphosgene, $(Cl_3CO)_2C=O$, is a relatively safe substitute for the notorious toxic gas phosgene. It is stable at room temperature, and its handling and storage do not demand meticulously anhydrous conditions, thus making it a very convenient reagent for typical laboratory and industrial scale operations.[25] In addition, this reagent has been used to achieve various functional group interconversions, particularly the insertion of the carbonyl moiety.[26]

Driven by our interest in the utilisation of triphosgene to synthesise urea-containing compounds, we recently explored a mild method for the construction of symmetrical diaryl ureas by triphosgene in the presence of triethylamine, which led to the rapid and clean production of the target products in good yields (Scheme 1). In most cases, the reactions proceed to completion in less than 1 h at room temperature except for the aryl amine containing nitro group.

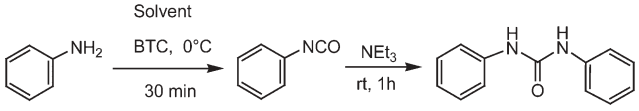
Results and discussion

Initially, we investigated the reaction of aniline with triphosgene to synthesise isocyanatobenzene in dichloromethane. After the aniline reacted completely with triphosgene by GC-MS monitoring, we added excess triethylamine as a base to the above mixture, and surprisingly, the symmetrical 1,3-diphenylurea was obtained rapidly in almost quantitative yield, 97% (Table 1, entry 4). Then we investigated the reaction in various solvents, and found that the reaction was tolerant of a wide variety of both polar and non polar solvents (Table 1). Furthermore, using dichloromethane not only got the best yield, but also was the most convenient procedure during the purification of the products from the reaction mixture.

We next investigated other tertiary amines, pyridine and inorganic base such as sodium carbonate, sodium bicarbonate, and found that 1,3-diphenylurea could also be obtained in the presence of other tertiary amines such as tripropylamine and tributylamine, instead of triethylamine. However, the yields were much lower than that with triethylamine. Interestingly, there was almost no diaryl urea generated when pyridine or inorganic base was used as a substitute for triethylamine (Table 2, entries 9–11). Instead, the reaction just produced the intermediate 1-isocyanatobenzene even if the reaction time was prolonged.

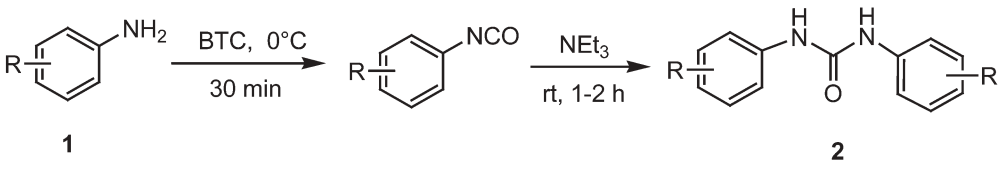
With our preferred conditions in hand, we investigated a range of different aryl primary amines. As shown in Tables 3 and 4, the reaction was highly tolerant of the monosubstituted or disubstituted aromatic primary amine structure, and most of the products were obtained in excellent yields, even weak nucleophilic amine such as 2-nitroaniline or 3-nitroaniline reacted in yield 85% (Table 3, entries 19 and 20), only

Table 1 Investigation of the effect of various solvents



Entry	Solvent	Yield/%[a]
1	THF	95
2	Acetic ether	87
3	Acetonitrile	76
4	DCM	97
5	Pyridine	75
6	Toluene	80
7	DCM/pyridine = 4/1	77
8	THF/pyridine = 4/1	75

[a] Isolated yield.



Scheme 1

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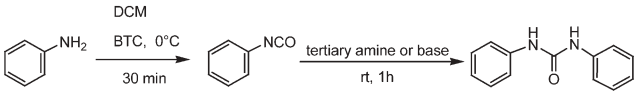
Table 2 Investigation of the effect of tertiary amines and inorganic bases



Entry	Tertiary amine or base	Yield/%[a]
1	Triethylamine	97
2	Tripropylamine	75
3	*T*ributylamine	71
4	*N,N*–Dimethylaniline	61
5	*N,N*-Diethylaniline	69
6	*N,N*-Diisopropylethylamine	66
7	*N,N*-dimethylethylamine	65
8	*N,N*-Dimethylbutylamine	68
9	Pyridine	Trace
10	$NaHCO_3$	0
11	Na_2CO_3	0

[a] Isolated yield.

4-methyl-2-nitrobenzenamine and 4-methoxy-2-nitrobenzenamine reacted in moderate yield, 77% and 75%, respectively (Table 4, entries 9 and 10).

