Synthesis X. Min et al. Paper

One-Pot Assembly towards ω-Substituted Arylbiurets from Aromatic Amines, Potassium Cyanate, and Glacial Acetic Acid

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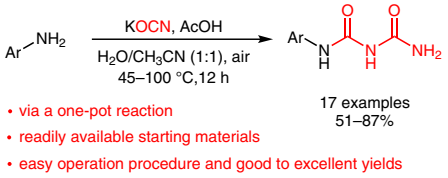

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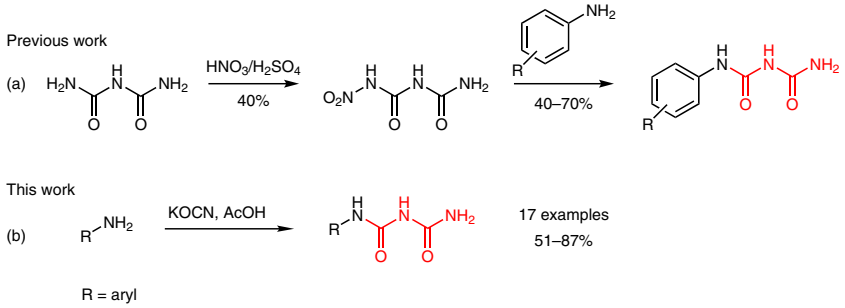
Abstract A novel, simple, and highly efficient method has been designed for the synthesis of ω-substituted arylbiurets in a one-pot reaction. The primary features of this protocol include readily available starting materials, an easy work-up procedure, and yields of 51 to 87%. ω-Substituted arylbiurets can be selectively prepared with an excess of potassium cyanate (KOCN). However, use of an excess of glacial acetic acid (AcOH) switches the reaction towards the formation of N-monosubstituted urea.

Key words ω-substituted biuret, N-monosubstituted urea, potassium cyanate, dicyanic acid, selective reactions

Over the past several decades, ω-substituted arylbiurets have attracted considerable attention because of their importance in organic synthesis and material sciences. In particular, arylated biurets are of much value because of their unique and excellent properties such as their tendency to form organic supramolecular networks with highly efficient energy transfer,[1] active photoresponsive compounds,[2] and nanofilm structures.[3] Moreover, these types of compounds have been widely used as key intermediates for the synthesis of cyanuric acid, derivatives of which are important compounds in medicinal and synthetic chemistry.[4]

Very few methods are known for the synthesis of ω-substituted arylbiurets. The most common route involves a two-step preparation (nitration followed by reaction with aniline),[5] starting from the unsubstituted biurets (Scheme 1, a).[1–3,6] However, the first nitration step requires the presence of large amounts of concentrated H_2SO_4 and HNO_3.[7] Given the use of strong acids and the excess of strong base needed for the following work-up procedure, this route cannot meet the requirements of green synthesis. Furthermore, because N-nitro compounds are potentially explosive, this procedure must be carried out behind a safety shield.[8] In addition, the efficiency of the conversion for the entire reaction process is not satisfactory, with maximum yields of 40%.[9] Furthermore, this route is only suitable for condensation reactions with partially substituted aniline, thereby restricting the range of potential substrates. Therefore, a more effective protocol for the synthesis of ω-substituted arylbiurets through an easy procedure with good yield is highly desirable.

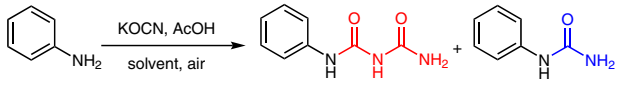


Scheme 1 Synthetic approach to ω-substituted arylbiuret derivatives

It is well known that KOCN can be converted into cyanate acid with excess acid in aqueous solution. If KOCN reacts with amines, N-monosubstituted ureas could be generated.[10] In addition, according to Davis and Blanchard,[11] HOCN dimerizes in solution to form dicyanic acid, with one molecule of HOCN functioning in the usual manner in urea formation and the second as an ammonia derivative. Inspired by these two observations, we hypothesized that the use of dicyanic acid to react with amine may lead to ω-substituted biuret. Here, we report an efficient and simple method for the preparation of ω-substituted arylbiurets (Scheme 1, b). The key features of the reaction include readily available and safer starting materials, easy operational procedure, and good to excellent yields.

Initially, this investigation was carried out by using aniline (**1a**) as a substrate to optimize the reactions conditions, including the amount of reagents, temperature, solvent, and acid type (Table 1). In our screening for the optimal amount of KOCN and AcOH, we observed that the yield of **2a** was not significantly increased when only the amount of KOCN was increased. To our surprise, the yield of **2a** unexpectedly decreased when the amounts of both KOCN and AcOH were increased (Table 1, entries 1–3).

