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Graphical Abstract

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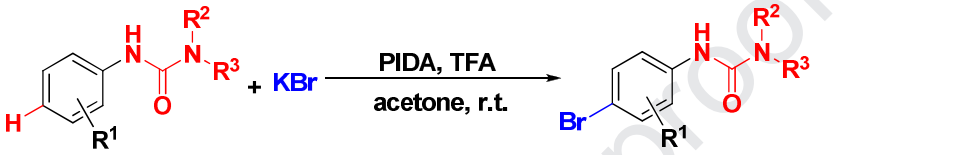

19 examples, up to 86% yield
metal-free, gram scale
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Regioselective Bromination of Aryl Ureas with Phenyliodine(III) Diacetate and Potassium Bromide

Chun-Meng Wang[a,b], Jian-Yao Du[a,b], Jin-Yang Zhang[a] , Kai-Xiang Tang[a] , Tian-Hong Gao[a], Yun-Gen Xu[a,*], Li-Ping Sun[a,*]

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ABSTRACT

An efficient regioselective and operationally simple urea bromination method utilizing PIDA and potassium bromide is reported. This protocol proved to be effective on a broad range of substituted ureas in acetone at room temperature, forming the *p*-brominated compounds in 44–86% yields.

1. Introduction

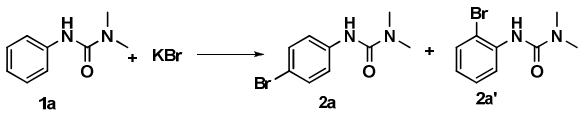
Urea derivatives are an important compounds which are widely used in many roles such as biologically active compounds, pharmaceuticals and agricultural pesticides[1]. Therefore, urea derivatives attract scientists' attention in organic synthesis. Some methods have been established that use ureas as directing groups to introduce aryl groups[2], alkenyl groups[3] and other functional groups[4] to the aryl ring of ureas. However, the direct bromination of ureas is still limited[5].

Aryl bromides are versatile structural motifs since they have been widely utilized as important precursors for the synthesis of pharmaceuticals and biologically active compounds. Furthermore, brominated arenes and heteroarenes can be found in a variety of drugs, pesticides and explosives. The classic method for the direct bromination of aromatic rings employs Br_2, which is a volatile, toxic, corrosive and polluting agent[6]. To overcome these problems, in recent years, a series of transition-metal-catalyzed C-H halogenation are reported with some halogen source such as NBS[7] and bromate[8]. However, for the transition-metal-catalyzed reactions, they suffered from the use of expensive metal catalysis which hamper the application in a way. In contrast, the metal-free catalyzed methods was able to avoid these problems. Though some protocols using oxidants with bromate have been established such as H_2O_2[9], Oxone[10], $K_2S_2O_8$[11] and others[12], PIDA-mediated the C-Br bond formation of ureas with KBr has not been reported. Herein, we report the regioselective *para*-bromination of ureas, which proceeds under convenient conditions in the presence of PIDA with KBr utilized as the halogen source.

2. Results and Discussion

We commenced our investigation by selecting 1,1-dimethyl-3-phenylurea (**1a**) as a model compound for the optimization of the reaction conditions (Table 1). At the outset of the study, KBr was chosen as the halogen source and TFA was added as the additive. In the set of oxidants screening, only

