Highly Stereoselective 7-Membered Ring Synthesis Based upon the Oxidopyrylium–Alkene [5+2]Cycloaddition Reaction

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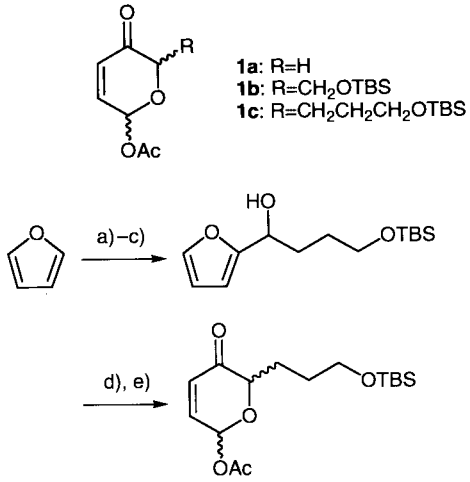
The [5+2]cycloaddition reaction of 2-substituted-3-oxidopyrylium betaine with dialkyl fumarates was found to proceed with stereoselectivity up to 15.5:1. The stereoselectivity became higher as either the 2-substituent of the 3-oxidopyrylium or the alkoxy group of the fumarate became larger. The stereoselectivity could be rationalized by considering these steric effects.

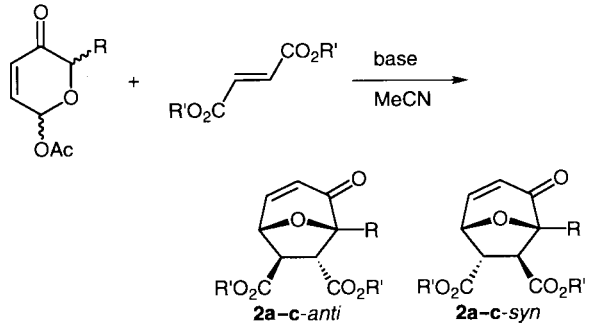
[5+2]Cycloaddition based upon the reaction of 3-oxidopyrylium, generated in situ from derivatives of 6-hydroxy-2*H*-pyran-3(6*H*)-ones, with alkenes has emerged as an efficient method of constructing 7-membered ring units,[1,2] and the application of this method has led to the elegant synthesis of some natural products.[3] However, most reported applications are either of intramolecular nature or of intermolecular reactions involving electron-rich alkenes, and the examination of electron-deficient alkenes has been limited.[1,4] The use of disubstituted alkenes potentially could give rise to up to four stereo centers in one transformation. Stemming from our interest in natural products bearing distinctly hydrophilic and hydrophobic moieties[5] and the application of the [5+2]cycloaddition reaction,[6] we have initiated synthetic studies directed towards CP-263,114, a potential anti-tumor agent, which features a 7-membered ring in the core.[7] During our examinations, a key [5+2]reaction of 3-oxidopyrylium with dimethyl fumarate was found to proceed with 13:1 stereoselectivity. In order to elucidate the effects underlying this selectivity, we have carried out a systematic investigation of the effect of the 2-substituent of the 3-oxidopyrylium betaines and the alkoxy moiety of the fumarate. Herein we describe our results.



Scheme 1. a) (i) *n*-BuLi, (ii) γ-butyrolactone, 69%; b) TBSCl, 99%; c) $NaBH_4$, 92%; d) mCPBA, 96%; e) Ac_2O, pyridine, 69%.

3-Oxidopyrylium betaine precursors **1a–c** were examined, as a function of chain size. Compound **1a** was prepared by known procedures.[4b] The preparation of compound **1b** was carried by the reaction of α-lithiofuran with TBS protected hydroxyacetaldehyde. The diastereomeric ratio was ca. 2:1. Since the stereochemistry here is lost in the subsequent cycloaddition reaction, the stereochemical identity of the diastereomers was not determined. Compound **1c** was prepared in five steps from furan as outlined in Scheme 1, in a similar diastereomeric ratio of ca. 2:1.

The reaction between compound **1c** and dimethyl fumarate was examined in order to optimize reaction conditions (Scheme 2). First of all, Et_3N, which is a standardly used base for this reaction was looked over. The reaction in MeCN was found to proceed at reflux temperature to give the adduct in 4:1 isomeric ratio and 84% yield (Table 1, Entry 7). This reaction and all the reactions that followed were found to be completely stereospecific in regards with the double bond geometry and no product in which the carboxylates were positioned *cis* could be isolated, thus verifying that the reaction is indeed concerted even for our system which is somewhat sterically congested. Assignment of the stereochemistry of the major compound was done on the basis of coupling constants and confirmed with NOE measurements.[8]



Scheme 2.

Table 1. [5+2] Reactions with Fumarates

Entry	Oxo-pyran	R'	Conditions[a]	Yield (%)	Ratio[b] *anti:syn*
1	**1a**	Me	rt, 2d	98	2:1
2	**1a**	*i*-Pr	rt, 2d	76	2:1
3	**1a**	*t*-Bu	rt, 2d	77	1:1.3
4	**1b**	Me	refluxed, 2d	85	13:1
5	**1b**	*i*-Pr	refluxed, 2d	63	15:1
6	**1b**	*t*-Bu	refluxed, 2d	55	15.5:1
7	**1c**	Me	refluxed, 2d	84	4:1
8	**1c**	*i*-Pr	refluxed, 2d	68	7:1
9	**1c**	*t*-Bu	refluxed, 2d	63	14:1

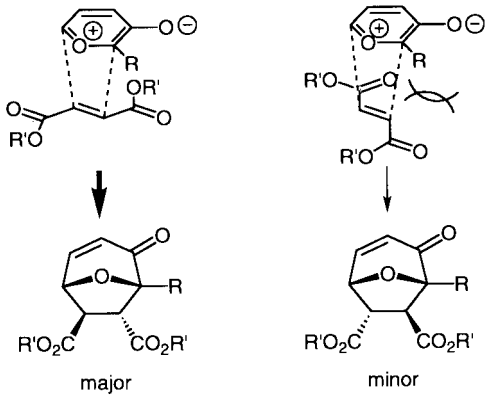
[a]Et_3N was used as base. [b]*anti:syn* designation is based upon the relative relationship between the R group and the adjacent carboxylate.

