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STRUCTURE OF AZAHETEROCYCLES OF THE PIPERIDINE-2,4-DIONE TYPE AND THEIR USE AS DRUGS

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Abstract: A current review summarizes recent results in the synthesis of piperidine-based azaheterocycles of the piperidine-2,4-diones type. For simple and efficient preparation of heterogeneous compounds in racemic and enantiopure forms, both traditional (change of carbonyl compounds) and new (rearrangement of anion enolate) addition methods are available. Due to their unique structure and related reactivity profile, dione-type molecules are a convenient modern platform for the construction of piperidine-type functional systems with high synthetic and medicinal properties. This potential is successfully implemented in the creation of highly biologically active pharmaceutical compounds and synthesis of natural products.

Keywords: Piperidine, carbonyl-compounds, pharmaceutical compounds, molecule, condensation

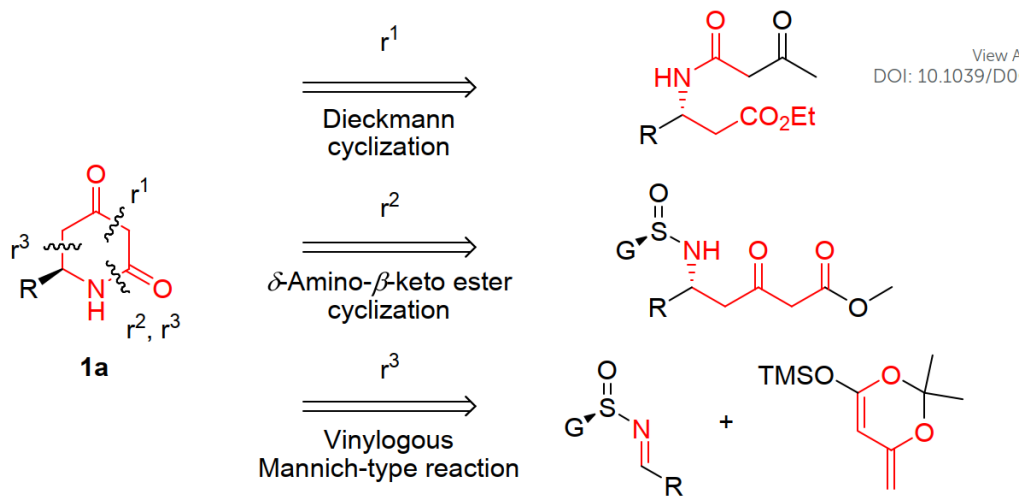
Introduction.

Azaheterocyclic systems provide the basis for the development of a variety of useful compounds and materials.[1] Among the numerous heterocyclic systems, piperidines occupy a privileged place, since they predominate in structures of natural products and medicinal substances.[2] Their carbonyl derivatives are also structural fragments of many natural products and synthetic molecules with a wide spectrum of biological activity. A large number of publications, including several reviews, have been devoted to the methods of construction of piperidine-2-ones and quinoline-2,4-diones.[3] In contrast, the piperidine-2,4-dione (1a) and 6- amino-2,3-dihydro-4-pyridin(thi)ones (1b,c) syntheses have not been reviewed up to date. Due to tautomerism, structures of these molecules are ambiguous and exist in equilibrium of tautomeric forms (I-IV) (Scheme 1). Preference for one form or another strongly depends on the nature of substituents in the heterocycle. Synthetically almost all positions of the piperidine ring can be useful. The reactivity of both carbonyls and methylene groups in the molecule are essentially different and therefore they can be selectively modified. Moreover 6-substituted 1a and 2-substituted 1b,c heterocycles are of particular interest. They possess configurationally stable chiral centers, that makes them an attractive object for preparation of chiral pharmaceutically relevant compounds. Other chiral centers in the ring are not so stable (except quaternary centers) and can be epimerized during the synthesis. Given the significance of these carbonyl compounds, an overview of the synthetic routes towards the piperidinone scaffold would be of great interest to the field.

Results and discussion.

Methods for synthesis of 1a using carbonyl compounds. There are several common approaches leading to formation of 1a (Scheme 1) such as Dieckmann condensation (r1), δ-amino-β-ketoester cyclization (r2) and vinylogous Mannich-type

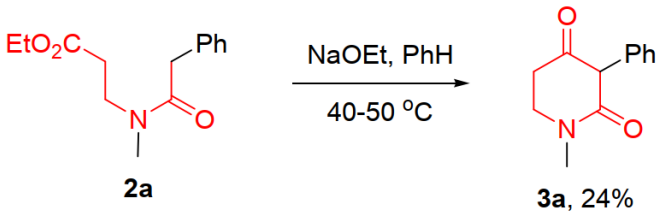
reaction (r3). All of these routes are reliable and effective and are used with different success in asymmetric synthesis of diones 1a.



