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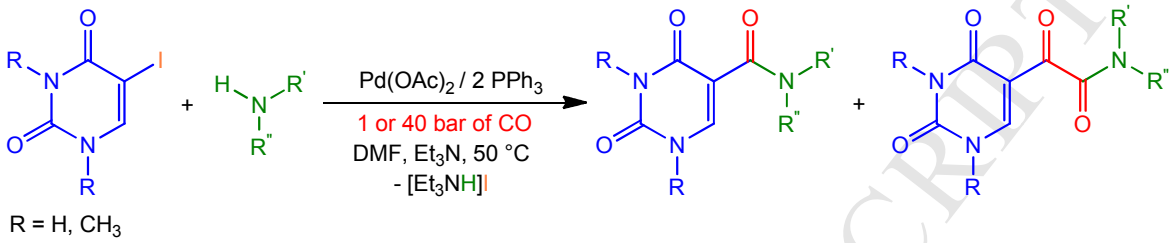
Graphical abstract



Functionalisation of the Uracil Ring via Palladium-Catalysed Aminocarbonylation.

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Abstract: Iodouracil derivatives (5-iodouracil, 5-iodo-1,3-dimethyluracil) were aminocarbonylated using a set of primary and secondary amines in the presence of *in situ* palladium(0) catalysts. The formation of carboxamides via single CO insertion was favoured at atmospheric CO pressure. The chemoselectivity toward double CO insertion can be increased by using 40 bar of CO pressure, in this way up to 60% selectivity toward 2-ketocarboxamide was achieved. In the case of 5-iodouracil the corresponding 5-glyoxylamido-uracil derivatives were exclusively formed at 40 bar CO pressure. The only exception is the less basic aniline nucleophile which provided the corresponding carboxamide exclusively. A typical side-reaction took place when 5-iodouracil was used as substrate: this heterocycle, existing in lactam-lactim tautomeric forms, underwent deiodination providing the parent uracil as side-product.

Key-words: palladium, uracil, carbonylation, carbon monoxide, carboxamide

1. Introduction

Pd-catalysed aminocarbonylation of aryl halides (preferably iodides) was discovered more than four decades ago[1] and had become one of the most investigated carbonylation reactions. The facile introduction of the carboxamide functionality into various skeletons made this reaction of synthetic importance and discussed in several review papers[2] and book chapters.[3]

In spite of the aminocarbonylation of alkenyl halides (or their synthetic surrogates, enol triflates) which gave generally carboxamides,[4] the same reaction of aryl halides (or triflates) was always accompanied by the formation of the corresponding 2-ketocarboxamides due to double CO insertion.[5]

Recently, our interest turned to the functionalisation of skeletons of biological importance, therefore, the potential of using halouracil derivatives as substrate is reviewed here. The antimicrobial and anticancer properties of N-substituted 5-iodouracils, as well as their development for practical applications was discussed.[6] 5-Functionalised uracil derivatives were synthesised from 5-iodouracil using halogen-magnesium exchange and consecutive reaction with various electrophiles.[7] The same substrate underwent direct arylation via photochemical reaction.[8] In addition to conventional synthetic procedures, palladium-copper catalysed coupling of terminal alkynes with protected 5-iodouracil nucleosides was carried out.[9] Furthermore, the large-scale preparation of 5-ethynyluracil, which is a potent inhibitor of dihydropyrimidine dehydrogenase enzyme playing key role in the metabolism of 5-fluorouracil, using Sonogashira coupling of trimethylsilylacetylene and 5-iodouracil followed by a simple deprotection was developed.[10] Similarly, 5-iodouracil peptide nucleic acid monomer was reacted with terminal alkynes in Sonogashira reaction.[11] Palladium-dba precursors without adding further ligands were used for direct arylation of 5-halouracil derivatives and 5-halouracil nucleosides.[12] Catalytic amination of 5-iodouracil in the presence of Cu(I) or Ni(0) complexes was carried out.[13] 5-Alkenyl-, 5-alkynyl- and 5-aryluracil derivatives were synthesised in Stille-coupling.[14] The reactivity of 5-bromo- and 5-iodouracil in Suzuki- and Stille-couplings was compared.[15]

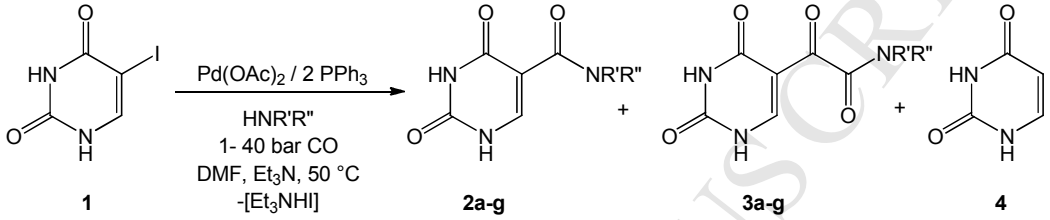
The synthesis of uridine-5-carboxamides was described by Matsuda and coworkers in the reaction between 5-(2,2,2-trifluoroethoxycarbonyl)-2'-deoxyuridine and various primary amines in acetonitrile.[16] 5-Carboxamidouracil derivatives were synthesised by using uracil-5-carboxylic acid and amines in the presence of 1,1'-carbonyldiimidazole as a coupling agent.[17] Although the palladium-catalysed aminocarbonylation reaction has found wide application in synthetic chemistry providing an easy route for the functionalisation of biologically important skeletons, to the best of our knowledge, no efforts were made for the synthesis of carboxamides of nucleotide bases.

In this work, the aminocarbonylation of the parent 5-iodouracil and its dimethyl-substituted derivative will be described. During the systematic catalytic investigations, the influence of the reaction conditions on reactivity and selectivity was explored.

2. Results and discussion

2.1. Aminocarbonylation of 5-iodouracil with primary and secondary amines as N-nucleophiles

5-Iodouracil (**1**) was reacted with various primary (*tert*-butylamine (**a**), aniline (**b**), methyl glycinate (**e**), methyl alaninate (**f**)) and secondary (piperidine (**c**), morpholine (**d**), methyl prolinate (**g**)) amines under carbon monoxide atmosphere (*Scheme 1*). A highly durable, low-ligated palladium(0) catalyst, prepared *in situ* from palladium(II) acetate and triphenylphosphine, was used.[18] Although the palladium(II)-palladium(0) reduction might also occur upon action of amine or carbon monoxide as reducing agents, it has been proved by cyclic voltammetry and NMR measurements that one of the two phosphine ligands acts as reducing agent while it is oxidized to phosphine oxide. Using solvents with good donor properties such as DMF, the formation of a highly active, coordinatively unsaturated $Pd(0)(PPh_3)(solvent)_n$ catalyst was supposed.



	R'	R"
a	H	tBu
b	H	Ph
c	-(CH$_2$)$_5$-	
d	-(CH$_2$)$_2$O(CH$_2$)$_2$-	
e	H	CH$_2$COOCH$_3$
f	H	CH(CH$_3$)COOCH$_3$
g	-CH(COOCH$_3$)(CH$_2$)$_3$-	

Scheme 1. Aminocarbonylation of 5-iodouracil (**1**)

The aminocarbonylation of **1** in the presence of *tert*-butylamine (**a**) and piperidine (**c**) resulted in the formation of the corresponding carboxamides (**2a**, **2c**) in low yields (<30%) under atmospheric carbon monoxide pressure (*Table 1*, entries 1 and 4). The carbonylation reactions are accompanied by deiodination providing the parent uracil (**4**). It has to be noted that it was found as major product at atmospheric CO pressure.

In order to achieve double carbonylation 40 bar of carbon monoxide pressure was needed. Under these conditions 2-ketocarboxamides (**3a-3g**) were found as exclusive carbonylated products, *i.e.*, no carboxamides were formed. The only exception in this amine set was aniline, which gave carboxamide (**2b**) via single CO insertion in highly selective reaction (*Table 1*, entry 3). The same phenomenon was observed recently with various iodoaromatics[19] and iodoheteroaromatics[20] also in our laboratory. Longer reaction times (>40 h) were

needed to reach complete conversion. Not only unfunctionalised amines (**a-d**), but also amino acid methyl esters (**e-g**) have been easily converted to the corresponding 2-ketoamide (except **b**).

