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FURTHER INVESTIGATION OF PYRANONE ACTIVATION

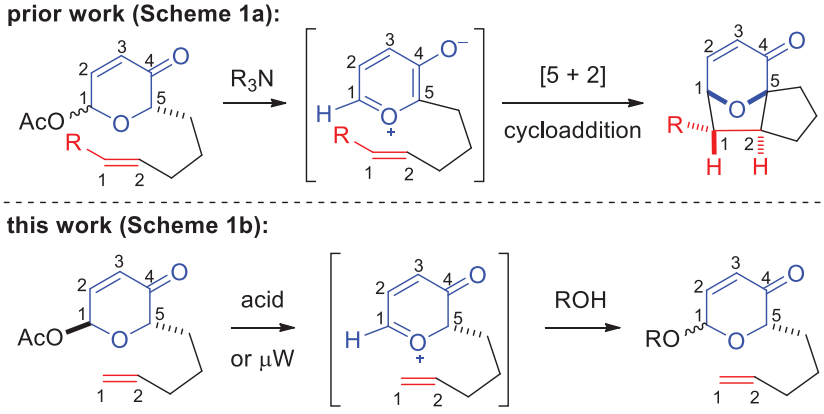
Justin A. Simanis, Christian R. Zwick, Erica L. Woodall, John R. Goodell, and T. Andrew Mitchell*

Department of Chemistry, Illinois State University, Normal, IL 61790-4160; tmitche@ilstu.edu

Abstract – As part of our ongoing investigation into the activation parameters of pyranones to the corresponding oxidopyryliums, various means were investigated. Screening of acid mediators revealed limited efficiency, with HCl providing the best result. Additional acid-mediated and microwave-assisted studies provided evidence that oxocarbenium formation is a key mechanistic event thwarting formation of oxidopyrylium intermediates. A μW-assisted exchange process was discovered allowing for the rapid synthesis of potentially useful alkoxypyranones.

Although oxidopyrylium-alkene [5+2] cycloaddition reaction[1] are used extensively to access biologically active natural products[2] containing a diverse range of bridged polycyclic ether substitution patterns, relatively little is known about the requisite activation parameters.[3] The most common method to generate oxidopyrylium intermediates is base-mediated activation of acetoxypyranones.[4] However, acylation of sterically hindered hydroxypyranone precursors has proven to be problematic[5] since tertiary hydroxypyranones are known to undergo ring fragmentation upon exposure to amine bases required for acylation.[6] Given this limitation of acetoxypyranone substitution at the acetal carbon,[7] we sought to explore tertiary hydroxypyranone substrates in greater detail toward oxidopyrylium activation and subsequent [5+2] cycloaddition. An interesting solution demonstrated by Magnus involved the activation of a tertiary hydroxypyranone directly to an oxidopyrylium by exposure to trifluoroacetic acid.[5b] Except for an earlier example by Sammes that was likely a result of thermal rather than acid-activation,[4b] to our knowledge this TFA-mediated case[5b] is the sole example of acid-mediated hydroxypyranone activation to an oxidopyrylium intermediate. Intrigued by this potential alternative to base-mediated activation, we sought to explore this mode of activation en route to novel oxidopyrylium-alkene [5+2] cycloadditions. Intramolecular cycloadditions were utilized as model reactions due to an inherent entropic advantage that

increases the rate of cycloaddition thus enhancing the probability of intercepting the proposed transient oxidopyrylium intermediate.[4b] Although acid-mediated activation gave poor conversion of desired cycloadduct, the insight gleaned shed light on acid-mediated,[5b] microwave-assisted,[8] and base-mediated activation.[9] Herein, we report these results and a μW-assisted formation of alkoxypyranones (Scheme 1).

