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A Catalytic Route to Ampakines and Their Derivatives

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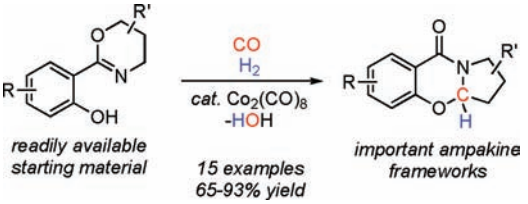
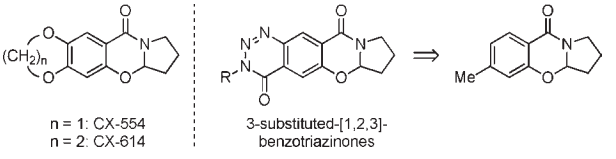
ABSTRACT



A catalytic domino reaction that efficiently provides access to an important class of heterocycles, the ampakines, is reported. Our approach is based on the cobalt-catalyzed hydroformylation of dihydrooxazines and allows for the facile synthesis of the pharmaceutically interesting compound CX-614 and related substances.

Neurodegenerative diseases such as Alzheimer's or Parkinson's are on the rise globally and will lead to substantial financial and societal costs if effective treatments are not found in the near future.[1] One promising therapy currently under investigation is the administration of ampakines.[2] These compounds allow positive allosteric modulation of α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors and could help alleviate the symptoms of these diseases by restoring diminished glutamatergic neurotransmission.[2b,d] Important examples of ampakines are CX-554[3] and CX-614[4] (Scheme 1), and their effects on cell receptors and potential medicinal applications are well documented. Structurally related to CX-614, 3-substituted-[1,2,3]-benzotriazinones, derived from simple ampakines (Scheme 1), also show potential for the treatment of neurodegenerative diseases by modulating AMPA receptors at even nanomolar concentrations.[5a]

Scheme 1. Examples of Ampakines



As part of our research efforts to use carbon monoxide as a feedstock for the preparation of synthetically useful

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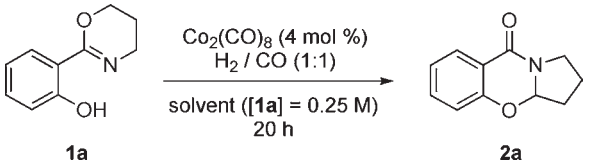
intermediates,[6] we recently reported the carbonylative ring expansion of 2-substituted oxazolines to oxazinones[7,8] and hydroformylation of 2-oxazolines to *N*-acylated aminoaldehydes.[9] Based on these findings we proposed that the in situ generation of an aminoaldehyde moiety followed by cyclization could produce the desired ampakine targets or synthetic precursors shown in Scheme 1. This methodology would be very atom economical, as opposed to current synthetic routes which use hard-to-obtain precursors,[5] suffer from low yields,[10] or require stoichiometric,[11] toxic,[12] or expensive[13] reagents. In this report we describe a domino reaction[14] that readily yields the desired ampakine framework while using simple starting materials and $Co_2(CO)_8$ as an inexpensive precatalyst.

Table 1. Influence of Solvent, Pressure, and Temperature



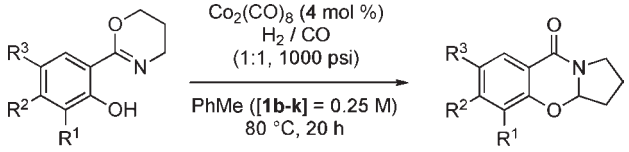
1a **2a**

entry	solvent	pressure (psi)	temp (°C)	yield (%)[a]
1	MeCN	1000	80	<1[b]
2	*n*-Hexane	1000	80	<1[b]
3	THF	1000	80	50
4	1,4-Dioxane	1000	80	70
5	PhMe	1000	80	81, 81[c]
6	PhMe	1000	60	23[b]
7	PhMe	800	80	61[b]

[a] Isolated yield for reactions carried out on a 0.5 mmol scale. [b] Determined by ^{1}H NMR spectroscopy. [c] 7.5 mmol scale.

