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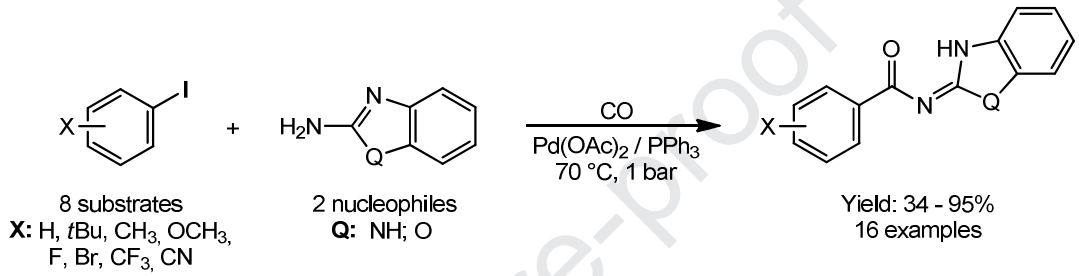
Graphical abstract



2-Aminobenzimidazole and -benzoxazole as *N*-nucleophile in palladium-catalysed aminocarbonylation

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Abstract:

Palladium-catalysed aminocarbonylation of aryl iodides in the presence of 2-aminobenzimidazole and 2-aminobenzoxazole as *N*-nucleophile was carried out. Single CO insertion took place, however, instead of the expected carboxamides (C(O)NH) the corresponding *N*-acyl-imine (C(O)N=C) derivatives were obtained. The structure of the latter compounds can be explained by tautomerization involving the heterocyclic ring. The above structures without amide-NH moieties were proved by methylation at the NH groups of the heterocycle. The resulted mono- and dimethylated benzimidazole derivatives, as well as monomethylated benzoxazole derivatives, like the parent *N*-acylated compounds, were fully characterised including single crystal X-ray crystallography.

Keywords: carbonylation**,** palladium**,** triazole, carbon monoxide, tautomerization

1. Introduction

Benzimidazole and benzoxazole derivatives are among the most investigated heterocycles[1] and have high biological (pharmaceutical) significance.[2] Regarding our title compounds, especially 2-aminobenzimidazole derivatives possess biological effects in a wide spectrum. In this way, these compounds have shown immunotropic, diuretic and antihistaminic properties. Moreover, several derivatives have exhibited antiproliferative properties. Several compounds have been evaluated for antiviral activities.[3] As functionalised (carbonylated) compounds are related directly to our recent investigations, it has to be noted that benzimidazole- and benzoxazole-based carboxamides and carbamates also have significant pharmacological importance (*Figure 1*).[4]

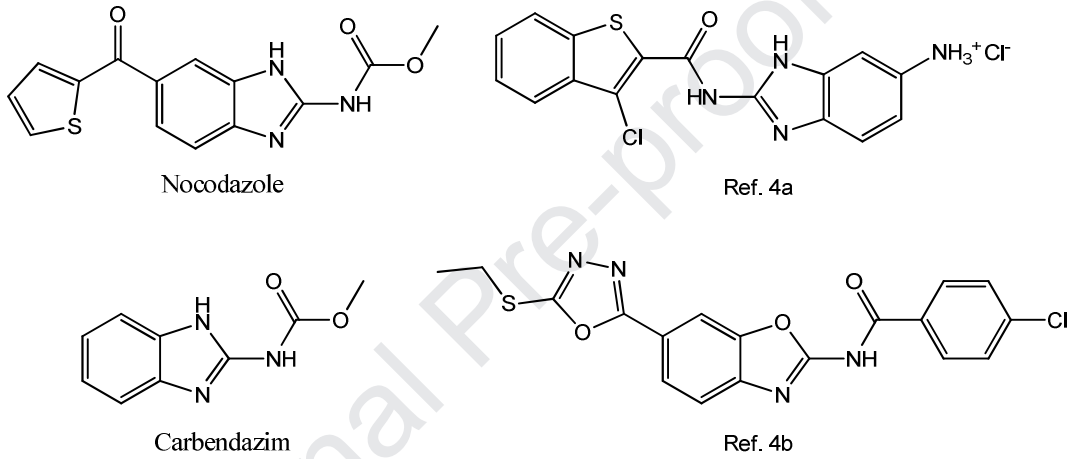


Figure 1. Benzimidazole and benzoxazole derivatives of practical importance bearing carbamate and carboxamide functionality.