Table 1. Optimization of reaction conditions

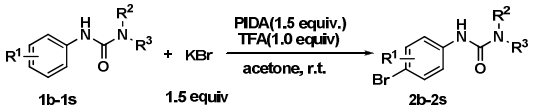


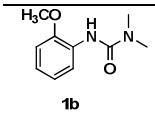
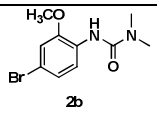
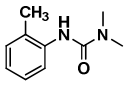
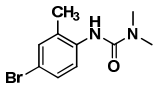
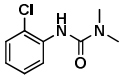
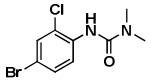
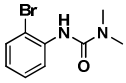
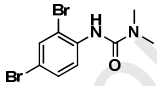
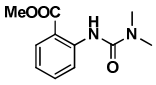
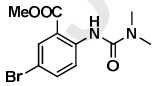
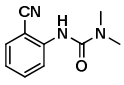
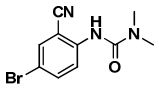
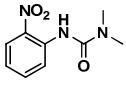
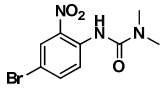
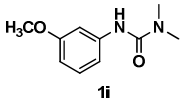
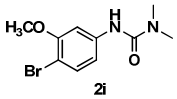
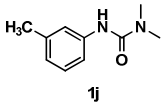
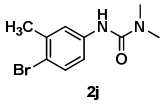
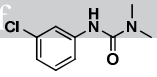
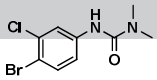
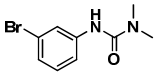
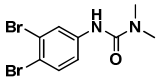
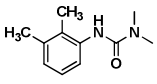
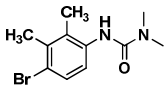
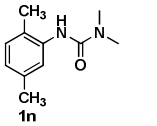
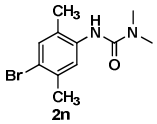
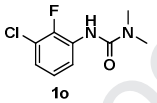
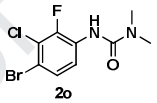
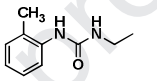
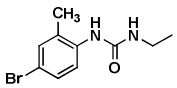
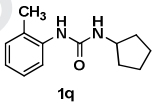
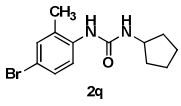
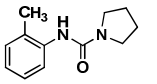
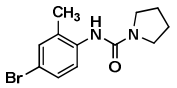
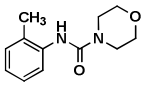
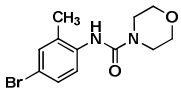
Entry	Oxidant	Additive	Solvent	Yield[b]	
				2a	2a'
1	PIDA	TFA	acetone	64	11
2	PIDA	AcOH	acetone	56	8
3	PIDA	PivOH	acetone	44	9
4	PIDA	*p*-TSA	acetone	34	9
5	PIDA	$BF_3{\cdot}OEt_2$	acetone	25	9
6[c]	PIDA	TFA	acetone	58	12
7[d]	PIDA	TFA	acetone	--	--
8[e]	PIDA	TFA	acetone	48	10
9	PIDA	TFA	DCM	--	--
10	PIDA	TFA	DCE	--	--
11	PIDA	TFA	toluene	--	--
12	PIDA	TFA	THF	53	9
13	PIDA	TFA	DMF	53	8
14	PIDA	TFA	H_2O	50	8

[a]Reaction conditions: 1,1-dimethyl-3-phenylurea (**1a**) (0.18 mmol, 1 equiv), KBr (0.27 mmol, 1.5 equiv), PIDA (0.27 mmol, 1.5 equiv), additive (0.18 mmol, 1 equiv), solvent (3 mL), r.t. [b]Isolated yield. [c]TFA (0.54 mmol, 3 equiv). [d]TFA (0.045 mmol, 0.25 equiv). [e]the temperature of reaction was 56 °C.

PIDA gave the brominated product in comparison to DDQ, CAN, Oxone and $K_2S_2O_8$. Sequentially, additives such as AcOH, PivOH, *p*-TSA and $BF_3{\cdot}OEt_2$ were used and no better yield was obtained (Table 1, entries 1–5). Then the loading of TFA was changed and obviously improved yield was not found (Table 1, entries 6 and 7). Next the solvent screening showed that acetone could get the best result among DCM, DCE, toluene, THF, DMF and H_2O tested (Table 1, entries 9–14). Finally, the standard reaction conditions for the synthesis was identified as follows: 1.5 equiv. KBr as the halogen source, 1.5 equiv. PIDA as the oxidant, 1 equiv. TFA as the additive and acetone as the solvent under an air atmosphere at room temperature.

Table 2. Substrate Scope of the Bromination.

