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Application of the ring-closing metathesis to the formation of 2-aryl-1*H*-pyrrole-3-carboxylates as building blocks for biologically active compounds

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A B S T R A C T

Ring-closing metathesis (RCM) is a powerful tool for the preparation of cyclic organic compounds. Yet, one of the major limitations of this method is the difficulty to prepare large quantities of target molecules. Herein we describe a comprehensive study regarding the gram-scale synthesis of 2-aryl-1*H*-pyrrole-3-carboxylates based on the ring-closing metathesis of the corresponding β-amino esters as a key step. This study includes evaluation of solvent and catalyst as well as reaction kinetics on the RCM. After an aromatization step, this methodology allowed for an efficient generation of variously substituted and unprecedented 2-aryl-1*H*-pyrrole-3-carboxylates in good yields and cost-effectiveness. The resulting molecules might serve as key building blocks for the generation of CNS-oriented compound libraries.

1. Introduction

Olefin metathesis has become an efficient tool for the formation of carbon–carbon double bonds. In particular, ring-closing metathesis (RCM) has a large impact on the pharmaceutical industry because this reaction allows formation of medium-to-large size carbocycles and heterocycles from acyclic dienes.[1] One of the first applications of RCM in the synthesis of biologically active compounds concerned the synthesis of Ciluprevir (BILN-2061), a pseudopeptide inhibitor of HCV NS3 protease (Fig. 1).[2] This method stimulated intense generation of Ciluprevir analogs, among which Vaniprevir (MH-7009) is now evaluated in phase III clinical trials.[3] It is worth noting that development of various Hepatitis C inhibitors is currently a subject of intense research in medicinal chemistry.[4] Another eminent example of biologically active compound obtained by RCM process is represented by Tamiflu (oseltamivir phosphate), which behaves as glycosidase inhibitor and is used for the treatment of influenza.[5] RCM was also applied as a central transformation in the synthesis of seven-member heterocyclic ring of SB-462795, a cathepsin K inhibitor, a drug candidate for the treatment of osteoporosis.[6]

Since the first reports of phosphine-containing ruthenium complexes for metathesis reaction,[7] a number of new catalysts have been developed.[8] A major breakthrough was the replacement of the phosphine ligand with a N-heterocyclic carbene (NHC), giving rise to second generation catalysts such as **G-II** (Fig. 2).[9] Such modification increased air and moisture stability of the corresponding complexes. Replacement of the benzylidene moiety with an indenylidene (Fig. 2, **M2** and **M2$_0$**)[8b,10a–d] or 2-isopropoxystyrene derivatives[11] (Fig. 2, **NO$_2$-Grela** and **M5$_1$**) led to new catalyst families with improved stability and activity. However, RCM is a highly substrate depending reaction and despite the wide variety of catalysts, there is no universal one applicable to all kind of dienes.[12] Moreover, cost of the ruthenium complexes constitutes a major limit of the process and studies for determining the proper reaction conditions, which allow for minimal catalyst loading are an important research area with regard to economical issues.

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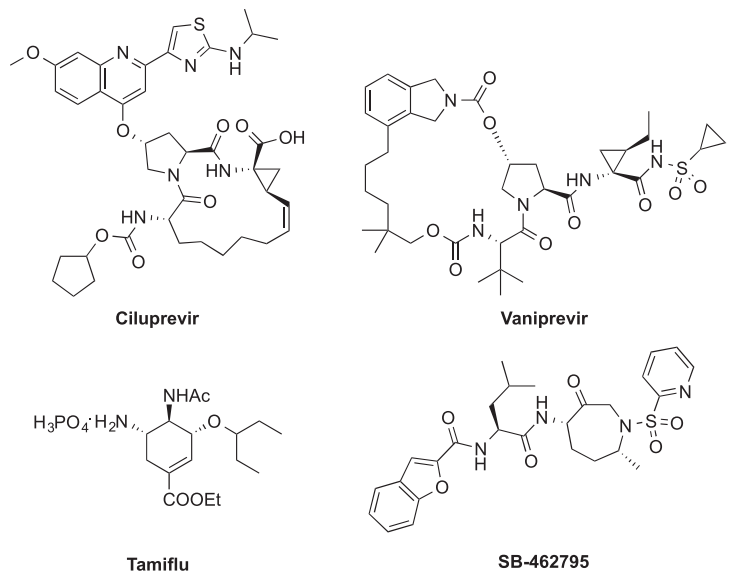


Fig. 1. Selected biologically active compounds obtained *via* RCM method.

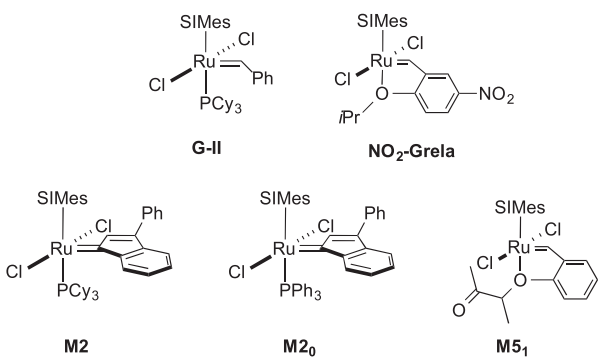
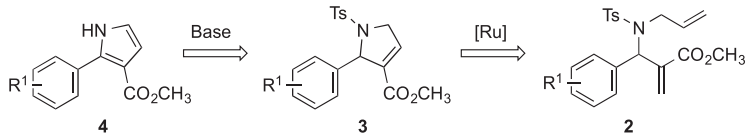


Fig. 2. Structure of catalysts used in this study.

cyclization of homopropargyl azides, although highly efficient, needed either 24 h reaction time or the use of toxic mercury as catalyst.[20]

During our recent study on the synthesis of 1*H*-pyrrolo[3,2-*c*] quinolines as 5-HT_6 receptor antagonists,[21] we found that RCM could be an efficient pathway to obtain pyrroles. We thus decided to optimize a method for the generation of 2-aryl-1*H*-pyrrole-3-carboxylates **4** involving RCM of **2** followed by base-induced aromatization (Scheme 1). These scaffolds should represent key intermediates for the synthesis of biologically active compounds targeted on CNS receptors. This approach has already proven its efficiency in the preparation of aromatic and heteroaromatic structures.[22]

Taking into account our interest in olefin metathesis[23] as well as economic limitations of this process, we wished to find optimal reaction conditions to obtain differently substituted pyrroline derivatives **3** in a gram-scale, in satisfactory yields, using a reduced



Scheme 1. Retrosynthetic approach for the formation of pyrrole derivatives **4**.

