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Synthesis of tetrahydrophthalazine and phthalamide (phthalimide) derivatives via palladium-catalysed carbonylation of iodoarenes

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ABSTRACT

1,2,3,4-Tetrahydrophthalazin-1-one and 1,2,3,4-tetrahydrophthalazin-1,4-dione derivatives were synthesised in high (up to 85%) and low yields using 2-iodobenzyl bromide and 1,2-diiodobenzene as bifunctional substrates, respectively. Iodoarenes, carbon monoxide and various hydrazine derivatives as *N*-nucleophiles were used in a three-component palladium-catalysed cascade hydrazinocarbonylation. A similar palladium-catalysed reaction, the aminocarbonylation of 1,2-diiodobenzene, resulted mainly in the formation of two types of major products depending on the amine *N*-nucleophiles: the use of primary amines yielded *N*-substituted phthalimides in double carbonylation, while secondary amines react with one of the iodoarene functionalities affording the corresponding 2-iodobenzamides. Due to double carbon monoxide insertion at one or both iodoarene functionalities, ketocarboxamide-carboxamide or bis-ketocarboxamide derivatives could be isolated by the modification of the reaction conditions. Some mechanistic details of the ring-closure reactions and the conditions leading to side-products are also discussed.

1. Introduction

Phthalazine and tetrahydrophthalazine skeletons, containing a hydrazine moiety in the ring system, are incorporated in compounds of biological importance, such as pseudopeptides[1] and C-nucleosides.[2] A recent method uses microwave irradiation for the synthesis of phthalazine-1,4-diones based on phthalic anhydride.[3] The protonated forms of 1-hydrazinophthalazine and phthalazone hydrazone derivatives were also studied.[4]

The transition metal-catalysed processes, containing a key-step of carbonylation of iodoarenes in the presence of hydrazine derivatives, provide an excellent route to the above *N*-heterocycles. The efficient synthesis of *N*-aminoisoindolone and phthalazone derivatives from iodoarenes were reported recently, depending on whether monosubstituted hydrazine or 1,2-disubstituted hydrazine was used,[5] via a cascade process, involving the carbonylation of an aryl iodide/Michael acceptor to give an acylpalladium species, which is intercepted by a hydrazine nucleophile.

The palladium-catalysed hydrazinocarbonylation of steroidal iodoalkenes, leading to cyclized derivatives, was studied also in our group[6–8] and reviewed recently.[9]

The synthesis of *N*-aryl-substituted phthalimides in palladium-catalysed aminocarbonylation was described using 1,2-diiodobenzene and a range of 4-substituted anilines as *N*-nucleophiles.[10] Substituted indenones were synthesised from the same substrate with alkynes and carbon monoxide in the presence of nickel carbonyl.[11] Recently, high-yielding palladium-catalysed double carbonylation of *ortho*-dihaloarenes were carried out in phosphonium salt ionic liquids resulting in *N*-substituted phthalimides.[12]

It should be noted, that 1,2-diiodobenzene, one of the substrates used in our present study as well, is a building block in conventional synthesis[13,14] and a ligand in iridium-catalysed Nazarov cyclization.[15,16] Its isomer, 1,4-diiodobenzene is widely used in various homogeneous catalytic reactions, e.g., in Sonogashira coupling,[17] in a three-component domino Heck Diels–Alder reaction,[18] in homocoupling reaction[19] and in single and double Suzuki–Miyaura coupling.[20]

Although it is well-known since the early discovery of Heck,[21] that amides and esters could be obtained in high yields from aromatic iodides, nucleophiles (amines or alcohols, respectively) and carbon monoxide in the presence of Pd(0) and Pd(II) catalysts, the functionalization of bifunctional substrates still provide challenging routes for the synthesis of derivatives of practical importance. In this paper we describe the systematic investigation of the cyclo-aminocarbonylation of bifunctional 2-iodobenzyl bromide and 1,2-diiodobenzene substrates towards tetrahydrophthalazinone (tetrahydrophthalazindione) and phthalimide derivatives, respectively.

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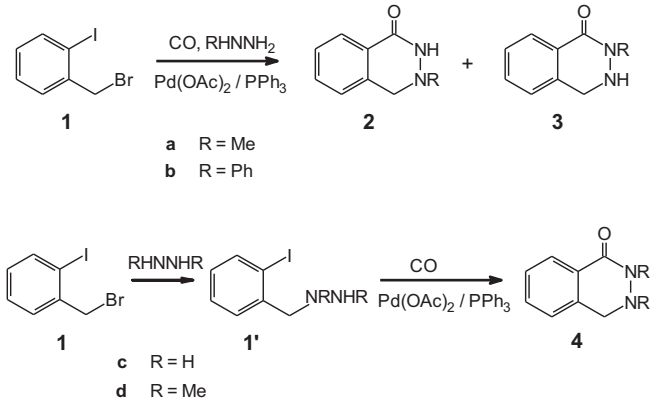
2. Results and discussion

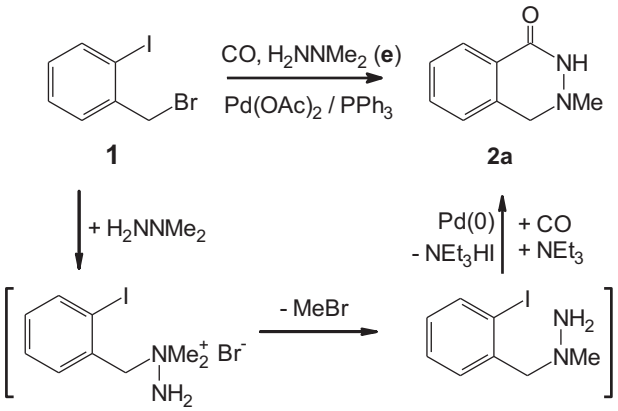
2.1. Hydrazinocarbonylation of 2-iodobenzyl bromide leading to 1,2,3,4-tetrahydrophthalazine-1-one

2-Iodobenzyl bromide (**1**) was reacted with hydrazine derivatives, such as methylhydrazine (**a**), phenylhydrazine (**b**), hydrazine (**c**), 1,2-dimethylhydrazine (**d**) and 1,1-dimethylhydrazine (**e**) under atmospheric carbon monoxide pressure in DMF in the presence palladium(0) catalysts generated in situ from palladium(II) acetate catalytic precursor (Schemes 1 and 3). It is worth noting that although the reduction of Pd(II) precursors to Pd(0) species has been proved in the presence of various phosphines while they have been oxidised to P(V) derivatives (monophosphine oxides or diphosphine oxide/hemioxide),[22–25] the exact mechanism of reduction under reductive conditions (carbon monoxide, hydrazine or amine derivatives) is still not known.