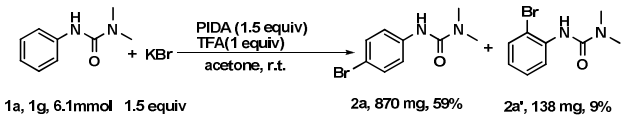


Substrate	Product	Yield
 1b	 2b	67
 1c	 2c	82
 1d	 2d	82
 1e	 2e	72
 1f	 2f	85
 1g	 2g	69
 1h	 2h	44
 1i	 2i	52
 1j	 2j	70
 1k	 2k	82
 1l	 2l	64
 1m	 2m	86
 1n	 2n	58
 1o	 2o	65
 1p	 2p	67
 1q	 2q	54
 1r	 2r	58
 1s	 2s	72

With the optimized reaction conditions established, we set out to investigate the scope and functional groups compatibility of this protocol (Table 2). To our satisfaction, substrates containing all kinds of functional groups including electron-withdrawing and electron-donating groups work well to provide products (**2b-2l**) in moderate to good yields (44-85%). Disubstituted substrates bearing methyl groups at diverse positions also provided the products (**2m** and **2n**) in good yields (86% and 58%). Besides, a disubstituted substrate bearing fluoro and chloro groups at the 4- and 3-positions also provided the product (**2o**) in 65% yield.

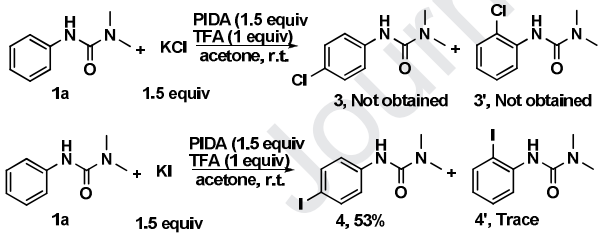
Next, we investigated the application of ureas equipped with different alkyl substituents on the nitrogen atom. Changing the dimethylamino moiety to secondary cyclic diamines had no influence on the reaction, and piperidine and morpholine urea derivatives reacted excellently to provide **2r** and **2s** in 58% and 72% yields. At the same time, ureas which were constituted by primary amines were also studied. We found that *N*-ethyl and *N*-cyclopentyl ureas could be transformed smoothly to **2p** and **2q** under the bromination conditions.

To fully demonstrate the synthetic potential of the present method, we tried the bromination of **1a** at the gram-scale (Scheme 1). To our delight, brominated product **2a** and **2a'** were obtained in 59% and 9% yields, respectively. Besides, the sort of halogen source was taken into consideration (Scheme 2). Unfortunately, when the KBr was replaced by KCl, *para*-chlorination product **3** was not obtained. To our delight, we got *para*-iodination product **4** in a moderate yield by using KI as the halogen source.



Scheme 1. Gram scale reaction

To gain more insight into the reaction mechanism, a series of control experiments were carried out. 2,2,6,6-tetra-methylpiperidine *N*-oxide (TEMPO) was added in the reaction as the radical quencher to investigate whether these reactions proceeded via radical pathways (Scheme 3, a). With 1.5 equiv. of TEMPO, the yield of the desired products was not decreased obviously. This result suggests that the reactions may not follow a radical pathway. Next, when phenyl dimethylcarbamate **5** was used as a substrate, the bromination products were not obtained (Scheme 3, b), indicating that the NH group of ureas is indispensable for the regioselective bromination. Besides, the *para*-bromination of acetanilide could also be obtained in moderate yield (Scheme 3, c). Since Br^- could also be oxidized to Br^+, in order to verify whether the reaction was performed via electrophilic substitution, bromine was used as the halogen source and the result showed that no bromination occurred at room temperature (Scheme 3, d). Based on this result, another common bromination reagent NBS was used, and the *para*-bromination product can only be obtained in 27% yield (Scheme 3, e).