The pyrrole scaffold has focused a special attention as a privileged structure in medicinal chemistry, since several pyrrole-containing compounds displayed antipsychotic, anxiolytic, anticancer and antibacterial activity.[13] Among them, 2-arylpyrrole core was present in a series of 5-phenyl pyrrole-3-carboxamides and 2,5-disubstitued phenyl-1-*H*-pyrroles were classified as dopamine D_2 receptor ligands[14] and D_3 receptor antagonists,[15] respectively. Furthermore, compound TAK-438 (Venoprazan), displaying high H^+/K^+-ATP-ase inhibitory activity is currently evaluated in phase III clinical trials for its efficacy in digestive disorders.[16] Moreover, 2-arylpyrrole derivatives behaved as potent progesterone receptor modulators.[17]

The synthetic procedures described for 2-arylpyrroles generally consist in C2 arylation of the heterocyclic core involving palladium catalyzed coupling[18] or cyclization of *N*-allylimine under oxidative conditions.[19] Nevertheless, these methods required either harsh conditions or prolonged reaction times. The metal-catalyzed catalyst loading. Herein we report a comparative study of selected metathesis catalysts, as well as the influence of solvent and reaction kinetics on RCM.

2. Results and discussion

Compound **2a** bearing a nitro-substituent in the C2 position of the phenyl ring was selected as a model substrate for the preliminary RCM experiments. Indeed, this substrate has already been used for the synthesis of pyrroloquinoline scaffolds, using the NO_2 moiety as an extra functional group for further transformations.[23d] In addition, the RCM of **2a** was found challenging since the nitro-substituent was suspected to poison the ruthenium catalyst. At that time, RCM of **2a** to yield **3a** was performed in dichloromethane, either at room temperature, in the presence of 10 mol % of **G-II** for 12 h, or at 100 °C with 4 mol % of **G-II** under microwave activation in

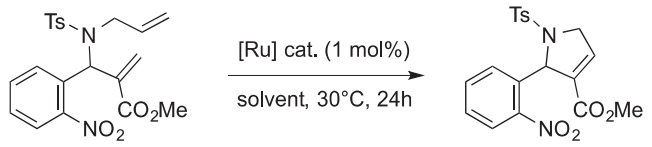
a sealed reactor for 2 h. The latter strategy allowed the preparation of the desired product **3a** in good yield (84%). It is worth noting, that microwave heating allows for the acceleration of the RCM process.[24] Nevertheless, this method suffers from some disadvantages with regard to the scale-up of the reaction. First of all, high catalyst loading, 4–10 mol %, implicates high cost for the scaled-up synthesis. Furthermore, microwave irradiation using sealed tubes is limiting in scale and thus would require splitting of the reaction mixture into several batches, thus reducing the user-friendly aspect of the whole process. The above observations prompted us to elaborate a suitable method for larger scale synthesis.

In order to optimize the catalyst loading, preliminary studies on the RCM of **2a** were performed under microwave irradiation, using an open-vessel mode, in the presence of either **G-II** or **NO_2-Grela** catalysts (Table 1).[25] To directly find the best catalyst loading for scalability, experiments were conducted on 0.5 g and 2.5 g of **2a**. Interestingly, on 0.5 g scale, while the decrease of **G-II** loading from 4 to 1 mol % did not significantly affect the HPLC conversion, it was reduced from quantitative to 77% in the presence of **NO_2-Grela** (Table 1). However, the importance of scaling-up reactions was demonstrated with experiments using 2.5 g of **2a** since **G-II** and **NO_2-Grela** behaved rather similarly on such scale, with a decrease in conversion concomitant with the lowering of catalyst loading. At this scale, **NO_2-Grela** performed better than **G-II** when 1 mol % was used, and **3a** could be isolated in 65% yield (Table 1, entry 6). The slightly lower yields compared to HPLC conversions were probably due to isolation issues since no cross-metathesis side-products were observed. Interestingly, only a 10% drop in the yield of isolated compound was observed when changing **NO_2-Grela** loading from 4 to 1 mol %. It is noteworthy that the obtained yields remained satisfactory from a preparative perspective. Indeed, TON (turn-over number) values of 65 and 18.5 could be obtained with 1 mol % and 4 mol % of **NO_2-Grela**, respectively, proving that the cost-effectiveness (ratio of catalyst cost per isolated yield of product) of the former reaction conditions was better than the latter ones. A 1 mol % catalyst loading was thus kept for further experiments.

To further optimize the RCM process, two more parameters were explored: the nature of the solvent and of the catalysts. One of the key considerations in industry is the use of green solvents to replace environmentally unfriendly ones.[26] Dichloromethane and toluene, which are both toxic, are the most widespread solvents employed for RCM. Nevertheless, some reports describe application of alternative innocuous solvent in this reaction.[23a,c,27] Among them, dimethyl carbonate (DMC) and ethyl acetate (AcOEt) seemed to be the most practical greener media for RCM transformation.[28] Additionally, these environmentally friendly solvents were reported in some cases to improve the reaction yields.[27]

Thus, the RCM of **2a** was attempted in DCM, DMC and AcOEt on a 50 mg scale using 1 mol % of **G-II** or **NO_2-Grela** at 30 °C for 24 h (Table 2). In order to avoid the use of a microwave reactor that would represent a limit for scale-up, the study was continued using traditional heating. Among the solvent tested, AcOEt gave the best yields in the RCM reactions catalyzed by both **G-II** (Table 2, entry 2, 73%) and **NO_2-Grela** (Table 2, entry 5, 65%). Nevertheless, **NO_2-Grela** yielded comparable results in DMC (63%) and AcOEt (Table 2, entries 5 and 6). In the syntheses performed at the industrial scale, the choice of the solvent is of particular importance and, among other issues, the costs of purchase, purification and drying should be carefully considered. Taking into account the availability and low boiling point of AcOEt, this solvent was selected for further study.