Scheme 1. The synthesis of substituted 1,2,3,4-tetrahydrophthalazin-1-one derivatives in the hydrazinocarbonylation of 2-iodobenzyl bromide with mono- and 1,2-disubstituted hydrazines.

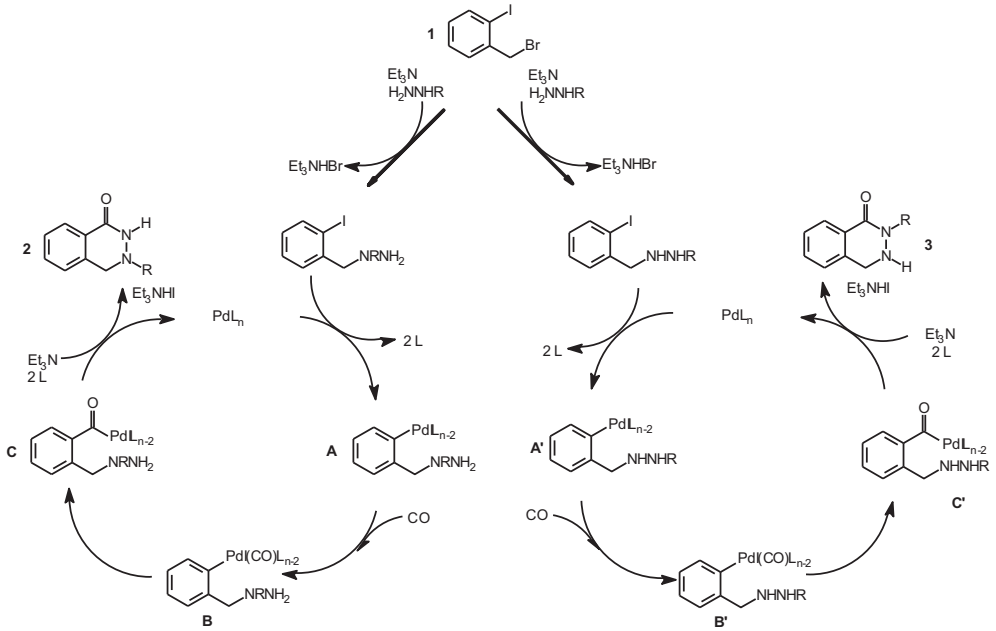
Highly selective reactions were observed with methylhydrazine (**a**) and 1,2-dimethylhydrazine (**d**) resulting in the major formation of **2a** and **4d**, respectively. Accordingly, both compounds were isolated in high yields. However, when phenylhydrazine (**b**) was used as the *N*-nucleophile, **2b** and **3b** was obtained in a ratio of 25/75.



Scheme 3. The hydrazinocarbonylation of 2-iodobenzyl bromide (**1**) with 1,1-dimethylhydrazine (**e**).

The formation of the tetrahydrophthalazinones can be interpreted by a simplified mechanism depicted in Scheme 2. The hydrazines are benzylated by **1**. In case of **a** the alkylation takes place selectively on the more nucleophilic nitrogen bearing the methyl substituent. A facile alkylation is observed also with **d**. Unexpectedly, the benzylation of **b** with **1** occurs on both nitrogen atoms. The (2-iodobenzyl)hydrazine derivatives react with the coordinatively unsaturated palladium(0) complex, formed in situ, resulting in aryl–palladium intermediates (**A**, **A′**) in oxidative addition. It is followed by carbon monoxide activation leading to carbonyl complexes (**B**, **B′**) and the insertion of carbon monoxide into the palladium(II)–aryl bond. The formed palladium-acyl derivatives (**C**, **C′**) are intercepted by the NH_2 (**a**, **b**) or NHR (**b**, **d**) fragment in intramolecular hydrazinocarbonylation yielding the products (**2**, **3**). The abstraction of HI with base (triethylamine) provides the palladium(0) complex via reductive elimination step.

The hydrazinocarbonylation with 1,1-dimethylhydrazine (**e**) yielded the same product (**2a**) as methylhydrazine (**a**) (Scheme 3). With the above reaction mechanism in hand, it means that the



Scheme 2. The simplified reaction mechanism of *cyclo*-hydrazinocarbonylation of **1** leading to tetrahydrophthalazinones.

benzylation step occurred exclusively on the more nucleophilic NMe_2 nitrogen forming a quaternary salt. The loss of methyl iodide yielded 1-(2-iodobenzyl)-1-methylhydrazine, which reacted as *N*-nucleophile in carbonylative cyclization.

As shown in Table 1, excellent isolated yields were obtained with hydrazines **a** and **e** due to the complete conversion resulting in a sole product (entries 1 and 6). The less nucleophilic **b** led to two isomers (**2b** and **3b**) and much lower isolated yields (entry 2). The ring-closure derivative of expected structure (**4c**) could not be isolated when the parent hydrazine (**c**) was used as *N*-nucleophile (entry 3). (Waxy polymeric material was obtained, except for 1,2-bis(2-iodophenyl)ethane, the coupled product of **1**.) Using 1,2-dimethylhydrazine (**d**) and short reaction time, the benzylated intermediate (**1′d**) could also be detected in addition to the final phthalazinone product (**4d**) (entry 4). Interestingly, the double demethylation of the hydrazine moiety was observed when increased reaction times (168 h) were used, leading to **4c** as minor product (entry 5). Thus, **4c** can be synthesised although in low yields in a roundabout way by using **d**, but not in a direct pathway in the presence of **c** as *N*-nucleophile.

