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Directed diversity-oriented synthesis. Ring-fused 5- to 10-membered rings from a common peptidomimetic 2-pyridone precursor

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ABSTRACT

A variety of ring-fused 2-pyridone-based central fragments were prepared using a strategy inspired by diversity-oriented synthesis. The produced compounds are diverse, yet focused, analogs of biologically active peptidomimetic 2-pyridones.

2-Pyridones are privileged structures in medicinal chemistry,[1] and many biologically active ring-fused 2-pyridones exist, for example, the natural product derived anti-cancer drug, topotecan,[2] and the acetylcholinesterase inhibitor, huperzine A.[3] The ring-fused 2-pyridones **1** and **2** (Fig. 1) belong to a class of compounds designed as peptidomimetics.[4] This type of thiazolo ring-fused 2-pyridone has various biological effects depending on their substitution pattern, for example, as antibacterials—targeting bacterial virulence,[5,6] and as modulators of the fibrillation of amyloid proteins, such as Alzheimer β-peptides[7] and the Parkinson's associated α-synuclein.[8] Previous synthetic efforts to improve, or to alter the biological activity of these compounds have focused on variation of the substituents[9] as well as changes of the central fragment itself.[10,11] Here, we report the synthesis of a series of central fragment analogs of compounds **1** and **2** using a strategy inspired by the concepts of diversity-oriented synthesis (DOS).[12,13]

The aim with DOS is to prepare compound collections with widely diverse central fragments to find biologically active substances without having a pre-determined target.[14] Considering the diverse biological activities of the thiazolo ring-fused 2-pyridones, we believe that further exploration of the chemical space around this class will generate many new compounds that are active in a variety of biological assays. In efforts toward this goal, we have developed a strategy involving directed diversity-oriented synthesis, where the produced compounds are relatively close to compounds **1** and **2** in the chemical space, but still considerably more varied than what is usually achieved by substituent variation. Inspired by the use of a 2-fluorobenzene sulfonyl chloride as a two-sited electrophile in the preparation of a DOS-library,[15] compound **3** was prepared in analogy with previously prepared compounds,[16,17] and then formylated[18] to give compound **4**, which contains two different electrophilic sites (Scheme 1). This key starting material allowed the synthesis of compounds with large variations of the left-hand side of the peptidomimetic 2-pyridone by orthogonally reacting the two electrophilic groups to form various ring-structures.

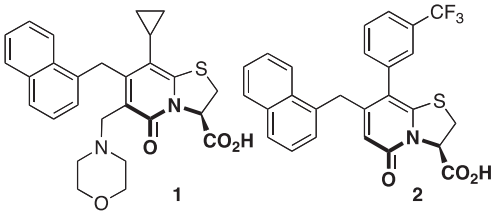

Figure 1. Biologically active thiazolo ring-fused 2-pyridones with peptidomimetic backbones (highlighted).

To start with, two new heteroaromatic scaffolds were prepared. Heteroaromatics are often easily functionalized and give rigid compounds, which can be beneficial for biological activity.[19] Ring-fused pyrroles have been prepared from other compounds with two electrophilic sites,[20,21] and reaction of **4** with primary amines under basic conditions gave the pyrroles **5** and **6** (Scheme 2A).

The corresponding ring-fused thiophene **7** was obtained by reaction with potassium thioacetate followed by cleavage of the

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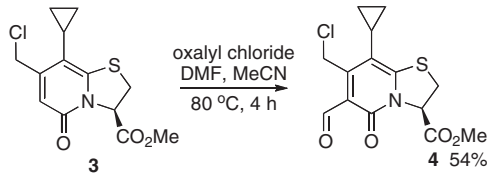
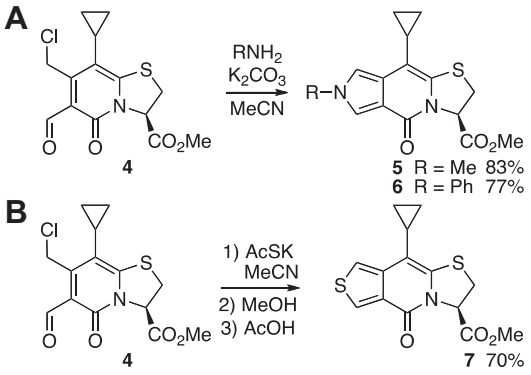
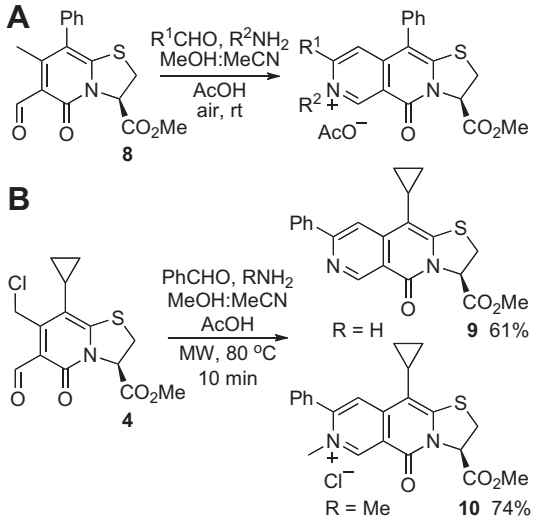