Table 2
Evaluation of selected solvents in the RCM of **2a**[a]



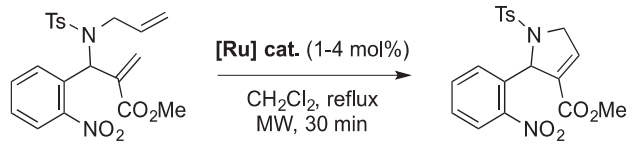
2a **3a**

Entry	Cat.	Solvent	HPLC conv. (%)[b]	NMR yield (%)[b,c]
1	**G-II**	CH_2Cl_2	62	63
2		AcOEt	74	73
3		DMC	68	66
4	**NO_2-Grela**	CH_2Cl_2	56	48
5		AcOEt	64	65
6		DMC	63	63

[a] Reaction conditions: **2a** (50 mg), Ru catalyst (1 mol %), 30 °C, 24 h.
[b] Mean from two experiments.
[c] Based on CH_2Br_2 as internal standard.

With these data in hands, additional catalysts, namely indenylidene-based catalysts **M2** and **$M2_0$**, and boomerang-type catalyst **$M5_1$**, featuring a *N,N*-bis[2,4,6-(trimethyl)-phenyl]imidazolin-2-ylidene (SIMes) ligand, were investigated in the RCM of **2a** on a 2.5 g scale (Fig. 2). Moreover, the catalysts were added in three equal portions over a period of 7 h to maximize reaction yield by decreasing catalyst decomposition.[29] Although **M2** catalyst gave the best HPLC results after 24 h, the conversion measured after 4 h of stirring was significantly lower when compared with other catalysts (Table 3, entry 3). This result might reflect the high stability

Table 1
Evaluation of the catalyst loading in the RCM of **2a**[a]

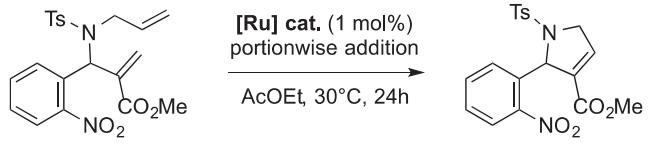


2a **3a**

Entry	Cat.	Loading (mol %)	0.5 g scale	2.5 g scale		
			Conv. (%)[b]	Conv. (%)[b]	Yield (%)[c]	TON[d]
1	**G-II**	4	100	98	75	18.8
2	**NO_2-Grela**		100	94	74	18.5
3	**G-II**	3	99	94	74	24.7
4	**NO_2-Grela**		94	86	73	24.3
5	**G-II**	1	96	72	59	59
6	**NO_2-Grela**		77	77	65	65

[a] Reaction conditions: **2a** (0.5 or 2.5 g), Ru catalyst (1–4 mol %), CH_2Cl_2, reflux, MW open vessel mode, 30 min.
[b] Mean from two experiments, conversion was determined by HPLC.
[c] Isolated yield upon crystallization from diethyl ether.
[d] TON=[(mmol of **3a**/mmol of **2a**)/mmol of [Ru]].

Table 3
Evaluation of selected ruthenium catalysts in the RCM of **2a**[a]



2a **3a**

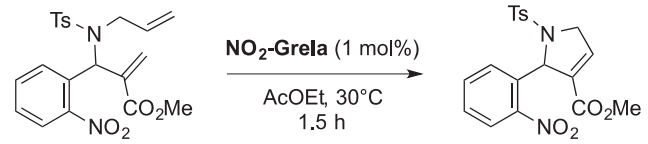
Entry	Cat.	HPLC conv. (%)[b]			NMR yield (%)[b,c]	Yield (%)[b,d]
		4 h[b]	7 h[b]	24 h[b]		
1	**G-II**	30	48	63	71	47
2	**NO_2-Grela**	34	52	62	71	53
3	**M2**	9	48	68	80	36
4	**$M2_0$**	34	50	62	65	52
5	**$M5_1$**	37	54	59	75	44

[a] Reaction conditions: **2a** (2.5 g), Ru catalyst (1 mol %), AcOEt, 30 °C, 24 h.
[b] Mean from two experiments.
[c] Based on CH_2Br_2 as internal standard.
[d] Isolated yield upon crystallization from diethyl ether.

and slow initiation rate of **M2**. Even though no side-product was detected during the RCM, the isolated yield obtained with this catalyst was the lowest. The best yields were obtained using **NO_2-Grela** and **$M2_0$** catalysts (Table 3, entries 2 and 4). **G-II** and **$M5_1$**, which are slightly less stable than the other catalysts tested, gave lower isolated yields (Table 3, entries 1 and 5).

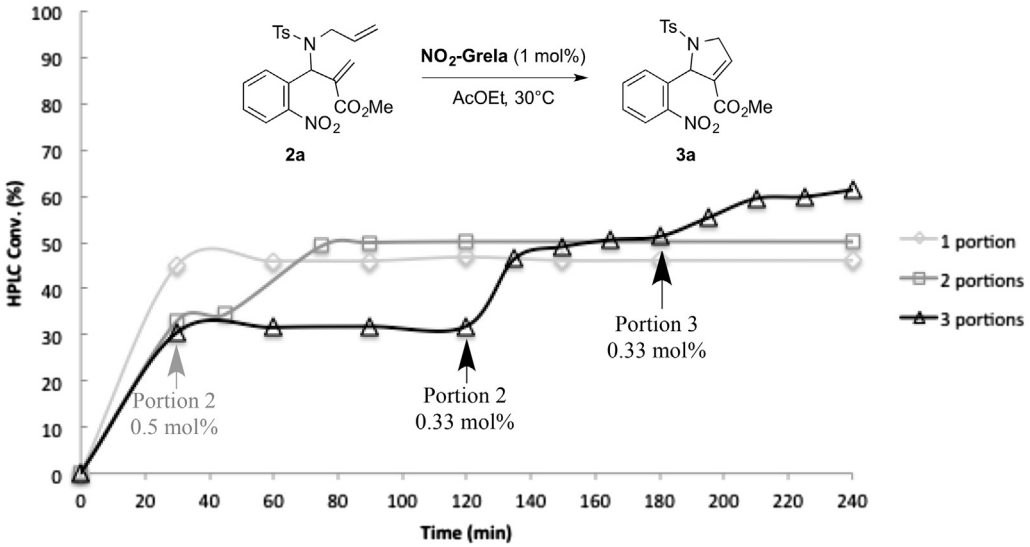
The beneficial effect of the portionwise addition of the catalyst was monitored on a 2.5 g scale experiment, using 1 mol % of **NO_2-Grela** in AcOEt (Scheme 2). When a single portion of **NO_2-Grela** was added at the beginning of the reaction, the conversion stabilized at 46% in less than 1 h as shown by HPLC. With a two-portion addition (second portion added after 45 min), the final conversion slightly increased to 50%. Gratifyingly, the three-portion addition (second and third addition after 2 h and 3 h, respectively) gave the best result with 61% conversion after 4 h of reaction. Such condition allowed isolation of **3a** in 54% yield.

