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Solid-Phase Synthesis of Pyridones and Pyridopyrazines as Peptidomimetic Scaffolds

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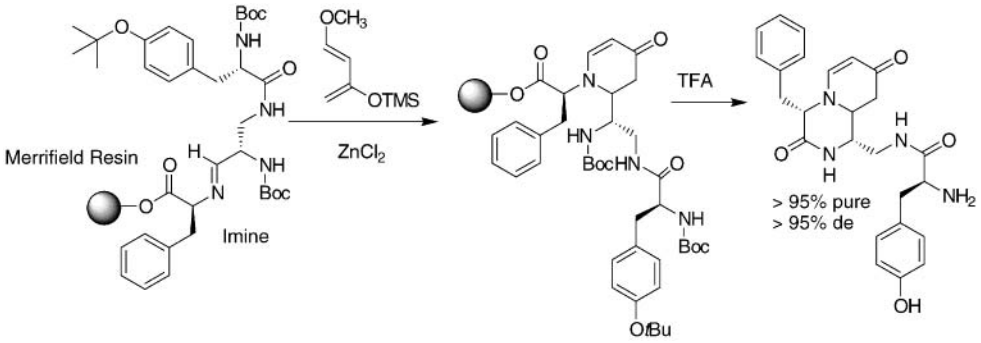
ABSTRACT



We report the syntheses of peptidomimetic opioids containing the core structure *N*-alkyl-2-alkyl-2,3-dihydro-4-pyridone. By employing imines bound on a solid support and the Danishefsky diene, this [4 + 2] cyclocondensation reaction facilitates the synthesis of novel complex heterocycles. The central reaction is carried out under mild conditions and employs readily available building blocks. In this study we demonstrate the suitability of *N*-alkyl-2-alkyl-2,3-dihydro-4-pyridones as a central scaffold for peptidomimetics and establish the scope of this [4 + 2] cyclocondensation reaction with imino acids on a solid phase. We also combine the synthesis of diketopiperazines with the [4 + 2] cyclocondensation reaction to form a 9,9a-dihydro-2*H*-pyrido-[1,2*a*]-pyrazine-3,8(1,4-dialkyl)dione, a bicyclic molecule containing a pyridopyrazine core structure.

It is a major focus of our research group to design and synthesize ligands possessing modified peptide structures with functional groups recognized at target sites (e.g., somatostatins, opioids, or proteases).[1] This approach involves the construction of a nonpeptidic central scaffold to attach and display the appropriate pharmacophores.[2] Replacement of the peptide backbone results in compounds with enhanced biostability and bioavailability.[3] Such scaffolds also introduce conformational constraints which provide information on structure−activity relationships.[4,5]

For scaffold-bound peptidomimetics synthesized on a polymer support, it is desirable to carry out the central reaction in relatively few steps.[6] The synthesis should be amenable to reactions in solution and on solid supports. It should be carried out under mild reaction conditions and with readily available building blocks.[7] The synthesis of *N*-alkyl-

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(5) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.; Lubell, W. D. *Tetrahedron* **1995**, 2937−2940.

(6) For comprehensive reviews on reactions carried out on the solid phase, see: Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, 4527−4554. Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1997**, 5643−5678. Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Reese, D. C. *Tetrahedron* **1998**, 15385−15443.

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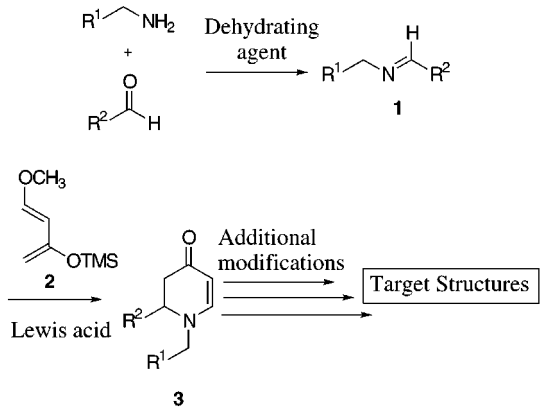
2-alkyl-2,3-dihydro-4-pyridone by the Diels−Alder type condensation described by Danishefsky and co-workers meets these requirements.[8−10]

In this Letter, we establish the scope and breadth of the [4 + 2] cyclocondensation utilizing natural and unnatural amino acid imines. We also combine the solid-phase chemistries of formation of diketopiperazines[11] with *N*-alkyl-2-alkyl-2,3-dihydro-4-pyridones. The combination of these chemistries allows for cyclization−cleavage[12] of 9,9a-dihydro-2*H*-pyrido-[1,2*a*]-pyrazine-3,8(1,4-dialkyl)diones from the resin. This eliminates the final purification step since only the desired product cleaves from the resin while byproducts of the synthesis are either trapped on the resin or washed away in the step prior to amino deprotection.

