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IBX OXIDATIONS FOR THE SYNTHESIS OF SUBSTITUTED 2H-PYRANS

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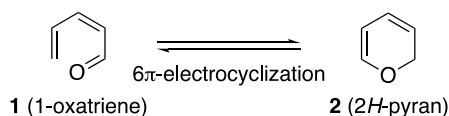
Abstract – Facile oxidation of highly substituted 3,5-hexadien-1-ols using 3-iodoxybenzoic acid (IBX) in DMSO has resulted in a one-pot preparation of 2,3,4,6-tetrasubstituted 2H-pyrans. Cycloisomerizations of the 1-oxatriene moiety, produced in the oxidation, spontaneously occur via a disrotatory oxa-electrocyclization. The 2H-pyran products of Table 1 features three differentiated carbonyl substituents.

In Celebration of Professor Yasuyuki Kita on His 77th Birthday

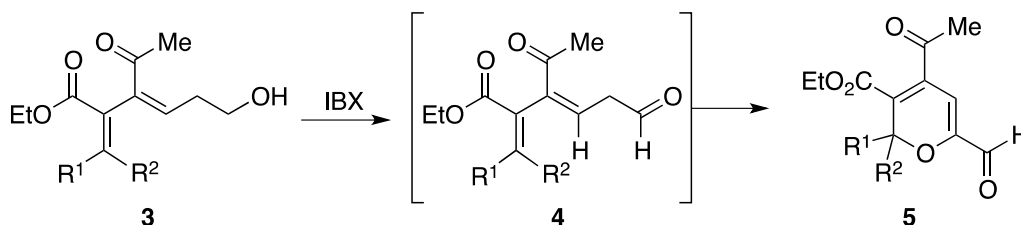
The pyran heterocycle is a common structural motif found within pharmaceuticals, agrichemicals, and biologically active natural products. Several reviews have summarized a variety of techniques for the preparation of substituted pyrans.¹ Methods for the synthesis of tetrahydropyrans have been extensively explored, and we have previously described a general strategy using asymmetric S_E' allylation reactions for enantiocontrolled syntheses of substituted tetrahydropyrans^{2,3} Similarly, the formation of dihydropyrans has attracted much attention because these structural motifs also appear within naturally-occurring macrolactones of biological interest.⁴ While syntheses of tetrahydropyrans and dihydropyrans are often focused on issues of stereochemistry and efficient strategies for regiocontrolled substitutions, the increased unsaturation of 2H-pyrans results in the characterization of notably less stable species. Successful methods toward substituted derivatives of this reactive family of pyrans are generally limited in scope.

In this communication, we report an efficient preparation of 2H-pyrans stemming from 3-iodoxybenzoic acid (IBX) oxidations of highly substituted 3,5-hexadien-1-ols with *in situ* electrocyclicization. The formation of 2H-pyrans via the oxa-electrocyclization reaction has been reported by several investigators in the course of studies for natural product synthesis,⁵ and a recent review has compiled key strategies for accessing 2H-pyrans as monocyclic as well as polycyclic structures via this cycloisomerization.⁶ One

reason for the instability of these substances is the observed valence isomerization between the 1-oxatrienes **1** and the ring-closed *2H*-pyrans **2**. Krasnaya⁷ has described significant studies of steric and electronic factors that influence the equilibria of these interconversions.



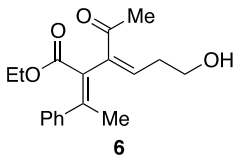
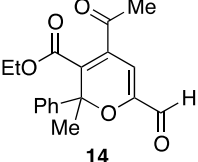
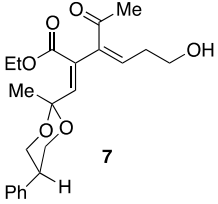
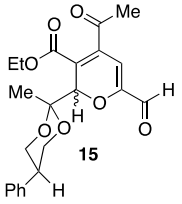
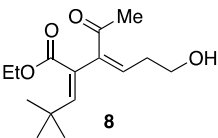
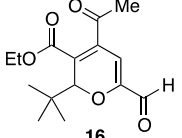
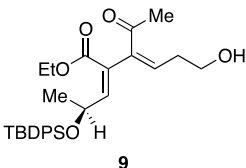
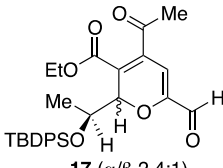
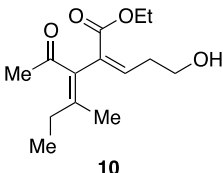
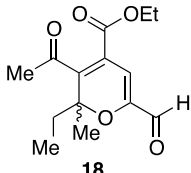
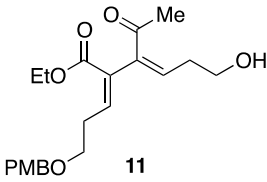
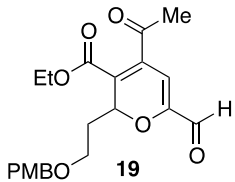
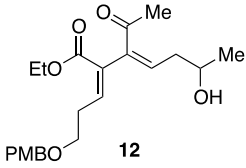
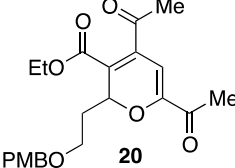
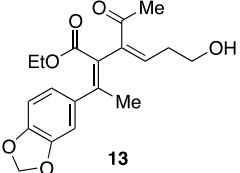
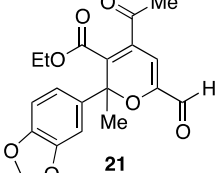
Recently, we have reported general methodology for the synthesis of α -linked bisenone systems via a ligandless palladium cross coupling.⁸ This reaction facilitates the formation of highly substituted, electron-deficient 1,3-dienes. These dienes undergo regio- and stereocontrolled condensations with indoles to afford complex tetrahydrocarbazoles in a single step via a tandem Michael–Mannich reaction.⁹ We sought to extend these studies to intramolecular processes which entailed the oxidation of the primary alcohol of **3** to provide aldehyde **4**. To our surprise, the use of one equivalent of IBX reagent in DMSO at room temperature readily produced the substituted *2H*-pyran **5** with the recovery of much of the alcohol. Poor conversion to the aldehyde **4** (less than 10%) was observed due to an overoxidation of the desired product.



