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A regioselective etherification of pyridoxine via an ortho-pyridinone methide intermediate

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The catalyst-free, regioselective synthesis of 4'-O-substituted pyridoxine derivatives under solventless conditions is described. The methodology relies on the highly regioselective formation of the ortho-pyridinone methide from pyridoxine and subsequent oxa-Michael addition of alcohol nucleophiles. This methodology provides good to excellent yields for primary and secondary alcohols and moderate yields for tertiary alcohols.

Introduction

Pyridoxine 1, a vitamer of B6, is one of the eight water-soluble B vitamins and is an important nutrient. Of the six forms of the vitamin, the main active vitamer, pyridoxal 5-phosphate, is a cofactor in over 100 enzyme-catalyzed reactions involved in metabolism and regulatory functions.1 Pyridoxine 1 possesses significant biological activity in its own right as a cofactor for several enzymes and a participant in the biosynthesis of neurotransmitters and the production of nucleic acids. Recently, pyridoxine's potent antioxidant activity against superoxide2 and singlet oxygen3 has been documented. Additionally, pyridoxine can be prescribed to treat certain medical disorders. It is used as an antidote for hydrazine exposure from incidents involving isoniazid (INH) overdose and Gyromitra mushroom poisoning.4 Pyridoxine is also administered to treat ginkgotoxin 2 induced seizures that can be caused from consumption of Ginkgo biloba seeds.5

The derivatization of the vitamin B6 3-pyridinol core has generated considerable interest due to the broad range of biological activity displayed with instructive examples highlighted in Fig. 1. The aminomethylated derivative, pyridoxamine 3, is used to treat diabetic kidney disease.6 Bananin 4 has been shown to inhibit SARS-CoV ATPase activity and viral replication leading to its investigation as an anti-SARS agent.7 Other derivatives have demonstrated utility as HIV-integrase inhibitors,8 antibiotics9 and enzyme mimics.10

The functionalization of pyridoxine can be challenging. As a practical consideration, the high water-solubility of pyridoxine can be problematic in extractions leading to significant mass loss.11 Pyridoxine is not soluble in many conventional organic solvents which can complicate reaction optimization. A key selectivity issue

Figure 1. Pyridoxine and selected biologically active derivatives.
is the differentiation of the two primary alcohols. Obtaining regioslectivity at the 4- and 5-hydroxymethyl groups typically requires a ketalization protection strategy of the 4-hydroxymethyl and the phenol. A rare example of selective derivatization at the 5-hydroxymethyl moiety without the use of protecting groups is the lipase-catalyzed acylation of pyridoxine reported by Sun and coworkers. Pyridinone methide chemistry holds promise as a potential method for protecting group-free derivatization of pyridoxine since theoretical studies have shown that the energy barrier for the ortho-pyridinone methide is 8 kcal/mol lower than the meta-pyridinone methide. While this reactivity has been noted prior to this report, only three primary alcohol substrates have been synthesized in the past 75 years and in low to moderate yields. Herein, we investigate the scope and limitations of the catalyst-free synthesis of 4'-O-substituted pyridoxine derivatives via thermal formation of a highly regioselective ortho-pyridinone methide (o-PM) intermediate and subsequent oxa-Michael addition of alcohol nucleophiles (Scheme 1).

While o-quinine methide chemistry is well-precedented in the literature, examples of o-pyridinone methides are rare. The thermal o-pyridinone methide reactivity of pyridoxine was first noted by Harris who synthesized ginkgotoxin HCl salt in a 12% yield by heating in the presence of sodium methoxide in 1940. Pyridinone methide formation and trapping with ortho-quinone methide is 8 kcal/mol lower than the meta-pyridinone methide. While this reactivity has been noted prior to this report, only three primary alcohol substrates have been synthesized in the past 75 years and in low to moderate yields. Herein, we investigate the scope and limitations of the catalyst-free synthesis of 4'-O-substituted pyridoxine derivatives via thermal formation of a highly regioselective ortho-pyridinone methide (o-PM) intermediate and subsequent oxa-Michael addition of alcohol nucleophiles (Scheme 1).

The low to moderate yields might be caused by the weak nucleophilicity of the alcohols as well as the observed reversibility of the C-O bond formation in the presence of water. Due to the biological importance of pyridoxine analogs, we sought to investigate the feasibility of expanding this alkoxylation reactivity to generate a broad scope of 4'-O-substituted ether derivatives. In particular, a scalable synthesis of ginkgotoxin was desired since the natural product is required as an analytic standard for GC–MS analysis of Ginkgo biloba. Currently, ginkgotoxin is only available in limited quantities commercially (63.50 USD/10 mg, Sigma-Aldrich). An evaluation of the steric and functional group limitations of the reaction was desired to generate a library of analogs to facilitate the study of the biological activity of this intriguing class of compounds.

**Results and discussion**

An examination to determine the most suitable reaction parameters commenced with an analysis of solvent and temperature. Without the use of a catalyst, the temperature required to achieve formation of the o-pyridinone methide was determined to be 105 °C in protic solvents. In aprotic solvents, the o-pyridinone methide did not form to an appreciable extent at comparable temperatures. The high solubility of pyridoxine in alcohols enabled the coupling partner to be utilized without the need for a traditional organic solvent.