With the objective of achieving higher selectivity at possibly lower temperatures, which should be preferable for possible asymmetric efforts, other reaction conditions were examined. Other bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), and *N*-methylmorpholine were also studied. However, either there was little difference with the results of Et_3N (DABCO, methylmorpholine) or the yield was inferior (DBU, TMEDA). The use of acidic conditions, instead of basic, with trifluoroacetic acid[3c] and trifluoromethanesulfonic acid lead to decomposition of the oxopyran substrate. The use of $LiClO_4$ in neither ether nor MeCN resulted in any enhancement of reactivity under neutral conditions, and induced decomposition when used in conjunction with Et_3N. The use of a solvent of low polarity, namely CH_2Cl_2, lead to retardation of rate. Thus, we could not establish milder conditions and decided to continue our investigations using Et_3N in MeCN.

The reaction of the oxidopyrylium precursor **1a** unsubstituted at the 2-position was found to proceed at room temperature, however with low selectivity (Table 1, Entries 1–3). The size of the alkoxy group of the fumarates had no effect in increasing selectivity. A reversal of selectivity was actually seen for the bulky di-*t*-butyl fumarate. As for **1c**, on changing the alkyl group to isopropyl and then to *t*-butyl led to a large enhancement, up to 14:1 for the latter. In the case of **1b**, where the presence of the TBS group establishes the substrate to be of larger hindrance than **1c**, the use of dimethyl fumarate already had led to a high ratio as mentioned above (13:1). The use of bulkier esters led to a modest but steady increase up to 15.5:1 (*t*-Bu).

With the expectation that the *cis*-dicarboxylate diastereomer would be furnished, the reaction of dimethyl maleate was also examined. To our surprise, it was found to be completely unreactive towards **1c**. Since sterics seem to play a major role in reactivity, it could be that the hindrance exerted by the inability of both carbonyl units to simultaneously come in coplanarity with the alkene moiety leads to the low reactivity. Other electron-deficient alkenes that could be regarded as equivalents leading to the *cis*-dicarboxylate diastereomer such as maleic anhydride, *N*-benzyl maleimide, *N*-phenylmaleimide, and γ-butenolide either decomposed or were unreactive under reaction conditions examined for **1a–c**.

From these results, the stereoselectivity can be rationalized by the transition state (TS) models depicted in Scheme 3. In the TS leading to the minor product, a severe pseudo-eclipse interaction between the R group of the oxidopyrylium betaine and one of the carboxylate groups of the fumarate can be envisioned, whereas the relation between these two groups in the TS leading to the major diastereomer is gauche. The fact that higher selectivity is achieved as either R (**1b** > **1c** > **1a**) or the alkoxy group of the fumarate (*t*-Bu > *i*-Pr > Me) gets larger, is in good agreement with this assumption. An additional attractive interaction between the betaine oxide oxygen atom and the ester group mediated by the ammonium hydrogen (of the amine base) by hydrogen bonding could also be operative. This could account for the slight preference for the major diastereomer in the reaction of **1a** with dimethyl and diisopropyl fumarate, since sterics should favor the opposite, as observed for the reaction of **1a** with di-*t*-butyl fumarate.



Scheme 3.

In summary, we have developed a method of preparing 7-membered carbocycles bearing multiple number of stereocenters with high stereoselectivity by adjusting the size of the alkoxy groups of the fumarates. Application of these carbocycles are currently under investigation.

NMR and HRMS were measured at the Instrument Center for Chemical Analysis of Hiroshima University.

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8 Selected data for **2c** (R' = Me): For major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 9.8, 4.6 Hz, 1 H), 6.06 (d, *J* = 9.8 Hz, 1 H), 5.07 (dd, *J* = 4.6, 0.9 Hz, 1 H), 3.78 (s, 3 H), 3.65 (s, 3 H), 3.70 (d, *J* = 4.3 Hz, 1 H), 3.67–3.62 (m, 2 H), 3.59 (dd, *J* = 4.3, 0.9 Hz, 1 H), 2.35 (ddd, *J* = 14.3, 11.3, 4.6 Hz, 1 H), 1.97 (ddd, *J* = 14.3, 11.3, 4.6 Hz, 1 H), 1.71–1.49 (m, 2 H), 0.90 (s, 9 H), 0.05 (s, 3 H), 0.05 (s, 3 H). For minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 9.8, 4.3 Hz, 1 H), 6.07 (dd, *J* = 9.8, 0.6 Hz, 1 H), 5.08 (dd, *J* = 7.0, 4.3 Hz, 1 H), 4.13 (t, *J* = 7.0 Hz, 1 H), 3.77 (s, 3 H), 3.69 (s, 3 H), 3.67–3.62 (m, 2 H), 3.23 (d, *J* = 7.0 Hz, 1 H), 2.27 (ddd, *J* = 13.4, 11.3, 4.6 Hz, 1 H), 1.71–1.50 (m, 2 H), 1.41 (ddd, *J* = 13.4, 11.3, 4.6, 1 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.05 (s, 3 H). Anal. Calcd for $C_{20}H_{32}O_7Si$: C, 58.23; H, 7.82%. Found: C, 58.39; H, 7.72%.