This [4 + 2] cyclocondensation reaction is carried out by allowing an amine to condense with an aldehyde in the presence of a dehydrating agent to form an imine **1** (Scheme 1).[13] Imine **1** is then allowed to react with a silyloxydiene

Scheme 1

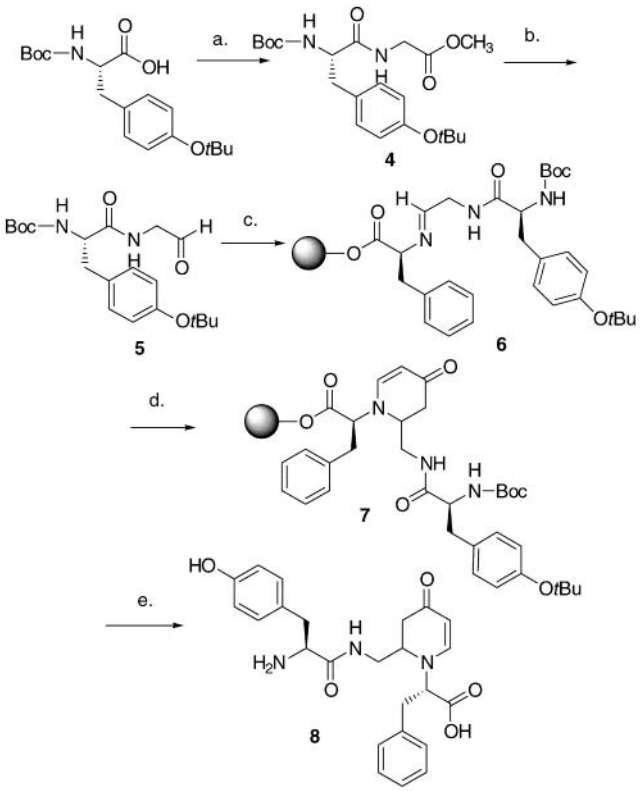


such as the Danishefsky diene **2** in the presence of a Lewis acid. The cyclocondensation reaction is carried out at 4 °C to produce *N*-alkyl-2-alkyl-2,3-dihydro-4-pyridones **3** with yields in the 50−95% range.

We have adapted this methodology to generate pyridone scaffolds in an effort to create molecularly diverse peptidomimetic structures. A family of pyridone-based opioid analogues were synthesized to illustrate the scaffold-based peptidomimetic approach and to identify lead opioids. These compounds were subjected to binding assays and were found to exhibit modest binding and selectivity to the opioid receptor subtypes. This Letter describes the utility of this [4 + 2] cyclocondensation reaction for peptidomimetic scaffold syntheses.

Scaffold-Based Peptidomimetic Opioids. The [4 + 2] cyclocondensation reaction was employed to synthesize representative opioid ligands. The pharmacophores associated with opioid ligands include amino, benzyl, and phenolic functional groups.[14] Scheme 2 illustrates the successful

Scheme 2[a]



[a] (a) H-Gly-OMe, EDC, HOBt, TEA in CH_2Cl_2, 95%; (b) DIBAL-H −78 °C, THF quantitative; (c) H-Phe-Wang resin 1:1 CH_2Cl_2/$HC(OCH_3)_3$; (d) the Danishefsky diene, $ZnCl_2$ (0.5 M) in THF 24 h 4 °C; (e) TFA/ DCM 1:1. RP-HPLC 55% overall, >95% de.

synthesis of opioid pyridone **8**. Using peptide coupling conditions, Boc-Tyr(*t*Bu)-OH was allowed to react with H-Gly-OMe to produce dipeptide **4**. Aldehyde **5** was produced in quantitative yield using DIBAL-H at −78 °C and was immediately condensed with H-Phe-Wang resin in the presence of trimethyl orthoformate to form imine **6**. Imine **6** was allowed to react with the Danishefsky diene in the presence of $ZnCl_2$ to form pyridone **7**.[15] Cleavage from the resin and removal of the Boc and *tert*-butyl protecting groups

