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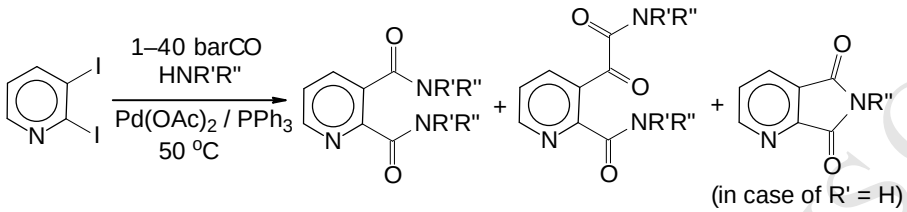
Graphical abstract



Palladium-catalysed aminocarbonylation of diiodopyridines

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Abstract:

The aminocarbonylation of 2,5- and 2,3-diiodopyridine, as well as 2-chloro-3,4-diiodopyridine with carbon monoxide and various primary and secondary amines was carried out using palladium-catalysed aminocarbonylation. The formation of the products containing carboxamide and ketocarboxamide functionalities was accompanied by the formation of imides when *ortho*-diiodo compounds were used as substrates. In spite of several possible reaction pathways, most of the products were synthesised as major product in yields of synthetic interest by the appropriate modification of the reaction conditions.

Key-words: carbonylation**,** cycloaminocarbonylation**,** palladium**,** carbon monoxide, diiodopyridine.

1. Introduction

The activation of carbon monoxide and its use as C1 building block in various model reactions as well as procedures of practical use is one of the success stories of homogeneous catalysis. In this way, carbonylations have become widely used text-book reactions for the synthesis of carboxylic acids and their derivatives (esters, amides), aldehydes and ketones.[1] Since the early discovery of Heck *et al*,[2] aminocarbonylation of aryl halides and haloalkenes, as well as that of their synthetic surrogates such as aryl triflates and alkenyl triflates, has proved to be an efficient tool for the synthesis of carboxamides with various structures.[3] The most common catalysts used for the synthesis of carboxamides are based on Pd(0) 'pre-formed' complexes or *in situ* formed systems. They show high tolerance regarding the structure of *N*-nucleophiles and substrates (aryl halides/triflates, alkenyl halides/triflates).[4]

Aminocarbonylation as a key reaction for the synthesis of α,β-unsaturated carboxamides and aryl carboxamides was investigated also in our laboratory.[5] Recently, the functionalization of *N*-heterocycles, due to their practical importance[6] (*e.g*. the synthesis of indole- and quinoline-based carboxamides, nicotinamide derivatives, *etc*.), is in the forefront of our research interest.[7]

As a part of our continuing interest in the systematic investigation of the synthesis of poly-substituted pyridine-based carboxamides, as well as to explore structure–reactivity and structure–selectivity relations, the aminocarbonylation of diiodopyridine derivatives were investigated in the presence of palladium catalysts. Since a variety of side-reactions including double carbon monoxide insertion, intramolecular ring-closure reactions, *etc*. may take place using these substrates, a special focus is given to the careful analysis of the product composition (even to compounds in trace amounts) to analyse selectivity issues of the reaction.

2. Results and discussion

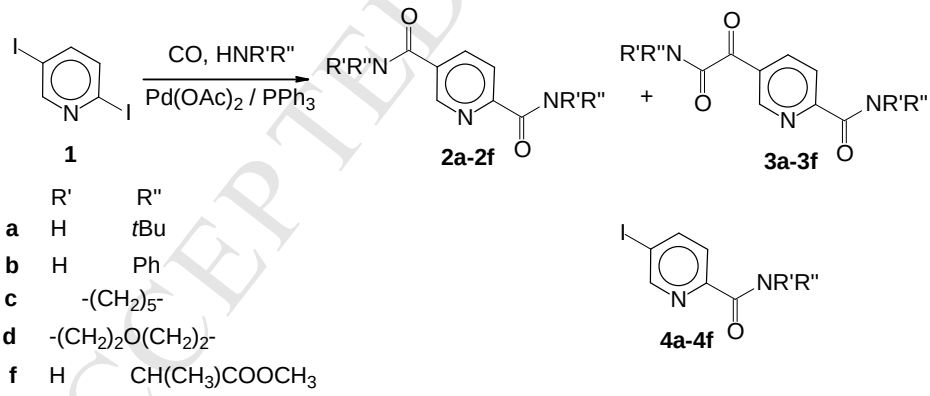
*2.1. Aminocarbonylation of 2,5-diiodopyridine(**1**) in the presence of various nucleophiles*

2,5-Diiodopyridine (**1**) was reacted with carbon monoxide and various primary and secondary amines as *N*-nucleophiles (*tert*-butylamine (**a**), aniline (**b**), piperidine (**c**), morpholine (**d**), methyl alaninate (**f**)) in the presence of palladium catalysts. (*Scheme 1*). Palladium(II) acetate was used as catalyst precursor and its reduction to catalytically active palladium(0) species took place 'in situ' as described previously.[8]

Based on detailed GC-MS studies, the formation of three different products was observed. In addition to the expected 2,5-dicarboxamide (**2**) and 2-carboxamide-5-ketocarboxamide (**3**) derivatives 5-iodo-2-carboxamide (**4**) product was also detected. Their ratio is strongly dependent on the type of the amine. The less reactive amine is the less basic **b** providing 5-iodo-2-carboxamide (**4b**) only from the abovementioned carbonylated products with low conversion under atmospheric conditions in 24 hours. Using longer reaction time **4b** was converted to the expected 2,5-dicarboxamide (**2b**) (*entries 4 and 5*). Applying 40 bar of carbon monoxide pressure the distribution of the carbonylated products were similar as under atmospheric conditions

(*entries 6 and 7*). However, practically full conversion was obtained in shorter reaction time (95 h) and the 2,5-dicarboxamide (**2b**) product was selectively formed (*entry 7*). Due to this low reactivity, the reaction sequence can be clearly seen: the carbonylation in position-2 takes place first, followed by the aminocarbonylation in position-5 resulting in **2b** in highly selective reaction (*entries 3-5 and 6-7*).

Using more basic primary (**a**) and secondary amines (**c, d**) the mixture of carbonylated products was obtained both at low and high CO pressure. However, one of the components can be synthesised as major product by the variation of the conditions. For instance, a **2a**/**3a** ratio of 66/34 was obtained at atmospheric pressure which can be shifted towards carboxamide-ketocarboxamide product (**3a**) (**2a**/**3a** = 24/76) (*entries 1 and 2*). It has to be noted that double CO insertion leading to ketocarboxamide functionality was observed in position-5, exclusively. The iodoarene functionality adjacent to 'ring-nitrogen' of the heteroaromatic ring (position-2) underwent aminocarbonylation with simple CO insertion, exclusively (*entries 8-11*). Using methyl alaninate (**f**) much lower reactivity was observed both under mild and more severe conditions resulting in the formation of 5-iodo-2-carboxamide (**4f**) accompanied with carbonylation in position-5 as well. The identification of the **4f** product was carried out by detailed NMR measurements including 2D NMR techniques (HMBC, HSQC). As expected, an increased amount of double carbonylated product was detected at the higher CO pressure (*entries 12 and 13*). The formation of **4f**, applicable in further functionalization reactions due to its 5-iodoaryl functionality, can be increased by reducing the amine to substrate ratio to 1.1/1 ((*entries 14 and 15*).



	R'	R"
a	H	*t*Bu
b	H	Ph
c	-(CH$_2$)$_5$-	
d	-(CH$_2$)$_2$O(CH$_2$)$_2$-	
f	H	CH(CH$_3$)COOCH$_3$

Scheme 1. Aminocarbonylation of 2,5-diiodopyridine(**1**)

Table 1. Aminocarbonylation of 2,5-diiodopyridine (**1**) in the presence of $Pd(OAc)_2$ +2 PPh_3 'in situ' catalyst [a)]

Entry	Amine	R. time [h]	Pressure [bar]	Conv. [b)] [%]	Ratio of the carbonylated products [b)]; (isolated yield [c)]) [%]		
					2,5-Dicarboxamide (**2**)	2-Amide-5-ketocarboxamide (**3**)	5-Iodo-2-carboxamide (**4**)
1	*t*-BuNH_2 (**a**)	24	1	100	66 (**2a**);(60)	34 (**3a**)	0 (**4a**)
2	*t*-BuNH_2 (**a**)	24	40	100	24 (**2a**)	76 (**3a**); (33)	0 (**4a**)
3	aniline (**b**)	24	1	28	0 (**2b**)	0 (**3b**)	100 (**4b**)
4	aniline (**b**)	50	1	60	27 (**2b**)	0 (**3b**)	73 (**4b**)
5	aniline (**b**)	170	1	100	100 (**2b**); (61)	0 (**3b**)	0 (**4b**)
6	aniline (**b**)	24	40	81	19 (**2b**)	0 (**3b**)	81 (**4b**)
7	aniline (**b**)	95	40	100	100 (**2b**); (61)	0 (**3b**)	0 (**4b**)
8	piperidine (**c**)	24	1	100	65 (**2c**)	16 (**3c**)	19 (**4c**)
9	piperidine (**c**)	24	40	100	46 (**2c**); (35)	54 (**3c**); (34)	0 (**4c**)
10	morpholine (**d**)	24	1	100	47 (**2d**)	28 (**3d**)	25 (**4d**)
11	morpholine (**d**)	24	40	100	44 (**2d**); (36)	56 (**3d**); (17)	0 (**4d**)
12	AlaOMe (**f**)	98	1	66	15 (**2f**)	3 (**3f**)	73 [d)] (**4f**)
13	AlaOMe (**f**)	24	40	88	16 (**2f**)	22 (**3f**); (12)	62 (**4f**)
14 [e)]	AlaOMe (**f**)	94	1	66	17 (**2f**); (9)	<1 (**3f**)	77 [f)] (**4f**)
15 [e)]	AlaOMe (**f**)	24	40	76	6 (**2f**)	12 (**3f**)	82 (**4f**); (13)

