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New Synthesis of Aryl and Heteroaryl *N*-Acylureas *via* Microwave-Assisted Palladium-Catalysed Carbonylation

David Liptrot,[a] Lilian Alcaraz,[a] and Bryan Roberts[a,*]

[a] Department of Chemistry, AstraZeneca R&D Charnwood, Bakewell Road, Loughborough, Leics, LE11 5RH, United Kingdom
Fax: (+44)-1509-645-571; phone: (+44)-1509-644-542; e-mail: bryan.roberts@astrazeneca.com

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Abstract: A new, practical synthesis of aryl and heteroaryl *N*-acylureas has been developed *via* palladium-catalysed carbonylation of aryl or heteroaryl halides in the presence of urea nucleophiles. A range of reactions illustrating the wide scope of this reaction was carried out under microwave irradiation, using either carbon monoxide gas in a vessel equipped with a gas inlet adapter, or molybdenum hexacarbonyl as the carbon monoxide source in standard microwave vials. The reactions proceeded in good to excellent yields. To illustrate the usefulness of this method a one-step synthesis of the important insecticide diflubenzuron is reported.

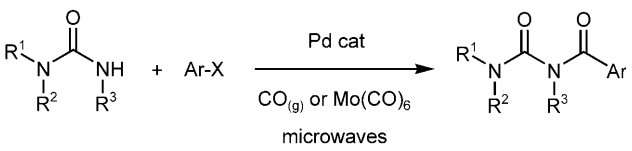
Keywords: *N*-acylureas; carbonylation; homogenous catalysis; microwave heating; palladium; ureas

The *N*-acylurea moiety is an important functional group in the fields of medicinal chemistry[1] and phytochemistry.[2] Some *N*-acylureas are known to possess analgesic, anti-inflammatory, anti-fungal, and anthelmintic properties.[3] Moreover, a number of benzoylureas show promising anti-tumour properties[4] and some have found commercial use in agriculture as insecticides.[5]

To date *N*-acylureas are classically prepared by acylating ureas with suitably activated carboxylic acids such as acid chlorides, anhydrides and carbodiimides.[6] The condensation of amines with acyl isocyanates[7] or *S*-allyl *N*-acylmonothiocarbamates[8] is also known to give *N*-acylureas. Other routes starting from ureas involve acylation with alkenyl esters[9] and boronic acid-catalysed condensation with acids.[10] When using these routes to synthesise *N*-acylureas the yields are often variable and the use of stoichiometric amounts of coupling agents or hazardous isocyanates often make these methods environmentally undesirable. Moreover, the scope of these transformations is often limited by the availability and stability of the required carboxylic acids which can, in some cases, be difficult to handle or are prone to facile decarboxylation.

Continuing our work in the area of palladium-catalysed carbonylation,[11] we report the first synthesis of aryl and heteroaryl *N*-acylureas from aryl and heteroaryl halides *via* microwave-assisted, palladium-catalysed carbonylation with urea nucleophiles using either carbon monoxide gas in pre-pressurised microwave vials or $Mo(CO)_6$ in standard microwave vials (Scheme 1).

Heck and co-workers[12] first reported the palladium-catalysed reaction of carbon monoxide, aryl halides, and alcohols or amines to give the respective benzoate and benzamide products. Since then the scope of the reaction has been developed such that a wide range of nucleophiles can be used, enabling the efficient synthesis of numerous carbonyl compounds.[13] We began by examining the reaction shown in Table 1. Using bromobenzene as a model aryl halide for reactions with substituted urea **1a**, triethylamine as base, 1,4-dioxane as solvent and $PdCl_2(dppf)\cdot CH_2Cl_2$ as the palladium catalyst. The carbon monoxide pressure was fixed at 65 psi and an optimisation of the reaction was carried out in the microwave system with respect to time and temperature. A temperature of 100 °C and reaction time of 4 h



Scheme 1. Synthesis of aryl and heteroaryl *N*-acylureas *via* microwave-assisted palladium-catalysed carbonylation.