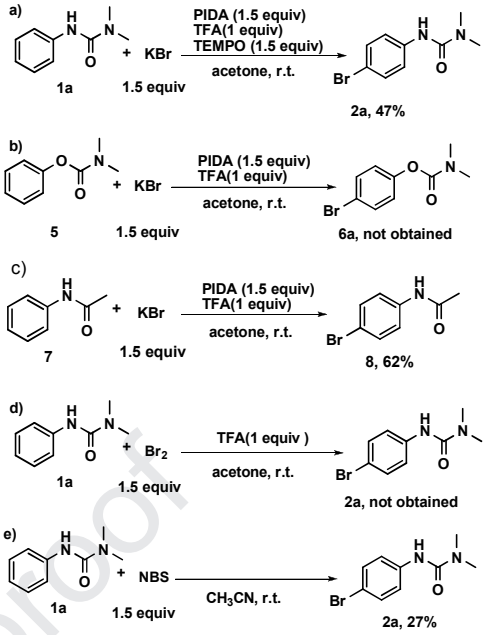


Scheme 2. The changes of the halogen sources

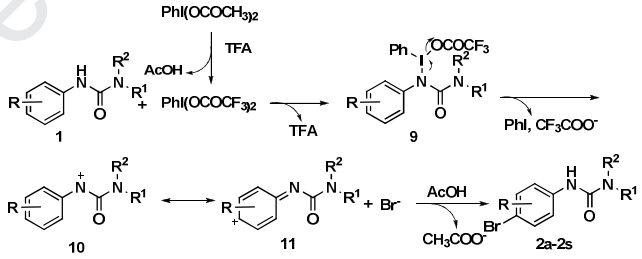
Although details about the mechanism remained to be ascertained, on the basis of these observations and earlier precedents[13], a plausible mechanism for this reaction was depicted in Scheme 4. As shown in the scheme, firstly, a nucleophilic attack of urea 1 forms the iodonium intermediate **9**. Then cleavage of the N–I bond furnishes iodobenzene and a nitrenium ion **10**, which is stabilized by the charge delocalization on the phenyl ring. Finally, the extensively charge delocalized intermediate **11** reacted with Br^- to give the *para*-brominated products **2**.

3. Conclusion

In summary, a novel and efficient protocol of metal-free aryl C–H bond bromination of ureas has been developed, in which simple and readily available bromide salt is employed as the bromine source. This convenient condition makes this protocol become easy to handle and practical. Besides, the present method tolerates a variety of functional groups and allows the synthesis of diverse 4-brominated urea derivatives in moderate to excellent yields. This method represents an important extension of the chemistry of urea compounds and these products can offer a platform for further functionalization.



Scheme 3. Control experiments



Scheme 4. Proposed mechanism

4. Experimental

4.1. General

Unless otherwise noted, all chemical reagents were commercially purchased and used without further purification. Analytical TLC was carried out by using pre-254 coated plates and visualized with UV light. Melting points (uncorrected) were determined on a RY-1 MP apparatus. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-300 spectrometer at 300 MHz and 75 MHz, respectively. Chemical shifts are reported in δ (ppm), relative to the internal standard of TMS. The signals observed are described as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiple). Coupling constants are reported as J values in units of Hz. Mass spectrometry was obtained by using a Q-TOF high-resolution mass spectrometer. Flash column chromatography was performed over silica gel 200-300 m.

4.2. General Procedure for the Bromination

To a mixture of ureas 1(0.2 mmol, 1 equiv), KBr (0.3 mmol, 1.5 equiv) and PIDA (0.3 mmol, 1.5 equiv) in acetone (2 mL) was added TFA (0.2 mmol, 1 equiv), then, the resultant mixture was stirred at room temperature for 0.5 to 6 hours. Then the mixture was treated with saturated $NaHCO_3$ (10 mL) solution and extracted with DCM (3 × 10 mL). The combined organic phase was dried over Na_2SO_4 and then evaporated of the solvent under reduced pressure. Next, purification of the crude residue

by flash column chromatography on silica gel afforded the desired products **2**.

3-(4-bromophenyl)-1,1-dimethylurea (2a): Eluent: dichloromethane: ethyl acetate (120:1). White solid, 28 mg, yield: 64%. mp: 170-172 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.38 (s, 1H), 3.03 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5, 138.4, 131.7, 121.5, 115.3, 36.4. HRMS (ESI-QTOF): m/z $(M + H)^+$ calcd for $C_9H_{12}BrN_2O$: 243.0133; found: 243.0130.

3-(2-bromophenyl)-1,1-dimethylurea (2a'): White solid, 5 mg, yield: 11%. mp: 89-90 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.01 (s, 1H), 6.85-6.91 (m, 1H), 3.03 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.0, 137.1, 131.9, 128.3, 123.4, 120.9, 113.0, 36.4. HRMS (ESI-QTOF): m/z $(M + H)^+$ calcd for $C_9H_{12}BrN_2O$: 243.0133; found: 243.0140.

