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Cyclic acetal formation between 2-pyridinecarboxyaldehyde and γ-hydroxy-α,β-acetylenic esters

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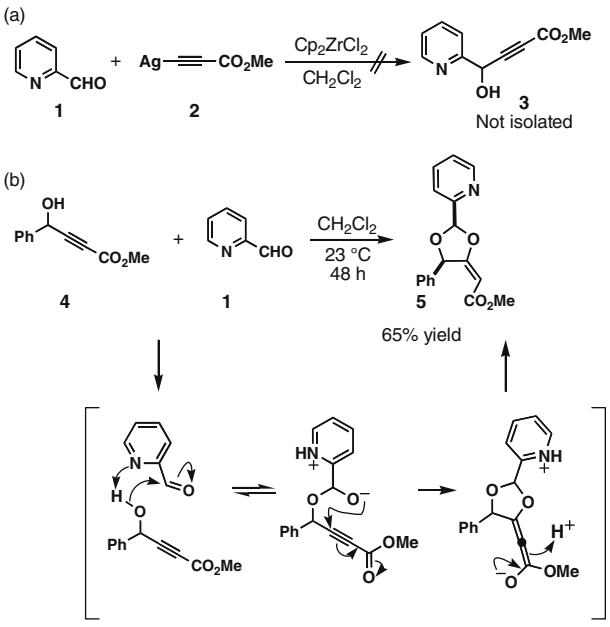
ABSTRACT

A new transformation between 2-pyridinecarboxyaldehyde and γ-hydroxy-α,β-acetylenic esters to form highly functionalized cyclic acetals was discovered. This transformation proceeds under very mild conditions without any additives and is promoted by the basic nature of the pyridine ring.

Electron-deficient propargylic alcohols such as γ-hydroxy-α,β-alkenyl esters are important intermediates in organic synthesis due to their potential for further functionalization.[1–4] As such, development of new synthetic methodologies toward the preparation of these important synthetic intermediates is of interest to many research groups including ours. For example, we showed that highly functionalized γ-hydroxy-α,β-acetylenic esters could be prepared by the coupling of aldehydes, ketones, or epoxides with silver acetylides in the presence of Cp_2ZrCl_2 and AgOTf.[5,6] The Trost group later developed an enantioselective method to prepare these compounds.[7] γ-Hydroxy-α,β-acetylenic esters are precursors for γ-hydroxy-α,β-alkenyl esters,[8] *cis*-γ-oxo-α,β-alkenyl esters,[9,10] and *trans*-γ-oxo-α,β-alkenyl esters.[9,11,12] In our laboratory, γ-hydroxy-α,β-alkenyl esters played a pivotal role in the synthesis of FR901464.[13–15] While studying the scope of zirconium/silver-promoted alkynylation of aldehydes and ketones, we found the interesting reactivity of 2-pyridinecarboxyaldehyde toward γ-hydroxy-α,β-acetylenic esters, which is the subject of this Letter.

In our efforts to develop zirconium/silver-promoted alkynylations of functionalized carbonyl compounds with silver acetylides,[6] the coupling between 2-pyridinecarboxyaldehyde (**1**) and Ag–C≡C–CO_2Me (**2**) in the presence of Cp_2ZrCl_2 gave an intractable mixture (Scheme 1a). We hypothesized that the expected product **3** could react with **1**, thereby producing the mixture. To test this hypothesis, a mixture of **4** and **1** (1:1, 0.3 M each) was stirred at 23 °C in CH_2Cl_2 for 4 d (Scheme 1b). These reaction conditions produced the highly functionalized product **5** in 65% yield, whose structure was confirmed by X-ray crystallography (Fig. 1). Interestingly, compound **4** did not react with either 3- or 4-pyridinecarboxyaldehyde. Similar compounds were produced by Evans et al. by using alcohol substrates and potassium *t*-butoxide with an aldehyde to form 6-membered cyclic acetals.[16] Another work to form a very similar 6-membered ring 1,3-dioxan-4-ylidenes was accomplished by Kwon et al. under phosphine catalysis.[17] These examples demonstrate the importance of cyclic acetals in organic synthesis.

