Bioorganic & Medicinal Chemistry Letters 19 (2009) 3848–3851

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Hypervalent iodine-catalyzed oxylactonization of ketocarboxylic acids to ketolactones

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ARTICLE INFO

Article history:
Received 26 February 2009
Revised 14 March 2009
Accepted 31 March 2009
Available online 5 April 2009

ABSTRACT

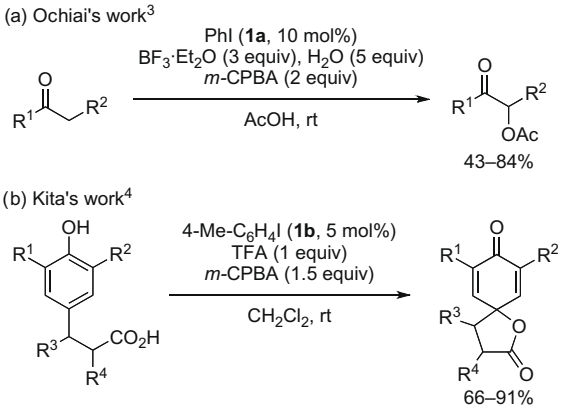
The hypervalent iodine-catalyzed oxylactonization of ketocarboxylic acids to ketolactones was achieved in the presence of iodobenzene (10 mol %), *p*-toluenesulfonic acid monohydrate (20 mol %) and *meta*-chloroperbenzoic acid as a stoichiometric co-oxidant.

Over the past two decades, hypervalent iodine compounds have been the focus of great attention due to their mild and chemoselective oxidizing properties and their environmentally benign nature in contrast to toxic metal reagents.[1] In particular, the reactivities of trivalent iodines resemble those of Hg(II), Tl(III) and Pb(IV).[1] In 2004, Kita's group introduced *meta*-chloroperbenzoic acid (*m*-CPBA) as a co-oxidant for the preparation of iodine(III) compounds.[2] The next year, Ochiai's group[3] and Kita's group[4] independently, reported the first hypervalent iodine-catalyzed oxidative coupling reactions with the successful use of *m*-CPBA as a co-oxidant. Ochiai's group developed the in situ-generated iodine(III)-catalyzed α-oxyacetylation of ketones in the presence of 10 mol % of iodobenzene (**1a**), 3 equiv of $BF_3{\cdot}Et_2O$, 5 equiv of water and 2 equiv of *m*-CPBA in acetic acid (Scheme 1a).[3] On the other hand, Kita's group developed the in situ-generated iodine(III)-catalyzed oxidative spirocyclization of phenol derivatives in the presence of 5 mol % of 4-iodotoluene (**1b**), 1 equiv of trifluoroacetic acid (TFA) and 1.5 equiv of *m*-CPBA in dichloromethane (Scheme 1a).[4] Since 2005, rapid progress has been made in the development of hypervalent iodine(III or V)-catalyzed oxidation reactions.[5] Very recently, we reported the 2-iodoxybenzenesulfonic acid (IBS)-catalyzed highly efficient and chemoselective oxidation of alcohols to carbonyl compounds with Oxone.[6]

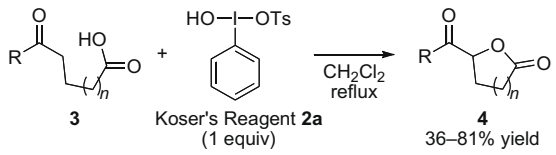
Lactones are abundant in nature and the lactonization methodology plays an important role in synthetic organic chemistry.[7] In 1990, Moriarty's group reported the [hydroxy(tosyloxy)iodo]benzene (**2a**, HTIB or Koser' reagent)-promoted oxylactonization of ketocarboxylic acids **3** to ketolactones **4** (Scheme 2).[8] In connection with our ongoing study of hypervalent iodine-catalyzed oxidations, we have been interested in the development of a catalytic oxylactonization of ketocarboxylic acids. To the best of our knowledge, there are no successful examples of a catalytic hypervalent iodine system for oxylactonization.[9,10]

First, we examined the oxylactonization of 5-oxo-5-phenylpentanoic acid (**3a**) to 5-benzoyldihydrofuran-2(3*H*)-one (**4a**) under Kita's spirocyclization conditions (Scheme 3).[4] However, undesired Baeyer–Villiger oxidation proceeded, and desired **4a** was not obtained.