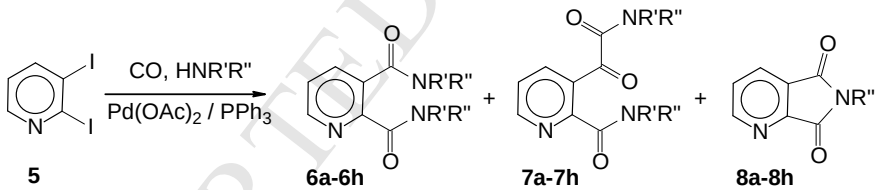
a) Reaction conditions (unless otherwise stated): 1 mmol substrate (**1**), amine nucleophile: 6 mmol of **a** (or 4 mmol of **b** / 3 mmol of **c**, **d** / 2.2 mmol of **f**), 0.025 mmol of $Pd(OAc)_2$, 0.05 mmol of PPh_3, 0.5 mL of Et_3N, 10 mL of DMF, 50 ^oC, 40 bar of CO.
b) Determined by GC-MS
c) Yields of the isolated target compound (based on the substrate (**1**))
d) 2-Iodo-5-(*N*-(1'-methoxycarbonylethyl)carboxamido)pyridine was also formed in 9%
e) 1.1 mmol of AlaOMe is used.
f) 2-Iodo-5-(*N*-(1'-methoxycarbonylethyl)carboxamido)pyridine was also formed in 6%

*2.2. Aminocarbonylation of 2,3-diiodopyridine (**5**)*

To investigate the structure–selectivity relation in the aminocarbonylation of diiodopyridines, a substrate (**5**) containing the two iodoarene functionalities in *ortho* position was aminocarbonylated under conditions described in 2.1. (*Scheme 2*). In order to achieve yields of synthetic interest, the reaction had to be carried out under 40 bar carbon monoxide pressure in 24 hours. Thus, practically full conversion was obtained in all cases with a product distribution shown in *Table 2*. The primary amines behave in a completely different way: **a** provided the two carboxamide derivatives (**6a** and **7a**) accompanied by the formation of some imide (**8a**) derivative, while **b**, **e-h** gave the corresponding imide derivatives (**8b**, **8e-8h**, respectively) in a highly selective cycloaminocarbonylation (*entries 3, 6-9*). The imide formation goes probably via the 3-iodo-2-carboxamide intermediate as detected in case of **g.** That is, **8g** was formed via cycloamidocarbonylation of the 3-iodo-2-carboxamide derivative (*entry 8*). (See also *Scheme 4* below)

The secondary amines (**c** and **d**) gave the 2-carboxamide-3-ketocarboxamide products (**7c** and **7d**, respectively) as major, and the dicarboxamide derivatives (**6c** and **6d**, respectively) as minor products. Regarding the major products, their isomers, *i.e.*, the 2-ketocarboxamide-3-carboxamide products were also detected as trace products by GC-MS.

In general, it has to be noted that double CO insertion is favoured in position-3 while the aminocarbonylation of the 2-iodo functionality resulted in the highly selective formation of the 2-carboxamide functionality in all cases.



	R'	R"		R'	R"
a	H	*t*Bu	**e**	H	CH_2COOCH_3
b	H	Ph	**f**	H	$CH(CH_3)COOCH_3$
c		$-(CH_2)_5-$	**g**	H	$CH(COOCH_3)CH(CH_3)_2$
d		$-(CH_2)_2O(CH_2)_2-$	**h**	H	CH_2(4-Py)

Scheme 2. Aminocarbonylation of 2,3-diiodopyridine(**5**)

*Table 2.*Aminocarbonylation of 2,3-diiodopyridine (**5**) in the presence of $Pd(OAc)_2$ + 2 PPh_3 'in situ' catalyst [a)]

Entry	Amine	Substrate / amine ratio	Ratio of the carbonylated products [b)]; (isolated yield [c)]) [%]		
			2,3-Dicarboxamide (**6**)	2-Amide-3-ketocarboxamide (**7**)	Imide (**8**)
1	*t*-BuNH_2 (**a**)	1/6	86 (**6a**);(48)	13 (**7a**)	1 (**8a**)
2	*t*-BuNH_2 (**a**)	1/3	93 (**6a**);(54)	3 (**7a**)	4 (**8a**)
3 [d)]	aniline (**b**)	1/2	12 (**6b**); (9)	0 (**7b**)	88 (**8b**); (66)
4 [e)]	piperidine (**c**)	1/3	39 (**6c**); (39)	60 (**7c**); (29)	0 (**8c**)
5 [f)]	morpholine (**d**)	1/3	12 (**6d**)	81 (**7d**); (63)	0 (**8d**)
9	GlyOMe (**e**)	1/1.1	0 (**6e**)	0 (**7e**)	100 (**8e**); (57)
10	AlaOMe (**f**)	1/1.1	0 (**6f**)	0 (**7f**)	100 (**8f**); (58)
11 [e) g)]	ValOMe (**g**)	1/1.1	0 (**6g**)	0 (**7g**)	84 (**8g**); (57)
12 [e)]	4-picolylamine (**h**)	1/1.5	0 (**6h**)	0 (**7h**)	100 (**8h**); (69)

a) Reaction conditions (unless otherwise stated): 1 mmol substrate (**5**), amine nucleophile: 3 or 6 mmol of **a** (or 2 mmol of **b** / 3 mmol of **c**, **d** / 1.1 mmol of **e**, **f**, **g**, **h**), 0.025 mmol of $Pd(OAc)_2$, 0.05 mmol of PPh_3, 0.5 mL of Et_3N, 10 mL of DMF, 50 ^oC, 40 bar of CO. The reaction time was 24 h. Practically complete conversion was observed in all cases.
b) determined by GC-MS
c) yields of the isolated target compound (based on the substrate (**5**))
d) The reaction time was 116 h.
e) The 2-ketocarboxamide-3-carboxamide type product (**7'c**) was also detected in traces (<1%).
f) The 2-ketocarboxamide-3-carboxamide type product (**7'd**) was also formed in 14 %.
g) 3-Iodo-2-carboxamide type product was detected in the reaction mixture (16 %).

*2.3. Aminocarbonylation of 2-chloro-3,4-diiodopyridine (**9**)*

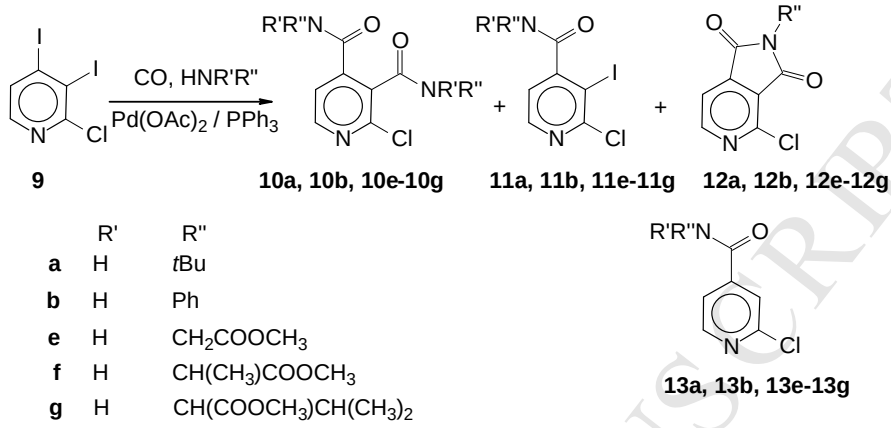
As a part of our structure–selectivity studies on the aminocarbonylation of heterocyclic iodoarenes, a further diiodopyridine derivative, 2-chloro-3,4-diiodopyridine (**9**) was reacted under conditions described in 2.1. The reaction carried out at atmospheric CO pressure resulted in the formation of dicarboxamide (**10**), 3-iodo-4-carboxamide (**11**), imide (**12**) and 4-carboxamide (**13**) derivatives (*Scheme 3*). Compounds **10** and **11** are the expected carboxamide products obtained in the aminocarbonylation of both iodoarene (in position-3 and 4) and the less sterically crowded 4-iodoarene functionalities, respectively. The imide derivative (**12**) is also generally formed when the two iodoarene functionalities are in *ortho*-position. It has been revealed by detailed analysis of the reaction mixture that some dehydrohalogenation in position-3 took place. The 2-chloroarene moiety remained intact in case of all four products. The chemoselectivities towards the above products are rather different depending on the amine nucleophile and reaction conditions.