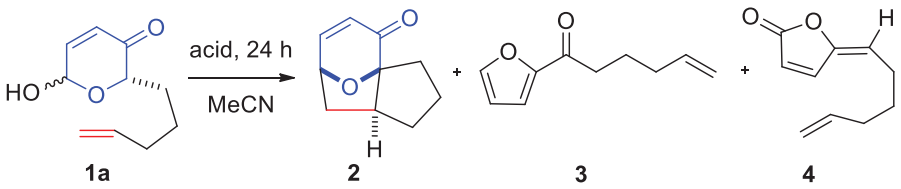


Scheme 1. Acetoxypyranone Modes of Activation

Hydroxypyranone **1a** was synthesized as a mixture of diastereomers (dr 2:1) in two steps. Acetoxypyranone **1b** was prepared by treatment of **1a** with acetyl chloride and pyridine. Flash column chromatography delivered diastereomerically pure *anti*- and *syn*-**1b**.[9] The major acetoxypyranone, *anti*-**1b** (>19:1), was utilized to probe the mechanism of activation (*vide infra*). Reaction of hydroxypyranone **1a** with various acids provided multiple outcomes (Table 1). AcOH provided only recovered starting material (entry 1), whereas HCl (entry 2) and CSA (entry 3) afforded minimal cycloadduct **2** along with by-products **3** and **4**.[10] Perchloric and triflic acids (entries 4 and 5) led to decomposition of starting material. Alternatives such as HCl salts of amines and Lewis acids (not shown) showed little promise to afford cycloadduct **2**. In similar reactions with *anti*-**1b**, hydroxypyranone **1a** was detected by ^{1}H NMR analysis of crude reaction mixtures thus signifying its potential as an intermediate en route to cycloadduct **2**. Consequently, our next objective was to ascertain whether acetoxypyranone *anti*-**1b**, in the presence of acid and water, was converted to hydroxypyranone **1a** via an oxocarbenium intermediate[11] or through simple hydrolysis. Thus, we screened various conditions utilizing high concentration of nucleophilic solvent in order to capture potential transient oxocarbenium intermediates. We found that *anti*-**1b** (dr >19:1) was readily converted to **1a** (dr ~2:1) upon exposure to a range of acids and high concentration of H_2O (Table 2, entries 1-4). Similar acidic conditions provided methoxypyranone **1c** (dr ~1:1),[10] albeit with lower yields presumably due to side reactions of the enone moiety (entries 5-8). The formation of acetal **1c** from *anti*-**1b** provides critical information[12] since it is incapable of forming as a result of hydrolysis. This supports oxocarbenium formation as the first mechanistic event in acid-mediated pyranone activation since nucleophilic attack at sp^2-hybridized oxocarbenium intermediates would be

expected to provide a mixture of diastereomers, while hydrolysis would maintain stereochemical fidelity. Interestingly, the diastereomeric ratio of hydroxypyranone **1a** produced via acid-mediated exchange was similar to that observed when synthesized by previously reported methods.[9] Analogous acid-mediated reactions of hydroxypyranone **1a** led to decomposition of starting material. These results provide evidence that oxocarbenium formation plays a crucial role in the conversion to pyranones **1a** and **1c**.

Table 1. Acid-Mediated Activation of Hydroxypyranone **1a**

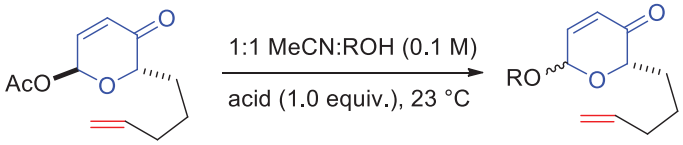


1a **2** **3** **4**

entry	acid	temp. (°C)	% yield[a]			
			1a	**2**	**3**	**4**
1	AcOH	60	69	ND[b]	ND[b]	ND[b]
2	HCl[c]	40	0	21	10	19
3	CSA[d]	60	0	11	14	20
4	TfOH[e]	-40	decomposition[f]			
5	$HClO_4$	-40	decomposition[f]			

[a] Determined by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as the internal standard. [b] Not detected [c] 0.5 equiv. of HCl was utilized with 25 μL of H_2O. [d] Camphorsulfonic acid. [e] Trifluoromethanesulfonic acid [f] Determined by ^{1}H NMR analysis of crude reaction mixtures.