3-(4-bromo-2-methoxyphenyl)-1,1-dimethylurea (2b): Eluent: dichloromethane: petroleum ether (4:1). Purple oil, 36 mg, yield: 67%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.7 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 1H), 7.0 (s, 1H), 6.97 (s, 1H), 3.87 (s, 3H), 3.05 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.2, 148.2, 128.3, 123.8, 119.8, 113.8, 113.1, 56.0, 36.3. HRMS (ESI-QTOF): m/z $(M + H)^+$ calcd for $C10H_{14}BrN_2O_2$: 273.0239; found: 273.0233.

3-(4-bromo-2-methylphenyl)-1,1-dimethylurea (2c): Eluent: dichloromethane: petroleum ether (15:1). White solid, 42 mg, yield: 82%. mp: 90-92 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, *J* = 9.2 Hz, 1H), 7.28 (s, 2H), 6.14 (s, 1H), 3.02 (s, 6H), 2.02 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.6, 136.4, 132.8, 130.5, 129.5, 124.0, 116.3, 36.4, 17.6. HRMS (ESI-QTOF): m/z $(M + H)^+$ calcd for $C_{10}H_{14}BrN_2O$: 257.0290; found: 257.0283.

3-(4-bromo-2-chlorophenyl)-1,1-dimethylurea (2d): Eluent: dichloromethane: petroleum ether (100:1). White solid, 45 mg, yield: 82%. mp: 74-76 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.9 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.35 (dd, *J* = 2.0, 8.8 Hz, 1H), 6.95 (s, 1H), 3.07 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.6, 135.3, 131.0, 130.7, 122.6, 121.7, 114.2, 36.4. HRMS (ESI-QTOF): m/z $(M + H)^+$ calcd for $C_9H_{11}BrClN_2O$: 276.9743; found: 276.9738.

3-(2,4-dibromophenyl)-1,1-dimethylurea (2e): Eluent: dichloromethane: petroleum ether (8:1).White solid, 47 mg, yield: 72%. mp: 80-81 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.9 Hz, 1H), 7.62 (d, *J* = 1.3 Hz, 1H), 7.37 (dd, *J* = 1.5, 8.9 Hz, 1H), 6.96 (s, 1H), 3.06 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.7, 136.4, 133.9, 131.3, 121.8, 114.7, 113.2, 36.4. HRMS (ESI-QTOF): m/z $(M + H)^+$ calcd for $C_9H_{11}Br_2N_2O$: 322.9218; found: 322.9212.

methyl 5-bromo-2-(3,3-dimethylureido)benzoate (2f): Eluent: dichloromethane: petroleum ether (15:1). White solid, 51 mg, yield: 85%. mp: 143-144 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.62 (s, 1H), 8.57 (d, *J* = 9.2 Hz, 1H), 8.13 (d, *J* = 2.2 Hz, 1H), 7.60 (dd, *J* = 2.2, 9.2 Hz, 1H), 3.94 (s, 1H), 3.11 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 155.2, 142.7, 137.2, 133.0, 121.1, 115.2, 112.6, 52.4, 36.3. HRMS (ESI-QTOF): m/z $(M + H)^+$ calcd for $C_{11}H_{14}BrN_2O_3$: 301.0188; found: 301.0185.

3-(4-bromo-2-cyanophenyl)-1,1-dimethylurea (2g): Eluent: dichloromethane. White solid, 37 mg, yield: 69%. mp: 118-120 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (d, *J* = 9.6 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.59 (s, 1H), 6.96 (s, 1H), 3.06 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0, 141.6, 137.2, 133.7, 121.7, 115.6, 114.2, 102.4, 36.5. HRMS (ESI-QTOF): m/z $(M + H)^+$ calcd for $C_{10}H_{11}BrN_3O$: 268.0085; found: 268.0078.