All the products were characterised by ^{1}H NMR, ^{13}C NMR and High-resolution mass spectrometry (HRMS). In order to confirm the structure of the compounds, the crystal structure of 1,3-bis(2,5-dichlorophenyl)urea (**4a**) as a representative example was determined by X-ray crystallography. Crystal of **4a** was obtained from a mixture of ethyl acetate and ethanol (1:3). An ORTEP view of the molecule together with the atom numbering is presented in Fig. 1, the crystal data and structure refinement is shown in Table 5. In the molecule (Fig. 1), both the two phenyl rings (C_1–C_6 and C_{1A}–C_{6A}) are almost planar with the RMS deviations of 0.0036 Å, the dihedral angle between the two planes is 84.7°. The adjacent molecules are linked by intermolecular N1–H1…O1 hydrogen bond interactions to stabilise the crystal structure.

Conclusions

In conclusion, we have developed a highly practical and convenient synthesis of symmetrical diaryl ureas by the reaction of triphosgene and various aromatic primary amines with triethylamine as a reduction for the isocynate-containing intermediates. Note that the reaction in high yield is tolerant of a wide range of aromatic primary amines, and could take place under extremely mild conditions.

Experimental

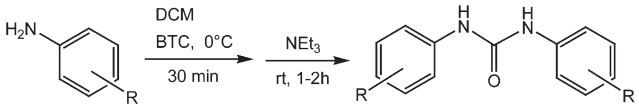
All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. IR spectra were run on a Bruker Equinox 55 using KBr pellets. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) analyses were recorded on a Bruker AVANCE 500 spectrometor in DMSO-d_6 with TMS as internal standard. Mass spectra were obtained on a Bruker micrOTOF-Q II instrument. The crystallographic data were collected on a Bruker Smart-Apex CCD diffractometer. Melting points were recorded on a digital melting point apparatus WRS-1B and are uncorrected. The progress of the reactions was detected by TLC using silica gel GF 254 plates.

Synthesis of the compounds **2** *and* **4***; general procedure*

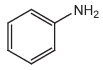
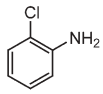
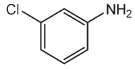
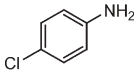
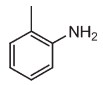
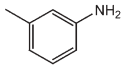
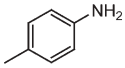
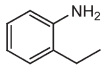
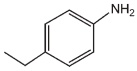
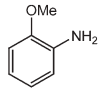
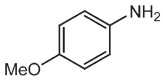
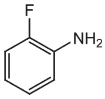
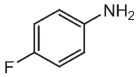
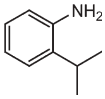
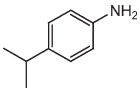
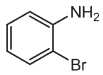
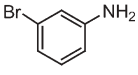
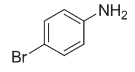
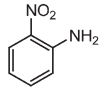
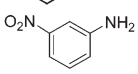
Bis(trichloromethyl) carbonate (BTC) (5.0 mmol 1.48 g) was dissolved in DCM (30 mL). The aromatic primary aniline (10.0 mmol) in DCM (20 mL) was added dropwise to the above solution at 0 °C over 30 min. After the aryl primary aniline reacted completely (monitored by GC), triethylamine (25.0 mmol, 2.53g) was added dropwise to the above mixture and stirred for 1–2 h at room temperature (monitored by TLC). The solid was obtained after distillation of DCM, washing by water (2×10 mL), and filtration.

1,3-Diphenylurea (**2a**): White solid; yield 97%, m.p. 245.0–245.4 °C (lit.[1] 240–241 °C); IR (KBr, cm^{-1}): 3282, 3046, 1644, 1594, 1547,

Table 3 Investigation of the scope of the monosubstituted aryl primary amine

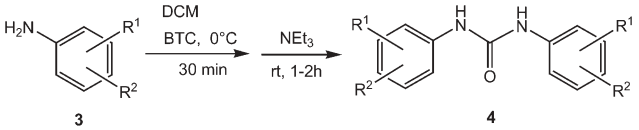


1 2

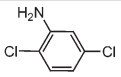
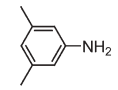
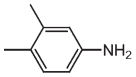
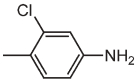
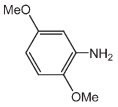
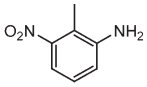
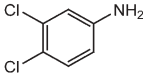
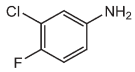
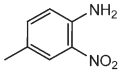
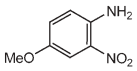
Entry	Starting material	2	Yield/%[a]
1		**2a**	97
2		**2b**	95
3		**2c**	82
4		**2d**	86
5		**2e**	99
6		**2f**	88
7		**2g**	92
8		**2h**	86
9		**2i**	82
10		**2j**	87
11		**2k**	87
12		**2l**	88
13		**2m**	94
14		**2n**	97
15		**2o**	90
16		**2p**	82
17		**2q**	84
18		**2r**	83
19		**2s**	85
20		**2t**	85

[a] Isolated yield.