Table 1. Pd-catalysed carbonylation of urea **1a** with aryl halides using method A.[a]

1a

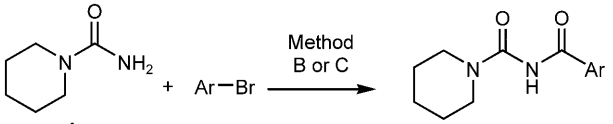
Entry	Ar–X	Yield [%][b]
1	C_6H_5Br	74
2	3-Cl-C_6H_4Br	76
3	3-MeO-C_6H_4Br	55
4	3-CF_3-C_6H_4Br	69
5	3-NC-C_6H_4Br	60
6	3-Me-C_6H_4Br	53
7	4-Cl-C_6H_4Br	72
8	4-MeO-C_6H_4Br	50
9	4-CF_3-C_6H_4Br	60
10	4-NC-C_6H_4Br	74
11	4-$Me_2NC(O)$-C_6H_4Br	85
12	4-*t*-Bu-C_6H_4Br	57
13	2-Cl-C_6H_4Br	30
14	2-F-C_6H_4Br	46
15	2-MeO-C_6H_4Br	45
16	2-*c*-Hex-C_6H_4Br	50
17	2-Me-C_6H_5Br	52
18	2-naphthyl-Br	65
19	2,6-F_2-C_6H_3Br	0
20	2,6-Me_2-C_6H_3Br	0
21	4-MeO-C_6H_4Cl	0
22	4-NC-C_6H_4Cl	68[c]

[a] Method A: aryl halide (1 equiv.), urea (**1a**, 2 equiv.), 1,4-dioxane (0.3 M), $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.1 equiv.), triethylamine (3 equiv.), CO 65 psi, 100 °C, 4 h.
[b] Isolated and purified products.
[c] 20 h.

(method A) gave complete conversion of bromobenzene and afforded the desired acyl urea in 74% yield (Table 1, entry 1).

To establish the scope of this transformation, the reaction conditions were applied to a range of aryl halides (Table 1). A variety of functional groups were tolerated and both electron-donating and electron-withdrawing groups on the aryl bromide gave moderate to good isolated yields. *meta*- (Table 1, entries 2–6) and *para*-substituted (Table 1, entries 7–12) systems performed well in the reaction. In the preceding examples the complete chemoselectivity observed for bromine over chlorine is worth noting (Table 1, entries 2 and 7). However, *ortho*-substituted aryl bromides, were not as well tolerated in the reaction (Table 1, entries 13–17) giving only modest yields of product. Attempts to use unactivated aryl chlorides met with no success, just recovery of the starting halide (Table 1, entry 21). This is not too suprising since carbonylation of aryl chlorides usually requires more forcing conditions, and/or alternative palladium catalysts.[14] However, an activated aryl chloride did provide a resonable yield of product, albeit with a longer reaction time (Table 1, entry 22). 2,6-Disubstituted aryl bromides (Table 1, entries 19 and 20) were not converted using our protocol. We believe the modest yields obtained with *ortho*-substituted and no reaction with 2,6-disubstituted aryl bromides are due to steric hindrance around the intermediate acyl-palladium species. It is worth noting that increasing reaction temperature or reaction times gave no improvement in yields for these substrates. Guided by our previous experience and reports in the literature,[15] a second optimisation on these difficult substrates was carried out, in one case using the same reagents but with the addition of DMAP, with these conditions a reaction time of 7 h was optimal (method B). In a second case we used $Pd(OAc)_2$/Xantphos reported by Buchwald as a useful carbonylation catalyst,[16] with these conditions a reaction time of 4 h was optimal (method C). Gratifyingly both of these new reaction conditions provided the *ortho*-substituted products with much improved yields (Table 2 entries 1-4). For method B we postulate that DMAP reacts with the intermediate acyl-palladium species thus reducing steric effects and allowing the urea nucleophile to react more readily. Application of method B to other aryl bromides (Table 2, entry 5) also gave an increased yield, in comparison to Table 1, entry 8. Interestingly we saw differences when these methods were applied to 2,6-disubstituted aryl bromides. Using method B, no products were isolated whereas with

Table 2. Pd-catalysed carbonylation of urea **1a** with aryl bromides using methods B and C.