Table 1 Optimization of the Reaction Conditions[a]



1a **2a** **3a**

Entry	Solvent	Temp (°C)	Time (h)	**2a** (%)	**3a** (%)
1	H_2O/CH_3CN (1:1)	50	0.5	63	33
2[c]	H_2O/CH_3CN (1:1)	50	0.5	64	31
3[d]	H_2O/CH_3CN (1:1)	50	0.5	42	55
4	H_2O/CH_3CN (1:1)	40	12	57	40
5	H_2O/CH_3CN (1:1)	60	12	70	24
6	H_2O/CH_3CN (1:1)	70	12	74	20
7	H_2O/CH_3CN (1:1)	80	12	76	16
8	H_2O/CH_3CN (1:1)	90	12	70	25
9	H_2O	80	12	30	67
10	H_2O/DMF (1:1)	80	12	61	36
11	H_2O/DMSO (1:1)	80	12	74	23
12[e]	H_2O/CH_3CN (1:1)	80	12	65	31
13[f]	H_2O/CH_3CN (1:1)	80	12	67	32
14[g]	H_2O/AcOH	45	12	–	80
15[h]	H_2O/CH_3CN (1:1)	45	12	–	–

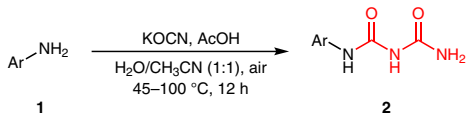
[a] Reaction conditions: phenylamine (**1a**; 102 mg, 1.1 mmol), KOCN (5.28 mmol), H_2O (6 mL), CH_3CN (6 mL), 80 C add glacial AcOH (2.64 mmol), after 1 h a second portion of glacial AcOH (2.64 mmol) was added.
[b] Yield of isolated product.
[c] Reaction conditions: KOCN (777 mg, 9.6 mmol), glacial AcOH (2.64 mmol), after 1 h a second portion of glacial AcOH (2.64 mmol) was added.
[d] Reaction conditions: KOCN (712 mg, 8.8 mmol), glacial AcOH (264 mg, 4.4 mmol), after 1 h a second portion of glacial AcOH (264 mg, 4.4 mmol) was added.
[e] HCl instead of AcOH.
[f] TsOH instead of AcOH.
[g] H_2O (6 mL) and glacial AcOH (87 mmol) as solvent.
[h] NaOH (120 mg, 3 mmol) was added.

The influence of the reaction temperature was then investigated. The yields increased gradually as the temperature increased, but the positive effect was not obvious if the temperature was increased to more than 80 °C (Table 1, entries 4–8). Solvent effects were then studied. To keep the reaction system homogeneous and to avoid reaction with the HOCN, the solvent should be carefully chosen to be miscible with water and must not contain hydroxyl, amino, or thiol groups.[12] After careful comparison, we selected the mixture of water and acetonitrile (1:1) as our reaction medium. The use of water alone lowered the yield to 30%, but the mixture with two other polar aprotic solvents, including DMF and DMSO, gave the corresponding biuret in 61% and 74% yield, respectively (entries 9–11). Although the addition of DMF and DMSO made the product distribution more favorable toward **2a** instead of **3a** (entries 9–11), the acetonitrile–water mixture was finally chosen because of its slightly better effect (entry 7 vs. entries 9–11). Next, we examined the type of acid used (entries 12 and 13). HCl and TsOH gave almost identical results, with yields of 65% and 67%, respectively. Therefore, of the several acids investigated, AcOH appeared to be optimal, because of the weaker acidity, which met the pH requirements of this system.[13] However, if AcOH was present in excess, no desired **2a** was isolated (entry 14). In contrast, this kind of reaction also failed in the presence of NaOH, indicating the possible involvement of cyanic acid in this reaction (entry 15). All of the above reactions were performed under air without protection from an N_2 atmosphere.

