CONCISE AND PRACTICAL AVENUES TO 5,5-SPIRO-α-PROLINES

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Keywords: α-proline; 5,5-spirocyclic α-prolines, scaffold hopping, medchem relevant building blocks, conformational restrictions.

Abstract

Scaffold hopping and three-dimensionality are one of dominating notions in contemporary drug discovery process. Following these concepts is a verified and generally robust avenue to improve the biological activity of a lead against a protein target, selectivity issues as well as ADMET properties. Unfortunately, the freedom of medicinal chemists to replace molecular fragments responsible for the properties is restricted due to unrevealed areas of chemical space existing for even simple building blocks. This paper contributes to the support of drug discovery workflow and describes concise and practical synthetic approaches toward multigram preparation of value-added conformationally constrained 5,5-spirocyclic α-prolines from readily accessible starting materials. Direct carboxylation of 2-spiropyrrolidines was found to be a novel and promising approach to achieve the purpose and is the most fruitful for substrates with no acidic centers within a part spiro linked to pyrrolidine core. The method allows for quick and one-step preparation of the target chemicals in good yields. For substrates inapplicable to the straightforward method, an alternative synthetic avenue was designed. This 4-steps protocol deals with common for laboratory practice transformations and is comparable in its efficiency with the carboxylation method. The paper concludes a series of our works on the elaboration of efficient methods for the construction of spiro proline frameworks.

Introduction

Spiro compounds are a crucial family of synthetic and natural chemicals that consist of two rings sharing a single atom, mostly carbon. Since 1900 when *Adolf von Baeyer* firstly coined the term "spiro" and accomplished the synthesis of the first 'artificial' member of the class,[1] spirocyclic compounds have come to spotlight of different branches of chemical industry and have even become an indispensable part of our daily life.[2] For instance, recent comprehensive reviews emphasize the role of spirocyclic compounds in fragrance, agricultural and food chemistry.[3,4] However, majority of efforts in the field are being made by medicinal chemists, who generate the lion's share of spirocyclic topologies. This is by no means serendipitous, as foundation of the trend was laid in far 1950th with the creation of mineralocorticoid receptor antagonist spironolactone.[5,6] Over the following years, evolution of the spirocyclic medicines concept has led to a significant increase in number of approved drugs, including such renowned pharmacological agents as buspirone, fenspiride, griseofulvin and irbesartan. Besides that, the interest in compounds containing spiro-conjunction was in some extent fueled by multiple instances of natural products with incorporated spirocyclic framework and highly pronounced biological properties.[7,8] With all the mentioned, spirocyclic compounds have become frequent guests in scientific papers that is evidenced by steadily increasing number of records in the Reaxys® database for the keyword "*spiro*" within the period from early 1900th to the present days and with the peak reached in 2022.[9] Similar tendency is observed for works specifically related to MedChem investigations.[10] Interestingly, the highest popularity of the topic occurred in 2008-2010 years that precisely match the period when milestone paper by *Frank Lovering et al.* was released.[11] This publication introduced the "escape from flatland" idea later becoming 'viral' and proposed that higher three-dimensionality is critical for a chemical species to succeed in the drug development scenario and get promoted from the discovery stage to approval by a drug office. This statement has a ground of tetrahedral nature of the spirolinked carbon leading to orthogonality of the ring planes and high level of the carcass rigidity. Such architecture has biomedical consequences and imparts several advantages to the molecule. In particular, its conformational restriction reduces entropy penalty while binding to a protein substrate. Additionally, low number of conformations the molecule can adopt improves its potency and selectivity. Nevertheless, the situation did not (and perhaps could not) change significantly over the last years and the chemists continue producing large amount of relatively 'flat' screening compounds with a high degree of unsaturation for high-throughput screening as well as (hetero)aromatic building blocks for fragment-based drug discovery. The apparent reason behind the "flat inertia" phenomenon dominating in synthetic community is well-developed protocols for the creation of such compounds. On the other hand, despite procedures toward spirocyclic compounds are adequately documented, our

experience proves that the process of their generation still remains a bottleneck within medicinal chemistry programs, especially when it comes to simple low-molecular-weight building blocks.[12] Apparently, this status quo results from existing difficulties in assembly spirocyclic frameworks and the construction of spiro-centers often represents by itself a formidable synthetic challenge. Therefore, the synthetic community has directed their efforts on creating novel practical approaches to reach a variety of spirocyclic topologies and expand achievable chemical space.

In our continuous pursuit of design and synthesis of advanced building blocks for medicinal chemistry needs, we focused on pyrrolidines with a spirocyclic moiety. This direction has a rational ground as derivatives of such building blocks are represented with potent agents demonstrating a wide range of biological effects. Moreover, a number of bioactive natural product families incorporate similar azaspirocyclic ring system, e.g. cephalotaxine, cylindricine A, polycitorol A etc. Our endeavors have led to practical protocols of constructing an impressive series of structurally diverse and functionalized pyrrolidines with a spiro-linkage in α- and β-positions that employ easily available starting compounds and handy procedures (Figure 1, A).[13],[14],[15] A prominent example of pyrrolidine-based compounds is a small though impactful molecule of proline. This proteinogenic amino acid is a unique member of the class being the only one with cyclic structure and secondary α-amino group. The peculiar cyclic structure of proline's side chain provides it an exceptional conformational rigidity that in turn affects the secondary structure of proteins near a proline residue and consequently their physical characteristics and enzymatic activity. In this regard, the outlined structural features predetermined application of proline in numerous MedChem programs, e.g. dealing with creation of peptidomimetics[16] and natural products modification[17,18]. Design and construction of proline analogs is another branch of ongoing investigations that has a purpose of imparting new qualities to proline-containing hybrides, including their enhanced metabolic stability, bioactivity, safety profile etc. For instance, *Liu with co-workers* have recently demonstrated that survival of a proline derived phosphoinositide-3-kinase delta in human liver microsomes improves in more than 4 times when a single methyl group is introduced in the position 5 of the pyrrolidine moiety.[19] In this way, installing a strained spiro conjunction to proline framework may enable the engineering of new generation of proline building blocks with advantageous attributes that would be impossible for flatter monocyclic or condensed proline counterparts. This idea has already been reflected in several MedChem projects initiated by pharmaceutical giants.[20,21] Considering unquestionable utility of spiro prolines, we decided to include them in our in-house research program on construction of enzyme inhibitors. However, while searching for a robust method for the synthesis of new spirocycles, we noticed a surprising 'data vacuum' in this area. Existing strategies did not satisfy our needs and suffered from multistep protocols, low yields and/or loads, narrow scope, or non-practical methodologies. Thereby, as a branch of our "spiro pyrrolidine"

program we have recently elaborated convenient multigram procedures toward spiro prolines featuring 3- and 4-spiro conjunction and utilizing readily available starting compounds (Figure 1, B).[22,23] This work completes review of our achievements in the field and illustrates concise and practical synthetic avenues to 5-spiro fused prolines.