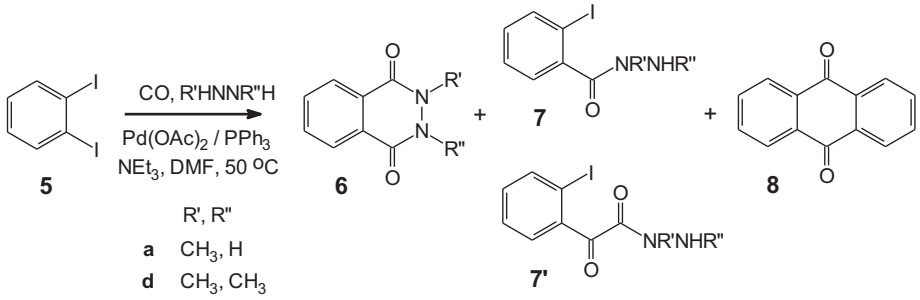
Table 1
Palladium-catalysed hydrazinocarbonylation of **1** with hydrazine *N*-nucleophiles[a]

Entry	Hydrazine	R. time[b] [h]	Composition of the r. mixture[c] [%]	Isolated yield[d] (amide) [%]
1	**a**	24	100 (**2a**)	85 (**2a**)
2	**b**	120	25 (**2b**); 75 (**3b**)	52 (**3b**)
3	**c**	120	0 (**4c**)	—
4	**d**	24	80 (**4d**), 20 (**1′d**)	66 (**4d**)
5	**d**	168	83 (**4d**), 17 (**4c**)	70 (**4d**)
6	**e**	24	100 (**2a**)	82 (**2a**)

[a] Reaction conditions: 0.025 mmol $Pd(OAc)_2$, 0.05 mmol PPh_3, 1 mmol substrate (**1**), 1.2 mmol hydrazine derivative (**a**–**e**), 0.5 mL triethylamine, 10 mL DMF; temperature: 50 °C, p(CO)=1 bar.
[b] Practically complete conversion (>99%) determined by GC–MS was obtained in all cases.
[c] Determined by GC–MS.
[d] Based on the amount of the substrate (**1**) used.

2.2. Hydrazino- and aminocarbonylation of 1,2-diiodobenzene

1,2-Diiodobenzene (**5**) was reacted with hydrazines (**a**, **d**) (Scheme 4), as well as primary (Scheme 5) and secondary amines (Scheme 6). The three types of *N*-nucleophiles led to completely different products.



Scheme 4. Hydrazinocarbonylation of **5**.

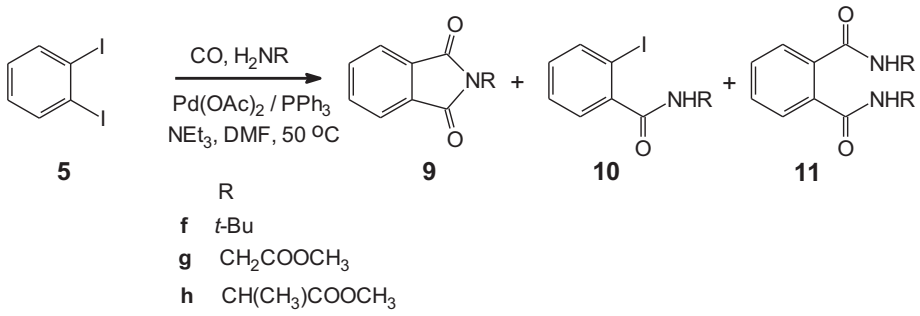
The *cyclo*-hydrazinocarbonylation of **5** with hydrazine derivatives (**a** and **d**) provided the expected phthalazindione derivatives, 2-methyl-1,2,3,4-tetrahydrophthalazin-1,4-dione (**6a**) and 2,3-dimethyl-1,2,3,4-tetrahydrophthalazin-1,4-dione (**6d**), respectively. However, due to the formation of side-products, such as monohydrazide (**7**), 2-ketohydrazide (**7′**) and anthraquinone (**8**), as well as to the low conversions, very low isolated yields were obtained for **6a** and **6d** (Scheme 4, Table 2). In spite of the limited synthetic interest, the following points are worth to be addressed from a catalytic point of view. (i) The reactivity of the two hydrazine nucleophile is strikingly different: **a** is more reactive providing carbonylated products even under atmospheric carbon monoxide pressure, while **d** is unreactive under similar conditions (entries 1 and 3). (ii) The formation of hydrazinocarbonylated products is accompanied by the formation of anthraquinone (**8**). (iii) Instead of the complete formation of the ring-closure product (**6d**), a double carbonylation resulting in ketohydrazide (**7′d**) under higher carbon monoxide pressure was observed (entries 4 and 5). (iv) Surprisingly, the slight excess of methylhydrazine (**a**) could serve as methyl source resulting in dimethylhydrazide (**7d**), which is the expected product with **d** (entry 2).

Primary amines, such as *tert*-butylamine (**f**), methyl glycinate (**g**) and methyl alaninate (**h**) were used in aminocarbonylation of **5** under atmospheric carbon monoxide pressure using the same catalytic system as above (Scheme 5). *N*-Substituted phthalimides (**9f**–**h**) were obtained in moderate yields (Table 3). The isolated yields are definitely lower than expected on the basis of previous investigations carried out with aniline derivatives.[9] A further compound was isolated in all cases: while the formation of **9f** was accompanied with that of **11f** (entry 1), the amino acid derivatives (**g** and **h**) provided the iodobenzamide intermediates, **10g** and **10h**, respectively (entries 2 and 3).

