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Synthesis of a Novel Tricyclic Peptidomimetic Scaffold

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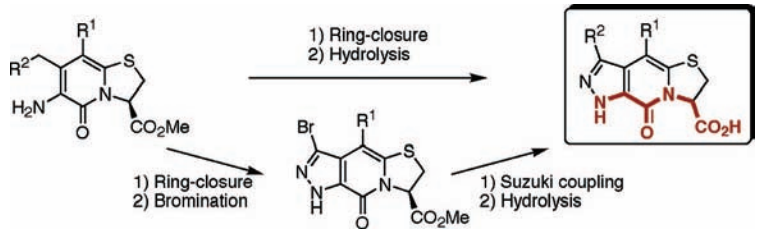
ABSTRACT



An efficient method to synthesize a novel rigid tricyclic peptidomimetic scaffold through ring-closure of amino-functionalized bicyclic 2-pyridones has been discovered. The scaffold can function as a peptide backbone mimetic (highlighted) with two substituents independently variable to fine-tune biological response. Halogenation of the pyrazolo ring followed by Suzuki couplings made it possible to introduce substituents with variable electronic properties late in the synthetic route, which is preferable in library synthesis.

Small molecules designed to mimic the behavior of peptides, i.e., peptidomimetics, are interesting as drug candidates. Peptidomimetics can offer improved pharmacological properties compared to peptides by introduction of conformational restrains and replacement of metabolically sensitive groups.[1] We have previously described bicyclic 2-pyridone **1** (Figure 1) that is active as a novel type of antibacterial agent, targeting virulence.[2] Similar heterocyclic systems have been used as peptidomimetics active, as e.g., human rhinovirus (HRV) 3C protease inhibitors[3] (compound **2**) and hepatitis C virus (HCV) NS3 protease inhibitors.[4]

Here, we report the synthesis of a novel ring-fused pyrazole-2-pyridone−thiazoline scaffold. Biologically active ring-fused pyrazole-2-pyridones have previously been reported. For instance, **3** (Figure 1) intercalates DNA[5] and inhibits proliferation of human pulmonary carcinoma cells and **4** functions as a benzodiazepine receptor inhibitor.[6] Our new scaffold constitutes a rigid peptide backbone mimetic.

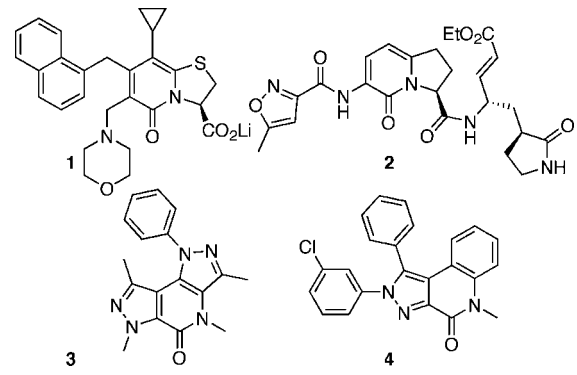


Figure 1. Examples of biologically active ring-fused 2-pyridones.

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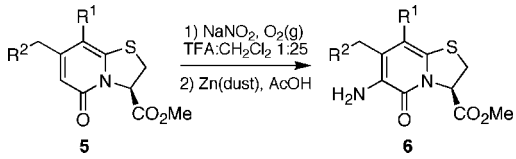
Rigidity is often beneficial for drug potency, as long as the bioactive conformation is still adaptable.[7] A recent study indicates that rigidity might be important for activity also for our antibacterial compounds.[8]

Ring-fused 2-pyridones **5** (Table 1) are easily prepared from acyl Meldrum's acid derivatives and thiazolines,[9] and we have previously described the synthesis of amino-functionalized bicyclic 2-pyridone **6a**.[10]

We found that attempted Sandmeyer reactions on **6** resulted in ring-closure to form pyrazoles. Diazomethyl quinolinones have previously been thermally converted to ring-fused pyrazole−quinolinones. It is noteworthy, however, that attempted ring-closure of 1-methyl-4-diazomethyl-2-pyridone failed under the same conditions.[11] Electron-deficient 2-methylaniline derivatives efficiently form indazoles when treated with aqueous $NaNO_2$ in acetic acid.[12] Under similar conditions, we successfully converted aminopyridones **6** into a novel heterocyclic scaffold (Table 2).

Table 1. Synthesis of Amino-Functionalized Pyridones

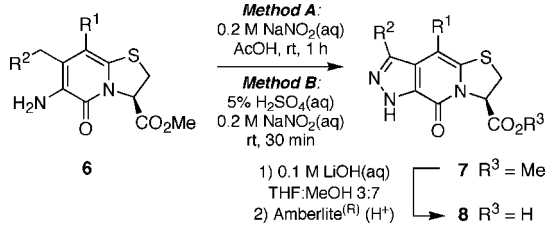


5 **6**

entry	R^1	R^2	product	yield[a] (%)
1	cyclopropyl	1-naphthyl	**6a**	75
2	Ph	H	**6b**	71
3	Ph	isobutyl	**6c**	67

[a] Isolated yields (%).

