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Iodine(III)-Mediated Contraction of 3,4-Dihydropyranones: Access to Polysubstituted γ-Butyrolactones

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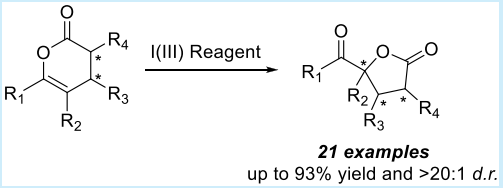
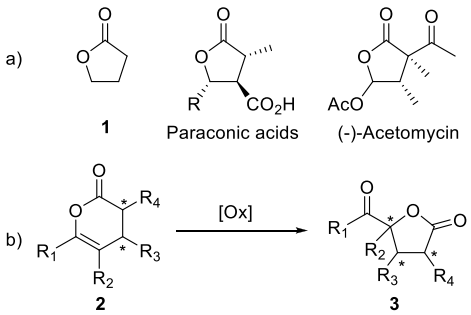
Supporting Information

ABSTRACT: Functionalized γ-butyrolactones are privileged structures in the field of medicinal chemistry; they are found in numerous natural products and synthetic compounds with diverse biological activities. The oxidative ring contraction of 3,4-dihydropyran-2-one derivatives represents a promising yet underappreciated strategy to access these compounds. To the best of our knowledge, very few examples of this strategy have been reported, with limited investigation of the influence of stereogenic centers on the starting dihydropyranones. We investigated the iodine(III)-mediated contraction of a representative set of dihydropyranone derivatives. The method gives rapid access to functionalized γ-butyrolactones in good yields. The reaction scope was investigated, and the method was found to support various levels of substituents, even enabling access to sterically congested quaternary centers. The stereoselectivity was investigated using chiral substrates and a chiral iodine(III) reagent.

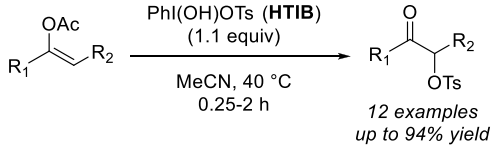


The γ-butyrolactone motif (Scheme 1a, **1**) is a privileged structure in the field of medicinal chemistry; it is found in numerous natural products and synthetic compounds with diverse biological activities.[1] Consequently, efforts have been devoted to developing methods to access this high-value scaffold.[2] One promising yet underappreciated strategy has been the oxidative ring contraction of 3,4-dihydropyran-2-ones (Scheme 1b, **2** → **3**). To the best of our knowledge, very few examples of this strategy have been reported,[3,4] with very limited investigation of the stereocontrol from R_3 or R_4. Recent developments, particularly in the field of NHC organocatalysis,[5] are giving access to numerous chiral nonracemic 3,4-dihydropyran-2-one derivatives, making this strategy quite relevant.

Scheme 1. (a) Useful γ-Butyrolactones and (b) Concept of Oxidative Contraction of Dihydropyranones



In the field of oxidative methodologies, hypervalent iodine compounds have become reagents.[6] They tend to have lower environmental impact.[7] In particular, numerous efforts have been invested in developing stereoselective methodologies.[8] Our group has been involved in the development of iodine(III)-mediated processes to access chiral nonracemic α-functionalized carbonyl compounds.[9] These products are of particular interest because of their ubiquity in nature and potential in synthesis. In our initial work in this area, we reported chiral iodoarene precatalysts to promote the direct enantioselective α-tosyloxylation of ketone compounds.[10] This has been an area of active research in the past 20 years, as α-tosyloxy ketones are high-value chiral precursors.[11] More recently, to solve the long-standing selectivity problem involved with this methodology, we reported that enol ester derivatives can serve as enol surrogates,[12] much like silyl enol ethers, initially reported by Moriarty et al.[13] and more recently by Wirth et al.[14] The enol esters can be easily converted to their corresponding α-tosyloxy ketone derivatives under stoichiometric (eq 1) and catalytic conditions.