Scheme 1. Common approaches for construction of 6-substituted piperidine-2,4-diones 1a

Dieckmann condensation is the most general method for construction of 1a; it consists

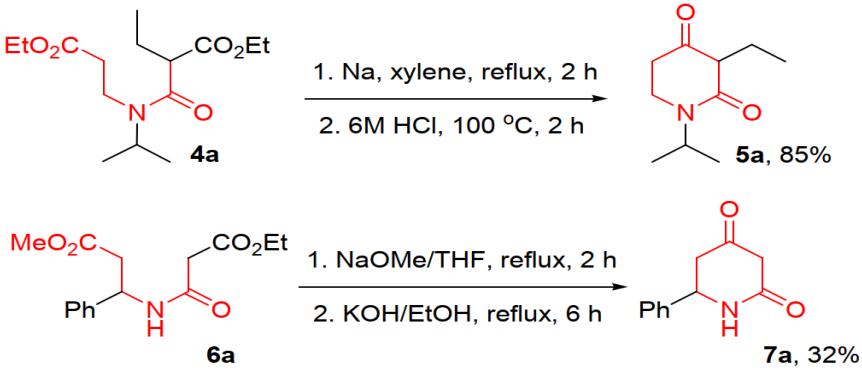
in various kinds of cyclization of β-amino acids (Scheme 2).[4] In 1963, Hohenlohe-Oehringen et al.[5] were the first to report the condensation of ester 2a into dione 3a (24%) (Scheme 2). The modest yield of 3a was connected with side reactions - intermolecular condensation and retro- Michael elimination, arising from deprotonation of similary acidic CH-groups both in ester and amide fragments.



Scheme 2. The first example of the Dieckmann cyclization in synthesis of 3a

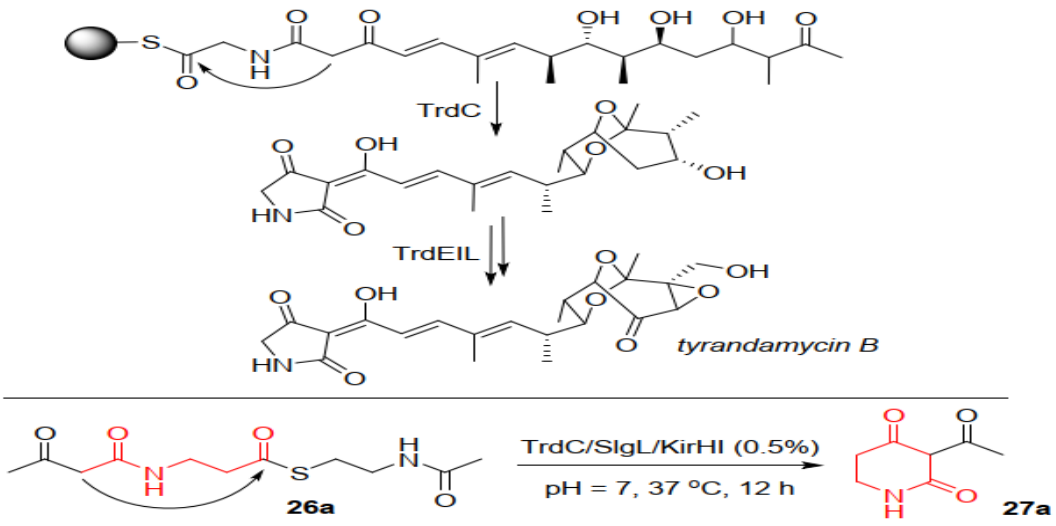
In subsequent studies in 1989 and 1991, it was found that the use of more acidic malonic acid amide 4a can significantly increase the yield of cyclization product 5a (85%),[6] and even unsubstituted NH-derivatives such as 6a can produce diones type

7a (32%)[7] (Scheme 3), although in these cases an extra stage of carboxyl group removal is required.



