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Sequential catalytic carbonylation reactions for sustainable synthesis of biologically relevant entities

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ABSTRACT

The sustainable synthesis of highly functionalised formylcarboxamide compounds with biological relevance is reported through a sequential aminocarbonylation/hydroformylation approach. The optimisation of palladium-catalysed aminocarbonylation of iodoaromatic substrates, using allylamine as nucleophile was first performed, with molybdenum hexacarbonyl as alternative CO source *versus* gaseous carbon monoxide. The combination of microwave irradiation with molybdenum hexacarbonyl allowed to selectively prepare a set of *N*-heterocyclic-based allylcarboxamides. Subsequent rhodium-catalysed hydroformylation of the allylcarboxamide intermediates led to the preparation of new pyridine, pyrazoline and chalcone derivatives containing both carboxamide and formyl moieties.

1. Introduction

Carbonyl compounds, such as carboxamides and aldehydes, are among the most relevant synthons for preparation of highly functionalised molecules with potential applications in medicinal chemistry [1–6]. Particularly, those containing *N*-heterocycles [7–14] and chalcone [15–17] cores are frequently present in important pharmacological entities, such as antibiotics, antibacterial, anti-hypertensive, anti-inflammatory and anticancer drugs (Fig. 1).

Therefore, there has been an increasing interest in the search for efficient and sustainable chemical processes for preparing such molecules. Among them, transition metal catalysed hydroformylation [18–25] and aminocarbonylation [26–34] reactions are two paradigmatic examples of efficient one-pot and versatile synthetic approaches to get access to carbonyl compounds, such as aldehydes and carboxylic acid derivatives. Regarding these topics, it should be highlighted the relevant contribution of Kollár, with more than 300 published papers [35].

Furthermore, the development of sequential carbonylation reactions have led to significant reduction in costs, purification steps and waste formation. Such sequential reactions present higher atom economy, allowing to improve the general processes efficiency and sustainability [36–44]. It should be also noted that the global demands for implementation of more sustainable synthetic processes have boosted the search for alternative CO sources [45–49], including metal-carbonyl compounds [50–53] and the development of energetically favourable processes, such as microwave-assisted carbonylation reactions [54–58].

Along the last years, we have been focused on the development of efficient transition-metal catalysed carbonylation-based sequential processes applied to biologically relevant substrates for the preparation value-added products with biological activity and/or industrial interest, including hydroformylation/arylation [59], hydroformylation/isomerisation [60], hydroformylation/reductive amination [61, 62], hydroformylation/Strecker [62], hydroformylation/hydrogenation [63] and aminocarbonylation/cyclisation [64].

As part of our continuing research in this field, herein we report an original sequential process for preparation of biologically relevant formylcarboxamide compounds comprising *N*-heterocycle and chalcone scaffolds, through microwave-assisted palladium-catalysed aminocarbonylation of iodoaromatic substrates with allylamine, followed by rhodium-catalysed hydroformylation of the

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[1] Dedicated to Professor Laszló Kollár, on the occasion of his 65th birthday.

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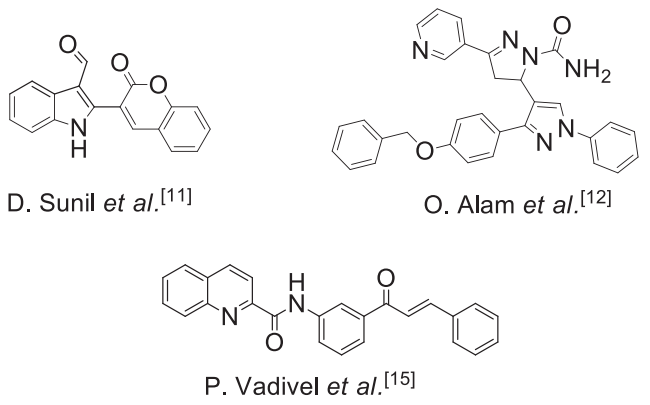


Fig. 1. Examples of *N*-heterocyclic and chalcone-based carbonyl compounds with pharmacological activity.

allylcarboxamide intermediates, to obtain carbonylated products containing both formyl and carboxamide motifs (Scheme 1).