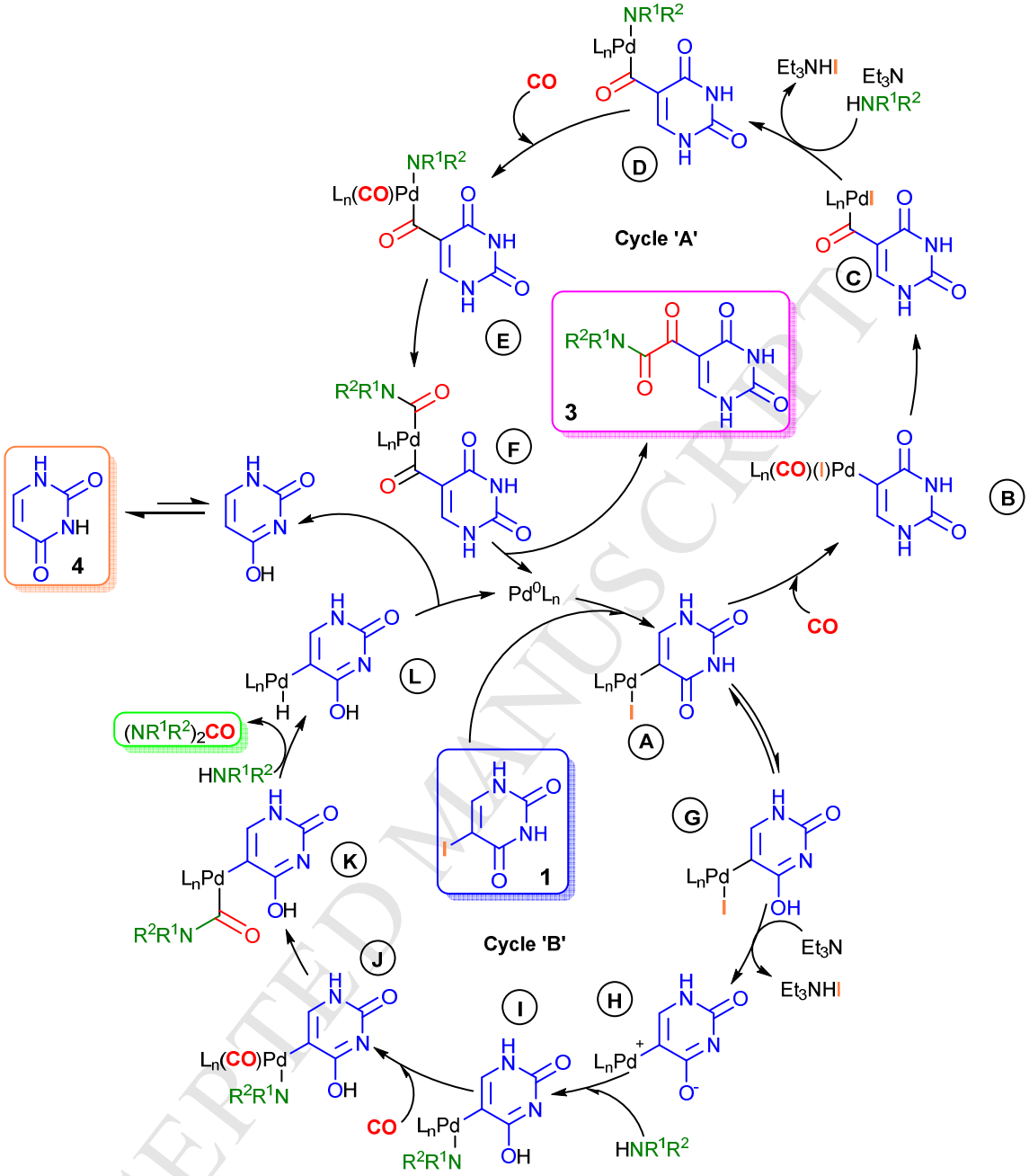
Table 1. Aminocarbonylation of **1** in the presence of various amines[a)]

Entry	Amine	R. time [h]	p(CO) [bar]	Conv. [%]	Ratio of the carbonylated products[b)] [%]		
					carboxamide (**2a-h**)	2-keto-carboxamide (**3a-h**)	uracil (**4**)
1	*t*-BuNH$_2$ (**a**)	42	1	>98	30 (**2a**)	0 (**3a**);	70 (**4**)
2	*t*-BuNH$_2$ (**a**)	40	40	>98	0 (**2a**)	95 (**3a**), 73[c)]	5 (**4**)
3	aniline (**b**)	48	40	>98	70 (**2b**), 60[c)]	0 (**3b**)	30 (**4**)
4	piperidine (**c**)	50	1	90	<5 (**2c**)	0 (**3c**)	>95 (**4**)
5	piperidine (**c**)	42	40	>98	0 (**2c**)	76 (**3c**), 64[c)]	24 (**4**)
6	morpholine (**d**)	48	40	>98	0 (**2d**)	72 (**3d**), 65[c)]	28 (**4**)
7	GlyOMe (**e**)	69	40	>98	0 (**2e**)	>98 (**3e**), 52[c)]	<5 (**4**)
8	AlaOMe (**f**)	68	40	>98	0 (**2f**)	>95 (**3f**), 68[c)]	<5 (**4**)
9	ProOMe (**g**)	68	40	>98	0 (**2g**)	>95 (**3g**), 63[c)]	<5 (**4**)

a) Reaction conditions (unless otherwise stated): 1 mmol of substrate (**1**), amine nucleophile: 3 mmol of **a** or 2 mmol of **b**/1.5 mmol of **c**, **d**/1.1 mmol of **e-g**), 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.
b) Determined by ^1H NMR.
c) Yields of the isolated target compounds (%), based on the substrate (**1**).

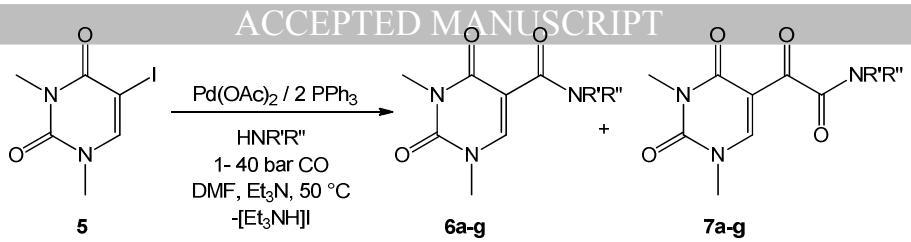
The formation of the double carbonylated (**3**) and the deiodinated products (**4**) can be rationalised on the basis of the generally accepted reaction mechanism depicted in *Scheme 2*. The 5-iodouracil (**1**) is oxidatively added to the *in situ* formed palladium(0) complex (Cycle 'A'). The coordination of the carbon monoxide to the palladium(II)-aryl complex (**A**) and its insertion into the Pd-C bond resulted in the formation of palladium(II)-acyl complex (**C**). This catalytic intermediate is apt to coordinate the amine nucleophile providing a palladium(II)-amido-acyl complex (**D**) accompanied by HX elimination in the presence of triethylamine. The coordination of the second carbon monoxide (**E**) is followed by its insertion into the Pd-N bond giving a palladium(II)-acyl-carbamoyl complex (**F**), which undergoes reductive elimination leading the formation of 2-ketocarboxamide type product (**3**) while the coordinatively unsaturated palladium(0) complex is re-formed. Deiodination has also been occurred, which can be explained on the basis of an earlier work of our research group.[21] The following plausible reaction mechanism (Cycle 'B'), including of the OH moiety formed in the lactim-lactam tautomerism of the uracil ring, is suggested for the deiodination. The tautomerism of the uracil ring in palladium(II)-aryl complex (**A**) could be resulted in **G** catalytic intermediate containing a 2-hydroxy-4-oxo-uracil moiety. Its deiodination in the presence of triethylamine leads to **H** species, which activates the amine nucleophile by providing palladium(II)-amido complex (**I**). The activation of carbon monoxide as a terminal ligand (**J**) is followed by its insertion into Pd-N bond forming the corresponding palladium(II)-carbamoyl complex (**K**). This species reacts with the second primary or

secondary amine providing the 'urea-type' product and the palladium(II)-aryl-hydrido complex (**L**), which undergoes reductive elimination forming uracil (**4**) and the palladium(0) complex. Consequently, the hydrogen derived from the amine nucleophile is necessary to formal deiodination.