Table 4 Investigation of the scope of the disubstituted aryl primary amine



3 4

Entry	Starting material	4	Yield/%[a]
1		**4a**	82
2		**4b**	98
3		**4c**	91
4		**4d**	87
5		**4e**	85
6		**4f**	80
7		**4g**	84
8		**4h**	82
9		**4i**	77
10		**4j**	75

[a] Isolated yield.

1497, 1315, 1227, 895, 781, 691; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.68 (s, 2H), 7.48 (d, 4H, J = 8.0 Hz), 7.29 (t, 4H, J = 8.0 Hz), 6.97 (t, 2H, J = 7.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.7, 139.9, 128.9, 122.0, 118.4; HRMS (ESI) exact mass calcd for $(C_{13}H_{13}N_2O)^+$ requires m/z 213.1028, found m/z 213.1017.

1,3-Bis(2-chlorophenyl)urea (**2b**): White solid; yield 95%, m.p. 242.0–242.3 °C (lit.[1] 226–227 °C); IR (KBr, cm^{-1}): 3248, 3016, 1640, 1580, 1460, 1405, 1264, 1222, 1080, 871, 800, 729; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.07 (s, 2H), 8.10 (d, 2H, J = 8.0 Hz), 7.45 (d, 2H, J = 7.5 Hz), 7.30 (t, 2H, J = 7.5 Hz), 7.04 (t, 2H, J = 8.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.4, 136.0, 129.5, 127.6, 123.9, 123.0, 122.7; HRMS (ESI) exact mass calcd for $(C_{13}H_{10}Cl_2N_2ONa)^+$ requires m/z 303.0068, found m/z 303.0060.

1,3-Bis(3-chlorophenyl)urea (**2c**): White solid; yield 82%, m.p. 253.2–252.6 °C (lit.[1] 245–246.5 °C); IR (KBr, cm^{-1}): 3324, 3076, 1635, 1578, 1550, 1478, 1403, 1284, 1224, 1070, 870, 789; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.96 (s, 2H), 7.74 (s, 2H), 7.29–7.28 (m, 4H), 7.02–7.00 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.5, 141.2, 133.5, 130.5, 121.9, 118.0, 117.0; HRMS (ESI) exact mass calcd for $(C_{13}H_{10}Cl_2N_2ONa)^+$ requires m/z 303.0068, found m/z 303.0060.

1,3-Bis(4-chlorophenyl)urea (**2d**): White solid; yield 86%, m.p. 284.3–284.7 °C (lit.[1] 301–302 °C); IR (KBr, cm^{-1}): 3240, 3056, 1655, 1605, 1568, 1500, 1448, 1401, 1294, 1214, 1075, 826, 729; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.87 (s, 2H), 7.51 (d, 4H, J = 9.0 Hz), 7.33 (d, 4H, J = 8.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.5, 138.7, 128.8, 125.7, 120.0; HRMS (ESI) exact mass calcd for $(C_{13}H_{10}Cl_2N_2ONa)^+$ requires m/z 303.0068, found m/z 303.0059.

1,3-Di-o-tolylurea (**2e**): White solid; yield 99%, m.p. 258.4–258.9 °C (lit.[1] 235–236 °C); IR (KBr, cm^{-1}): 3215, 3086, 2966, 2863, 1652, 1562, 1438, 1294, 1200, 906, 751; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.26 (s, 2H), 7.79 (d, 2H, J = 7.5 Hz), 7.17 (d, 2H, J = 7.0 Hz), 7.13 (t, 2H, J = 7.5 Hz), 6.94 (dd, 2H, J = 7.5, 1.0 Hz), 2.26 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 153.1, 137.7, 130.3, 127.9, 126.2, 122.8, 121.7, 18.2; HRMS (ESI) exact mass calcd for $(C_{15}H_{17}N_2O)^+$ requires m/z 241.1341, found m/z 241.1324.

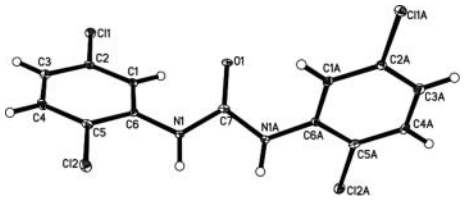


Fig. 1 X-ray crystal structure of **4a**, showing displacement ellipsoids at the 50% probability.

