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

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ABSTRACT

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 B_6, 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 superoxide[2] and singlet oxygen[3] 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 B_6 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] antibiotics[9] 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

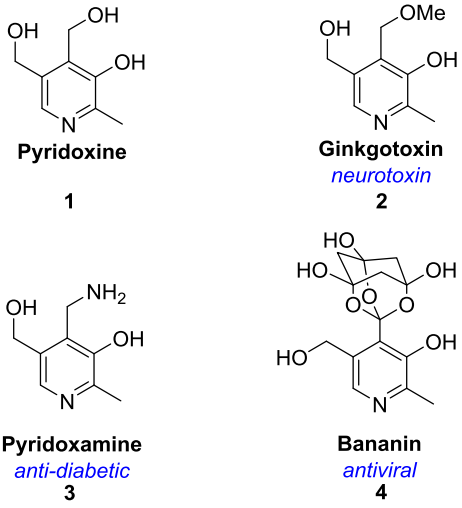

Figure 1. Pyridoxine and selected biologically active derivatives.

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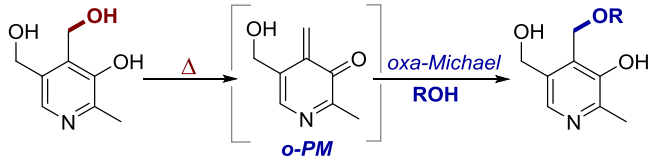


Scheme 1. Thermal *ortho*-pyridinone methide formation and trapping with alcohols.

is the differentiation of the two primary alcohols. Obtaining regioselectivity at the 4- and 5-hydroxymethyl groups typically requires a ketalization protection strategy of the 4-hydroxymethyl and the phenol.[9] 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.[11] 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.[12] 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[13] synthesis of 4′-O-substituted pyridoxine derivatives *via* thermal formation of a highly regioselective *o*-pyridinone methide (*o*-PM) intermediate and subsequent oxa-Michael addition of alcohol nucleophiles (Scheme 1).

While *o*-quinone methide chemistry is well-precedented in the literature,[14] 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.[15] This reactivity was further developed by Frater-Schröder and Mahrer-Busato in conjunction with toxicological studies in 1975. They demonstrated that heating pyridoxine to 120–130 °C in the presence of *n*-butanol and isoamyl alcohol with tetralin as a cosolvent provided the 4′-O-substituted products albeit in a 49% and 36% yield, respectively.[16] This report is significant as the first catalyst-free formation of these products; however, the report is limited to two substrates and the authors note the presence of dimerization of pyridoxine and other byproducts at such high temperatures. Recently, a microwave-assisted *p*-toluenesulfonic acid-catalyzed synthesis of ginkgotoxin was accomplished providing 56% yield.[17] 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.[16]

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.

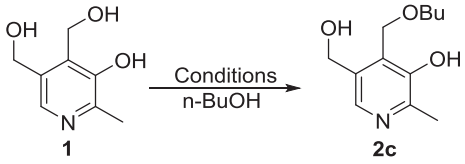
Results and discussion

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.[16] 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,[18] 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

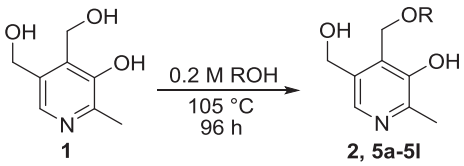
Table 1
Optimization Screen.[a]



Entry	Catalyst	Time (h)	Temp (°C)	Yield (%)
1	none	24	105	51
2	none	96	105	83
3	dibenzoyl peroxide	96	50	0
4	dibenzoyl peroxide	96	105	65
5	AIBN, *hv*	48	50	0
6	phenylboronic acid	96	105	58
7	p-TSA	96	105	53

[a] All reactions were conducted $[\mathbf{1}]_0$ = 0.2 M on a 0.3 mmol scale under air.