Carrying out the reaction using **a** as nucleophile at atmospheric CO a strong dependence on the substrate to amine ratio was observed. Using a ratio of 1/3, the 3-iodo-4-carboxamide (**11a**) was the major product in 20 h (*entry 1*), which can be converted to **10a** and to the imide derivative (**12a**) (*entries 2 and 3*). Changing the substrate to amine ratio to 1/6 the amount of the imide (**12a**) substantially decreased and the formation of dicarboxamide (**10a**) was favoured (*entries 4 and 5*). In other words, the aminocarbonylation of both functionalities to **10a** is dominating over aminocarbonylation–amidocarbonylation sequence providing **12a** when the primary amine nucleophile is present in excess. Applying 40 bar CO pressure **10a** is still the main product accompanied by the formation of **13a** (*entry 6*). It is worth noting that the decrease in the amount of imides cannot be explained by the nucleophilic attack of the amine used in excess, *i.e.*, by the conversion of imides (**12**) to dicarboxamides (**10**). The isolated imides did not show any reaction with the corresponding nucleophiles under the reaction conditions used and the imides were recovered quantitatively.

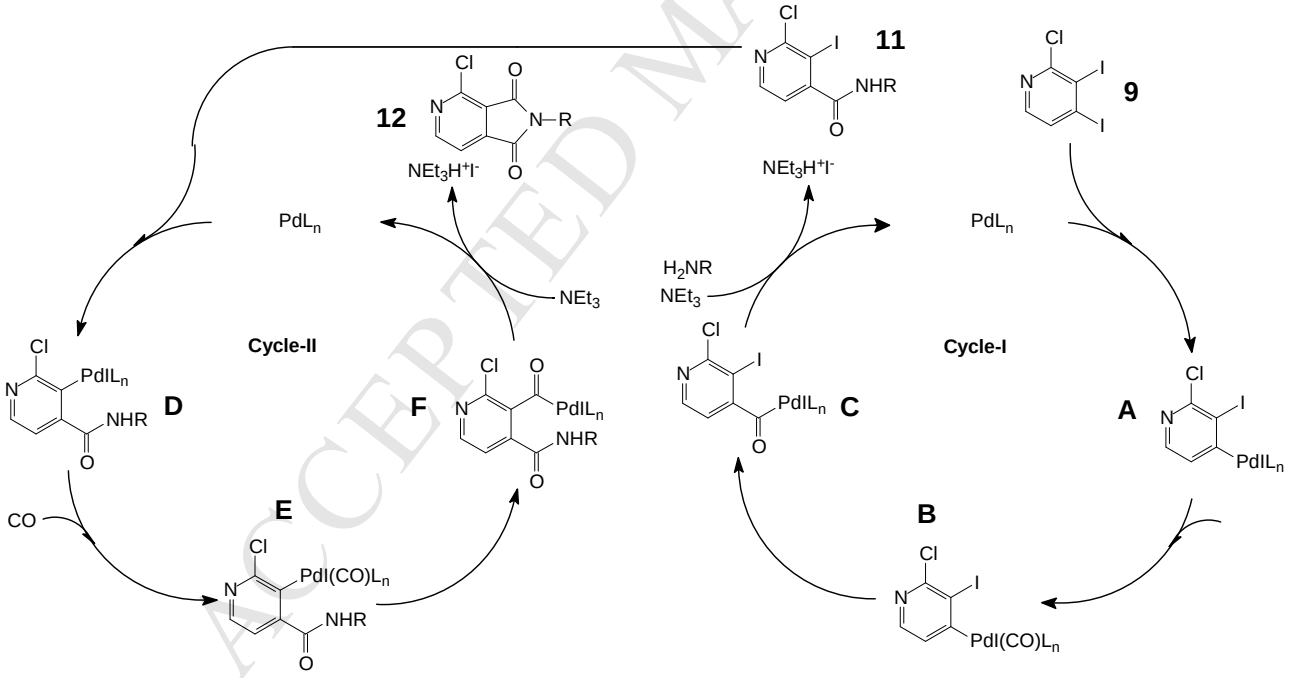
The 2-chloro-4-carboxamido derivative, formed via dehydroiodination in position-3, was obtained in highest amount when **b** was used as nucleophile although imide **12b** was the major product (*entries 7 and 8*). Using amino acid methyl esters (**f**, **g**) the 3-iodo-4-carboxamide intermediates (**11f** and **11g**) were detected in substantial amount which can be converted to imides **12f** and **12g** in longer reaction time. As above, the 4-carboxamide formed first acts as a nucleophile in the carbonylation of the adjacent 3-iodo functionality resulting in an intramolecular dicarbonylation (*Scheme 4*).

The formation of the imide derivatives can be rationalised by a simplified catalytic cycle (*Scheme 4*). The oxidative addition of the 4-iodo functionality of **9** onto the palladium(0) species resulted in the palladium(II)-aryl derivative (**A**) which reacts with carbon monoxide yielding the terminal carbonyl complex (**B**). A palladium(II)-acyl intermediate (**C**) is formed via carbon monoxide insertion. Its reaction with the activated primary amine gave carboxamide (**11**) and a palladium-hydrido-iodo intermediate which undergoes reductive elimination and the palladium(0) species are reformed (cycle-I). The 3-iodo-4-carboxamide derivative (**11**) entered into cycle-II via oxidative addition of the 3-iodo functionality forming the corresponding

palladium(II)-aryl derivative (**D**). It is followed by CO activation (**E**) and its insertion into palladium-carbon bond provided the acyl derivative (**F**). The close proximity of palladium-acyl and 3-C(O)NHR functionality enables the nucleophilic attack of the amide moiety forming **12** and hydrido-iodo-species. Reductive elimination took place providing the palladium(0) key-intermediate.



Scheme 3. Aminocarbonylation of 2-chloro-3,4-diiodopyridine(**9**)



Scheme 4. Simplified catalytic cycles leading to iodocarboxamide (**11**) and imide (**12**) products

*Table 3.*Aminocarbonylation of 2-chloro-3,4-diiodopyridine (**9**) in the presence of primary amines[a)]

Entry	Amine	Substrate/ amine ratio	Reaction time [h]	Ratio of the carbonylated products [b)]; (isolated yield [c)]) [%]			
				2-chloro-3,4-di-carboxamide (**10**)	2-chloro-3-iodo-4-carboxamide (**11**)	Imide (**12**)	2-Chloro-4-carboxamide (**13**)
1 [d)]	*t*-BuNH$_2$ (**a**)	1/3	20	12 (**10a**)	67 (**11a**); (45)	6 (**12a**)	15 (**13a**)
2 [d)]	*t*-BuNH$_2$ (**a**)	1/3	70	17 (**10a**)	43 (**11a**)	18 (**12a**)	22 (**13a**)
3 [d)]	*t*-BuNH$_2$ (**a**)	1/3	96	17 (**10a**)	37 (**11a**)	20 (**12a**); (13)	26 (**13a**)
4 [d)]	*t*-BuNH$_2$ (**a**)	1/6	20	86 (**10a**)	2 (**11a**)	4 (**12a**)	8 (**13a**)
5 [d)]	*t*-BuNH$_2$ (**a**)	1/6	91	91 (**10a**);(66)	0 (**11a**)	2 (**12a**)	7 (**13a**)
6 [e)]	*t*-BuNH$_2$ (**a**)	1/6	24	71 (**10a**)	0 (**11a**)	8 (**12a**)	17 (**13a**)
7	aniline (**b**)	1/2	23	0 (**10b**)	0 (**11b**)	65 (**12b**)	35 (**13b**)
8	aniline (**b**)	1/2	46	0 (**10b**)	0 (**11b**)	59 (**12b**); (36)	41 (**13b**)
9	GlyOMe (**e**)	1/1.1	20	0 (**10e**)	30 (**11e**); (18)	64 (**12e**); (34)	6 (**13e**)
10	AlaOMe (**f**)	1/1.1	23	0 (**10f**)	44 (**11f**)	45 (**12f**)	11 (**13f**)
11	AlaOMe (**f**)	1/1.1	70	0 (**10f**)	0 (**11f**)	89 (**12f**); (72)	11 (**13f**)
12	ValOMe (**g**)	1/1.1	21	0 (**10g**)	56 (**11g**)	30 (**12g**)	14 (**13g**)
13	ValOMe (**g**)	1/1.1	44	0 (**10g**)	0 (**11g**)	84 (**12g**); (54)	16 (**13g**)

a) Reaction conditions (unless otherwise stated): 0.5 mmol substrate (**7**), primary amines, 0.025 mmol of $Pd(OAc)_2$, 0.05 mmol of PPh_3, 40 bar of CO, 0.5 mL of Et_3N, 10 mL of DMF, 50 ^oC. Practically complete conversion was observed in all cases.
b) Determined by GC-MS
c) Yields of the isolated target compound (based on the substrate (**9**))
d) 1 bar of CO
e) 4% of carboxamide/ketocarboxamide type product was formed.

Conclusions

The reaction of 2,5-, 2,3- and 3,4-diiodopyridines with carbon monoxide and various primary and secondary amines provided the expected aminocarbonylated products such as dicarboxamides and carboxamide-ketocarboxamide derivatives. The formation of imides were observed in the presence of *ortho*-diiodo compounds (2,3- and 3,4-diiodopyridines) using primary amines in double cycloaminocarbonylation. It is worth mentioning that, in spite of several reaction pathways leading to various carbonylated derivatives, most of the products can be synthesised as major product in yields of synthetic interest by the appropriate modification of the reaction conditions (amine to substrate ratio, temperature, carbon monoxide pressure).