We speculated that the weakly basic pyridine nitrogen atom could transiently deprotonate the hydroxy group of alcohol **4**, promoting addition to the aldehyde (Scheme 1b). The resulting hemiacetal anion could then undergo a conjugate addition toward the α,β-acetylenic esters to form product **5** with the indicated cis relationship of the pyridine and phenyl group and the trans olefin. This could explain why 3- or 4-pyridinecarboxyaldehyde did not react.



Scheme 1. (a) Attempted alkynylation. (b) Plausible mechanism for the cyclic acetal formation.

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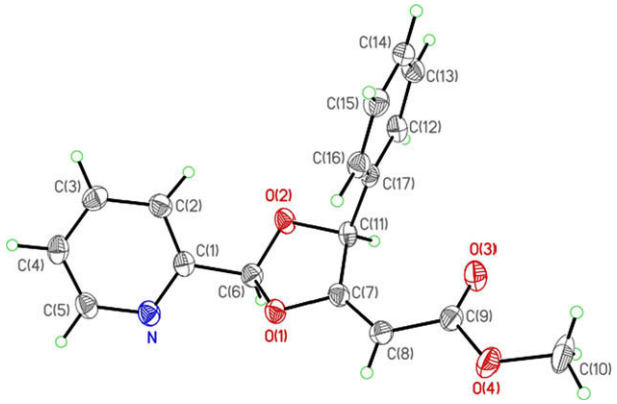


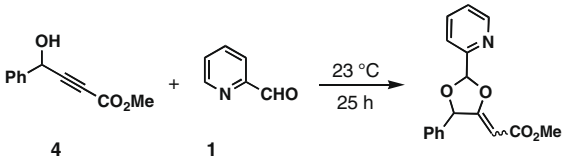
Figure 1. ORTEP representation of **5**.

The selectivity for the trans olefin geometry may occur because the lone pair electrons on the oxygen of the acetal and oxygen of the ester carbonyl repel each other if the olefin were cis.[24] The phenyl and pyridine rings are cis to each other possibly because as the alkoxide attacks in a 1,4-fashion, both rings prefer to be in the pseudo-equatorial positions. [25,26]

Although the reaction proceeded in CH_2Cl_2, we asked if other solvents would be more suitable. Solvents were screened by ^1H NMR analysis in the respective deuterated solvent. Compounds **1** and **4** were dissolved in each of the deuterated solvents listed in Table 1, with a final reaction concentration of 0.5 M (with respect to the alkyne) in the presence of Bn_2O as an internal standard, and the reactions were monitored at 23 °C. After 25 h in CD_2Cl_2, 33% of **4** was consumed. In C_6D_6 and CD_3OD, 38% and 44% conversion of **4** was observed, respectively. The reaction solution in CH_2Cl_2 turned black after approximately 1 d, which may be a sign of polymeric material being formed from the alkynoate; a similar observation was noted by Garcia-Tellado and co-workers in their domino process approach for their synthesis of 1,3-dioxolane.[18] This probable polymeric material production was dramatically reduced when switching to MeOH as a solvent.

We next examined the scope of the reaction of 2-pyridinecarboxyaldehyde with various γ-hydroxy-α,β-acetylenic esters in MeOH. As can be seen in Table 2, the reaction is well-tolerable in the presence of cyclohexyl (entry 1) and aromatic side chains (entries 2–7) and even proceeds with the bulky *t*-butyl group (entry 8). With respect to the aromatic side chains, both electron-donating and electron-withdrawing substituents are withstood in the reaction and proceed with similar yield.

Table 1
Solvent effect

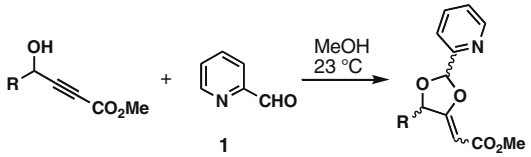


4 **1** (1.2 equiv)

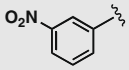
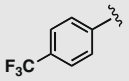
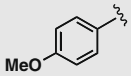
Entry	Solvent	% Conversion (by ^1H NMR)
1	$CDCl_3$	20
2	CD_2Cl_2	33
3	C_6D_6	38
4	DMSO-d_6	5
5	CD_3OD	44

[**4**] = 0.5 M. Bn_2O (0.5 mmol) was used as an internal standard.