1a

Entry	Ar–Br	Yield [%][a]	
		Method B[b]	Method C[c]
1	2-Cl-C_6H_4Br	70	not done
2	2-MeO-C_6H_4Br	90	not done
3	2-Me-C_6H_4Br	90	70
4	2-F-C_6H_4Br	89	70
5	4-MeO-C_6H_4Br	82	not done
6	2,6-F_2-C_6H_3Br	0	50
7	2,6-Me_2-C_6H_3Br	0	4

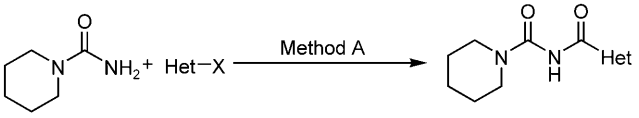
[a] Isolated and purified product.
[b] Method B: aryl halide (1 equiv.), urea (**1a**, 2 equiv.), 1,4-dioxane (0.3 M), Pd(dppf) (0.1 equiv.), triethylamine (3 equiv.), DMAP (1 equiv.), CO 65 psi, 100 °C, 7 h.
[c] Method C: aryl halide (1 equiv.), urea (**1a**, 2 equiv.), 1,4-dioxane (0.3 M), $Pd(OAc)_2$ (0.1 equiv.), Xantphos (0.15 equiv.), triethylamine (1 equiv.), CO 65 psi, 100 °C, 4 h.

method C, a moderate yield of product was isolated from 2,6-difluorobromobenzene (Table 2 entries 6 and 7).

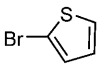
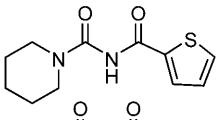
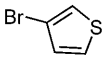
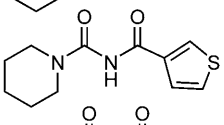
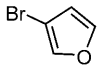
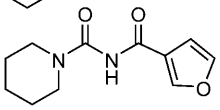
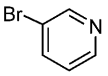
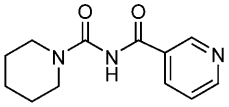
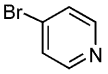
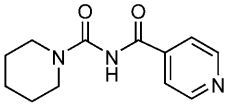
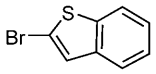
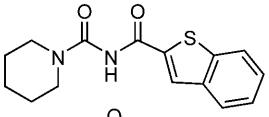
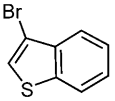
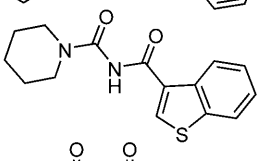
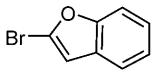
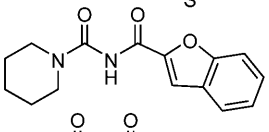
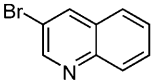
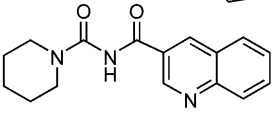
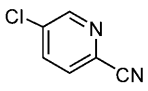
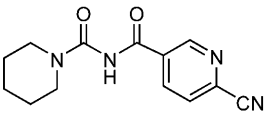
Having established a wide scope with aryl bromides, application of the methods to heteroaryl halides was performed (Table 3). Gratifyingly the conditions optimised for aryl bromides (method A) provided moderate to good yields of heteroaryl *N*-acylureas without further optimisation. As shown in Table 3 the methodology is applicable to a wide range of heterocyles such as 5-membered (Table 3, entries 1–3), 6-membered (Table 3, entries 4 and 5) and fused systems (Table 3, entries 6–9). However, the one heteroaryl chloride studied only achieved modest conversion after an extended time. (Table 3, entry 10).

Next we turned our attention to the urea partner in these carbonylation reactions. A selection of ureas wase subjected to our initial reaction conditions (method A), using bromobenzene as a representative aryl halide (Table 4).Variations to the dialkylated portion of the urea did not significantly affect the outcome of the reaction (Table 4, entry 1). A range of

Table 3. Pd-catalysed carbonylation of urea **1a** with heteroaryl halides using method A.