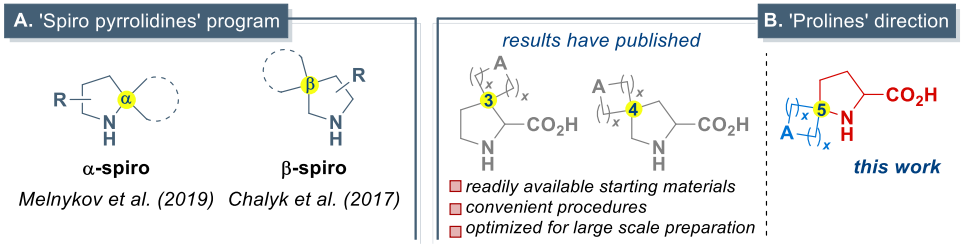


Figure 1. Background of the work

Known rare approaches to assemble the spirocyclic core of 5-spiro proline share similar idea of ring closure *via* nucleophilic attack of NH group and are summarized in Figure 2. The historically first approach was described for the preparation of spiro-cyclohexane linked proline by *Nuhrich et al.* in 1991 (Figure 2, A).[24] It started from methyl cyclohexanecarboxylate and led to the spiro proline *via* a regiospecific 5-*exo*-tet ring closure of the key intermediate *N*-tosyl-oxiranepropylamine. Although, the method opens up an efficient entry to the proline and is expected to find its place in synthetic methodologies, it has obvious weaknesses. The research group of *David W. Knight* made further step on elaborating methods for the construction of the discussed topology.[25,26] Thus, exploiting *G. Stork* procedure for the generation of Δ^4-unsaturated *N*-Ts-protected amino acids,[27] they involved the latter into triflic acid induced 5-*endo*-trig cyclization to give a desired spiro proline (Figure 2, B). The same ring closure can also be accomplished as 5-*endo*-iodocyclisations, though requiring much more time for the reaction to be completed. The method was still tested against cyclohexane derivatives and *sub*-gram quantities of the starting compounds. The following improvement of the acid-catalyzed protocol appeared with the work by *Z. Wang et al*.[28] First, the authors employed a ruthenium-alkylidene-catalysed cross-metathesis reaction to furnish homoallylic precursors, and, second, they expanded the reaction scope to 5- and 7-membered carbospirocycles. Moreover, one should give the research group a credit for high yields and elaboration of a telescopic procedure for the "cross-metathesis/acid-catalyzed cyclisation" sequence. Nonetheless, the reaction scale remained less than 100 mg, and the utilization of the expensive, potentially harmful Ru-containing catalyst reduce MedChem attractiveness of the method at that. Several works coping with the preparation of naturally occurring products (fasicularin, lepadiformine, and histrionicotoxin alkaloids) described preparation of 5-spiroprolines as intermediates to the target compounds.[29,30,31,32] All those strategies are definitely elegant, however, as we believe, impractical.

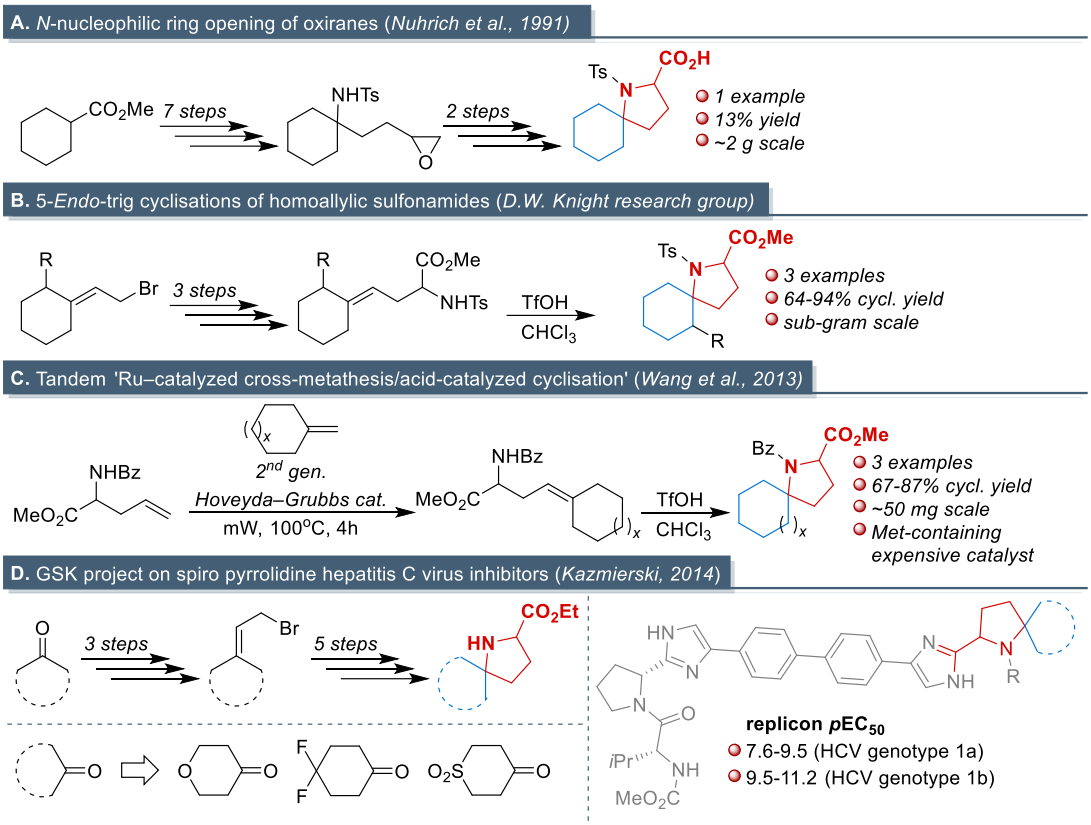


Figure 2. Outline of 5-spiro proline topic

Recent GlaxoSmithKline project on HCV replication inhibitors has revealed novel potent agents with diverse spiro-pyrrolidine motifs.[33] Amazingly, spiro derivatives turned out to be much more potent replication inhibitors than their analog with monocyclic pyrrolidine fragment daclatasvir (sold under the brand name Daklinza®). One group of the identified inhibitors comprised α-spiro pyrrolidine moiety and was obtained from corresponding 5-spiro prolines. The synthesis of the latter mostly relied on the *D. Knight* protocols and commenced from simple cyclic ketones (Figure 2, D). In this regard, the paper extends the number of achievable 5-spiro prolines to heterocyclic and *gem-di*-F-cyclohexane derivatives. Apparently, this finding will breathe new life into 5-spiro prolines as further structure optimization and SAR analysis requires substantial structural variations of the starting prolines and, hence, efficient protocols for their construction.

A modern medicinal chemistry vision claims a crucial role of available building blocks diversity as this is a key element influencing the efficiency of synthesizing a target compound; otherwise, a brilliant molecule can be lost or become less attractive. Furthermore, such a boost to reagent libraries opens up access to new areas of chemical space and reinforce SAR research in truly gigantic contemporary MedChem programs. Thereby, with full comprehension of value and prospects of 5-spiroproline framework and driven by the outlined medicinal chemistry requirements to new molecular entities, herein we report novel concise and practical synthetic

strategies to the molecular platform, which are supported by our previous findings on synthesis of α-spiropyrrolidines[15].