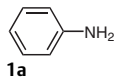
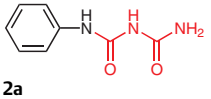
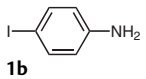
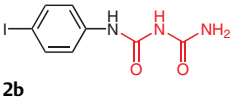
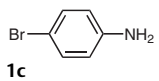
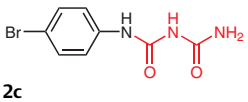
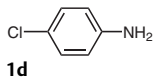
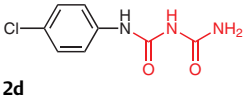
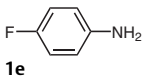
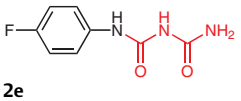
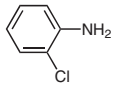
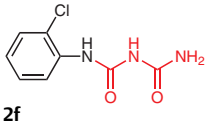
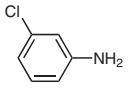
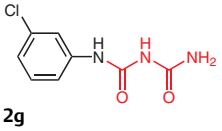
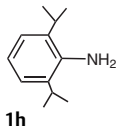
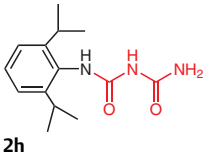
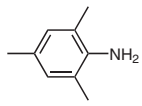
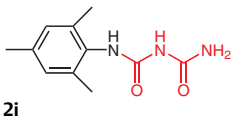
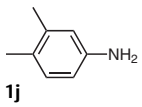
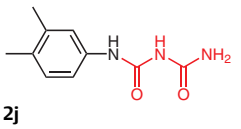
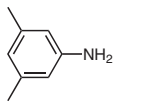
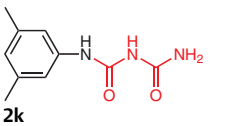
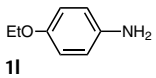
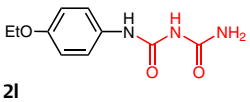
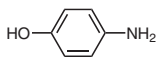
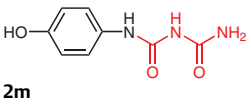
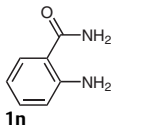
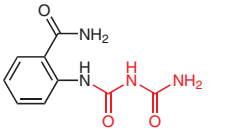
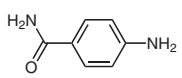
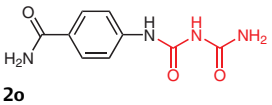
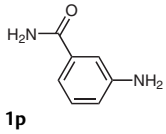
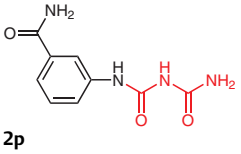
With the optimal conditions in hand, we investigated the versatility of this methodology by using different aromatic amines. A collection of ω-substituted arylbiurets was easily prepared in good to high yields as shown in Table 2. When the reaction of **1a** was conducted under the optimized conditions, **2a** was obtained in 76% yield (entry 1). A series of halogenated anilines was then studied. Whereas the yields of **2b**, **2f**, and **2g** were all greater than 80% (entries 2, 6, and 7), the yields of **2c**, **2d** and **2e** were not ideal at first (ca. 60%) because of incomplete conversion. When the reaction temperature was reduced to 70 °C and the amounts of both KOCN and AcOH were increased, satisfactory yields were obtained (83, 86, and 82% for **2c**, **2d** and **2e**, respectively, entries 3–5). Alkyl substituted anilines **1h–k** were conducive to the occurrence of this reaction, and the products **2h–j** were obtained in excellent yield of more than 80%, with the exception of **2k**, for which a somewhat diminished yield was obtained (69%) (entries 8–11). Surprisingly, **1h** and **1i** showed better selectivity and only afforded ω-substituted biuret without simultaneously obtaining N-monosubstituted ureas. Sterically demanding aniline with 2,6-diisopropyl (**1h**) underwent the reaction in high yield,

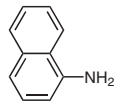
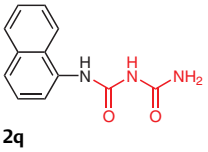
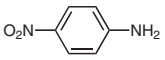
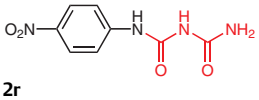
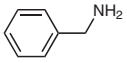
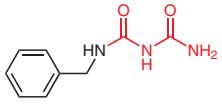
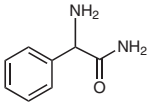
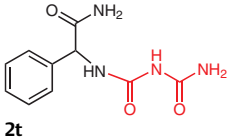
indicating that no specific stereo effects were observed in these transformations (entry 8). As the electron-donating ability of the anilines increases, a decrease in the yields for **2l** and **2m** were observed (41 and 42% at 70 and 80 °C, respectively). The yields could be slightly improved to 51 and 55%, respectively, when the amount of KOCN and AcOH were reduced and the temperature was increased to 100 °C (entries 12 and 13). When an electron-withdrawing group such as a carbamyl on the phenyl was present, as in **1n–p**, the reaction did not occur when the reaction temperature exceeded 60 °C for **1n** and **1o**. When the reaction temperature was reduced to 45 °C while the amounts of KOCN and AcOH were increased, the yields of ω-substituted biuret increased to 84 and 76%, respectively. For compound **1p**, the influence of the electron-withdrawing group on the aniline is small, so that the strong nucleophilic ability of the amino group is maintained and the ω-substituted biuret compound can be obtained at relatively high temperatures (entries 14–16). The reaction also proceeded well with naphthylamine **1q** (entry 17). For compound **1r**, with strong electron-withdrawing groups, such reactions did not occur (entry 18). This reaction did not proceed with aliphatic amines or benzyl amines under the same reaction conditions. When phenylglycinamide (**1s**) and benzyl amine (**1t**) were subjected to a mixture of KOCN and AcOH, no arylbiurets were isolated; instead, only N-monosubstituted ureas **3s** or **3t**, respectively, were obtained (entries 19 and 20). Given the stronger nucleophilic nature of the aliphatic amines, they probably reacted fast with cyanic acid to give N-monosubstituted urea before the resulting dicyanic acid was formed.