Scheme 2. Aminocarbonylation and deiodination of 5-iodouracil (**1**) rationalized by generally accepted catalytic steps

2.2. Aminocarbonylation of 5-iodo-1,3-dimethyluracil with primary and secondary amines as N-nucleophiles



	R'	R"
a	H	tBu
b	H	Ph
c	-(CH$_2$)$_5$-	
d	-(CH$_2$)$_2$O(CH$_2$)$_2$-	
e	H	CH$_2$COOCH$_3$
f	H	CH(CH$_3$)COOCH$_3$
g	-CH(COOCH$_3$)(CH$_2$)$_3$-	

Scheme 3. Aminocarbonylation of 5-iodo-1,3-dimethyluracil (**5**)

A strikingly different behaviour was observed using **5** as substrate. The aminocarbonylation of **5** resulted in the formation of carboxamides (**6a-g**) and 2-ketocarboxamides (**7a-g**) due to single and double CO insertion, respectively (*Scheme 3*). That is, the formation of the deiodination product (1,3-dimethyluracil) was not observed under various conditions. The mixture of mono and double carbonylated derivatives (carboxamides and 2-ketocarboxamides, respectively) were formed depending on the CO pressure and amine (*Table 2*).

Using simple primary (**a**, **b**) and secondary (**c**, **d**) amines practically full conversions were observed both under atmospheric (entries 2, 5, 8) and high pressure conditions (entries 3, 4, 6, 10) after 24 hours.

As above, the use of aniline (**b**) as N-nucleophile resulted in the chemospecific formation of carboxamide (**6b**) (entry 4). In general, the prevailed formation of carboxamides was observed at atmospheric CO pressure. The chemoselectivity can be shifted toward 2-ketocarboxamides at 40 bar CO pressure.

Using amino acid methyl esters as nucleophile lower reactivity was observed under atmospheric conditions: after 24 hours lower than 8% conversions were occurred (entries 12, 16). After longer reaction time (120 h) full conversion was observed by using methyl alaninate (**f**) (entry 17), while the methyl prolinate (**g**) has shown low reactivity (entry 14) under same conditions. Elevated carbon monoxide pressure had to be used to reach full conversion after 24 hours (entries 11, 15, 18).

Table 2. Aminocarbonylation of 5-iodo-1,3-dimethyluracil (**5**) in the presence of various amines under atmospheric and 40 bar carbon monoxide pressure [a)]

Entry	Amine	R. time [h]	p(CO) [bar]	Conv. [%]	Ratio of the carbonylated products[b)] [%]	
					carboxamide (**6a-h**)	2-ketocarboxamide (**7a-h**)
1	*t*-BuNH$_2$ (**a**)	8	1	72	71 (**6a**)	29 (**7a**)
2	*t*-BuNH$_2$ (**a**)	24	1	97	83 (**6a**), 46[c)]	17 (**7a**)
3	*t*-BuNH$_2$ (**a**)	8	40	>98	43 (**6a**)	57 (**7a**), 38[c)]
4	aniline (**b**)	24	40	>98	100 (**6b**), 49[c)]	0 (**7b**)
5	piperidine (**c**)	24	1	>98	77 (**6c**); 45[c)]	23 (**7c**)
6	piperidine (**c**)	24	40	>98	43 (**6c**)	57 (**7c**); 49[c)]
7	morpholine (**d**)	8	1	73	82(**6d**)	18 (**7d**)
8	morpholine (**d**)	24	1	>98	82(**6d**); 43[c)]	18 (**7d**)
9	morpholine (**d**)	8	40	94	48(**6d**)	52 (**7d**)
10	morpholine (**d**)	24	40	>98	52(**6d**)	48 (**7d**); 28[c)]
11	GlyOMe (**e**)	24	40	>98	40 (**6e**); 30[c)]	60 (**7e**); 29[c)]
12	AlaOMe (**f**)	24	1	8	>99 (**6f**)	<1 (**7f**)
13	AlaOMe (**f**)	48	1	22	88 (**6f**)	12 (**7f**)
14	AlaOMe (**f**)	120	1	>98	90 (**6f**); 39[c)]	10 (**7f**)
15	AlaOMe (**f**)	24	40	>98	40 (**6f**)	60 (**7f**); 34[c)]
16	ProOMe (**g**)	24	1	<2%	100 (**6g**)	0
17	ProOMe (**g**)	120	1	13	100 (**6g**)	0
18	ProOMe (**g**)	24	40	>98	46 (**6g**); 25[c)]	54 (**7g**); 21[c)]

a) Reaction conditions (unless otherwise stated): 1 mmol of substrate (**1**), amine nucleophile: 3 mmol of **a** or 2 mmol of **b**/1.5 mmol of **c**, **d**/1.1 mmol of **e**-**g**), 0.025 mmol of Pd(OAc)$_2$, 0.05 mmol of PPh$_3$, 0.5 mL of Et$_3$N, 10 mL of DMF, 50 ^{o}C.
b) Determined by GC-MS.
c) Yields of the isolated target compounds (%), based on the substrate (**5**). (n.i. = not isolated)

To compare the reactivity of a primary (**a**) and a secondary (**d**) amine both under atmospheric and high pressure conditions, samples were taken from the reaction mixture after 1, 2, 4, 8, 24 hours. The influence of the carbon monoxide pressure on the conversion can be clearly seen (*Figure 1* and *Figure 2*): while 24 hours was necessary to reach practically complete conversion under atmospheric conditions, very high conversion (> 82%) was observed at 40 bar CO pressure after 4 hours. In spite of the quite higher basicity of the *tert*-butylamine, there is no striking difference between the reactivity of **a** and **d**.

Figure 1. Conversion as a function of time in the aminocarbonylation of **5** with *tert*-butylamine (**a**)

