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Novel Lactonization with Phenonium Ion Participation Induced by Hypervalent Iodine Reagents

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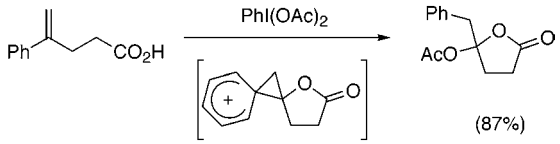
ABSTRACT



A novel lactonization of 4-aryl-4-pentenoic acids is described using aryl-λ³-iodanes as reagents for this transformation. The hypervalent iodine species acts as a hypernucleofuge, generating intermediate phenonium ions, which react to aryl-migrated lactones.

The participation of aryl groups in reactions involving carbocations was proposed by Cram some time ago.[1] Different interpretations led to controversial discussions, and many reports on phenonium ions have been published.[2] The presence of phenonium ions in reactions has now been shown by different experimental, spectroscopic, and computational methods.[2b,c] Despite the variety of studies in phenonium ion chemistry, the ion has not been widely applied to synthetic chemistry. In this paper, we report such an application in a novel cyclization of aryl-substituted unsaturated carboxylic acids induced by hypervalent iodine compounds.

Hypervalent iodine compounds are well-known for their mild oxidative properties.[3] These compounds can also be used as electrophilic reagents, and various cyclizations of unsaturated systems have been carried out.[4] We investigated the cyclization of the unsaturated carboxylic acid **1** using (diacetoxyiodo)benzene as the hypervalent iodine reagent. The formation of lactone **3** was anticipated after replacement of the hypervalent iodine moiety (a super-leaving group)[5] in intermediate **2** with the acetate nucleophile. However, the formation of product **5** was observed. The formation of **5** can be rationalized by a participation of the phenyl moiety, which results in the formation of a phenonium ion intermediate **4**. An interesting solvent effect, similar to those already described by Koser[6] and Moriarty,[7] was noted in this reaction. When the reaction is performed at higher dilution, the yields of **5** are quite low. In a minimum amount of solvent, the reaction favors the formation of product **5** (87% yield).

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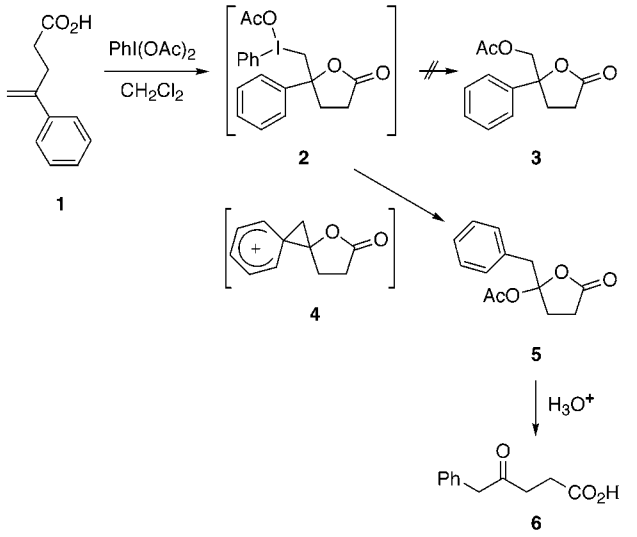
Table 1. Reaction of **1** with Various Hypervalent Iodine Reagents

entry	reagent	product (low concentration, ~0.04 M)	product (high concentration, ~4 M)
1	$PhI(OAc)_2$	**5** (20%)	**5** (87%)
2	PhI(OH)OTs	**6** (35%)	**6** (52%)
3	$PhI(OCOCF_3)_2$	complex mixture	**6** (86%)
4	IBX[a]	no reaction	no reaction

[a] IBX: 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide.

Compound **5** was identified by its spectroscopic data[8] as well as by acidic hydrolysis, which resulted in the formation of the known carboxylic acid **6**.[9] We have also investigated other hypervalent iodine reagents in the lactonization of **1**. The results are summarized in Table 1.