To introduce various functionalities into a heterocycle backbone a great variety of homogeneous catalytic reactions can be used effciently.[5] Since the carboxamido-substituted derivatives are among the most investigated ones even in this family, the palladium-catalysed aminocarbonylation ('Heck-carbonylation') provided an efficient methodology to obtain these compounds.[6]

The aminocarbonylation of iodoaromatics can provide both carboxamides and 2-ketocarboxamides via single and double CO insertion, respectively.[7,8] The chemoselectivity is strongly dependent on the structure of both the substrate and nucleophile, and reaction conditions such as CO pressure and reaction temperature. In general, both mono and double carbonylated compounds are formed even under mild conditions (low CO pressure) using primary and secondary amines of high basicity. However, aryl amines of low basicity provide carboxamides exclusively. (From mechanistic point of view, the formation of Pd(II)-acyl-carbamoyl catalytic intermediates, providing 2-ketocarboxamides in reductive elimination, is not favoured using aryl amines.)

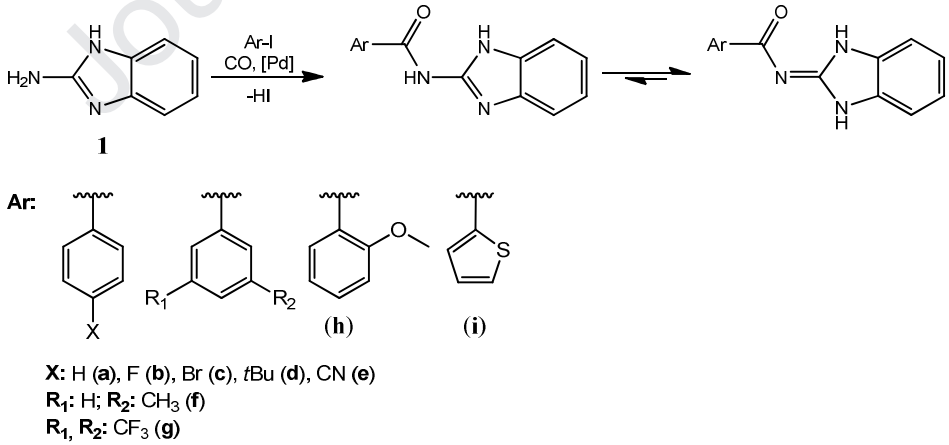
Among these *N*-nucleophiles, amino-heteraromatics are of special importance yielding conjugates (hybrides) with two moieties of equal biological importance.[9,10]

Both the high efficiency of the aminocarbonylation reaction toward the synthesis of carboxamides and the preliminary experiences of our laboratory in this field prompted us to investigate the amino-substituted heterocycles as *N*-nucleophiles. Furthermore, the structural features of the products were investigated in detail since the close proximity of the carboxamide functionality and the imidazolyl (oxazolyl) moiety allows tautomerization.

2. Results and discussion

*2.1. Aminocarbonylation using 2-aminobemzimidazole (**1**) as N-nucleophile*

Iodobenzene (**a**) and substituted iodobenzenes such as 4-fluoroiodobenzene (**b**), 4-bromoiodobenzene (**c**), 4-*tert*-butyliodobenzene (**d**), 4-cyanoiodobenzene (**e**), 3-methyliodobenzene (**f**), 3.5-bis(trifluoromethyl)iodobenzene (**g**), 2-methoxyiodobenzene (**h**) and 2-iodothiophene (**i**) were reacted with 2-aminobenzimidazole (**1**) as *N*-nucleophile in palladium-catalysed aminocarbonylation under mild conditions (1 bar CO, 70 ^{o}C) in the presence of a Pd(0) catalyst formed *in itu* from palladium(II) acetate and triphenylphosphine (*Scheme 1*).[11] Regarding the number of carbon monoxide molecules embedded in the substrate molecule, the reaction is completely chemoselective toward monocarbonylation yielding carbonyl compounds (**1a-i**) exclusively in 60-98% isolated yields (*Figure 2*). Since an amine nucleophile of low basicity was used, chemoselectivities similar to those obtained with anilines were expected. Accordingly, no double CO insertion leading to 2-ketocarboxamides was observed.