Table 4
Evaluation of scale-up effect in the RCM of **2a**[a]



Entry	Scale	HPLC conv. (%)[b]	NMR yield (%)[b,c]	Yield (%)[b,d]
1	2.5 g	61	70	54
2	15 g	63	60	53

[a] Reaction conditions: **2a** (15 g), **NO_2-Grela** (1 mol %), AcOEt, 30 °C, 1.5 h.
[b] Mean from two experiments.
[c] Based on CH_2Br_2 as internal standard.
[d] Isolated yield upon crystallization from diethyl ether.



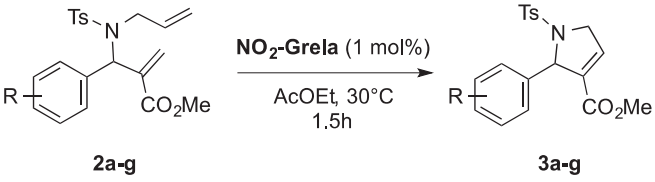
Scheme 2. Kinetic study of RCM of **2a** with portionwise addition of **NO_2-Grela**.

As already witnessed in the literature for **G-II**,[30] kinetic data from Scheme 2 confirmed that the product concentration reached a constant level 30 min after each catalyst addition. Thus, the best compromise for the experimental conditions and catalyst loading, evaluated for the RCM reaction of 2-nitro-substituted substrate **2a** involved portionwise addition of 1 mol % of **NO_2-Grela** catalyst (3 equal portions), with 30 min intervals, over a period of 1.5 h at 30 °C in AcOEt.

In order to evaluate the influence of reaction scale-up on the outcome of RCM of **2a**, we next performed the experiment using 15 g of 2-nitro-substituted substrate, maintaining 1 mol % of catalyst loading added in 3 portions in every 30 min, while stirring the mixture in AcOEt at 30 °C (Table 4). We were pleased to see that under these conditions, the RCM product **3a** was obtained with 53% isolated yield.

Encouraged by these findings, we next investigated the synthetic utility of the evaluated method for the RCM of variously substituted dienes **2a**–**g**, obtained through a three-component aza-Baylis–Hillman reaction followed by allylation. It is noteworthy that any substituent might modify biological activity of the final compounds or could be used as a functional handle for further synthetic transformations. In addition to **2a**, non-substituted β-amino ester **2b** as well as its analogs bearing methoxy groups (**2c**–**e**) or chlorine atoms (**2f**–**g**) as substituents of the phenyl ring were evaluated (Table 5). The reaction was performed on 0.5 g of substrates using portionwise addition of 1 mol % of **NO_2-Grela** while stirring the mixture in AcOEt at 30 °C for 1.5 h.

Table 5
Application of the optimized conditions to the synthesis of pyrrolines **3b**–**g**[a]



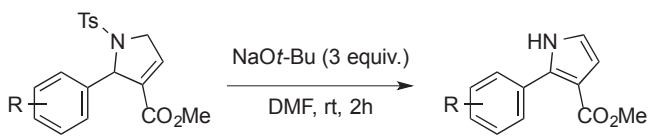
Entry	Product	R	HPLC conv. (%)[b]	NMR yield (%)[b,c]	Yield (%)[b,d]
1	**3a**[e]	*o*-NO_2	61	70	54
2	**3b**	H	58	71	58
3	**3c**	*o*-OMe	48	60	39
4	**3d**	*m*-OMe	52	65	43
5	**3e**	*p*-OMe	52	n.d.[f]	46
6	**3f**	*m*-Cl	65	75	66
7	**3g**	*p*-Cl	66	81	64

[a] Reaction conditions: **2a**–**g** (0.5 g), **NO_2-Grela** (1 mol %), AcOEt, 30 °C, 1.5 h.
[b] Mean from two experiments.
[c] Based on CH_2Br_2 as internal standard.
[d] Isolated yield upon crystallization from diethyl ether.
[e] Reported in Ref. 23d.
[f] n.d.=not determined.

The RCM reaction was not affected by the position of the substituent on the phenyl ring, as similar yields were obtained when the chloro or methoxy groups were either in *ortho*, *meta* or *para* position (Table 5, entries 3–8). Compounds **3c**–**e**, bearing a methoxy group, were isolated in about 43% yield while their chloro congeners **3f**–**g** were obtained in more or less 64% yield. When no substituent was present on the aromatic moiety, an intermediate yield of 54% for **3b** was obtained (Table 5, entry 2). It should be noted that in all cases, purification of compounds **3a**–**g** was not performed via column chromatography but simple crystallization in diethyl ether, thus improving the feasibility of the whole process on a larger scale.

Pyrrolines **3a**–**g** were then converted into corresponding pyrroles **4a**–**g** using NaO*t*-Bu in DMF, under air to promote deprotection and aromatization in a one-pot sequence (Table 6). Corresponding pyrrole derivatives could be isolated efficiently, with 60–70% yield, in solely 2 h. It is important to highlight that this methodology, involving RCM followed by base-mediated deprotection/aromatization, allowed to synthesize new pyrrole derivatives **4c**–**f**, which could serve as diversity platforms for further transformations.

Table 6
Deprotection–aromatization for the preparation of pyrroles **4a**–**g**[a]



3a-g **4a-g**

Entry	Product	R	Yield (%)[b,c]
1	**4a**	*o*-NO_2	65
2	**4b**	H	60
3	**4c**	*o*-OMe	70
4	**4d**	*m*-OMe	68
5	**4e**	*p*-OMe	67
6	**4f**	*m*-Cl	65
7	**4g**	*p*-Cl	63

[a] Reaction conditions: **3a**–**g** (0.3 mmol), NaO*t*-Bu (0.9 mmol), DMF, rt, 2 h.
[b] Isolated yield upon purification by column chromatography.
[c] Mean from two experiments.