The different reactivity of the two iodoarene functionalities enabled the synthesis of partially aminocarbonylated intermediates (iodo-carboxamido derivatives) which are applicable in further synthetic reactions (*e.g*. cross-coupling reactions due to the iodoarene functionality).

Although in general iodoarene functionalities can be involved in both simple and double carbon monoxide insertion (even under mild reaction conditions) resulting in carboxamide and 2-ketocarboxamide functionalities, respectively, double carbon monoxide insertion occurs favourably in position-3 or position-5 (but not in position-2 adjacent to nitrogen)[7] of pyridine.

3. Experimental

3.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance III 500 spectrometer at 500 and 125.7 MHz, respectively. Chemical shifts δ are reported in ppm relative to $CHCl_3$ (7.26 and 77.00 ppm for ^{1}H and ^{13}C, respectively). Elemental analyses were measured on a 1108 Carlo Erba apparatus. Samples of the catalytic reactions were analysed with a Hewlett Packard 5830A gas chromatograph fitted with a capillary column coated with OV-1 (internal standard: naphthalene; injector temp 250 ˚C, oven: starting temp 50 ˚C (hold-time 1 min), heating rate 15 ˚C min^{-1}, final temp 320 ˚C (hold-time 11 min); detector temp 280 ˚C, carrier gas: helium (rate: 1 mL min^{-1})).The FT-IR spectra were taken in KBr pellets using an IMPACT 400 spectrometer (Nicolet) applying a DTGS detector in the region of 400-4000 cm^{-1}, the resolution was 4 cm^{-1}. The amount of the samples was *ca*. 0.5 mg.

The diiodopyridine substrates (2,5-diiodopyridine, 2,3-diiodopyridine and 2-chloro-3,4-diiodopyridine), as well as the amine nucleophiles were purchased from Sigma-Aldrich and were used without further purification.

3.2. Aminocarbonylation of diiodopyridine derivatives in the presence of various amines as N-nucleophiles under atmospheric carbon monoxide pressure

In a typical experiment $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), triphenylphosphine (13.1 mg, 0.05 mmol), 2,5-diiodopyridine (**1**) (331 mg, 1 mmol) (or 2,3-diiodopyridine (**5**) (331 mg, 1 mmol) or 2-chloro-3,4-

diiodopyridine (**9**) (182.75 mg, 0.5 mmol), amine nucleophile (see above in the tables) and triethylamine (0.5 mL) were dissolved in DMF (10 mL) under argon in a three-necked flask equipped with a gas inlet, reflux condenser with a ballon (filled with argon) at the top. The atmosphere was changed to carbon monoxide. The reaction was conducted for the given reaction time upon stirring at 50 ˚C and analysed by GC-MS (internal standard: naphthalene). The mixture was then concentrated and evaporated to dryness. The residue was dissolved in chloroform (20 mL) and washed with water (3 x 20 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated to a crystalline material or a waxy residue. All compounds were subjected to column chromatography (Silicagel 60 (Merck), 0.063-0.200 mm), EtOAc/$CHCl_3$, or EtOAc/MeOH/$CHCl_3$ (the exact ratios are specified in Section Characterization (3.4) for each compound). It has to be noted that some of the products are known compounds as indicated by the appropriate references. However, due to some novel analytical details the full characterization is given also in these cases.

3.3. Aminocarbonylation of diiodopyridine derivatives in the presence of various amines as N-nucleophiles under high carbon monoxide pressure

In a typical experiment, $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), triphenylphosphine (13.1 mg, 0.05 mmol), 2,5-diiodopyridine (331 mg, 1 mmol), 2,3-diiodopyridine (331 mg, 1 mmol) or 2-chloro-3,4-diiodopyridine (182.75 mg, 0.5 mmol), amine nucleophile (see above in the tables; 3 mmol of **a** / 2 mmol of **b** / 1.5 mmol of **c**, **d** / 1.1 mmol of **e**, **f**, **g**, **h**) and triethylamine (0.5mL) were dissolved in DMF (10 mL) under argon in a 100 mL autoclave. The atmosphere was changed to carbon monoxide and the autoclave was pressurized to the given pressure by carbon monoxide. The reaction was conducted for the given reaction time upon stirring at 50 ˚C and analysed by GC-MS (internal standard: naphthalene). The mixture was then concentrated and evaporated to dryness and worked-up as described in Section 3.2.

3.4. Characterization of the products

2,5-Bis-(*N-tert*-butylcarboxamido)pyridine (**2a**).[9] Yield: 168 mg (60%); white crystals, mp. 181 ˚C; [Found: C, 64.86; H, 8.58; N, 14.95; $C_{15}H_{23}N_3O_2$ requires C, 64.95; H, 8.36; N, 15.15%]; R_f (10% EtOAc, 90% $CHCl_3$) 0.22; δ_H (500 MHz, $CDCl_3$) 8.87 (1 H, d, 1.4 Hz, Py), 8.20 (1 H, d, 8.1 Hz, Py), 8.12 (1 H, dd, 8,1 Hz, 2.0 Hz, Py), 6.00 (1 H, brs, NH), 1.51 (18 H, s, 2x $C(CH_3)_3$); δ_C (125.7 MHz, $CDCl_3$) 164.4, 162.6 152.5, 146.6, 133.6, 131.1, 121.3, 52.3, 51.1, 28.8, 28.7; IR (KBr, ν (cm^{-1})): 3329 (NH), 1642 (CON); MS m/z (rel int.): 277 (22, M^+), 262 (100), 234 (8), 220 (6), 205 (35), 192 (22), 177 (35), 162 (6), 149 (12), 121 (10), 105 (6), 77 (12), 57 (35).

2-(*N-tert*-Butylcarboxamido)-5-(*N-tert*-butylglyoxylamido)pyridine (**3a**). Yield: 91 mg (33%); beige crystals, mp. 145 ˚C; [Found: C, 62.77; H, 7.50; N, 13.61; $C_{16}H_{23}N_3O_3$ requires C, 62.93; H, 7.59; N, 13.76%]; R_f (10% EtOAc, 90% $CHCl_3$) 0.60; δ_H (500 MHz, $CDCl_3$) 9.39 (1 H, d, 1.4 Hz, Py), 8.78 (1 H, dd, 8.2 Hz, 2.0 Hz, Py), 8.76 (1 H, d, 8.2 Hz, Py), 7.01 (1 H, brs, NH), 1.51 (9 H, s, $C(CH_3)_3$), 1.47 (9 H, s, $C(CH_3)_3$); δ_C

(125.7 MHz, $CDCl_3$) 186.9, 162.2, 159.8, 153.8, 150.4, 140.1, 130.7, 121.1, 51.9, 51.2, 28.6, 28.3; IR (KBr, ν (cm^{-1})): 3282 (NH), 1672 (br, CO + CON); MS m/z (rel int.): 279 (71, M^+), 262 (100), 222 (9), 205 (36), 177 (36), 149 (12), 121 (10), 100 (5), 77 (12), 57 (29)

2,5-Bis-(*N*-phenylcarboxamido)pyridine (**2b**).[10] Yield: 193 mg (61 %); off-white crystals, mp. >250 ˚C; [Found: C, 71.76; H, 4.90; N, 13.05; $C_{19}H_{15}N_3O_2$ requires C, 71.91; H, 4.76; N, 13.24%]; R_f (10% EtOAc, 90% $CHCl_3$) 0.22; δ_H (500 MHz, DMSO-d_6) 10.78 (1 H, brs, NH), 10.65 (1 H, brs, NH), 9.21 (1 H, d, 1.6 Hz, Py), 8.56 (1 H, dd, 8.1 Hz, 2.1 Hz, Py), 8.31 (1 H, d, 8.1 Hz, Py), 7.94 (2 H, d, 7.7 Hz, Ph (*ortho*)), 7.80 (2 H, d, 7.7 Hz, Ph (*ortho*)), 7.43-7.36 (overlapping 4 H, m, Ph (*meta*)), 7.19-7.12 (overlapping 2 H, m, Ph (*para*)); δ_C (125.7 MHz, DMSO-d_6) 163.9, 162.4, 152.3, 148.2, 139.1, 138.7, 137.8, 133.5, 129.3, 129.2, 124.7, 124.6, 122.6, 120.9 (overlapping of two signals); IR (KBr, ν (cm^{-1})): 3362, 3317 (NH), 1642 (CON); MS m/z (rel int.): 317 (100, M^+), 281 (3), 225 (17), 198 (51), 120 (12), 105 (5), 77 (25), 65 (10), 51 (7).

