Multigram Synthesis of 4,4-disubstituted-3-oxopyrrolidones – efficient starting material for diverse 3 functionalized pyrrolidones

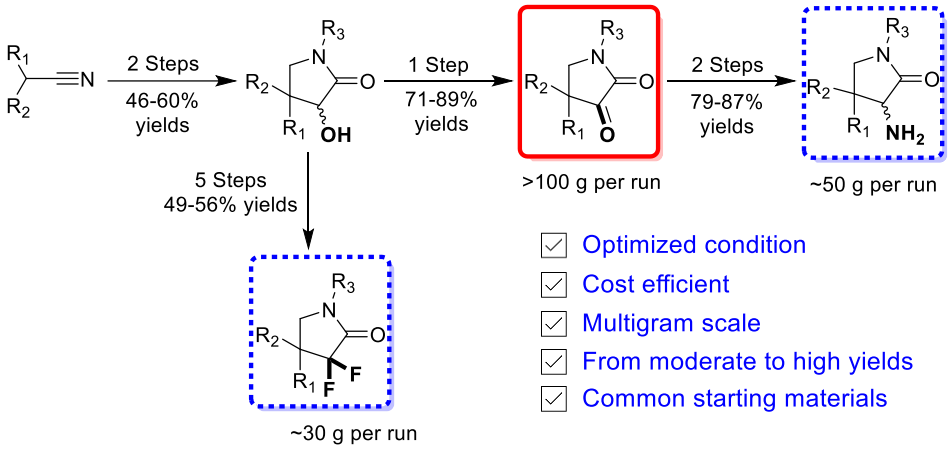
Semen S. Bondarenko[a,b], Anatolii M. Fedorchenko[a], Pavlo O. Novosolov[a,b], Oleksandr V. Marchenko[a,b], Anton I. Hanopolskyi[b,c], Yulian M. Volovenko[b], Dmytro M. Volochnyuk[a,b,d], Serhiy V. Ryabukhin*[a,b,d]

[a] *Enamine Ltd, 78 Winston Churchill str., 02660 Kyiv, Ukraine*

[b] *Taras Shevchenko National University of Kyiv, 60 Volodymyrska str., 01033 Kyiv, Ukraine*

[c] *Preci LLC, 9 Amosova Street, 03038 Kyiv, Ukraine*

[d] *Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Academik Kukhar street 5, 02660 Kyiv, Ukraine*



Abstract:

The practical rapid development of chemical leads for drug discovery is strongly dependent on scalable procedures for building block synthesis. N-heterocyclic moieties, especially unsaturated ones, remain essential tools in the hands of screening and medicinal chemists. Here, we report four novel chemical block families and the interconversions between them. 4,4-disubstituted-3-oxopyrrolidones synthesis was an essential milestone in the diversity-oriented production of 3-aminopyrrolidones, 3-hydroxypyrrolidones and 3,3'-difluoropyrrolidines. Those can be functionalized with conformationally flexible spirocyclic substituents. We developed the multigram procedure for 4,4-disubstituted-3-oxopyrrolidones from commercially accessible and cost-saving reagents via the short three-step procedure. Also, here we are reporting the robust conversion procedure of 3-oxopyrrolidones to 3-aminopyrrolidones, 3,3'-difluoropyrrolidones and 3-hydroxypyrrolidones, involving a minimal amount of steps. We demonstrate the scope and limitations and further perspectives for such synthetic approaches.

Keywords: pyrrolidone derivatives, 3-oxopyrrolydones, 3-aminopyrrolidones, 3,3'-difluoropyrrolidines, building blocks.

Introduction:

The development of diversity-oriented organic synthesis crucially impacts modern drug development. The building block approach in combinational chemistry is the leading method to

achieve library diversity rapidly[1]. Exploration of different building blocks helps to identify the promising blocks and to determine the route for further screening[2]. Different block-design strategies constantly highlight some new potent compounds for medicinal chemistry research[3,4]. Analysis of modern screening reagents motivates the empirical chemical space exploration of low Fsp^3, low molecular weight (M<200), 3D shaped or chiral compounds[3].