Scheme 1. Aminocarbonylation of iodoaromatics (**a-i**) in the presence of 2-aminobenzimidazole (**1**)

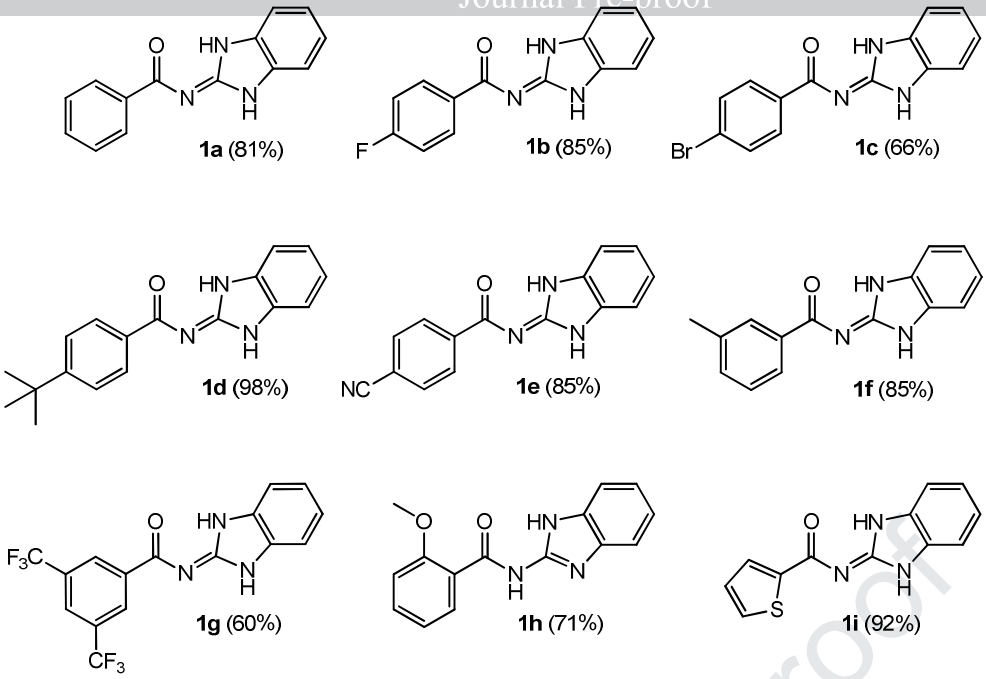
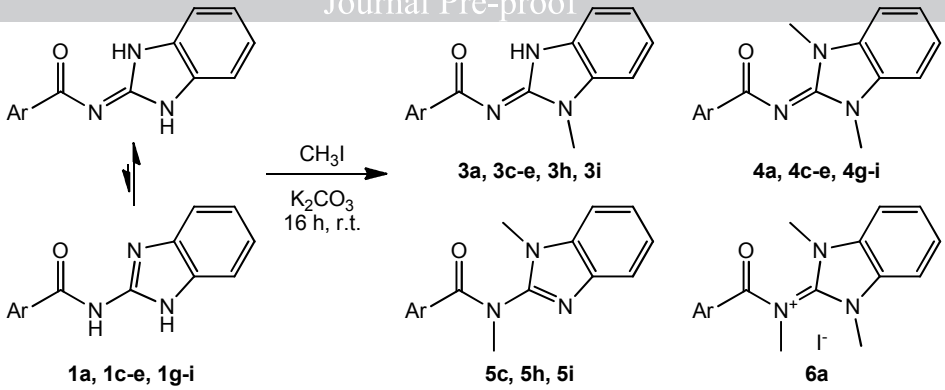


Figure 2. Products isolated in aminocarbonylation using 2-aminobenzimidazole (**1**) as *N*-nucleophile

Single crystal X-ray diffraction study for the compounds of which suitable crystal could be grown revealed that in several cases instead of the expected benzimidazole-based carboxamides possessing the C(O)NH functionality (**1h**), a C(O)N=C functionality was identified (**1e**, **1g**). That is, the (1,3-dihydro-2H-benzimidazole-2-ylidene)benzamide isomer of the expected products were obtained. Based on this information detailed NMR investigations were performed and supported the presence of C=N-acyl moiety for further derivatives (**1a-d**, **1f, 1i**)) in solution, too.