Further studies have explored this transformation, and our preliminary results are compiled in Table 1. IBX oxidations are optimized in DMSO with three equivalents of reagent at 22 °C. Reactions are typically completed within approximately 8 hours, and the pyran products are isolated following flash silica gel chromatography. Common protecting groups are tolerated in the reaction, including ketals, silyl ethers, and PMB ethers.

The dienes of Table 1 have been prepared as pure C=C isomers via Stille cross couplings which retain the olefin geometry of the starting alkenyl iodides and stannanes.¹⁰ A facile overoxidation of the homoallylic alcohols present in compounds **6–13** (Table 1) has produced the tetrasubstituted *2H*-pyrans **14–21** which are distinguished by the introduction of a carboxaldehyde at C-6 (entries 1–6) or methyl ketone (entry 7). Entries 1, 5, and 8 illustrate the participation of tetrasubstituted alkenes in the ring closure process, and the presence of an adjacent center of chirality in **9** leads to a modest stereochemical

Table 1. The formation of 2*H*-pyrans

Entry ^a	Starting Diene ^b	Product ^c	Yield ^d
1	 6	 14	81%
2	 7	 15	52%
3	 8	 16	71%
4	 9	 17 (α/β 2.4:1)	60%
5	 10	 18	48%
6	 11	 19	81%
7	 12	 20	56%
8	 13	 21	60%

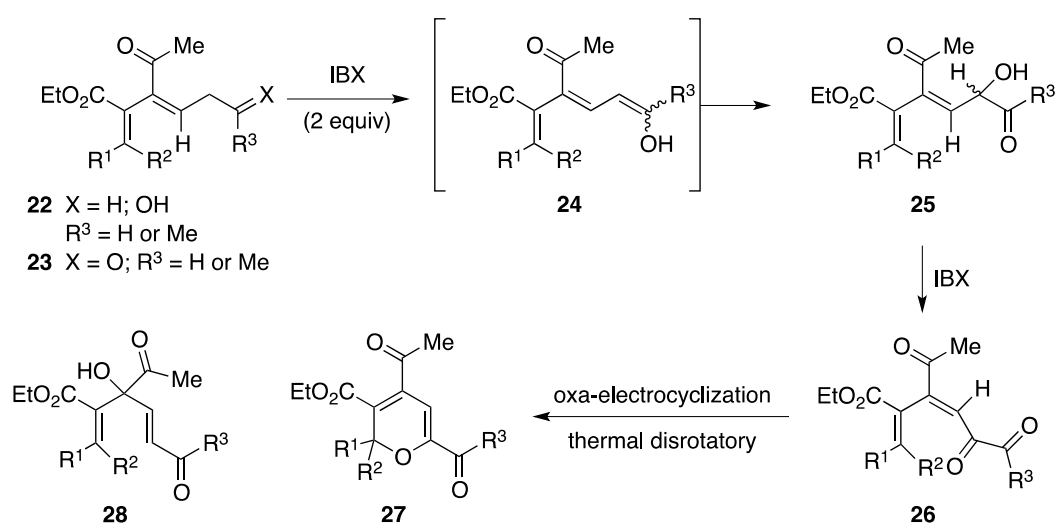
^a Reaction conditions: Dienes were treated with IBX (3.25 equiv) in DMSO at 22 °C for approximately

h. ^b Starting dienes were prepared according to our published procedure of reference 8, and purified and

characterized by proton and carbon NMR spectroscopy prior to use. ^c Pyran products were purified by flash chromatography (gradient elution 5% EtOAc to 30% EtOAc in Hexanes), and were characterized by ¹H and ¹³C NMR analysis. ^d Yields are reported for purified product, based on starting diene, using the general reaction conditions.