Table 2. Formation of Ring-Fused Pyrazoles



6

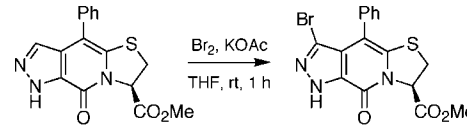
				yield[a] method			
entry	R^1	R^2	product	A	B	product	yield[a] (%)
1	cyclopropyl	1-naphthyl	**7a**	61	46/82[b]	**8a**	94
2	Ph	H	**7b**	31	85	**8b**	95
3	Ph	isobutyl	**7c**	54	61	**8c**	97

[a] Isolated yields (%). [b] THF used as cosolvent.

Both aliphatic and aromatic R^2 groups were well tolerated, but for R^2 = H the yield dropped significantly (31%), possibly due both to nitrosation and dimerization of the pyrazole as indicated by LC−MS. Dimerization has previously been reported during formation of other ring-fused pyrazoles by reaction of the pyrazole derivative with intermediate diazonium salt.[13] Fortunately, performing the reaction in aqueous sulfuric acid instead of acetic acid significantly increased the yield of the desired product. To achieve high yields of **7a**, addition of THF to improve solubility was necessary. The methyl esters **7** were subsequently hydrolyzed to reveal the peptidomimetic scaffold **8** in excellent yields (94−97%).

With the improved synthesis of **7b** in hand, a way of introducing new substitiuents in the pyrazole ring by bromination followed by Suzuki couplings was in sight. This allows introduction of new R^2 substitiuents, including electron-rich substituents incompatible with the nitration step in synthesis of **6** (Table 1). It also introduces a late diversification point in the synthetic route, which is important in library synthesis. Bromination was accomplished by treatment of **7b** with bromine in the presence of potassium acetate as acid scavenger (Scheme 1).

Scheme 1. Bromination of the Ring-Fused Pyrazole **7b**



7b **9** (83%)

Suzuki couplings of ring-fused thiazolo-2-pyridones have proven difficult, but the use of S-Phos[14] and $Pd(OAc)_2$ in THF have previously been successful.[15] Unfortunately, applying these conditions did not result in any conversion of **9**.

Unprotected ring-fused pyrazoles have been subjected to Suzuki couplings using $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ in dioxane with phosphate base and microwave heating.[16] Utilizing these conditions, coupling of **9** with phenylboronic acid was observed. However, the coupling was sluggish with significant precipitation of palladium black. When 10 mol % of

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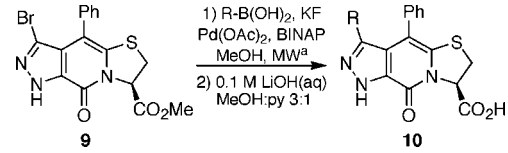
palladium was used, only 25% coupling product was isolated. The use of 20 mol % of palladium resulted in approximately 60% conversion according to crude ^{1}H NMR. Pd(dppf)-Cl_2•CH_2Cl_2 could be exchanged for $Pd(OAc)_2$ and BINAP with similar results. Turning to the more heat-stable Herrmann catalyst[17] did not give any conversion of starting material. Instead, a range of different solvents was tested together with $Pd(OAc)_2$ and BINAP as catalysts. The use of DMF and acetonitrile resulted in mixtures of methylated products as indicated by LC−MS, presumably via deprotonation and nucleofilic attack of the pyrazole on the solvent. In acetone very low conversion was detected, and in formamide almost exclusive dehalogenation of **9** to give **7b** was observed. Methanol proved to be a good choice of solvent with good conversion of starting material. Competing dehalogenation was detected as well as hydrolysis of the methyl ester. The latter was avoided by the use of potassium fluoride as a boronic acid activator[18] rather than phosphate, carbonate, or hydroxide bases. Using these conditions, electron-rich, electron-poor, and heteroaromatic boronic acids were coupled (Table 3). Even the sterically demanding *ortho*-tolylboronic acid could be coupled; however, prolonged reaction time was needed for full conversion. The coupled products were directly hydrolyzed before reversed-phase HPLC purification.

In conclusion, we have shown that ring-fused pyrazole-2-pyridone scaffolds can be made by diazotation of amino-functionalized 2-pyridones, resulting in a novel rigid peptidomimetic scaffold. This new scaffold could be further functionalized through Suzuki couplings with both heteroaryls and aryls with different electronic and steric properties. The resulting molecules are rigid, substituted heterocyclic structures with potential to function as peptidomimetics. By changing the substitution pattern this scaffold has potential to target a variety of biological systems.

Table 3. Suzuki Couplings[a]



9 **10**

entry	R	product	yield[b] (%)
1	Ph	**10a**	61
2	4-MeOPh	**10b**	55
3	3-NO_2Ph	**10c**	37
4	3-furyl	**10d**	53
5	2-MePh	**10e**	32[c]

[a] 2.0 equiv of boronic acid, 10 mol % of $Pd(OAc)_2$, heated for 3 min at 50 °C and then 20 min at 140 °C. [b] Isolated yields (%) over two steps. [c] Heated for 3 min at 50 °C and 60 min at 140 °C.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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