The methylation of these compounds with methyl iodide leads to the corresponding 1-methyl- and 1,3-dimethylbenzimidazole compounds as primary products, *i.e.*, methylation takes place at the heterocycle nitrogen atoms (**4a**, **4c-e**, **4g**, **4**i) and not at the amide-NH which was proved by X-ray diffraction study for compound **4e**. In some cases (**5a**, **5d**, **5i**), due to the tautomeric equilibrium, amide-NH methylation have been carried out as well (*Scheme 2, Figure 3*). It has to be noted that in some cases even the minor products of methylation were isolated in analytically pure form, obviously in low isolated yields, and fully characterised. When the parent iodobenzene (**1a**) was used, trimethylation of the corresponding acylated derivative took place resulting in **6a**.



Scheme 2. Methylation of acylated methylbenzimidazol derivatives **1** (depicted in Fig. 2)

As mentioned above, in addition to conventional characterization methods, several compounds of the above series **1e, 1g, 1h** (parent carbonylation compounds), and **4e** (methylated compounds in the benzimidazole series) were charaterised by single crystal X-ray crystallography as well. (Similarly, the crystal structure od the parent (**2e**) and methylated compound (**7e**) were determined also in the benzoxazole series (See 2.2.).)

The differentiation between C(O)NH and C(O)N= functionalities was unambigous on the basis of bond length data.[12] Peaks on the difference electron density map were also observed indicating the place of hydrogen atoms on the heterocyclic ring nitrogen. In the amide tautomers the N1-C12 distance is significantly shorter, for **1h** 1.3601(18) Å, than that of the acylated C=N (acylated guanidine) tautomers, in the range of 1.30-1.34 Å (Figure 4 shows the numbering scheme, see also Table S2 and Table S3).

For more recent information search on the Cambridge Structural Database [13] (Version 5.40 updates February, 2019) was performed using the Conquest software [14] (Ver 2.02) and the results vere analysed and visualized using the Mercury package.[15]

It was also observed, that in the acylated C=N (acylated guanidine) tautomers the C12-N11 and C12-N13 bond distances are equal within experimental error. It is noteworthy, that both in solution and in the solid state the noted tautomeric form was observed for our compounds. The similar tautomeric equilibrium has been studied by Koeller et al.[16] among amido-benzimidazole derivatives at half-equivalence point and it was concluded, that added salts have crucial effect on the equilibrium. According to our results simple crystallization resulted only one tautomer which can be explained by solubility differences. In structure **6a** the planarity of the molecule is lost because of the repulsion of methyl substituents. The solid state structures are stabilized by weak C-H..O interactions.