1,3-Di-m-tolylurea (**2f**): White solid; yield 88%, m.p. 225.6–226.1 °C (lit.[1] 262–263 °C); IR (KBr, cm^{-1}): 3255, 3056, 2961, 2931, 2869, 1635, 1550, 1401, 1290, 1227, 763, 748; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.59 (s, 2H), 7.34 (s, 2H), 7.26 (d, 2H, J = 8.5 Hz), 7.16 (t, 2H, J = 8.0 Hz), 6.78 (d, 2H, J = 7.5 Hz), 2.28 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.7, 139.9, 138.1, 128.8, 122.7, 118.9, 115.6, 21.4; HRMS (ESI) exact mass calcd for $(C_{15}H_{17}N_2O)^+$ requires m/z 241.1335, found m/z 241.1325.

1,3-Di-p-tolylurea (**2g**): White solid; yield 92%; m.p. 271.6–273.3 °C (lit.[1] 268–269 °C); IR (KBr, cm^{-1}): 3319, 3056, 2933, 2869, 1635, 1594, 1556, 1516, 1406, 1305, 1230, 814, 776, 751; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50 (s, 2H), 7.35 (d, 4H, J = 8.0 Hz), 7.08 (d, 4H, J = 7.5 Hz), 2.24 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.8, 137.4, 130.7, 129.3, 118.4, 20.5; HRMS (ESI) exact mass calcd for $(C_{15}H_{17}N_2O)^+$ requires m/z 241.1341, found m/z 241.1324.

1,3-Bis(2-ethylphenyl)urea (**2h**): White solid; yield 86%, m.p. 237.9–238.3 °C (lit.[2] 177–179 °C); IR (KBr, cm^{-1}): 3255, 3056, 2961, 2931, 2870, 2831, 1631, 1585, 1537, 1446, 1290, 1118, 751; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.21 (s, 2H), 7.75 (d, 2H, J = 8.0 Hz), 7.19 (d, 2H, J = 7.5 Hz), 7.14 (t, 2H, J = 7.5 Hz), 7.01 (t, 2H, J = 7.5 Hz), 2.64 (q, 4H, J = 7.5 Hz), 1.19 (t, 6H, J = 7.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 153.7, 136.9, 134.4, 128.5, 126.1, 123.4, 123.0, 24.0, 14.4. HRMS (ESI) exact mass calcd for $(C_{17}H_{21}N_2O)^+$ requires m/z 269.1650, found m/z 269.1647.

1,3-Bis(4-ethylphenyl)urea (**2i**): White solid; yield 82%, m.p. 224.2–224.4 °C; IR (KBr, cm^{-1}): 3268, 3016, 2912, 2872, 2855, 1631, 1585, 1547, 1456, 1406, 1296, 1230, 1064, 826, 760; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.52 (s, 2H), 7.37(d, 4H, J = 8.0 Hz), 7.10 (d, 4H, J = 8.0 Hz), 2.54 (q, 4H, J = 7.5 Hz), 1.15 (t, 6H, J = 7.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.8, 137.6, 137.2, 128.1, 118.5, 27.7, 15.9. HRMS (ESI) exact mass calcd for $(C_{17}H_{21}N_2O)^+$ requires m/z 269.1654, found m/z 269.1646.

1,3-Bis(2-methoxyphenyl)urea (**2j**): Light yellow solid; yield 87%, m.p. 187.6–188.1 °C (lit.[1] 187–188 °C); IR (KBr, cm^{-1}): 3292, 2936, 2834, 1644, 1591, 1534, 1456, 1321, 1286, 1252, 1227, 1108, 1024,

Table 5 Crystal data and structure refinement for **4a**

Empirical formula	C_{13} H_8 Cl_4 N_2 O
Formula weight	350.01
Temperature/K	298(2)
Wavelength/Å	0.71073
Crystal system	Monoclinic
Space group	C 2
Volume/Å^3	670.76(13)
Z	2
Calculated density/Mg m^{-3}	1.733
Unit cell dimensions	a = 24.874(3) Å, b = 4.6225(5) Å c = 5.8692(7) Å α = 90 °, β = 96.310(2)°, γ = 90°
Absorption coefficient/mm^{-1}	0.876
F(000)	352
Index ranges	$-30 \le h \le 25$ $-5 \le k \le 5$ $-6 \le l \le 7$
Goodness-of-fit on F^2	1.012
Final R indices	R^1 = 0.0225, wR^2 = 0.0808
R indices (all data)	R^1= 0.0255, wR^2 = 0.0971

735; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.94 (s, 2H), 8.18 (dd, 2H, J = 8.0, 1.5 Hz), 7.00 (dd, 2H, J = 8.0, 1.5 Hz), 6.96 (td, 2H, J = 8.0, 1.5 Hz), 6.91 (td, 2H, J = 7.5, 1.5 Hz), 3.87 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.9, 148.4, 129.1, 122.1, 120.6, 119.4, 111.0, 55.8. HRMS (ESI) exact mass calcd for $(C_{15}H_{16}N_2O_3Na)^+$ requires *m/z* 295.1059, found *m/z* 295.1046.