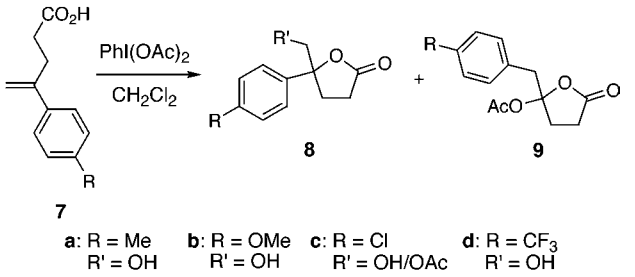
Scheme 1. Rearrangement Induced by Hypervalent Iodine Reagents



Only aryl-λ^3-iodanes can be used as efficient reagents for a lactonization reaction of **1**, whereas IBX,[10] an aryl-λ^5-iodane (entry 4), is too weak an electrophile to promote the reaction. In the case of [hydroxy(tosyloxy)iodo]benzene (Koser reagent, entry 2) and [bis(trifluoroacetoxy)iodo]-benzene (entry 3), the lactonization with subsequent aryl migration is followed by direct hydrolysis of the ketal and the 4-oxocarboxylic acid **6** is the only product isolated in these reactions.

After the encouraging results obtained with (diacetoxy-iodo)benzene as a reagent, we investigated different substituted 4-aryl-4-pentenoic acids of type **7** in the lactonization reaction. The reaction with **1** proceeded very quickly at room temperature, but the reactions with *para*-substituted aryl alkenoic acids **7** were found to be more sluggish and starting material usually was recovered. Additionally, both unrearranged compounds **8** and rearranged compounds **9** were found as reaction products. 4-Aryl-4-pentenoic acids **7** have

Scheme 2. Electronically Different Substrates **7** for Cyclization and Rearrangement



been synthesized by Suzuki reactions[11] of 4-bromo-4-pentenoic acid ethyl ester[12] and the appropriate *para*-substituted phenylboronic acids with subsequent cleavage of the ethyl esters. The methyl-substituted carboxylic acid **7a** (R = Me) gave only 10% yield of the rearranged product **9a**,[13] together with 9% yield of product **8a** (R = Me, R′ = OH, no rearrangement), and 59% of the carboxylic acid **7a** was recovered after the reaction. It was expected that electron-donating substituents should stabilize the phenonium

(8) Spectroscopic data of acetic acid 2-benzyl-5-oxo-tetrahydrofuran-2-yl ester **5**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.99 (s, 3H, $COOCH_3$), 2.09−2.75 (m, 4H, CH_2CH_2), 3.18 (d, 1H, J = 14 Hz, $PhCH_2$), 3.28 (d, 1H, J = 14 Hz, $PhCH_2$), 7.19−7.28 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.7, 28.6, 30.1, 44.4, 109.3, 127.4, 128.5, 130.7, 133.2, 169.3, 175.3. IR ($CHCl_3$): ν 3684, 3028, 2400, 1794, 1751 cm^{-1}. MS: *m/z* (rel intensity) 252 (65, [M + NH_4^+]), 209 (42), 192 (100), 77 (5). HRMS: ($C_{13}H_{14}O_4$ + NH_4^+) calcd, 252.1236; found, 252.1234.

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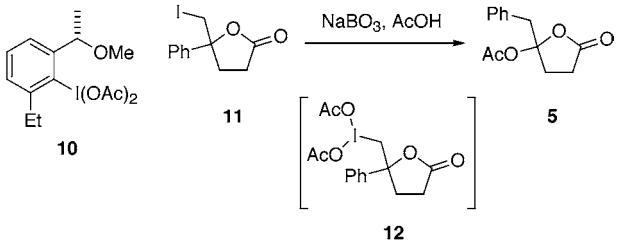
(13) Representative procedure: A slurry of **7a** (19.9 mg, 0.105 mmol), (diacetoxyiodo)benzene (52.5 mg, 0.163 mmol) and methylene chloride (0.05 mL) was stirred for 2 h at room temperature before adding a small amount of water. After extraction with methylene chloride (three times), the combined organic phases were dried over magnesium sulfate and concentrated in vacuo. Silica gel chromatography (1:4 ethyl acetate/pentane) yielded 2.2 mg (9%) of **8a** and 2.4 mg (10%) of **9a** as oils. **5-Hydroxy-methyl-5-(4-methyl-phenyl)-furan-2-one (8a).** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.28 (s, 3H, $ArCH_3$), 2.29−2.74 (m, 4H, CH_2CH_2), 3.65 (d, 1H, J = 14 Hz, $HOCH_2$), 3.75 (d, 1H, J = 14 Hz, $HOCH_2$), 7.13−7.20 (m, 4H, ArH). IR ($CHCl_3$): ν 3524, 3018, 2242, 2253, 1725 cm^{-1}. **5-Acetoxy-5-(4-methyl-phenyl)-dihydrofuran-2-one (9a).** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.00 (s, 3H, $COOCH_3$), 2.11−2.72 (m, 4H, CH_2CH_2), 2.28 (s, 3 H, $ArCH_3$), 3.14 (d, 1H, J = 14 Hz, $ArCH_2$), 3.22 (d, 1H, J = 14 Hz, $ArCH_2$), 7.06−7.12 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.5, 22.2, 29.1, 30.5, 44.4, 110.0, 129.6, 130.5, 131.0, 138.1, 169.5, 175.8. MS: *m/z* (rel intensity) 266 (80, [M + NH_4^+]), 224 (5), 223 (35), 206 (100), 188 (9). HRMS: ($C_{14}H_{16}O_4$ + NH_4^+) calcd, 266.1392; found, 266.1389.