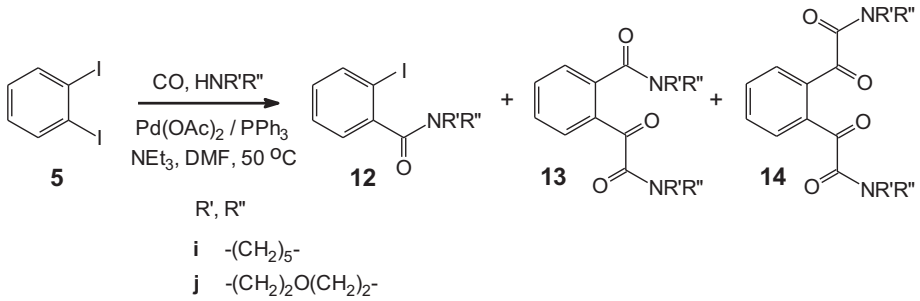
Three products were detected and isolated using secondary amines, such as piperidine (**i**) and morpholine (**j**) in the aminocarbonylation of **5** (Scheme 6). 2-Iodobenzamides (**12**) and the ketocarboxamide-carboxamide derivatives (**13**) were formed and isolated with both amines (Table 3, entries 4 and 5). The formation of the latter compound can be rationalised via mono and double carbon monoxide insertion into the palladium–aryl bond in position-1 and position-2, respectively. Furthermore, bis(ketocarboxamide) (**14j**) was also formed when **j** was used as the nucleophile under higher pressure of CO (entries 6 and 7). Surprisingly, the presence of 1,2-bis-carboxamides was not observed under the reaction conditions investigated.

3. Conclusions

It has been shown that 2-iodobenzyl bromide can be transformed via a palladium-catalysed intramolecular hydrazinocarbonylation to give 1,2,3,4-tetrahydrophthalazine-1-one derivatives. The same reaction with 1,2-diiodobenzene as substrate resulted in complicated reaction mixtures containing various hydrazides in addition to the targeted 1,2,3,4-tetrahydrophthalazin-1,4-dione derivatives. The aminocarbonylation of 1,2-diiodobenzene in the presence of primary amines brought about the expected phthalimide, as well as iodocarboxamide and dicarboxamide. The same reaction in the presence of secondary amines yielded iodocarboxamides and ketocarboxamides. The appropriate choice of the reaction conditions enabled the isolation of all above mentioned aminocarbonylated compounds.



Scheme 5. Aminocarbonylation of **5** using primary amines.



Scheme 6. Aminocarbonylation of **5** using secondary amines.

Table 2
Palladium-catalysed intramolecular hydrazinocarbonylation of **5** with hydrazine *N*-nucleophiles[a]

Entry	Hydrazine	p(CO) [bar]	R. time [h]	Composition of the r. mixture[b,c] [%]	Isolated yield[d] [%]
1	**a**	1	96	12 (**6a**), 88 (**8**)	**6a** (n.d.)
2	**a**	40	96	22 (**6a**), 50 (**7a**), 28 (**7d**)	**6a** (15), **7a** (40), **7d** (20)
3	**d**	1	70	0 (**6d**), 0 (**7d**), 0 (**8**)	
4	**d**	40	72	16 (**6d**), 21 (**7d**), 7 (**7′d**), 11 (**8**)	**6d** (n.d.), **7d** (18)
5	**d**	60	96	27 (**6d**), 25 (**7d**), 4 (**7′d**), 13 (**8**)	**6d** (n.d.), **7d** (21)

[a] Reaction conditions: 0.025 mmol $Pd(OAc)_2$, 0.05 mmol PPh_3, 1 mmol substrate (**5**), 1.2 mmol hydrazine derivative (**a**, **d**), 0.5 mL triethylamine, 10 mL DMF; temperature: 50 °C.
[b] The amounts of the products are indicated in the table, the rest is unconverted substrate.
[c] Determined by GC–MS.
[d] Based on the amount of the substrate (**5**) used.

Table 3
Palladium-catalysed aminocarbonylation of **5** with primary (**f**, **g**, **h**) and secondary (**i**, **j**) amines as *N*-nucleophiles[a]

Entry	Amine	p(CO) [bar]	R. time [h]	**1**/amine ratio	Composition of the r. mixture[b,c] [%]	Isolated yield[d] [%]
1	**f**	1	72	1/6	38 (**9f**), 62 (**11f**)	30 (**9f**), 51 (**11f**)
2	**g**	1	72	1/2.2	39 (**9g**), 53 (**10g**)	31 (**9g**), 48 (**10g**)
3	**h**	1	96	1/2.2	38 (**9h**), 49 (**10h**)	32 (**9h**), 40 (**10h**)
4	**i**	1	72	1/3	54 (**12i**), 40 (**13i**)	46 (**12i**), 30 (**13i**)
5	**j**	1	96	1/3	34 (**12j**), 57 (**13j**)	30 (**12j**), 51 (**13j**)
6	**j**	40	24	1/3	4 (**12j**), 31 (**13j**), 65 (**14j**)	n.d.(**12j**), n.d.(**13j**), 60(**14j**)
7	**j**	40	96	1/3	47 (**13j**), 53 (**14j**)	40 (**13j**), 48 (**14j**)

n.d.=not determined (i.e., the target compound was not isolated as a pure substance).
[a] Reaction conditions: 0.025 mmol $Pd(OAc)_2$; 0.05 mmol PPh_3, 1 mmol substrate (**5**); 0.5 mL triethylamine; 10 mL DMF; temperature: 50 °C.
[b] Determined by GC–MS.
[c] The amounts of the products are indicated in the table, the rest is unconverted substrate.
[d] Based on the amount of the substrate (**5**) used.

4. Experimental

4.1. General procedures

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Inova 400 spectrometer at 400.13 MHz and 100.62 MHz, respectively. Chemical shifts δ are reported in parts per million relative to $CHCl_3$ (7.26 and 77.00 ppm for ^1H and ^{13}C, respectively). Elemental analyses were measured on an 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. 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.

2-Iodobenzyl bromide (**1**), 1,2-diiodobenzene (**5**), hydrazine derivatives (**a**–**e**), amines (**f**, **i**, **j**), amino acid esters (**g**, **h**) were purchased from Sigma–Aldrich. The products of known structure (**2a**,[26] **6d**[27] and **9f**[28]) gave identical spectra with those given in the literature. However, where further analytical data for the target compounds are available, the isolated compounds with full characterisation are given below.