2,5-Bis-(*N*,*N*-pentane-1',5'-diylcarboxamido)pyridine (**2c**). Yield: 106 mg (35%); off-white crystals, mp. 146 ˚C; [Found: C, 71.26; H, 7.98; N, 14.56; $C_{17}H_{23}N_3O_2$ requires C, 71.55; H, 8.12; N, 14.72%]; R_f (2% MeOH, 98% $CHCl_3$) 0.16; δ_H (500 MHz, $CDCl_3$) 8.60 (1 H, s, Py), 7.81 (1 H, dd, 7.9 Hz, 1.5 Hz, Py), 7.60 (1 H, d, 7.9 Hz, Py), 3.80-3.64 (4 H, brs, N-CH_2), 3.45-3.39 (2 H, m, N-CH_2), 3.39-3.23 (2 H, brs, N-CH_2), 1.72-1.61 (8 H, brs, CH_2), 1.61-1.49 (4 H, brs, CH_2); δ_C (125.7 MHz, $CDCl_3$) 167.0, 166.8, 155.3, 146.4, 135.8, 132.7, 122.9, 48.8, 48.3, 43.3, 43.2, 26.5, 26.4, 25.5, 24.5, 24.4; IR (KBr, ν (cm^{-1})): 1625 (br, CON); MS m/z (rel int.): 301 (5, M^+), 273 (1), 256 (3), 234 (1), 217 (16), 190 (8), 164 (1), 131 (1), 84 (100).

2-(*N*,*N*-Pentane-1',5'-diylcarboxamido)-5-(*N*,*N*-pentane-1',5'-diylglyoxylamido)pyridine (**3c**). Yield: 112.8 mg (34 %); orange viscous oil; [Found: C, 65.56; H, 7.18; N, 12.55; $C_{18}H_{23}N_3O_3$ requires C, 65.63; H, 7.04; N, 12.76%]; R_f (2% MeOH, 98% $CHCl_3$) 0.51; δ_H (500 MHz, $CDCl_3$) 9.09 (1 H, d, 1.2 Hz, Py), 8,33 (1 H, dd, 8.1 Hz, 2.0 Hz, Py), 7.7 (1 H, d, 8.1 Hz, Py), 3.77-3.68 (4 H, m, N-CH_2), 3.60-3.54 (2 H, m, N-CH_2), 3.36-3.29 (2 H, m, N-CH_2), 1.78-1.62 (12 H, m, CH_2); δ_C (125.7 MHz, $CDCl_3$) 189.5, 166.3, 164.1, 159.3, 150.1, 137.7, 128.9, 123.4, 48.2, 47.1, 43.3, 42.5, 26.3, 25.5, 25.4, 24.4, 24.3; IR (KBr, ν (cm^{-1})): 1684 (CO), 1647 (br, CON); MS m/z (rel int.): 329 (7, M^+), 301 (3), 245 (7), 217 (3), 189 (2), 112 (10), 84 (100), 56 (7).

2,5-Bis-(*N*,*N*-pentane-3'-oxa-1',5'-diylcarboxamido)pyridine (**2d**). Yield: 100 mg (36%); white crystals, mp. 160 ˚C; [Found: C, 59.26; H, 6.48; N, 13.60; $C_{15}H_{19}N_3O_4$ requires C, 59.01; H, 6.27; N, 13.76 %]; R_f (3% MeOH, 97% $CHCl_3$) 0.32; δ_H (500 MHz, $CDCl_3$) 8.61 (1 H, s, Py), 7.83 (1 H, dd, 8.0 Hz, 2.0 Hz, Py), 7.81 (1 H, d, 8.1 Hz, Py), 3.89-3.70 (8 H, brs, O-CH_2), 3.70-3.64 (4 H, brs, N-CH_2), 3.64-3.50 (4 H, brs, N-CH_2); δ_C (125.7 MHz, $CDCl_3$) 167.0, 166.5, 154.7, 146.6, 136.1, 131.9, 123.9, 66.9, 66.7, 48.2, 47.7, 42.8, 42.7; IR (KBr, ν (cm^{-1})): 1626 (CON); MS m/z (rel int.): 277 (22, M^+), 305 (19, M^+), 247 (1), 219 (34), 192 (38), 161 (2), 134 (7), 86 (100).

2-(*N*,*N*-Pentane-3'-oxa-1',5'-diylcarboxamido)-5-(*N*,*N*-pentane-3'-oxa-1',5'-diylglyoxylamido)pyridine (**3d**). Yield: 55 mg (17%); orange crystals, mp. 122 ˚C; [Found: C, 57.56; H, 5.59; N, 12.55; $C_{16}H_{19}N_3O_5$ requires C, 57.65; H, 5.75; N, 12.61 %]; R_f (3% MeOH, 97% $CHCl_3$) 0.24; δ_H (500 MHz, $CDCl_3$) 9.11 (1 H, d,

1.3 Hz, Py), 8.36 (1 H, dd, 8.2 Hz, 2.1 Hz, Py), 7.80 (1 H, d, 8.1 Hz, Py), 3.81-3.78 (8 H, m, O-*CH*$_2$), 3.72-3.68 (4 H, m, N-*CH*$_2$), 3.62-3.58 (2 H, m, N-*CH*$_2$), 3.46-3.42 (2 H, m, N-*CH*$_2$); δ_C (125.7 MHz, $CDCl_3$) 188.5, 166.1, 163.8, 158.2, 149.9, 138.0, 129.1, 124.3, 66.9, 66.7, 66.6, 66.4, 47.7, 46.3, 42.8, 41.9; IR (KBr, ν (cm^{-1})): 1678 (CO), 1644 (CON); MS m/z (rel int.): 333 (18, M^+), 305 (1), 247 (18), 220 (16), 191 (1), 161 (1), 134 (1), 114 (18), 86 (100)

2,5-Bis-(*N*-(1'-methoxycarbonylethyl)carboxamido)pyridine **(2f)**. Yield: 29.7 mg (9%); yellow viscous oil; [Found: C, 53.26; H, 5.50; N, 12.15; $C_{15}H_{19}N_3O_6$ requires C, 53.41; H, 5.68; N, 12.46%];R_f (50% EtOAc, 50% $CHCl_3$) 0.31; δ_H (500 MHz, $CDCl_3$) 8.99 (1 H, d, 1.3 Hz, Py), 8.50 (1 H, d, 7.7 Hz, NH); 8.24 (1 H, dd, 8.1 Hz, 2.1 Hz, Py), 8.1 (1 H, d, 8.1 Hz, Py), 7.17 (1 H, d, 7.1 Hz, NH); 4.81 (overlapping, 2x quintets, 2 H, m, N-*CH*); 3.81 (3 H, s, O-*CH*$_3$), 3.79 (3 H, s, O-*CH*$_3$),1.56 (overlapping, 2x doublets, 6 H, t, 6.6 Hz, CH*CH*$_3$); δ_C (125.7 MHz, $CDCl_3$) 173.4, 173.1, 164.4, 163.1, 151.5,147.3, 136.3, 131.8, 122.0, 52.7, 52.6, 48.7, 48.2, 18.3, 18.2; IR (KBr, ν (cm^{-1})): 3342 (NH), 1747 (COO), 1663 (CON); MS m/z (rel int.): 337 (1, M^+), 322 (1), 306 (1), 278 (100), 235 (30), 207 (31), 192 (1), 175 (1), 162 (1), 148 (8), 133 (1), 120 (2), 77 (8), 59 (1).

2-(*N*-(1'-Methoxycarbonylethyl)carboxamido)-5-(*N*-(1'-methoxycarbonylethyl)glyoxylamido)pyridine (**3f**). Yield: 45 mg (12%); yellow viscous oil; [Found: C, 52.40; H, 5.48; N, 11.25; $C_{16}H_{19}N_3O_7$ requires C, 52.60; H, 5.24; N, 11.50%]; R_f (50% EtOAc, 50% $CHCl_3$) 0.57; δ_H (500 MHz, $CDCl_3$) 9.49 (1 H, d, 1.3 Hz, Py), 8.79 (1 H, dd, 8.1 Hz, 2.0 Hz, Py), 8.55 (1 H, d, 7.7 Hz, NH), 8.30 (1 H, d, 8.1 Hz, Py), 7.69 (1 H, d, 7.5 Hz, NH),4.82 (1 H, quintet, 7.4 Hz, N-*CH*), 4.69 (1 H, qi, 7.4 Hz, N-*CH*), 3.82 (3 H, s, O-*CH*$_3$), 3.81 (3 H, s, O-*CH*$_3$),1.58(3 H, d, 7.3 Hz, CH*CH*$_3$), 1.56(3 H, d, 7.3 Hz, CH*CH*$_3$); δ_C (125.7 MHz, $CDCl_3$) 185.3, 172.9, 172.2, 162.8, 159.9, 152.7, 150.9, 140.1, 130.9, 121.9, 52.8, 52.6, 48.3, 48.2, 18.4, 18.0. IR (KBr, ν (cm^{-1})): 3371 (NH), 1744 (overlapping COO, CO), 1676 (CON); MS m/z (rel int.): 365 (1, M^+), 334 (1), 306 (100), 288 (1), 263 (2), 235 (25), 208 (2), 192 (1), 175 (2), 148 (17), 120 (2), 102 (17), 77 (17), 59 (10).