Table 2
Reaction of 2-pyridinecarboxyaldehyde with γ-hydroxy-α,β-acetylenic esters



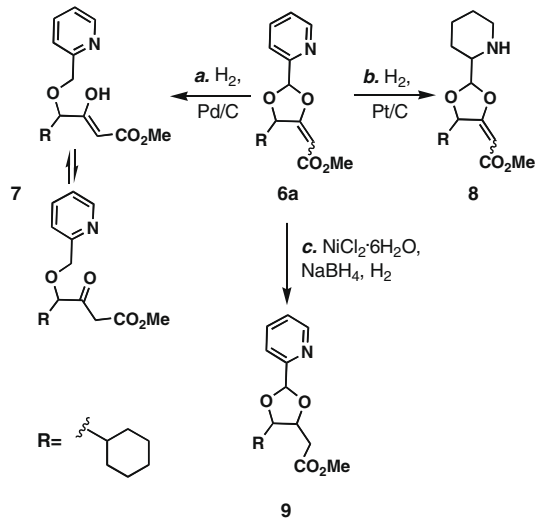
1 (1.2 equiv)

Entry	R	Time (d)	Yield[a] (%)
1		5.3	84 (60)
2		2.9	79 (61)
3		2.8	82 (60)
4		3.2	99 (83)
5		2.9	82 (65)
6		1.9	76 (40)
7		2.8	88 (67)
8		5.9	47 (34)

[a] Yields for major diastereomer are shown in ( ). The yields of combined diastereomers are listed outside ( ).

We then studied the reactivity of this novel 2-pyridylacetal functionality. Standard hydrogenolysis conditions with Pd/C and H_2 reductively cleaved one of the two acetal C–O bonds to form ether **7** in 40% yield as a mixture of tautomers (Scheme 2), with the rest being the starting material. Structurally similar compound has been shown to behave as an *anti*-ischemic and *anti*-hypertensive activity,[23] indicating that this synthetic method may provide a library of compounds closely related to these *anti*-ischemic and *anti*-hypertensive drugs. Hydrogenation with Pt/C reduced the pyridine ring to form amine **8** in 33% yield with the rest being the starting material. Similar results were obtained when palladium-black was used. From these results, it is concluded that unlike benzyl ethers, pyridylmethyl ethers are difficult to cleave under the typical hydrogenolysis conditions. Acetal **6a** was inert toward acidic conditions (e.g., CSA and TFA) presumably because the protonated pyridine destabilizes the carbocation at the benzylic position. Attempts to methylate the pyridine nitrogen with MeI and treating with base gave no sign of reaction besides partial methylation of the nitrogen.[19] Conjugate reduction of enoate **6a** with $NiCl_2{\cdot}6H_2O$ and $NaBH_4$[20] resulted in **9** as a mixture of two separable diastereomers. The major diastereomer was isolated in 30% yield. The remaining is a mixture of a minor amount of different diastereomer and the unreacted starting material.

In conclusion, we have discovered an interesting reactivity between 2-pyridinecarboxyaldehdye and γ-hydroxy-α,β-acetylenic esters. The reactions were promoted by the basicity and proximity of the pyridine group. The acetal product **6a** represents the reactivity of these acetal compounds under various reaction conditions. Although these results indicate that reaction conditions are needed



Scheme 2. Derivatizations of **6a**. Reagents and conditions: (a) H_2, Pd/C (10 mol %), EtOAc, 23 °C, 44 h, 40%; (b) H_2, Pt/C (10 mol %), EtOAc, 23 °C, 22 h, 33%; (c) $NiCl_2{\cdot}6H_2O$ (7.0 equiv) $NaBH_4$ (7.0 equiv), H_2, MeOH, 23 °C, 46.5 h, 30%.

to use the pyridine acetals as protecting groups, the acetals provide an interesting scaffold for diversity-oriented synthesis[21] because this moiety has been shown to be important in biologically active molecules.[22,23]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.008.

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24. Kwon et al. observed similar trans selectivity in Ref. 17.
25. We presume the relation between the pyridinyl and the different R groups in Table 2 is cis.
26. The relationship between the phenyl and pyridine group and olefin geometry of the other minor diastereomer was not determined.