4.2. Hydrazinocarbonylation of 2-iodobenzyl bromide (1) under atmospheric carbon monoxide pressure

In a typical experiment $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.05 mmol), 2-iodobenzyl bromide (297 mg, 1 mmol), 1.2 mmol of hydrazine derivative (**a**–**d**) and 0.5 mL triethylamine were dissolved in DMF (10 mL) under argon in a 100 mL three-necked flask equipped with a gas inlet and a reflux condenser with a balloon 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. The mixture was then concentrated and evaporated to dryness. The residue was dissolved in chloroform (20 mL) and washed with water (3×20 mL). The organic phase was dried over Na_2SO_4 and evaporated to a crystalline material or to a waxy residue. All compounds were subjected to column chromatography using the solvent mixture indicated for the R_f values in Section 4.6.

4.3. Hydrazinocarbonylation of 1,2-diiodobenzene (5) under atmospheric carbon monoxide pressure

In a typical experiment $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.05 mmol), 1,2-diiodobenzene (330 mg, 1 mmol), 1.2 mmol of hydrazine derivative (**a**–**d**) and 0.5 mL triethylamine were dissolved in DMF (10 mL) under argon in a 100 mL three-necked flask equipped with a gas inlet, reflux condenser with a balloon at the top. The atmosphere was changed to carbon monoxide. The mixture was then concentrated and evaporated to dryness. The residue was dissolved in chloroform (20 mL) and washed with water (20 mL). The organic phase was thoroughly washed twice with 5% aq HCl (20 mL), satd aq $NaHCO_3$ (20 mL), satd aq brine (20 mL), and dried over Na_2SO_4 and evaporated to a crystalline material or to a waxy residue. All compounds were subjected to column chromatography using the solvent mixture indicated for the R_f values in Section 4.6.

4.4. Aminocarbonylation of 1,2-diiodobenzene (5) in the presence of primary and secondary amines under atmospheric carbon monoxide pressure

In a typical experiment $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.05 mmol), 1,2-diiodobenzene (330 mg, 1 mmol), 6 mmol of *tert*-butylamine (**f**) (or 2.2 mmol of amino acid methyl ester hydrochloride (**g**, **h**) or 3 mmol of secondary amine (**i**, **j**)) and 0.5 mL triethylamine were dissolved in DMF (10 mL) under argon in a 100 mL three-necked flask equipped with a gas inlet, reflux condenser with a balloon 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. The work-up procedure was identical with those described in Section 4.3.

4.5. Aminocarbonylation of 1,2-diiodobenzene (5) in the presence of primary and secondary amines under high carbon monoxide pressure

The above amounts of catalyst, substrate and amines 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 40 bar with carbon monoxide. The reaction was conducted for the given reaction time upon stirring at 50 °C and analysed by GC–MS. The work-up procedure was identical with those described in Section 4.3.

4.6. Characterisation of the products

*4.6.1. 3-Methyl-1,2,3,4-tetrahydrophthalazin-1-one (**2a**).* ^{1}H NMR ($CDCl_3$) δ: 8.05 (1H, d, J=7.5 Hz, Ar–H), 7.67 (1H, br s, NH), 7.53 (1H, t, J=7.5 Hz, Ar–H), 7.42 (1H, t, J=7.5 Hz, Ar–H), 7.20 (1H, d, J=7.5 Hz, Ar–H); 4.21 (2H, s, CH_2), 2.61 (3H, s, Me). ^{13}C NMR ($CDCl_3$) δ: 164.4, 135.2, 133.0, 127.9, 127.1, 126.9, 126.1, 55.8, 45.0. IR (KBr, ν (cm^{-1})): 3420 (v br, NH), 1670 (CON). MS m/z (rel int.): 162 (32, M^+), 161 (100), 118 (20), 90 (46). Analysis calculated for $C_9H_{10}N_2O$ (162.19): C, 66.65; H, 6.21; N, 17.27. Found: C, 66.47; H, 6.43; N, 17.48. R_f (4% EtOH/$CHCl_3$) 0.56. Beige crystals, mp 111 °C. Yield: 130 mg (85%).

*4.6.2. 3-Phenyl-1,2,3,4-tetrahydrophthalazin-1-one (**2b**).* ^{1}H NMR ($CDCl_3$) δ: 8.03 (1H, d, J=7.6 Hz, Ar–H), 7.60–7.40 (3H, m, Ar–H+NH), 7.30–7.10 (3H, m, Ar–H+Ph(*meta*)), 6.91 (1H, t, J=7.6 Hz, Ph(*para*)), 6.72 (2H, d, J=7.6 Hz, Ph(*ortho*)), 4.62 (2H, s, CH_2). ^{13}C NMR ($CDCl_3$) δ: 167.6, 146.4, 135.9, 132.0, 129.0 (double intensity), 128.2, 127.9, 124.1, 123.0, 116.6, 113.3 (double intensity), 51.1. IR (KBr, ν (cm^{-1})): 3254 (v br, NH), 1662 (CON). MS m/z (rel int.): 224 (100, M^+), 223 (34), 132 (25), 118 (9), 93 (29). Analysis calculated for $C_{14}H_{12}N_2O$ (224.26): C, 74.98; H, 5.39; N, 12.49. Found: C, 74.77; H, 5.53; N, 12.20. R_f (4% EtOH/$CHCl_3$) 0.65. Orange crystals, mp 152 °C. Yield: 116 mg (52%).

*4.6.3. 2-Phenyl-1,2,3,4-tetrahydrophthalazin-1-one (**3b**).* Compound **3b** (characterised in a 60/40 mixture of **2b**/**3b**): ^{1}H NMR ($CDCl_3$): δ: 7.91 (1H, d, J=7.6 Hz, Ar–H), 7.62–7.40 (3H, m, Ar–H+NH), 7.08–7.25 (3H, m, Ar–H+Ph(*meta*)), 7.02 (2H, d, J=7.6 Hz, Ph(*ortho*)), 6.90 (1H, t, J=7.6 Hz, Ph(*para*)), 4.86 (2H, s, CH_2). MS m/z (rel int.): 224 (77, M^+), 223 (100), 118 (25), 90 (36).