More than 75% of recent drug candidates contain at least one N-heterocycle[5]. A lot of papers are devoted to produce N-heterocycles or to optimize their synthesis[6–8]. Nonplanar, nonaromatic molecules are currently attracting huge attention in drug development. The flexibility of those blocks allows them to adapt more easily to complex binding sites[9]. Among others, spirocyclic blocks become abundant in the drug scaffolds[10]. They have higher affinity to the three-dimensional binding site of the target and secure the functionality of the ligand inside the protein[11]. The conformational freedom of such building blocks decreases the sterical constraint of the protein-ligand complex and decreases the binding free energy. The molecules of interest for medicinal chemistry often involve the N-heterocycles as a part of the spirocyclic system[12]. One of the earliest examples is the anti-psychotic, fluspirilene, which contains 1,3,8-triazaspiro[4.5]decan-4-one block[13]. Pirrolidine-containing sitafloxacine (Garcevit) is a promising antibiotic and another instance of the utility of the spirocyclic scaffold[14]. Recently, we reported novel effective approaches for the synthesis of spirocyclic pyrrolidines[15].

Pyrrolidones are well-represented in the pharmaceutical industry and in natural products. Among the most famous, anti-epileptics are levitiracetam, piracetam and its derivatives, phenylpiracetam and carbacetam[16]. Lactacystine, a pyrrolidone-containing natural product from the *Streptomyces* bacteria is known for its antineoplastic activity[17]. Another compound, Ceftobiprole, is a β-lactam antibiotic containing 3-substituted pyrrolidone[18].

However, there are no effective procedures for the preparative production of 3-oxopyrrolidones, and disubstituted in the 4-position derivatives are extremely rare in the literature. Those compounds can enlarge the chemical space significantly via the multiple ways for their modification and structural interchanges (Figure 1b). Keto-moiety in α-position to amide results in opportunities for racemic or enantioselective reduction, amination and difluoration. Thus, a number of new chemical blocks are made available immediately from the scalable precursor.

This work expands the opportunity for the synthesis of substituted 2,3-diketopyrrolidines and 2-pyrrolidone-3-amines. Those scaffolds are still underrepresented in industrial chemicals and modern drug research. Ranirestat (AS-3201, Dainippon Sumitomo Pharma)[19] and isatin dyes drivatives[20] contain the pyrrolidone ring in their structure. Zhu et al exploited α-oxo-γ-butyrolactam as a precursor for the synthesis of indoloquinolizidines[21]. Southwick and Crouch reported an approach to the production of N-substituted 3-oxopyrrolidones. Their synthesis involved the reaction of β-alanine methyl ester and dimethyloxalate. Further decarboxylation produced 3-oxopyrrolidones[22]. Later, Sundberg investigated the possibility to attach the removable benzyl or Boc substituent to Nitrogen. This procedure afforded pyrrolidine-2,3-dione after the deprotection[23]. Unfortunately, this method cannot be applied to synthesize 4-substituted analogues of those compounds. Here, we describe the straightforward and cost-effective procedure for the diversity-oriented synthesis of these compounds. Moreover, this method enables the synthesis of pyrrolidone-based spyrocyclic compounds.

This work also expands the knowledge about the conversion of 3-oxo-pyrrolidones to 3-amino-pyrrolidones. Previously, compounds of such a type were synthesized through the cyclization of α,γ-diamino-n-butyric acid and its esters in various acidic conditions[24]. Later, Font-Bardia et al developed a procedure that allows the production of enantiopure 3-amino-4,4-dimethylpyrrolidin-2-one, starting from 3-hydroxy-4,4-dimethyldihydrofuran-2(3H)-one. The procedure involves the generation of N-substituted 3-oxo-pyrrolidone after the oxidation. Then this compound undergoes the imine condensation, followed by the reduction[25]. Here, we improved the scope of those groups of compounds as well. We believe that the new procedure will become a useful aid for the incorporation of new heterocyclic compounds into drug research as potent building blocks.