3. Conclusion

In conclusion, we developed a convenient protocol for the preparation of 2-arylpyrrole derivatives based on a scaled-up RCM reaction, with reduced catalyst loading in a non-toxic solvent. The study allowed to decrease the catalyst loading from 4 mol % to 1 mol % and to replace **G-II** catalyst with its **NO_2-Grela** alternative. Dichloromethane, which is commonly used in RCM, could also be changed for ethyl acetate, an environmentally friendly solvent. Additionally, the optimized conditions were successfully applied to differently substituted β-amino esters, providing the corresponding pyrrolines in satisfactory yields. Finally, 2-aryl-1*H*-pyrrole-3-carboxylates, which are important building blocks for the generation of CNS-oriented compound libraries, were obtained through a one-pot sequence deprotection/aromatization.

4. Experimental section

4.1. General remarks

Organic transformations were carried out at ambient temperature, unless indicated otherwise. Organic solvents used in this study (from Sigma–Aldrich and Chempur) were of reagent grade and were used without purification. All other commercially available reagents were of the highest purity (from Sigma–Aldrich, Alfa Aesar, Fluorochem, TCI). Metathesis catalysts used were either purchased from Sigma Aldrich, Apeiron-Synthesis (**NO_2-Grela**) or given by Umicore AG & Co. All workup and purification procedures were carried out with reagent-grade solvents under ambient atmosphere.

Melting points were determined with a Büchi apparatus and are uncorrected.

Analytical HPLC analyses were run on an Alliance Waters 2695 Separations Module equipped with a Chromolith Speed ROD RP 18.5 μm column (4.6×50 mm). Standard conditions were as follows: eluent system A (water/0.1% TFA), system B (MeCN/0.1% TFA). A flow rate of 5 ml/min with a gradient of (0–100)% B over 3 min was used. Detection was performed with a Waters 2998 Photodiode Array Detector.

LC/MS analyses were carried out on a system consisting of a Waters Acquity UPLC coupled with a Waters TQD mass spectrometer (electrospray ionization mode ESI-tandem quadrupole). All of the analyses were carried out with an Acquity UPLC BEH C_{18}, 50×2.1 mm column at 40 °C. A flow rate of 0.3 ml/min and a gradient of (5–95)% B over 13 min was used. The mobile phase conditions were as follows: eluent A: water/0.1% HCO_2H; eluent B: MeCN/0.1% HCO_2H. Retention times (t_R) are reported in minutes.

^{1}H NMR and ^{13}C NMR spectra were recorded either at 300 MHz and 75 MHz (Varian BB 200 spectrometer) or 400 MHz and 100 MHz (Bruker Avance AM) using $CDCl_3$ as solvent. The *J* values are reported in Hertz (Hz), and the splitting patterns are designated as follows: s (singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet), br s (broad singlet).

4.2. General procedure for preparation of compounds 2a–g

This procedure was similar to the one used in Ref. 21.

In a dried flask *p*-toluenesulfonamide (18 g, 105 mmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (1.78 g, 15.7 mmol, 0.15 equiv) were mixed together with the previously activated molecular sieves (4 Å, 21 g). The mixture was suspended in isopropanol (300 ml), followed by addition of benzaldehyde derivative (105 mmol, 1 equiv) and methyl acrylate (10.7 ml, 115 mmol, 1.1 equiv). Subsequently, titanium isopropoxide (Ti(*i*OPr)$_4$) was added as a freshly prepared solution in isopropanol (0.6 ml, 2.1 mmol, 0.02 equiv). The flask was filled with nitrogen and the mixture was stirred at room temperature for 36 h. Then, a mixture was filtered through Celite which was rinsed with CH_2Cl_2. The solvent was evaporated and the remaining crude was dissolved in AcOEt (400 ml), washed three times with 1 M $KHSO_4$, once with saturated $NaHCO_3$, water and brine and dried over Na_2SO_4. Evaporation of the solvent gave a yellow oil which was subsequently dissolved in AcOEt (300 ml) and precipitated upon portionwise addition of *n*-hexane (300 ml). The appearing white precipitate was filtered, dried under vacuum and was pure enough to be directly engaged in the next step.

β-Aminoester (25.6 mmol, 1 equiv) was dissolved in DMF (100 ml), followed by addition of K_2CO_3 (76.5 mmol, 3 equiv). Subsequently, allyl bromide (51.2 mmol, 2 equiv) was added dropwisely. The reaction was stirred at room temperature for 6 h. The mixture was diluted with ethyl acetate (300 ml) and washed 5× with water and brine. The organic phase was filtered and evaporated. The remaining yellow residue was dissolved in AcOEt (70 ml) and precipitated upon portionwise addition of *n*-hexane (70 ml). The obtained white solid was filtered and dried under vacuum.

4.3. Characterization of 2a–g

4.3.1. Methyl-2-[(N-allyl-N-tosylamino)(2-nitrophenyl)-methyl]acrylate (2a).[23d,31] White solid, 95% yield, t_R=7.48, Mp 83–85 °C, $C_{21}H_{22}N_2O_6S$, MW 430.47.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.40 (s, 3H), 3.52 (s, 3H), 3.92–4.23 (m, 2H), 4.89–5.01 (m, 2H), 5.42–5.57 (m, 2H), 6.42 (s, 1H), 6.80 (s, 1H), 7.19–7.27 (m, 2H), 7.41–7.50 (m, 1H), 7.59–7.69 (m, 3H), 7.76 (d, *J*=7.62 Hz, 1H), 7.92 (dd, *J*=7.91 Hz, 1.47 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.5, 50.8, 52.1, 58.4, 118.7, 125.3, 127.7, 128.7, 129.3, 130.4, 133.2, 133.6, 134.4, 137.8, 138.3, 143.3, 148.0, 165.4.

Monoisotopic Mass 430.12, $[M+H]^+$ 430.8. HRMS calcd for $C_{21}H_{23}N_2O_6S$ 431.1277; found: 431.1277.

*4.3.2. Methyl-2-{[(N-allyl-4-methylphenyl)sulfonamido](phenyl)methyl}acrylate (**2b**).*[32] White solid, 95% yield, t_R=7.90, Mp 67–69 °C, $C_{21}H_{23}NO_4S$, MW 385.46.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.43 (s, 3H), 3.60 (s, 3H), 3.77–3.85 (m, 2H), 4.78–4.88 (m, 2H), 5.19–5.35 (m, 1H), 5.73 (d, *J*=1.76 Hz, 1H), 6.11 (s, 1H) 6.44 (s, 1H), 7.0 (dd, *J*=6.45, 2.93 Hz, 2H), 7.19–7.30 (m, 5H), 7.69 (d, *J*=8.21 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.5, 48.7, 52.0, 61.8, 117.6, 127.5, 128.0, 128.5, 129.4, 134.3, 137.1, 137.9, 139.2, 143.2, 166.3.