Results and discussion

While planning a synthetic avenue toward new chemical entities, one should keep in mind practicality of the protocol as this attribute plays a vital role in defining the impact of synthesis. Despite the fact that many simple to complex structures are achievable now, in a deep ocean of chemical information, only those protocols 'survive' that can afford a compound of interest in a practical fashion, hence securing easy and quick accessibility of valuable agents for a wide range of scientific and commercial purposes. In this way, organic chemistry history witnessed several milestones, like emergence and development of 'multicomponent reactions' and 'domino reactions' concepts, which brought synthetic methodology to a new level, thus enabling preparation of a synthetic target from simple inexpensive precursors. Unfortunately, these highly efficient approaches are not applicable for some topologies, at least so far. Therefore, one should rely on available starting materials and select those allowing preparation in "*one simple, safe, environmentally acceptable and resource-effective operation that proceeds quickly and in quantitative yield*".[34] Back to the discussed 5-spiro prolines. We did not manage to find suitable methodology matching all our requirements. For this reason, we turned our attention to α-spiropyrrolidines, for preparation of which we worked out efficient multigram procedures utilizing readily available *in bulk* precursors. Close look at those structures reveals the fact that they are possible substrates for the direct carboxylation reaction as the result of activated α-CH bond functionalization of *N*-protected pyrrolidines. This transformation meets all requirements of the above statement, as carbon dioxide is an available, abundant, and renewable C1 resource. Due to many advantages of the method, several strategies for chemical fixation of CO_2 have been reported, including transition-metal-catalyzed and Brønsted-base mediated reactions, light-driven carboxylation, photoredox catalyzed and/or electrochemical transformations.[35,36] Among them, base-promoted carboxylation seems the most attractive to reach highly value-added carboxylic acids as it is environmentally friendly and operationally simple strategy employing low-toxicity bases rather than transition metal containing ligands and other co-catalysts.[37] Thereby, having the synthetic plan to achieve our goal, we next outlined the substrate scope to test viability of the strategy. Besides well-documented cyclohexane derivative, as the research objects we also selected pyrrolidines with small 3- to 5-membered spiro-linked carbocycles as well as *gem-di*-F-cyclohexane and pyrane derivatives (Figure 3). Despite the synthesis of prolines with the last two spirocyclic fragments have been reported in the GSK MedChem project, neither synthetic procedures, nor spectral and physicpochemical data are provided.

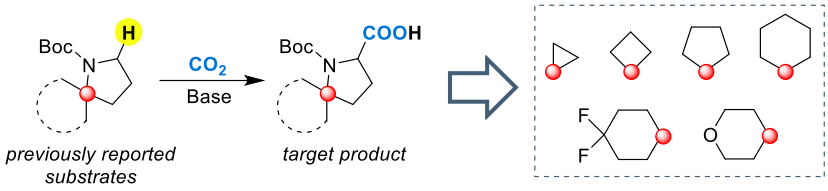


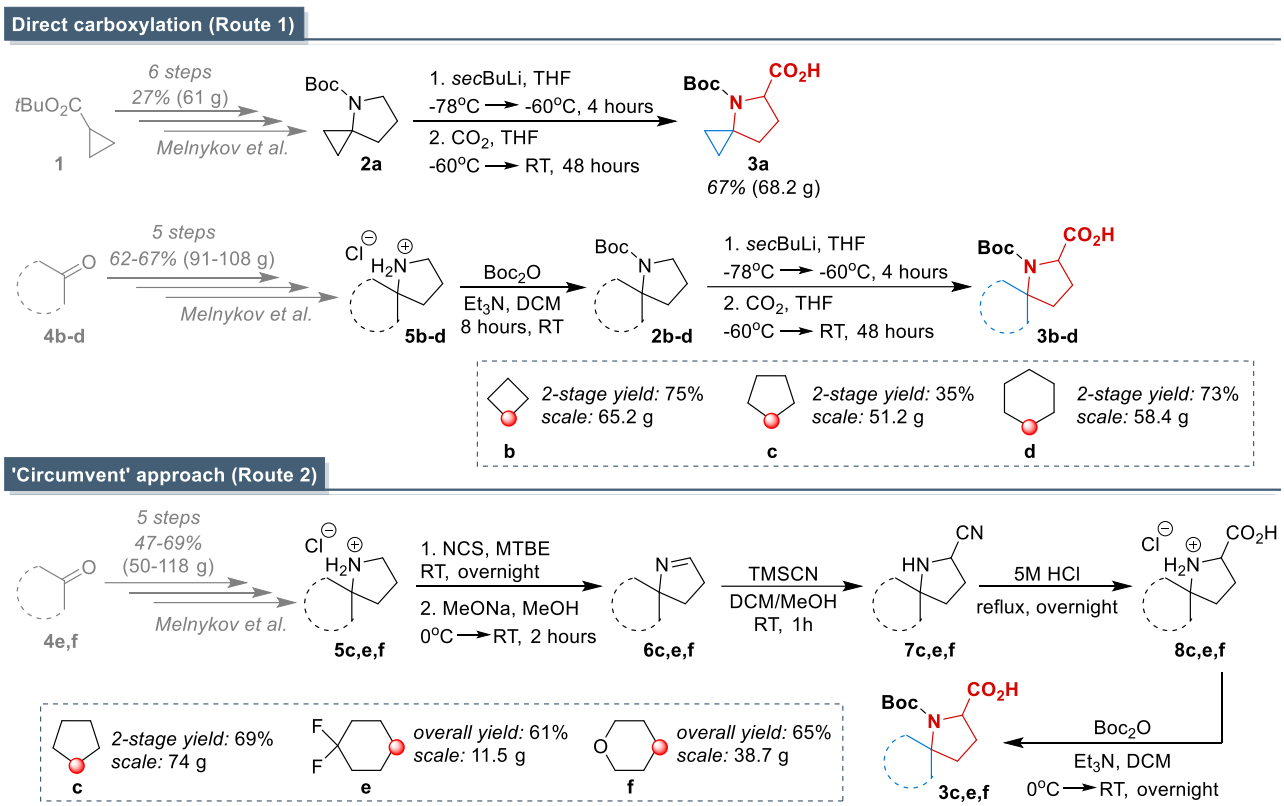
Figure 3. Strategy and the substrate scope

According to the outlined strategy, first step was the search for workable conditions for the carboxylation of the pyrrolidines (Scheme 1, *Route 1*). To this end, several bases, auxiliary complexing agents, reaction times and temperature modes were examined. All the optimization experiments were carried out with cyclopropane derivative **2a**. According to them, the best results we achieved when *sec*BuLi was used as a base and TMEDA as a ligand for Li ions, thus enhancing ability of the base to abstract the C-H proton. In the described protocol, the base acted as a reagent, rather than catalyst, and was used in small 20% excess. Additionally, one should point out that other tested bases used in common laboratory practice, e.g. potassium *tert*-butoxide, LDA, LiTMP, LiHMDS, KHMDS, *n*BuLi, did not give satisfactory outcomes. Moreover, the presence of the ligand is crucial for the reaction success as its exclusion from the protocol resulted in only recovery of the starting material. Overall, the reaction did not require a high pressure of CO_2 gas and proceeded at atmospheric pressure, and completed within 48 hours, as it was determined by LCMS and ^{1}H NMR monitoring of the reaction progress. The one-step protocol furnished the target *N*-Boc-protected spiro proline **3a** in good 69% yield. Remarkably, the interaction was conveniently scaled to multigram amounts without a tangible change in the product yield. In this way, we succeeded to obtain up to 68 g of the azaspiro derivative **3a** in a single run.