2. Results and discussion

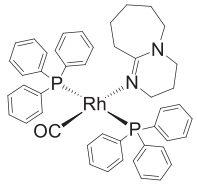
The palladium-catalysed aminocarbonylation step was first optimised, using iodobenzene (**1**) as a model substrate, allylamine as nucleophile, palladium (II) acetate as catalytic precursor, DBU as base and dioxane as solvent. The reactions were carried out in the presence of carbon monoxide or molybdenum hexacarbonyl as alternative CO carbonyl source, at 125 °C, using either conventional heating or microwave irradiation. Conversion and selectivity were determined by GC-MS analysis of the crude mixtures and the results are presented in Table 1.

Using a CO pressure of 3 bar and conventional heating, a conversion of 79% was obtained in 60 min (TOF = 32 h^{-1}), with 69% selectivity for the carboxamide product (**2**) (Table 1, entry 1). Under microwave irradiation (150 W), a similar conversion was obtained in just 5 min, leading to a substantial increase in TOF (365 h^{-1}), although a slightly slower selectivity (62%) was observed (Table 1, entry 2). Alternatively, the use of $Mo(CO)_6$ complex as alternative carbonyl source, under conventional heating, provided full conversion in 60 min (TOF = 40 h^{-1}), with 82% selectivity for the carboxamide (**2**) (Table 1, entry 3). In addition, under microwave irradiation, the reaction proceeded with full conversion in 5 min (TOF = 475 h^{-1}) and with 76% selectivity for the carboxamide product (**2**) (Table 1, entry 4). In sum, microwave irradiation allowed to significantly reduce the required reaction time from 60 min to 5 min with enhancement of the activity (TOF = 40 and 475 h^{-1} respectively), maintaining the reaction selectivity.

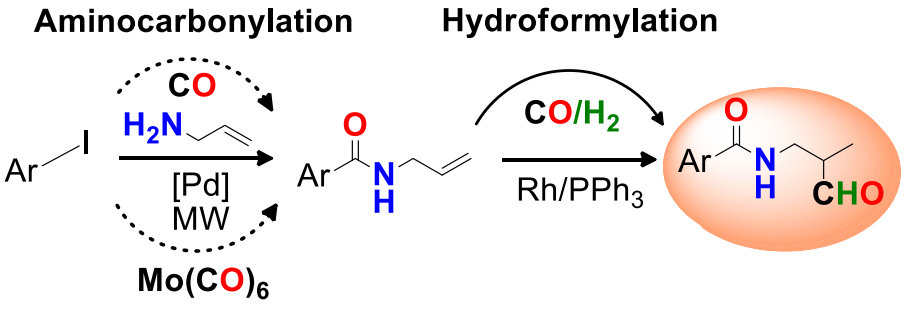
With optimised conditions, microwave-assisted Pd-catalysed aminocarbonylation reactions, using $Mo(CO)_6$ as carbonyl source, were applied to different iodoaromatic substrates with biologically relevant scaffolds, including 1-bromo-4-iodo benzene (**3**), 4-iodoanisole (**4**), iodopyridine (**5**), 7-iodoindole (6), 5-iodoindole (**7**), iodopyrazoline (**8**) and iodochalcone (**9**) [68]. Conversion and yields were determined by GC-MS analysis of the crude mixtures and the results are presented in Table 2.

The microwave-assisted aminocarbonylation reactions proceeded with *ca.* 99% conversion in 5 min and allylcarboxamide derivatives were obtained as major products in all cases, in yields ranging from 65% (for product **11**) to 87% (for product **13**). In addition, the aminocarbonylation of substrates **3** and **5** led to predominant formation mono-carbonylated products **10** and **12**, respectively (Table 2, entries 2 and 4), which indicate that oxidative addition to the palladium complex occurs mainly through the most reactive C—I bond, while C—Br and C—Cl bonds remain unchanged under these conditions. Moreover, in the case of iodopyrazoline (**8**), the reaction required 1 h, under microwave irradiation, to obtain the corresponding allylcarboxamide product (**15**), obtained in 70% yield. In all cases, GC-MS indicated the formation of ketocarboxamides as minor products (up to *ca.* 10%), corroborated by the ^{13}C NMR spectra which presented typical signals around 190 ppm. After work up and purification by column chromatography in silica gel, using EtOAc/*n*-hexane or EtOAc/CH_2Cl_2 mixtures as eluents, the carboxamide products **2** and **10**—**16** have been isolated and fully characterised. In sum, microwave-assisted palladium-catalysed aminocarbonylation of iodoaromatic substrates, using allylamine as a nucleophile, allowed optimising the first step of the sequential process and provided the access to a set of allylcarboxamide products.

