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3,4- and 3,5-disubstituted 2-pyridones using an intermolecular cycloaddition/cycloreversion strategy: toward the synthesis of aristopyridinone A

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The intermolecular cycloaddition of pyrazinone precursors with alkyne substrates was evaluated. The resulting regioisomeric [2.2.2]-diketopiperazine alkene cycloadducts were diverted into 2-pyridone products through cycloreversion of the [2.2.2]-bicyclic intermediates. New insights into the regioselectivity of pyrazinone azadiene Diels–Alder reactions as well as cycloreversion reactivity were revealed in this study. Synthetic sequences using this [4+2]/[4+2] strategy were determined that can produce predominately the 3,5-disubstituted 2-pyridone alkaloid structures; pyridones featuring the 3,4-substitution pattern are observed as the minor regioisomeric products.

We recently developed a general synthetic method for the construction of 2-pyridone derivatives via cycloaddition of pyrazinone intermediates and subsequent cycloreversion of the intermediate [2.2.2]-diazabicycloalkene cycloadduct. These preliminary efforts focused primarily on intramolecular pyrazinone Diels–Alder reactions, where cycloaddition regiochemistry was not assessed. We viewed 1 as an instructive disubstituted 2-pyridone model in which to explore the extension of this synthetic strategy to include an intermolecular Diels–Alder/retro-Diels–Alder process. The 2-pyridone core is a medicinally privileged scaffold and we predicted that a synthesis directed toward 1 would provide material to assess the bioactivity and also prove useful in the construction of other 2-pyridone-containing molecules.

Our approach toward pyridone 1 is outlined below (Scheme 1). We anticipated that the requisite Diels–Alder precursor could be prepared by aldol condensation of the differentially-protected glycine-derived diketopiperazine (DJP) 3 with arylacetaldehyde 2 followed by alkyne isomerization of the exocyclic alkene to give the necessary endocyclic azadiene apparent in pyrazinone 4. Diels–Alder cycloaddition with a suitable alkyne substrate would afford the regioisomeric intermediate [2.2.2]-bicyclic adducts 5a and 5b. The cycloadducts could deliver the 3,4- and 3,5-disubstituted pyridones 6a and 6b following cycloreversion and selective extrusion of one lactam bridge (illustrated as the lactim ether). Final O- and N-deprotection of the aryl ether and dimethoxybenzyl residues in isomer 6a as well as any necessary functionalization to reveal the hydroxymethyl at C4 of the pyridone would complete

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aristopyridinone A. At the time we initiated this study, there were insufficient data to reliably predict which regioisomeric cycloadduct 5a or 5b would dominate. Because pyrazinones (e.g., 4) are reactive with both electron-rich and electron-deficient dieneophiles, we anticipated that we could explore different electronic properties of the alkyne dieneophile where the substituent would be either an electron-donating or electron withdrawing group. In this way, we envisioned potential control of regioselection in the Diels–Alder event.

In order to validate our general synthetic plan, we first initiated a model sequence starting with DKP 3 and benzaldehyde (Scheme 2). The aldol condensation was completed in a three-step operation that involved enolization, aldol addition, acetylation, and elimination of the derived β-acetoxy derivative with DBU to give 7. Based on our experience with aldol condensations with DKP substrates, we expected DKP alkylidene intermediate 7 to isomerize under the basic elimination reaction conditions (DBU) to the endocyclic alkene 8.9 We were somewhat surprised that we did not observe pyrazinone 8 directly from the elimination reaction. The equilibrium between 7 and 8 is operational as evidenced by production of cycloadducts 9a and 9b on heating DKP 7 with DBU in the presence of propargyl alcohol. Heating with DBU in the absence of propargyl alcohol returned only starting material DKP 7. We can thus conclude that the exocyclic alkene in 7 is thermodynamically more favorable than the isomeric pyrazinone 8.