Table 2 Substrate Scope[a]



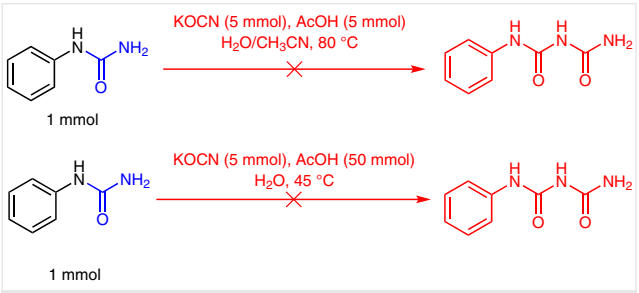
1 2

Entry	Substrate	Product	Yield (%)[b]
1	 **1a**	 **2a**	76
2	 **1b**	 **2b**	83
3[c]	 **1c**	 **2c**	83
4[c]	 **1d**	 **2d**	86
5[c]	 **1e**	 **2e**	82
6	 **1f**	 **2f**	85
7	 **1g**	 **2g**	81
8	 **1h**	 **2h**	86
9	 **1i**	 **2i**	87
10	 **1j**	 **2j**	80
11	 **1k**	 **2k**	69
12[d]	 **1l**	 **2l**	51
13[d]	 **1m**	 **2m**	55
14[e]	 **1n**	 **2n**	84
15[e]	 **1o**	 **2o**	76
16[c]	 **1p**	 **2p**	75

Entry	Substrate	Product	Yield (%)[b]
17	 **1q**	 **2q**	86
18	 **1r**	 **2r**	0
19	 **1s**	 **2s**	0
20	 **1t**	 **2t**	0

[a] Reaction conditions: **1** (1.1 mmol), KOCN (5.28 mmol), H_2O (6 mL), CH_3CN (6 mL), upon reaching 80 °C, glacial AcOH (2.64 mmol) added, after 1 h a second portion of glacial AcOH (2.64 mmol) was added, 12 h.
[b] Isolated yield after chromatography.
[c] Reaction conditions: **1** (1.1 mmol), KOCN (7.92 mmol), upon reaching 70 °C glacial AcOH (3.96 mmol) added, after 1 h a second portion of glacial AcOH (3.96 mmol) was added, 12 h.
[d] Reaction conditions: **1** (1.1 mmol), KOCN (3.96 mmol), upon reaching 100 °C glacial AcOH (1.98 mmol) added, after 1 h a second portion of glacial AcOH (1.98 mmol) was added, 12 h.
[e] Reaction conditions: **1** (1 mmol), KOCN (8 mmol), upon reaching 45 °C glacial AcOH (8 mmol) was added, 12 h.

Before we moved on to study the reaction mechanism, some additional reactions needed to be performed. As shown above, this type of reaction yields the ω-substituted biuret in the presence of excess potassium cyanate. However, N-monosubstituted urea was obtained with excess AcOH (Table 1, entry 14). This selectivity was further confirmed by some more examples when the reaction was performed in excess AcOH (Scheme 2). Aniline (**1a**), 4-amidinophenol (**1m**), and 2-aminobenzamide (**1n**) all gave the corresponding arylureas selectively: **3a**, **3m**, and **3n**, with electron-neutral (for **3a**), electron-donating (for **3m**), and electron-withdrawing group (for **3n**) on the phenyl ring. Clearly, this reaction is selective, depending on the amount of reagents used. Excess KOCN is a very important factor to obtain biurets when AcOH was used (Scheme 2). In addition, when a control experiment was performed with 1-phenylurea with KOCN in the presence of AcOH, the reaction did not occur (Scheme 3). This provides useful information to show that the arylurea is not an intermediate on the way to the arylbiurets.

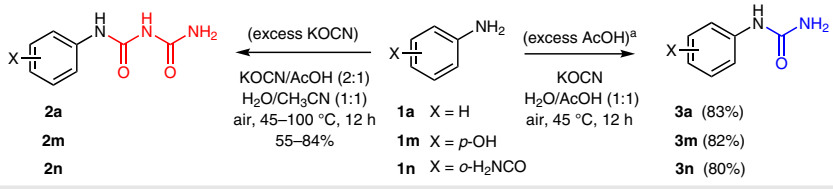


Scheme 3 Control experiment with 1-phenylurea and cyanic acid

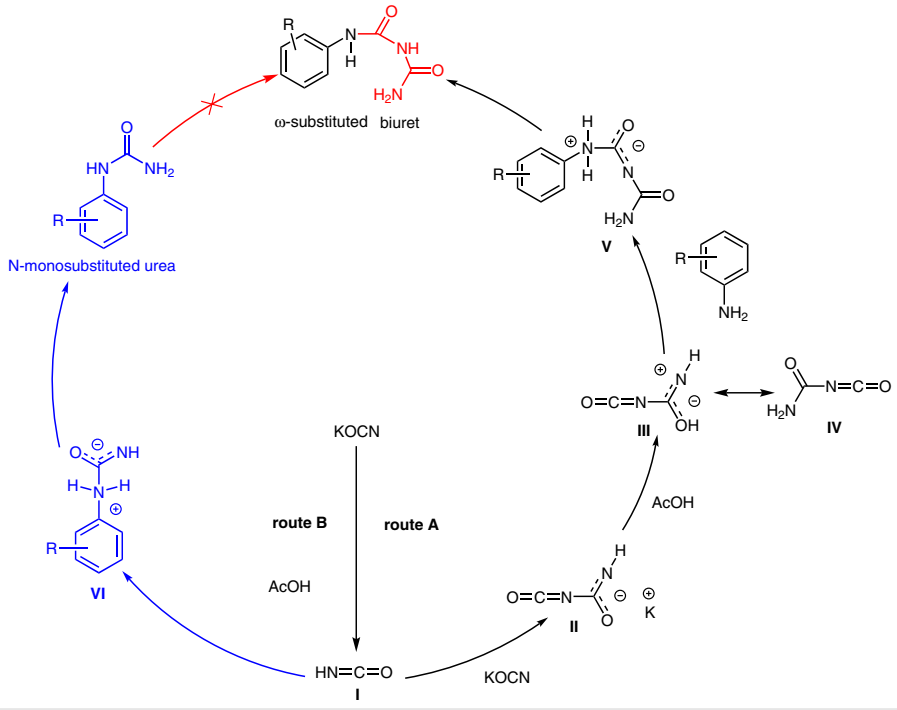
Based on the results of the validation experiments described above, as well as on previous reports, we propose a plausible mechanism for this one-pot reaction, as depicted in Scheme 4.[10,12]