Monoisotopic Mass 385.13, $[M+H]^+$ 386.1.

*4.3.3. Methyl-2-{[(N-allyl-4-methylphenyl)sulfonamido](2-methoxyphenyl)methyl}acrylate (**2c**).* White solid, 90% yield, t_R=7.97, Mp 85–87 °C, $C_{21}H_{25}NO_5S$, MW 415.50.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.39 (s, 3H), 3.51 (s, 3H), 3.60 (s, 3H), 3.74–3.98 (m, 2H), 4.76–4.85 (m, 2H), 5.30–5.47 (m, 1H), 5.96–6.00 (m, 1H), 6.25 (s, 1H), 6.49–6.53 (m, 1H), 6.66 (dd, *J*=8.21, 0.77 Hz, 1H), 6.80–6.87 (m, 1H), 7.09 (dd, *J*=7.57, 1.67 Hz, 1H), 7.14–7.26 (m, 3H), 7.50–7.57 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.5, 50.0, 51.9, 54.8, 56.9, 110.2, 117.3, 120.1, 124.8, 127.6, 128.9, 129.4, 129.7, 134.4, 138.4, 139.8, 142.4, 157.3, 166.4.

Monoisotopic Mass 415.15, $[M+H]^+$416.2.

HRMS calcd for $C_{21}H_{25}NO_5S$ 416.1532; found: 416.1530.

*4.3.4. Methyl-2-{[(N-allyl-4-methylphenyl)sulfonamido](3-methoxyphenyl)methyl}acrylate (**2d**).*[32] White solid, 90% yield, t_R=7.97, Mp 71–73 °C, $C_{21}H_{25}NO_5S$, MW 415.50.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.42 (s, 3H), 3.63 (d, *J*=8.98 Hz, 6H), 3.80 (d, *J*=6.16 Hz, 2H), 4.81–4.84 (m, 1H), 4.86–4.90 (m, 1H), 5.22–5.37 (m, 1H), 5.75 (d, *J*=1.28 Hz, 1H), 6.06 (s, 1H), 6.42–6.49 (m, 2H), 6.58–6.63 (m, 1H), 6.73–6.78 (m, 1H), 7.13 (t, *J*=7.95 Hz, 1H), 7.23–7.31 (m, 2H), 7.67–7.74 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.5, 48.7, 52.0, 55.0, 61.7, 113.9, 114.0, 117.6, 120.7, 127.6, 128.0, 129.4, 129.5, 134.4, 137.8, 138.5, 139.2, 143.2, 159.7, 166.3.

Monoisotopic Mass 415.15, $[M+H]^+$416.3.

*4.3.5. Methyl-2-{[(N-allyl-4-methylphenyl)sulfonamido](4-methoxyphenyl)methyl}acrylate (**2e**).*[32] White solid, 90% yield, t_R=7.97, Mp 91–92 °C, $C_{21}H_{25}NO_5S$, MW 415.50.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.42 (s, 3H), 3.60 (s, 3H), 3.75 (s, 3H), 3.77–3.81 (m, 2H), 4.81 (t, *J*=1.28 Hz, 1H), 4.84–4.89 (m, 1H), 5.17–5.32 (m, 1H), 5.75 (dd, *J*=1.80, 0.51 Hz, 1H), 6.03 (s, 1H), 6.38–6.42 (m, 1H), 6.70–6.77 (m, 2H), 6.87–6.94 (m, 2H), 7.23–7.29 (m, 2H), 7.65–7.72 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.5, 48.6, 52.0, 55.2, 61.3, 113.9, 117.6, 127.3, 127.5, 128.9, 129.4, 129.9, 134.4, 137.8, 139.4, 143.2, 159.3, 166.4.

Monoisotopic Mass 415.15. $[M+H]^+$416.2.

*4.3.6. Methyl-2-{[(N-allyl-4-methylphenyl)sulfonamido](3-chlorophenyl)methyl}acrylate (**2f**).*[32] White solid, 93% yield, t_R=8.30, Mp 58–60 °C, $C_{21}H_{22}ClNO_4S$, MW 419.92.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.43 (s, 3H), 3.60–3.64 (m, 3H), 3.83 (d, *J*=6.41 Hz, 2H), 5.28–5.43 (m, 1H), 5.73 (d, *J*=1.80 Hz, 1H), 6.04 (s, 1H), 6.47 (d, *J*=1.03 Hz, 1H), 6.87 (t, *J*=1.67 Hz, 2H), 6.92–6.97 (m, 2H), 7.13–7.29 (m, 4H), 7.62–7.70 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.5, 49.0, 52.1, 61.2, 117.9, 126.7, 127.4, 128.2, 128.7, 129.5, 129.7, 134.1, 134.4, 137.6, 138.5, 139.3, 143.5, 166.0.

Monoisotopic Mass 419.10, $[M+H]^+$ 420.2.

*4.3.7. Methyl-2-{[(N-allyl-4-methylphenyl)sulfonamido](4-chlorophenyl)methyl}acrylate (**2g**).*[32] White solid, 93% yield, t_R=8.30, Mp 87–89 °C, $C_{21}H_{22}ClNO_4S$, MW 419.92.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.43 (s, 3H), 3.58–3.63 (m, 3H), 3.78–3.84 (m, 2H), 4.81–4.90 (m, 2H), 5.22–5.40 (m, 1H), 5.72 (d, *J*=1.80 Hz, 1H), 6.04 (s, 1H), 6.45 (d, *J*=1.28 Hz, 1H), 6.93–7.00 (m, 2H), 7.23 (s, 4H), 7.63–7.68 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.5, 49.0, 52.1, 61.1, 117.9, 128.5, 128.7, 129.5, 129.9, 133.9, 134.1, 136.0, 137.7, 139.0, 143.4, 166.1.

Monoisotopic Mass 419.10, $[M+H]^+$ 420.3.

4.4. General procedure for preparation of compounds 3a–g

Compound **2a–g** (2.5 g, 1 equiv) was dissolved in AcOEt (25 ml) and **NO_2-Grela** catalyst (1 mol %) was added in three portions over a period of 1.5 h with 30 min time intervals. The reaction was quenched with ethyl vinyl ether (50 equiv/Ru) and stirred for additional 1 h. The solution was evaporated and the remaining residue was dissolved in CH_2Cl_2 and filtered through a layer of silica gel. The obtained product was triturated with diethyl ether to give white precipitate which was filtered and dried under vacuum.