1,3-Bis(4-methoxyphenyl)urea (**2k**): White solid; yield 87%, m.p. 242.4–242.7 °C (lit.[1] 240 °C); IR (KBr, cm^{-1}): 3309, 3065, 2956, 2844, 1638, 1603, 1553, 1503, 1301, 1243, 1105, 1027, 823, 723; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.39 (s, 2H), 7.36 (d, 4H, J = 8.5 Hz), 6.87 (d, 4H, J = 8.0 Hz), 3.71(s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.6, 153.2, 133.1, 120.1, 114.2, 55.3. HRMS (ESI) exact mass calcd for $(C_{15}H_{16}N_2O_3Na)^+$ requires *m/z* 295.1059, found *m/z* 295.1045.

1,3-Bis(3-fluorophenyl)urea (**2l**): White solid; yield 88%, m.p. 197.1–197.4 °C; IR (KBr, cm^{-1}): 3314, 3277, 3065, 1649, 1597, 1541, 1485, 1442, 1312, 1270, 1178, 1135, 1046, 940, 864, 762; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.00 (s, 2H), 7.53(dt, 2H, J = 11.5, 2.0 Hz), 7.32 (dd, 2H, J = 15.0, 8.0 Hz), 7.16 (dd, 2H, J = 8.0, 1.5 Hz), 6.81 (td, 2H, J = 8.5, 2.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.6 (d, $^1J_{FC}$ = 240.0 Hz), 152.5, 141.5 (d, $^3J_{FC}$ = 11.3 Hz), 130.5 (d, $^3J_{FC}$ = 8.8 Hz), 114.3 (d, $^4J_{FC}$ = 2.5 Hz), 118.5 (d, $^2J_{FC}$ = 21.3 Hz), 105.3 (d, $^2J_{FC}$ = 26.3 Hz); HRMS (ESI) exact mass calcd for $(C_{13}H_{11}F_2N_2O)^+$ requires *m/z* 249.0839, found *m/z* 249.0816.

1,3-Bis(4-fluorophenyl)urea (**2m**): White solid; yield 94%, m.p. 268.3–269.1 °C; IR (KBr, cm^{-1}): 3267, 3151, 1625, 1606, 1562, 1503, 1409, 1296, 1205, 1152, 1088, 829, 789, 729; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.73 (s, 2H), 7.52 (dd, 4H, J = 9.0, 5.0 Hz), 7.13 (t, 4H, J = 9.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.6 (d, $^1J_{FC}$ = 236.3 Hz), 153.0, 136.3 (d, $^4J_{FC}$ = 2.25 Hz), 120.3 (d, $^3J_{FC}$ = 7.5 Hz), 115.4 (d, $^2J_{FC}$ = 22.3 Hz); HRMS (ESI) exact mass calcd for $(C_{13}H_{11}F_2N_2O)^+$ requires *m/z* 249.0839, found *m/z* 249.0816.

1,3-Bis(2-isopropylphenyl)urea (**2n**): White solid; yield 97%, m.p. 229.5–229.6 °C; IR (KBr, cm^{-1}): 3317, 3046, 2933, 2835, 1643, 1605, 1542, 1501, 1418, 1300, 1227, 1049, 863, 725; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.19 (s, 2H), 7.62 (dd, 2H, J = 8.0, 1.5 Hz), 7.28 (dd, 2H, J = 7.5, 1.5 Hz), 7.13 (dd, 2H, J = 7.5, 1.5 Hz), 7.07 (dd, 2H, J = 7.5, 1.0 Hz), 3.20 (hept, 2H, J = 6.5 Hz), 1.21 (d, 12H, J = 6.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.2, 139.9, 135.9, 125.8, 125.4, 124.2, 124.1, 27.0, 23.3. HRMS (ESI) exact mass calcd for $(C_{19}H_{25}N_2O)^+$ requires *m/z* 297.1967, found *m/z* 297.1957.