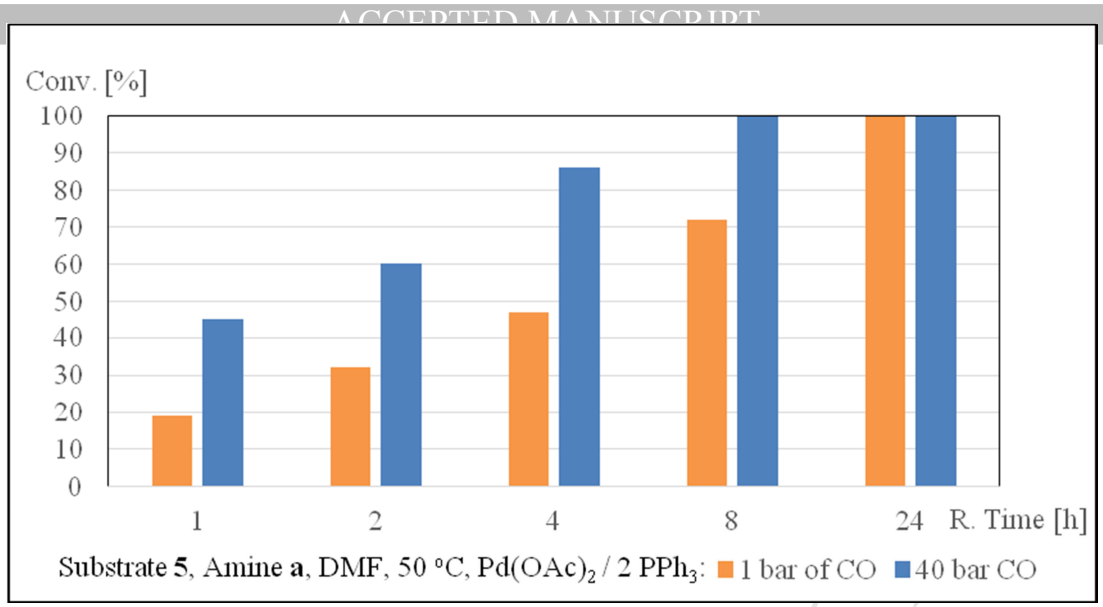
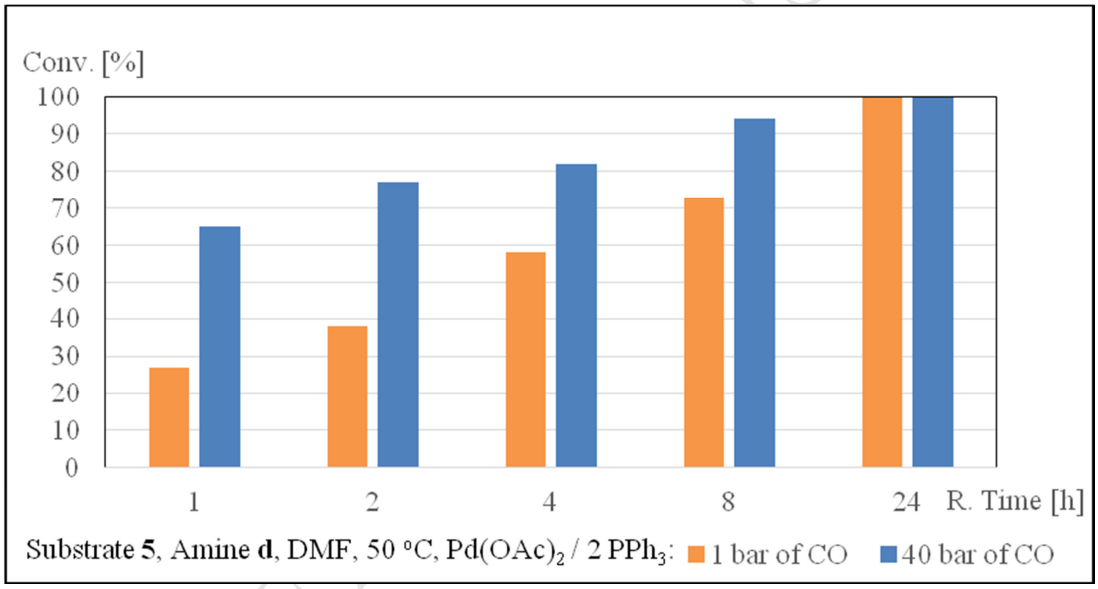


Figure 2. Conversion as a function of time in the aminocarbonylation of **5** with morpholine (**d**)



2.3. Conclusions

In summary, the uracil ring can be efficiently functionalised by carboxamido and 2-ketocarboxamido substituents under aminocarbonylation conditions in the presence of $Pd(OAc)_2$ / PPh_3 catalysts.

In the aminocarbonylation of 5-iodouracil under atmospheric carbon monoxide the deiodination process dominates. Increasing the carbon monoxide pressure (40 bar) the double carbon monoxide insertion, resulting in the 5-glyoxylamido-uracil derivatives, is highly favoured over deiodination side reaction. The formation of deiodinated products can be rationalised by a reaction mechanism based on generally accepted elementary steps. In our suggestion, the OH moiety of the 5-iodouracil formed in tautomerization has an important role in the deiodination resulting in the uracil as a side product.

A strikingly different behaviour can be observed in the aminocarbonylation of 1,3-dimethyl-5-iodouracil. A mixture of carbonylated products was observed both at low (1 bar) and high (40 bar) carbon monoxide pressure. The product formation can be shifted toward the corresponding 5-glyoxylamido-1,3-dimethyluracil derivatives by using 40 bar of carbon monoxide pressure. Deiodination did not occur due to the lack of the lactim-lactam tautomerism. It has to be added, that the isolation procedures in case of 1,3-dimethyl-5-iodouracil were not optimized, *i.e.* the yields added in *Table 2.* were obtained under these conditions.

3. Experimental

3.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO 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) or to DMSO (2.50 and 39.50 ppm for ^{1}H and ^{13}C, respectively). Mass spectrometry data have been obtained using either a GC-MS system consisting of a Perkin Elmer AutoSystem XL gas-chromatograph or an Agilent 6300 Series Ion Trap LC/MSD XCT Plus mass spectrometer (Agilent Technologies, Germany) equipped with an electrospray ion source and controlled with the Agilent LC/MSD Trap software 5.3 (in case of the isolated compounds of the catalytic reactions of 5-iodouracil). Elemental analyses were measured on a 1108 Carlo Erba apparatus. 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. Melting points are uncorrected and were measured with a Büchi apparatus. TLC plates (silica gel on TLC aluminium foil with fluorescence indicator 254 nm) were purchased from Sigma-Aldrich. The eluents used in thin-layer chromatography are specified below.

5-Iodouracil (**1**), 5-iodo-1,3-dimethyluracil (**5**) substrates and amine nucleophiles (**a-g**) were purchased from Sigma-Aldrich and were used without further purification.

*3.2. Aminocarbonylation of iodouracil derivatives (**1, 5**) under atmospheric pressure of carbon monoxide.*

In a typical experiment $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), triphenylphosphine (13.2 mg, 0.05 mmol), 5-iodouracil (**1**) or 5-iodo-1,3-dimethyluracil (**5**) substrates (1 mmol), amine nucleophiles (see above in tables) and triethylamine (0.5 mL) were dissolved in DMF (10 mL) under argon in a 100 mL three-necked flask equipped with reflux condenser connected to a balloon filled with argon. 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 and GC-MS. The cooled reaction mixture was then concentrated and evaporated to dryness under reduced pressure.

Method **A.** (**2b**, **3a**, **3c-3g**): Chloroform (10 mL) was added to the residue and the insoluble material (product) was filtered, washed with absolute ethanol and dried.

Method **B.** (**6a-6g**, **7a-3g**): The residue was dissolved in chloroform (15 mL) and washed twice with water (15 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure to a solid material. All compounds were subjected to column chromatography (Silicagel 60 (Sigma), 0.063-0.200 mm), $CHCl_3$/EtOAc/MeOH or hexane/EtOAc/MeOH eluent mixtures (the exact ratios are specified in *Characterization* (3.4) for each compound).

*3.3. Aminocarbonylation of iodouracil derivatives under high carbon monoxide pressure (a general synthetic methodology for the synthesis of **3a-3g** and **7a-7g**).*

In a typical experiment $Pd(OAc)_2$, triphenylphosphine, iodouracil derivatives (**1, 5**), amine nucleophiles (**a-g**) and triethylamine were used in the same amount as above and were dissolved in 10 mL of DMF under argon in a 100 mL autoclave. The atmosphere was changed to carbon dioxide and the autoclave was pressurized to the given pressure with carbon monoxide. (Caution: High pressure carbon monoxide should only be used with adequate ventilation (hood) using CO sensors as well.) The reaction was conducted for the given reaction time upon stirring at 50 °C. After the given reaction time the reaction mixture was cooled to room temperature and the autoclave was carefully depressurized in a well-ventilated hood. The product mixture was analysed by GC and GC-MS. The work-up of the reaction mixture was identical to that discussed for the atmospheric experiments.

3.4. Characterisation of the products

3.4.1. 5-(*N-tert*-Butylglyoxylamido)uracil (**3a**)

Yield: 175 mg (73%), Off white powder, m.p. 270-271 °C; R_f (15% MeOH/$CHCl_3$) 0.65. δ_H (500 MHz, DMSO-d6) 11.82 (1H, br s, *NH*), 11.42 (1H, br s, *NH*), 8.20 (1H, s, NH*CH*), 7.98 (1H, s, CO*NH*), 1.31 (9H, 3 x *(CH)*$_3$). δ_C NMR (125.7 MHz) 186.6, 165.7, 161.3, 150.9, 150.6, 108.8, 51.1, 28.7. IR (KBr, ν (cm^{-1})): 3375 (NH), 1734, 1700, 1669 (CO), 1653 (Amide I.), 1616 (C=C), 1499 (Amide II.); MS m/z (rel. int.): 238 (100, $[M–H]^-$), MS/MS (rel. int.) 238 (19), 223 (10), 195 (32), 123 (8), 111 (100).