4.5. Characterization of 3a–g

*4.5.1. Methyl 2,5-dihydro-2-(2-nitrophenyl)-1-tosyl-1H-pyrrole-3-carboxylate (**3a**).*[21,23d,31] White solid, 54% yield, Mp 125–127 °C, t_R=6.83, $C_{19}H_{18}N_2O_6S$, MW 402.42.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.43 (s, 3H), 3.53 (s, 3H), 4.33–4.65 (m, 2H), 6.69–6.72 (m, 1H), 6.75–6.76 (m, 1H), 7.35 (d, *J*=8.0 Hz, 2H), 7.39–7.44 (m, 1H), 7.55–7.57 (m, 2H), 7.81 (d, *J*=8.0 Hz, 2H), 7.90 (d, *J*=8.0 Hz 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.7, 52.2, 55.8, 62.5, 124.7, 127.9, 128.7, 129.8, 130.2, 133.2, 133.5, 135.2, 135.8, 136.7, 144.4, 148.9, 161.7.

Monoisotopic Mass 402.09, $[M+H]^+$ 403.3. HRMS calcd for $C_{19}H_{19}N_2O_6S$ 403.0964; found: 403.0967.

*4.5.2. Methyl 2-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**3b**).*[33] White solid, 58% yield, t_R=7.03, Mp 111–113 °C, $C_{19}H_{19}NO_4S$, MW 357.42.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.36 (s, 3H), 3.58 (s, 3H), 4.33–4.43 (m, 1H), 4.47–4.57 (m, 1H), 5.72–5.75 (m, 1H), 6.76–6.80 (m, 1H), 7.14 (d, *J*=8.21 Hz, 2H), 7.20–7.25 (m, 5H), 7.38–7.45 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 51.8, 54.9, 69.0, 127.1, 127.7, 128.3, 129.5, 135.6, 135.7, 139.4, 143.3, 162.2.

Monoisotopic Mass 457.10, $[M+H]^+$ 358.2.

*4.5.3. Methyl 2-(2-methoxyphenyl)-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**3c**).* White solid, 39% yield, t_R=6.93, Mp 115–117 °C, $C_{20}H_{21}NO_5S$, MW 387.45.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.38 (s, 3H) 3.56 (s, 6H), 4.30–4.56 (m, 2H), 5.99 (m, 1H), 6.66 (dd, *J*=8.72, 0.77 Hz, 1H), 6.75

(m, 1H), 6.87 (m, 1H), 7.11 (d, J=7.95 Hz, 2H), 7.16–7.27 (m, 2H), 7.33–7.41 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.4, 51.6, 55.2, 65.0, 111.0, 120.4, 126.8, 127.1, 129.1, 129.3, 130.4, 134.2, 135.7, 136.1, 142.8, 157.4, 162.4.

Monoisotopic Mass 387.11, $[M+H]^+$ 388.3.

HRMS calcd for $C_{20}H_{21}NO_5S$ 388.1219, found 388.1217.

*4.5.4. Methyl 2-(3-methoxyphenyl)-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**3d**).* White solid, 43% yield, t_R=6.93, Mp 79–81 °C, $C_{20}H_{21}NO_5S$, MW 387.45.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.36 (s, 3H), 3.55–3.64 (m, 3H), 3.71 (s, 3H), 4.31–4.56 (m, 2H), 5.68–5.74 (m, 1H), 6.64–6.69 (m, 1H), 6.71–6.89 (m, 3H), 7.08–7.21 (m, 3H), 7.42 (d, J=8.46 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.5, 51.9, 55.0, 55.1, 68.9, 113.2, 133.5, 120.3, 127.1, 129.3, 129.4, 135.5, 135.8, 140.7, 143.3, 159.5, 162.2.

Monoisotopic Mass 387.11, $[M+H]^+$ 388.3.

HRMS calcd for $C_{20}H_{21}NO_5S$ 388.1219, found 388.1219.

*4.5.5. Methyl 2-(4-methoxyphenyl)-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**3e**).* White solid, 46% yield, t_R=6.93, Mp 85–87 °C, $C_{20}H_{21}NO_5S$, MW 387.45.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.34 (s, 3H), 3.56 (s, 3H), 3.71–3.79 (m, 3H), 4.27–4.40 (m, 1H), 4.41–4.52 (m, 1H), 5.61–5.72 (m, 1H), 6.69–6.79 (m, 3H), 7.06–7.18 (m, 4H), 7.42 (d, J=8.21 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.4, 51.8, 54.8, 55.2, 68.5, 113.7, 127.1, 128.9, 129.5, 131.6, 135.5, 135.6, 143.2, 159.4, 162.3.

Monoisotopic Mass 387.11, $[M+H]^+$ 388.3.

HRMS calcd for $C_{20}H_{21}NO_5S$ 388.1219, found 388.1216.

*4.5.6. Methyl 2-(3-chlorophenyl)-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**3f**).* White solid, 66% yield, t_R=7.49, Mp 112–114 °C, $C_{19}H_{18}ClNO_4S$, MW 391.87.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.41 (s, 3H), 3.53–3.66 (m, 3H), 4.32–4.60 (m, 2H), 5.68 (m, 1H), 6.75–6.85 (m, 1H), 7.04 (s, 1H), 7.09–7.28 (m, 5H), 7.34–7.51 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.5, 51.9, 55.03, 68.4, 126.3, 127.0, 127.6, 128.2, 129.5, 134.2, 135.2, 135.4, 136.2, 141.3, 143.6, 162.0.

Monoisotopic Mass 391.06, $[M+H]^+$ 392.2.

HRMS calcd for $C_{19}H_{18}ClNO_4S$ 392.0723, found 392.0727.

*4.5.7. Methyl 2-(4-chlorophenyl)-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**3g**).* White solid, 64% yield, t_R=7.49, Mp 109–111 °C, $C_{19}H_{18}ClNO_4S$, MW 391.87.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.39 (s, 3H), 3.59 (s, 3H), 4.33–4.44 (m, 1H), 4.46–4.56 (m, 1H), 5.69 (dt, J=5.57, 2.20 Hz, 1H), 6.78 (q, J=2.15 Hz, 1H), 7.10–7.23 (m, 6H), 7.41–7.49 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 51.9, 55.0, 68.3, 127.1, 128.5, 129.1, 129.6, 133.9, 135.3, 136.0, 138.1, 143.6, 162.0.