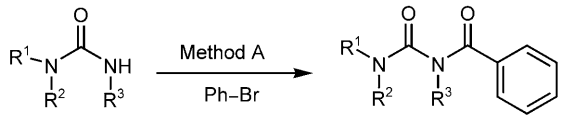


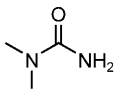
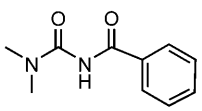
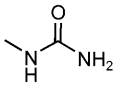
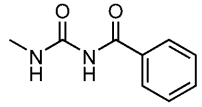
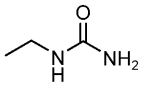
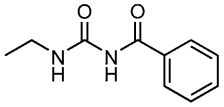
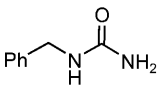
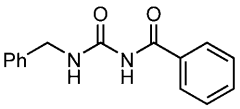
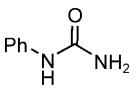
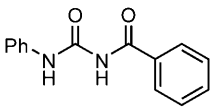
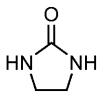
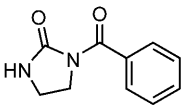
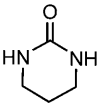
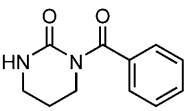
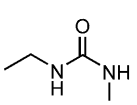
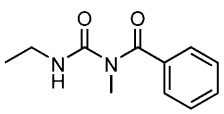
1a

Entry	Het–X	Product	Yield [%][a]
1			61
2			75
3			85
4			76
5			84
6			66
7			88
8			67
9			89
10[b]			35

[a] Isolated and purified product.
[b] 20 h.

Table 4. Pd-catalysed carbonylation of substitued ureas with bromobenzene using method A.



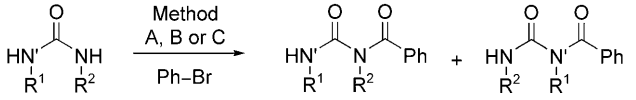
Entry	Urea	Product	Yield [%][a]
1			62
2			91
3			96
4			58
5			57
6			64
7			51
8			23

[a] Isolated and purified product.

monosubstituted alkyl (Table 4, entries 2–4) and phenyl substrates (Table 4, entry 5) also performed well. It is worth noting that in all these cases complete regioselectivity was observed with the reaction taking place on the least substituted nitrogen. This regioselectivity is possibly due to steric effects around the intermediate acyl-palladium species. Exploring the steric requirements of this reaction further, cyclic ureas gave moderate yields of product (Table 4, entries 6 and 7). However increasing the urea substitution further by using an *N,N′*-disubstituted urea (Table 4, entry 8) gave a low yield of product representing a limitation of these conditions.

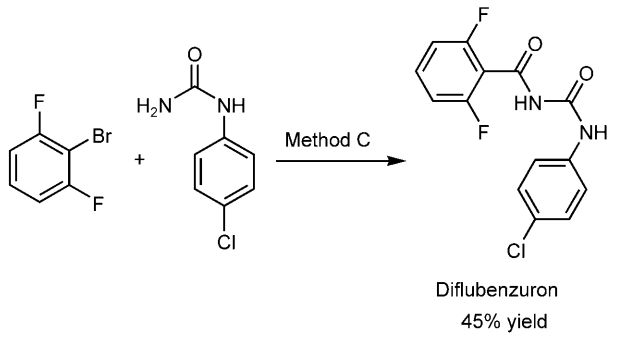
Guided by our previous experience for overcoming steric effects on the aryl bromide we synthesised a series of *N,N′*-disubstituted ureas[17] and subjected them to the 3 newly developed reaction conditions, using bromobenzene as a representative aryl halide (Table 5). When the disubstituted *N′*-ethyl-*N*-methyl-urea was subjected to the 3 reaction conditions we saw that with method A, regioselectivity was retained, reaction taking place on the least hindered nitrogen but the yield was poor (Table 5, entry 1). It should be noted that increasing the reaction time was detrimental to the yield. Using methods B and C the yield of product was much improved but the regioselectivity was lost giving a 4:3 mixture of products in favour of the least hindered nitrogen (Table 5, entries 2 and 3). A similar pattern was seen with the *N′*-propyl-*N*-methyl-disubstituted urea (Table 5 entries 4–6). These results suggest that method B and method C lead to a less sterically demanding intermediate acyl-palladium species when compared with method A. Interestingly when a monosubstituted urea was subjected to the 3 reaction conditions, the yields of isolated product were consistent and there was no change in regioselectivity with the reaction taking place exclusively at the unsubstituted position (Table 5, entries 7–9).

Table 5. Pd-catalysed carbonylation of substitued ureas with bromobenzene using methods A, B and C.