Scheme 3. Use of malonic acid derivatives in Dieckmann cyclization

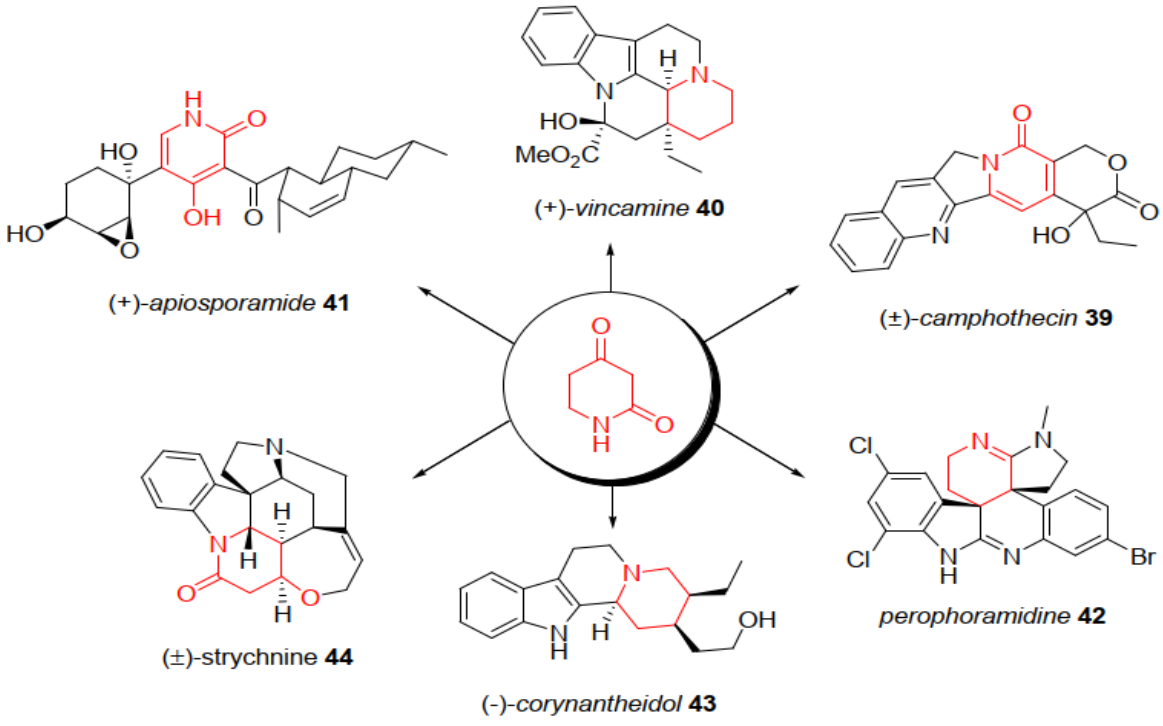
In 2015, Ju et al.[17] discovered a new family of Dieckmann cyclases that provide biosynthesis of actinomycete-derived compounds containing pyrrolidine- and piperidine-2,4- dione scaffolds, such as tyrandamycin B (TrdC enzyme), kirromycin (KirHI enzyme) and streptolidigin (SlgL enzyme) (Scheme 4). The authors[17] found that TrdC-, KirHI- and FacHI- catalyzed transformations of thioether 26a to dione 27a can be carried out in vitro for 12 hours at 37 °C in neutral medium



Scheme 4. Biosynthetic Dieckmann cyclization

Almost all of these biologically active compounds mentioned above were synthesizeddirectly from piperidine-2,4-diones. The easiness of its functionalization in different position of the cycle makes the dione's core an attractive object for synthetic transformations.[8]

The last feature enables to use piperidine-2,4-diones as building blocks in total syntheses of natural products such as (±)-camptothecin 39,[9] (+)-vincamine 40,[10] (+)-apiosporamide 41,[11] RS-15385[11] (Scheme 5). The formal syntheses of allopumiliotoxin[12] and emetine[8c] were carried out as well. Approaches have been developed to create skeletons of such alkaloids as perophoramidine 42,[13] (-)-corynantheidol 43,[14] citrinadin B,[15] thebaine analogue,[16] 2,4- dioxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine,[17] (±)-strychnine 44.[17]



Scheme 5. Application of piperidine-2,4-dione scaffold in syntheses of natural products Such a variety of natural products and biologically active molecules among the

piperidine-2,4-dione derivatives speaks of the importance of developing approaches to the synthesis of this framework.

Conclusions

Piperidine-2,4-diones and their derivatives – 6-amino-2,3-dihydro-4-pyridin(thi)ones are valuable building blocks possessing high synthetic and medicinal potential. Different reactivity of the reactive centers allows the selective functionalization of the piperidine ring, that makes these molecules a convenient platform for construction of functionalized piperidine-type systems. There are several convenient preparative methods providing an access to racemic or enantiomerically enriched keto-derivatives. Traditional synthetic approaches to diversely

decorated dione's scaffold (e.g. Dieckmann cyclization and δ-amino-β-ketoestor condensation have been employed for many years, but these can be low yielding and limited by reactive dicarbonyl-containing intermediates. Therefore, an effective and general complementary approach based on transformation of alkenyl and alkynyl amines via enolate rearrangements was developed. Significant biological activity of piperidine-2,4-diones has been reported, varying from antimicrobial properties to the inhibition of proliferation. 6-Amino-2,3-dihydro-4- pyridin(thi)ones represent prospective but an underexplored class of compounds, because of limited access to this type of molecules. We hope that this literature overview will stimulate the exploration of new synthetic avenues towards novel piperidine-based functionalized molecules.

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