3.4.2. 5-(*N*-Phenylcarboxamido)-uracil (**2b**)

Yield: 140 mg (60%), Beige powder, m.p. > 300 °; R_f (15% MeOH/$CHCl_3$) 0.65. δ_H (500 MHz, DMSO-d6) 11.86 (2H, br s, 2 x *NH*), 10.91 (1H, s, CO*NH*), 8.26 (1H, s, NH*CH*), 7.64 (2H, s, Ph (*ortho*)), 7.35 (2H, s, Ph (*meta*)), 7.10 (1H, s, Ph (*para*)). δ_C NMR (125.7 MHz) 165.0, 160.7, 150.8, 149.0, 138.6, 129.5, 124.2, 120.9, 104.6. IR (KBr, ν (cm^{-1})): 3221 (NH), 1718, 1696 (CO), 1653 (Amide I.), 1617 (C=C), 1553 (Amide II.); MS m/z (rel. int.): 229.9 (100, $[M–H]^-$), MS/MS (rel. int.) 186.9 (46), 143.0 (100).

3.4.3. 5-(*N,N*-Pentane-1',5'-diylglyoxylamido)-uracil (**3c**)

Yield: 160 mg (64%), Off white powder, m.p. 281-282 °C; R_f (15% MeOH/$CHCl_3$) 0.50. δ_H (500 MHz, DMSO-d6) 12.05 (1H, br s, *NH*), 11.52 (1H, s, *NH*), 8.22 (1H, s, NH*CH*), 3.43 (2H, s, CH_2), 3.15 (2H, s, CH_2), 1.66-1.42 (6H, br m, 3 x CH_2). δ_C NMR (125.7 MHz) 188.1, 166.0, 161.8, 151.0, 150.8, 108.7, 46.3, 41.6, 25.4, 24.9, 24.4. IR (KBr, ν (cm^{-1})): 1768, 1728, 1680 (CO), 1660 (Amide I.), 1626 (C=C); MS m/z (rel. int.): 250.0 (100, $[M–H]^-$), MS/MS (rel. int.) 250.0 (56), 222.0 (20), 206.9 (100), 205.9 (61), 179.0 (10), 163.0 (19), 139.0 (32), 121.1 (8).

3.4.4. 5-(*N,N*-Penta-3'-oxa-1',5'-diylglyoxylamido)-uracil (**3d**)

Yield: 165 mg (65%), Pale brown powder, m.p. 248-249 °C; R_f (15% MeOH/$CHCl_3$) 0.44. δ_H (500 MHz, DMSO-d6) 12.05 (1H, br s, *NH*), 11.57 (1H, s, *NH*), 8.26 (1H, s, NH*CH*), 3.68-3.60 (2H, m, CH_2), 3.58-3.52 (2H, m, CH_2), 3.50-3.44 (2H, m, CH_2), 3.25-3.17 (2H, m, CH_2). δ_C NMR (125.7 MHz) 187.7, 166.4, 162.0, 151.0, 150.9, 108.7, 66.0, 65.9, 48.8, 41.3. IR (KBr, ν (cm^{-1})): 1772, 1727, 1679 (CO), 1663

(Amide I.), 1624 (C=C), 1114 (COC); MS m/z (rel. int.): 251.9 (100, [M–H]$^-$), MS/MS (rel. int.) 252.0 (26.4), 208.9 (100), 207.9 (89), 181.9 (13).

3.4.5. 5-(*N*-(Methoxycarbonylmethyl)-glyoxylamido)-uracil (**3e**)

Yield: 132 mg (52%), Brown powder, m.p. 135-136 °C; R_f (15% MeOH/$CHCl_3$) 0.35. δ_H (500 MHz, DMSO-d6) 11.86 (1H, br s, *NH*), 11.44 (1H, s, *NH*), 9.00 (1H, br s, CO*NH*), 8.39 (1H, s, NH*CH*), 3.95 (2H, s, *CH_2*), 3.67 (3H, s, *OCH_3*). δ_C NMR (125.7 MHz) 185.1, 170.1, 165.3, 161.0, 152.0, 150.7, 108.2, 52.4, 40.9. IR (KBr, ν (cm^{-1})): 3114 (NH), 1735 (ester CO), 1726, 1699, 1668 (CO), 1648 (Amide I.), 1610 (C=C), 1506 (Amide II.); MS m/z (rel. int.): 253.9 (100, [M–H]$^-$), MS/MS (rel. int.) 221.9 (7), 210.9 (100), 196.9 (4), 178.9 (9), 177.9 (11), 111.1 (3).

3.4.6. 5-(*N*-(1'-Methoxycarbonylethyl)-glyoxylamido)-uracil (**3f**)

Yield: 183 mg (68%), Off white powder, m.p. 223-224 °C; R_f (15% MeOH/$CHCl_3$) 0.49. δ_H (500 MHz, DMSO-d6) 11.85 (1H, br s, *NH*), 11.45 (1H, s, *NH*), 8.99 (1H, br s, CO*NH*), 8.30 (1H, s, NH*CH*), 4.39 (1H, s, *CH*CH_3), 3.66 (3H, s, *OCH_3*), 1.35 (3H, s, CH*CH_3*). δ_C NMR (125.7 MHz) 1885.8, 172.8, 165.2, 161.1, 151.7, 150.8, 108.73, 52.5, 47.8, 17.1 IR (KBr, ν (cm^{-1})): 3327 (NH), 1735 (ester CO), 1720, 1685, 1678 (CO), 1654 (Amide I.), 1634 (C=C), 1527 (Amide II.); MS m/z (rel. int.): 268 (100, [M–H]$^-$), MS/MS (rel. int.) 235.9 (6) 224.9 (100), 192.9 (31), 191.9 (49), 149.0 (7), 111.0 (15).

3.4.7 5-(*N*-(1'-Methoxycarbonyl-butan-1',4'-diyl)-glyoxylamido)-uracil (**3g**) (ca.1/3 mixture of two C(O)N rotamers)

Yield: 185 mg (63%), White solid material, m.p. 245-246 °C; R_f (15% MeOH/$CHCl_3$) 0.56. δ_H (500 MHz, DMSO-d6) 12.08 (1H, br s, *NH*), 11.54/12.52 (major/minor) (1H, s, *NH*), 8.23/8.21 (major/minor) (1H, s C*CH*), 4.41-4.37/4.36-4.32 (major/minor) (1H, m, N*CH*), 3.68/3.61 (major/minor) (3H, s, O*CH_3*), 3.58 (2H, m, NCH_2, overlapping with the water content of DMSO-d6), 2.31-2.20/2.19-2.12 (major/minor) (2H, m, *CH_2*), 2.00-1.99/1.97-1.83 (minor/major) (2H, m, *CH_2*). δ_C NMR (125.7 MHz) 187.2/187.0 (major/minor), 172.3/172.2 (minor/major), 165.7/165.5 (major/minor), 161.6/161.5 (minor/major), 151.7/151.3 (major/minor), 150.8/150.6 (major/minor), 108.4/108.1 (minor/major), 59.2/58.2 (minor/major), 52.6/52.5 (minor/major), 47.0/46.1 (major/minor), 30.8/29.2 (minor/major), 24.9/22.4 (major/minor). IR (KBr, ν (cm^{-1})): 1738 (ester CO), 1728, 1695, 1682 (CO), 1640 (Amide I.), 1605 (C=C); MS m/z (rel. int.): 294.0 (100, [M–H]$^-$), MS/MS (rel int) 261.9 (31), 251.0 (22), 237.0 (6), 233.9 (5), 218.9 (8), 217.9 (100), 205.9 (10), 174.9 (66).

3.4.8. 1,3-Dimethyl-5-(*N-tert*-butylcarboxamido)uracil (**6a**)

Yield: 110 mg (46%), White solid, m.p. 184-185 °C; [Anal. Calcd. for $C_{11}H_{17}N_3O_3$:C, 55.22; H, 7.16; N, 17.56. Found: C, 55.98; H, 6.57; N, 16.78]; R_f (5% MeOH, 35% EtOAc, 60% hexane) 0.64. δ_H (500 MHz, $CHCl_3$) 8.80 (1H, br s, CO*NH*), 8.36 (1H, s, *CH*), 3.51 (3H, s, N*CH_3*), 3.38 (3H, s, N*CH_3*), 1.43 (9H, 3 x *$(CH)_3$*). δ_C NMR (125.7 MHz), 163.1, 160.8, 151.0, 148.3, 106.0, 51.1, 37.7, 28.8, 28.2. IR (KBr, ν (cm^{-1})): 3292 (NH), 1699 (br, CO + Amide I.), 1620 (C=C), 1554 (Amide II.); MS m/z (rel. int.): 239 (2, M^+), 224 (46), 182 (8), 167 (100), 140 (2), 110 (4), 82 (4), 53 (4).