Monoisotopic Mass 391.06, $[M+H]^+$ 392.2.

HRMS calcd for $C_{19}H_{18}ClNO_4S$ 392.0723, found 392.0722.

4.6. General procedure for preparation of compounds 4a–g

To a solution of 2,5-dihydropyrrole 3 (2.5 g, 6.2 mmol, 1 equiv) in DMF (40 ml) potassium *tert*-butoxide (2.09 g, 18.7 mmol, 3 equiv) was added. The reaction was carried for 2 h under TLC monitoring. The mixture was diluted with ethyl acetate, neutralized with 1 M $KHSO_4$, washed with saturated solution of $NaHCO_3$ (1×), water (3×) and brine (1×). The organic layer was dried under Na_2SO_4 and evaporated. The obtained crude product was purified on silica gel with AcOEt/Hex (4/6) as a developing solvent.

4.7. Characterization of 4a–g

*4.7.1. Methyl 2-(2-nitrophenyl)-1H-pyrrole-3-carboxylate (**4a**).*[21,23d,31] Yellow solid, 65% yield, t_R=5.72, $C_{12}H_{10}N_2O_4$, MW 246.22.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.63 (s, 3H), 6.74 (t, J=2.95 Hz, 1H), 6.82–6.84 (m, 1H), 7.43–7.48 (m, 1H), 7.52–7.60 (m, 1H), 7.62–7.68 (m, 1H), 8.01 (dd, J=8.21, 1.28 Hz, 1H), 8.50–8.68 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 51.0, 111.4, 113.5, 118.7, 124.4, 127.3, 129.5, 132.4, 149.5, 164.8.

Monoisotopic Mass 246.06, $[M+H]^+$ 247.3.

*4.7.2. Methyl 2-phenyl-1H-pyrrole-3-carboxylate (**4b**).*[23e] White oil, yield 60%, t_R=5.34, $C_{12}H_{11}NO_2$, MW 201.23.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.71 (s, 3H), 6.66–6.74 (m, 2H), 7.31–7.37 (m, 2H), 7.38–7.41 (m, 1H), 7.52–7.55 (m, 1H), 7.56–7.58 (m, 1H), 8.68 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 51.0, 111.7, 112.1, 117.8, 128.1, 128.9, 132.0, 137.2, 165.6.

Monoisotopic Mass 201.08, $[M+H]^+$ 202.0.

*4.7.3. Methyl 2-(2-methoxyphenyl)-1H-pyrrole-3-carboxylate (**4c**).* White oil, yield 70%, t_R=5.21, $C_{13}H_{13}NO_3$, MW 231.25.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.72 (s, 3H), 3.81 (s, 3H), 6.69–6.78 (m, 2H), 6.92–7.07 (m, 2H), 7.26–7.37 (m, 1H), 7.64 (dd, J=7.62, 1.76 Hz, 1H), 9.01 (br s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 50.8, 55.7, 111.1, 111.5, 112.6, 117.2, 120.5, 120.2, 129.6, 132.3, 133.3, 156.4, 165.5.

Monoisotopic Mass 231.09, $[M+H]^+$ 232.1.

HRMS calcd for $C_{13}H_{13}NO_3$ 232.0974, found 232.0972.

*4.7.4. Methyl 2-(3-methoxyphenyl)-1H-pyrrole-3-carboxylate (**4d**).* White oil, yield 68%, t_R=5.47, $C_{13}H_{13}NO_3$, MW 231.25.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.64 (s, 3H), 3.78 (s, 3H), 6.52–6.56 (m, 1H), 6.82–6.87 (m, 1H), 6.88–6.94 (m, 1H), 7.14–7.22 (m, 2H), 7.26–7.34 (m, 1H), 11.50–11.71 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 51.0, 55.5, 111.4, 111.9, 113.8, 114.9, 119.0, 121.7, 129.3, 133.6, 136.5, 159.2, 165.1.

Monoisotopic Mass 231.09, $[M+H]^+$ 232.1.

HRMS calcd for $C_{13}H_{13}NO_3$ 232.0974, found 232.0971.

*4.7.5. Methyl 2-(4-methoxyphenyl)-1H-pyrrole-3-carboxylate (**4e**).* White oil, yield 67%, t_R=5.40, $C_{13}H_{13}NO_3$, MW 231.25.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.72 (s, 3H), 3.82 (s, 3H), 6.69 (quin, J=2.64 Hz, 2H), 6.87–6.94 (m, 2H), 7.46–7.53 (m, 2H), 8.46–8.67 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 50.5, 55.3, 111.2, 111.9, 113.6, 117.4, 124.5, 130.2, 137.3, 159.6, 165.6.

Monoisotopic Mass 231.09, $[M+H]^+$ 232.1.

HRMS calcd for $C_{13}H_{13}NO_3$ 232.0974, found 232.0972.

*4.7.6. Methyl 2-(3-chlorophenyl)-1H-pyrrole-3-carboxylate (**4f**).* White oil, yield 65%, t_R=6.21, $C_{12}H_{10}ClNO_2$, MW 235.67.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.74 (s, 3H), 6.69–6.76 (m, 2 H), 7.27–7.34 (m, 2H), 7.42–7.49 (m, 1H), 7.53–7.57 (m, 1H), 8.59–8.78 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 51.1, 112.4, 118.3, 127.2, 128.2, 128.8, 129.4, 133.7, 165.3.

Monoisotopic Mass 235.04. $[M+H]^+$ 236.0.

HRMS calcd for $C_{12}H_{10}ClNO_2$ 236.0478, found 236.0478.

*4.7.7. Methyl 2-(4-chlorophenyl)-1H-pyrrole-3-carboxylate (**4g**).*[23e] White oil, yield 63%, t_R=6.18, $C_{12}H_{10}ClNO_2$, MW 235.67.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.73 (s, 3H), 6.69–6.75 (m, 2H), 7.30–7.38 (m, 2H), 7.45–7.52 (m, 2H), 8.55–8.72 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 51.0, 112.3, 118.1, 128.4, 130.2, 130.4, 134.2, 135.9, 165.4.

Monoisotopic Mass 235.04. $[M+H]^+$ 236.0.

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References and notes

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