Scheme 1. Preparation of a 2-pyridone with two electrophilic sites.



Scheme 2. Ring-fused five-membered heteroaromatics.



Scheme 3. Improved syntheses of naphthyridones and naphthyridonium salts.

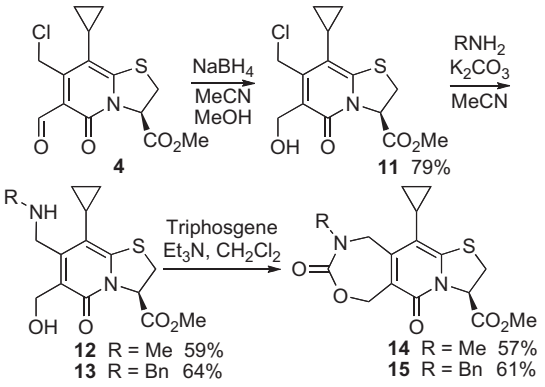
acetyl group and dehydration in a one-pot procedure (Scheme 2B). The use of sodium sulfide instead of potassium thioacetate gave significant amounts of a dimeric compound (according to LC–MS).

We previously described a three-component reaction that produced dihydronaphthyridones from methyl and formyl substituted 2-pyridones such as **8**. Subsequent oxidation with air, or more generally, with chloranil, gave naphthyridones and naphthyridonium salts (Scheme 3A).[22] Compound **4** participated in similar reactions when reacted with aldehydes and amines under mildly acidic conditions (Scheme 3B). The naphthyridone **9** and the naphthyridonium salt **10** were formed without the need of an extra oxidation step, thus providing a more straightforward route to these types of compounds.

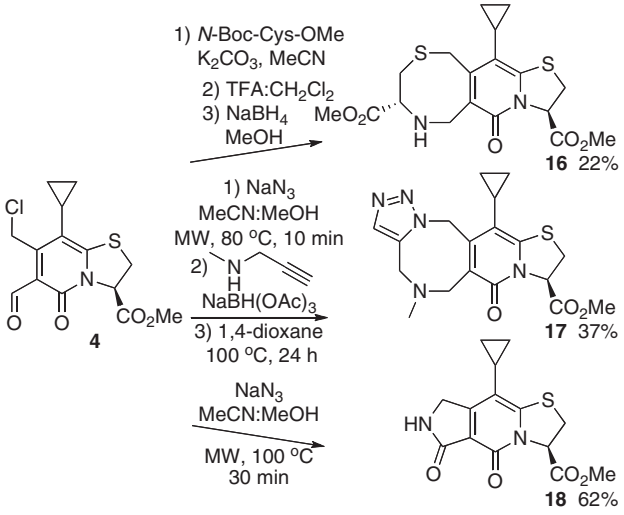
Although new heteroaromatic scaffolds are valuable in medicinal chemistry,[23] compounds with a higher proportion of sp^3-carbons and stereochemical complexity often interact more specifically with proteins.[24] A higher proportion of saturated carbons also decreases structural planarity, which typically improves aqueous solubility.[25] By preparing medium-sized rings with saturated carbons, less planar compounds with restricted flexibility were created. To synthesize the seven-membered carbamates **14** and **15**, compound **4** was reduced to the alcohol **11**, reacted with an amine, and then ring-closed with triphosgene ($Cl_3COCOOCCl_3$) (Scheme 4).

Two compounds containing eight-membered rings were synthesized by nucleophilic substitution of the chloride followed by reductive amination of the aldehyde (Scheme 5). Thus, Boc-protected cysteine methyl ester was reacted with **4** and then deprotected with trifluoroacetic acid. Ring-closure to compound **16** was accomplished with sodium borohydride in methanol. The use of non-protected cysteine gave several by-products. Triazole **17** was prepared by displacement of the chloride with sodium azide followed by reductive amination with *N*-methyl propargylamine. A thermal intramolecular Huisgen cyclization[26,27] then gave the ring-closed product **17**. During the first step in the synthesis of **17**, small amounts of the ring-fused pyrrolidone **18** were formed. This type of transformation usually requires acidic conditions and is then regarded an intramolecular Schmidt rearrangement,[28] but in our case acid did not promote the formation of **18**. However, it was found that slightly elevated temperatures and longer reaction times increased the amount of this product and allowed its isolation in 62% yield.