Cycloadducts 9a and 9b were produced as an inseparable mixture (ratio 1:3) favoring 9b. Cleavage of the lactim O-methyl ether with KI in AcOH (110 °C) provided lactams 10a and 10b, which could be separated by chromatography. Lactam activation and cycloreversion were accomplished on major isomer 10b on heating (110 °C) with Ac2O and pyridine to afford the 3,5-substituted pyridone 11 (97% yield). Our initial communication on the cycloreversion of [2.2.2] - diketopiperazine alkene substrates to give 2-pyridone products employed microwave heating (max. temp. ~200 °C).6 The modified thermolysis conditions reported in this Letter are an improvement in efficiency and employ more manageable temperatures for cycloreversion (110 °C).

The synthesis of pyridone 11 validated our general strategy, although we wanted to determine cycloaddition reaction conditions that would reverse the regioselectivity and ultimately provide access to pyridones with 3,4-substitution as the major product, the structural pattern present in aristopyridinone A (1). Toward this end, a modified aldol condensation sequence was performed with 4-methoxyphenylacetaldehyde (2) and could deliver pyrazinone 4 in one reaction vessel (Scheme 3). Because pyrazinone 4 is somewhat oxygen-sensitive and decomposes on silica gel, in practice we found it more convenient to isolate and purify the intermediate β-acetoxy adduct 12. As needed, reserves of intermediate 12 were converted to pyrazinone 4 by elimination of the β-acetoxy residue and alkene isomerization with DBU. The intermediate exocyclic alkene product was not observed in this sequence and the equilibrium appears to favor pyrazinone 4.

The cycloaddition of pyrazinone 4, which was used directly without purification, was explored with three electronically distinct dieneophiles. Using ethyl propiolate, a mixture of cycloadducts 13a and 13b was obtained in a 1:2 ratio (63% combined yield). In agreement with our model system, cycloaddition of 4 with propargyl alcohol afforded adducts 14a and 14b (1:4 ratio, 78% combined yield). The β-acetoxy intermediate 12 was used as
the starting material for this sequence; acetal elimination, isomerization, and Diels–Alder cycloaddition with propargyl alcohol were accomplished in domino fashion in the same reaction vessel.

The dominant regiosomer possessed 3,5-substitution for the cycloaddition with both propiolate and propargyl alcohol. Methyl 2-nitroacrylate can be used as a synthetic equivalent of propiolate that possesses the opposite electronic properties and is often an effective tool in reversing cycloaddition regioselectivity.10 In our hands, the nitroacrylate was more reactive and cycloaddition with pyrazinone 4 was achieved near ambient temperatures; however, we observed little influence on regioselecton and an approximate 1:1 mixture of 15a and 15b was obtained (56% combined yield).

We decided to move forward toward the cycloreversion with 13a and 13b (1:2 ratio), the cycloadducts derived from ethyl propiolate (Scheme 4). Toward this end, the lactim O-methyl ether was cleaved with KI in AcOH (110 °C) to give lactams 16a and 16b. We were unable to effectively separate isomers by chromatography and the mixture (1:2 ratio) was submitted to the reaction conditions that promote cycloreversion (Ac2O, pyr, 110 °C). Isomers 16a and 16b behaved differently under the reaction conditions and products 19 and 20 were afforded (12% and 64% yield). The 3,5-disubstituted pyridone 20 is the result of cycloreversion of 16b via the derived activated intermediate 17b. Formation of the 3,4,6-trisubstituted pyridone 19 from 16a can be explained by N-C3 bond cleavage, followed by loss of the C6-proton. The divergent reaction pathways for isomers 16a and 16b are intriguing and we see two possible explanations for this differing reactivity.