Initially, the reaction of AcOH with an excess of KOCN gives cyanic acid **I**. The negative charge on the nitrogen of KOCN attacks the carbon atom of the carbonyl group to give the adduct **II**. Protonation of this salt produces the zwitterionic intermediate **III**, which can be isomerized to more stable dicyanic **IV**.[10,13] The nitrogen atom attacks the cyanic acid fragment to form a dipolar intermediate **V**. A simple proton-transfer enables the conversion of the zwitterionic intermediate **V** into the uncharged biuret product. This pathway is consistent with our previous results obtained using excessive AcOH. The other path starts with the nucleophilic addition of aniline to the C=O double bond of the HOCN to afford phenylurea, which further attacks another molecule of HOCN to give the biuret. This latter path can be ruled out by the control experiment shown in Scheme 3, because the reaction starting from phenylurea does not yield the biuret.

In conclusion, we have developed a one-pot reaction for the synthesis of arylbiuret using KOCN and AcOH with various substrates. The salient feature of this reaction is the use of the readily available KOCN and AcOH instead of the dan-



Scheme 2 Comparison of the formation of ω-substituted arylbiuret derivatives and arylureas. [a] *Reagents and conditions*: **1** (4 mmol), H_2O (6 mL), glacial AcOH (87 mmol), after reaching 45 °C KOCN (6 mmol) was added; after a further 2 h a second portion of KOCN (3 mmol) was added, 12 h. Yield of isolated product.



Scheme 4 Plausible reaction mechanism

gerous N-nitro compounds, as well as the absence of any expensive catalysts. In addition, this reaction provided some experimental evidence to confirm the possible reaction mechanism.

All reactions were carried out in 25 mL Schlenk type tubes under an air atmosphere, unless otherwise indicated (Schlenk type tubes were used simply as a reaction container). An oil bath was used as heating source. All reagents were purchased from commercial sources and used without further treatment. NMR spectra were recorded with a Bruker Avance II 400 NMR spectrometer (400 MHz for ^{1}H; 100 MHz for ^{13}C); DMSO-d_6 was used as solvent. The chemical shift is reported in parts per million. Data are reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiple; br, broad), coupling constant (hertz, Hz), integration. Melting points were measured with a Beijing Tektronix X-4 digital microscopic melting-point apparatus. High-resolution mass spectra (HRMS) were recorded with a quadrupole analyzer using an ESI source (Agilent TechnologiesG6224A). TLC was performed with commercially prepared 100–400 mesh silica gel GF254 (Qingdao Haiyang Chemcal Co. Ltd.) plates, and visualization was effected at 254 nm.

Synthesis of 2a, 2b, 2f–k, 2p, 2q, 3s, 3t; General Procedure A

A 25 mL Schlenk type tube equipped with a magnetic stir bar was charged with arylamine (1.1 mmol, 1 equiv), KOCN (5.28 mmol, 4.8 equiv), H_2O (6 mL), and CH_3CN (6 mL), and glacial AcOH (2.64 mmol, 2.4 equiv) was added when the temperature reached 80 °C; after an additional 1 h, a second portion of glacial AcOH (2.64 mmol, 2.4 equiv) was added. The mixture was stirred at 80 °C for 10 h, and the progress of the reaction was monitored by TLC. Upon completion of the reaction, the resulting solution was cooled to r.t. and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo. The resulting mixture was purified by chromatography (silica gel, mixture of EtOAc/CH_2Cl_2/EtOH as eluent) to afford the target products.

Synthesis of 2c–e; General Procedure B

A 25 mL Schlenk type tube equipped with a magnetic stir bar was charged with arylamine (1.1 mmol, 1 equiv), KOCN (7.92 mmol, 7.2 equiv), H_2O (6 mL), and CH_3CN (6 mL), and glacial AcOH (3.96 mmol, 3.6 equiv) was added when the temperature reached 70 °C; after an additional 1 h, a second portion of glacial AcOH (3.96 mmol, 3.6 equiv) was added. The mixture was stirred at 70 °C for 10 h and the progress of the reaction was monitored by TLC. Upon completion of the reaction, the resulting solution was cooled to r.t. and the solution was extracted with EtOAc (3 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo. The resulting mixture was purified by chromatography (silica gel, mixture of EtOAc/CH_2Cl_2/EtOH as eluent) to afford the target products.