(1)

With this in mind, we envisioned that iodine(III) reagents could serve to promote the contraction of 3,4-dihydropyran-2-ones **2** to the corresponding γ-butyrolactones **3** (Scheme 1b, [Ox] = iodine(III) reagent). Additionally, we hypothesized that they could provide unique reactivity and selectivity

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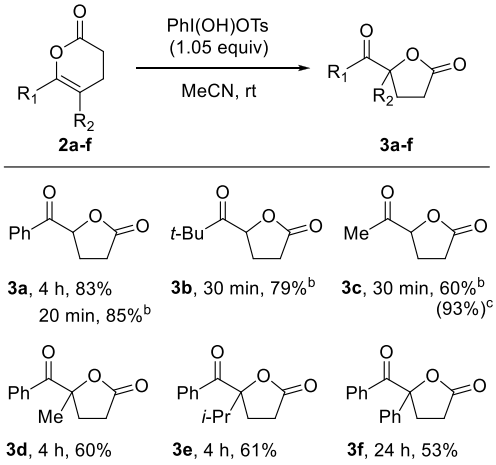
Org. Lett. XXXX, XXX, XXX−XXX

profiles. In this communication, we report our preliminary investigation of the iodine(III)-mediated oxidative contraction of 3,4-dihydropyranones to their corresponding polysubstituted γ-butyrolactone products as well as an investigation of the effect of steric and electronic modifications on both the substrate and the iodine(III) reagent on the stereoselectivity.

We initially selected a small set of dihydropyranones to investigate the feasibility of the reaction. The substrates (**2a–f**) were made using reported synthetic routes.[15] We submitted these compounds to the standard oxidation protocol previously developed for enol esters, using a slight excess of [(hydroxy)-tosyloxyiodo]benzene (HTIB) at room temperature. The results are illustrated in Scheme 2. Gratifyingly, when

Scheme 2. Preliminary Scope[a]



[a]Isolated yields are reported. [b]0.1 equiv of $TsOH·H_2O$ was added to the reaction mixture. [c]The yield was determined by ^1H NMR analysis using an internal standard.

dihydropyranone **2a** (R_1 = Ph, R_2 = H) was submitted to the contraction conditions, it was converted to the corresponding γ-butyrolactone **3a** within 4 h using a slight excess of HTIB. In analogy to our work with acyclic enol esters, the addition of a catalytic quantity of $TsOH·H_2O$ drastically increased the rate of the reaction, leading to completion in 20 min. The method tolerates an enolizable alkyl group at the R_1 position (**3c**), the lower yield being due to product volatility. We evaluated the possibility of making γ-butyrolactones bearing quaternary centers ($R_2 \neq H$) using substrates **2d–f**. The desired products were obtained, albeit in lower yields. Almost no elimination product was observed in the crude products, in contrast to the results observed with acyclic enol esters.[9]

With these promising results in hand, we investigated substrates bearing a stereogenic center α to the enol to measure the level of achievable diastereoselectivity. Substrate **2g** was first used to assess the effect of the reaction conditions on the selectivity. Iodine(III) reagents **4a–e**[16] were synthesized and used for the investigation to explore the effect of the nature of the iodine(III) reagent on the selectivity (Figure 1).

Dihydropyranone **2g** was submitted to various oxidative contraction conditions. The results are described in Table 1. Under the standard oxidation protocol, described in Scheme 2, a good yield of the contraction product **3g** was obtained, with a selectivity of 4.7:1 in favor of the *trans* diastereoisomer. The

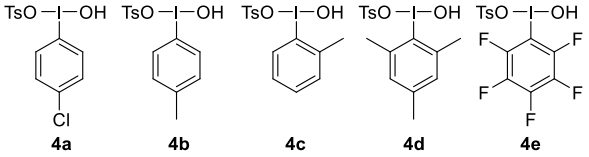
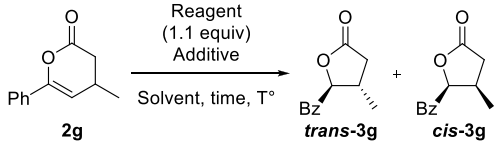


Figure 1. Iodine(III) reagents used for the study.