Entry	Urea R^1	Urea R^2	Method	Product Ratio N:N′	Yield [%][a]
1	Et	Me	A	1:0	23
2	Et	Me	B	4:3	70
3	Et	Me	C	4:3	50
4	Pr	Me	A	1:0	17
5	Pr	Me	B	1:1	50
6	Pr	Me	C	1:1	70
7	Me	H	A	1:0	91
8	Me	H	B	1:0	93
9	Me	H	C	1:0	70

[a] Isolated and purified product.



Scheme 2. Synthesis of the insecticide diflubenzuron.

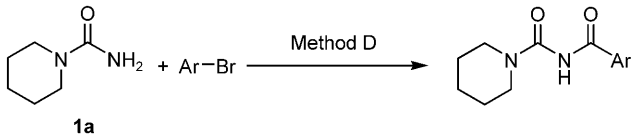
The usefulness of this methodology was illustrated by a single-step synthesis of the important insecticide diflubenzuron in 45% yield from commercially available starting materials (Scheme 2).

Finally, whilst the methods outlined are simple and efficient with a wide substrate scope they do require the use of specialised carbonylation equipment which is not available in all laboratories. Furthermore, the methods are not easily adaptable to parallel synthesis and automation often required in modern medicinal chemistry laboratories. In order to address these issues we investigated the use of a solid source of CO in the palladium-catalysed carbonylation.

In recent years a number of CO gas-free carbonylative conditions have been reported using formamides or solid metal carbonyls as CO sources.[18] The palladium-catalysed $Mo(CO)_6$-mediated carbonylative coupling of aryl and heteroaryl halides with a variety of nucleophiles under microwave-assisted conditions is now well established in the literature and ideally suited to small-scale laboratory reactions, parallel synthesis and semi-automation.[19]

We started our optimisation of the reaction using conditions reported recently for the synthesis of aryl and heteroaryl acylsulfonamides.[20] Using bromobenzene as a model aryl halide, for reactions with urea **1a**, DBU as base, 1,4-dioxane as solvent, $Mo(CO)_6$, as CO source, {Pd(OAc)[P(*o*-tolyl)$_3$]$_2$} as the palladium source and P(*t*-Bu)$_3$[HBF$_4$] as ligand, an optimisation of the reaction was performed in the microwave with respect to time and temperature. A reaction time of 2.5 h and a temperature of 100 °C gave complete conversion of bromobenzene but only 51% yield of the desired acylurea. Further optimisation of the reaction using identical conditions but with the addition of DMAP (method D) gave an improved yield (Table 6, entry 1). In order to establish the scope of this transformation, these reaction conditions were applied to a small set of aryl and heteroaryl bromides (Table 6). The reaction tolerated a range of functional groups and both electron-donating and electron-withdrawing groups gave moderate to excellent isolated yields (Table 6, entries 2–6).

Table 6. Pd-catalysed $Mo(CO)_6$-mediated carbonylative coupling of urea **1a** with aryl and heteroaryl bromides using method D.



Entry	Ar–Br	Yield [%][a,b]
1	C_6H_5Br	83 (51)[c]
2	3-Cl-C_6H_4Br	71
3	4-MeO-C_6H_4Br	55
4	4-CF_3-C_6H_4Br	60
5	2-Me-C_6H_4Br	78
6	3-thienyl-Br	60

[a] Isolated and purified product.
[b] Method D: aryl bromide (1 equiv.), urea (**1a**, 2 equiv.), 1,4-dioxane (0.3 M), {Pd(OAc)[P(*o*-tolyl)$_3$)]$_2$} (0.1 mmol), P(*t*-Bu)$_3$[HBF_4] (0.2 mmol), DBU (3 equiv.), $Mo(CO)_6$ (1 equiv.) in 1,4-dioxane (0.3 M), 100 °C, 2.5 h.
[c] DMAP not added.

In summary, we have developed a new, efficient route to aryl and heteroaryl *N*-acylureas *via* a palladium-catalysed carbonylation of readily available aryl or heteroaryl bromides in the presence of urea nucleophiles. The reaction tolerates a wide range of substituted ureas and substituted aryl or heteroaryl halides. The reactions can be carried out using either CO gas or $Mo(CO)_6$. We anticipate that this new method will find broad application for the synthesis of a wider variety of aryl and heteroaryl *N*-acylureas than currently accessible through the known methodologies.