1,3-Bis(4-isopropylphenyl)urea (**2o**): White solid; yield 90%, m.p. 237.9–238.6 °C; IR (KBr, cm^{-1}): 3267, 3080, 2930, 2831, 1641, 1591, 1547, 1506, 1415, 1302, 1234, 1049, 833, 785; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.54 (s, 2H), 7.40 (d, 4H, J = 8.0 Hz), 7.14 (d, 4H, J = 8.5 Hz), 2.82 (hept, 2H, J = 7.0Hz), 1.19 (d, 12H, J = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.8, 141.9, 137.7, 126.6, 118.5, 33.0, 24.2. HRMS (ESI) exact mass calcd for $(C_{19}H_{25}N_2O)^+$ requires *m/z* 297.1967, found *m/z* 297.1959.

1,3-Bis(2-bromophenyl)urea (**2p**): White solid; yield 82%, m.p. 232.2–232.8 °C (lit.[2] 229–232 °C); IR (KBr, cm^{-1}): 3319, 3059, 1644, 1581, 1534, 1475, 1434, 1280, 1224, 1027, 748, 732; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.91 (s, 2H), 7.97 (d, 2H, J = 8.0 Hz), 7.63 (d, 2H, J = 8.0 Hz), 7.35 (t, 2H, J = 7.5 Hz), 7.01 (t, 2H, J = 7.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.6, 137.1, 132.7, 128.1, 124.8, 123.8, 114.3. HRMS (ESI) exact mass calcd for $(C_{13}H_{11}Br_2N_2O)^+$ requires *m/z* 368.9238, found *m/z* 368.9232.

1,3-Bis(3-bromophenyl)urea (**2q**): Light yellow solid; yield 84%, m.p. 275.5–276.4 °C; IR (KBr, cm^{-1}): 3279, 3059, 1631, 1572, 1539, 1475, 1396, 1284, 1224, 1064, 873, 851, 785, 682; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.95 (s, 2H), 7.89 (s, 2H), 7.34 (d, 2H, J = 8.5 Hz), 7.23 (t, 2H, J = 8.0 Hz), 7.15 (d, 2H, J = 7.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.4, 141.3, 130.8, 124.8, 121.9, 120.9, 117.4. HRMS (ESI) exact mass calcd for $(C_{13}H_{11}Br_2N_2O)^+$ requires *m/z* 368.9238, found *m/z* 368.9231.

1,3-Bis(4-bromophenyl)urea (**2r**): Light yellow solid; yield 83%, m.p. 283.0–283.3 °C (lit.[1] 292–293 °C); IR (KBr, cm^{-1}): 3239, 3039, 1719, 1687, 1581, 1509, 1431, 1287, 1177, 1024, 742; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.89 (s, 2H), 7.45 (d, 8H, J = 9.0 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.4, 139.1, 131.7, 120.4, 113.6. HRMS (ESI) exact mass calcd for $(C_{13}H_{11}Br_2N_2O)^+$ requires *m/z* 368.9238, found *m/z* 368.9232.

1,3-Bis(2-nitrophenyl)urea (**2s**): Light yellow solid; yield 85%, m.p. 225.4–226.1 °C; IR (KBr, cm^{-1}): 3342, 3049, 1667, 1579, 1515, 1471, 1277, 1227, 899, 801; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.08 (s, 2H), 8.05 (dd, 2H, J = 8.0, 1.5 Hz), 7.97 (d, 2H, J = 8.0 Hz), 7.71 (t, 2H, J = 8.5 Hz), 7.30 (t, 2H, J = 8.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.1, 140.1, 134.7, 133.2, 125.4, 124.1, 123.8. HRMS (ESI) exact mass calcd for $(C_{13}H_{10}N_4O_5Na)^+$ requires *m/z* 325.0549, found *m/z* 325.0543.

1,3-Bis(3-nitrophenyl)urea (**2t**): Yellow solid; yield 85%, m.p. 242.0–243.5 °C (lit.[1] 231–232 °C); IR (KBr, cm^{-1}): 3312, 3029, 1669, 1576, 1510, 1475, 1257, 1217, 829, 741; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.40 (s, 2H), 8.57 (s, 2H), 7.86 (dd, 2H, J = 8.0, 1.5 Hz), 7.77 (d, 2H, J = 8.0 Hz), 7.59 (t, 2H, J = 8.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.6, 148.3, 140.8, 130.2, 124.8, 116.9, 112.7. HRMS (ESI) exact mass calcd for $(C_{13}H_{10}N_4O_5Na)^+$ requires *m/z* 325.0549, found *m/z* 325.0545.