3-(4-bromo-2-nitrophenyl)-1,1-dimethylurea (2h): Eluent: dichloromethane: petroleum ether (15:1). Yellow solid, 25 mg, yield: 44%, mp: 103-105 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$): δ

10.17 (s, 1H), 8.68 (d, *J* = 9.2 Hz, 1H), 8.37 (d, *J* = 1.5 Hz, 1H), 7.70 (dd, *J* = 2.2, 9.2 Hz, 1H), 3.13 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.3, 138.8, 136.6, 135.7, 128.0, 122.8, 113.1, 36.5. HRMS (ESI-QTOF): m/z $(M + H)^+$ calcd for $C_9H_{10}BrN_3O_3$: 287.9984; found:287.9977.

3-(4-bromo-3-methoxyphenyl)-1,1-dimethylurea (2i): Eluent: dichloromethane: petroleum ether (10:1). White solid, 28 mg, yield: 52%. mp: 140-142 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (s, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 6.64 (dd, *J* = 1.8, 8.4 Hz, 1H), 6.51 (s, 1H), 3.87 (s, 1H), 3.03 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.0, 155.4, 140.0, 112.4, 112.3, 104.1, 56.2, 36.5. HRMS (ESI-QTOF): m/z $(M + H)^+$ calcd for $C_{10}H_{14}BrN_2O_2$: 273.0239; found: 273.0237.

3-(4-bromo-3-methylphenyl)-1,1-dimethylurea (2j): Eluent: dichloromethane: petroleum ether (2:1). White solid, 36 mg, yield: 70%. mp: 149-151 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.6 Hz, 1H), 7.22 (s, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.13 (s, 1H), 2.90 (s, 6H), 2.23 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5, 138.4, 138.2, 132.3, 122.1, 118.8, 117.9, 36.5, 23.0. HRMS (ESI-QTOF): m/z $(M + H)^+$ calcd for $C_{10}H_{14}BrN_2O$: 257.0290; found: 257.0286.

3-(4-bromo-3-chlorophenyl)-1,1-dimethylurea (2k): Eluent: dichloromethane: petroleum ether (15:1). White solid, 45 mg, yield: 82%. mp: 165-167 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.56 (s, 1H), 7.86 (s, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 2.92 (s, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.6, 142.1, 133.7, 133.0, 120.8, 120.0, 112.7, 36.6. HRMS (ESI-QTOF): m/z $(M + H)^+$ calcd for $C_9H_{11}BrClN_2O$: 276.9743; found: 276.9735.

3-(3,4-dibromophenyl)-1,1-dimethylurea (2l): Eluent: dichloromethane: petroleum ether (1:2). White solid, 41 mg, yield: 64%. mp: 175-177 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.23 (t, *J* = 9.2, 7.3 Hz, 1H), 6.44 (s, 1H), 3.00 (s, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.6, 142.0, 133.6, 124.0, 123.6, 120.4, 115.1, 36.6. HRMS (ESI-QTOF): m/z $(M + H)^+$ calcd for $C_9H_{11}Br_2N_2O$: 322.9218; found: 322.9217.

3-(4-bromo-2,3-dimethylphenyl)-1,1-dimethylurea (2m): Eluent: dichloromethane: ethyl acetate (120:1). White solid, 47 mg, yield: 86%. mp: 182-184 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.6 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 6.00 (s, 1H), 2.89 (s, 6H), 2.26 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 136.4, 136.2, 131.5, 129.9, 123.4, 121.2, 36.5, 20.4, 15.3. HRMS (ESI-QTOF): m/z $(M + H)^+$ calcd for $C_{11}H_{16}BrN_2O$: 271.0466; found: 271.0438.

3-(4-bromo-2,5-dimethylphenyl)-1,1-dimethylurea (2n): Eluent: dichloromethane: petroleum ether (15:1). White solid, 31 mg, yield: 58%. mp: 112-113 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.30 (s, 1H), 6.08 (s, 1H), 3.03 (s, 6H), 2.34 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7, 136.3, 135.9, 133.3, 127.6, 124.6, 118.9, 36.4, 22.6, 17.0. HRMS (ESI-QTOF): m/z $(M + H)^+$ calcd for $C_{11}H_{16}BrN_2O$: 271.0466; found: 271.0441.

