

Stereoselective Synthesis of Tetrahydropyran-4-ones from Dioxinones Catalyzed by Scandium(III) Triflate

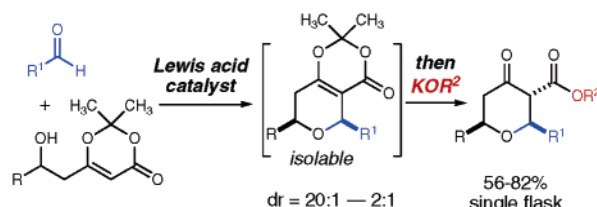
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ABSTRACT



A scandium triflate catalyzed, diastereoselective cyclization between aldehydes and β -hydroxy dioxinones has been discovered. This process capitalizes on the untapped nucleophilicity of the embedded enol ether within the dioxinone core. The bicyclic compounds from the resulting cyclization can be isolated, or alternatively, alkoxide nucleophiles can be directly added. This in situ addition fragments the dioxinone rings and delivers the 3-carboxy-substituted tetrahydropyran-4-ones in good yields with high levels of diastereoselectivity.

Tetrahydropyrans and related tetrahydropyran-4-ones are key structural elements in numerous bioactive natural products and medicinal compounds.¹ Because of their prevalence, there are multiple strategies for the construction of these six-membered ring systems, including Prins cyclizations,² hetero-Diels–Alder reactions,³ and intramolecular nucleophilic reactions.⁴ Inspired by the natural product targets currently being pursued in our laboratory and encouraged by the numerous bioactive compounds containing tetrahydropyrans, we desired a direct method for the synthesis of various carboxy-substituted tetrahydropyran-4-ones. Although exist-

ing methods might be employed to access these structures, we envisioned an efficient and mild approach to our targets that would capitalize on the previously untapped nucleophilic character of dioxinones such as **1**.⁵ We report herein the realization of this strategy as a one-pot, diastereoselective synthesis of tetrahydropyran-4-ones (**4**) from β -hydroxy-dioxinones (**1**) and aldehydes (**2**) catalyzed by a Lewis acid (Scheme 1, eq 1).

To install the desired 3-carboxy substituent directly, we sought to capitalize on the potential nucleophilicity of the α -position of the dioxinone ring system.⁶ Although an enol ether moiety is contained within the dioxinone nucleus of **1**, a survey of the literature revealed that, surprisingly, the use

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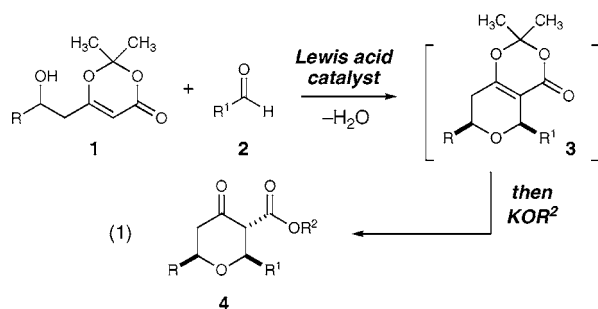
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(5) The appended carboxy substituent significantly attenuates the reactivity of dienes related to **1**, thereby rendering a hetero-Diels–Alder strategy to compounds such as **4** currently untenable under numerous Lewis acid catalyzed conditions surveyed.

Scheme 1



of dioxinones as nucleophiles is exceedingly rare.⁷ From a practical perspective, the β -hydroxy-dioxinones employed in this strategy are more stable than related β -keto esters and can be directly accessed from catalytic asymmetric additions of dienolates to aldehydes.⁸ Finally, the addition of nucleophilic alkoxides directly to the reaction flask would then convert intermediate **3** to the targeted 2,6-disubstituted tetrahydropyran-4-ones with an appended carboxy substituent.

Our initial investigations focused on identifying optimal carbon–carbon bond-forming conditions to generate stable species with the general structure of **3** (Table 1, eq 2). While stoichiometric quantities of BF₃·OEt₂ promoted the cyclization of β -hydroxy-dioxinone **1a** and aldehyde (**2a**, entry 1), we were delighted to discover that catalytic amounts of scandium(III) trifluoromethanesulfonate afforded high yields of the desired heterocycle **3a** (entries 2–5). Gratifyingly, the diastereoselectivity of the overall process is excellent (20:1), affording the 2,6-*cis* relative stereochemistry.⁹ A survey of the catalyst loadings indicated that 10 mol % of Sc(OTf)₃ was optimal in terms of yield and reaction time. The use of other metal triflate salts in the reaction, such as Sm(OTf)₃, La(OTf)₃, Mg(OTf)₂, and Zn(OTf)₂, did not provide significant quantities of the desired cyclized product, **3a**. It is important to note that the choice of dehydrating agent (CaSO₄) is crucial for obtaining high yields of the pyrone products under catalytic conditions.¹⁰ Utilizing molecular sieves or anhydrous magnesium sulfate consistently afforded lower yields of **3a** in a variety of solvents.