3.4.9. 1,3-Dimethyl-5-(*N*-*tert*-butylglyoxylamido)uracil (**7a**)

Yield: 101 mg (38%), White solid, m.p. 142-143 °C; [Anal. Calcd. for $C_{12}H_{17}N_3O_4$:C, 53.92; H, 6.41; N, 15.72. Found: C, 53.28; H, 6.17; N, 15.25]; R_f (5% MeOH, 35% EtOAc, 60% hexane) 0.41. δ_H (500 MHz, $CHCl_3$) 9.21 (1H, s, *CH*), 7.08 (1H, br s, CO*NH*), 3.56 (3H, s, N*CH*$_3$), 3.39 (3H, s, N*CH*$_3$), 1.44 (9H, 3 x *(CH)*$_3$). δ_C NMR (125.7 MHz), 182.1, 160.8, 159.6, 152.9, 150.4, 108.0, 51.7, 38.72, 28.3, 28.1. IR (KBr, ν (cm^{-1})): 3329 (NH), 1718, 1688, 1670 (CO), 1661 (Amide I.), 1626 (C=C), 1552 (Amide II.); MS m/z (rel. int.): 167 (70, M^+-100), 140 (100), 110 (6), 82 (12), 57 (22).

3.4.10. 1,3-Dimethyl-5-(*N*-*tert*-phenylcarboxamido)uracil (**6b**)

Yield: 126 mg (49%), White solid, m.p. 216-217 °C; [Anal. Calcd. for $C_{13}H_{13}N_3O_3$:C, 60.23; H, 5.05; N, 16.21. Found: C, 59.60; H, 4.79; N, 15.67.]; R_f (30% EtOAcH/$CHCl_3$) 0.44. δ_H (500 MHz, $CDCl_3$) 10.94 (1H, s, CO*NH*), 8.52 (1H, s, *CH*), 7.70 (2H, d, 7.4 Hz, Ph (*ortho*)), 7.39 (2H, t, 7.4 Hz, Ph (*meta*)), 7.16 (1H, t, 7.4 Hz, Ph (*para*)) 3.50 (3H, s, N*CH*$_3$), 3.28 (3H, s, N*CH*$_3$). δ_C NMR (125.7 MHz) 163.2, 160.0, 150.9, 149.2, 137.9, 129.0, 124.3, 120.4, 105.2, 38.0, 28.4. IR (KBr, ν (cm^{-1})): 3265 (NH), 1705, 1695 (CO), 1622 (Amide I.), 1596 (C=C), 1527 (Amide II.); MS m/z (rel. int.): 259 (65, M^+), 167 (100), 140 (1), 110 (6), 82 (2), 65 (6), 53 (5).

3.4.11. 1,3-Dimethyl-5-(*N*-pentane-1',5'-diylcarboxamido)uracil (**6c**)

Yield: 119 mg (45%), Off white solid, m.p. 123-124 °C; [Anal. Calcd. for $C_{12}H_{17}N_3O_3$:C, 57.36; H, 6.82; N, 16.72. Found: C, 57.36; H, 6.35; N, 16.23.]; R_f (10% MeOH, 45% EtOAc, 45% hexane) 0.46. δ_H (500 MHz, $CHCl_3$) 7.56 (1H, s, NH*CH*), 3.64 (2H, br s, *CH*$_2$), 3.43 (3H, s, N*CH*$_3$), 3.35 (3H, s, N*CH*$_3$), 3.28 (2H, br s, *CH*$_2$), 1.71-1.54 (6H, br m, 3 x *CH*$_2$). δ_C NMR (125.7 MHz) 162.8, 159.9, 151. 3, 144.8, 111.4, 48.7, 43.4, 37.3, 28.1, 26.3, 25.4, 24.4. IR (KBr, ν (cm^{-1})): 1703, 1655 (CO), 1645 (Amide I.), 1620 (C=C); MS m/z (rel. int.): 251 (91, M^+), 167 (23), 140 (9), 112 (2), 84 (100), 82 (2), 56 (7).

3.4.12. 1,3-Dimethyl-5-(*N*-pentane-1',5'-diylglyoxylamido)uracil (**7c**)

Yield: 135 mg (49%), White solid, m.p. 190-191 °C; [Anal. Calcd. for $C_{13}H_{17}N_3O_4$:C, 575.91; H, 6.14; N, 15.05. Found: C, 56.08; H, 5.89; N, 14.40.]; R_f (10% MeOH, 45% EtOAc, 45% hexane) 0.69. δ_H (500 MHz, $CHCl_3$) 8.24 (1H, s, NH*CH*), 3.63 (2H, br s, *CH*$_2$), 3.53 (3H, s, N*CH*$_3$), 3.34 (3H, s, N*CH*$_3$), 3.28 (2H, br s, *CH*$_2$), 1.69 (4H, br s, 2 x *CH*$_2$), 1.61 (2H, br s, *CH*$_2$). δ_C NMR (125.7 MHz) 187.3, 165.8, 160.4, 150.9, 150.0, 109.3, 46.8, 42.1, 38.1, 28.0, 25.5, 24.9, 24.5. IR (KBr, ν (cm^{-1})): 1722, 1683, 1654 (CO), 1634 (Amide I.), 1612 (C=C); MS m/z (rel. int.): 279 (40, M^+), 207 (1), 167 (82), 140 (4), 112 (100), 84 (30), 69 (73), 56 (15).

3.4.13. 1,3-Dimethyl-5-(*N*-penta-3'-oxa-1',5'-diylcarboxamido)uracil (**6d**)

Yield: 86 mg (43%), Off white solid, m.p. 216-217 °C; [Anal. Calcd. for $C_{11}H_{15}N_3O_4$:C, 52.17; H, 5.97; N, 16.59. Found: C, 51.80; H, 5.66; N, 16.27.]; R_f (5% MeOH, 10% EtOAc, 85% $CHCl_3$) 0.38. δ_H (500 MHz, $CHCl_3$) 7.66 (1H, s, NH*CH*), 3.73 (6H, br s, 3 x *CH*$_2$), 3.45 (3H, s, N*CH*$_3$), 3.35 (5H, br s, overlapping of N*CH*$_3$ and *CH*$_2$). δ_C NMR (125.7 MHz) 163.2, 159.9, 151. 1, 146.3, 110.2, 66.9, 66.6, 48.1, 43.1, 37.5,

28.3. IR (KBr, ν (cm^{-1})): 1722, 1683, 1669 (CO), 1653 (Amide I.), 1634 (C=C), 1111 (COC); MS m/z (rel. int.): 253 (2, M^+), 207 (9), 167 (100), 154 (10), 140 (17), 86 (68), 74 (22), 56 (15).

3.4.14. 1,3-Dimethyl-5-(*N*-penta-3'-oxa-1',5'-diylglyoxylamido)uracil (**7d**)

Yield: 78 mg (28%), Off white solid, m.p. 156-157 °C; [Anal. Calcd. for $C_{12}H_{15}N_3O_5$:C, 52.24; H, 5.38; N, 14.94. Found: C, 51.53; H, 5.34; N, 14.23.]; R_f (5% MeOH, 10% EtOAc, 85% $CHCl_3$) 0.49. δ_H (500 MHz, $CHCl_3$) 8.24 (1H, s, NH*CH*), 3.85-3.80 (2H, m, *CH_2*), 3.74-3.70 (2H, m, *CH_2*), 3.57 (3H, s, N*CH_3*), 3.49-3.44 (2H, m, *CH_2*), 3.38 (5H, br s, overlapping of N*CH_3* and *CH_2*). δ_C NMR (125.7 MHz) 186.9, 166.0, 160.6, 150. 8, 150.0, 109.2, 66.8, 66.5, 46.5, 41.5, 38.2, 28.1. IR (KBr, ν (cm^{-1})): 1707, 1653, (CO), 1634 (Amide I.), 1627 (C=C), 1111 (COC); MS m/z (rel. int.): 281 (18, M^+), 253 (1), 224 (1), 196 (2), 167 (100), 140 (2), 114 (21), 86 (5), 70 (32), 56 (5).