*4.6.4. 2,3-Dimethyl-1,2,3,4-tetrahydrophthalazin-1-one (**4d**).* ^{1}H NMR ($CDCl_3$) δ: 8.04 (1H, d, J=7.5 Hz, Ar–H), 7.49 (1H, t, J=7.5 Hz, Ar–H), 7.40 (1H, t, J=7.5 Hz, Ar–H), 7.17 (1H, d, J=7.5 Hz, Ar–H), 4.21 (2H, s, CH_2), 3.25 (3H, s, Me), 2.52 (3H, s, Me). ^{13}C NMR ($CDCl_3$) δ: 163.1, 134.6, 132.4, 127.8, 127.4, 127.2, 125.8, 55.1, 40.5, 33.5. IR (KBr, ν (cm^{-1})): 1643 (CON). MS m/z (rel int.): 176 (100, M^+), 161 (29), 132 (13), 118 (79), 90 (60). Analysis calculated for $C_{10}H_{12}N_2O$ (176.22): C, 68.16; H, 6.86; N, 15.90. Found: C, 68.07; H, 6.95; N, 15.66. R_f (50% EtOAc/$CHCl_3$) 0.62. Pale-yellow crystals, mp 79 °C. Yield: 124 mg (70%).

*4.6.5. 2-Methyl-1,2,3,4-tetrahydrophthalazin-1,4-dione (**6a**).* ^{1}H NMR ($CDCl_3$) δ: 8.10–7.78 (4H, m, Ar–H), 7.67 (1H, br s, NH), 3.12 (3H, s, Me). ^{13}C NMR ($CDCl_3$) δ: 170.7, 169.2, 139.1, 135.1, 134.9, 128.4, 34.7. MS m/z (rel int.): 176 (19, M^+), 148 (90), 130 (100), 104 (45), 76 (48). R_f (50% EtOAc/$CHCl_3$) 0.56. Brown-yellow viscous material. Yield: 27 mg (15%).

*4.6.6. N-Methyl-2-iodobenzhydrazide (**7a**).* ^{1}H NMR ($CDCl_3$) δ: 7.81 (1H, d, J=7.8 Hz, Ar–H), 7.39 (1H, t, J=7.8 Hz, Ar–H), 7.21 (1H, d, J=7.8 Hz, Ar–H), 7.05 (1H, t, J=7.8 Hz, Ar–H), 2.82, 3.15 (3H, s, CH_3) (two singlets due to C(O)N hindered rotation), 1.62 (2H, br s, NH_2). ^{13}C NMR ($CDCl_3$) δ: 170.7, 142.8, 139.1, 130.0, 128.4, 127.0, 92.4, 38.4, 34.7 (two methyl signals due to C(O)N hindered rotation). MS m/z (rel int.): 276 (4, M^+) 275 (51), 274 (70), 231 (100), 203 (32). R_f (50% EtOAc/$CHCl_3$) 0.72. Yellow viscous material. Yield: 117 mg (40%).

*4.6.7. 2,3-Dimethyl-1,2,3,4-tetrahydrophthalazin-1,4-dione (**6d**).* Compound **6d** (characterised in a 1/2 mixture of **6d**/**7d**): MS m/z (rel int.): 190(M^+)/60, 162/21, 132/12, 104/100, 76/51.

*4.6.8. N,N′-Dimethyl-2-iodobenzhydrazide (**7d**).* ^{1}H NMR ($CDCl_3$) δ: 7.82–7.75 (2H, m, Ar–H+NH), 7.40 (1H, t, J=7.4 Hz, Ar–H), 7.23 (1H, d, J=7.4 Hz, Ar–H), 7.07 (1H, d, J=7.4 Hz, Ar–H), 3.01 (3H, s, CH_3), 2.77 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.1, 139.2, 133.3, 130.8, 127.2,

123.6, 92.3, 36.1, 35.5. IR (KBr, ν (cm^{-1})): 1652 (CON). MS *m*/*z* (rel int.): 290 (14, M^+), 261 (41), 231 (100), 203 (30). R_f (50% EtOAc/$CHCl_3$) 0.40. Brown-yellow viscous material. Yield: 58 mg (21%).

*4.6.9. N,N′-Dimethyl-2-iodophenylglyoxylhydrazide (**7′d**).* Compound **7′d** (identified in the catalytic mixture obtained in the hydrazinocarbonylation of **5** (Table 2, entry 4)) MS *m*/*z* (rel int.): 318 (12, M^+), 261 (19), 231 (100), 203 (32).

*4.6.10. N-(tert-Butyl)phthalimide (**9f**).* ^{1}H NMR ($CDCl_3$) δ: 7.75 (2H, d, *J*=3.5 Hz, Ar–H), 7.65 (2H, d, *J*=3.5 Hz, Ar–H), 1.68 (9H, s, *t*-Bu). ^{13}C NMR ($CDCl_3$) δ: 169.6, 133.6, 132.1, 122.5, 57.8, 29.1. IR (KBr, ν (cm^{-1})): 1637 (CON). MS *m*/*z* (rel int.): 203 (22, M^+), 188 (100), 148 (66), 130 (73). Analysis calculated for $C_{12}H_{13}NO_2$ (203.24): C, 70.92; H, 6.45; N, 6.89. Found: C, 70.87; H, 6.65; N, 6.68. R_f (50% EtOAc/$CHCl_3$) 0.85. White needle-like crystals, mp 203 °C. Yield: 61 mg (30%).

*4.6.11. N,N′-Bis(tert-butyl)-phthalamide (**11f**).* ^{1}H NMR ($CDCl_3$) δ: 7.54 (2H, d, *J*=3.2 Hz, Ar–H), 7.42 (2H, d, *J*=3.2 Hz, Ar–H), 6.63 (2H, br s, NH), 1.45 (9H, s, *t*-Bu). ^{13}C NMR ($CDCl_3$) δ: 168.6, 135.1, 129.7, 128.2, 51.9, 28.6. IR (KBr, ν (cm^{-1})): 3291 (br, NH), 1636 (CON). MS *m*/*z* (rel int.): 276 (5, M^+) 204 (18), 148 (100), 130 (19). Analysis calculated for $C_{16}H_{24}N_2O_2$ (276.38): C, 69.53; H, 8.75; N, 10.14. Found: C, 69.37; H, 8.92; N, 9.92. R_f (50% EtOAc/$CHCl_3$) 0.77. Yellow powder, mp 224 °C. Yield: 140 mg (51%).