Table 1. Screening of Conditions[a]



entry	reagent	solvent	time (min)	yield of **3g** (%)[b]	*trans*:*cis*[c]
1[d]	HTIB	MeCN	240	80	4.7:1
2	HTIB	MeCN	15	75	4.5:1
3[e]	HTIB	MeCN	5	77	4.3:1
4	HTIB	CH_2Cl_2	20	82	7.8:1
5	HTIB	$CHCl_3$	20	80	5.4:1
6[f]	DIB	MeCN	60	72	4.5:1
7[g]	DIB	MeCN	5	75	3.4:1
8	**4a**	MeCN	30	83	3.8:1
9	**4b**	MeCN	30	82	3.7:1
10	**4c**	MeCN	30	82	6.0:1
11	**4c**	CH_2Cl_2	60	81	7.5:1
12	**4d**	MeCN	30	75	5.6:1
13	**4e**	MeCN	180	45	1.9:1
14	Br_2	CCl_4	720	77	1.1:1
15	*m*-CPBA	CH_2Cl_2	720	61	1.1:1

[a]Unless otherwise stated, the reaction was performed at room temperature using 0.1 equiv of $TsOH·H_2O$ as the additive. [b]Isolated yields of combined diastereoisomers. [c]Diastereomeric ratios were determined by ^1H NMR analysis of the crude products. [d]The reaction was performed without an additive. [e]Additive: $TsOH·H_2O$ (1 equiv). [f]Additive: $MsOH·H_2O$ (2 equiv). [g]Additive: $H_2SO_4·H_2O$ (2 equiv).

relative stereochemistry of the major diastereoisomer was unambiguously assigned using X-ray diffraction analysis.

A catalytic amount of $TsOH·H_2O$ increased the reaction rate and had a marginal effect on the diastereoselectivity. It was possible to obtain an extremely fast reaction (~5 min) by using a stoichiometric quantity of $TsOH·H_2O$, with a slight decrease in diastereoselectivity. We currently hypothesize that the role of $TsOH·H_2O$ is to increase the effective concentration of the reactive iodine(III) species.[9] We obtained increased selectivities in less polar solvents (Table 1, entries 4 and 5). HTIB equivalents can be generated in situ from (diacetoxyiodo)-benzene (DIB) and a strong acid (entries 6 and 7). The use of MsOH resulted in almost identical diastereoselectivity, whereas lower selectivity was obtained using sulfuric acid.

We evaluated the use of HTIB derivatives **4a–e** (Table 1, entries 8–13). The influence of the electronic properties of the iodine(III) reagent led to a small cost in terms of selectivity. Conversely, the use of bulkier reagents (entries 10–12) led to an increase in selectivity. We evaluated the use of a less polar solvent with the most selective reagent (**4c**); it did lead to an increase in selectivity (entry 11) but did not surpass what could be obtained with HTIB under the same conditions (entry 4). We also investigated the effect of lower reaction temperature with both HTIB and **4c**, but it did not result in increased selectivity. The partial solubility of the iodine(III)

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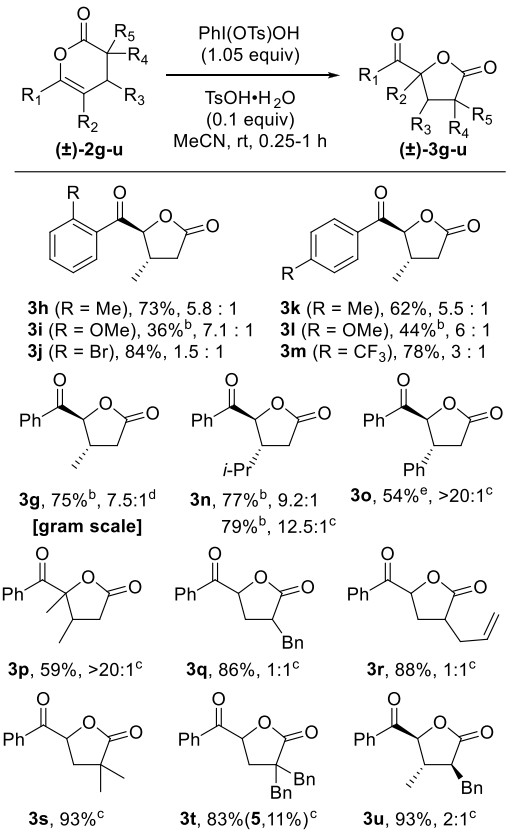
Org. Lett. XXXX, XXX, XXX–XXX

reagents could explain this surprising behavior. Finally, we investigated the oxidative contractions reported in the literature using Br_2[3] (entry 14) and *m*-CPBA[4] (entry 15) as the oxidants. Interestingly the selectivities were modest; the use of a bulkier iodine(III) reagent is thus clearly advantageous to access synthetically useful selectivities.