3-(4-bromo-3-chloro-2-fluorophenyl)-1,1-dimethylurea (2o): Eluent: dichloromethane: petroleum ether (15:1). White solid, 38 mg, yield: 65%. mp: 126-128 ^{o}C. ^{1}H NMR (300 MHz,

$CDCl_3$): δ 8.04 (t, *J* = 8.8, 8.2 Hz, 1H), 7.36 (dd, *J* = 1.6, 8.8 Hz, 1H), 6.55 (s, 1H), 3.06 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.5, 148.6(d, *J* = 240 Hz), 128.3, 128.2, 119.8, 115.1, 36.5. ^{19}F NMR (282 MHz, $CDCl_3$): δ -127.39—127.43(m). HRMS (ESI-QTOF): m/z $(M + H)^+$ calcd for $C_9H_{10}BrClFN_2O$: 294.9649; found: 294.9648.

1-(4-bromo-2-methylphenyl)-3-ethylurea (2p): Eluent: dichloromethane: ethyl acetate (80:1). White solid, 34 mg, yield: 67%. mp: 184-185 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 7.78 (d, *J* = 8.7 Hz, 1H), 7.59 (s, 1H), 7.18 (d, *J* = 8.9 Hz, 1H), 6.52 (s, 1H), 3.06-3.00 (m, 2H), 2.10 (s, 3H), 0.99 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.5, 138.3, 132.7, 129.5, 129.1, 122.1, 113.5, 34.4, 18.0, 15.8. HRMS (ESI-QTOF): m/z $(M + H)^+$ calcd for $C_{10}H_{14}BrN_2O$: 257.0290; found: 257.0281.

1-(4-bromo-2-methylphenyl)-3-cyclopentylurea (2q): Eluent: dichloromethane. White solid, 32 mg, yield: 54%. mp: 128-130 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 7.88 (d, *J* = 8.3 Hz, 1H), 7.54 (s, 1H), 7.30 (s, 1H), 7.22 (d, *J* = 6.8 Hz, 1H), 6.67 (d, *J* = 5.3 Hz, 1H), 3.90 (d, *J* = 5.5 Hz, 1H), 2.49 (s, 1H), 1.81 (s, 2H), 1.54-1.59(m, 4H), 1.35 (s, 2H),. ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.1, 138.3, 132.7, 129.1, 128.9, 121.6, 113.2, 51.3, 33.3, 23.6, 18.0. HRMS (ESI-QTOF): m/z $(M + H)^+$ calcd for $C_{13}H_{18}BrN_2O$: 297.0603; found: 297.0595.

N-(4-bromo-2-methylphenyl)pyrrolidine-1-carboxamide (2r): Eluent: dichloromethane. White solid, 33 mg, yield: 58%. mp: 135-137 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.26(s, 1H), 5.96 (s, 1H), 3.44 (s, 4H), 2.09 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.7, 136.4, 132.7, 129.6, 123.3, 115.8, 45.8, 25.6, 17.5. HRMS (ESI-QTOF): m/z $(M + H)^+$ calcd for $C_{12}H_{16}BrN_2O$: 283.0446; found: 283.0440.

N-(4-bromo-2-methylphenyl)morpholine-4-carboxamide (2s): Eluent: dichloromethane. White solid, 43 mg, yield: 72%. mp: 160-162 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.7 Hz, 1H), 7.31 (s, 1H), 7.29 (d, *J* = 8.7 Hz, 1H), 6.16(s, 1H), 3.74 (t, *J* = 4.6, 4.8 Hz, 4H), 3.46 (t, *J* = 4.6, 4.8 Hz, 4H), 2.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.1, 135.9, 133.0, 131.3, 129.7, 117.1, 66.5, 44.3, 17.6. HRMS (ESI-QTOF): m/z $(M + H)^+$ calcd for $C_{12}H_{16}BrN_2O_2$: 299.0395; found: 299.0392.

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Regioselective Bromination of Aryl Ureas with Phenyliodine(III) Diacetate and Potassium Bromide

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A novel and efficient protocol of metal-free aryl C–H bond bromination of ureas has been developed, in which simple and readily available bromide salt is employed as the bromine source. This convenient conditions make this protocol very easy to handle and practical. Besides, the present method tolerates a variety of functional groups and allows the synthesis of diverse 4-brominated urea derivatives in moderate to excellent yields.