1,3-Bis(2,5-dichlorophenyl)urea (**4a**): White solid; yield 82%, m.p. 292.0–292.6 °C; IR (KBr, cm^{-1}): 3289, 3084, 1641, 1581, 1549, 1461, 1406, 1262, 1217, 1089, 873, 804, 738; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.31 (s, 2H), 8.23 (d, 2H, J = 2.5 Hz), 7.52 (d, 2H, J = 8.5 Hz), 7.14 (dd, 2H, J = 8.5, 2.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.1, 137.0, 132.0, 130.8, 123.6, 121.5, 121.2. HRMS (ESI) exact mass calcd for $(C_{13}H_9{}^{35}Cl_3{}^{37}ClN_2O)^+$ requires *m/z* 350.9440, found *m/z* 350.9419.

1,3-Bis(3,5-dimethylphenyl)urea (**4b**): White solid; yield 98%, m.p. 281.7–282.0 °C; IR (KBr, cm^{-1}): 3284, 3081, 2963, 2916, 2857, 2823, 1635, 1553, 1513,1444, 1312, 1274, 1218, 851, 839; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.46 (s, 2H), 7.06 (s, 4H), 6.60 (s, 2H), 2.23 (s, 12H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.6, 139.7, 137.9, 123.5, 116.0, 21.3. HRMS (ESI) exact mass calcd for $(C_{17}H_{21}N_2O)^+$ requires *m/z* 269.1654, found *m/z* 269.1645.

1,3-Bis(3,4-dimethylphenyl)urea (**4c**): White solid; yield 91%, m.p. 243.4–243.9 °C; IR (KBr, cm^{-1}): 3292, 3151, 2964, 2914, 2852, 2808, 1638, 1588, 1534, 1444, 1403, 1301, 1218, 1024, 999, 870, 801, 782; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.43 (s, 2H), 7.26 (s, 2H), 7.19 (d, 2H, J = 8.0 Hz), 7.02 (d, 2H, J = 8.5 Hz), 2.20 (s, 6H), 2.16 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.8, 137.7, 136.5, 129.8, 129.5, 119.7, 115.9, 19.8, 18.8. HRMS (ESI) exact mass calcd for $(C_{17}H_{21}N_2O)^+$ requires *m/z* 269.1654, found *m/z* 269.1642.

1,3-Bis(3-chloro-4-methylphenyl)urea (**4d**): White solid; yield 87%, m.p. 271.1–271.3 °C; IR (KBr, cm^{-1}): 3275, 3062, 2948, 1628, 1553, 1491, 1440, 1378, 1271, 1045, 867, 820; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.79 (s, 2H), 7.70 (d, 2H, J = 2.0 Hz), 7.23 (d, 2H, J = 8.0 Hz), 7.20 (dd, 2H, J = 8.0, 2.0 Hz), 2.26 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.5, 138.9, 133.3, 131.3, 128.5, 118.5, 117.2, 18.9. HRMS (ESI) exact mass calcd for $(C_{15}H_{15}Cl_2N_2O)^+$ requires *m/z* 309.0554, found *m/z* 309.0561.

1,3-Bis(2,5-dimethoxyphenyl)urea (**4e**): Grey solid; yield 85%, m.p. 206.5–207.5 °C; IR (KBr, cm^{-1}): 3292, 3092, 2936, 2834, 1669, 1598, 1535, 1454, 1417, 1279, 1198, 1123, 1045, 867, 820; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.99 (s, 2H), 7.85 (d, 2H, J = 2.5 Hz), 6.90 (d, 2H, J = 9.0Hz), 6.50 (dd, 2H, J = 9.0, 3.0Hz), 3.81 (s, 6H), 3.70 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 153.5, 152.8, 142.6, 129.9, 111.7, 106.2, 105.7, 56.4, 55.4. HRMS (ESI) exact mass calcd for $(C_{17}H_{21}N_2O_5)^+$ requires *m/z* 333.1450, found *m/z* 333.1441.

1,3-Bis(2-methyl-3-nitrophenyl)urea (**4f**): Light yellow solid; yield 80%, m.p. 290.6–291.6 °C; IR (KBr, cm^{-1}): 3316, 3067, 2923, 2831, 1659, 1585, 1515, 1464, 1345, 1251, 1084, 832, 781; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.74 (s, 2H), 8.04 (d, 2H, J = 8.0 Hz), 7.59 (d, 2H, J = 7.5 Hz), 7.41 (t, 2H, J = 8.0 Hz), 2.34 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 153.0, 151.2, 139.1, 126.9, 126.8, 123.2, 118.8, 13.7. HRMS (ESI) exact mass calcd for $(C_{15}H_{14}N_4O_5Na)^+$ requires *m/z* 353.0862, found *m/z* 353.0854.

1,3-Bis(3,4-dichlorophenyl)urea (**4g**): White solid; yield 84%, m.p. 271.0–271.9 °C; IR (KBr, cm^{-1}): 3324, 3086, 1670, 1607, 1577, 1544, 1471, 1390, 1290, 1026, 884, 854, 808; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.10 (s, 2H), 7.87(s, 2H), 7.50 (d, 2H, J = 9.5 Hz), 7.35 (d, 2H, J = 9.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.2, 139.7, 131.2, 130.7, 123.7, 119.8, 118.7. HRMS (ESI) exact mass calcd for $(C_{13}H_9{}^{35}Cl_3{}^{37}ClN2O)^+$ requires *m/z* 350.9440, found *m/z* 350.9419.

1,3-Bis(3-chloro-4-fluorophenyl)urea (**4h**): White solid; yield 82%, m.p. 237.1–237.6 °C; IR (KBr, cm^{-1}): 3322, 3027, 1649, 1600, 1554, 1494, 1402, 1217, 1053, 868, 825, 755; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.95 (s, 2H), 7.80–7.78 (m, 2H), 7.36–7.30 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.7 ($^1J_{FC}$ = 240.0 Hz), 152.6, 136.9 ($^4J_{FC}$ = 2.5 Hz), 120.0, 119.3 ($^2J_{FC}$ = 17.5 Hz), 118.9 ($^3J_{FC}$ = 6.25 Hz), 117.0 ($^2J_{FC}$ = 22.5 Hz). HRMS (ESI) exact mass calcd for $(C_{13}H_9Cl_2F_2N_2O)^+$ requires *m/z* 317.0060, found *m/z* 317.0036.

1,3-Bis(4-methyl-2-nitrophenyl)urea (**4i**): Light yellow solid; yield 77%, m.p. 234.6–235.0 °C; IR (KBr, cm^{-1}): 3305, 3077, 2933, 2823, 1657, 1575, 1512, 1474, 1337, 1271, 1234, 1153, 1088, 892, 829, 801; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.92 (s, 2H), 7.86 (s, 2H), 7.82 (d, 1H, J = 8.5 Hz), 7.52 (d, 2H, J = 8.5 Hz), 2.35 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.2, 139.9, 135.3, 133.6, 130.8, 125.0, 124.1, 20.0. HRMS (ESI) exact mass calcd for $(C_{15}H_{14}N_4O_5Na)^+$ requires *m/z* 353.0862, found *m/z* 353.0854.

1,3-Bis(4-methoxy-2-nitrophenyl)urea (**4j**): Light yellow solid; yield 75%, m.p.229.3–229.8 °C; IR (KBr, cm^{-1}): 3307, 3112, 2958, 2849, 1650, 1578, 1503, 1479, 1350, 1268, 1209, 1027, 836, 801, 751; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.71 (s, 2H), 7.83 (d, 2H, J = 9.0 Hz), 7.53 (d, 2H, J = 2.5 Hz), 7.33 (dd, 2H, J = 9.0, 3.0Hz), 3.84 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.0, 152.6, 141.0, 126.4, 126.2, 121.6, 121.5, 108.9, 108.8, 56.1. HRMS (ESI) exact mass calcd for $(C_{15}H_{14}N_4O_7Na)^+$ requires *m/z* 385.0760, found *m/z* 385.0734.

Crystal structure determination and refinement

A single crystal having dimension of 0.25 × 0.21 × 0.15 mm was mounted on a glass fibre. All measurements were made on a Bruker Smart Apex diffractometer with graphite monochromated MoKα (λ = 0.71073 Å) radiation with an ω-scan technique. The data were collected at 298(2) K to maximum θ value of 25.49°. Determination of the crystal class, orientation matrix, and cell dimensions were performed according to the established procedures. Lorentz polarisation and absorption corrections were applied. Absorption corrections were applied by fitting a pseudoellipsoid to the ψ-scan data of selected strong reflections over a range of 2θ angles. The structure was solved by direct method and expanded using Fourier techniques. Most of the non-hydrogen atoms in the crystal structure were located with the direct methods, and subsequent Fourier syntheses were used to derive the remaining non-hydrogen atoms. All of non-hydrogen atoms were refined anisotropically, and all of the hydrogen atoms were held stationary and included in the final stage of full-matrix least-squares refinement based on F^2 using the SHELXS-97 and SHELXL-97 programs[27].

The CIF file has been deposited with the Cambridge Crystallographic Data Centre. Supplementary data are available from the CCDC, on request, quoting the deposition number 906920. NMR spectra of the compounds are available directly from the correspondent.

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