In order to minimise product losses by work-up and purification procedures, a sequential catalytic aminocarbonylation/hydroformylation methodology was then carried out, without work-up or purification of the allylcarboxamide intermediates. Thus, using iodobenzene (**1**) as a model substrate, the crude mixture obtained in the microwave-assisted aminocarbonylation step was directly subjected to hydroformylation conditions (8 bar H_2/CO) with a rhodium/triphenylphosphine catalyst, at 50 °C. However, in a first attempt, no conversion was observed after 6 h. This was attributed to the formation of a sterically hindered rhodium/DBU complex of type **17** [65,66], which leads to formation of catalytically inactive species.

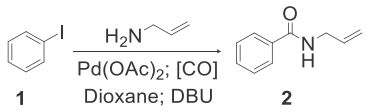


17



Scheme 1. Sequential aminocarbonylation/hydroformylation approach for the synthesis of formylcarboxamides.

Table 1
Aminocarbonylation of iodobenzene (**1**) using allylamine as nucleophile.[a]



1 2

Entry	Carbonyl source	Heating	Time (min)	Conversion (%)	Selectivity (%)	TOF (h^{-1})
1	CO (3 bar)	Conv.	60	79	69	32
2	CO (3 bar)	MW (150 W)	5	76	62	365
3	$Mo(CO)_6$	Conv.	60	99	82	40
4	$Mo(CO)_6$	MW (150 W)	5	99	76	475

[a] Reaction conditions: iodobenzene (0.4 mmol), allylamine (0.6 mmol), $Pd(OAc)_2$ (0.01 mmol), $Mo(CO)_6$ (0.4 mmol), DBU (0.2 mL), dioxane (3 mL), 125 °C.

To overcome this issue, the crude mixture, resulting from the aminocarbonylation step, was passed through a silica-pad prior to hydroformylation. Following this procedure, full substrate conversion was obtained in 5 h, with 72% chemoselectivity for oxo-products and 44% regioselectivity for the branched aldehyde (**18**) (Table 3, entry 1). Then, aiming the preparation of biologically relevant formylcarboxamide molecules, the scope of this sequential aminocarbonylation/hydroformylation methodology was expanded to iodopyridine (**5**), iodopyrazoline (**8**) and iodochalcone (**9**) substrates.

In a typical sequential aminocarbonylation/hydroformylation experiment, the iodo-substrate, allylamine, $Pd(OAc)_2$, $Mo(CO)_6$ and DBU were dissolved in dioxane and placed inside a microwave vial. The mixture was then subjected to microwave irradiation (P = 150 W), the reaction proceeding at 125 °C for 5 min. After cooling down to room temperature, the obtained mixture was filtered through a silica pad and the residue was introduced *via* cannula into an autoclave containing the precursor, $Rh(CO)_2acac$ and triphenylphosphine (PPh_3). The autoclave was then pressurised with 8 bar H_2/CO and kept at 50 °C for 5 h (or 12 h). At the end, the solvent was evaporated and the crude mixture was analysed by ^1H and ^{13}C NMR spectroscopy.

The sequential aminocarbonylation/hydroformylation processes proceeded with complete conversions and the chemoselectivity for oxo-products was in the range 56–73%. The regioselectivity for the branched aldehydes varied from 36 to 51% (Table 3, entries 2–4). Upon purification by column chromatography in silica gel, the branched formylcarboxamide products **18**–**21** were isolated in yields ranging from 19 to 22%. These low yields can be explained by the significant formation of linear aldehydes and the respective cyclisation products (not isolated), resultant from intramolecular condensation between the carboxamide and formyl moiety of the linear aldehydes, which leads to the formation of a stable 5 membered ring (Scheme 2) [67], evidenced by ^1H NMR and GC-MS.

It is worth mentioning that, in the case of chalcone-derived substrate (**9**), the hydroformylation of the allyl moiety occurred concomitantly with reduction of the conjugated internal C=C double bond, which resulted in the formation of formylcarboxamide **21**, obtained as major product (Table 3, entry 4).