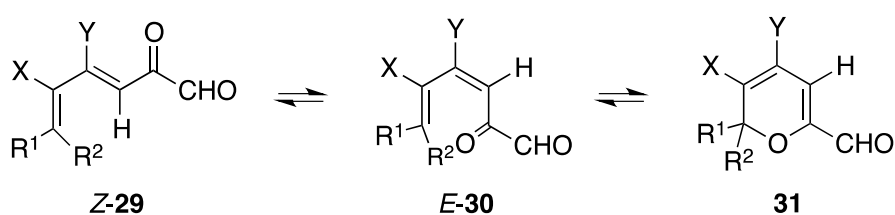
preference for the 2(*S*)-isomer of **17** (α/β ratio 2.4:1). The 2*H*-pyrans **14–21** (Table 1) have been characterized by ¹H and ¹³C NMR spectroscopy and via HRMS analysis.¹¹ Proton NMR spectroscopy reveals a distinctive singlet for the vinylic C-5 hydrogen, typically appearing in the region of δ 6.02–6.57 ppm whereas the methine C-2 hydrogen of compounds **15–17**, and **19** and **20** is observed in the range of δ 5.19–5.55 ppm.

Scheme 1 illustrates a proposed pathway for pyran formation. The initial oxidation of the homoallylic alcohol introduces a carbonyl group which readily undergoes enolization to provoke the IBX-induced α -hydroxylation¹² to afford intermediate **25** for conversion to the α -dicarbonyl compound **26**. A facile C=C isomerization must occur for oxa-electrocyclization of **26** to provide the 2*H*-pyran product **27**. In some cases, we have found evidence for the production of side products which have tentatively been identified as the tertiary alcohols **28**. Resubmission of these substances to the IBX conditions do not proceed to pyran formation in spite of the apparent ease of isomerization of allylic alcohol **28**. Further experimentation is underway to probe this aspect particularly in view of the precedented [3,3]-rearrangement of intermediates anticipated from initial reactions of **28** with additional oxidant.



Scheme 1. Proposed rationale for the formation of 2*H*-pyrans

We have investigated this reversible electrocyclization via computational studies because our experiments did not observe the *Z*- or *E*-isomers **29** and **30** to suggest an equilibrium involving the *2H*-pyran **31** ($X = \text{CO}_2\text{Et}$; $Y = \text{COMe}$). Our initial computational efforts have examined the specific transformations of **6** to pyran **14**, and **8** to the *t*-butyl substituted **16**. Free energy (ΔG) for the conversion of *Z*-**29** to yield **31** is calculated as -4.56 kcal/mol and -10.64 kcal/mol, respectively. Enthalpies ΔH [$H^\circ(\mathbf{31}) - H^\circ(\mathbf{29})$] for these examples are -7.36 kcal/mol and -14.76 kcal/mol, respectively.¹³ These parameters are in general agreement with data described by Krasnaya,⁷ and may suggest a steric destabilization of the starting dienone. Further refinements are anticipated to evaluate electronic criteria.



However, we postulate the presence of electron-withdrawing carbonyl substituents at C-3, C-4 and C-6 may favor *2H*-pyran formation. In our case, the use of aprotic polar solvent (DMSO) does not shift the equilibrium toward the ring-opened dienones as previously observed.⁶

In summary, our studies have described the IBX oxidations of 3,5-hexadien-1-ols resulting in the formation of tetrasubstituted *2H*-pyrans via the oxa-electrocyclization of 1-oxatriene intermediates. These cyclizations proceed with a crucial C=C isomerization to achieve a concerted transition state geometry. Reactions are successful in spite of considerable steric interactions. Computational studies reveal a thermodynamic preference for pyran products in this family, displaying three distinct carbonyl substituents. Further studies will explore electronic effects in the scope of this reaction.

ACKNOWLEDGEMENTS

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SUPPORTING INFORMATION

Supplementary data (general experimental procedures for the preparation of the starting 3,5-dien-1-ols of Table 1 and the IBX oxidation reaction to obtain *2H*-pyran products, proton and carbon NMR data, FTIR and HRMS characterizations) associated with this article can be found, in the online version, at URL: <https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27093/103/2>

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- A general procedure for the cross coupling and characterization data for the starting dienes of Table 1 can be found in the Supporting Information.
- See Supporting Information for a general procedure and characterization data for the 2*H*-pyrans of Table 1.
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- DFT calculations optimized the lowest PM603 energy structures at the ωb 97xd/6-31⁺g(d,p) level

using SMD DMSO solvent modeling. Calculations have suggested enthalpic and entropic favorability of the *2H*-pyran structures. Full DFT computations of the specific interconversions of **Z-29**, **E-30**, and **31** are underway.