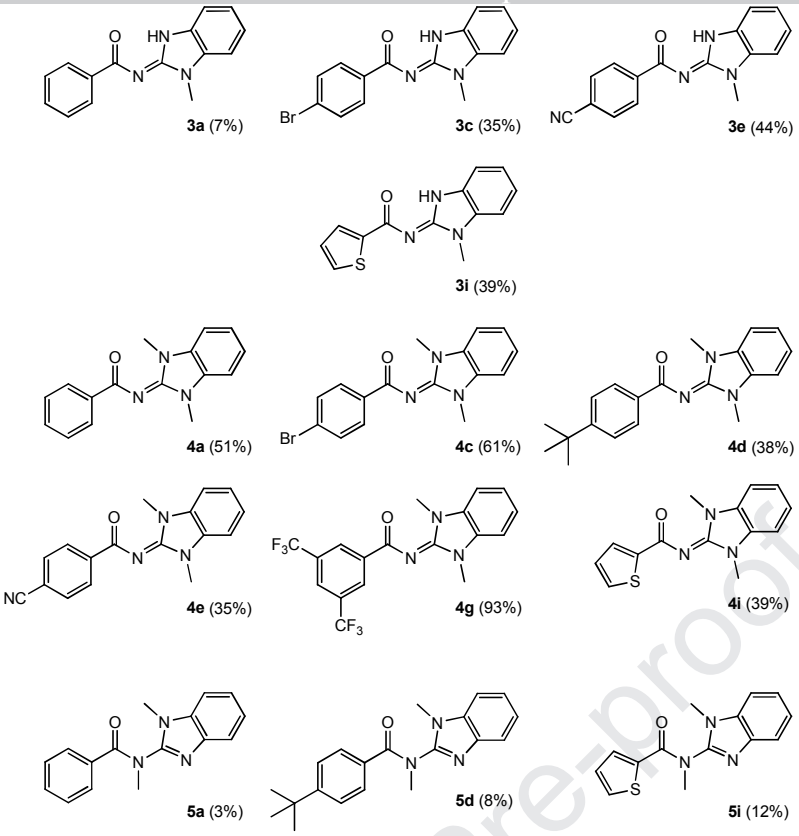


Figure 3. Products isolated in methylation of selected acylated 2-aminobenzimidazoles (isolated yields in brackets)

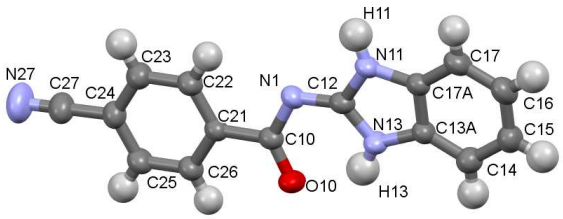


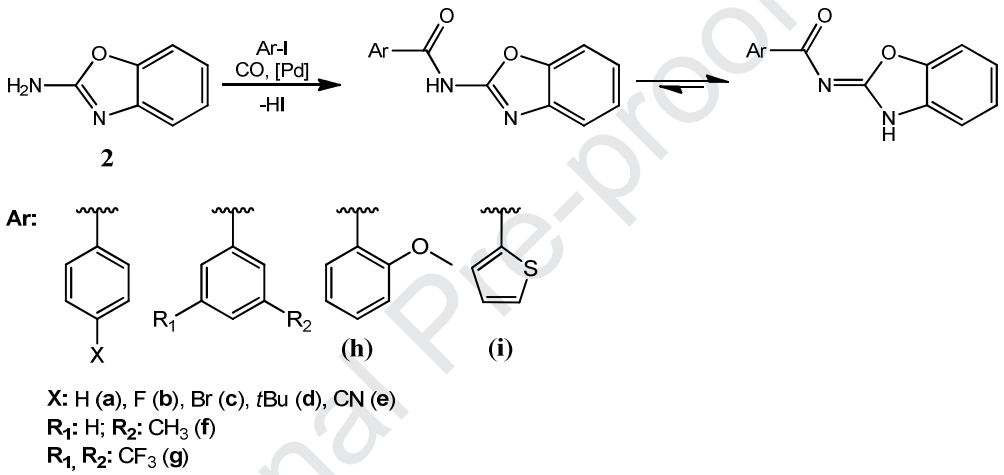
Figure 4. ORTEP view of **1e** structure at 50% probability level with numbering scheme

*2.2. Aminocarbonylation using 2-aminobenzoxazole (**2**) as N-nucleophile*

To widen the scope of the above reaction, as well as to produce novel compounds of practical interest, a further nucleophiles of similar structure, 2-aminobenzoxazole (**2**) was used (Scheme 3). This nucleophile proved to be efficient in aminocarbonylation providing carboxamides depicted in Figure 5. However, the introduction of the oxygen atom into the heterocycle resulted in a dramatic change in reactivity of the

nucleophile. While close to complete conversions can be obtained with **1** under the given conditions, typically conversions lower than 50% can be obtained using **2** as nucleophile (Table 1) with the axception of iodoaromatics **g** and **h**. Therefore, the isolation of the aminocarbonylation profucts in the **2a-i** series in analytically pure form can be performed with low yields only. (It has to be noted that the yields can be substantially increased (up to 70%) by using elevated reaction times (72 h).)

Surprisingly, in case of iodoaromatics **h** possessing a 2-methoxy substituent, the 'conventional' carboxamide (ArC(O)NH) functionality was identified by single crystal X-ray diffraction studies. That is, the close proximity of the oxygen (OMe) enables the formation of a weak hydrogen bond to amide-NH stabilising the amide tautomer, and consequently, the tautomerization toward the acylimine =NC(O)Ar form cannot be observed under normal conditions.



Scheme 3. Aminocarbonylation of iodoaromatics (**a-i**) in the presence of 2-aminobenzoxazole (**2**).