Table 2. Acid-Mediated Exchange via Oxocarbenium Intermediate



anti-**1b** (dr >19:1)

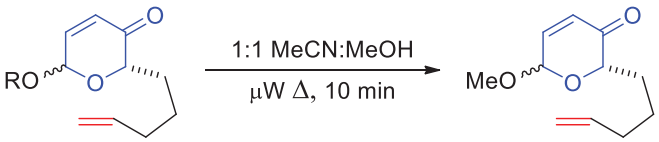
1a R = H
1c R = Me

entry	ROH	acid	temp. (°C)	time (h)	% yield **1a/1c**[a]	dr[a]
1	H_2O	HCl	23	3	63	2.3:1
2	H_2O	TFA	23	3	87	2.0:1
3	H_2O	AcOH	23	3	ND[b]	NA[c]
4	H_2O	AcOH	60	24	80	1.9:1
5	MeOH	HCl	23	3	8	1.6:1
6	MeOH	TFA	23	3	79	1.0:1
7	MeOH	AcOH	23	24	ND[b]	NA[a]
8	MeOH	AcOH	60	24	11	1:1.2

[a] Determined by ^{1}H NMR analysis utilizing 1,3,5-trimethoxybenzene as the internal standard. [b] Not detected [c] Not applicable.

Based on acid-mediated exchange results that suggest initial oxocarbenium en route to oxidopyrylium generation, an analogous study was conducted to determine if μW-assisted conditions would proceed in similar fashion. Toward this end, pyranones **1a** and *anti*-**1b** were subjected to microwave irradiation[10] in MeCN:MeOH (1:1) for ten minutes (Table 3). Heating to 100 °C was insufficient to obtain significant conversion of either **1a** or **1b** to methoxypyranone **1c** (entries 1, 5). As compared to *anti*-**1b**, hydroxypyranone **1a** was more readily converted to **1c** at elevated temperatures (entries 2-3, 6-7). In contrast, upon heating to 160 °C and isolation of methoxypyranone **1c**,[10] greater efficiency with *anti*-**1b** was observed as compared to **1a** (entries 4, 8). Similar to the acid-mediated activation, isolation of a diastereomeric mixture suggests that oxocarbenium intermediates are formed in these reactions. In order to explore the scope of this exchange process, we attempted to substitute various alcohols (Table 4). Upon increasing the concentration (0.1 → 1 M), moderate yield was obtained with just two equivalents of MeOH (entry 1). Isopropanol afforded a similar result (entry 2) and other primary alcohols were successful (entries 3-5). In all cases, minimal cycloadduct **2** was observed further demonstrating the lack of efficiency of oxocarbenium conversion to oxidopyrylium. Other nucleophiles (not shown) were unproductive: trifluoroethanol afforded low yield and *N*-hydroxyphthalimide gave decomposition.

Table 3. μW-Assisted Exchange *via* Oxocarbenium Formation



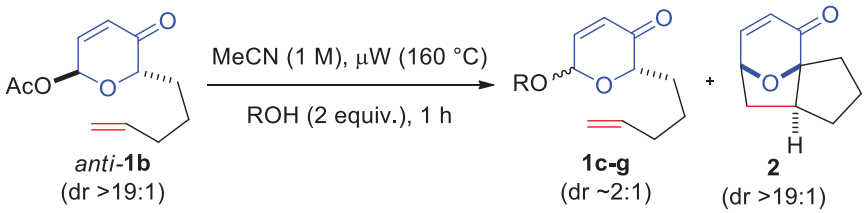
1a R = H
1b R = Ac

1c

entry	pyranone	temp. (°C)	% yield **1a/1b**[a]	% yield **1c**[a]	dr[a]
1	**1a**[b]	100	79	ND[d]	NA[e]
2	**1a**[b]	120	39	32	1.4:1
3	**1a**[b]	140	30	44	1.5:1
4	**1a**[b]	160	<5[f]	70[g]	1.7:1
5	**1b**[c]	100	100	ND[d]	NA[e]
6	**1b**[c]	120	81	ND[d]	1.0:1
7	**1b**[c]	140	48	21	1.1:1
8	**1b**[c]	160	ND[d]	89[g]	1.2:1

[a] Determined by ^{1}H NMR analysis utilizing 1,3,5-trimethoxybenzene as the internal standard. [b] dr 2.4:1. [c] *anti* (>19:1). [d] Not detected. [e] Not applicable. [f] Trace quantity detected by ^{1}H NMR analysis of crude reaction mixture. [g] Isolated yield.