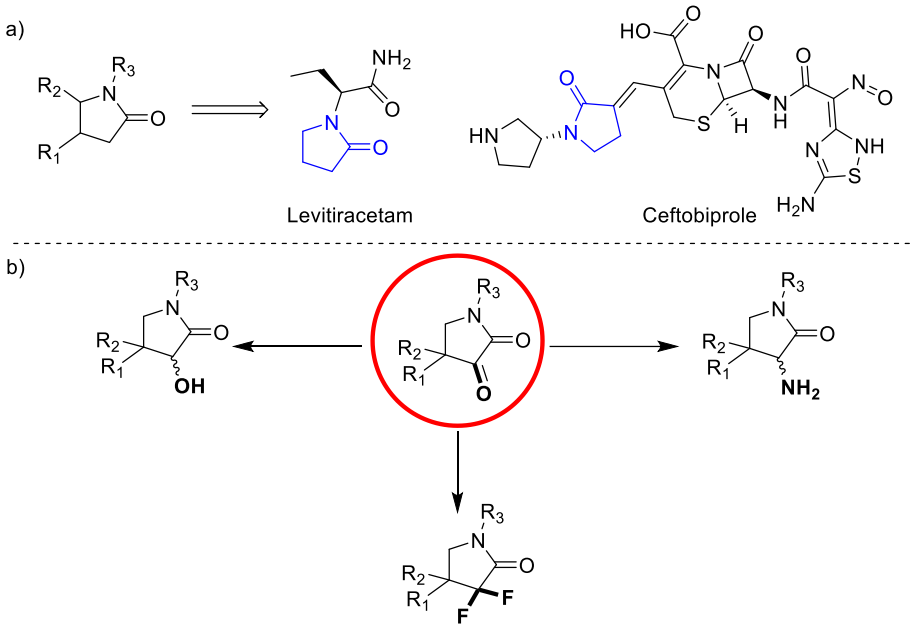


Figure 1. a) Common molecules, containing pyrrolidone structures in the scaffold, b) possible structural scaffolds from 4,4-disubstituted 3-oxopyrrolidone available via the proposed procedure.

Results and Discussion

After the retrosynthetic analysis of the potential approaches to 3-oxopyrrolidones we decided to follow Sunberg's chemical logic (Figure 2a)[22,23]. For optimal derivatisation positions 2,3 and 4,5 should come from different substrates in aldol condensation-type of the reactions. In such a case, potential substituents in positions 4 and 5 will depend on the synthon.

As for the synthon for the positions 2 and 3, we selected ethyl glyoxylate. In contrast to Crouch-Sundberg's dimethyl oxalate-based procedure, our approach guarantees higher efficiency of condensation with a broader range of substrates. We evaluated the use of a technical grade commercial form of ethyl glyoxylate for the gram scale aldol condensation step. We saw little difference between freshly distilled compound and commercial form. Thus, all of the procedures in this work are described for the technical ethyl glyoxylate.

The opposite of synthon in our approach is alpha-functionalized nitrile. The combination of long shelf-life time and controllable reactivity makes nitriles optimal substrates for the development of wide-scope procedures (Figure 2b).