The optimized protocol was then applied to the homologous pyrrolidines **5b-d** with 4-, 5-, and 6-membered carbocyclic rings, respectively. Prior to the key carboxylation step, in-ring nitrogen atom was conventionally protected with Boc-group in high yields (compounds **2b-d**). The following functionalization with CO_2 maintained its efficiency in all the cases affording spiro prolines **3b,d** in 73-77% yield. Surprisingly, cyclopentane species **2c** featured moderate yield of the carboxylated product **3c** being 35% with no obvious reason for such behavior. Nevertheless, we believe that this yield is still acceptable for the synthetically appealing direct carboxylation giving straightforward access to the value-added building blocks. In full accordance with project objectives, the 'carboxylation' protocol was reproduced for compounds **3b-d** at more than 50 g scale and with insignificant variation of the above-stated yields (Scheme 1).

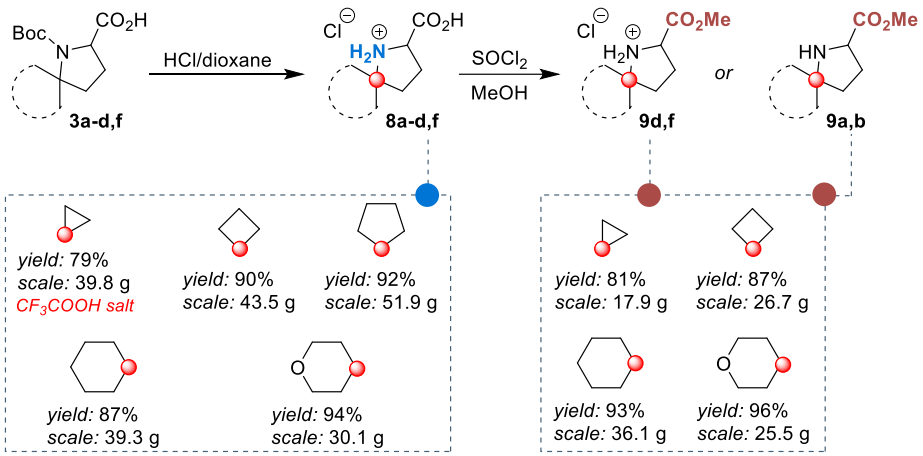
Unfortunately, the straightforward protocol (Scheme 1, *Route 1*) turned out to be fruitless for the substrates bearing difluorocyclohexane (**5e**) and pyrane (**5f**) moieties. In these cases, the carboxylation reaction did not yield the desired prolines, but mixture of several products. Evidently, as follows from HPLC data, the mixture does contain the target carboxylic acids, however their content was too low to

consider subsequent isolation step reasonable. Apparent cause behind the emerged problem is the presence of another acidic center in the molecule of initial pyrrolidines, namely C-H bond adjacent to the oxygen and CF_2 group. Doubtlessly, this ambiguous reactivity has led to the loss of reaction selectivity and, hence to the formation of numerous carboxylated products. All our attempts to make the reaction back on track by means of varying reaction parameters, e.g. time, temperature, and the rate of adding reagents, did not improve the situation significantly. Therefore, we required an alternative synthetic strategy to circumvent the encountered problematic issue. The answer arose from an idea disclosed in our previous work coping with the synthesis of 4-spiro proline topology. In that work installation of the carboxyl function in a ready-made spirocyclic system was realized *via* nucleophilic addition of the cyanide species (in the form of TMSCN or KCN) across endocyclic C=N bond followed by hydrolysis step. In this regard, the generation of corresponding imines **6e,f** from substrates **5e,f** was achieved as 2-step process involving '*N*-chlorination/dehydrochlorination' sequence similarly to a method reported earlier for a proline ester[38]. However, in contrast to the literature method making use of concomitant chlorination and elimination in the presence of NCS/Et_3N setup, compounds **5** required much stronger base to be converted into enamines, presumably as a result of lower acidity of α-proton. The reaction occurred as a one-pot process and led to high yields of imines **6**. The following step of trimethylsilyl cyanide addition proceeded smoothly and took a short time to complete affording nitriles **7**, which were employed in subsequent basic hydrolysis without additional purification. Crude amino acids **8** were purified by means of formation of the target *N*-Boc derivatives **3**. Overall, the alternative route is handy and characterized by quick and convenient transformations, common reagents set, and, as we see, after some optimization can be performed as a through process. Besides that, it is likely to be an excellent method of choice for substrates not applicable to the *Route 1*. Following this stepwise approach spiro prolines **3e,f** were prepared in 61% (11.5 g) and 65% (38.7 g) yields, respectively, starting from hydrochlorides **5**. Considering insufficient yield of cyclopentane containing spiro proline **3c** in *Route 1*, we made the effort to improve it and tested *Route 2* for its relevance to pyrrolidine **5c**. Luckily, the experiment turned out to be productive and allowed to obtain compound **3c** in 69% yield and 74 g scale.



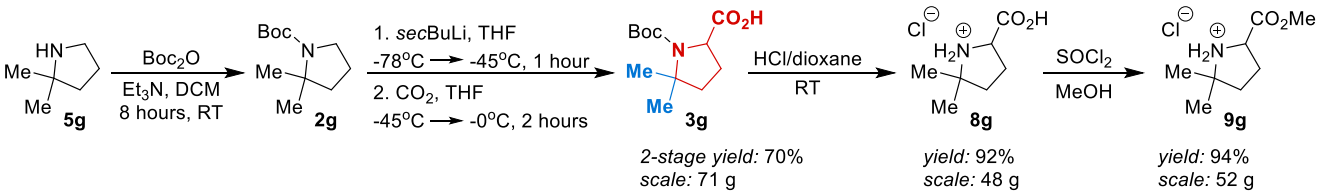
Scheme 1. Approaches to the target 5-spiro proline derivatives

While *N*-Boc protected prolines **3** are well suitable for transformations occurring at COOH function, both unprotected counterparts and especially amino acid esters are convenient for certain types of reactions. In particular, availability of amino acid derivatives with protected *N*- and *C*-sides is crucial for peptide synthesis to efficiently control the direction of peptide chain elongation. Thereby, derivatization of the *N*-Boc amino acids **3** was performed (Scheme 2). Thus, the Boc-group was removed by means of HCl solution in dioxane yielding amino acids hydrochlorides **8**. One should mention that for cyclopropane derivative **8a** trifluoroacetate salt appeared to be more convenient for isolation and handling. The salts were next converted to methyl esters, which were isolated either as hydrochlorides (**9d,f**) or free amines (**9a,b**).



Scheme 2. Synthesis of amino acids hydrochlorides **8** and methyl esters **9**

Installation of a spiro linkage is indeed an efficient way to impart conformational rigidity to proline containing compounds that allows to manage predominating shape of a molecule. In this way, 5,5-dimethylproline, featuring topology close that of spiro analogs, was the first conformationally constrained amino acid with proline backbone exploited to control peptide shape.[39] In particular, its role was the restriction of a peptide group exclusively to the *cis*-conformation, which, in turn, results in a chain reversal, a structural characteristic that is expected to dictate the formation of early folding intermediates and to determine productive protein folding pathways.[40] However, as far as we know, there is no practical access to multigram quantities of 5,5-dimethylproline. Thereby, we decided to test elaborated one-step carboxylation protocol for the preparation of this valuable building block. Multigram access to initial 2,2-dimethylpyrrolidine was achieved as a result of our in-house project, which will be reported in due course. The starting material **5g** was first protected, and *N*-Boc derivative **2g** was then promoted to the carboxylation stage (Scheme 3). Our experiments have demonstrated that the carboxylation reaction proceeded expectedly under previously outlined conditions with formation of the desired 5,5-dimethylproline derivative **3g** in a good yield of 72% even for a large-scale protocol. The product **3g** was modified similarly to the spiro analogs, thus providing amino acid **8g** and methyl ester **9g**. Promising results of the experiment open up great opportunities for the preparation of other 5,5-dialkylprolines, which are currently unknown.



Scheme 3. Synthesis and transformation of 5,5-dimethylproline – a structural mimic of spiro prolines

Conclusions

Currently, synthetic organic chemistry does a great deal of work and it is difficult to find a simple organic compound, which is poorly studied regarding its preparation, chemical properties or is even unknown. As a part of our ongoing investigations on expanding chemical space of medicinally relevant building blocks, we encountered such a problem for 5-spirocyclic prolines. There are a couple of well-reported derivatives and, furthermore, existing procedures are mostly impractical and inappropriate for our purposes. This state of affairs resulted in development of two efficient synthetic approaches commencing from spirocyclic pyrrolidines. The first one is a straightforward base-promoted carboxylation and the second consists of four simple synthetic steps. Carboxylation methodology was optimal for substrates without extra acidic centers in spiro-linked moiety, aside from α-position of the

pyrrolidine ring. Stepwise approach is an excellent option for other spirocyclic pyrrolidines. Realization of both strategies furnished seven *N*-Boc protected spiro prolines as ready-to-use 'bricks' for MedChem purposes with yields 61-77% and at the multigram scale. Additionally, applicability of the carboxylation protocol for the multigram synthesis of 5,5-dimethylproline – a mimic of the spirocyclic analogs – has been demonstrated. Synthetic procedures for conversion of the prepared prolines to the corresponding amino acid hydrochlorides and esters have been communicated as well. Considering accessibility of initial pyrrolidines, as well as the practicality of the elaborated protocols, we surely expect that they will shortly find application in drug discovery projects in both academic institutions and industry.

Experimental part

All starting compounds were obtained from commercial sources and used without additional purification, unless stated otherwise. All solvents were purified according to the standard procedures.

^{1}H NMR spectra were recorded on a Varian Unity Plus 400 (400 MHz) or a Bruker 170 Avance 500 (500 MHz) instrument; ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 (126 MHz) or an Agilent ProPulse 600 (151 MHz) spectrometer. The NMR chemical shifts are referenced using the solvent signals at 7.26 and 77.1 ppm for ^{1}H and ^{13}C nuclei, respectively, in $CDCl_3$, and 2.48 and 39.5 ppm for ^{1}H and ^{13}C nuclei, respectively, in DMSO-d_6. LCMS and GCMS analyses were performed with assistance of an Agilent LC/MSD SL 1100 instrument (atmospheric pressure electrospray ionization (ES-API)) or an Agilent 5890 Series II 5972 GCMS instrument (electron impact (EI) ionization (70eV)), respectively. Results for elemental analysis were obtained at the Analytical Laboratory of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine. A composition of the hydrochloride salts was established by an acid-base titration method. Melting points were determined on an MPA100 OptiMelt automated melting point system.

According to ^{13}C and ^{19}F NMR spectra, *N*-Boc amino acids 3 exist as two major rotameric forms in the solution.

General procedure for the synthesis of *N*-Boc protected pyrrolidines

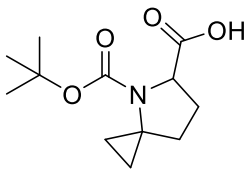
The starting pyrrolidine (1.0 equiv) was placed in a round-bottom flask and dissolved in DCM (~1 mL per 1 mmol of the pyrrolidine). Then triethylamine (1.2 equiv) and Boc_2O (1.1 equiv) were added dropwise to the solution and the mixture was stirred at room temperature for 8 hours. Upon completion, the reaction mixture was washed with water and brine, the organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was then distilled at 1 atm, thus furnishing pure *N*-Boc amine as a pale-yellow oil.

Spectral and physicochemical characteristics of the compounds are in full agreement with the literature data.

The general procedure for the carboxylation of pyrrolidines 2

N-Boc protected pyrrolidine **2** (1.0 equiv) was dissolved in THF (~2.1 mL per 1 mmol of the pyrrolidine) and the solution was added to a three-necked reactor under argon atmosphere. Then TMEDA (1.2 equiv) was added to the reactor and the mixture was cooled to -78°C. After that *sec*-BuLi (1.2 equiv) was added dropwise and the reaction mixture was warmed to -60°C and kept at this temperature for 4 hours. Then the mixture was bubbled with CO_2 for 30 minutes and left at room temperature for 48 hours with stirring. Upon completion, the volatile components were evaporated *in vacuo*, water was added to the residue and the mixture was washed twice with MTBE. The aqueous layer was separated, acidified with aq. $NaHSO_4$, and extracted three times with MTBE. The combined organic phases were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The resulting powder was washed with pentane giving the target proline derivative.

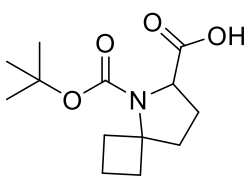
4-(tert-Butoxycarbonyl)-4-azaspiro[2.4]heptane-5-carboxylic acid (**3a**)



Compound **3a** was synthesized from *tert*-butyl 4-azaspiro[2.4]heptane-4-carboxylate (**2a**) (81.3 g, 0.412 mol), TMEDA (57.5 g, 0.494 mol), *sec*-BuLi (353 mL:, 1.4 M in cyclohexane) and THF (900 mL). Proline derivative **3a** was obtained in a yield of 69% (68.2 g, 0.283 mol) as a beige powder.