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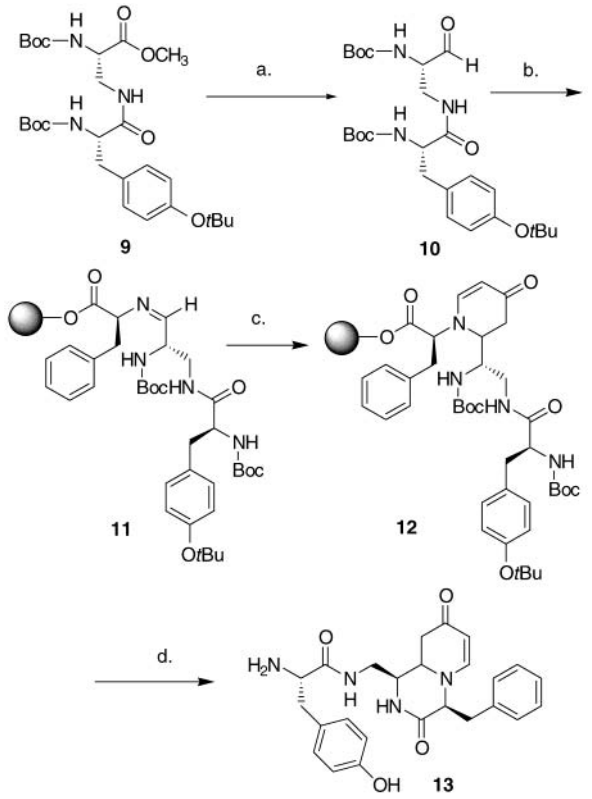
(15) We explored the syntheses of pyridones using a variety of Lewis acids. In our hands $ZnCl_2$ performed much better than $Yb(OTf)_3$ as a catalyst for pyridone formation. A discussion of this study will be published at a later date.

Scheme 3[a]



[a] (a) DIBAL-H −78 °C in THF; (b) H-Phe-Merrifield resin, 1:1 CH_2Cl_2/HC$(OCH_3)_3$; (c) the Danishefsky diene, $ZnCl_2$ (0.5M) in THF 24 h 4 °C; (d) TFA/ CH_2Cl_2 1:1, 12 h, 45% overall, >95% de.

were achieved using TFA to produce opioid pyridone **8** in a 55% yield after RP-HPLC purification.[16]

Scheme 3 illustrates the synthesis of a peptidomimetic opioid with a pyridopyrazine scaffold in which pyridone synthesis is combined with diketopiperazine formation. The synthesis was initiated by reaction of α-Boc-diaminopropionic acid methyl ester (Boc-Dpr-OMe) with Boc-Tyr(*t*Bu)-OH to produce **9** in 95% overall yield. Dipeptide **9** was subjected to DIBAL-H to reduce the ester to aldehyde **10** in quantitative yield. The crude aldehyde **10** was immediately condensed with H-Phe-Merrifield resin in the presence of trimethyl orthoformate to form imine **11**. Imine **11** was allowed to react with the Danishefsky diene in the presence of $ZnCl_2$ to form pyridone **12**. Acidolysis of the Boc protecting groups initiated cyclization to produce the pyridopyrazine opioid **13** in 45% overall yield. It is important to note that the cyclization and subsequent cleavage reaction yielded pure pyridopyrazine (compound**13**) for the reasons noted above.[17]

Compounds **8** and **13** were subjected to a [^{3}H]diprenorphine competitive binding assay. Compound **8** exhibits a K_i at the δ opioid receptor of 7 μM and no binding at the μ or κ receptors. Compound **13** is selective for the μ receptor with a K_i of 6 μM and exhibits no binding to the δ and κ receptors.