Synthesis of 2l–m; General Procedure C

A 25 mL Schlenk type tube equipped with a magnetic stir bar was charged with arylamine (1.1 mmol, 1 equiv), KOCN (3.96 mmol, 3.6 equiv), H_2O (6 mL), and CH_3CN (6 mL), and glacial AcOH (1.98 mmol, 1.8 equiv) was added when the temperature reached 100 °C; after an additional 1 h, a second portion of glacial AcOH (1.98 mmol, 1.8 equiv) was added. The mixture was stirred at 100 °C for 10 h, and the progress of the reaction was monitored by TLC. Upon completion of the reaction, the resulting solution was cooled to r.t. and the solution was extracted with EtOAc (3 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated in

vacuo. The resulting mixture was purified by chromatography (silica gel, mixture of EtOAc/CH_2Cl_2/EtOH as eluent) to afford the target products.

Synthesis of 2n–p; General Procedure D

A 25 mL Schlenk type tube equipped with a magnetic stir bar was charged with arylamine (1.1 mmol, 1 equiv), KOCN (8 mmol, 8 equiv), H_2O (6 mL), and CH_3CN (6 mL), and glacial AcOH (8 mmol, 8 equiv) was added when the temperature reached 45 °C; The mixture was stirred at 45 °C for 10 h, and the progress of the reaction was monitored by TLC. Upon completion of the reaction, the resulting solution was cooled to r.t., the liquid was filtered and washed with cold H_2O, and the filtrate was dried to afford the target products.

Synthesis of 3a, 3m, and 3n; General Procedure E

A 25 mL Schlenk type tube equipped with a magnetic stir bar was charged with arylamine (4 mmol, 1 equiv), H_2O (6 mL), and glacial AcOH (87 mmol, 21.7 equiv), and KOCN (6 mmol, 1.5 equiv) was added when the temperature reached 45 °C; after an additional 1 h, a second portion of KOCN (3 mmol, 0.75 equiv) was added. The mixture was stirred at 45 °C for 10 h, and the progress of the reaction was monitored by TLC. Upon completion of the reaction, the resulting solution was cooled to r.t. and the solution was extracted with EtOAc (3 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo. The resulting mixture was purified by chromatography (silica gel, mixture of EtOAc/CH_2Cl_2/EtOH as eluent) to afford the target products.

N-Phenylimidodicarbonic Diamide(2a)[14]

Yield: 150 mg (76%); white powder; mp 184–185 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.82 (s, 1 H), 8.72 (s, 1 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.16 (t, *J* = 7.8 Hz, 2 H), 6.90 (t, *J* = 7.3 Hz, 1 H), 6.65 (br, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.9, 152.4, 138.6, 129.3, 123.4, 119.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_8H_9N_3O_2Na$: 202.0592; found: 202.0590.

N-(Iodophenyl)imidodicarbonic Diamide (2b)[6]

Yield: 277 mg (83%); white powder; mp 296–297 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.05 (s, 1 H), 8.92 (s, 1 H), 7.62 (d, *J* = 8.7 Hz, 2 H), 7.29 (d, *J* = 8.7 Hz, 2 H), 6.72 (br, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.8, 152.3, 138.5, 137.9, 121.7, 86.7.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_8H_7IN_3O_2$: 303.9583; found: 303.9596.

N-(4-Bromophenyl)imidodicarbonic Diamide (2c)[1]

Yield: 234 mg (83%); white powder; mp 293–294 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.09 (s, 1 H), 8.94 (s, 1 H), 7.48 (d, *J* = 8.9 Hz, 2 H), 7.43 (d, *J* = 9.0 Hz, 2 H), 6.72 (br, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.8, 152.3, 138.0, 132.1, 121.4, 115.0.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_8H_7BrN_3O_2$: 255.9722; found: 255.9733.

N-(4-Chlorophenyl)imidodicarbonic Diamide (2d)[15]

Yield: 200 mg (86%); white powder; mp 218–219 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.09 (s, 1 H), 8.94 (s, 1 H), 7.48 (d, *J* = 8.9 Hz, 2 H), 7.35 (d, *J* = 8.8 Hz, 2 H), 6.72 (br, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.8, 152.4, 137.6, 129.2, 127.0, 121.0.

HRMS (ESI): *m*/*z*: [M – H]$^-$ calcd for $C_8H_7ClN_3O_2$: 212.0227; found: 212.0236.

N-(4-Fluorophenyl)imidodicarbonic Diamide (2e)[16]

Yield: 176 mg (82%); white powder; mp 225–226 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.96 (s, 1 H), 8.86 (s, 1 H), 7.48–7.41 (m, 2 H), 7.12 (t, *J* = 8.8 Hz, 2 H), 6.70 (br, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 158.4 (d, *J* = 239.6 Hz), 155.9, 152.5, 134.9 (d, *J* = 2.5 Hz), 121.4 (d, *J* = 8.0 Hz), 115.9 (d, *J* = 22.3 Hz).