*4.6.12. N-(Methoxycarbonylmethyl)phthalimide (**9g**).* ^{1}H NMR ($CDCl_3$) δ: 7.85 (2H, d, *J*=3.5 Hz, Ar–H), 7.74 (2H, d, *J*=3.5 Hz, Ar–H), 4.42 (2H, s, NCH_2), 3.73 (3H, s, OCH_3). ^{13}C NMR ($CDCl_3$) δ: 167.6, 167.4, 134.2, 131.9, 123.5, 52.6, 38.7. IR (KBr, ν (cm^{-1})): 1732 (COO), 1644 (CON). MS *m*/*z* (rel int.): 219 (9, M^+), 160 (100), 133 (5), 104 (10). Analysis calculated for $C_{11}H_9NO_4$ (219.20): C, 60.28; H, 4.14; N, 6.39. Found: C, 60.07; H, 4.33; N, 6.17. R_f (50% EtOAc/$CHCl_3$) 0.83. Yellow crystals, mp 96 °C. Yield: 68 mg (31%).

*4.6.13. N-(Methoxycarbonylmethyl)-2-iodobenzamide (**10g**).* ^{1}H NMR ($CDCl_3$) δ: 7.83 (1H, d, *J*=8.2 Hz, Ar–H), 7.41–7.30 (2H, m, Ar–H), 7.08 (1H, t, *J*=7.6 Hz, Ar–H), 6.48 (1H, br s, NH), 4.18 (1H, s, NCH_2), 3.73 (3H, s, OCH_3). ^{13}C NMR ($CDCl_3$) δ: 169.9, 169.2, 141.2, 139.9, 131.3, 128.4, 128.1, 92.3, 52.4, 41.6. IR (KBr, ν (cm^{-1})): 3254 (NH), 1732 (COO), 1646 (CON). MS *m*/*z* (rel int.): 319 (51, M^+), 260 (27), 231 (100), 203 (26), 104 (6). Analysis calculated for $C_{10}H_{10}INO_3$ (319.10): C, 37.64; H, 3.16; N, 4.39. Found: C, 37.57; H, 3.26; N, 4.18. R_f (50% EtOAc/$CHCl_3$) 0.72. Yellow crystals, mp 104 °C. Yield: 153 mg (48%).

*4.6.14. N-(1-(Methoxycarbonyl)-ethyl)phthalimide (**9h**).* ^{1}H NMR ($CDCl_3$) δ: 7.84 (2H, d, *J*=3.3 Hz, Ar–H), 7.73 (2H, d, *J*=3.3 Hz, Ar–H), 4.97 (1H, q, *J*=7.2 Hz, C*H*CH_3), 3.72 (3H, s, OCH_3), 1.68 (3H, d, *J*=7.2 Hz, $CHCH_3$). ^{13}C NMR ($CDCl_3$) δ: 170.1, 167.3, 134.1, 131.9, 123.5, 52.7, 47.4, 15.2. IR (KBr, ν (cm^{-1})): 1747 (COO). MS *m*/*z* (rel int.): 233 (5, M^+), 174 (100), 147 (25), 130 (30), 104 (12). Analysis calculated for $C_{12}H_{11}NO_4$ (233.22): C, 61.80; H, 4.75; N, 6.01. Found: C, 61.57; H, 4.83; N, 5.88. R_f (20% EtOAc/$CHCl_3$) 0.85. Pale-yellow viscous material. Yield: 75 mg (32%).

*4.6.15. N-(1-(Methoxycarbonyl)-ethyl)-2-iodobenzamide (**10h**).* ^{1}H NMR ($CDCl_3$) δ: 7.86 (1H, d, *J*=8.1 Hz, Ar–H), 7.32–7.41 (2H, m, Ar–H), 7.09 (1H, d, *J*=7.5 Hz, Ar–H), 6.43 (1H, br s, NH), 4.78 (1H, qi, *J*=7.1 Hz, C*H*CH_3), 3.78 (3H, s, OCH_3), 1.55 (3H, d, *J*=7.1 Hz, $CHCH_3$). ^{13}C NMR ($CDCl_3$) δ: 173.1, 168.5, 141.4, 139.9, 131.3, 128.3, 128.1, 92.3, 52.6, 48.5, 18.4. IR (KBr, ν (cm^{-1})): 3270 (v br, NH), 1739 (COO), 1648 (CON). MS *m*/*z* (rel int.): 333 (19, M^+), 274 (73), 231 (100), 203 (23). Analysis calculated for $C_{11}H_{12}INO$ (301.13): C, 43.88; H, 4.02; N, 4.65. Found: C, 43.67; H, 4.25; N, 4.58. R_f (20% EtOAc/$CHCl_3$) 0.73. Pale-yellow powderlike crystals, mp 127 °C. Yield: 133 mg (40%).

*4.6.16. N,N-(Pentan-1,5-diyl)-2-iodobenzamide (**12i**).* ^{1}H NMR ($CDCl_3$) δ: 7.79 (1H, d, *J*=7.5 Hz, Ar–H), 7.35 (1H, t, *J*=7.5 Hz, Ar–H), 7.15 (1H, d, *J*=7.5 Hz, Ar–H), 7.03 (1H, t, *J*=7.5 Hz, Ar–H), 3.80–3.60 (2H, m, $N(CH_2)$), 3.12–3.05 (2H, m, NCH_2), 1.72–1.40 (6H, m, $(CH_2)_3$). ^{13}C NMR($CDCl_3$) δ: 169.1, 142.7, 139.1, 129.9, 128.2, 126.8, 92.4, 47.9, 42.4, 26.2, 25.3, 24.4. IR (KBr, ν (cm^{-1})): 1636 (CON). MS *m*/*z* (rel int.): 315 (37, M^+) 314 (100), 231 (65), 188 (24). Analysis calculated for $C_{12}H_{14}INO$ (315.15): C, 45.73; H, 4.48; N, 4.44. Found: C, 45.57; H, 4.60; N, 4.18. R_f (50% EtOAc/$CHCl_3$) 0.78. Brown viscous material. Yield: 126 mg (40%).