2-(*N*-(1'-methoxycarbonylethyl)carboxamido)-5-iodopyridine (**4f**). Yield: 45 mg (13%) off-white viscous oil; [Found: C, 35.81; H, 3.57; N, 8.25; $C_{10}H_{11}IN_2O_3$ requires C, 35.95; H, 3.32; N, 8.38%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.78; δ_H (500 MHz, $CDCl_3$) 8.80 (1 H, d, 1.7 Hz, Py), 8.37 (1 H, d, 7.1 Hz, NH); 8.19 (1 H, dd, 8.1 Hz, 2.0 Hz, Py), 7.95 (1 H, d, 8.1 Hz, Py), 4.79 (1 H, qi, 7.4 Hz, N-*CH*); 3.79 (3 H, s, O-*CH*$_3$),1.55(3 H, d, 7.3 Hz, CH*CH*$_3$); δ_C (125.7 MHz, $CDCl_3$) 173.1, 163.4, 154.3, 148.3, 145.8, 124.0, 97.3, 52.5, 48.1, 18.4; IR (KBr, ν (cm^{-1})): 3384 (NH), 1743 (COO), 1683 (CON); MS m/z (rel int.): 334 (1, M^+), 319 (1), 306 (1), 291 (1), 275 (100), 257 (1), 232 (43), 204 (40), 191 (1), 177 (1), 164 (1), 148 (2), 133 (1), 120 (1), 105 (1), 92 (1), 77 (17), 64 (1), 50 (2).

2,3-Bis-(*N*-*tert*-butylcarboxamido)pyridine (**6a**)**.** Yield: 134 mg (48 %); cream-colored crystals; [Found: C, 64.77; H, 8.18; N, 15.02; $C_{15}H_{23}N_3O_2$ requires C, 64.95; H, 8.36; N, 15.15%]; mp. 113 ˚C; R_f (3 % MeOH, 97 % $CHCl_3$) 0.58; δ_H (500 MHz, $CDCl_3$) 8.54 (1 H, dd, 4.9 Hz, 1.4 Hz, *Py*), 8.16 (1 H, dd, 7.7 Hz, 1.4 Hz, *Py*), 7.68 (1 H, brs, *NH*), 7.45 (2 H, overlapping dd és brs, 7.7 Hz, 4.9 Hz, *Py, NH*), 1.49 (9 H, s, *C(CH*$_3$*)*$_3$), 1.48 (9 H, s, *C(CH*$_3$*)*$_3$); δ_C (125.7 MHz, $CDCl_3$)165.9, 165.2, 148.8, 148.5, 139.0, 133.2, 125.3, 51.6, 51.5,

28.7, 28.6; IR (KBr, ν (cm^{-1})): 3353, 3267 (NH), 1663, 1635 (CON). MS m/z (rel int.): 277 (4, M^+), 220 (4), 205 (30), 177 (26), 149 (100), 133 (5), 121 (4), 105 (3), 93 (6), 58 (13).

2,3-Bis-(*N*-phenylcarboxamido)pyridine (**6b**) Yield: 27 mg (9%); off-white crystals; [Found: C, 71.76; H, 4.59; N, 13.05; $C_{19}H_{15}N_3O_2$ requires C, 71.91; H, 4.76; N, 13.24%]; mp. 218-219 ^oC; R_f (20% EtOAc, 80% $CHCl_3$) 0.46; δ_H (500 MHz, DMSO-d_6) 10.66 (1 H, brs, NH), 10.43 (1 H, brs, NH), 8.80 (1 H, dd, 4.9 Hz, 1.4 Hz, *Py*), 8.08 (1 H, dd, 7.7 Hz, 1.4 Hz, *Py*), 7.82 (2 H, d, 7.7 Hz, Ph (*ortho*)), 7.75 (1 H, dd, 7.7 Hz, 4.9 Hz,*Py*), 7.69 (2 H, d, 7.7 Hz, Ph (*ortho*)), 7.37-7.31 (overlapping 4 H, m, Ph (*meta*)), 7.13-7.08 (overlapping 2 H, m, Ph (*para*)); δ_C (125.7 MHz, DMSO-d_6) 166.4, 163.3, 149.2, 148.9, 139.9, 139.0, 137.5, 134.2, 129.2, 129.1, 126.4, 124.3, 123.9, 120.5, 120.0; IR (KBr, ν (cm^{-1})): 3311 (NH), 1672 (CON).

6-Phenyl-5*H*-pyrrolo[3,4-b]pyridine-5,7(6*H*)-dion **(8b).** Yield: 148 mg (66%); beige crystals; [Found: C, 69.46; H, 3.78; N, 12.35; $C_{13}H_8N_2O_2$ requires C, 69.64; H, 3.60; N, 12.49%]; mp. 212-213 ˚C; R_f (20% EtOAc, 80% $CHCl_3$) 0.54; δ_H (500 MHz, $CDCl_3$) 9.06 (1 H, dd, 4.9 Hz, 1.4 Hz, *Py*), 8.28(1 H, dd, 7.7 Hz, 1.4 Hz,*Py*), 7.71 (1 H, dd, 7.7 Hz, 4.9 Hz, *Py*), 7.55 (2 H, d, 7.7 Hz,Ph (*ortho*)), 7.50-7.41 (overlapping 3 H, m, Ph (*meta*) + Ph (*para*)); δ_C (125.7 MHz, $CDCl_3$)165.2, 165.1, 155.8, 151.2, 131.7, 131.1, 129.3, 128.5, 127.8, 127.0, 126.5; IR(KBr, ν (cm^{-1})): 1745, 1712 (CON); MS m/z (rel int.): 224 (100, M^+), 196 (10), 180 (39), 167 (6), 154 (3), 140 (5), 119 (3), 105 (20), 91 (9), 77 (45).

2,3-Bis-(*N*,*N*-pentane-1',5'-diylcarboxamido)pyridine (**6c**). Yield: 101 mg (34%); yellow crystals; [Found: C, 67.66; H, 7.58; N, 13.75; $C_{17}H_{23}N_3O_2$ requires C, 67.75; H, 7.69; N, 13.94%]; mp. 94-96 ˚C; R_f (5% MeOH, 15% EtOAc, 80% $CHCl_3$). 0.40; δ_H (500 MHz, $CDCl_3$) 8.55 (1 H, dd, 4.9 Hz, 1.5 Hz, Py), 7.59 (1 H, dd, 7.7 Hz, 1.4 Hz, Py), 7.30 (1 H, dd, 7.7 Hz, 4.9 Hz Py), 3.70-3.62 (4 H, brs, N-CH_2), 3.30-3.21 (4 H, m, N-CH_2), 1.67-1.58 (12 H, m, CH_2); δ_C (125.7 MHz, $CDCl_3$) 166.9, 166.5, 152.9, 148.7, 134.4, 131.9, 123.1, 48.7, 48.2, 42.9, 42.8, 26.0, 25.9, 25.4, 25.3, 24.5, 24.4; IR (KBr, ν (cm^{-1})): 1635 (CON); MS m/z (rel int.): 301 (8, M^+), 277 (1), 245 (1), 231 (1), 217 (33), 188 (17), 161 (17), 149 (8), 131 (8), 106 (17), 84 (100), 69 (2)

2-(*N*,*N*-Pentane-1',5'-carboxamido)-3-(*N*,*N*-pentane-1',5'-diylglyoxylamido)pyridine (**7c**). Yield: 95 mg (29%); orange viscous oil; [Found: C, 65.46; H, 7.28; N, 12.61; $C_{18}H_{23}N_3O_3$ requires C, 65.63; H, 7.04; N, 12.76%]; R_f (5% MeOH, 15% EtOAc, 80% $CHCl_3$). 0.51; δ_H (500 MHz, $CDCl_3$) 8.68 (1 H, dd, 4.8 Hz, 1.5 Hz, Py), 8.27 (1 H, dd, 7.9 Hz, 1.5 Hz, Py), 7.43 (1 H, dd, 7.9 Hz, 4.8 Hz, Py), 3.61-3.52 (4 H, m, N-CH_2), 3.59-3.56 (2 H, m, 2xN-CH_2), 3.41-3.35 (2 H, m, N-CH_2), 3.35-3.29 (2 H, m, N-CH_2); 1.66-1.60 (12 H, m, CH_2). δ_C (125.7 MHz, $CDCl_3$) 198.9, 166.5, 164.1, 156.2, 151.5, 138.9, 130.0, 123.8, 48.2, 47.2, 42.9, 42.5, 25.8, 25.7, 25.3, 25.2, 24.5, 24.4; IR (KBr, ν (cm^{-1})): 1684 (CO), 1642 (CON); MS m/z (rel int.): 329 (1, M^+), 301 (1), 277 (1), 246 (1), 232 (1), 217 (100), 207 (1), 189 (1), 161 (17), 134 (2), 106 (6), 84 (17), 69 (6).

2-(*N*,*N*-Pentane-3'-oxa-1',5'-diylcarboxamido)-3-(*N*,*N*-pentane-3'-oxa-1',5'-diylglyoxylamido)pyridine (**7d**). Yield: 210 mg (63%); off-white crystals; mp. 124-125 ^oC; [Found: C, 57.56; H, 5.66; N, 12.55; $C_{16}H_{19}N_3O_5$ requires C, 57.65; H, 5.75; N, 12.61%]; R_f (5% MeOH, 15% EtOAc, 80% $CHCl_3$) 0.16; δ_H (500 MHz, $CDCl_3$) 8.69 (1 H, dd, 4.8 Hz, 1.4 Hz, Py), 8.30 (1 H, dd, 7.9 Hz, 1.5 Hz, Py), 8.12 (1 H, dd, 7.9 Hz, 4.8

Hz, Py), 3.82-3.75 (8 H, m, O-*CH*$_2$), 3.71-3.66 (8 H, m, N-*CH*$_2$); δ_C (125.7 MHz, $CDCl_3$) 187.8, 166.7, 164.0, 155.0, 151.1, 138.9, 131.6, 124.5, 66.8, 66.7, 66.5, 66.4, 47.8, 46.5, 42.6, 42.1; IR (KBr, ν (cm^{-1})): 1763 (CO), 1677, 1642 (CON); MS m/z (rel int.): 219 (100, M^+-114), 191 (1), 183 (1), 148 (6), 114 (2), 106 (8), 86 (4), 78 (11), 70 (8).

