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Selenium-Catalyzed Regioselective Cyclization of Unsaturated Carboxylic Acids Using Hypervalent Iodine Oxidants

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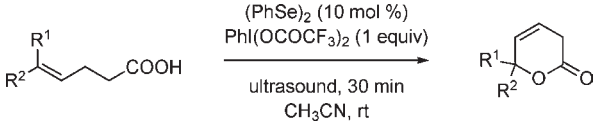
ABSTRACT



A new and convenient selenium-catalyzed regioselective cyclization of γ,δ-unsaturated carboxylic acids to the corresponding 3,6-dihydro-2*H*-pyran-2-ones is described. The cyclization products have been obtained in good to excellent yields using diphenyl diselenide as a catalyst and [bis(trifluoroacetoxy)iodo]benzene as a stoichiometric oxidant.

In the past few decades, organoselenium chemistry has been developed into an important tool in synthetic organic chemistry. Several organoselenium reagents have been employed in various useful synthetic transformations such as selenenylations, selenocyclizations, selenoxide eliminations, and 2,3-sigmatropic rearrangements.[1] Recently, organoselenium reagents have been used catalytically in various synthetic transformations such as oxidation of alcohols,[2] olefins,[3] and carbonyl compounds;[4] elimination reactions of diols;[5] Diels–Alder reactions;[6] and Baylis–Hillman[7] and radical chain reactions.[8] Recently, we have reported the selenium-catalyzed synthesis of butenolides[9] and isocoumarins[10] by cyclization of β,γ-butenoic acids and stilbene carboxylic acids, respectively. The cyclization of γ,δ-unsaturated pentenoic acids with selenium reagents as catalysts is still unexplored. Our target was to achieve the synthesis of 2*H*-pyran-2-ones by cyclization of γ,δ-unsaturated pentenoic acids using selenium reagents as a catalyst. The 2*H*-pyran-2-one scaffolds are known for various biological properties, and this structural motif is found in several natural products.[11] In addition, the

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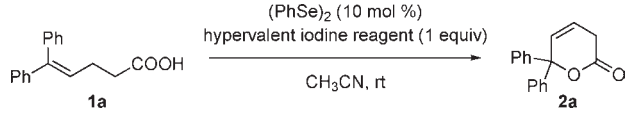
2*H*-pyran-2-one system can be used as a synthetic precursor in Diels–Alder reactions and other ring transformations.

Herein, we report a convenient way to cyclize a series of γ,δ-unsaturated pentenoic acids **1** to the corresponding 3,6-dihydro-2*H*-pyran-2-ones **2** using diphenyl diselenide as a catalyst. The synthesis of 3,6-dihydro-2*H*-pyran-2-ones **2** has been reported via a cationic, palladium-catalyzed [2 + 2] cycloaddition–allylic rearrangement sequence of ketene with α,β-unsaturated aldehydes and ketones.[12]

The synthesis of the required γ,δ-unsaturated pentenoic acids **1** was achieved by Wittig reactions of benzophenones with the ylide generated from (3-carboxypropyl)(triphenyl)-phosphonium bromide in THF using *n*-butyllithium as base.[13] The reaction products **1a**–**g** were isolated in good yields. Due to the small difference in substituents, the NMR spectra of compounds **1b**–**g** are confirming an almost equal mixture of *E* and *Z* isomers. The synthesis of (*E*)-5-phenylpent-4-enoic acid **1h** was achieved by a palladium-catalyzed Heck reaction of iodobenzene and 4-pentenoic acid in 52% yield.

Initially, optimal reaction conditions and reagents for the diphenyl diselenide catalyzed cyclization were established using 5,5-diphenylpent-4-enoic acid **1a** as a model substrate. The cyclization reactions were performed with **1a** in acetonitrile using 10 mol % of diphenyl diselenide as a catalyst and 1 equiv of a hypervalent iodine reagant as an oxidant at room temperature. The isolated product was characterized as the six-membered, cyclized compound 6,6-diphenyl-3,6-dihydro-2*H*-pyran-2-one **2a** as shown in Scheme 1.