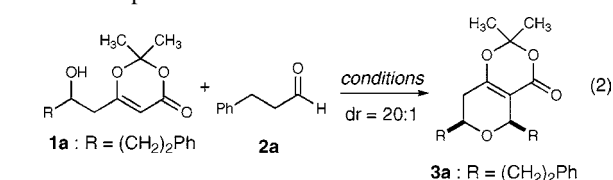
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(9) As determined by ¹H NMR (500 MHz) NOE experiments.

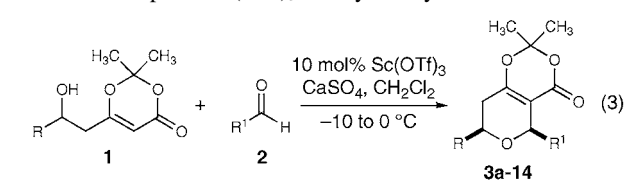
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Table 1. Optimization of Reaction Conditions^a

entry	conditions	yield (%) ^b
1	2 equiv of BF ₃ ·OEt ₂ , CH ₂ Cl ₂ , 0 °C, 2 h	51
2	20 mol % Sc(OTf) ₃ , H ₃ CCN, 4Å sieves, 0 °C, 3 h	45
3	20 mol % Sc(OTf) ₃ , CH ₂ Cl ₂ , CaSO ₄ , ^c –20 °C, 3 h	93
4	10 mol % Sc(OTf) ₃ , CH ₂ Cl ₂ , CaSO ₄ , ^c –20 °C, 4 h	80
5	5 mol % Sc(OTf) ₃ , CH ₂ Cl ₂ , CaSO ₄ , ^c –20 to 23 °C, 24 h	79

^a Reactions performed at 0.2 M. ^b Isolated yield. ^c Anhydrous.

With efficient Lewis acid catalyzed conditions identified, the influence of aldehyde structure on the transformation to **3** was probed (Table 2, eq 3). Saturated aldehydes participate in the cyclization, with linear systems (entries 1, 2, and 8) being superior to α -branched substrates (entry 9) in terms of yield. The overall diastereoselectivity of the reaction is dependent on the structure of the aldehyde. For example, *p*-anisaldehyde, 1-naphthaldehyde, and isobutyraldehyde provide reduced levels of selectivity compared to unbranched saturated or electron-deficient substrates. Various dioxinones (**1**) with alkyl chains (linear and branched) or aromatic rings (such as phenyl) flanking the hydroxyl group are good substrates and do not adversely impact diastereoselectivity of the resulting bicyclic compounds.

Table 2. Scope of Sc(OTf)₃-Catalyzed Cyclization

entry	R	R ¹	yield (%) ^b	dr (<i>cis:trans</i>) ^c	product
1	Ph(CH ₂) ₂	Ph(CH ₂) ₂	80	20:1	3a
2	Ph(CH ₂) ₂	<i>n</i> -hexyl	85	20:1	5
3	Ph(CH ₂) ₂	Ph	71	6:1	6
4	Ph(CH ₂) ₂	4-Cl-Ph	73	20:1	7
5	Ph(CH ₂) ₂	4-FI-Ph	83	20:1	8
6	Ph(CH ₂) ₂	4-MeO-Ph	54	2:1	9
7	Ph(CH ₂) ₂	1-Naphthyl	81	3:1	10
8	Ph(CH ₂) ₂	BnO(CH ₂) ₃	80	20:1	11
9	Ph(CH ₂) ₂	<i>i</i> -Pr	75	2:1	12
10	Ph	Ph(CH ₂) ₂	64	20:1	13
11	cyclohexyl	Ph(CH ₂) ₂	70	20:1	14

^a Reactions performed at 0.2 M. ^b Isolated yield after chromatographic purification. ^c As determined by ¹H NMR (500 MHz).

Table 3. One-Pot Cyclization/Ring Opening^a

entry	1,3-dioxin-4-one (1)	aldehyde (2)	nucleophile (KOR ₂)	yield (%) ^b	dr: (cis/trans) ^c	keto/enol ^d
1			KOEt	78% (15)	95 : 5	4 : 1
2			KOEt	72% (16)	95 : 5	4 : 1
3			KOEt	60% (17)	95 : 5	6 : 1
4			KOEt	67% (18)	93 : 7	2 : 1
5			KOCH ₂ Ph	82% (19)	94 : 6	4 : 1
6			KO(CH ₂) ₂ SiMe ₃	72% (20)	95 : 5	3 : 1

^a Reactions performed from -10 to 0 °C at 0.2 M; 4 equiv of KOR² added directly to reaction after conversion of **1**. ^b Isolated yield after chromatographic purification. ^c 2,6 relationship. ^d Enol/keto ratio determined by ¹H NMR (500 MHz).