Next, we examined the oxylactonization of **3a** under modified conditions that originated in Ochiai's α-oxyacetylation (Scheme 4).[3] Dichloromethane was used as a solvent instead of acetic acid to prevent the α-oxyacetylation of **3a**. Fortunately, **4a** was



Scheme 1. In situ-generated iodine(III)-catalyzed oxidative coupling reactions.



Scheme 2. HTIB **2a**-promoted oxylactonization of **3**.

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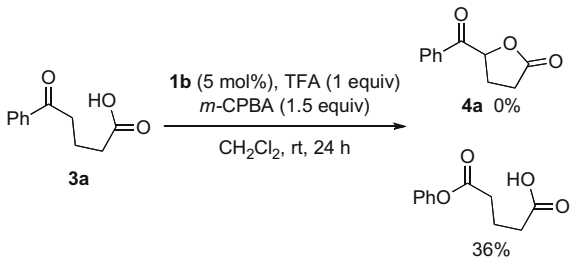
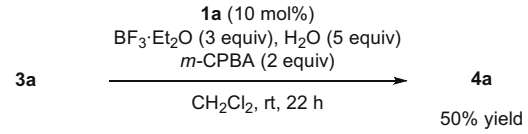
doi:10.1016/j.bmcl.2009.03.148



Scheme 3. Oxylactonization of **3a** under Kita's coupling conditions.[4]



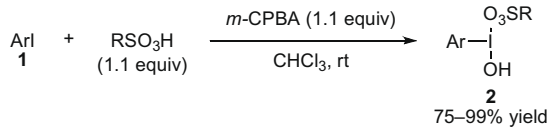
Scheme 4. Oxylactonization of **3a** under Ochiai's coupling conditions.[3]

obtained in 50% yield along with several byproducts (Baeyer–Villiger oxidation products, etc.).

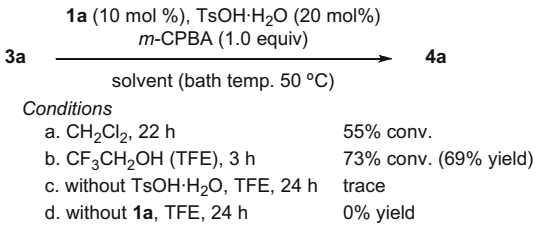
According to Togo's report,[11,12] various [hydroxy(sulfonyloxy)iodo]arenes (**2**) can be efficiently prepared from a mixture of iodoarenes (**1**), *m*-CPBA and sulfonic acids at room temperature (Scheme 5).

Based on Togo's significant findings,[11] we examined Moriarty's oxylactonization of **3a** in the catalytic manner of **2a** (Scheme 6). When **3a** was heated in the presence of 1 equiv of *m*-CPBA, 10 mol % of **1a** and 20 mol % of *p*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$) in dichloromethane at 50 °C for 22 h, **4a** was obtained in 55% conversion. The oxylactonization reaction proceeded more rapidly in 2,2,2-trifluoroethanol (TFE), and **4a** was obtained in 73% conversion.[13] In contrast, Baeyer–Villiger oxidation products were obtained instead of **4a** in the absence of **1** or $TsOH{\cdot}H_2O$. These results mean that the combination of both **1** and acid catalysis is essential for the present reaction.