2-(*N*,*N*-Pentane-3'-oxa-1',5'-diylglyoxylamido)-3-(*N*,*N*-pentane-3'-oxa-1',5'-diylcarboxamido)pyridine (**7'd**). Yield: 46 mg (14%); orange viscous oil; [Found: C, 57.46; H, 5.58; N, 12.45; $C_{16}H_{19}N_3O_5$ requires C, 57.65; H, 5.75; N, 12.61%]; R_f (5% MeOH, 15% EtOAc, 80% $CHCl_3$) 0.08; δ_H (500 MHz, $CDCl_3$) 8.80 (1 H, dd, 4.7 Hz, 1.4 Hz, Py), 7.79 (1 H, dd, 7.7 Hz, 1.4 Hz, Py), 7.61 (1 H, dd, 7.8 Hz, 4.7 Hz, Py), 3.89-3.74 (8 H, m, O-*CH*$_2$), 3.70-3.66 (2 H, m, N-*CH*$_2$),3.62-3.60 (2 H, m, N-*CH*$_2$), 3.41-3.39 (2 H, m, N-*CH*$_2$), 3.25-3.22 (2 H, m, N-*CH*$_2$); δ_C (125.7 MHz, $CDCl_3$) 190.6, 166.6, 165.6, 150.1, 147.5, 136.1, 133.3, 127.8, 66.6, 66.5, 66.3 (double intensity), 47.1, 46.1, 42.2, 41.7; IR (KBr, ν (cm^{-1})): 1702 (CO), 1650, 1644 (CON); MS m/z (rel int.): 247 (38, M^+-86), 219 (100), 191 (1), 185 (2), 148 (7), 114 (5), 106 (14), 86 (9), 78 (18), 70 (18).

Methyl-2-(5,7-dioxo-5*H*-pyrrolo[3,4-b]pyridine-6(7*H*)-yl)acetate (**8e**).[11] Yield: 125 mg (57%); pale brown crystals; [Found: C, 54.36; H, 3.78; N, 12.65; $C_{10}H_8N_2O_4$ requires C, 54.55; H, 3.66; N, 12.72%]; mp. 100-101 ˚C; R_f (2% MeOH, 18% EtOAc, 80% $CHCl_3$) 0.68; δ_H (500 MHz, $CDCl_3$) 8.94 (1 H, dd, 4.9 Hz, 1.5 Hz, *Py*), 8.17 (1 H, dd, 7.6 Hz, 1.5 Hz, *Py*), 7.63 (1 H, dd, 7.6 Hz, 4.9 Hz, *Py*), 4.46 (2 H, s, *CH*$_2$), 3.71 (3 H, s, O*CH*$_3$); δ_C (125.7 MHz, $CDCl_3$) 167.3, 165.4, 165.2, 155.5, 151.5, 131.5, 127.7, 127.3, 52.8, 38.8; IR (KBr, ν (cm^{-1})): 1792 (COO), 1759, 1721 (CON); MS m/z (rel int.): 220 (12, M^+), 189 (1), 161 (100), 133 (5), 106 (28), 78 (22), 51 (10).

Methyl-2-(5,7-dioxo-5*H*-pyrrolo[3,4-b]pyridine-6(7*H*)-yl)propanoate (**8f**). Yield: 134 mg (58 %); white crystals; [Found: C, 56.21; H, 4.18; N, 11.77; $C_{11}H_{10}N_2O_4$ requires C, 56.41; H, 4.30; N, 11.96%]; mp. 90-91 ˚C; R_f (2% MeOH, 18% EtOAc, 80% $CHCl_3$) 0,66; δ_H (500 MHz, $CDCl_3$) 9.00 (1 H, dd, 4.9 Hz, 1.4 Hz, *Py*), 8.20 (1 H, dd, 7.7 Hz, 1.4 Hz, *Py*), 7.66 (1 H, dd, 7.7 Hz, 4.9 Hz, *Py*), 5.06 (1 H, q, 7.4 Hz N-*CH*), 3.76 (3 H, s, O*CH*$_3$),1.74 (3 H, d, 7.4 Hz CH*CH*$_3$). δ_C (125.7 MHz, $CDCl_3$) 169.8, 165.4, 165.3, 155.5, 151.5, 131.5, 127.6, 127.2, 52.9, 47.7, 15.3; IR (KBr, ν (cm^{-1})): 1791 (COO), 1758, 1712 (CON); MS m/z (rel int.): 234 (4, M^+), 175 (100), 148 (22), 131 (15), 105 (11), 78 (14), 51 (5).

Methyl-2-(5,7-dioxo-5*H*-pyrrolo[3,4-b]pyridine-6(7*H*)-yl)-3-methylbutanoate (**8g**). Yield: 124 mg (57 %); beige crystals; [Found: C, 59.26; H, 5.57; N, 10.60; $C_{13}H_{14}N_2O_4$ requires C, 59.54; H, 5.38; N, 10.68%]; mp. 82-83 ˚C; R_f (20% EtOAc, 80% $CHCl_3$) 0.62; δ_H (500 MHz, $CDCl_3$) 9.03 (1 H, dd, 4.9 Hz, 1.4 Hz, *Py*), 8.22 (1 H, dd, 7.6 Hz, 1.4 Hz, *Py*), 7.68 (1 H, dd, 7.6 Hz, 4.9 Hz, *Py*), 4.68 (1 H, d, 8.3 Hz, N*CH*), 3.74 (3 H, s, O*CH*$_3$), 2.87-2.75 (1 H, m, *CH*(CH_3)$_2$), 1.19 (3H, d, 6.7 Hz, CH(*CH*$_3$)$_2$), 0.95 (3 H, d, 6.8 Hz CH(*CH*$_3$)$_2$); δ_C (125.7 MHz, $CDCl_3$) 168.9, 165.7, 165.6, 155.6, 151.3, 131.5, 127.6, 127.0, 57.9, 52.5, 28.6, 20.9, 19.4. IR(KBr, ν (cm^{-1})): 1783 (CON), 1751 (COO), 1720 (CON); MS m/z (rel int.): 262 (7, M^+), 230 (3), 203 (100), 188 (13), 149 (42), 133 (13), 105 (20), 77 (22), 55 (8).

6-(Pyridine-4-ylmethyl)-5*H*-pyrrolo[3,4-b]pyridine-5,7(6*H*)-dione (**8h**):[12] Yield: 166 mg (69%); beige crystals; [Found: C, 65.20; H, 3.98; N, 17.55; $C_{13}H_9N_3O_2$ requires C, 65.27; H, 3.79; N, 17.56%]; mp.172-173 ˚C; R_f (3% MeOH, 97% $CHCl_3$) 0.60; δ_H (500 MHz, $CDCl_3$) 9.00 (1 H, dd, 4.9 Hz, 1.4 Hz, *Py*), 8.56 (2 H, dd, 4.4 Hz, 1.5 Hz, *Py*), 8.19 (1 H, dd, 7.7 Hz, 1.4 Hz, *Py*), 7.65 (1 H, dd, 7.7 Hz, 4.9 Hz, *Py*,), 7.31 (2 H, dd, 4.4 Hz, 1.5 Hz, *Py*), 4.90 (2 H, s, CH_2); δ_C(125.7 MHz, $CDCl_3$)165.7, 165.6, 155.6, 151.5, 150.3, 144.2, 131.5, 127.7, 127.3, 123.1 40.7; IR(KBr, ν (cm^{-1})): 1784, 1713 (CON); MS m/z (rel int.): 239 (100, M^+), 211 (17), 189 (31), 161 (6), 155 (7), 131 (3), 105 (18), 79 (45), 51 (7).

2-Chloro-3,4-bis-(*N-tert*-butylcarboxamido)pyridine (**10a**). Yield: 104 mg (66%); off-wihte crystals; [Found: C, 57.66; H, 7.38; N, 13.35; $C_{15}H_{22}ClN_3O_2$ requires C, 57.78; H, 7.11; N, 13.48%]; mp. 209 ˚C; R_f (3% MeOH, 97% $CHCl_3$) 0.44; δ_H (500 MHz, $CDCl_3$) 8.22 (1 H, d, 5.0 Hz, Py), 7.32 (1 H, d, 5.0 Hz, Py), 7.09 (1 H, brs, NH), 6.88 (1 H, brs, NH), 1.53 (9 H, s, $C(CH_3)_3$), 1.42 (9 H, s, $C(CH_3)_3$); δ_C (125.7 MHz, $CDCl_3$) 165.1, 163.6, 149.7, 147.9, 144.4, 129.8, 122.1, 53.1, 52.5, 28.5, 28.4; IR (KBr, ν (cm^{-1})): 3274 (CON), 1654, 1642 (CON); MS m/z (rel int.): 311 (2, M^+), 296 (1), 276/274 (9/3), 241/239 (6/18), 185/183 (34/100), 167/165 (2/6), 140 (6), 112 (4), 74 (4), 58 (44).