Scheme 1. Catalytic Cyclization of **1a** Using Different Hypervalent Iodine Reagents



In order to find the best reaction conditions, we performed the same reaction by using different cyclic and acyclic hypervalent iodine reagents (Table 1). The cyclized product **2a** was obtained in 80% yield with [bis-(trifluoroacetoxy)iodo]benzene (Table 1, entry 2) while the yield was lower (23%) using the less reactive (diacetoxyiodo)benzene. When the reaction was carried out in an ultrasonic bath, the reaction was complete in 30 min and the cyclized product **2a** was isolated in 85% yield (Table 1, entry 3). The fully fluorinated and more soluble reagent [bis(trifluoroacetoxy)iodo]pentafluorobenzene was also used, but **2a** was obtained in only 73% yield. The cyclic hypervalent iodine IBA as well as the iodine(V) reagent IBX did not activate the diselenide sufficiently, although the cyclic product **2a** was obtained in 32% yield with more reactive cyclic FIBA.[14]

Table 1. Different Hypervalent Iodine Compounds in the Cyclization of **1a**

entry	oxidant	reaction time (min)	**2a** yield (%)
1	$PhI(OAc)_2$	30	23
2	$PhI(OCOCF_3)_2$	30	80
3[d]	$PhI(OCOCF_3)_2$	30	85
4	$C_6F_5I(OCOCF_3)_2$	30	73
5	IBA[a]	180	traces
6	IBX[b]	180	–
7	FIBA[c]	30	32

[a] IBA: 1-Hydroxy-1,2-benziodoxol-3-(*1H*)-one. [b] IBX: 1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one 1-oxide. [c] FIBA: 5,6,7,8-Tetrafluoro-1-hydroxy-1,2-benziodoxol-3-(1*H*)-one 1-oxide. [d] Additional use of ultrasonic bath.

In addition, different polar and nonpolar solvents were used for the cyclization of **1a** using [bis(trifluoroacetoxy)iodo]benzene (Table 2). The cyclization reaction proceeded well in polar and aprotic solvents such as acetonitrile and dichloromethane (Table 2, entries 1 and 7). The reaction was not working properly in polar and protic solvents such as diethyl ether, tetrahydrofuran, and methanol which might be explained by their ability to coordinate to the phenylselenenyl cation (Table 2, entries 2, 4, and 6). The cyclized product **2a** was observed in 15% yield in the nonpolar and aprotic solvent toluene.

Table 2. Different Solvents for the Cyclization of **1a** Using [Bis(trifluoroacetoxy)iodo]benzene

entry	solvent	reaction time (min)	**2a** yield (%)
1	MeCN	30	85
2	THF	180	15
3	DMSO	180	63
4	Et_2O	180	42
5	toluene	180	15
6	MeOH	180	24
7	CH_2Cl_2	30	83

Finally, to optimize the amount of diphenyl diselenide we also attempted the reaction shown in Table 2, entry 1 with 8 and 5 mol % of diphenyl diselenide, and the cyclized product was obtained in reduced yields of 80% and 58%, respectively. No reaction was observed in the absence of diphenyl diselenide. Optimal conditions for the cyclization of **1a** to **2a** were found to consist of 1 equiv of [bis(trifluoroacetoxy)iodo]benzene with 10 mol % diphenyl diselenide

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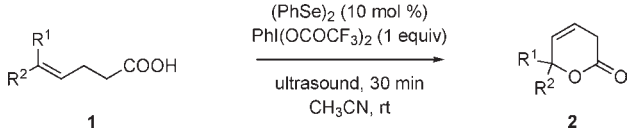
in acetonitrile irradiated with ultrasound for 30 min. A series of γ,δ-unsaturated pentenoic acids **1b**–**h** were successfully cyclized to yield the products **2b**–**h** in 51–87% yield as shown in Scheme 2. Unsymmetrically substituted acids **1b**–**1e** and **1g** were prepared and used as mixtures of *E*- and *Z*-isomers (ratio ~1:1).