We explored the scope using HTIB in both MeCN and CH_2Cl_2. The results are illustrated in Scheme 3. We first

Scheme 3. Substrate Scope Study[a]



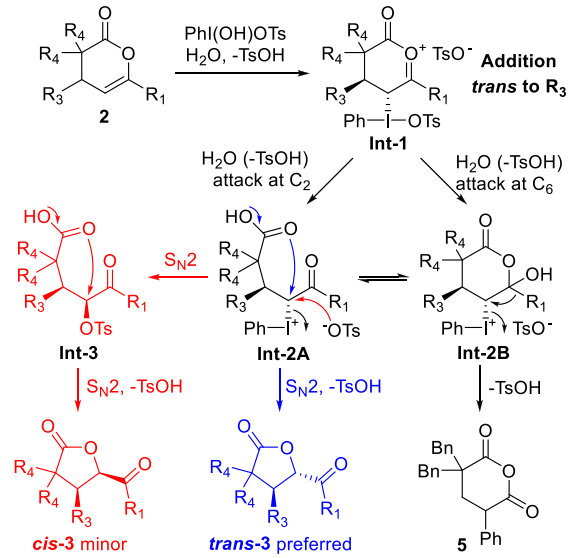
[a]Isolated yields of combined products are reported. Selectivities (*trans*:*cis*) were determined by ^{1}H NMR analysis of the crude products. [b]Isolated yield of the pure *trans* product. [c]The reaction was performed in CH_2Cl_2. [d]The reaction was performed in CH_2Cl_2 on a 15 mmol (2.8 g) scale. [e]Combined yield of *trans*-**3o** and 5,6-diphenyl-2-pyrone (1:1.5).

investigated the effect of different substitution patterns on an aromatic ring at the R_1 position. In analogy to our work on enol acetates,[9] we found that dihydropyranones bearing an electron-rich aromatic ring (substrates **2h**, **2i**, **2k**, and **2l**) were much more reactive toward HTIB, the reaction being complete within minutes. The crude products presented noticeable degradation, but surprisingly, this increased reactivity was also met with increased selectivity. In analogy, substrates possessing more electron-deficient aromatic rings (**2j** and **2m**) were less reactive and less selective. Increasing the size of the R_3 group resulted in a noticeable enhancement of the selectivity with respect to **2g** (R_3 = Me), affording up to 12.5:1 in CH_2Cl_2 for **2n** (R_3 = *i*-Pr). Contraction of **2o**, bearing a phenyl at R_3, provided the desired lactone product as a single diastereoisomer (*trans*-**3o**) along with 5,6-diphenyl-2-pyrone as a major side product originating from phenyl migration.[17] We have reported the combined yield for *trans*-**3o** and 5,6-diphenyl-2-pyrone, as separation proved difficult. We evaluated the influence of 1,2-allylic strain on the selectivity using a substrate possessing methyl groups at both R_2 and R_3. A drastic increase in selectivity (product **3p** was obtained as a single diastereoisomer) was observed compared with model substrate **2g**. We then evaluated the effect of substitution at R_4/R_5. As could be expected, no selectivity was obtained. Interestingly, an allyl moiety was tolerated under the reaction conditions (**3r**).

The presence of a quaternary center α to the lactone carbonyl is felt, however, as the oxidation rate is lower, leading to reaction times of up to 1 h (products **3s** and **3t**). Interestingly, the phenyl migration product **5** could be isolated in 11% yield when **2t** was subjected to the oxidation conditions.[17] In contrast to substrate **2p**, addition of a stereocenter at R_4 while having a stereocenter at R_3 (substrate **2u**) resulted in lowered selectivity compared with **2g**. Finally, it is noteworthy that the contraction is easily scalable; performing a 15 mmol scale contraction of **2g** provided pure *trans*-**3g** in 75% isolated yield.