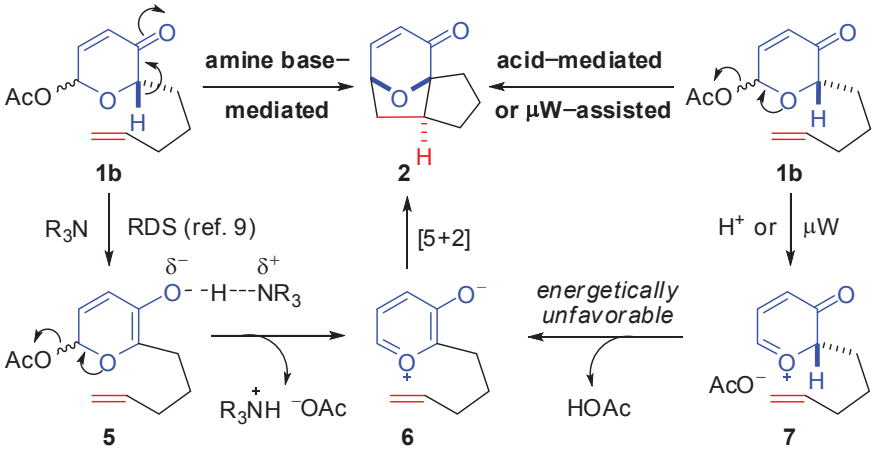
Table 4. μW-Assisted Synthesis of Alkoxypyranones **1c-g**



entry	ROH	% yield **1c-g**[a]	% yield **2**[b]	dr[b]
1	MeOH	70 (**c**)	14	2.3:1
2	*i*PrOH	68 (**d**)	13	2.4:1
3	5-hexen-1-ol	62 (**e**)	14	2.6:1
4	ethyl glycolate	44 (**f**)[c]	6	2.1:1
5	2-allyloxyethanol	73 (**g**)[c]	14	2.4:1

[a] Isolated yield. [b] Estimated by ^{1}H NMR analysis of the crude reaction mixture. [c] Inseparable mixture with cycloadduct **2**.

Taken together, these results stand in stark contrast to previous findings utilizing base-mediated activation (Scheme 2).[9] Specifically, we used kinetic isotope effects to demonstrate that abstraction of the α-hydrogen is involved in the rate-determining step of oxidopyrylium generation. Elimination of the acetoxy from dienolate **5** provides oxidopyrylium **6**, which undergoes [5+2] cycloaddition to tricyclic ether **2**. In contrast, both acid-mediated and microwave-assisted activation of pyranones **1a** and **1b** (*vide supra*) suggest that oxocarbenium **7** is formed prior to oxidopyrylium **6**. Although not a direct correlation, inference from the calculated ground-state conformation of oxocarbenium **7**[13] suggests that an energetically unfavorable deprotonation of the α-proton[10] may explain the fact that oxocarbenium **7** inefficiently progresses toward oxidopyrylium **6**. Hydroxypyranones utilized in previous examples[4b,5b] contain structural features that likely explain the increased yields as compared to our model system (*vide supra*). In these cases, the alkene tether is appended to the same carbon as the hydroxyl group. Consequently, it seems plausible that two α-hydrogens may allow for a lower activation energy barrier of deprotonation due to increased orbital overlap with the adjacent ketone toward oxidopyrylium formation.



Scheme 2. Mechanism for Acetoxypyranone Modes of Activation

Activation parameters of various pyranones were investigated. Screening of acid mediators in a model reaction revealed limited cycloaddition with multiple by-products. Multiple experiments utilized both acid-mediated and microwave-assisted methods to provide evidence suggestive of oxocarbenium formation as the initial mechanistic event toward the generation of oxidopyrylium intermediates. This is contrary to our previous results with base-mediated processes which suggest initial deprotonation of the α-proton en route to oxidopyrylium intermediates. Both of these studies, taken together, aid our understanding of the activation parameters of acetoxypyranones, which will be further investigated synthetically and computationally. As a more complete description of these parameters emerges, this will inevitably lead to advances toward novel cycloaddition processes.