The observed rearrangement of 16a (in preference to retrograde Diels–Alder) suggests a highly asynchronous transition state for the thermolysis. In isomer 16a, the bridgehead proton becomes aligned for deprotonation. Intermediate 18 illustrates complete ionization of the N-C3, although partial ionization may be sufficient to permit deprotonation at C6. If intermediate 18 is operational, the thermodynamic acidity of the C6 proton would be very high (<10 pK<sub>a</sub>) and enolization would be rapid. Alternatively, ionization of N-C3 bond in the isomeric intermediate 17b might be destabilized by developing adjacent electrostatic side groups (from the β-carbon of the unsaturated ester). This would potentially shift the reaction pathway toward cycloreversion and explain why the 3,5-disubstituted pyridone 20 is the observed product with isomer 17b. The DMB protecting group provides useful protection of the pyridone N–H throughout our sequence. We found that the DMB group is most effectively removed under acidic conditions as demonstrated by the conversion of pyridone 20 into 21 (TFA, CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>3</sub>SiH, 130 °C, micro, 30 min, 99% yield).

The thermolysis reaction of 16a and 16b revealed that an electron withdrawing group at C4 of the [2.2.2]-diketopiperazine alkene intermediate (such as 16a) will not undergo cycloreversion. We performed the analogous sequence starting from cycloadducts 14a and 14b (ca. 1:4 ratio), which bear hydroxymethyl substitution at the alkene (Scheme 5). Cycloreversion of the lactam intermediates derived from 14a and 14b occurred on both isomeric substrates and afforded the 3,4- and 3,5-pyridones 22a and 22b. Separation of the isolomers was accomplished after removal of the acetox residue (K<sub>2</sub>CO<sub>3</sub>, MeOH) gave products 23a and 23b in 28% and 53% isolated yields.

Formation of 23a and 23b demonstrates that cycloreversion is effective with hydroxymethyl (or acetoxymethyl) substitution on the derived intermediate [2.2.2]-diazabicyclic structure. Accordingly, this reaction sequence offers a method to access either 3,4- or 3,5-substituted pyridone products from the corresponding regioisomeric [2.2.2]-diazabicyclic cycloadducts. The limitations of this chemistry (at least with the dieneophiles explored in this study) show that construction of 3,5-disubstituted 2-pyridone products is the major product and 3,4-disubstituted products are afforded as minor regioisomeric products. Although intermediate 23a could potentially be converted to aristopyridinone A (1) in a few operations, in order to execute an efficient synthesis an alternative and more selective route toward 1 is warranted.

In summary, we have revealed a method to prepare 2-pyridones with a synthetic sequence that intercepts an intermolecular pyrazinone [4+2] cycloaddition, followed by cycloreversion of the derived intermediate [2.2.2]-bicycloalkene adducts. The reaction conditions employed for cycloreversion (Ac2O, pyr, 110 °C) are more expeditious and easier to execute than the conditions previously employed. We gained new insight into both the cycloaddition and cycloversion operations. In particular, we revealed that propargyl alcohol and propiolate give the same dominant regioisomer for cycloaddition (leading to 3,5-disubstituted pyridones). This result suggests that the regioselectivity in the cycloaddition of pyrazinone intermediates is not especially responsive to the electronic nature of the alkyne dieneophile. We also revealed

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**Scheme 4.** Divergent reactivity with isomeric [2.2.2]-bicycloadducts.

(a) TFA/CH<sub>2</sub>Cl<sub>2</sub> (1:2), Et<sub>3</sub>SiH, 130 °C, microwave, 30 min (99% yield)

**Scheme 5.** Synthesis of 3,4- and 3,5-substituted pyridones.

(a) KI, AcOH, 100 °C (69% yield); (b) Ac2O, pyr, 110 °C (88% yield)
that an electron-withdrawing residue at C4 of a [2.2.2]-bicycloalkene cycloadduct promotes a rearrangement in preference to extrusion of the lactam bridge (cycloreversion). The chemistry revealed in this synthetic exercise is useful for the construction of both [2.2.2]-diazabicyclic intermediates and 2-pyridone structures, in particular, those structures bearing 3,5-substitution.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.067.

References and notes

8. Diketopiperazine 6 can be prepared in 4 steps from glycine methyl ester in 55% overall yield. See Ref. 6.