3. Conclusions

We have developed an innovative catalytic aminocarbonylation/hydroformylation sequential approach to prepare new formylcarboxamide molecules. The optimisation of the first step of the catalytic sequence was achieved through microwave-assisted palladium-catalysed aminocarbonylation of iodoaromatic substrates, using allylamine as nucleophile and $Mo(CO)_6$ as alternative carbonyl source, which provided an efficient strategy for the synthesis of allylcarboxamide derivatives. The subsequent Rh/triphenylphosphine-catalysed hydroformylation of the allylcarboxamide intermediates allowed the synthesis of a set of new *N*-heterocyclic and chalcone-based formylcarboxamides, including 6-chloro-*N*-(2-methyl-3-oxopropyl)nicotinamide, 4-(1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-*N*-(2-methyl-3-oxopropyl)benzamide and (*E*)-*N*-(2-methyl-3-oxopropyl)-4-(3-oxo-3-phenylprop-1-en-1-yl)benzamide. In sum, this transition-metal catalysed aminocarbonylation/hydroformylation sequential process opens new perspectives regarding the preparation of biologically relevant molecules containing both carboxamide and formyl motifs.

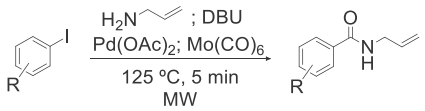
4. Experimental section

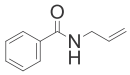
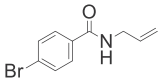
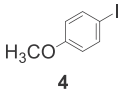
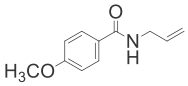
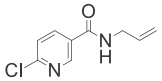
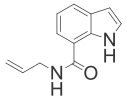
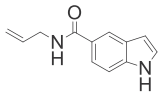
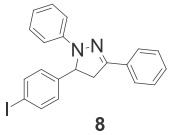
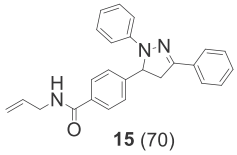
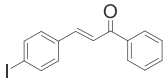
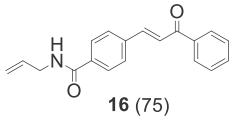
4.1. General

Manipulation of all moisture sensitive reagents was carried out under nitrogen atmosphere by using Schlenk techniques. Glassware was dried in an oven at 200 °C and cooled under a nitrogen atmosphere. Palladium (II) acetate, triphenylphosphine, $Mo(CO)_6$, iodobenzeno, 1-bromo-4-iodobenzene, 4-methoxyiodobenzene, 2-chloro-5-iodopyridine, 7-iodoindole, 5-iodoindole, DBU and dioxane were purchased from Merck and used without further purification. The iodopyrazoline **8** and iodochalcone **9** substrates were synthesised through a mechanochemical synthetic methodology, recently developed by some of us [68].

Microwave-assisted experiments were performed in thick-walled glass vials under closed-vessel conditions, using a CEM Discover® SP Focused Microwave™ Synthesis System. NMR spectra were recorded on a Bruker Avance 400 spectrometer, operating at 400.13 MHz for ^1H NMR and 100.62 MHz for ^{13}C NMR. Chemical shifts (δ) are reported in ppm relatively to $CDCl_3$ (7.260 and 77.16 ppm for ^1H and ^{13}C, respectively) or tetramethylsilane (TMS). High-resolution mass spectrometry analysis was carried out on a Bruker Microtof apparatus, equipped with selective ESI detector. Samples of the reactions were analysed by: a) gas chromatography carried out on Agilent-7820A GC System equipped with a non-polar capillary HP-5 column (5% diphenyl and 95% dimethylpolysiloxane), with 30 m length and 0.32 mm inside diameter and using nitrogen as carrier gas, and equipped with an FID detector; or b) gas chromatography coupled with mass spectrometry (GC-MS) using an Agilent 7820A GC System, equipped with a HP-5 MS column, coupled to an Agilent 5975 MSD System Technologies spectrometer, using EI (70 eV) and helium as carrier gas. Carboxamide derivatives were analysed by gas chromatography using the following methods: a) GC-FID method: injector temp 250 °C, oven: starting temp 50 °C (hold-time 2 min), heating rate 30 °C min^{-1}, final temp 280 °C (hold-time 9 min); detector temp 280 °C, carrier gas:

Table 2
Microwave-assisted Pd-catalysed aminocarbonylation using allylamine as nucleophile.[a]



Entry	Substrate	Product (yield, %)[b]
1	 **1**	 **2** (76)
2	 **3**	 **10** (71)
3	 **4**	 **11** (65)
4	 **5**	 **12** (76)
5	 **6**	 **13** (87)
6	 **7**	 **14** (72)
7[c]	 **8**	 **15** (70)
8	 **9**	 **16** (75)

[a] Reaction conditions: substrate (0.4 mmol), allylamine (0.6 mmol), $Pd(OAc)_2$ (0.01 mmol), $Mo(CO)_6$ (0.4 mmol), DBU (0.2 mL), dioxane (3 mL), 125 °C, 5 min, 150 W.
[b] Yield determined by GC-MS analysis of crude mixtures.
[c] 1 h.

nitrogen (rate: 1.6 mL min^{-1}); b) GC-MS method: injector temp 250 °C, oven: starting temperature 50 °C (hold-time 1 min), heating rate 15 °C min^{-1}, final temp 280 °C (hold-time 15 min); detector temp 280 °C, carrier gas: helium (rate: 1 mL min^{-1}).

4.2. Microwave-assisted palladium-catalysed aminocarbonylation

The iodoaryl substrate (0.4 mmol), allylamine (45 μL, 0.6 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), $Mo(CO)_6$ (105.6 mg, 0.4 mmol), DBU (180 μL, 1.2 mmol) were dissolved in dioxane (3 mL) and placed into a microwave vial. The mixture was subjected to microwave irradiation (Initial Power = 150 W) and the reaction was conducted at 125 °C for 5 min. The mixture was then cooled to room temperature, filtered through a small plug of Celite and evaporated to dryness with the crude being analysed by GC-MS and/or GC-FID (methods described in Section 5.1). The residue obtained was dissolved in dichloromethane (20 mL) and washed with water (3 × 20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to a solid material or to a waxy residue. The reaction products were isolated and purified by column chromatography (Silicagel 60 (Merck), 0.063–0.200 mm), using EtOAc/*n*-hexane or EtOAc/CH_2Cl_2 mixtures as the eluents (specified below for each compound).

4.3. General procedure of sequential aminocarbonylation/hydroformylation

For the sequential aminocarbonylation/hydroformylation process the iodoaromatic substrate (0.4 mmol), allylamine (45 μL, 0.6 mmol, 1.5 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), $Mo(CO)_6$ (105.6 mg, 0.4 mmol), DBU (180 μL, 1.2 mmol) and dioxane (3 mL) were placed into a microwave vial. The mixture was subjected to microwave irradiation (Initial Power = 150 W) and the reaction was conducted at 125 °C for 5 min. After cooled down to room temperature, the aminocarbonylation crude mixture was filtered through a small plug of silica gel and introduced *via* cannula into the autoclave. The rhodium precursor $Rh(acac)(CO)_2$ (4×10^{-3} mmol, 1.03 mg) and triphenylphosphine (0.02 mmol, 5.24 mg) were dissolved in dioxane (3 mL), under argon atmosphere, and introduced *via* cannula into the autoclave. After purging the system with three cycles of vacuum/*syngas* the reactor was pressurised with 8 bar of H_2/CO (1:1) and kept at 50 °C. After 5 h, the reactor was cooled to room temperature and slowly depressurised. The reaction mixture was evaporated to dryness analysed by ^{1}H NMR spectroscopy. The reaction products were isolated and purified by column chromatography (Silicagel 60 (Merck), 0.063–0.200 mm), using EtOAc/*n*-hexane or EtOAc/CH_2Cl_2 mixtures as the eluents (specified below for each compound).

4.3.1. Characterisation of products

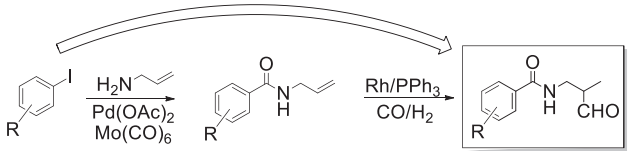
The spectroscopic data of **2**, **10** and **11** are in agreement with that previously reported [69,70,71].