As our experimental results shown in Schemes 3, 4 and 6, $TsOH{\cdot}H_2O$ was more effective than $BF_3{\cdot}Et_2O$–H_2O as a co-activator for the iodine(III)-catalyzed oxylactonization of **3a**. Thus, the reaction conditions shown in Scheme 6 were optimized (Table 1). Initially, we investigated the substituent effect of iodobenzene **1a** in TFE (entries 1–7). Electron-donating group-substituted iodobenzenes such as 4-Me–C_6H_4I (**1b**) and 4-MeO–C_6H_4I (**1c**) were inferior

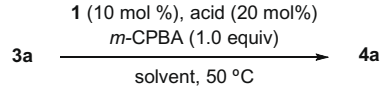


Scheme 5. Facile preparation of **2**.[10]



Scheme 6. Catalytic use of **1a** and $TsOH{\cdot}H_2O$ for the oxylactonization of **3a**.

Table 1
Optimization of in situ-generated hypervalent iodine-catalyzed oxylactonization of **3a** to **4a**[a]



Entry	ArI **1**	Acid	Solvent, time (h)	**4a**, conv[b] (%)
1	C_6H_5I (**1a**)	$TsOH{\cdot}H_2O$	TFE, 3	73 (69)
2	4-Me–C_6H_4I (**1b**)	$TsOH{\cdot}H_2O$	TFE, 4	57
3	4-MeO–C_6H_4I (**1c**)	$TsOH{\cdot}H_2O$	TFE, 4	49
4	4-CF_3–C_6H_4I (**1d**)	$TsOH{\cdot}H_2O$	TFE, 4	74
5	3,5-$(CF_3)_2$–C_6H_4I (**1e**)	$TsOH{\cdot}H_2O$	TFE, 4	48
6	2-HO_2C–C_6H_4I (**1f**)	$TsOH{\cdot}H_2O$	TFE, 10	0[c]
7	2-HO_3S–C_6H_4I (**1g**)	$TsOH{\cdot}H_2O$	TFE, 10	0[c]
8	**1a**	$TsOH{\cdot}H_2O$[d]	TFE, 3	19
9	**1a**	Tf_2NH	TFE, 3	63
10	**1a**	Tf_3CH	TFE, 3	52
11	**1a**	HBF_4	TFE, 3	42
12	**1a**	$BF_3{\cdot}Et_2O$	TFE, 3	60
13	**1a**	TFA	TFE, 8	0[c]
14	**1a**	$TsOH{\cdot}H_2O$	CH_3CN, 22	59
15	**1a**	$TsOH{\cdot}H_2O$	CH_3NO_2, 6	70
16[e]	**1a**	$TsOH{\cdot}H_2O$	CH_3NO_2, 23	99 (90)
17[e]	**1a**[f]	$TsOH{\cdot}H_2O$[f]	CH_3NO_2, 28	86 (80)

[a] Unless otherwise noted, a mixture of **3a** (0.5 mmol) and *m*-CPBA (0.5 mmol) in the solvents (2.5 mL) described in the table was heated at 50 °C in the presence of **1** (0.05 mmol) and acid (0.1 mmol).
[b] ^1H NMR analysis. The isolated yields of analytically pure product **4a** are shown in parentheses.
[c] Baeyer–Villiger oxidation compounds of **3a** were obtained as main products.
[d] 10 mol % of $TsOH{\cdot}H_2O$ was used.
[e] *m*-CPBA (1.3 equiv) was added portion-wise (6 portions were added as 0.2 equiv per 2 h, and finally 0.1 equiv was added).
[f] 2 mmol scale of **3a**; **1a** (2 mol %) and $TsOH{\cdot}H_2O$ (10 mol %) were used.

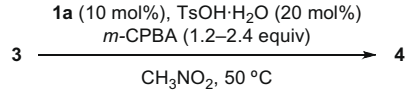
to **1a** (entries 2 and 3). In contrast, the catalytic activity of 4-CF_3–C_6H_4I (**1d**) was similar to that of **1a** (entry 4). However, the use of 3,5-$(CF_3)_2$–C_6H_4I (**1e**) gave **4a** in modest yield (entry 5). Interestingly, 2-(HO_2C)–C_6H_4I (**1f**) and 2-(HO_3S)–C_6H_4I (**1g**) were inert (entries 6 and 7).