Table 2
Synthesis of 4′-O-pyridoxine derivatives *via* thermal *o*-PM.[a]



1 **2, 5a-5l**

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

[a] All reactions were conducted $[\mathbf{1}]_0 = 0.2$ M.
[b] Isolated yield.
[c] Ran for 144 h.

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 *o*-quinone methide formation;[19] 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*-Toluenesulfonic acid (entry 7), the catalyst used in the microwave-assisted synthesis of ginkgotoxin,[17] provided a 53% yield. Basic conditions, as utilized by Harris,[10] 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 *o*-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 geraniol (**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-methoxyethanol (**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.

Acknowledgments

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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.

References and notes

1. (a) Clayton PT. *J Inherit Metab Dis*. 2006;29:317–326(b) NIH, Office of dietary supplements. Dietary Supplement Fact Sheet: Vitamin B6 (accessed Nov 20, 2016). http://ods.od.nih.gov/factsheets/VitaminB6-HealthProfessional/.
2. Jain SK, Lim G. *Free Radical Biol Med*. 2001;30:232–237.
3. (a) Matxain JM, Ristilä M, Strid Å, Eriksson LA. *Chem-Eur J*. 2007;13:4636–4642; (b) Ohta BK, Foote CS. *J Am Chem Soc*. 2002;124:12064–12065.
4. Lheureux P, Penaloza A, Gris M. *Eur J Emerg Med*. 2005;12:78–85.
5. (a) Leistner E, Drewke C. *J Nat Prod*. 2010;73:86–92; (b) Jang H-S, Roh SY, Jeong EH, Kim B-S, Sunwoo MKJ. *Epilepsy Res*. 2015;5:104–106.
6. Williams ME, Bolton WK, Khalifah RG, Degenhardt TP, Schotzinger RJ, McGill JB. *Am J Nephrol*. 2007;27:605–614.
7. (a) Kesel AJ. *Curr Med Chem*. 2005;12:2095–2162; (b) Wang Z, Huang J-D, Wong K-L, et al. *FEBS J*. 2011;278:383–389.
8. Stranix B, Beaulieu F, Bouchard JE, Milot G, Zhigang W, Ruel R. US 2011/0178120A1; 2011.
9. (a) Pugachev MV, Shtyrlin NV, Sysoeva LP, et al. *Bioorg Med Chem*. 2013;21:4388–4395; (b) Pugachev MV, Shtyrlin NV, Sapozhnikov SV, et al. *Bioorg Med Chem*. 2013;21:7330–7342.
10. Lui L, Breslow R. *Bioorg Med Chem*. 2004;12:3277–3287.
11. Zhang D-H, Bai S, Dong X-Y, Sun Y. *J Agric Food Chem*. 2007;55:4526–4531.
12. Wu M, Xu Q, Strid Å, Martell JM, Eriksson LA. *J Phys Chem A*. 2011;115:13556–13563.
13. (a) Gawande MB, Bonifácio VDB, Luque R, Branco PS, Varma RS. *ChemSusChem*. 2014;7:24–44; (b) Sarkar A, Santra S, Kundu SK, et al. *Green Chem*. 2016;18:4475–4525.
14. (a) Caruana L, Fochi M, Bernardi L. *Molecules*. 2015;20:11733–11764; (b) Wang Z, Sun J. *Synthesis*. 2015;47:3629–3644.
15. Harris SA. *J Am Chem Soc*. 1940;62:3203–3205.
16. Frater-Schröder M, Mahrer-Busato M. *Bioorg Chem*. 1975;4:332–341.
17. (a) Liu Y, Chen S-N, McAlpine JB, et al. *J Nat Prod*. 2014;77:611–617; (b) Liu Y, Friesen JB, Klein LL, et al. *J Chromatogr A*. 2015;1426:248–251.
18. Matxain JM, Ristilä M, Strid Å, Eriksson LA. *J Phys Chem A*. 2006;110:13068–13072.
19. Zheng H, Hall DG. *Tetrahedron Lett*. 2010;51:4256–4259.