In a multicomponent reaction approach,¹¹ 3-carboxy pyran-4-ones can be produced from a single reaction vessel by direct addition of potassium alkoxide salts (Table 3). This one-pot sequential process efficiently assembles three reaction components and can accommodate various substitutions on the dioxinone (**1**), aldehyde coupling partner (**2**), or alkoxide nucleophile (KOR²). By increasing the catalyst loading to 20 mol %, the overall process is accomplished in less than 10 h.¹² Presumably, the delivery of alkoxide promotes fragmentation of the dioxinone ring in situ to afford ethyl, benzyl, and trimethylsilyl ethyl esters in good yield (as keto/enol tautomers).

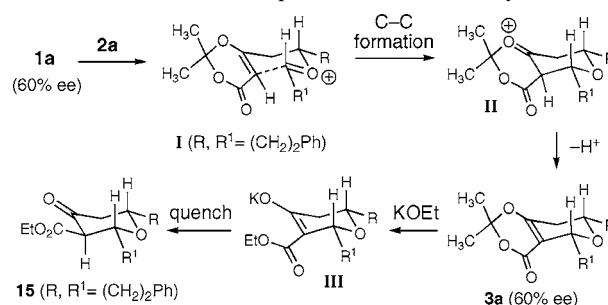
Our current working model of the reaction begins with the Lewis acid catalyzed formation of oxocarbenium ion **I**

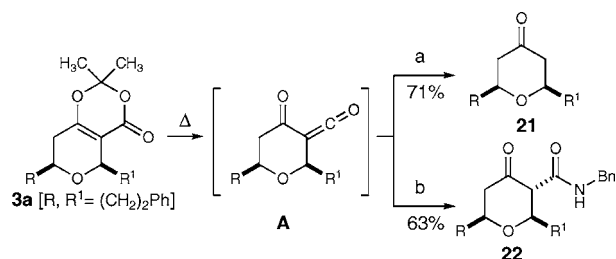
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(12) Lower catalyst loadings (5 and 10 mol %) increase reaction time but do not adversely affect yield or selectivity.

(13) An alternative mechanism may involve an oxonia-Cope rearrangement of **I** followed by ring closure; see: (a) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, 62, 3426–3427. (b) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, 3, 3815–3818 and references therein. (c) Roush, W. R.; Dilley, G. J. *Synlett* **2001**, 955–959. Further investigations to probe the operative reaction pathway are ongoing in our laboratory.

(Scheme 2). Presumably, C–C bond formation proceeds via a chairlike arrangement to afford dioxinone intermediate **II**. The elimination of a proton from this oxocarbenium species affords the bicyclic 2,6-*cis*-dioxinone **3a**.¹³ The addition of an alkoxide nucleophile (such as KOEt) to the reaction fragments the dioxinone ring, and protonation of the resulting enolate (**III**) upon quenching generates the thermodynamically favored equatorial ester (**4**).¹⁴ Gratifyingly, the original stereocenter of the β -hydroxy-dioxinone is completely conserved in **3a** when enantioenriched **1a**^{9c} is utilized in the

Scheme 2. Proposed Reaction Pathway

Scheme 3. Synthetic Transformations of Dioxinone **3a**^a

^a (a) DMSO, H₂O, 130 °C; (b) xylenes, reflux, H₂NCH₂Ph.

reaction. This stereochemical fidelity provides the foundation to synthesize desired optically active bicycles (such as **3a**) or carboxy-substituted tetrahydropyran-4-ones (such as **15**) from enantioenriched β -hydroxy-dioxinones.

A significant advantage to this methodology is that the dioxinone products **3a–14** are highly versatile platforms for further synthetic manipulations (Scheme 3). One avenue of transformation employs the exposure of the dioxinone core to heat, which presumably generates a reactive acylketene (**A**) via thermal reversion.¹⁵ Differentially trapping the acylketene from **3a** cleanly affords either unsubstituted tetrahydropyran-4-one **21** (71%) or β -keto amide **22** (63%) without affecting the diastereoselectivity established in **3a**. Interestingly, compounds such as **3a–14** have not been reported in the literature to date, and a full investigation of

(14) As a mixture of enol and keto tautomers. The configuration of this stereocenter is assigned based on large ¹H–¹H coupling values ($J \geq 10$ Hz) indicating a diaxial vicinal proton disposition.

(15) Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431–2435 and references therein.

the synthetic potential of these rigid reaction scaffolds should provide access to significant chemical diversity initiated by this new cyclization methodology.¹⁶

In summary, β -hydroxy-dioxinones and aldehydes undergo mild and stereoselective cyclizations in the presence of catalytic amounts of Sc(OTf)₃. This novel construction of the pyrone heterocycle capitalizes on the intrinsic, yet previous unexploited, nucleophilicity of the dioxinone moiety. The direct addition of a range of alkoxide nucleophiles to the reaction flask can convert the resulting bicyclic pyrans into carboxy-substituted tetrahydropyran-4-ones, thereby accessing a highly efficient three-component process. Alternatively, the intermediate pyrans can be isolated in good yield and converted into the related carboxamide or unsubstituted tetrahydropyran-4-ones by trapping the easily generated acylketenes. Applications of this new catalytic cyclization reaction to the synthesis of bioactive pyrones are in progress in our laboratory.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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