Scheme 2. Catalytic Cyclization of γ,δ-Unsaturated Pentenoic Acids **1** to 3,6-Dihydro-2*H*-pyran-2-ones **2**



1 **2**

The cyclization reactions were working smoothly with substrates **1** having halogen bearing aromatic substituents, and the products were isolated in good to excellent yields (Table 3, entries 2–5). In the cyclization of 5-phenyl-5-*p*-tolylpent-4-enoic acid **1g** the reaction product **2g** was obtained in 55% yield. However, in contrast to products **2a**–**2h**, the reaction product **2g** was not stable above room temperature. Surprisingly, the catalytic cyclization of (*E*)-5-phenylpent-4-enoic acid **1h** was relatively slow and full conversion was not achieved even after 5 h of reaction time/sonication (Table 3, entry 8). The cyclized product **1h** was obtained in only 51% yield. Interestingly, the six-membered selenocyclization product **8h** as a reaction intermediate was also isolated in 15% yield which supports the mechanistic proposal (Scheme 5). The cyclization of 4-pentenoic acid **1i** did not proceed at all under the reaction conditions, and the cyclized product was detected only in traces. This result clearly indicates that aryl substituents in **1** are necessary to achieve successful cyclizations to **2**. All reaction products were fully characterized.

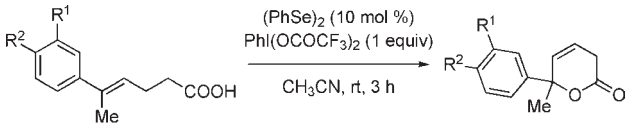
Table 3. Cyclization of γ,δ-Unsaturated Pentenoic Acids **1**

entry	**1**	**2** yield (%)
1	**1a**: $R^1 = R^2 =$ Ph	85
2	**1b**: $R^1 =$ Ph, $R^2 =$ 4-Br-C_6H_4	87
3	**1c**: $R^1 =$ Ph, $R^2 =$ 4-Cl-C_6H_4	79
4	**1d**: $R^1 =$ Ph, $R^2 =$ 4-F-C_6H_4	68
5	**1e**: $R^1 =$ Ph, $R^2 =$ 3-Cl-C_6H_4	73
6	**1f**: $R^1 = R^2 =$ 4-Cl-C_6H_4	81
7	**1g**: $R^1 =$ Ph, $R^2 =$ 4-Me-C_6H_4	55[a]
8	**1h**: $R^1 = H$, $R^2 =$ Ph	51[b]
9	**1i**: $R^1 = R^2 = H$	–

[a] Reaction was carried out in dichloromethane. [b] In addition to **2h**, the selenolactone intermediate was isolated in 15% yield.

We then investigated the cyclization of of trisubstituted γ,δ-unsaturated pentenoic acids **3** under similar reaction conditions (Scheme 3). The synthesis of acids **3** was achieved by the addition of arylmagnesium bromide reagents to cyclopropyl methyl ketone, ring opening/elimination by bromide, and elongation using carbon dioxide in three steps (see Supporting Information). The cyclization of compound **3a** was performed under the identical reaction conditions (ultrasound, 30 min) as described above for **1**, and the cyclized product **4a** was isolated in 57% yield. However, when the same substrate **3a** was treated with the reagent combination without ultrasound, the cyclized product **4a** was isolated in a slightly higher yield (68%). Subsequently, the cyclization of various acids **3b**–**d** to lactones **4** was performed in good yields. The reaction tolerated aryl substituents with differing electron demands as shown in Table 4. Interestingly, the presence of the methyl substituent at position C-5 in compounds **3** did not effect the course of the reaction and five-membered cyclization products were not observed.