A series of conditions was screened with instructive examples highlighted in Table 1. Pyridoxine 1 in n-butanol at 105 °C provided 5c in a 51% yield after 24 h (entry 1) with significant unreacted starting material isolated during purification. Allowing the control to run to completion by TLC analysis provided an 83% yield (entry 2) over 96 h. Despite the long reaction time, the reaction provides clean conversion to the ether products and avoids the dimerization and byproducts formation that occurs at higher temperatures. No reactivity was observed for temperatures under 100 °C regardless of reaction time. Increasing the temperature to 120–160 °C shortened the reaction time; however, this led to a higher degree of decomposition and a lower selectivity ratio of the ortho- to meta-substitution. We then sought to employ a catalyst to expedite the reaction time.

Using 0.2 M n-butanol and pyridoxine for the synthesis of 5c as a model system, an investigation to identify a suitable catalyst was undertaken. Since pyridoxine has been noted to form radicals in biological systems, we began the study with an analysis of radical initiators. Of the radical initiators attempted, dibenzoyl peroxide provided the highest yields and facilitated product formation.

![Scheme 1](image-url)
below 100 °C; however, the catalyst provided less 5c than the uncatalyzed conditions at both lower temperatures (entry 3) and at 105 °C (entry 4). Several boronic acid catalysts were also screened as they have been demonstrated as efficient promoters of α-quinone methide formation; these attempts provided lower yields than the uncatalyzed conditions (entry 6). A series of Brönsted and Lewis acid catalysis were attempted and most hindered the desired reactivity or provided a lower selectivity ratio of the ortho- to meta-substitution, p-Toluensulfonic acid (entry 7), the catalyst used in the microwave-assisted synthesis of ginkgotoxin, provided a 53% yield. Basic conditions, as utilized by Harris, provided a faster reaction, but favored decomposition with trace product formation. With suitable solventless, catalyst-free conditions in hand, an examination of the allowable steric and electronic parameters with respect to the alcohol coupling partner was undertaken. A variety of primary, secondary, and tertiary alcohols were submitted to the reaction conditions with the results compiled in Table 2.

The yields for the thermal α-pyridinone methide trapping with various alcohols ranged from 38 to 83%. Generally, the less substituted alcohols provided higher yields than those with higher substitution. Additionally, the lower boiling point alcohols (2, 5a, 5b, 5d) that required a pressurized vessel tended to provide lower yields than the higher boiling entries. Ginkgotoxin 2 was obtained in a 57% yield. The high boiling point primary alcohols, n-butanol, benzyl, and geranil (5c, 5g, 5h) provided excellent yields of 83%, 70%, and 82% respectively. The geranyl example (5h) is particularly encouraging since it contains sensitive functionality that may not work well under the previously reported Lewis acid/base-catalyzed conditions. The ether moiety of 2-methoxylethanol (5j) was tolerated by the reaction manifold and provided an acceptable yield of 52%. Propargylic alcohol provided an inseparable complex product mixture with the Diels-Alder adduct. Other 3-pyridinol derivatives, 4-methoxypyridin-2-yl)methanol and 2-(hydroxymethyl)pyridin-3-ol HCl were attempted in the reaction manifold but only trace product was observed after three days with n-butanol.

### Conclusion

The general synthesis of 4’-O-substituted pyridoxine derivatives with high regioselectivity under catalyst-free conditions is disclosed. This operationally-simple methodology enables access to a broad scope of ether analogs from inexpensive, commercially available pyridoxine and alcohols in moderate to excellent yields via the rare ortho-pyridinone methide intermediate. The substrate scope demonstrated good functional group compatibility with primary, secondary, and tertiary alcohols and ether and olefin moieties being well-tolerated. The analysis of the biological activities of these compounds and the incorporation of additional nucleophilic partners will be reported in due course.

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### A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [http://dx.doi.org/10.1016/j.tetlet.2017.04.082](http://dx.doi.org/10.1016/j.tetlet.2017.04.082).

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### Table 2

| Entry | Product | R        | Yield (%) |
|-------|---------|----------|-----------|
| 1     | 2       | Me<sup>c</sup> | 57        |
| 2     | 5a      | Et<sup>c</sup> | 58        |
| 3     | 5b      | i-Pr<sup>c</sup> | 44        |
| 4     | 5c      | n-Butanol | 83        |
| 5     | 5d      | t-Butanol  | 38        |
| 6     | 5e      | i-Amyl    | 79        |
| 7     | 5f      | s-Amyl    | 55        |
| 8     | 5g      | t-Amyl    | 46        |
| 9     | 5h      | Bu        | 70        |
| 10    | 5i      | Geranyl   | 82        |
| 11    | 5j      | β-Methallyl | 38        |
| 12    | 5k      | 2-Butenyl | 72        |
| 13    | 5l      | 2-Methoxethyl | 56    |

<sup>a</sup> All reactions were conducted [1] = 0.2 M.
<sup>b</sup> Isolated yield.
<sup>c</sup> Ran for 144 h.