Table 1. Conversions obtained in the aminocarbonylation of iodoaromatics (a-i) on.[a]

Iodoaromatics	Conversion[b] [%] Nucleophile	
	1	**2**
a	>98	24
b	>98	20
c	>98	36
d	>98	24
e	>98	41
f	>98	42
g	62	87
h	>98	>98
i	95	11

[a] Reaction conditions: 1 mmol substrate (**a-i**), 1.2 mmol nucleofile (**1**, **2**); 0.025 mmol of $Pd(OAc)_2$, 0.05 mmol of PPh_3, 0.5 mL of Et_3N, 10 mL of DMF, 1 bar CO, 70°C, reaction time 24 h.

[b] Determined by GC (dodecane as internal standard).

As in the benzimidazole series, several compounds from the benzoxazole acyl derivatives and their methylated compounds (**2e** and **7e**, respectively) were characterised by single crystal X-ray crystallography as well.

In structure **2e** the peak of the proton at the oxazole nitrogen could be found on the difference electrondensity map while in **7e** the place of the methyl group was unambigous. Bond length and bond angle data are in the expected range, see also Tables S2 and S3.

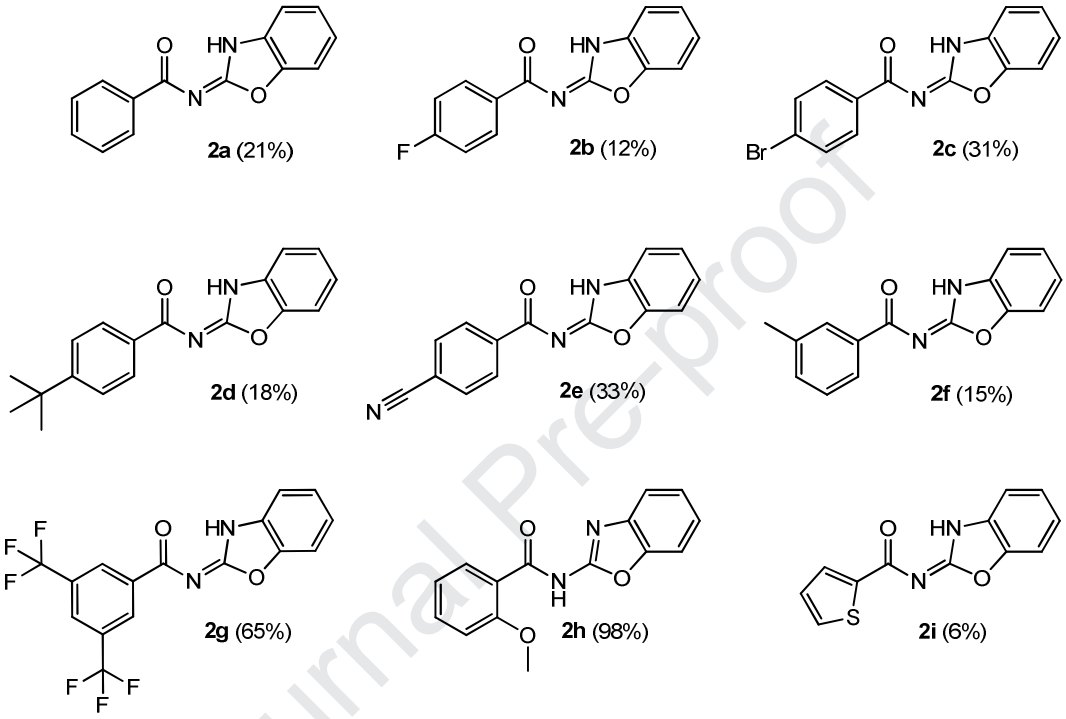
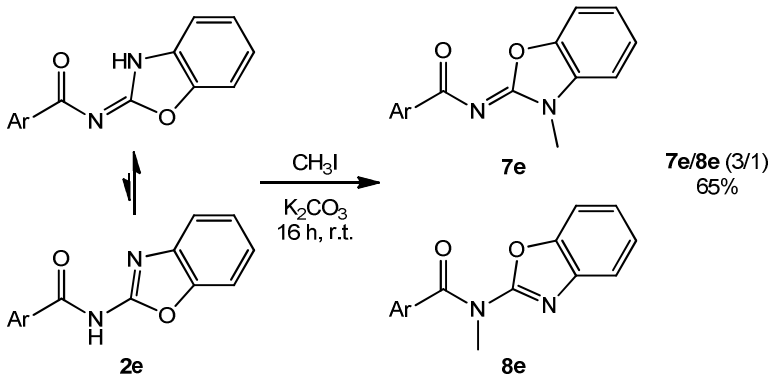