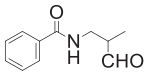
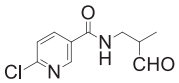
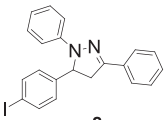
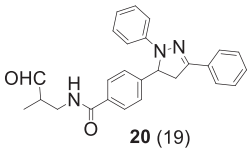
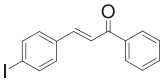
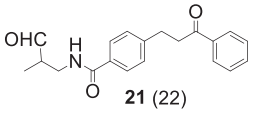
*4.3.1.1. N-allyl-6-chloronicotinamide (**12**).* Rf (CH_2Cl_2/EtOAc 1:1) = 0.74. Beige solid, Yield 23%, 18 mg (0.09 mmol). ^{1}H RMN (400 MHz, $CDCl_3$, ppm): δ 8.75 (d, *J* = 7.6 Hz, 1H), 8.10 (dd, *J* = 8.3, 2.5 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 6.18 (s, 1H), 5.97–5.90 (m, 1H), 5.28 (dd, *J* = 17.1, 1.2 Hz, 1H), 5.23 (dd, *J* = 10.2, 0.9 Hz, 1H), 4.12–4.08 (m, 2H). ^{13}C RMN (100 MHz, $CDCl_3$, ppm): δ 164.5; 154.5; 148.0; 138.1; 133.6; 129.2; 124.6; 117.6; 42.8. HRMS (ESI) (*m/z*): found 197.0477 $[M+H]^+$ (calcd. 197.0476).

*4.3.1.2. N-allyl-1H-indole-7-carboxamide (**13**).* Rf (EtOAc/*n*-hex 1:4) = 0.37. White solid. Yield 20%, 16 mg (0.08 mmol). ^{1}H RMN (400 MHz, $CDCl_3$, ppm): δ 10.32 (br s, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.33–7.32 (m, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 6.58–6.57 (m, 1H), 6.47 (s, 1H), 6.01–5.94 (m, 1H), 5.30 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.21 (dd, *J* = 10.2, 1.3 Hz, 1H), 4.16–4.13 (m, 2H). ^{13}C RMN (100 MHz, $CDCl_3$, ppm): δ 167.8; 135.6; 134.4; 129.7; 125.8; 125.0; 118.9; 118.8; 116.8; 115.9; 102.1; 42.2. HRMS (ESI) (*m/z*): found 201.1023 $[M+H]^+$ (calcd. 201.1022).

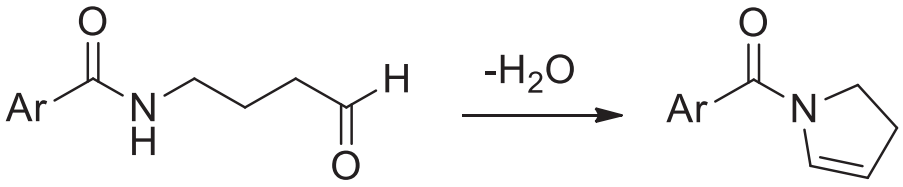
*4.3.1.3. N-allyl-1H-indole-5-carboxamide (**14**).* Rf (CH_2Cl_2/EtOAc 2:1) = 0.51. White solid. Yield 23%, 18 mg (0.09 mmol). ^{1}H RMN (400 MHz, $CDCl_3$, ppm): δ 8.53 (br s, 1H), 8.11 (s, 1H), 7.66 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.28–7.26 (m, 1H), 6.62 (s,

Table 3
Synthesis of formylcarboxamides by sequential aminocarbonylation/hydroformylation methodology.[a]



Entry	Substrate	Chemo (%)[b]	*iso*-Regio (%)[c]	Product (isolated yield, %)
1	 **1**	72	44	 **18** (21)
2	 **5**	73	51	 **19** (20)
3[d]	 **8**	56	46	 **20** (19)
4[d]	 **9**	64	36	 **21** (22)

[a] Reactions conditions: *aminocarbonylation step* substrate (0.4 mmol), allylamine (0.6 mmol), $Pd(OAc)_2$ (0.01 mmol), $Mo(CO)_6$ (0.4 mmol), DBU (0.2 mL), dioxane (3 mL), 125 °C, 150 W, 5 min,: *hydroformylation step:* $Rh(acac)(CO)_2/PPh_3$ = 1:5; Rh/substrate = 1:100; P = 8 bar H_2/CO; 50 °C, 5 h. Conversion was ca 99% in all cases.
[b] Chemoselectivity for oxo-products (determined by ^1H NMR).
[c] Regioselectivity for the branched aldehyde (*iso*) (determined by ^1H NMR).
[d] 12 h.



Scheme 2. Formation of 5-membered ring by intramolecular condensation.

1H), 6.23 (br s, 1H), 6.01–5.94 (m, 1H), 5.29 (dd, J = 17.1, 1.5 Hz, 1H), 5.19 (dd, J = 10.2, 1.3 Hz, 1H), 4.14–4.12 (m, 2H). ^{13}C RMN (100 MHz, $CDCl_3$, ppm): δ 168.6; 137.7; 134.7; 127.7; 126.6; 125.7; 121.2; 120.3; 116.6; 111.2; 103.8; 42.6. HRMS (ESI) (*m/z*): found 201.1024 $[M+H]^+$ (calcd. 201.1022).

*4.3.1.4. N-allyl-4-(1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)benzamide (**15**).* Rf (EtOAc/*n*-hex 1:1) = 0.66. Yellow solid. Yield 21%, 32 mg (0.08 mmol). ^1H RMN (400 MHz, $CDCl_3$, ppm): δ 7.73 (t, J = 7.3 Hz, 4H), 7.31–7.25 (m, 4H), 7.34 (d, J = 7.2 Hz, 2H), 7.20–7.16 (m, 3H), 7.04 (d, J = 7.8 Hz, 2H), 6.80 (t, J = 7.3 Hz, 1H), 6.19 (br s, 1H), 5.95–5.88 (m, 1H), 5.30 (dd, J = 12.4, 7.2 Hz, 1H), 5.24 (dd, J = 17.2, 1.4 Hz, 1H), 5.17 (dd, J = 10.2, 1.2 Hz, 1H), 4.07–4.04 (m, 2H), 3.86 (dd, J = 17.0, 12.4 Hz, 1H), 3.11 (dd, J = 17.1, 7.2 Hz, 1H). ^{13}C RMN (100 MHz, $CDCl_3$, ppm): δ 167.0; 146.9; 146.3; 144.7; 134.2; 134.0; 132.6; 129.1; 128.9; 128.7; 128.0; 126.3; 125.9; 119.5; 116.9; 113.5; 64.3; 43.5; 42.5. HRMS (ESI) (*m/z*): found 381.1835 $[M^+]$ (calcd. 381.1841).

*4.3.1.5. (E)-N-allyl-4-(3-oxo-3-phenylprop-1-en-1-yl)benzamide (**16**).* Rf (EtOAc/*n*-hex 1:1) = 0.56. Yellow solid. Yield 25%, 29 mg (0.1 mmol). ^1H RMN (400 MHz, $CDCl_3$, ppm): δ 8.04–8.02 (m, 2H), 7.85–7.79 (m, 3H), 7.70 (d, J = 8.2 Hz, 2H), 7.63–7.59 (m, 2H), 7.55 (d, J = 10.8 Hz, 1H), 7.51 (d, J = 7.3 Hz, 1H), 6.26 (s, 1H), 5.99–5.92 (m, 1H), 5.28 (dd, J = 17.1, 1.4 Hz, 1H), 5.21 (dd, J = 10.2, 1.2 Hz, 1H), 4.13–4.10 (m, 2H). ^{13}C RMN (100 MHz, $CDCl_3$, ppm): δ 190.4; 166.6; 143.4; 138.0; 137.9; 136.0; 134.1; 133.2; 128.8; 128.7; 128.6; 127.7; 123.8; 117.0; 42.7. HRMS (ESI) (*m/z*): found 292.13302 $[M+H]^+$ (calcd. 292.1332).

*4.3.1.6. N-(2-methyl-3-oxopropyl)benzamide (**18**).* Rf (CH_2Cl_2/EtOAc 7:3) = 0.54. Yellow oil. Yield 21%, 16 mg (0.08 mmol). ^{1}H RMN (400 MHz, $CDCl_3$, ppm): δ 9.71 (s, 1H), 7.74–7.72 (m, 2H), 7.50–7.46 (m, 1H), 7.40 (dd, J = 10.2, 4.6 Hz, 2H), 6.73 (br s, 1H), 3.75–3.69 (m, 1H), 3.57–3.50 (m, 1H), 2.82–2.74 (m, 1H), 1.21 (d, J = 7.5 Hz, 3H). ^{13}C RMN (100 MHz, $CDCl_3$, ppm): δ 204.5; 167.7; 134.3; 131.7; 128.7; 127.0; 46.9; 39.9; 11.6. HRMS (ESI) (m/z): found 214.08399 $[M+Na]^+$ (calcd. 214.0839).