EXPERIMENTAL

Pyranone 1c: Prepared according to the general procedure with *anti*-**1b** (208 mg, 0.927 mmol), MeOH (75 μL, 1.85 mmol), and MeCN (925 μL). Purification by flash column chromatography (hexanes:EtOAc 90:10) delivered *anti*-**1c** as a white solid (35 mg, 0.18 mmol, 20%, dr >19:1), and *anti*-**1c**/*syn*-**1c** mixture as a yellow oil (89 mg, 0.45 mmol, 49%, dr 1.4:1.0). Spectral data matched that obtained from the alternative conditions toward pure diastereomers of methoxypyranone **1c** (*vide supra*).

Pyranone 1d: Prepared according to the general procedure with *anti*-**1b** (200 mg, 0.892 mmol), *i*PrOH (107 mg, 1.78 mmol), and MeCN (890 μL). Purification by flash column chromatography (hexanes:EtOAc 90:10) delivered *anti*-**1d** as a pale yellow oil (49 mg, 0.22 mmol, 25%, dr >19:1), *anti*-**1d**/*syn*-**1d** mixture as a yellow oil (76 mg, 0.34 mmol, 38%, dr 1.7:1.0), and *anti*-**1d**/*syn*-**1d** mixture as a yellow oil (11 mg, 0.05 mmol, 5%, dr 0.13:1.0); Characterization data for *anti*-**1d**: $\mathbf{R_f}$ = 0.49 (hexanes:EtOAc 85:15); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.80 (dd, *J* = 10.2, 3.6 Hz, 1H), 6.06 (dd, *J* = 10.2, 0.6 Hz, 1H), 5.85-5.77 (m, 1H), 5.30 (dd, *J* = 3.6, 0.6 Hz, 1H), 5.03-4.99 (m, 1H), 4.97-4.94 (m, 1H), 4.44 (dd, *J* = 8.4, 3.6 Hz, 1H), 4.05 (qq, *J* = 6.3, 6.1 Hz, 1H), 2.15-2.05 (m, 2H), 2.01-1.95 (m, 1H), 1.72-1.64 (m, 1H), 1.60-1.49 (m, 2H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.23 (d, *J* = 6.1 Hz, 3H); **^{13}C NMR** (400 MHz, $CDCl_3$) δ 196.9, 144.0, 138.4, 127.5, 114.7, 91.3, 73.8, 70.8, 33.5, 29.1, 24.5, 23.3, 21.8; **IR (film)** $\mathbf{\nu_{max}}$ 1700, 1049 cm^{-1}; **ESI-HRMS** calculated for $C_{13}H_{20}O_3$ $[M+Li]^+$ 231.1567, found 231.1560.

Pyranone 1e: Prepared according to the general procedure with *anti*-**1b** (224 mg, 1.00 mmol, 1.0 equiv.), 5-hexen-1-ol (93.5 mg, 2.00 mmol, 2.0 equiv.), and MeCN (925 μL). Purification by flash column chromatography (hexanes:Et_2O 85:15) delivered *anti*-**1e** as a pale yellow oil (112 mg, 0.42 mmol, 42%, dr >19:1), and *anti*-**1e**/*syn*-**1e** mixture as a yellow oil (54 mg, 0.20 mmol, 20%, dr 0.21:1.0); Characterization data for *anti*-**1e**: $\mathbf{R_f}$ = 0.26 (hexanes:Et_2O 85:15); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.83 (dd, *J* = 10.2, 3.5 Hz, 1H), 6.07 (dd, *J* = 10.2, 0.6 Hz, 1H), 5.86-5.76 (m, 2H), 5.19 (dd, 3.5, 0.6 Hz, 1H), 5.04-4.99 (m, 2H), 4.98-4.95 (m, 2H), 4.40 (dd, *J* = 8.4, 3.6 Hz, 1H), 3.85-3.80 (m, 1H), 3.6-3.56 (m, 1H),

2.15-2.04 (m, 4H), 2.02-1.95 (m, 1H), 1.68-1.46 (m, 7H); **^{13}C NMR** (400 MHz, C_6D_6) δ 195.4, 142.9, 138.31, 138.30, 127.1, 114.6, 114.5, 93.1, 73.8, 68.7, 33.5, 33.4, 29.13, 29.05, 25.4, 24.5; **IR (film) ν_{max}** 1700, 1034 cm^{-1}; **ESI-HRMS** calculated for $C_{16}H_{24}O_3$ $[M+Li]^+$ 271.1880, found 271.1892.