HRMS (ESI): *m*/*z*: [M – H]$^-$ calcd for $C_8H_7FN_3O_2$: 196.0522; found: 196.0532.

N-(2-Chlorophenyl)imidodicarbonic Diamide (2f)

Yield: 198 mg (85%); white powder; mp 232–233 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.75 (s, 1 H), 9.27 (s, 1 H), 8.20 (d, *J* = 8.2 Hz, 1 H), 7.48 (d, *J* = 7.9 Hz, 1 H), 7.32 (t, *J* = 7.8 Hz, 1 H), 7.08 (t, *J* = 7.4 Hz, 1 H), 6.45 (br, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.3, 152.1, 135.5, 129.6, 128.1, 124.5, 122.6, 121.7.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_8H_7ClN_3O_2$: 212.0227; found: 212.0237.

N-(3-Chlorophenyl)imidodicarbonic Diamide (2g)

Yield: 176 mg (81%); white powder; mp 208–209 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.13 (s, 1 H), 8.96 (s, 1 H), 7.69 (s, 1 H), 7.31 (t, *J* = 8.0 Hz, 1 H), 7.24 (d, *J* = 8.5 Hz, 1 H), 7.08 (d, *J* = 7.9 Hz, 1 H), 6.71 (br, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.8, 152.4, 140.1, 133.7, 131.0, 123.1, 118.9, 118.0.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_8H_7ClN_3O_2$: 212.0227; found: 212.0236.

N-(2,6-Bis(1-methylethyl)phenyl)imidodicarbonic Diamide (2h)

Yield: 249 mg (86%); white powder; mp 241–242 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.09 (s, 1 H), 8.85 (s, 1 H), 7.23 (d, *J* = 7.6 Hz, 1 H), 7.14 (d, *J* = 7.7 Hz, 2 H), 6.82 (br, 2 H), 3.02 (q, *J* = 6.8 Hz, 2 H), 1.11 (d, *J* = 6.8 Hz, 12 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.2, 154.0, 146.4, 131.7, 128.0, 123.4, 31.1, 28.6.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{14}H_{20}N_3O_2$: 286.1532; found: 286.1529.

N-(2,4,6-Trimethylphenyl)imidodicarbonic Diamide (2i)

Yield: 211 mg (87%); white solid; mp 336–337 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.97 (s, 1 H), 8.82 (s, 1 H), 6.86 (m, 4 H, Ar-H and NH_2), 2.20 (s, 3 H), 2.10 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.1, 153.0, 135.8, 135.2, 131.9, 128.8, 20.9, 18.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{15}N_3O_2Na$: 244.1062; found: 244.1062.

***N*-(3,4-Dimethylphenyl)imidodicarbonic Diamide(2j)**

Yield: 183 mg (80%); white solid; mp 214–215 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.81 (s, 1 H), 8.81 (s, 1 H), 7.21–7.14 (m, 2 H), 7.04 (d, *J* = 8.0 Hz, 1 H), 6.84 (br, 2 H), 2.17 (d, *J* = 10.7 Hz, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.0, 152.3, 137.0, 136.2, 131.2, 130.2, 120.6, 116.9, 19.9, 19.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{13}N_3O_2Na$: 230.0905; found: 230.0904.

***N*-(3,5-Dimethylphenyl)imidodicarbonic Diamide (2k)**

Yield: 157 mg (69%); white powder; mp 213–214 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.85 (s, 1 H), 8.83 (s, 1 H), 6.85 (m, 5 H, Ar-H and NH_2), 2.21 (s, 5 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.0, 152.3, 138.4, 125.0, 117.0, 21.4.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{10}H_{12}N_3O_2$: 206.0930; found: 206.0937.

***N*-(4-Ethoxyphenyl)imidodicarbonic Diamide (2l)**[17]

Yield: 125 mg (51%); brown powder; mp 227–228 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.74 (s, 1 H), 8.77 (s, 1 H), 7.32 (d, *J* = 8.9 Hz, 2 H), 6.86 (br, 4 H, Ar-H, 2 H and NH_2, 2 H), 3.97 (q, *J* = 6.9 Hz, 2 H), 1.30 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.9, 154.9, 152.5, 131.4, 121.2, 115.0, 63.5, 15.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{13}N_3O_3Na$: 246.0855; found: 246.0854.

***N*-(4-Hydroxyphenyl)imidodicarbonic Diamide (2m)**

Yield: 157 mg (55%); red solid; mp 225–226 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.62 (s, 1 H), 9.19 (s, 1 H), 8.72 (s, 1 H), 7.20 (d, *J* = 8.8 Hz, 2 H), 6.88 (br, 2 H), 6.69 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.0, 153.8, 152.5, 129.9, 121.6, 115.7.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_8H_8N_3O_3$: 194.0566; found: 194.0575.