Mp: 122−124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.49 (s, 1H), 2.19 (s, 3H), 1.82 – 1.36 (m, 12H), 0.51 (dtd, J = 19.7, 10.2, 5.6 Hz, 2H) ppm, CO_2H proton is in exchange. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 80.56, 60.76, 43.29, 34.55, 27.75, 26.27, 9.02, 7.98 ppm. LCMS: $[M - H]^-$ 240.0. Anal. Calcd for $C_{12}H_{19}NO_4$, %: C 59.73, H 7.94, N 5.81. Found, %: C 59.52, H 8.03, N 5.92.

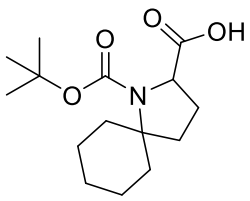
5-(tert-Butoxycarbonyl)-5-azaspiro[3.4]octane-6-carboxylic acid (**3b**)



Compound **3b** was synthesized from *tert*-butyl 5-azaspiro[3.4]octane-5-carboxylate (**2b**) (69.8 g, 0.33 mol), TMEDA (46 g, 0.396 mol), *sec*-BuLi (283 ml, 1.4 M in cyclohexane) and THF (700 mL). Proline derivative **3b** was obtained in a yield of 77% (65.2 g, 0.255 mol) as a yellow powder.

Mp: 116−118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.37 (s, 1H), 4.15 – 4.04 (m, 1H), 3.15 – 2.61 (m, 2H), 2.17 – 1.56 (m, 8H), 1.51 – 1.26 (m, 9H) ppm. $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6): δ 174.71, 174.17, 154.02, 153.10, 79.50, 79.03, 65.18, 63.91, 63.14, 61.18, 38.40, 34.33, 34.18, 32.87, 32.41, 28.57, 28.40, 26.61, 26.22, 13.55, 13.01 ppm. LCMS: $[M - H]^-$ 254.1. Anal. Calcd for $C_{13}H_{21}NO_4$, %: C 61.16, H 8.29, N 5.49. Found, %: C 61.26, H 8.35, N 5.34.

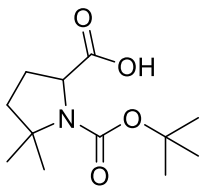
1-(tert-Butoxycarbonyl)-1-azaspiro[4.5]decane-2-carboxylic acid (**3d**)



Compound **3d** was synthesized from *tert*-butyl 1-azaspiro[4.5]decane-1-carboxylate (**2d**) (69.8 g, 0.33 mol), TMEDA (46 g, 0.396 mol), *sec*-BuLi (283 ml, 1.4 M in cyclohexane) and THF (700 mL). Proline derivative **3b** was obtained in a yield of 75% (58.4 g, 0.206 mol) as a yellow crystalline powder.

Mp: 121−123 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.55 – 4.27 (m, 1H), 2.68 – 0.99 (m, 23H) ppm, CO_2H proton is in exchange. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 179.24, 174.86, 156.00, 152.02, 81.27, 79.29, 65.43, 65.30, 60.71, 60.52, 35.72, 34.64, 33.75, 33.64, 32.15, 31.68, 27.98, 27.84, 26.28, 24.85, 24.56, 24.29, 24.13, 24.03, 23.68 ppm. LCMS: $[M - H]^-$ 282.2. Anal. Calcd for $C_{15}H_{25}NO_4$, %: C 63.58, H 8.89, N 4.94. Found, %: C 63.70, H 8.82, N 5.03.

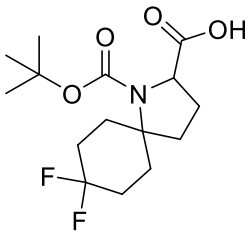
1-(tert-Butoxycarbonyl)-5,5-dimethylpyrrolidine-2-carboxylic acid (**3g**)



Compound **3g** was prepared from *tert*-butyl 2,2-dimethylpyrrolidine-1-carboxylate (81 g, 0.406 mol), TMEDA (56.68 g, 0.487 mol), *sec*-BuLi (348 mL, 1.4 M in cyclohexane) and THF (1 L). Dimethylproline **11a** was obtained in yield of 72% (71 g, 0.29 mol) as a white powder.

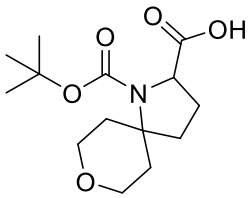
Mp: 75−77 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.47 – 4.25 (m, 1H), 2.29 – 1.69 (m, 4H), 1.58 – 1.23 (m, 15H) ppm, CO_2H proton is in exchange. $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 179.56, 175.51, 156.32, 152.54, 81.49, 79.76, 61.61, 61.46, 61.15, 40.95, 40.01, 28.45, 28.31, 27.58, 26.71, 26.22, 25.96, 25.89, 24.92 ppm. LCMS: $[M - H]^-$ 242.2. Anal. Calcd for $C_{12}H_{21}NO_4$, %: C 59.24, H 8.70, N 5.76. Found, %: C 59.38, H 8.59, N 5.81.

1-(*tert*-Butoxycarbonyl)-8,8-difluoro-1-azaspiro[4.5]decane-2-carboxylic acid (3e)



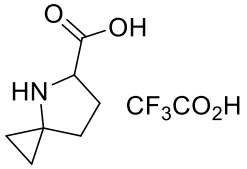
Yield: 11.5 g, 0.036 mol, 61%. Beige powder. Mp: 171−173 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.42 (s, 1H), 4.21 – 4.13 (m, 1H), 2.80 – 2.57 (m, 1H), 2.45 – 2.30 (m, 1H), 2.21 – 1.44 (m, 9H), 1.41 – 1.29 (m, 9H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 174.32, 173.90, 152.94, 151.85, 125.43, 123.52, 121.60, 79.19, 78.66, 63.07, 62.55, 60.79, 60.75, 33.90, 32.99, 31.52-30.87 (m), 29.43, 29.35, 28.50, 28.42, 28.01, 27.96, 27.88, 26.07, 25.54 ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ -91.57 (d, J = 233 Hz), -91.88 (d, J = 233 Hz), -101.11 (d, J = 232 Hz), -102.42 (d, J = 232 Hz) ppm. LCMS: [M - H]$^-$ 318.2. Anal. Calcd for $C_{15}H_{23}F_2NO_4$, %: C 56.42, H 7.26, N 4.39. Found, %: C 56.61, H 7.22, N 4.30.

1-(*tert*-Butoxycarbonyl)-8-oxa-1-azaspiro[4.5]decane-2-carboxylic acid (3f)



Yield: 38.7 g, 0.136 mol, 65%. Yellow crystalline powder. Mp: 71−74 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.57 – 4.33 (m, 1H), 3.95 (dd, J = 11.9, 5.2 Hz, 2H), 3.41 (dt, J = 39.5, 12.3 Hz, 2H), 3.12 – 2.43 (m, 2H), 2.41 – 1.76 (m, 4H), 1.68 – 1.14 (m, 11H) ppm, CO_2H proton is in exchange. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 178.40, 175.15, 155.29, 151.89, 81.60, 79.60, 65.71, 65.56, 62.39, 60.63, 60.40, 36.11, 34.37, 34.19, 33.27, 32.87, 28.02, 27.81, 26.04, 24.38 ppm. LCMS: [M - H]$^-$ 284.2. Anal. Calcd for $C_{14}H_{23}NO_5$, %: C 58.93, H 8.13, N 4.91. Found, %: C 58.80, H 8.20, N 5.05.