Pyranone 1f: Prepared according to the general procedure with *anti*-**1b** (206 mg, 0.917 mmol), ethyl glycolate (191 mg, 1.83 mmol), and MeCN (915 μL). Purification by flash column chromatography (hexanes:EtOAc 85:15) delivered *anti*-**1f**/*syn*-**1f** mixture (111 mg) contaminated with cycloadduct **2** (13 mg) as a pale yellow oil (calc. 98 mg, 0.37 mmol, 40%, dr 1.49:1.0) and *syn*-**1f** as a yellow oil (11 mg, 0.045 mmol, 4%, dr >19:1); Characterization data for *syn*-**1f**: $\mathbf{R_f}$ = 0.21 (hexanes:EtOAc 85:15); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.98 (dd, *J* = 10.4, 2.1 Hz, 1H), 6.15 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.84-5.74 (m, 1H), 5.46-5.45 (m, 1H), 5.04-4.99 (m, 1H), 4.98-4.94 (m, 1H), 4.37 (d, *J* = 16.4 Hz, 1H), 4.32 (d, *J* = 16.4 Hz, 1H), 4.27-4.21 (m, 2H), 4.08-4.04 (m, 1H), 2.15-2.01 (m, 2H), 1.97-1.78 (m, 2H), 1.65-1.48 (m, 2H), 1.30 (dd, *J* = 7.2, 7.1 Hz, 3H); **^{13}C NMR** (400 MHz, $CDCl_3$) δ 196.0, 169.7, 145.4, 138.2, 128.7, 114.9, 95.0, 79.0, 64.7, 61.2, 33.4, 31.1, 24.7, 14.2; **IR (film) ν_{max}** 1751, 1699, 1063 cm^{-1}; **ESI-HRMS** calculated for $C_{14}H_{20}O_5$ $[M+Li]^+$ 275.1466, found 275.1454.

Pyranone 1g: Prepared according to the general procedure with *anti*-**1b** (210 mg, 0.936 mmol), 2-allyloxyethanol (191 mg, 1.87 mmol) and MeCN (935 μL). Purification by flash column chromatography (hexanes:EtOAc 90:10) delivered *anti*-**1g**/*syn*-**1g** mixture (181 mg) contaminated with cycloadduct **2** (18 mg) as a pale yellow oil (calc. 163 mg, 0.61 mmol, 65%, dr 3.7:1.0) and *syn*-**1g** as a yellow oil (19 mg, 0.07 mmol, 8%, dr >19:1); Characterization data for *syn*-**1g**: $\mathbf{R_f}$ = 0.15 (hexanes:EtOAc 90:10); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.92 (dd, *J* = 10.3, 1.9, 1H), 6.12 (dd, *J* = 10.3, 1.7, 1H), 5.97-5.87 (m, 1H), 5.86-5.76 (m, 1H), 5.40-5.39 (m, 1H), 5.31-5.26 (m, 1H), 5.21-5.18 (m, 1H), 5.05-4.98 (m, 1H), 4.97-4.94 (m, 1H), 4.05-4.01 (m, 4H), 3.85-3.79 (m, 1H), 3.67-3.64 (m, 2H), 2.14-2.03 (m, 2H), 2.01-1.77 (m, 2H), 1.68-1.48 (m, 2H); **^{13}C NMR** (400 MHz, $CDCl_3$) δ 196.4, 146.6, 138.4, 134.6, 128.6, 117.3, 114.8, 96.0, 78.9, 72.3, 69.2, 68.1, 33.4, 30.7, 24.7; **IR (film) ν_{max}** 1700, 1051 cm^{-1}; **ESI-HRMS** calculated for $C_{15}H_{22}O_4$ $[M+H]^+$ 267.1596, found 267.1581.

ACKNOWLEDGEMENTS

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