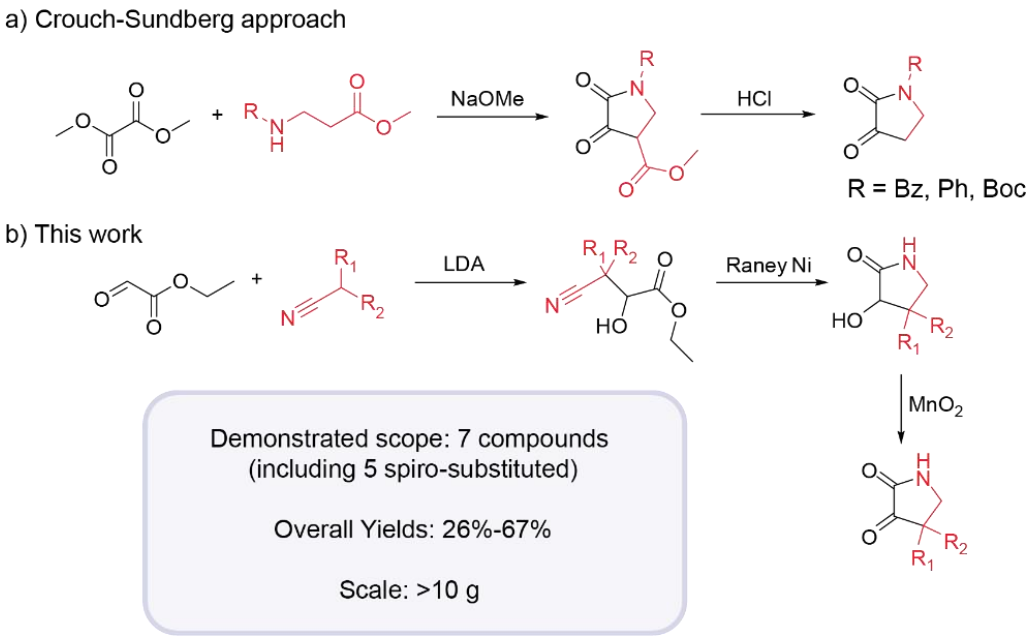


Figure 2. Comparison of earlier approach to 3-oxopyrrolidone and the approach highlighted in the current work

To our surprise, neither acetonitrile nor propionitrile provided a noticeable yield of condensation adducts. Whereas, isobutyronitrile resulted in a 64% yield. The lower acidity of primary and secondary α-nitriles probably restricts the 1,2-addition to ethyl 2-oxoacetate. The row of tertiary α-nitriles provided acceptable yields in this step. Following the limitations of this step, we concentrated our attention on the work with spiro-functionalized and 4,4-disubstituted derivatives.

Reactions with primary and secondary alpha-nitriles produce complex unresolvable mixtures of products. We did not manage to find our product in these mixtures. We hypothesize that the presence of hydrogen in the alpha-position to amine allows dehydration products to form, which later polymerize. This might be supported by the finding that altering the nature of the substituent in the alpha-position to nitrile does not change the course of the reaction. In the situation where R1=R2=(not)-H, the product of the aldol condensation forms with >50% yield. Neither of the products **5a-c** were formed under those conditions (Figure 3b)

Following the formation of 1,2-adduct nitrile, we searched for the procedure of selective reduction of nitrile with the subsequent or simultaneous cyclizations. Our in-house experience suggested that Raney-Nickel-catalyzed hydrogenation may be optimal for this reduction. Raney Nickel-catalyzed hydrogenation of nitriles is known for its selectivity towards other reducible groups. We tuned the conditions for this reaction towards 60 atm and 50 ºC. This reaction simultaneous ring closure with amide formation with >85% yield on all the compounds in the scope.

An additional step needs to be applied to convert 3-hydroxypyrrolidin-2-one cycle into pyrrolidine-2,3-dione. The most applicable oxidant in our hands for such oxidation appeared to be MnO_2.

The current sequence was validated on the compound **5e** (Figure 3c). This three-step procedure can be scaled up on >30 gram, whereas overall yields observed on the general scope of this reaction is higher than 26% on the worst example.

Products **5e-k** were successfully formed under current conditions. We additionally purified intermediates of the aldol condensations, using flash chromatography. The rest of the steps did not require any additional purification. The final product was recrystallized.