4-Azaspiro[2.4]heptane-5-carboxylic acid trifluoroacetate (8a)



4-(*tert*-butoxycarbonyl)-4-azaspiro[2.4]heptane-5-carboxylic acid (**3a**) (68.2 g, 0.283 mol, 1 equiv) was dissolved in DCM and trifluoroacetic acid (322.7 g, 2.83 mol, 10 equiv) was added. The reaction mixture was stirred for 1 hour at room temperature and then evaporated to dryness. The residual solid was washed with

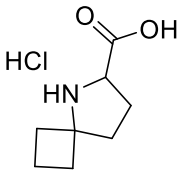
MTBE and dried in air to obtain the title trifluoroacetate as a light-brown powder in 79% yield (39.8 g, 0.224 mol).

Mp: 114−118 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.55 (s, 1H), 4.50 (t, J = 8.2 Hz, 1H), 2.41 (dtd, J = 13.5, 7.9, 5.8 Hz, 1H), 2.21 – 2.07 (m, 1H), 2.04 – 1.89 (m, 2H), 1.21 – 1.11 (m, 1H), 1.11 – 1.03 (m, 1H), 0.88 – 0.75 (m, 2H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 170.17, 59.36, 42.54, 30.10, 27.41, 9.28, 9.13 ppm. LCMS: $[M - CF_3CO_2]^+$ 142.0. Anal. Calcd for $C_9H_{12}F_3NO_4$, %: C 42.36, H 4.74, N 5.49. Found, %: C 42.27, H 4.79, N 5.59.

General procedure for removing *N*-Boc protecting group

Corresponding *N*-Boc protected carboxylic acid **3** was dissolved in a small amount of dioxane and then 3-fold excess of 4M HCl solution in dioxane was added. The mixture was left to stir for 8 hours at room temperature. Upon completion, MTBE was added and the mixture was stirred for 10 min. The precipitate formed was filtered off, washed with MTBE and dried in air providing the title salt as a white powder in 90% yield (43.5 g, 0.227 mol).

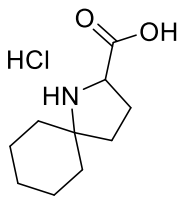
5-Azaspiro[3.4]octane-6-carboxylic acid hydrochloride (**8b**)



The title compound was obtained from 5-(*tert*-butoxycarbonyl)-5-azaspiro[3.4]octane-6-carboxylic acid (**3b**) (65.2 g, 0.255 mol) following the general procedure as a white powder in 90% yield (43.5 g, 0.227 mol).

Mp: 177−180 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.92 (s, 1H), 10.40 (s, 1H), 8.91 (s, 1H), 4.27 (t, J = 8.2 Hz, 1H), 2.58 – 2.52 (m, 1H), 2.48 – 2.42 (m, 1H), 2.40 – 2.26 (m, 1H), 2.12 – 1.89 (m, 5H), 1.88 – 1.72 (m, 2H) ppm. ^{13}C{^{1}H} NMR (126 MHz,DMSO-d_6): δ 170.48, 65.74, 56.99, 34.10, 30.82, 29.91, 25.96, 13.98 ppm. LCMS: $[M - Cl]^+$ 156.4. Anal. Calcd for $C_8H_{14}ClNO_2$, %: C 50.14, H 7.36, N 7.31. Found, %: C 50.01, H 7.43, N 7.27.

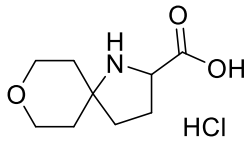
1-Azaspiro[4.5]decane-2-carboxylic acid hydrochloride (**8d**)



The title compound was obtained from 1-(*tert*-butoxycarbonyl)-1-azaspiro[4.5]decane-2-carboxylic acid (**3d**) (58.2 g, 0.205 mol) according to the general procedure as a beige powder in 87% yield (39.3 g, 0.179 mol).

Mp: 170–173 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.86 (s, 1H), 8.48 (s, 1H), 4.46 – 4.37 (m, 1H), 2.32 (dtd, J = 13.8, 8.6, 5.2 Hz, 1H), 2.07 (dq, J = 13.1, 8.0 Hz, 1H), 1.92 – 1.59 (m, 8H), 1.53 – 1.44 (m, 1H), 1.37 – 1.25 (m, 2H), 1.24 – 1.14 (m, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 171.00, 68.53, 57.70, 33.73, 33.62, 33.13, 26.67, 25.02, 22.85, 22.82 ppm. LCMS: [M - Cl]$^{+}$ 184.2. Anal. Calcd for $C_{10}H_{18}ClNO_2$, %: C 54.67, H 8.26, N 6.38. Found, %: C 54.81, H 8.19, N 6.31.

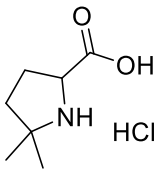
8-Oxa-1-azaspiro[4.5]decane-2-carboxylic acid hydrochloride (**8f**)



The title compound was obtained from 1-(*tert*-butoxycarbonyl)-8-oxa-1-azaspiro[4.5]decane-2-carboxylic acid (**3f**) (41.2 g, 0.144 mol) according to the general procedure as a light-brown powder in 94% yield (30.1 g, 0.136 mol).

Mp: 181–184 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.93 (s, 1H), 10.03 (s, 1H), 8.75 (s, 1H), 4.45 (s, 1H), 3.85 – 3.75 (m, 2H), 3.39 (q, J = 10.9 Hz, 2H), 2.42 – 2.31 (m, 1H), 2.17 – 2.06 (m, 1H), 2.04 – 1.83 (m, 4H), 1.73 (t, J = 13.8 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 170.33, 65.41, 63.68, 63.64, 56.99, 33.53, 33.41, 32.05, 25.94 ppm. LCMS: [M - Cl]$^{+}$ 186.2. Anal. Calcd for $C_9H_{16}ClNO_3$, %: C 48.76, H 7.28, N 6.32. Found, %: C 48.60, H 7.32, N 6.41.

5,5-Dimethylpyrrolidine-2-carboxylic acid hydrochloride (**8g**)



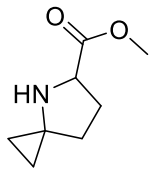
The title compound was obtained from 5-(*tert*-butoxycarbonyl)-5,5-dimethylpyrolidine-2-carboxylic acid (**3g**) (71.0 g, 0.292 mol)following the general procedure as a yellow crystalline powder in 92% yield (48 g, 0.267 mol).

Mp: 170–174 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.99 (s, 1H), 10.02 (s, 1H), 8.53 (s, 1H), 4.45 (t, J = 8.1 Hz, 1H), 2.44 – 2.30 (m, 1H), 2.12 (dq, J = 13.3, 8.3 Hz, 1H), 1.89 – 1.73 (m, 2H), 1.39 (s, 3H), 1.33 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 170.54, 64.80, 57.50, 36.72, 26.28, 24.41, 24.31 ppm. LCMS: [M - Cl]$^{+}$ 144.2. Anal. Calcd for $C_7H_{14}ClNO_2$, %: C 46.80, H 7.86, N 7.80. Found, %: C 46.89, H 7.81, N 7.90.