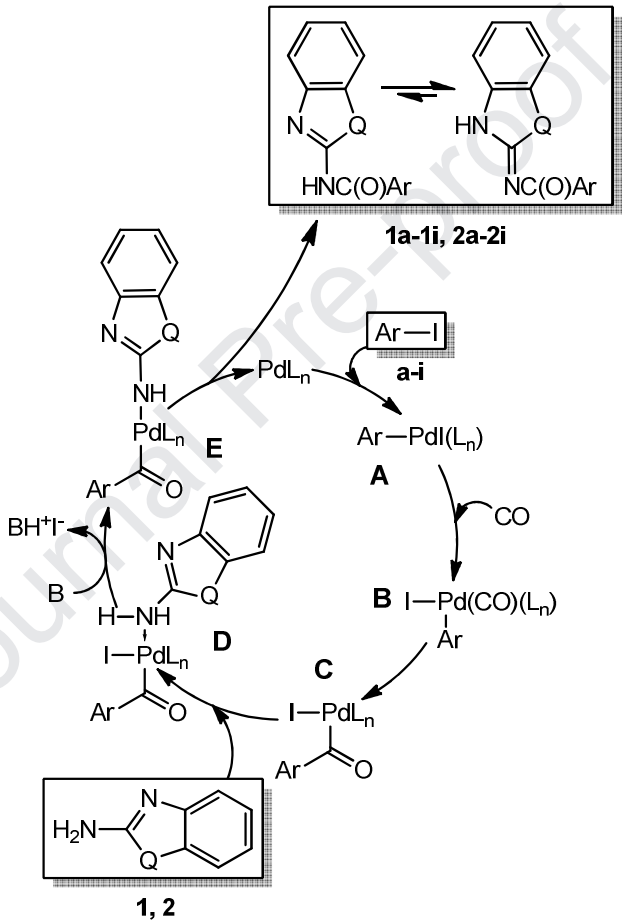
Figure 5. Products isolated in aminocarbonylation using 2-aminobenzoxazole (**2**) as *N*-nucleophile.

As above, methylation experiments were carried out with one of the acylated compounds, **2e**, Due to the equilibrium between the two tautomeric forms, monomethylation on both imidazole-NH and amide-NH took place and **7e** and **8e** (as a two-component mixture) were isolated, respectively (*Scheme 4*).



Scheme 4. Methylation of the acylation product **2e** resulting in a mixture of two monomethylatd compounds **7e**/**8e**

The high chemoselectivity can be rationalised on the basis of a generally accepted catalytic cycle (*Scheme 5*). That is, the oxidative addition of the iodoaromatics (**a-i**) onto *in situ* formed palladium(0) complexes resulted in the formation of aryl-iodo-palladium(II) intermediate (**A**). CO is activated as a terminal carbonyl ligand in **B**, then inserted into aryl-palladium bond yielding the acyl-complex (**C**). The coordination of the amine nucleophile (**1** or **2** in **D**) is followed by HI abstraction by a base (for instance Et_3N). The amido-acyl-palladium(II) intermediate (**E**) formed in this way undergoes reductive elimination in the product-forming step and the coordinatively unsaturated palladium(0) species are re-formed.



Scheme 5. A simplified catalytic cycle for the aminocarbonylation of iodoarenes with **1** and **2** as *N*-nucleophiles.

Conclusions

Iodoaromatics such as substituted iodobenzenes and 2-iodothiophene underwent aminocarbonylation in the presence of aminoheterocycles (2-aminobenzimidazole and 2-aminobenzoxazole) as *N*-nucleophiles. A single carbon monoxide insertion took place resulting in *N*-acylimine, the tautomer of the expected carboxamide.

The novel structures containing one and two NH groups in benzoxazole and benzimidazole, respectively, were proved by methylation experiments and full characterization including single crystal X-ray crystallography.