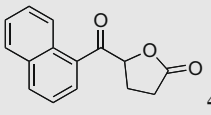
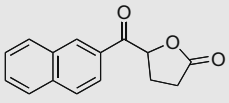
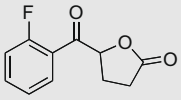
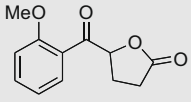
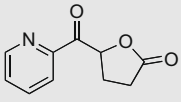
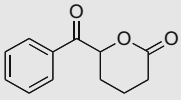
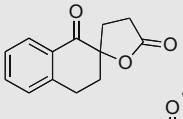
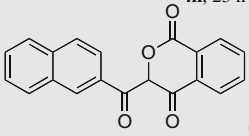
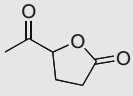
The addition of 20 mol % of $TsOH{\cdot}H_2O$ was required to promote the oxylactonization efficiently (entry 1). When 10 mol % of $TsOH{\cdot}H_2O$ was used, the reaction was quite slow (entry 8). Other Brønsted or Lewis acids were also screened under the conditions in entry 1. Although superacids such as Tf_2NH and Tf_3CH showed higher reactivity than $TsOH{\cdot}H_2O$ at the initial stage, the decomposition of *m*-CPBA was also accelerated under these conditions (entries 9 and 10). HBF_4 and $BF_3{\cdot}Et_2O$ were inferior to $TsOH{\cdot}H_2O$ (entries 11 and 12). TFA was inert (entry 13).

Although TFE was a suitable solvent,[13] the TFE ester of **3a** was also obtained in 2–18% yield (entries 1–12). Thus, other solvents were screened. Acetonitrile as well as dichloromethane was less effective than TFE (entry 14). We found that the decomposition of *m*-CPBA was much slower in nitromethane than in the other solvents screened,[14] and **4a** was obtained in 70% yield after 6 h (entry 15). However, the decomposition of *m*-CPBA was still competitive under the conditions in entry 15.[14] When 1.3 equiv of *m*-CPBA was added portion-wise, **4a** was obtained in 90% isolated yield (entry 16). Thus, the catalyst loadings of **1** and $TsOH{\cdot}H_2O$ could be reduced to 2 mol % and 10 mol %, respectively, to give **4a** in 80% yield (86% conv., TON of **1a** = 43; entry 17).

To explore the generality and the substrate scope of the in situ-generated iodine(III)-catalyzed oxylactonization, several ketocarboxylic acids **3** were prepared by standard methods[15] and examined as substrates under optimized conditions: **1a** (10 mol %), $TsOH{\cdot}H_2O$ (20 mol %) and portion-wise addition of *m*-CPBA (Table 2). 1-Napthyl and 2-napthyl ketones **3b** and **3c** gave corresponding ketolactones **4b** and **4c** in good yields (entries 1 and 2). 2-Fluorophenyl

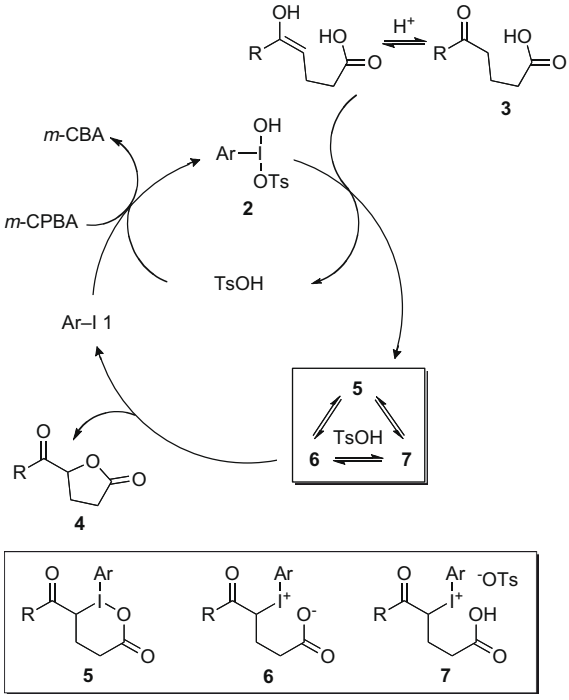
Table 2
In situ-generated hypervalent iodine-catalyzed oxylactonization of ketocarboxylic acids **3** to ketolactones **4**[a]