We propose a mechanism to account for the *trans* selectivity and formation of side product **5** (Scheme 4). We expect the

Scheme 4. Proposed Mechanism



iodine(III) reagent to react preferentially with the alkene face *trans* to the substituent at R_3, leading preferentially to **Int-1** (or species with identical relative configuration). Less polar solvents would result in stronger electrostatic interactions, leading to shorter substrate···iodine(III) distances and better facial discrimination. A water molecule would then attack at C_2 or C_6 on **Int-1**, leading to either **Int-2A** or **Int-2B**, respectively. Formation of **5** would originate from a 1,2-phenyl shift[18] on **Int-2B**. This is observed only for **2t** (R_1 = Ph, R_3 = H, R_4 = Bn); the increased steric bulk near C_2 could force the attack of H_2O at C_6, providing a kinetic preference for the formation of **Int-2B**. Alternatively, the Thorpe−Ingold effect could increase the effective concentration of **Int-2B**. Finally, we propose that the desired *trans* product is obtain by S_N2 attack from the free acid on **Int-2A** (blue arrow). It does suggest that the α-tosyloxylation (red arrow), leading to **Int-3**, is not dominant in this reaction.

Our method compares favorably with known methods to access γ-butyrolactones by direct oxidative cyclization of

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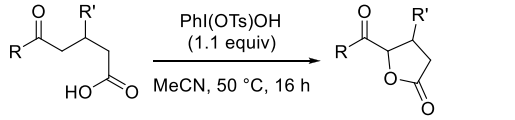
Org. Lett. XXXX, XXX, XXX−XXX

acyclic keto acids.[11d,f,19] We investigated lactonization of substrates **6a–c**; the results are presented in Scheme 5. The

Scheme 5. Lactonization of Keto Acids



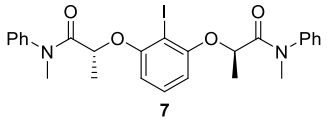
6a (R = Ph, R' = H)
6b (R = Me, R' = H)
6c (R = Ph, R' = Me)

3a, 91%
3c, 30%
3g, 84%, 1:1 *trans*:*cis*

method requires higher temperature and longer reaction times, but lactone **3a** could be obtained in high yield from **6a**. Substrate **6b**, with two enolizable positions, resulted in the formation of numerous side products, thus yielding the desired lactone **3c** in only 30% yield. Finally, the oxidative lactonization of keto acid **6c** resulted in the desired lactone **3g** in 84% yield, but with no diastereoselectivity. The oxidative contraction of 3,4-dihydropyran-2-ones thus provides numerous advantages in terms of both reaction rate and selectivity.

Finally, on the basis of our success in the enantioselective conversion of enol esters to enantioenriched α-tosyloxy ketones, we performed a preliminary evaluation of an enantioselective variant of the oxidative contraction of dihydropyranone **2a** (Scheme 6). Lactone **3a** was obtained

Scheme 6. Enantioselective Conditions



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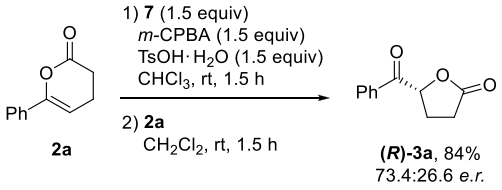

2a

(*R*)-3a, 84%
73.4:26.6 *e.r.*

in good yield with moderate enantioselectivity. This is a promising result that raises interesting questions concerning the mechanism and stereoinduction process.

In conclusion, we have developed an efficient iodine(III)-mediated method to perform the oxidative contraction of a variety of 3,4-dihydropyran-2-ones to rapidly access polysubstituted γ-butyrolactone derivatives. When using chiral substrates, our strategy provides unprecedented diastereoselectivities for this type of contraction. Furthermore, it is also advantageous in terms of selectivity compared with the equivalent lactonization of acyclic keto acids. Finally, we have demonstrated the first example of an enantioselective variant of the method. This new strategy will greatly complement the toolbox of synthetic chemists to access complex γ-butyrolactone intermediates. We are currently investigating the mechanism of this transformation as well as improving and studying extended stereoselective variants. These results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01893.

Experimental procedures and NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 1919362 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(17) See the Supporting Information for additional discussion of the reaction mechanism to rationalize the formation of 5,6-diphenyl-2-pyrone.

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