ion intermediates. Recently, several publications on intramolecular cyclizations have appeared and only stabilized phenonium ion intermediates were successfully employed in these cyclizations.[14] Reaction of the 4-methoxy-substituted derivative **7b** (R = OMe) with (diacetoxyiodo)benzene resulted in a 38% yield of rearranged product **9b**[15] together with 5% of an unrearranged product **8b**, which has either lost the acetoxy group during the workup or the intermediate phenonium ion has been trapped by water (R′ = OH). Also, reactions with carboxylic acids **7** bearing electron-withdrawing substituents (**7c**, R = Cl; **7d**, R = CF_3) have been carried out, but only small amounts of rearranged and unrearranged products (20−30%) have been detected by NMR along with unreacted starting material (35−40%). The effect of the *para*-substitution on the overall reaction is quite remarkable. While it was expected that the presence of electron-donating groups would facilitate the rearrangement process in these reactions, this was not the case. The presence of any substituent slowed, dramatically, the overall reaction, and mixtures of rearranged and unrearranged products were obtained for all substrates. Interestingly, these reactions represent the first examples of electron-deficient aryl groups (**7c**,**d**) participating in a phenonium ion rearrangement.

The chiral hypervalent iodine reagent **10**[16] in the cyclization of **1** described above led to the rearranged lactone **5** in 56% yield, but only to an enantiomeric excess of 4%.[17] To further prove the existence of an unstable hypervalent intermediate of type **2** in the reaction pathway, we synthesized iodolactone **11** by treatment of **1** with ICl.[18] We examined various methods for oxidizing **11** to the corresponding hypervalent intermediate **12**. While a ligand exchange reaction with (diacetoxyiodo)benzene was unsuccessful, oxidation with sodium perborate in glacial acetic acid[19] led to the formation of the rearranged compound **5**, which proves that the hypervalent iodine species **12** is a precursor for the phenonium ion intermediate.

Scheme 3. Stepwise Rearrangement by Iodolactonization and Subsequent Oxidation



In summary, we have presented a novel lactonization and subsequent rearrangement with phenonium ion participation. For the first time, phenonium ion intermediates have been generated using the feature of hypervalent iodine substituents being hypernucleofuges in organic synthesis.

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(15) Procedure as described in ref 13: **7b** (20.1 mg, 0.0975 mmol) and (diacetoxyiodo)benzene (47.7 mg, 0.148 mmol) gave 1.1 mg (5%) of **8b** and 9.7 mg (38%) of **9b**. **5-Hydroxymethyl-5-(4-methoxy-phenyl)-dihydro-furan-2-one (8b).** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.29−2.74 (m, 4H, CH_2CH_2), 3.59−3.79 (q, 2 H, $OHCH_2$), 3.75 (s, 3H, $ArOCH_3$), 6.84 (d, 2H, J = 8 Hz, ArH), 7.24 (d, 2H, J = 8 Hz, ArH). **5-Acetoxy-5-(4-methoxy-phenyl)-dihydro-furan-2-one (9b).** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.09 (s, 3H, $COOCH_3$), 2.19−2.80 (m, 4H, CH_2CH_2), 3.22 (d, 1H, J = 14.2 Hz, $ArCH_2$), 3.28 (d, 1H, J = 14.2 Hz, $ArCH_2$), 3.82 (s, 3H, $ArOCH_3$), 6.94 (d, 2H, J = 8 Hz, ArH), 7.22 (d, 2H, J = 8 Hz, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.2, 29.1, 30.4, 43.9, 55.6, 109.9, 114.3, 125.5, 132.2, 159.0, 169.6, 175.8. IR ($CHCl_3$): ν 3019, 2399, 1797, 1743, 1514, 1220 cm^{-1}.

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