We hypothesized that a dihydrooxazine bearing an *ortho*-substituted phenol would give the desired ampakine structure following stepwise hydroformylation and cyclization. To test this theory, a model substrate was synthesized and subjected to hydroformylation conditions in the presence of catalytic amounts of $Co_2(CO)_8$ (Table 1). Solvents of different polarities and Lewis basicities were investigated as these parameters are crucial in related carbonylation reactions.[15] Toluene proved to be the best solvent (entry 5), yielding the desired product in 81% isolated yield. Highly polar and nonpolar solvents both completely impeded the reaction (entries 1 and 2). Lowering the reaction temperature or the overall pressure decreased the yield (entries 6 and 7). Furthermore, adding molecular sieves (3 Å) to the reaction mixture led to no improvement, suggesting that the water produced in the reaction has no deleterious effect. Lastly, the transformation scales up well with virtually no loss in isolated yield (entry 5).

Table 2. Hydroformylation of Substituted 2-Aryl-dihydrooxazines



1b-k **2b-k**

entry	R^1	R^2	R^3	product	yield (%)[a]
1	H	H	F	**2b**	65
2	H	H	Me	**2c**	70, 73[b]
3	H	H	OMe	**2d**	68, 87[b]
4	H	H	Ph	**2e**	72[b]
5	H	Me	H	**2f**	72[b]
6	H	OMe	H	**2g**	43, 73,[b] 74[c]
7	Br	H	H	**2h**	79
8	H	(−OCH_2O−)		**2i**	76[b]
9	H	(−OCH_2CH_2O−)		**2j**	40, 71[b]
10	H	(−CH=CH−)$_2$		**2k**	64, 80[b]

[a] Isolated yield for reactions carried out on a 0.5 mmol scale. [b] [Substrate] = 0.12 M, 0.4 mmol scale. [c] 8 mol % $Co_2(CO)_8$, [substrate] = 0.12 M, 0.4 mmol scale.

Next, we subjected a variety of substituted dihydrooxazines to the optimized conditions (Table 2). The introduction of either electron-withdrawing (entry 1) or electron-donating (entries 3, 6, 9, and 10) substituents onto the aryl moiety of the dihydrooxazine decreased the isolated yield despite complete consumption of the corresponding starting materials.[16] The decrease in yield in entry 1 is consistent with observations made by Jia and coworkers for the carbonylative ring expansion of aryl-substituted 2-oxazolines.[8] In entries 3, 6, 9, and 10 the electron-donating substituents should increase the nucleophilicity of the dihydrooxazine which could facilitate initiation of unproductive ring-opening polymerization, a well-known reaction of oxazolines and oxazines.[17] Initiation of polymerization requires the attack of a substrate molecule on an already activated substrate molecule (Scheme 2, path A: S_N2 attack by **1a** in the place of Co $(CO)_4^-$; and path B: attack by **1a** at Co acyl).[17a] Consequently, we decided to decrease the overall substrate concentration to favor the desired hydroformylation pathway.

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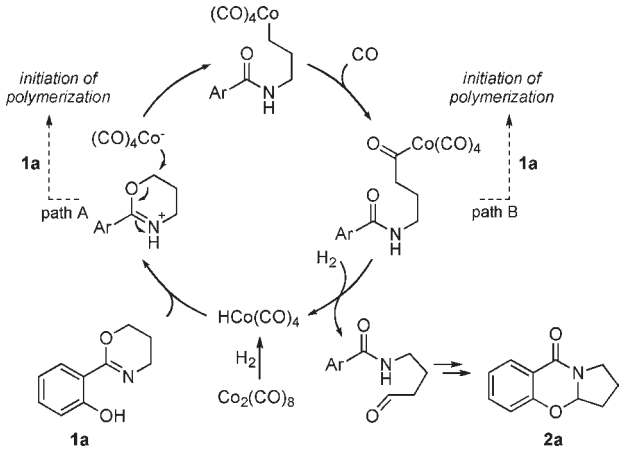
Scheme 2. Proposed Catalytic Cycle



This modification of the reaction conditions led to a pronounced increase in yield for substrates with electron-donating substituents (entries 3, 6, and 10) and furnished CX-554 (entry 8), CX-614 (entry 9), and the intermediate needed for the synthesis of benzotriazinones (entry 5) in good yield.