*4.6.17. 2-(N,N-Pentan-1,5-diylcarboxamido)-N,N-(pentan-1,5-diyl)-phenylglyoxylamide (**13i**).* ^{1}H NMR ($CDCl_3$) δ: 7.88 (1H, d, *J*=7.7 Hz, Ar–H), 7.57 (1H, t, *J*=7.7 Hz, Ar–H), 7.45 (1H, t, *J*=7.7 Hz, Ar–H), 7.29 (1H, d, *J*=7.7 Hz, Ar–H), 3.70 (2H, br s, $N(CH_2)$), 3.61 (2H, br s, NCH_2), 3.33 (2H, t, *J*=5.5 Hz, NCH_2), 3.19 (2H, t, *J*=5.5 Hz, NCH_2), 1.70–1.42 (12H, m, 2× $(CH_2)_3$). ^{13}C NMR ($CDCl_3$) δ: 191.2, 168.8, 164.8, 138.6, 133.7, 131.9, 131.7, 128.9, 127.2, 48.1, 47.0, 42.5, 42.2, 25.9, 25.7, 25.3, 25.2, 24.5, 24.3. IR (KBr, ν (cm^{-1})): 1768 (CO), 1642 (v br, CON). MS *m*/*z* (rel int.): 328 (2, M^+), 245 (8), 216 (100), 160 (40). Analysis calculated for $C_{19}H_{24}N_2O_3$ (328.41): C, 69.49; H, 7.37; N, 8.53. Found: C, 69.17; H, 7.55; N, 8.27. R_f (50% EtOAc/$CHCl_3$) 0.56. Yellow viscous material. Yield: 98 mg (30%).

*4.6.18. N,N-(3-Oxa-pentan-1,5-diyl)-2-iodobenzamide (**12j**).* ^{1}H NMR ($CDCl_3$) δ: 7.82 (1H, d, *J*=8.1 Hz, Ar–H), 7.39 (1H, t, *J*=7.4 Hz, Ar–H), 7.19 (1H, d, *J*=7.4 Hz, Ar–H), 7.08 (1H, t, *J*=7.4 Hz, Ar–H), 3.90–3.70 (5H, m, $O(CH_2)_2$+NCH), 3.62–3.56 (1H, m, NCH), 3.26 (1H, br s, NCH), 3.18 (1H, br s, NCH). ^{13}C NMR ($CDCl_3$) δ: 169.3, 141.8, 139.2, 130.3, 128.4, 127.0, 92.4, 66.7, 66.6, 47.2, 41.9. IR (KBr, ν (cm^{-1})): 1623 (CON). MS *m*/*z* (rel int.): 317 (40, M^+), 231 (100), 203 (28), 190 (9). Analysis calculated for $C_{11}H_{12}INO_2$ (317.43): C, 41.66; H, 3.81; N, 4.42. Found: C, 41.56; H, 3.93; N, 4.20. R_f (50% EtOAc/$CHCl_3$) 0.58. Yellow crystals, mp 82–83 °C. Yield: 95 mg (30%).

*4.6.19. 2-(N,N-(3-Oxa-pentan-1,5-diylcarboxamido))-N,N-(3-oxa-pentan-1,5-diyl)-phenylglyoxylamide (**13j**).* ^{1}H NMR ($CDCl_3$) δ: 7.95 (1H, d, *J*=7.7 Hz, Ar–H), 7.60 (1H, t, *J*=7.7 Hz, Ar–H), 7.52 (1H, t, *J*=7.7 Hz, Ar–H), 7.29 (1H, d, *J*=7.7 Hz, Ar–H), 3.65–3.80 (12H, m, OCH_2+NCH_2), 3.50 (2H, br s, $N(CH_2)$), 3.32 (2H, br s, NCH_2). ^{13}C NMR ($CDCl_3$) δ: 190.1, 169.1, 164.7, 137.4, 133.5, 132.4, 131.6, 129.6, 127.0, 66.6 (double intensity); 66.4 (double intensity); 47.8, 46.3, 42.2, 41.7. IR (KBr, ν (cm^{-1})): 1679 (CO), 1635 (v br, CON). MS *m*/*z* (rel int.): 332 (2, M^+), 247 (5), 218 (100), 174 (9). Analysis calculated for $C_{17}H_{20}N_2O_5$ (332.36): C, 61.44; H, 6.07; N, 8.43. Found: C, 61.55; H, 6.23; N, 8.19. R_f (6% EtOH/$CHCl_3$) 0.45. Yellow crystals, mp 129 °C. Yield: 170 mg (51%).

*4.6.20. 2,2′-(1,2-Phenylene)bis(1-morpholinoethane-1,2-dione) (**14j**).* ^{1}H NMR ($CDCl_3$) δ: 7.81 (2H, d, Ar–H), 7.68 (2H, d, Ar–H), 3.70 (8H, br s, OCH_2), 3.63 (8H, br s, NCH_2). ^{13}C NMR ($CDCl_3$) δ: 191.7, 163.6, 135.8, 133.3, 131.3, 66.7, 66.5, 46.2, 42.1. IR (KBr, ν (cm^{-1})): 1768 (CO), 1643 (v br, CON). MS *m*/*z* (rel int.): 360 (3, M^+), 246 (60), 218 (41), 147 (14); 114 (100). Analysis calculated for $C_{18}H_{20}N_2O_6$ (360.77): C, 59.99; H, 5.59; N, 7.77. Found: C, 59.87; H, 5.73; N, 7.58. R_f (6% EtOH/$CHCl_3$) 0.70. Brown viscous material. Yield: 216 mg (60%).

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