Conclusions

We have demonstrated that synthesis of peptidomimetics containing the core pyridone structure can be accomplished on a solid support in good yields. This [4 + 2] cyclocondensation reaction facilitates the synthesis of complex heterocycles in very few steps. The central reaction is carried out under mild conditions utilizing readily available building blocks. In this study we have shown the suitability of *N*-alkyl-2-alkyl-2,3-dihydro-4-pyridones as a central scaffold for peptidomimetic design. For the case of compound **13** the scaffold combines diketopiperazine and pyridone formation prepared on a solid support. To our knowledge this is the first time these two chemistries have been combined. The combination of pyridone and diketopiperazine offers a rigid scaffold amenable to extensive chemical diversity. The syntheses of peptidomimetic opioids were accomplished as an illustrative example of the approach. It is our goal to create new dienes allowing for multiple points of diversity on the pyridone scaffold and extend the method to other important ligands including somatostatin, RGD-like structures, and protease inhibitors.

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(16) **Compound 8:** ^{1}H NMR (500 MHz, DMSO-d_6, δ) 8.5 (s, 1H), 7.6 (t, 1H, J = 5.5 Hz), 6.8 (d, 1H, J = 6.7 Hz), 6.7 (m, 5H), 6.4 (d, 2H, J = 8.0 Hz), 6.2 (d, 1H, J = 7.5 Hz), 4.3 (d, 1H, J = 8.0 Hz) 4.1 (dd, 1H, J = 6.3 Hz, 8.2 Hz), 3.6 (m, 3H), 2.9 (m, 2H), 2.8 (m, 2H), 2.75 (m, 2H), 2.1 (dd, 1H J = 5.2 Hz, 8.3 Hz), 1.9 (d, 8.3). t_R = 12 min. HRMS (*m*/*z*): [M + Na]$^+$ calcd for $C_{24}H_{27}N_3O_5Na$ 460.1848, found, 460.1848.

(17) **Compound 13**. Synthesis of the pyridopyrazine **13** was initiated by condensation of Boc-Dpr(Boc-Tyr(tBu))aldehyde **10** (0.51 g, 1.0 mmol) with H-Phe-Merrifield resin (0.5 g, 0.27 mmol) (the H-Phe-Merrifield resin was pretreated with three washes of DCM and three washes of trimethyl orthoformate) in a 3:2 solution of trimethyl orthoformate:DCM for 3 h at 25 °C. The resin-bound imine **11** was washed with anhydrous THF (2 × 10 mL). The resin was suspended in 8 mL (4 °C) of 0.5 M $ZnCl_2$ in THF. Immediately, cold Danishefsky diene (1.0 g, 5 mmol) was added to the reaction vessel and allowed to react for 16 h at 4 °C. The resin containing the crude pyridone **12** was washed with DCM (2 × 10 mL), with 2% acetic acid in methanol (2 × 10 mL), and again with DCM (5 × 10 mL). Cleavage and cyclization were accomplished by allowing neat TFA (10 mL) to react with the resin-bound pyridone for 30 min at 25 °C. The TFA was collected, and the resin was suspended in DCM (10 mL) and placed on a wrist action shaker for 24 h. Pyridopyrazine **13** was extracted from the solid support with TFA (2 × 10 mL) and DCM (2 × 10 mL) washes. The extracts where then combined and concentrated on a rotary evaporator to produce 0.0678 g of a yellow oil (45% yield, >95% pure). ^{1}H NMR (500 MHz, DMSO-d_6, δ) 9.36 (s, 1H), 8.48 (t, 1H, J = 5.5 Hz), 8.10 (s, 3H), 7.7 (s, 1H) 7.2 (m, 5H), 7.0 (d, 2H, J = 8.0 Hz), 6.8 (d, 1H, J = 7.5 Hz), 6.7 (d, 2H, J = 8 Hz), 4.6 (d, 1H, J = 7.5 Hz), 4.2 (dd, 1H, J = 6.5 Hz, 8.5 Hz), 3.9 (m, 1H), 3.8 (m, 1H), 3.7 (m, 1H), 3.25 (m, 1H), 3.20 (m, 1H), 3.1 (m, 2H), 3.0 (dd, 1H, J = 6.0 Hz, 14 Hz), 2.8 (dd, 1H, J = 8.5 Hz, 14.5 Hz), 2.6 (dd, 1H, J = 7 Hz, 17.5 Hz), 2.45 (d, 1H, J = 3.5 Hz), 2.40 (d, 1H, J = 3.9 Hz). t_R = 17 min. HRMS (*m*/*z*): [M + Na]$^+$ calcd for $C_{25}H_{28}N_4O_4Na$ 471.2008, found, 471.1988.