2-Chloro-3-iodo-4-(*N-tert*-butylcarboxamido)pyridine (**11a**). Yield: 77 mg (45%); yellow crystals; [Found: C, 35.26; H, 3.78; N, 8.05; $C_{10}H_{12}ClIN_2O$ requires C, 35.47; H, 3.57; N, 8.27%]; mp. 202 ˚C; R_f (20% EtOAc, 80% $CHCl_3$) 0.56; δ_H (500 MHz, $CDCl_3$) 8.35 (1 H, d, 4.7 Hz, *Py*), 7.12 (1 H, d, 4.7 Hz, *Py*), 5.57 (1 H, brs, N*H*), 1.51 (9 H, s, $C(CH_3)_3$); δ_C (125.7 MHz, $CDCl_3$) 166.4, 156.1, 154.5, 149.1, 120.2, 93.7, 52.9, 28.6. IR (KBr, ν (cm^{-1})): 3297 (NH), 1657 (CON); MS m/z (rel int.): 340/338 (10/31, M^+), 325/323 (15/45),285/283 (13/39), 268/266 (33/100), 240/238 (6/18), 213/211 (2/8), 177 (2), 140 (6), 112 (6), 84 (12), 76 (7), 57 (12).

2-(*tert*-Butyl)-4-chloro-1*H*-pyrrolo[3,4-c]pyridine-1,3(2*H*)-dione (**12a**)**.** Yield: 15 mg (13%); pale brown crystals; [Found: C, 55.26; H, 4.58; N, 11.61; $C_{11}H_{11}ClN_2O_2$ requires C, 55.36; H, 4.65; N, 11.74%]; mp. 151 ˚C; R_f (20 % EtOAc, 80% $CHCl_3$) 0.82; δ_H (500 MHz, $CDCl_3$) 8.79 (1 H, d, 4.7 Hz, *Py*), 7.67 (1 H, d, 4.7 Hz, *Py*), 1.72(9 H, s, $C(CH_3)_3$); δ_C (125.7 MHz, $CDCl_3$) 166.4, 166.3, 155.1, 146.7, 142.8, 123.0, 115.6, 59.2, 28.9; IR (KBr, ν (cm^{-1})): 1779, 1711 (CON); MS m/z (rel int.): 240/238 (27, M^+), 225/223 (34/100), 185/183 (34/98), 167/165 (10/29), 147 (15), 119 (3), 104 (12), 84 (19), 76 (14), 56 (17).

2-Phenyl-4-chloro-1*H*-pyrrolo[3,4-c]pyridine-1,3(2*H*)-dione (**12b**). Yield: 45 mg (36%); orange crystals; [Found: C, 60.20; H, 2.93; N, 10.65; $C_{13}H_7ClN_2O_2$ requires C, 60.36; H, 2.73; N, 10.83%]; mp.250 ˚C; R_f (5% EtOAc, 95% $CHCl_3$) 0.59; δ_H (500 MHz, $CDCl_3$) 8.93 (1 H, d, 4.7 Hz, *Py*), 7.85 (1 H, d, 4.7 Hz, *Py*), 7.56 (2 H, t, 7.6 Hz, Ph (*meta*)), 7.44 (2 H, d, 7.6 Hz, Ph (*ortho*)), 7.38 (1 H, t, 7.6 Hz, Ph (*para*)); δ_C (125.7 MHz, $CDCl_3$) 164.3, 163.9, 155.9, 147.8, 142.4, 130.8, 129.3, 128.8, 126.5, 122.8, 116.4; MS m/z (rel int.): 260/258 (34/100, M^+), 216/214 (13/39), 179 (32), 141/139 (4/13), 113/111 (3/9), 104 (7), 84 (12), 76 (8).

Methyl-2-(4-chloro-1,3-dioxo-1*H*-pyrrolo[3,4-c]pyridin-2(3*H*)-yl)acetate (**12e**). Yield: 43 mg (34%); yellow crystalline solid; [Found: C, 47.06; H, 2.88; N, 10.85; $C_{10}H_7ClN_2O_4$ requires C, 47.17; H, 2.77; N,

11.00%]; mp. 133-134 ˚C; R_f (20% EtOAc, 80% $CHCl_3$) 0.70; δ_H (500 MHz, $CDCl_3$) 8.89 (1 H, d, 4.7 Hz, *Py*), 7.78 (1 H, d, 4.7 Hz, *Py*), 4.49 (2 H, s, *CH*$_2$), 3.81 (3 H, s, *CH*$_3$); δ_C (125.7 MHz, $CDCl_3$) 167.0, 164.5, 164.1, 155.9, 147.5, 142.5, 123.2, 116.3, 53.0, 39.2; IR (KBr, ν (cm^{-1})): 1785 (COO), 1749, 1727 (CON); MS m/z (rel int.): 256/254 (3/10, M^+), 223 (1), 197/195 (34/100), 170/168 (1/3), 141/139 (3/9), 114/112 (2/6), 84 (6), 76 (6), 59 (3).

2-Chloro-3-iodo-4-(*N*-(1'-Methoxycarbonylmethyl)carboxamido)pyridine (**11e**)**.** Yield: 30 mg (18%); pale yellow crystals; [Found: C, 30.26; H, 2.48; N, 7.69; $C_9H_8ClIN_2O_3$ requires C, 30.49; H, 2.27; N, 7.90%]; mp. 94-95 ˚C; R_f (20% EtOAc, 80% $CHCl_3$) 0.26; δ_H (500 MHz, $CDCl_3$) 8.39 (1 H, d, 4.7 Hz, *Py*), 7.19 (1 H, d, 4.7 Hz, *Py*), 6.56 (1 H, brs, *NH*), 4.27 (2 H, d, 5.3 Hz,*CH*$_2$,), 3.84 (3 H, s, CH_3). δ_C (125.7 MHz, $CDCl_3$) 169.5, 167.0, 156.4, 153.1, 149.1, 120.5, 93.7, 52.7, 41.6; IR (KBr, ν (cm^{-1})): 3281 (NH), 1738 (COO), 1646 (CON); MS m/z (rel int.): 356/354 (23/69, M^+), 297/295 (15/45), 268/266 (34/100), 240/238 (6/19), 213/211 (2/6), 167 (2), 142/140 (1/3), 113/111 (1/4), 86/84 (3/9), 76 (6), 59 (2).

Methyl-2-(4-chloro-1,3-dioxo-1*H*-pyrrolo[3,4-c]pyridin-2(3*H*)-yl)propanoate **12f**)**.** Yield: 96 mg (72%); yellow viscous oil; [Found: C, 49.29; H, 3.54; N, 10.25; $C_{11}H_9ClN_2O_4$ requires C, 49.18; H, 3.38; N, 10.43%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.72; δ_H (500 MHz, $CDCl_3$) 8.88 (1 H, d, 4.7 Hz, *Py*), 7.76 (1 H, d, 4.7 Hz, *Py*), 5,03 (1 H, q, 7.4 Hz, N-*CH*), 3.79 (3 H, s, O*CH*$_3$,), 1.74 (3 H, s, CH*CH*$_3$); δ_C (125.7 MHz, $CDCl_3$) 169.4, 164.4, 164.1, 155.8, 147.4, 142.5, 123.1, 116.3, 53.0, 48.1, 15.1; IR (KBr, ν (cm^{-1})): 1787 (COO), 1748, 1724 (CON); MS m/z (rel int.): 270/268 (1/3, M^+), 211/209 (33/100), 173 (17), 139 (6), 104 (6), 84 (5), 76 (5), 59 (1).

Methyl-2-(4-chloro-1,3-dioxo-1*H*-pyrrolo[3,4-c]pyridin-2(3*H*)-yl)-3-methylbutanoate (**12g**). Yield 80 mg (54%); yellow viscous oil; [Found: C, 52.44; H, 4.54; N, 9.30; $C_{13}H_{13}ClN_2O_4$ requires C, 52.62; H, 4.42; N, 9.44%]; R_f (5% EtOAc, 95% $CHCl_3$) 0.60; δ_H (500 MHz, $CDCl_3$) 8.87 (1 H, d, 4.7 Hz, *Py*), 7.76 (1 H, d, 4.7 Hz, *Py*), 4.61 (1 H, d, 8.2 Hz, N-*CH*), 3.73 (3 H, s, O*CH*$_3$,), 2.82-2.72 (1 H, m, *CH*(CH_3)$_2$), 1.15 (3 H, d 6.7 Hz, CH(*CH*$_3$)$_2$), 0.91 (3 H, d, 6.8 Hz CH(*CH*$_3$)$_2$); δ_C (125.7 MHz, $CDCl_3$) 168.5, 164.8, 164.5, 155.8, 147.4, 142.3, 122.9, 116.3, 58.2, 52.7, 28.6 , 20.9, 19.5; IR (KBr, ν (cm^{-1})): 1785 (COO), 1748, 1725 (CON); MS m/z (rel int.): 298/296 (2/7, M^+), 258/256 (4/11), 239/237 (33/100), 224/222 (6/19), 197/195 (8/24), 185/183 (16/48), 169/167 (6/19),141/139 (7/21), 114 (13), 84 (9), 76 (7), 55 (17).

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