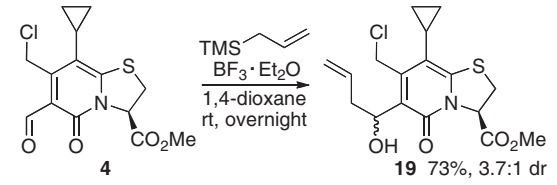
We planned to prepare a nine-membered ring system by ring-closing metathesis.[29] To introduce the alkenes for the metathesis,



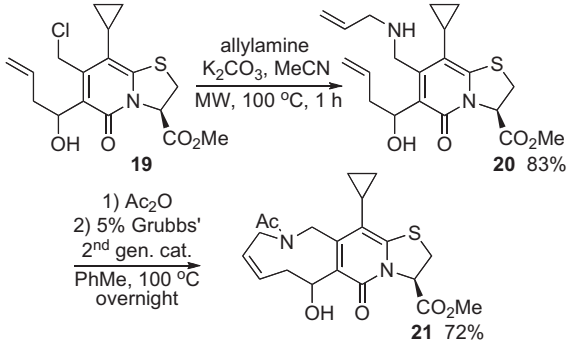
Scheme 4. Synthesis of seven-membered carbamates.



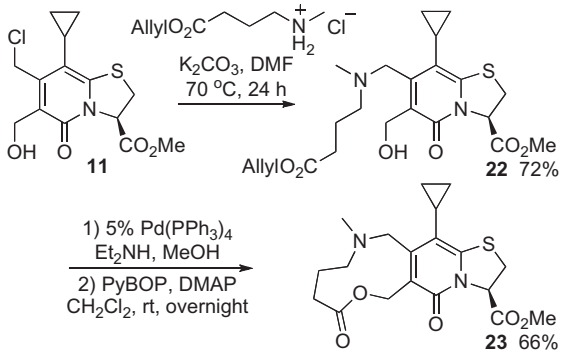
Scheme 5. Synthesis of eight-membered rings and a pyrrolidone ring-fused compound.



Scheme 6. Hosomi-Sakurai allylation of **4**.



Scheme 7. Ring-closing metathesis provided compound **21**.



Scheme 8. Lactonization into a 10-membered ring.

compound **4** was first allylated with allyltrimethylsilane.[30] Different conditions for the allylation were evaluated, and the best results were accomplished in 1,4-dioxane with $BF_3 \cdot Et_2O$ as the acid (Scheme 6). After purification, a 3.7:1 diastereomeric mixture of **19** was obtained in 73% yield (2.5:1 dr before purification). A lower diastereomeric ratio (1.8:1) was obtained in dichloromethane, and with $SnCl_4$ as the Lewis acid the diastereoselectivity inverted to give a 1:2.2 mixture.

Next, compound **19** was reacted with allylamine to introduce the second alkene needed for the metathesis. The resulting amine **20** was then *N*-acylated, and the ring-closing metathesis was realized by the use of Grubbs' second generation catalyst[31] in toluene (20 mM) to give **21** in 72% yield (Scheme 7).

For the 10-membered case, we considered a lactone ring-closure. Although medium-sized lactones are often difficult to prepare because of competing formation of dimeric species,[32] substrates with rigidifying elements such as *Z*-double bonds can give efficient reactions.[33] The 10-membered lactone **23** was prepared from the alcohol **11**, which was first reacted with the allyl ester of *N*-methyl-γ-aminobutyric acid to give **22**. This product was then subjected to palladium-catalyzed deallylation, followed by lactonization to give **23** using PyBOP as the coupling reagent[34] (Scheme 8). The ring-closure proceeded well using modest dilute conditions (50 mM) without the need for slow addition of the substrate.

In conclusion, we have applied a strategy of directed diversity-oriented synthesis to prepare a series of 5- to 10-membered ring-fused structural peptidomimetics starting from a chloromethyl and formylated compound. This type of two-sited electrophile can potentially be used to construct a wide range of ring-fused heterocycles. The compounds produced here are diverse analogs of biologically active 2-pyridones that will be evaluated in a variety of biological assays in the near future.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedure and spectral data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.100.

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