Experimental Section

General Remarks

For methods A, B and C reactions were performed with a CEM Discover single mode microwave reactor equipped with a 300 W source. A 10-mL fibre optic accessory was equipped with a gas inlet to allow introduction of carbon monoxide gas to the reaction vessel and each of the reactions was performed in a CEM 10-mL microwave reaction vial. All temperature measurements were performed with a fibre optic probe. For method D reactions were performed with a CEM Discover single mode microwave reactor equipped with a 300 W source set to 50 W. Each of the reactions was performed in a CEM 10-mL microwave reaction vial. All temperature measurements were performed with an infra-red probe.

Typical Procedure for Method A

A 10-mL microwave vial was charged with aryl halide (1 mmol), urea (**1a**, 2 mmol) and $PdCl_2$(dppf)·CH_2Cl_2 (0.1 mmol). The vial was then charged with anhydrous dioxane (3 mL) and triethylamine (3 mmol). The vial was pressurised with CO to 65 psi, then purged and refilled, 3 times. The reaction mixture was then microwave heated to 100 °C for 4 h. with stirring. The reaction mixture was allowed to cool and excess carbon monoxide vented. The crude mixture was concentrated under vacuum and neutralised with glacial acetic acid. This residue was dissolved in methanol, filtered and purified directly by RPHPLC on a Symmetry column eluted with a 5:95% gradient of acetonitrile/0.2% aqueous TFA to yield the corresponding aryl *N*-acylurea.

Typical Procedure for Method B

A 10-mL microwave vial was charged with aryl halide (1 mmol), urea (**1a**, 2 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (0.1 mmol) and DMAP (1 mmol). The vial was then charged with anhydrous dioxane (3 mL) and triethylamine (3 mmol). The vial was pressurised with CO to 65 psi then purged and refilled, 3 times. The reaction mixture was then microwave heated to 100 °C for 7 h; with stirring. The reaction mixture was allowed to cool and excess carbon monoxide vented. The crude mixture was concentrated under vacuum and neutralised with glacial acetic acid. This residue was dissolved in methanol, filtered and purified directly by RPHPLC on a Symmetry column eluted with a 5:95% gradient of acetonitrile/0.2% aqueous TFA to yield the corresponding aryl *N*-acylurea.

Typical procedure for Method C

A 10-mL microwave vial was charged with aryl halide (1 mmol), urea (**1a**, 2 mmol), $PdOAc_2$ (0.1 mmol) and Xantphos (0.15 mmol). The vial was then charged with anhydrous dioxane (3 mL) and triethylamine (3 mmol). The vial was pressurised with CO to 65 psi then purged and refilled, 3 times. The reaction mixture was then heated to 100 °C for 4 h. with stirring. The reaction mixture was allowed to cool and excess carbon monoxide vented. The crude mixture was concentrated under vacuum and neutralised with glacial acetic acid. This residue was dissolved in methanol, filtered and purified directly by RPHPLC on a Symmetry column eluted with a 5:95% gradient of acetonitrile/0.2% aqueous TFA to yield the corresponding aryl *N*-acylurea.

Typical Procedure for Method D

A 10-mL microwave tube was charged with aryl halide (1 mmol), urea **1a** (2 mmol), $Mo(CO)_6$ (1 mmol), DBU (3 mmol), DMAP (1 mmol), {Pd(OAc)[P(*o*-tolyl)$_3$]$_2$} (0.1 mmol), and P(*t*-Bu)$_3$[HBF_4] (0.2 mmol). 3 mL of 1,4-dioxane were then added. The vessel was sealed and microwave heated to 100 °C for 2.5 h ("hold time"). The reaction mixture was allowed to cool, and then taken up in ethyl acetate (40 mL). The resulting solution was washed with saturated $NaHCO_3$ solution (2 × 50 mL).The aqueous phase was acidified with 2 N HCl, and extracted with ethyl acetate (2 × 100 mL). The organic phase had the solvent removed under vacuum and was dissolved in methanol, filtered and purified by preparative RPHPLC on a Symmetry column eluted with a 5:95% gradient of acetonitrile/0.2% aqueous TFA to yield the corresponding aryl *N*-acylurea.

Supporting Information

Experimental procedures and full characterisation (^{1}H and ^{13}C NMR data and spectra, HR-MS and purity analysis) for all new compounds are provided in the Supporting Information.

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