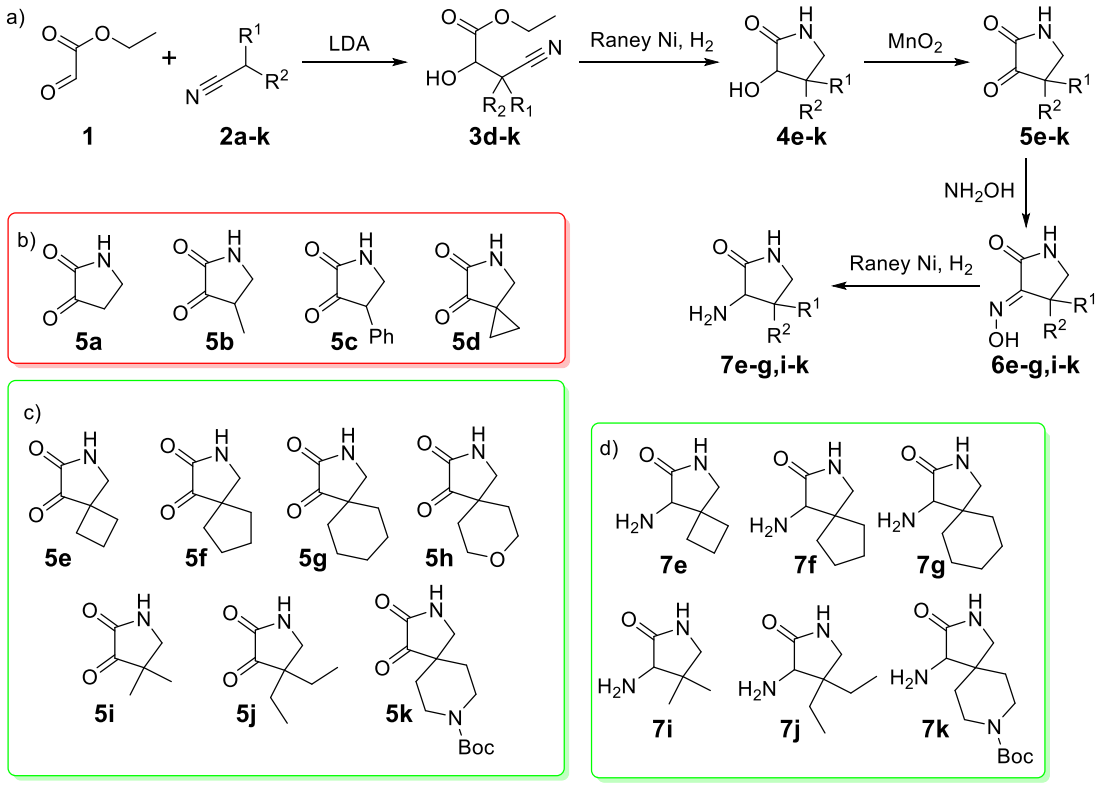


Figure 3. a) Shortened description of the procedure for the synthesis of 3-oxopyrrolidones and its conversion into 3-aminopyrrolidones, b) unsuccessful scope of the sequence (a), c) successful scope of the sequence (a), d) examples of successful aminations of the products (c).

Unfortunately, product **5d**, containing a cyclopropyl ring was not available, despite our efforts. The problems occurred on the hydrogenation step. Probably, ring-opening by 4-position can happen under the hydrogenation condition.

3-oxopyrrolidones are essential intermediates in the synthesis of 3-aminopyrrolidones. These blocks are highly drug-like since their scaffold contains the α-aminoamide group. Thus, their synthesis is important for building block libraries enrichment.

The keto-group in the compound **5e-g,i-k** is susceptible to oxime formation using hydroxylamine condensation. Those oximes could be easily reduced by Raney Nickel to form compounds **7e-g,i-k** (Figure 3d). We trust that the modification of compound **5h** is similar to those, presented in the current manuscript.