Scheme 3. Catalytic Cyclization of Trisubstituted γ,δ-Unsaturated Pentenoic Acids **3** to Lactones **4**

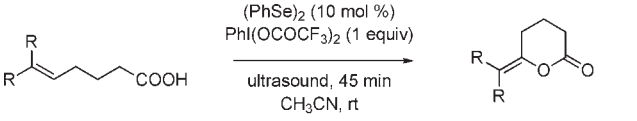


3 **4**

Table 4. Cyclization of (*E*)-5-Arylhex-4-enoic Acids **3**

entry	**3**	**4** yield (%)
1	**3a**: $R^1 = R^2 = H$	68
2	**3b**: $R^1 =$ F, $R^2 = H$	71
3	**3c**: $R^1 = H$, $R^2 =$ F	74
4	**3d**: $R^1 = H$, $R^2 =$ Et	81

Scheme 4. Catalytic Cyclization of 6,6-Diarylhex-5-enoic Acids **5** to 6-(Diarylmethylene)tetrahydro-2*H*-pyran-2-ones **6**

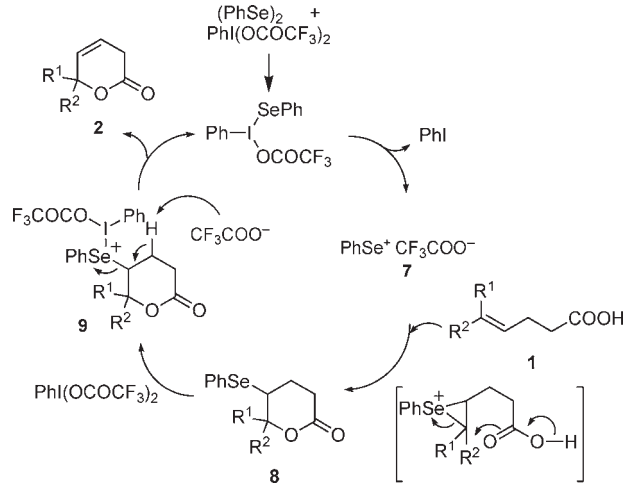


5a (R = Ph)
5b (R = 4-Cl-C_6H_4)

6a (R = Ph), 83%
6b (R = 4-Cl-C_6H_4), 71%

Additionally, this approach was extended to elongated acids **5** which were synthesized by a similar route to compounds **1**.[13] The cyclization of these acids **5** was performed under identical reaction conditions. The spectroscopical analysis of isolated products revealed that no seven-membered lactones have been obtained but that an *exo*-cyclization led to six-membered lactones **6** with an *exo* double bond in good yields (Scheme 4). Cyclizations of corresponding γ,δ-unsaturated alcohols at different temperatures and reaction conditions lead only to decomposition products.

Scheme 5. Proposed Mechanism for the Catalytic Cyclization of γ,δ-Unsaturated Pentenoic Acids **1**



On the basis of our previous research efforts[9a] and further evidenced by the isolation of a selenolactone as a reaction intermediate during the catalytic cyclization of (*E*)-5-phenylpent-4-enoic acid **1h**, we propose a catalytic cycle as shown in Scheme 5. The reaction is initiated by the formation of phenylselenenyl trifluoroacetate **7** which we have already proven by NMR experiments.[9a] Phenylselenenyl trifluoroacetate **7** reacts with the γ,δ-unsaturated pentenoic acid **1** to yield a selenolactone **8**. The selenide functionality of lactone **8** is then activated for elimination by [bis(trifluoroacetoxy)iodo]benzene *via* intermediate **9** to finally yield the 3,6-dihydro-2*H*-pyran-2-ones **2** as reaction products. The selenium electrophile **7** is regenerated by this process leading to the catalytic cycle (Scheme 5).

In summary, we have established a new approach for the facile synthesis of different six-membered lactones from γ,δ-unsaturated carboxylic acids using catalytic amounts of diphenyl diselenide. Our method to synthesize these scaffolds is very simple, economical, and metal-free. Research studies about the wider scope of this approach are currently in progress.

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Supporting Information Available. Experimental procedures and spectral data for compounds **1**–**6** and **8h**. This material is available free of charge via the Internet at http://pubs.acs.org.