Modifications to the dihydrooxazine backbone were well tolerated (Table 3, entries 1−4).[18] The observed diastereomeric ratios were relatively small, possibly due to the flexibility of the five-membered ring and the distance between the existing and the newly formed stereocenter. The position of the substituent had little effect on the ratio (entries 1 and 4), whereas changing the size of the substituent from methyl to phenyl roughly doubled the stereoselectivity (entries 1 and 2). Furthermore, the diastereomeric ratios seem to be primarily kinetically controlled. For example, in entry 1 the *cis*-isomer forms in 23% excess; a pure sample of this diastereomer is recovered unchanged when resubjected to our hydroformylation conditions but epimerizes to approximately a 1:1 mixture when exposed to *p*-toluenesulfonic acid at 40 °C. Consequently, the two diastereomers of a given substrate seemingly do not interconvert under our reaction conditions.

Based on previous literature reports,[7,8,13] we expect the first part of the domino reaction to proceed by the catalytic cycle depicted in Scheme 2. First, activation of the

(18) Introduction of a methyl or phenyl group onto the oxygen-bearing methylene group led to low yields or a mixture of products, respectively.

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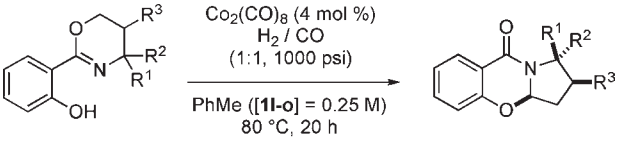
Table 3. Hydroformylation of Alkyl-Substituted 2-Dihydrooxazines



1l-o 2l-o

entry	R^1	R^2	R^3	product	yield (%)[a]
1	Me	H	H	**2l**	66, 90[b] (1.6:1)[c]
2	Ph	H	H	**2m**	80 (2.9:1)[c]
3	Me	Me	H	**2n**	93
4	H	H	Me	**2o**	80 (1.3:1)[c]

[a] Isolated yield for reactions carried out on a 0.5 mmol scale. [b] [Substrate] = 0.12 M, 0.4 mmol scale. [c] Diastereomeric ratio (*cis*/*trans*).

dihydrooxazine through protonation and subsequent ring opening *via* an S_N2-type pathway should give rise to a transient cobalt-alkyl species. Insertion of CO[19] followed by hydrogenolysis of the resulting cobalt-acyl intermediate[20,21] produces an *N*-acylaminoaldehyde. The presence of the Brønsted acid $HCo(CO)_4$ should then facilitate isomerization to the corresponding hemiaminal and subsequent formation of an iminium ion by loss of water. A fast second cyclization to the final product is likely given the close vicinity of the phenol group to the iminium ion.

In conclusion, we have developed an atom economical route to an important ampakine framework *via* hydroformylation of dihydrooxazines. Our methodology provides quick access to the pharmaceutically interesting compound CX-614 (Table 2, entry 9) and to a central building block for the synthesis of 3-substituted-[1,2,3]-benzotriazinones (Table 2, entry 5). In both cases, the modular nature of the starting materials allows for the synthesis of a wide range of derivatives.

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Supporting Information Available. Crystallographic data, experimental procedures, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Using in situ IR spectroscopy, we observed the buildup and subsequent persistence of an absorption peak centered around 1740 cm^{-1}. Attributing this peak to the cobalt-acyl species (cf. ref 15 and references therein), we suspect that the hydrogenolysis reaction might be the rate-determining step in our proposed catalytic cycle.