***N*-(2-Amidophenyl)imidodicarbonic Diamide (2n)**

Yield: 187 mg (84%); white solid; mp 246–247 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.95 (s, 1 H), 9.37 (s, 1 H), 8.08 (d, *J* = 8.2 Hz, 1 H), 8.04 (s, 1 H), 7.60 (d, *J* = 7.3 Hz, 1 H), 7.53 (s, 1 H), 7.42 (t, *J* = 7.3 Hz, 1 H), 7.09 (t, *J* = 7.1 Hz, 1 H), 6.81 (br, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.2, 155.3, 152.9, 138.0, 131.3, 128.5, 124.4, 122.7, 122.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{10}N_4O_3Na$: 223.0831; found: 223.0827.

***N*-(4-Amidophenyl)imidodicarbonic Diamide (2o)**

Yield: 168 mg (76%); white powder; mp 247–248 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.23 (s, 1 H), 9.01 (s, 1 H), 7.87 (s, 1 H), 7.83 (d, *J* = 8.6 Hz, 2 H), 7.50 (d, *J* = 8.7 Hz, 2 H), 7.23 (s, 1 H), 6.90 (br, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.8, 155.9, 152.4, 141.4, 129.0, 128.9, 118.9, 118.4.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_9H_9N_4O_3$: 221.0675; found: 221.0682.

***N*-(3-Amidophenyl)imidodicarbonic Diamide (2p)**

Yield: 165 mg (76%); white solid; mp 272–273 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.12 (s, 1 H), 8.94 (s, 1 H), 7.94 (s, 1 H), 7.84 (s, 1 H), 7.63 (d, *J* = 8.1 Hz, 1 H), 7.51 (d, *J* = 7.7 Hz, 1 H), 7.34 (d, *J* = 7.7 Hz, 2 H), 6.85 (br, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.0, 152.3, 138.4, 125.0, 117.0, 21.4.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_9H_9N_4O_3$: 221.0675; found: 221.0684.

***N*-1-Naphthalenylimidodicarbonic Diamide (2q)**

Yield: 216 mg (86%); white solid; mp 263–264 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.75 (s, 1 H), 9.20 (s, 1 H), 8.06 (d, *J* = 7.5 Hz, 1 H), 7.97 (t, *J* = 7.9 Hz, 2 H), 7.69 (d, *J* = 8.1 Hz, 1 H), 7.59 (m, 2 H), 7.49 (t, *J* = 7.9 Hz, 1 H), 6.87 (br, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.6, 152.7, 134.0, 133.5, 129.0, 126.7, 126.5, 126.3, 125.9, 124.1, 121.0, 117.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{11}N_3O_2Na$: 252.0749; found: 252.0751.

1-Phenylurea (3a)[12]

Yield: 451 mg (83%); white powder; mp 191–192 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.57 (s, 1 H), 7.39 (d, *J* = 7.7 Hz, 2 H), 7.20 (t, *J* = 7.9 Hz, 2 H), 6.87 (t, *J* = 7.3 Hz, 1 H), 5.86 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.4, 140.9, 129.0, 121.5, 118.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_7H_8N_2ONa$: 159.0534; found: 159.0532.

***N*-(4-Hydroxyphenyl)urea (3m)**[18]

Yield: 498 mg (82%); white solid; mp 287–288 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.91 (s, 1 H), 8.13 (s, 1 H), 7.13 (d, *J* = 8.6 Hz, 2 H), 6.61 (d, *J* = 8.6 Hz, 2 H), 5.63 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.7, 152.3, 132.5, 120.3, 115.4.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_7H_7N_2O_2$: 151.0508; found: 151.0514.

***N*-(2-Aminophenyl)urea (3n)**[19]

Yield: 498 mg (80%); white solid; mp 245–246 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.20 (s, 1 H), 8.25 (d, *J* = 8.4 Hz, 1 H), 8.09 (s, 1 H), 7.63 (d, *J* = 7.7 Hz, 1 H), 7.51 (s, 1 H), 7.35 (t, *J* = 7.8 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1 H), 6.41 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.3, 156.2, 141.6, 131.9, 128.6, 120.4, 120.3, 119.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_8H_9N_3O_2Na$: 202.0592; found: 202.0591.

1-Phenylmethylurea (3s)

Yield: 130 mg (79%); white solid; mp 145–151 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.36–7.28 (m, 2 H), 7.23 (dd, *J* = 14.4, 7.1 Hz, 3 H), 6.40 (t, *J* = 5.8 Hz, 1 H), 5.51 (s, 2 H), 4.18 (d, *J* = 6.1 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.1, 141.3, 128.6, 127.4, 126.9, 43.28.

Phenylureidoacetic Acid Amide (3t)

Yield: 157 mg (74%); white solid; mp 223–224 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.71 (s, 1 H), 7.40–7.29 (m, 4 H), 7.25 (t, *J* = 7.1 Hz, 1 H), 7.09 (s, 1 H), 6.75 (d, *J* = 8.2 Hz, 1 H), 5.70 (s, 2 H), 5.21 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.0, 158.1, 141.1, 128.5, 127.5, 127.0, 56.7.

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Supporting Information

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