Other important derivations of 3-oxopyrrolidones are difluorination products of the ketones. When pre-formed 3-hydroxypyrrolidone **4f** was subjected to the $LiAlH_4$ reduction alcohol **8f** was formed (Figure 4). We decided to proceed with the Swern oxidation to achieve the ketone for the following difluorination. Unfortunately, Swern oxidation is intolerant towards amines. We introduced Boc protection on amine to avoid side-reactions that can block targeted sequences. Product **9f** then can be successfully oxidized to compound **10f.** This product might be difluorinated to form the product **11f.**

Swern reaction and following DAST difluorination yielded 91% and 87% yields, respectively. Formed protected product **11f** can be cleaved with strong acid as HCl in dioxane to form the final product **12f** as a hydrochloride in near quantitative yield. Only column chromatography separation in this route is required for compound **11f**. Other intermediates were used as crude. The target compound **12f** was obtained in 56% the total yield starting from alcohol **4f**.

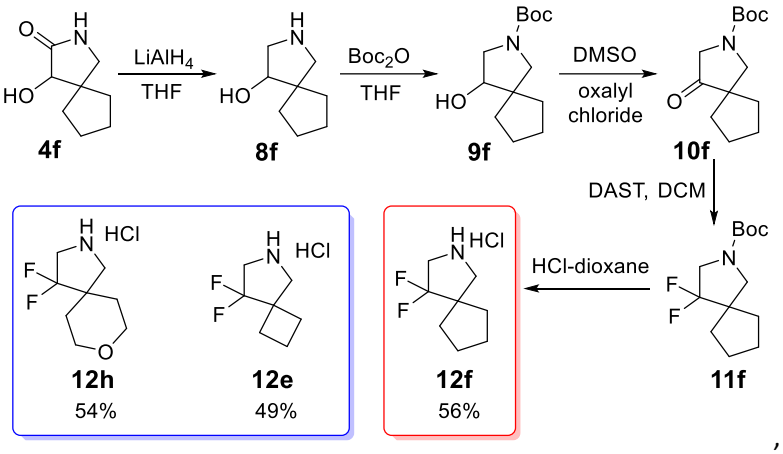


Figure 4. The approach for the preparation of difluoroderivatized pyrrolidines **12f, 12e** and **12h.**

This synthetic approach was also implemented for the synthesis of compounds **12e** and **12h.** Those products were obtained in 49% and 54% total yields as hydrochlorides respectively. The active amine group in those compounds can be immediately incorporated into the more complex scaffolds.

Conclusions

Earlier approaches to the 2,3-dioxopyrrolidines were inefficient from the point of substrate variety. For those reasons, seeking strategies to increase the available chemical space, we developed the procedure, based on aldol condensation with nitriles and the following hydrogenation-cyclization. The demonstrated scope of this procedure was a set of compounds, all of which are R1=R2≠H products. The initial aldol condensation procedure has not yielded acceptable yields with primary or secondary-substitute α-carbon. Nevertheless, this procedure was applicable towards the synthesis of products **5e-k**. Those are essential intermediates for the α-aminoamide cyclic building blocks **7e-g,i-k**. Those products can also be converted to 3,3'-difluoro-derived pyrrolidines **12e,f,h** with the selective substitution of ketone with DAST (Figure 4). All those blocks can be readily incorporated into the more complex scaffolds, using nucleophilic amino- or electrophilic keto-groups. We believe this procedure will result in applicable chemical moieties for future medicinal chemistry efforts and combinatorial screening.

ASSOCIATED CONTENT

Details of experiments and syntheses; spectral and analytical data for the synthesized compounds; copies of NMR spectra. This material is available free of charge via the Internet at.

AUTHOR INFORMATION

Corresponding Authors

Sergey V. Ryabukhin s.v.ryabukhin@gmail.com; s.ryabukhin@enamine.net

ORCID: 0000-0003-4281-8268.

Author Contributions

All authors have given approval to the final version of the manuscript.

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