3.4.15. 1,3-Dimethyl-5-(*N*-(methoxycarbonylmethyl)-carboxamido)-uracil (**6e**)

Yield: 75 mg (30%), Pale y ellow solid, m.p. 131-132 °C; [Anal. Calcd. for $C_{10}H_{13}N_3O_5$:C, 47.06; H, 5.13; N, 16.46. Found: C, 46.93; H, 4.79; N, 15.97.]; R_f (5% MeOH, 10% EtOAc, 85% $CHCl_3$) 0.55. δ_H (500 MHz, $CHCl_3$) 9.32 (1H, br s, CO*NH*), 8.43 (1H, s, NH*CH*), 4.19 (2H, d, 5.4 Hz, NH*CH_2*), 3.78 (3H, s, O*CH_3*), 3.54 (3H, s, N*CH_3*), 3.40 (3H, s, N*CH_3*). δ_C NMR (125.7 MHz) 170.0, 162.8, 162.6, 150.9, 149.2, 104.5, 52.4, 41.3, 37.9, 28.3. IR (KBr, ν (cm^{-1})): 3301 (NH), 1737 (ester CO), 1710, 1671 (CO), 1626 (Amide I.), 1618 (C=C), 1538 (Amide II.); MS m/z (rel. int.): 255 (7, M^+), 223 (11), 196 (38), 167 (100), 140 (4), 110 (4), 82 (4), 53 (6).

3.4.16. 1,3-Dimethyl -5-(*N*-(methoxycarbonylmethyl)-glyoxylamido)-uracil (**7e**)

Yield: 81 mg (29%), Beige solid, m.p. 145-146 °C; [Anal. Calcd. for $C_{11}H_{13}N_3O_6$:C, 46.65; H, 4.63; N, 14.84. Found: C, 45.53; H, 4.35; N, 14.01.]; R_f (5% MeOH, 10% EtOAc, 85% $CHCl_3$) 0.40. δ_H (500 MHz, $CHCl_3$) 9.12 (1H, s, NH*CH*), 7.76 (1H, br s, CO*NH*), 4.15 (2H, d, 5.4 Hz, NH*CH_2*), 3.80 (3H, s, O*CH_3*), 3.56 (3H, s, N*CH_3*), 3.38 (3H, s, N*CH_3*). δ_C NMR (125.7 MHz) 181.0, 169.2, 162.2, 159.6, 153.3, 150.5, 107.9, 52.6, 41.1, 38.3, 28.1. IR (KBr, ν (cm^{-1})): 3261 (NH), 1757 (ester CO), 1711, 1684, 1674 (CO), 1651 (Amide I.), 1616 (C=C), 1543 (Amide II.); MS m/z (rel. int.): 195 (2, M^+-88), 167 (100), 140 (49), 110 (7), 83 (11), 53 (11).

3.4.17. 1,3-Dimethyl 5-(*N*-(1'-methoxycarbonylethyl)-carboxamido)-uracil (**6f**)

Yield: 105 mg (39%), White solid, m.p. 152-153 °C; [Anal. Calcd. for $C_{11}H_{15}N_3O_5$:C, 49.07; H, 5.62; N, 15.61. Found: C, 49.23; H, 5.13; N, 15.50.]; R_f (5% MeOH, 10% EtOAc, 85% $CHCl_3$) 0.74. δ_H (500 MHz, $CHCl_3$) 9.32 (1H, d, 7.2 Hz, CO*NH*), 8.40 (1H, s, NH*CH*), 4.71 (1H, qi, 7.2 Hz, NH*CH*), 3.78 (3H, s, O*CH_3*), 3.54 (3H, s, N*CH_3*), 3.42 (3H, s, N*CH_3*), 1.52 (3H, d, 7.2 Hz, *CH_3*). δ_C NMR (125.7 MHz) 173.0, 162.8, 161.7, 150.9, 148.9, 104.7, 52.4, 48.2, 37.9, 28.3, 18.2. IR (KBr, ν (cm^{-1})): 3288 (NH), 1731 (ester CO), 1716, 1684 (CO), 1630 (Amide I.), 1617 (C=C), 1533 (Amide II.); MS m/z (rel. int.): 269 (1, M^+), 238 (1), 210 (64), 167 (100), 140 (3), 110 (3), 82 (2), 53 (3).

3.4.18. 1,3-Dimethyl 5-(*N*-(1'-methoxycarbonylethyl)-glyoxylamido)-uracil (**7f**)

Yield: 100 mg (34%), off white solid, m.p. 138-139 °C; [Anal. Calcd. for $C_{12}H_{15}N_3O_6$:C, 48.49; H, 5.09; N, 14.14. Found: C, 48.19; H, 4.92; N, 13.80.]; R_f (5% MeOH, 10% EtOAc, 85% $CHCl_3$) 0.56. δ_H (500 MHz, $CHCl_3$) 9.12 (1H, s, NH*CH*), 8.40 (1H, d, 7.2 Hz, CO*NH*), 4.59 (1H, qi, 7.2 Hz, NH*CH*), 3.80 (3H, s, O*CH*$_3$), 3.56 (3H, s, N*CH*$_3$), 3.38 (3H, s, N*CH*$_3$), 1.52 (3H, d, 7.2 Hz, *CH*$_3$). δ_C NMR (125.7 MHz) 181.0, 172.2, 161.3, 159.5, 153.1, 150.5, 108.0, 52.7, 48.3, 38.3, 28.1, 17.9. IR (KBr, ν (cm^{-1})): 3278 (NH), 1751 (ester CO), 1721, 1676, 1657 (CO), 1641 (Amide I.), 1612 (C=C), 1539 (Amide II.); MS m/z (rel. int.): 238 (2, M^+-59), 167 (100), 140 (76), 110 (6), 83 (12), 53 (9).

3.4.19. 1,3-Dimethyl 5-(*N*-(1'-methoxycarbonyl-butan-1',4'-diyl)-carboxamido)-uracil (**6g**) (ca.1/3 mixture of two C(O)N rotamers)

Yield: 71 mg (25%), Yellow viscous material; [Anal. Calcd. for $C_{11}H_{13}N_3O_5$:C, 49.44; H, 4.90; N, 15.72. Found: C, 50.08; H, 5.20; N, 15.29.]; R_f (5% MeOH, 10% EtOAc, 85% $CHCl_3$) 0.58. δ_H (500 MHz, $CHCl_3$) 7.71/7.61 (major/minor) (1H, s C*CH*), 4.58/4.51 (minor/major) (1H, br s, N*CH*), 3.73/3.71 (minor/major) (3H, s, O*CH*$_3$), 3.69-3.63 (2H, br s, NCH_2), 3.43/3.41 (minor/major) (3H, s, N*CH*$_3$), 3.32 (3H, s, N*CH*$_3$), 2.32-2.19/2.05-1.91 (minor/major) (4H, br s, 2 x *CH*$_2$). δ_C NMR (125.7 MHz) 173.0/172.5 (minor/major), 163.8/163.5 (minor/major), 159.8/159.5 (minor/major), 151.2/151.4 (minor/major), 146.1/143.7 (major/minor), 110.9/110.8 (minor/major), 59.7/59.5 (minor/major), 52.4/52.2 (minor/major), 48.1/47.0 (major/minor), 37.4/37.2 (major/minor), 31.1/29.2 (minor/major), 28.4/28.1 (minor/major), 24.6/22.5 (major/minor). IR (KBr, ν (cm^{-1})): 1745 (ester CO), 1710, 1661 (CO), 1654 (Amide I.), 1616 (C=C); MS m/z (rel. int.): 295 (4, M^+), 236 (12), 167 (100), 140 (3), 128 (69), 110 (4), 82 (2), 68 (8), 53 (4).