*4.3.1.7. 6-chloro-N-(2-methyl-3-oxopropyl)nicotinamide (**19**).* Rf (CH_2Cl_2/EtOAc 1:2) = 0.27. Beige solid. Yield 20%, 18 mg (0.08 mmol). ^{1}H RMN (400 MHz, $CDCl_3$, ppm): δ 9.70 (s, 1H), 8.73 (d, J = 2.2 Hz, 1H), 8.04 (dd, J = 8.3, 2.5 Hz, 1H), 7.39 (d, J = 8.3 Hz, 1H), 6.92 (s, 1H), 3.78–3.70 (m, 1H), 3.56–3.48 (m, 1H), 2.86–2.78 (m, 1H), 1.23 (d, J = 7.5 Hz, 3H). ^{13}C RMN (100 MHz, $CDCl_3$, ppm): δ 204.6; 164.8; 154.4; 148.2; 139.2; 129.3; 124.8; 46.7; 39.0; 11.7. HRMS (ESI) (m/z): found 227.0581 $[M+H]^+$ (calcd. 227.0582).

*4.3.1.8. 4-(1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-N-(2-methyl-3-oxopropyl)benzamide (**20**).* Rf (EtOAc/*n*-hex 2:1) = 0.44. Yellow solid. Yield 19%, 31 mg (0.08 mmol). ^{1}H RMN (400 MHz, $CDCl_3$, ppm): δ 9.69 (s, 1H), 7.73–7.66 (m, 4H), 7.39–7.34 (m, 5H), 7.19–7.15 (m, 2H), 7.03 (d, J = 7.8 Hz, 2H), 6.79 (t, J = 7.3 Hz, 1H), 6.60 (t, J = 5.9 Hz, 1H), 5.30 (dd, J = 12.5, 7.0 Hz, 1H), 3.86 (dd, J = 17.1, 12.4 Hz, 1H), 3.74–3.67 (m, 1H), 3.53–3.50 (m, 1H), 3.10 (dd, J = 17.1, 7.3 Hz, 1H), 2.80–2.74 (m, 1H), 1.21 (d, J = 7.5 Hz, 3H). ^{13}C RMN (100 MHz, $CDCl_3$, ppm): δ 204.5; 167.3; 152.3; 146.9; 146.4; 133.8; 133.8; 129.1; 128.9; 128.7; 128.0; 126.4; 125.9; 119.5; 113.5; 64.3; 46.9; 43.5; 39.9; 11.6. HRMS (ESI) (m/z): found 412.2020 $[M+H]^+$ (calcd. 412.2020).

*4.3.1.9. (E)-N-(2-methyl-3-oxopropyl)-4-(3-oxo-3-phenylprop-1-en-1-yl)benzamide (**21**).* Rf (CH_2Cl_2/EtOAc 1:1) = 0.6. Yellow solid. Yield 22%, 28 mg (0.09 mmol). ^{1}H RMN (400 MHz, $CDCl_3$, ppm): δ 9.71 (s, 1H), 7.95–7.93 (m, 2H), 7.67 (d, J = 8.2 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 6.63 (s, 1H), 3.73 (ddd, J = 13.7, 6.7, 4.3 Hz, 1H), 3.53 (ddd, J = 13.8, 8.0, 5.8 Hz, 1H), 3.30 (t, J = 7.5 Hz, 2H), 3.11 (t, J = 7.5 Hz, 2H), 2.81–2.76 (m, 1H), 1.22 (d, J = 7.5 Hz, 3H). ^{13}C RMN (100 MHz, $CDCl_3$, ppm): δ 204.5; 198.9; 167.5; 145.5; 136.8; 133.3; 132.2; 128.8; 128.8; 128.1; 127.3; 46.9; 40.0; 39.9; 30.0; 11.6. HRMS (ESI) (m/z): found: 324.1591 $[M+H]^+$ (calcd. 324.1594).

Declaration of competing interest

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.

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