General procedure for the preparation of methyl esters 9

Thionyl chloride (0.18 mL per 1 mmol of the substrate) was added dropwise slowly into a mixture of the corresponding proline and anhydrous methanol (~1 mL per 1 mmol of the substrate) with vigorous stirring at 0°C. Then the mixture was stirred overnight at room temperature. The excess methanol and thionyl chloride was removed under reduced pressure affording the desired ester hydrochlorides **9d,f,g**. To obtain compounds **9a,b** the residue was dissolved in minimal amount of $CHCl_3$, cooled down to 0°C and triethylamine (1.0 equiv) was added. After the solid was filtered off, and the filtrate was concentrated under reduced pressure. Distillation under vacuum provided the target methyl esters **9a,b**.

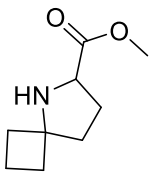
Methyl 4-azaspiro[2.4]heptane-5-carboxylate (**9a**)



The title compound was obtained following the general procedure from 4-azaspiro[2.4]heptane-5-carboxylic acid trifluoroacetate (**8a**) (36.4 g, 0.142 mol) as a colorless liquid in 81% yield (17.9 g, 0.115 mol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (t, J = 7.5 Hz, 1H), 3.81 – 3.70 (m, 3H), 2.44 (s, 1H), 2.40 – 2.26 (m, 1H), 2.10 – 1.97 (m, 1H), 1.88 – 1.77 (m, 1H), 1.73 – 1.62 (m, 1H), 0.86 – 0.76 (m, 1H), 0.71 – 0.55 (m, 2H), 0.50 – 0.40 (m, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.80, 59.54, 51.60, 42.40, 32.79, 31.11, 13.04, 9.92. ppm. LCMS: [M + H]$^+$ 156.2. Anal. Calcd for $C_8H_{13}NO_2$, %: C 61.91, H 8.44, N 9.03. Found, %: C 61.86, H 8.48, N 9.09.

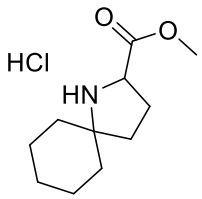
Methyl 5-azaspiro[3.4]octane-6-carboxylate (**9b**)



The title compound was obtained following the general procedure from 5-azaspiro[3.4]octane-6-carboxylic acid hydrochloride (**8b**) (34.7 g, 0.181 mol) as a colorless liquid in 87% yield (26.7 g, 0.158 mol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 – 3.78 (m, 1H), 3.72 (s, 3H), 2.35 (s, 1H), 2.24 – 2.04 (m, 3H), 2.03 – 1.95 (m, 2H), 1.94 – 1.79 (m, 3H), 1.76 – 1.57 (m, 2H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 175.51, 64.02, 58.36, 51.55, 36.35, 36.26, 35.59, 28.43, 13.20 ppm. GCMS: [M]$^{+\bullet}$ 169, [M – $C_3H_5NO_2$]$^{+\bullet}$ 82 (100%). Anal. Calcd for $C_9H_{15}NO_2$, %: C 63.88, H 8.93, N 8.28. Found, %: C 63.98, H 9.01, N 8.15.

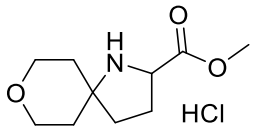
Methyl 1-azaspiro[4.5]decane-2-carboxylate hydrochloride (**9d**)



The title compound was obtained following the general procedure from 1-azaspiro[4.5]decane-2-carboxylic acid hydrochloride (**8d**) (36.5 g, 0.167 mol) as a beige powder in 93% yield (36.1 g, 0.155 mol).

Mp: 136−139 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.94 (s, 1H), 8.82 (s, 1H), 4.53 (s, 1H), 3.75 (s, 3H), 2.34 – 2.28 (m, 1H), 2.17 – 2.06 (m, 1H), 1.93 – 1.82 (m, 2H), 1.77 – 1.59 (m, 6H), 1.52 – 1.46 (m, 1H), 1.34 – 1.27 (m, 2H), 1.24 – 1.16 (m, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 169.28, 68.11, 56.81, 52.93, 33.08, 32.99, 32.36, 25.76, 24.49, 22.36, 22.25 ppm. LCMS: $[M - Cl]^+$ 198.1. Anal. Calcd for $C_{11}H_{20}ClNO_2$, %: C 56.53, H 8.63, N 5.99. Found, %: C 56.70, H 8.55, N 5.90.

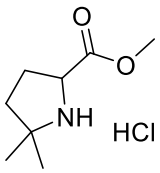
Methyl 8-oxa-1-azaspiro[4.5]decane-2-carboxylate hydrochloride (**9f**)



The title compound was obtained following the general procedure from 8-oxa-1-azaspiro[4.5]decane-2-carboxylic acid hydrochloride (**8f**) (25.1 g, 0.114 mol) as a beige powder in 96% yield (25.5 g, 0.109 mol).

Mp: 171−175 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.24 (s, 1H), 9.11 (s, 1H), 4.55 (t, J = 7.3 Hz, 1H), 3.86 – 3.77 (m, 2H), 3.75 (s, 3H), 3.44 – 3.34 (m, 3H), 2.42 – 2.31 (m, 1H), 2.21 – 2.10 (m, 1H), 2.05 – 1.85 (m, 4H), 1.79 – 1.69 (m, 2H) ppm. ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 169.65, 65.99, 64.19, 64.11, 57.12, 53.43, 33.99, 33.71, 32.29, 26.05 ppm. LCMS: $[M - Cl]^+$ 200.2. Anal. Calcd for $C_{10}H_{18}ClNO_3$, %: C 50.96, H 7.70, N 5.94. Found, %: C 51.04, H 7.75, N 5.81.

Methyl 5,5-dimethylpyrrolidine-2-carboxylate hydrochloride (**9g**)



The title compound was obtained following the general procedure from *5*,5-dimethylpyrrolidine-2-carboxylic acid hydrochloride (**8g**) (51.2 g, 0.286 mol) as a yellow powder in 94% yield (52.0 g, 0.269 mol).

Mp: 139−141 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.14 (s, 1H), 8.97 (s, 1H), 4.56 (t, J = 8.8 Hz, 1H), 3.76 (s, 3H), 2.43 – 2.30 (m, 1H), 2.16 (dq, J = 13.2, 8.2 Hz, 1H), 1.91 – 1.74 (m, 2H), 1.39 (s, 3H), 1.34 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ

169.33, 64.91, 57.12, 52.94, 36.51, 25.82, 24.24, 24.24 ppm. LCMS: $[M - Cl]^+$ 158.2. Anal. Calcd for $C_8H_{16}ClNO_2$, %: C 49.61, H 8.33, N 7.23. Found, %: C 49.70, H 8.29, N 7.15.

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