3.4.20. 1,3-Dimethyl 5-(*N*-(1'-methoxycarbonyl-butan-1',4'-diyl)-glyoxylamido)-uracil (**7g**) (ca.1/2 mixture of two C(O)N rotamers)

Yield: 68 mg (21%), Yellow viscous material; R_f (5% MeOH, 10% EtOAc, 85% $CHCl_3$) 0.68. δ_H (500 MHz, $CHCl_3$) 8.51/8.34 (major/minor) (1H, s, C*CH*), 4.64-4.56/4.55-4.50 (minor/major) (1H, m, N*CH*), 3.7/3.74 (minor/major) (3H, s, O*CH*$_3$), 3.65 (2H, br s, NCH_2), 3.44/3.41 (minor/major) (3H, s, N*CH*$_3$), 3.33 (3H, s, N*CH*$_3$), 2.35-2.22/2.07-1.96 (minor/major) (4H, m, 2 x *CH*$_2$). δ_C NMR (125.7 MHz) 186.3/186.0 (major/minor), 172.2/172.0 (minor/major), 165.3/165.1 (major/minor), 163.6/163.4 (major/minor), 151.7/151.4 (minor/major), 143.3/143.0 (minor/major), 101.1, 59.5/58.4 (minor/major), 52.5/52.4 (major/minor), 47.0/46.4 (major/minor), 38.3/38.2 (major/minor), 30.8/29.1 (minor/major), 28.4/ 28.0 (major/minor), 24.6/22.5 (major/minor). IR (KBr, ν (cm^{-1})): 1740 (ester CO), 1706, 1685, 1662 (CO), 1634 (Amide I.), 1615 (C=C); MS m/z (rel. int.): 323 (1, M^+), 295 (8), 264 (12), 236 (1), 207 (1) 167 (82), 128 (100), 110 (3), 82 (7), 68 (4), 53 (6).

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References

1. (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318-3326. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem*. **1974**, *39*, 3327-3331. (c) Schoenberg, A.; Heck, R. F. *J. Am. Chem. Soc*. **1974**, *96*, 7761-7764.
2. For recent reviews on Pd-catalyzed carbonylation reactions of aryl halides, see: (a) Wu, X.-F.; Neumann; H.; Beller, M. *Chem. Rev*. **2013**, *113*, 1-35. (b) Roy, S.; Roy, S.; Gribble, G. W. *Tetrahedron* **2012**, *68*, 9867-9923. (c) Wu, X.-F.; Neumann; H; Beller, M. *Chem. Soc. Rev*. **2011**, *40*, 4986-5009. (d) Magano, J.; Dunetz, J. R. *Chem. Rev*. **2011**, *111*, 2177-2250. (e) Grigg, R; Mutton, S. P. *Tetrahedron* **2010**, *66*, 5515-5548. (f) Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402-5422. (g) Skoda-Földes, R.; Kollár, L. *Curr. Org. Chem*. **2002**, *6*, 1097-1119. (h) Gadge; S. T.; Bhanage, B. M. *RSC Advances* **2014**, *4*, 10367-10389.
3. (a) Cornils, B.; Herrmann, W. A. (Eds.), *Applied Homogeneous Catalysis with Organometallic Compounds*, Wiley-VCH, Weinheim, 1996.; (b) Beller, M.; Bolm, C. (Eds.) *Transition Metals for Organic Synthesis (Vol. I-II.)*, Wiley-VCH, Weinheim, 1998.; (c) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation. Direct Synthesis of Carbonyl Compounds*. Plenum Press, New York and London, 1991. (d) Wu, X.-F.; Neumann, H.; Beller, M. *ChemSusChem* **2013**, *6*, 229-241.; (e) Gabriele, B.; Mancuso, R., Salerno, G. *Eur. J. Org. Chem.* **2012**, 6825-6839.; (f) Wu, X.-F.; Neumann, H. *ChemCatChem*, **2012**, *4*, 447-458.; (g) Liu, Q.; Zhang, H.; Lei, A. *Angew. Chem. Int. Ed*. **2011**, *50*, 10788-10799.; (h) Yan, G.; Wu, X.; Yang, M. *Org. Biomol. Chem*. **2013**, *11*, 5558-5578. (i) Wu, L.; Fang, X.; Liu, Q.; Jackstell, R.; Beller, M.; Wu, X.-F. *ACS Catal*. **2014**, *4*, 2977-2989.
4. Kiss, M.; Takács, A.; Kollár, L. *Curr. Green Chem*. **2015**, *2*, 319-338 and references cited therein.
5. (a) Ozawa, F.; Sugimoto, T.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1984**, *3*, 692-697. (b) Son, T.; Yanagihara, H.; Ozawa, F.; Yamamoto, A. *Bull. Chem. Soc. Jpn*. **1988**, *61*, 1251-1258.
6. Prachayasittikul, S.; Sornsongkhram, N.; Pingaew, R.; Worachartcheewan, A; Ruchirawat, S.; Prachayasittikul, V. *Molecules* **2009**, *14*, 2768-2779.
7. (a) Abarbri, M.; Knochel, P. *Synlett* **1999**, 1577-1578.; (b) Kopp, F.; Knochel, P. *Org. Lett*. **2007**, *9*, 1639-1641.
8. Yang, Q.; Wei, T.; He, Y.; Liang, Y.; Zhang, Z.-T. *Helvetica Chim. Acta* **2015**, 98, 953-960.
9. Robins, M. J.; Barr, P. J. *Tetrahedron Lett*. **1981**, *22*, 421-424.
10. Cooke, J.W.B.; Bright, R.; Coleman, M.J.; Jenkins, K.P. *Org. Process Res. Dev.* **2001**, 5, 383-386.
11. Hudson, R.H.E.; Li, G.; Tse, J. *Tetrahedron Lett*. **2002**, *43*, 1381-1386.
12. Liang, Y.; Gloudeman, J.; Wnuk, S.F. *J. Org. Chem*. **2014**, *79*, 4094-4103.
13. Arterburn, J.B.; Pannala, M.; Gonzalez, A.M. *Tetrahedron Lett*. **2001**, *42*, 1475-1477.
14. Farina, V.; Hauck, S.I. *Synlett* **1991**, 157-159.
15. Peters, D.; Hornfeldt, A.B.; Gronowitz, S. *J. Heterocycl. Chem.* **1990**, *27*, 2165-2173.
16. Nomura, Y.; Ueno, Y.; Matsuda A. *Nucleic Acids Res.* **1997**, 25, 2784-2791.

17. Tauraitė, D,; Dabužinskaitė, J.; Ražanas, R.; Urbonavičius, J.; Stankevičiūtė, J.; Serva, S.; Meškys, R. *CHEMIJA* **2015**, 26. 120-125.
18. (a) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, 11, 3009-3013. (b) Amatore, C.; Carre, E.; Jutand, A.; M'Barki, M. A.; Meyer, G. *Organometallics* **1995**, 14, 5605-5614. (c) Csákai, Z.; Skoda-Földes, R.; Kollár, L. *Inorg. Chim. Acta* **1999**, 286, 93-97 and references cited therein.
19. (a) Takács, A.; Abreu, A. R.; Peixoto, A. F.; Pereira, M. M.; Kollár, L. *Synthetic Communication* **2009**, 39, 1534-1548. (b) Marosvölgyi-Haskó, D.; Kégl, T.; Kollár, L. *Tetrahedron* **2016**, 72, 7509-7516.
20. (a) Takács, A.; Jakab, B.; Petz, A.; Kollár, L. *Tetrahedron* **2007**, 63, 10372-10378. (b) Takács, A.; Marosvölgyi-Haskó, D.; Kabak-Solt, Zs.; Damas, L.; Rodrigues F. M. S.; Carrilho, R. M. B.; Pineiro, M.; Pereira, M. M.; Kollár, L.; *Tetrahedron* **2016**, 72, 247-256. (c) Takács, A.; Varga, M. G.; Kardos, J.; Kollár, L. *Tetrahedron* **2017**, 73, 2131-2138.
21. Takács, A.; Szilágyi, A.; Ács, P.; Márk, L.; Peixoto, A. F.; Pereira, M. M.; Kollár, L. *Tetrahedron* **2011**, 67, 2402-2406.

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- Describing a proposed mechanism of deiodination side reaction
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