Entry	*m*-CPBA (equiv)[a]	Ketolactone **4**, time (h)	Yield[b] (%)
1	1.8	 **4b**, 14 h	71
2	1.8	 **4c**, 14 h	70
3	1.6	 **4d**, 28.5 h	81
4	1.8	 **4e**, 48 h	41[c]
5[d]	2.4	 **4f**, 47 h	38[e]
6[d]	1.4	 **4g**, 27 h	15[e,f]
7	1.8	 **4h**, 23 h	74
8	1.2	 **4i**, 10 h	40[e]
9	1.2	 **4j**, 12 h	<5[g]

[a] Unless otherwise noted, *m*-CPBA (1.2–2.4 equiv) was added portion-wise 6–12 × (0.2 equiv per 2 h) to a stirring mixture of **3** (0.5 mmol), **1a** (0.05 mmol) and $TsOH{\cdot}H_2O$ (0.1 mmol) in CH_3NO_2 (2.5 mL) at 50 °C.
[b] Isolated yields of analytically pure **4**.
[c] Baeyer–Villiger oxidation compounds of **3** were obtained as main products.
[d] **1a** (20 mol %) and $TsOH{\cdot}H_2O$ (50 mol %) were used.
[e] Unknown products were also obtained.
[f] Hydrolysis of **4g** to hydroxycarboxylic acid was also observed.[16]
[g] Compound **3j** was recovered mainly. Baeyer–Villiger oxidation products of **3j** were obtained as main products.

ketone **3d** was transformed to **4d** in 81% yield (entry 3). In contrast, 2-methoxyphenyl ketone (**3e**) was transformed to **4e** in only 41% yield, since Baeyer–Villiger products were obtained as main products (entry 4). Unfortunately, picolinoyl lactone **4f** and six-membered δ-lactone **4g** were obtained in only 38% and 15% yield, respectively (entries 5 and 6). Notably, the oxidation of **3h** gave spirolactone **4h** in 74% yield (entry 7). Additionally, the oxylactonization of 1,3-diketone **3i** gave **4i** in moderate yield (entry 8). Unfortunately, no sufficient results were observed with alkyl-keto



Scheme 7. A possible catalytic cycle for in situ-generated iodine(III)-catalyzed oxylactonization.

carboxylic acids such **3j** under our conditions. The yield was very low (<5%) and Baeyer–Villiger oxidation products were also obtained (entry 9).

A proposed catalytic cycle is depicted in Scheme 7. First, iodine(III) **2** should be generated by the oxidation of **1** with *m*-CPBA in the presence of TsOH. Next, the Moriarty's intermediate **5** might be generated via ligand exchange of **2** with an enol tautomer of **3**.[8] The intermediate **5** would be equilibrated with iodonium carboxylate **6** and/or iodonium tosylate **7**. The reductive elimination of **5** or S_N2 substitution of iodonium intermediates **6** or **7** would give **4** and **1**, which could be re-oxidized with *m*-CPBA to **2**.

In conclusion, for the first time, we achieved the oxylactonization of ketocarboxylic acids (**3**) to ketolactones (**4**) with hypervalent iodine compounds that were prepared in situ from catalytic amounts of iodoarenes **1** and $TsOH{\cdot}H_2O$ in the presence of *m*-CPBA as a stoichiometric co-oxidant. The chiral hypervalent iodine-catalyzed enantioselective oxylactonization of ketocarboxylic acids is under investigation in our laboratories.

Acknowledgments

Financial support for this project was provided by JSPS.KAKENHI (20245022), the GSC Project of METI, the Toray Science Foundation, the General Sekiyu Research and Development Encouragement and Assistance Foundation, the Showa Foundation, and the Global COE program of MEXT.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.03.148.

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