3. Experimental

3.1. General procedures

^{1}H, ^{19}F and ^{13}C NMR spectra were recorded in DMSO on a Bruker Avance III 500 spectrometer at 500, 470.4 and 125.7 MHz, respectively. Chemical shifts δ are reported in ppm relative to DMSO (2.50 and 39.50 ppm for ^{1}H and ^{13}C, respectively). 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. Mass spectrometry data have been obtained using a GC-MS system consisting of a Perkin Elmer AutoSystem XL gas-chromatograph. Melting points are uncorrected and were measured with a Büchi apparatus. TLC plates (silica gel on TLC Al foils with fluorescence indicator 254 nm) were purchased from Sigma-Aldrich. The eluents used in thin-layer chromatography are specified below. Iodoaromatics and 2-aminobenzimidazole and 2-aminobenzoxazole were purchased from Aldrich and used without further purification.

It has to be noted that several compounds below (**1a**[17-20], **1b**[20], **1h**[21], **2a**[18, 19, 22, 23], **2b**[23], **2d**[23], **2i**[23], **3a**[19]) have been already synthesised. In general, good agreement with analytical details published for these compounds can be observed. However, due to some missing data or partial characterization, all analytical details will be given below also in these cases.

*3.2. Aminocarbonylation of iodoaromatics using 2-aminobenzimidazole (**1**) (or 2-aminobenzoxazole (**2**)) 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), iodobenzene (**a**) (110 µL, 1.0 mmol) (or an other iodoaromatics, **b-i**) (1.0 mmol), nucleophile **1** (159.8 mg, 1.2 mmol) (or an other nucleophile, **2-3**) (1.2 mmol) and triethylamine (0.5 mL) 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 (filled with argon, connected via gas inlet) at the top. The argon atmosphere was changed to carbon monoxide by applying low vacuum/carbon monoxide flushing (three times) through the gas inlet (with tap) equipped to the flask. (The application of a carbon monoxide atmosphere is sufficient, no bubbling of CO is necessary.) The reaction was conducted for the given reaction time upon stirring at 70 ˚C and analysed by GC-MS (internal standard: dodecane). The cooled reaction mixture was then concentrated and evaporated to dryness under reduced pressure.

Method **A**. (**1d**, **1f**, **1h**, **2a**, **2d**, **2e**, **2h**): The residue was dissolved in chloroform (15 mL) and washed three times with water (30 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated under

reduced pressure to a solid material. Aforesaid compounds were subjected to column chromatography (Silicagel 60 (Merck), 0.063-0.200 mm), EtOAc/$CHCl_3$ eluent mixtures (the exact ratios are specified in Characterization for each compound; isolated yields are not optimized.

Method **B**. (**1a-1c**, **1e**, **1g**, **1i**, **2b**, **2c**, **2f**, **2g**, **2i**): Toluene (15 mL) was added to the residue, the insoluble material (product) was filtered, washed with water on the filter and dried. The powder-like material was dissolved in methanol, the palladium-black was filtered off and methanol was evaporated.

3.3. Methylation of the carbonylated products

In a typical experiment the carbonylated product **1a** (71.2 mg, 0.3 mmol) (or a similar compound of this series) was dissolved in acetone (10 mL) and potassium-carbonate (82.8 mg, 0.6 mmol) and methyl iodide (200 µL, 3.2 mmol) was added under argon. The reaction mixture was stired for 16 hours at room temperature. It was then filtered, evaporated to dryness under reduced pressure. The residue was dissolved in chloroform (10 mL) and washed three times with water (10 mL). See Method **A**.

Supporting Information

The Supporting Information is available free of charge on the Elsevier Publications website at ….

Experimental detailes of single crystal X-ray diffraction determinations, structures, as well as full analytical characterization of the compounds obtained in aminocarbonylation and consequent methylation can be found in the Supporting Information. In addition, ^{1}H and ^{13}C NMR spectra of all products are added. Structures **1e**, **1g**, **1h**, **2e**, **4e**, **6a**, **7e** have been deposited under deposition numbers 1969221-1969227, respectively, at CCDC/CSD.

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- Detailed analysis of the tautomeric forms of the products by NMR and X-ray crystallography.
- Synthesis of heterocyclic compounds of potential practical (pharmaceutical) importance.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: