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COMMUNICATION

A hypervalent iodine-mediated spirocyclization of 2-(4-hydroxybenzamido)-acrylates – unexpected formation of δ-spirolactones†

Christian Hempel,[a] Nicole M. Weckenmann,[a] C. Maichle-Moessmer[b] and Boris J. Nachtsheim*[a]

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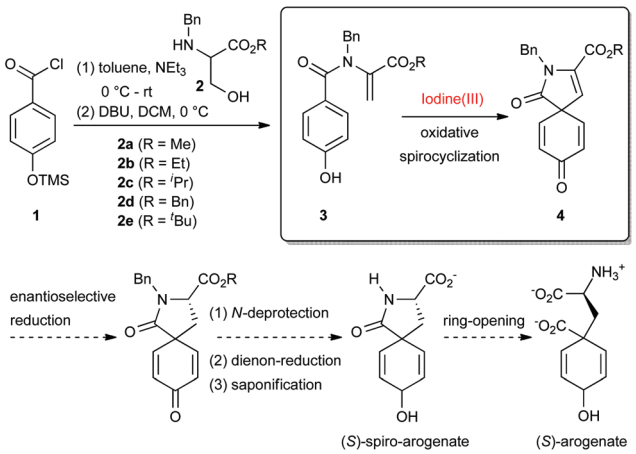
On the way towards a new total synthesis of (*S*)-arogenate, a novel aryl-λ^3-iodane-mediated oxidative spirocyclization of *para*-substituted phenol derivatives has been discovered. Starting from easy accessible 2-(4-hydroxybenzamido)acrylates we could construct spirocyclic lactams in up to 52% yield. Under alternative reaction conditions the same precursors underwent an unexpected oxidative spirocyclization yielding a novel δ-spirolactone in up to 70% yield.

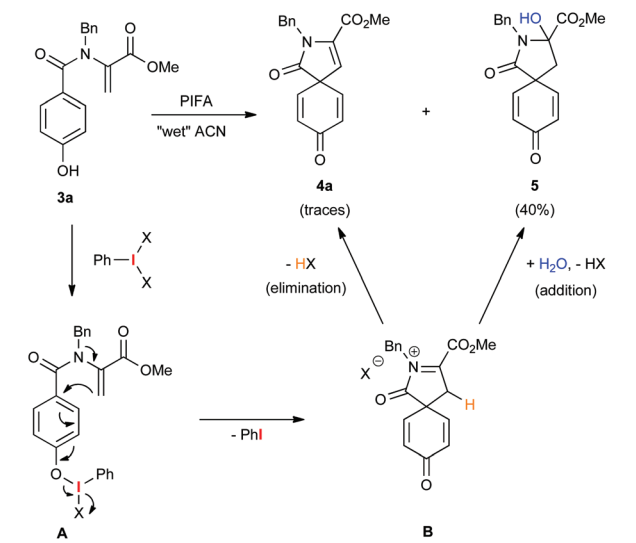
The construction of spirocyclic compounds *via* the oxidative dearomatization of phenols is an innovative approach that has found extensive application in natural product synthesis.[1] Various pioneering reaction methods based on hypervalent iodine(III) reagents have been reported recently.[2–4] Using this approach as a key tool, our group was interested in a novel synthesis of arogenate (pretyrosine),[5] a crucial biosynthetic precursor of the essential aromatic amino acids phenylalanine and tyrosine. So far two synthetic procedures for arogenate have been described.[6] Even though both of these pathways yield enantiopure (*S*)-arogenate, the critical steps in which the α-stereogenic center is installed were based on chiral auxiliary chemistry. Our synthetic strategy towards arogenate involved γ-spirolactam **4** as the prochiral key intermediate (Scheme 1) which after catalytic enantioselective hydrogenation and saponification should yield spiro-arogenate[7] and subsequently arogenate.

In this communication we present preliminary results towards a fast and efficient synthetic approach of **4** based on an iodine(III)-mediated oxidative spirocyclization of 2-(4-hydroxybenzamido)-acrylates **3**.[8] In addition we describe an unexpected but nonetheless highly interesting side reaction, namely a rare iodine(III)-mediated spirocyclization giving novel δ-spirolactones.

The synthesis of **3a** (R = Me) was realized through a fast two-step process starting from *N*-benzyl serine methyl ester **2a** and an excess of *O*-TMS protected 4-hydroxybenzoyl chloride **1** (Scheme 1). In a first oxidative cyclization experiment of **3a** two major reaction products could be isolated (Scheme 2). With



Scheme 1 A new synthetic proposal towards (*S*)-arogenate.



Scheme 2 First attempts on a PIFA-mediated spirocyclization of 2-(4-hydroxybenzamido)acrylates.

[a]*Eberhard Karls University, Institute of Organic Chemistry, Auf der Morgenstelle 18, Tuebingen, Germany. E-mail: boris.nachtsheim@uni-tuebingen.de; Fax: +49 7071 29-5897; Tel: +49 7071 29-72035*
[b]*Eberhard Karls University, Institute of Inorganic Chemistry, Auf der Morgenstelle 18, Tuebingen, Germany*

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stoichiometric amounts of the hypervalent iodine(III) reagent PIFA (phenyliodine bis(trifluoroacetate)) in acetonitrile the desired γ-spirolactam **4a** could only be observed in trace amounts (<10% yield). Instead we could isolate the monohydroxylated derivative **5** as the major product in 40% yield. Other hypervalent iodine reagents, in particular PIDA (phenyliodine diacetate) or Koser's reagent (hydroxy(tosyloxy)iodobenzene), did not yield **4a** or **5** in significant amounts.

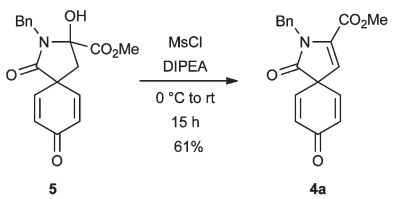
When taking a deeper look into the putative reaction mechanism both reaction products are plausible. In general iodine(III)-mediated spirocyclizations of *ortho*- or *para*-substituted phenols can be described in terms of a radical mechanism, as a dissociative reaction mechanism involving phenoxonium ions or in terms of an associative reaction mechanism as shown in Scheme 2.[3c] Typically ligand exchange on the hypervalent iodine(III) atom yields the phenolate bound intermediate **A**. With phenyliodide acting as a hypernucleofuge the oxidative C–C-bond forming step occurs with the β-carbon of the enamide acting as a carbon nucleophile. At this point the resulting *N*-acyliminium ion **B** can either eliminate a proton to give **4a** or be attacked by external nucleophiles *e.g.* traces of water from the solvent to give the α-hydroxylated derivative **5**.[9] Nonetheless it is worth mentioning that **5** could be easily converted into **4a** by *in situ* mesylation and subsequent elimination (Scheme 3).

However we were still interested in a direct synthesis of **4a** starting from **3a**. Thus further optimization studies were undertaken, this time under water-free conditions (Table 1).

During these optimization studies a second, unexpected side product occurred. Intensive 2D-NMR analysis and finally a single X-ray crystal structure proved this unknown structure to be the δ-spirolactone **6** (Fig. 1). In Table 1, yields for both reaction products are given. First we tried to optimize the reaction towards formation of the desired spirolactam **4a**. At ambient temperatures the reaction was quite slow and sluggish giving **4a** in only 20% yield (Table 1 – entry 1).

Raising the temperature to 60 °C gave **4a** in promising 49% yield (Table 1 – entry 2). *In situ* generation of PIFA with catalytic amounts of phenyl iodide and *m*CPBA as a co-oxidant gave **4a** in only 18% yield (Table 1 – entry 3).[10] Addition of TFA to the mixture did not improve yields (Table 1 – entry 4). Changing the solvent to propionitrile and raising the temperature to 90 °C finally gave **4a** in an acceptable yield of 52% (Table 1 – entry 5). However we still observed a major fraction (23%) of **6**, even under these optimized conditions. Thus we thought of varying the acrylates ester functionality in **4a**. In particular we wanted to increase its bulkiness in order to increase the steric demand around the esters carbonyl group to prevent it from acting as a concurring nucleophile. The results of these experiments are shown in Scheme 4. Unfortunately there was only a low impact of the ester residue on the outcome of this reaction.

Contrary to our initial thoughts we observed the best yield of **4a–d** with the least steric demanding methyl ester. For ethyl-, isopropyl-, and benzyl ester yields dropped slightly and ranged



Scheme 3 Elimination of **5** to the desired γ-spirolactam **4a**.

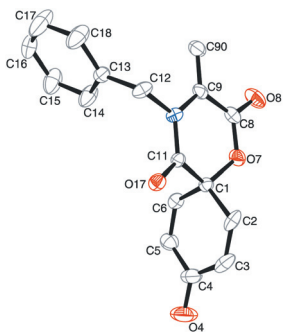
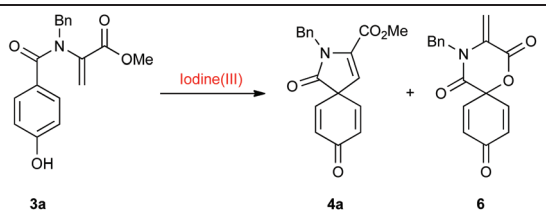


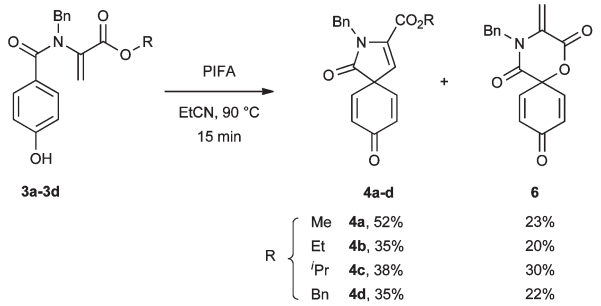
Fig. 1 Crystal structure of δ-spirolactone **6**.

Table 1 Optimization studies towards formation of the desired spirocyclic lactam **4a**



Entry[a]	Iodine(III)	Equiv.[d]	Solvent	*T* [°C]	*t* [min]	Yield **4a**[e] [%]	Yield **6**[e] [%]
1	PIFA	1.2	MeCN	rt	20	20	28
2	PIFA	1.2	MeCN	60	10	49	19
3[b]	PhI	0.2	MeCN	60	60	18	24
4[c]	PIFA	1.2	MeCN	60	10	17	21
5	PIFA	1.2	EtCN	90	10	52	23

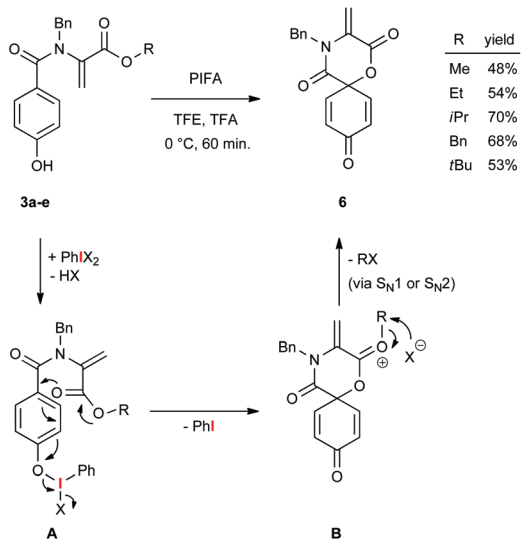
[a] General reaction conditions: 0.14 mmol **3a**, 0.17 mmol PIFA (1.2 equiv.), 2 mL solvent. [b] 2.0 equiv. of TFA was added. [c] 1.2 equiv. of TFA was added. [d] Equivalents of the iodine(III)-source. [e] Isolated yields after column chromatography.



Scheme 4 Influence of the ester residue on the formation of **4a–d** and **6**.

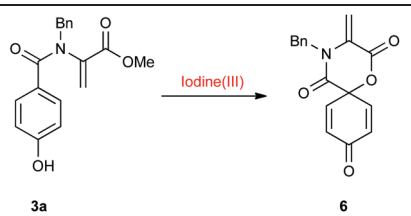
from 35–38%. Again the unexpected spirolactone **6** could be isolated in nearly constant yields ranging from 20–30%. Oxidative spirolactonization reactions mediated by aryl-λ^3-iodanes are well described. However an intensive literature search revealed to us that in general γ-spirolactones are preferentially built by iodane-mediated spirocyclizations,[11] while to the best of our knowledge, there is no example of an iodane-mediated synthesis of δ-spirolactones starting directly from carboxylic acid derivatives. As one rare example where a similar intermediate was postulated, Kita and co-workers recently presented a domino reaction of *para*-cyclobutanol substituted phenols leading to spiro-cyclohexadienone lactones.[12] The same group presented a 6-ring lactamization.[13] However our finding together with the fact that the observed δ-spirolactone **6** can be seen as an interesting synthetic intermediate that can be further derivatized along the exocyclic double bond prompted us to further optimize this originally undesired side reaction. The results of these optimization studies are given in Table 2. Surprisingly we could completely prevent formation of spirolactam **4a** when changing the solvent from propionitrile to TFE (2,2,2-trifluoroethanol) (Table 2 – entry 1). Even though fluorinated solvents have been described to have unique features in iodane-mediated spirocyclization reactions, this observation was surprising to us.[14] When TFA was added as an acid additive reaction yields increased slightly to 38% (Table 2 – entry 2). Adding PIFA and TFA in a twofold excess gave **6** in 44% yield (Table 2 – entry 3). Finally lowering the reaction temperature to 0 °C resulted in a cleaner reaction and formation of **6** in 48% yield (Table 2 – entry 4). HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) as an alternative fluorinated protic solvent had a negative impact on product yield (Table 2 – entry 5). It is worth mentioning that other hypervalent iodine compounds such as PIDA and Koser's reagent did not give **6** in promising yields, although with HTIB at least 23% of **6** could be isolated (Table 2 – entries 6 and 7).

Under these optimized reaction conditions we discovered the influence of the ester group on this novel spirolactonization reaction (Scheme 5). In sharp contrast to the conditions used for the formation of **4a–d** this time the ester functionality had a significant influence on spirolactone formation under the optimized



Scheme 5 Putative reaction mechanism for the formation of **6**.

Table 2 Optimization studies towards formation of the unexpected δ-spirolactone **6**



Entry[a]	Iodine(III)	Equiv.[b]	Solvent	Additive (equiv.)	*T* [°C]	*t* [min]	Yield **6**[c] [%]
1	PIFA	1.2	TFE	—	70	20	32
2	PIFA	1.2	TFE	TFA (1)	70	60	38
3	PIFA	2	TFE	TFA (2)	70	60	44
4	PIFA	2	TFE	TFA (2)	0	60	48
5	PIFA	2	HFIP	TFA (1)	0	180	35
6	PIDA	1.2	TFE	—	0 to 70	180	—
7	HTIB	1.2	TFE	—	70	15	23

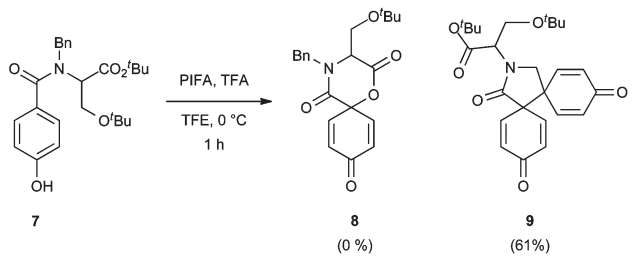
[a] General reaction conditions: 0.1 mmol **3a**, 0.12 mmol PIFA (1.2 equiv.) in 2 mL TFE. [b] Equivalents of the iodine(III)-source. [c] Isolated yields after column chromatography.

conditions we found in Table 2. Going from methyl- to ethyl and isopropyl ester yields of **6** increased significantly from 48 to 70%. The corresponding benzyl ester **3d** gave **6** in 68% yield while yields dropped to 53% when *tert*-butyl ester **3e** was used instead.

Thinking about the putative reaction mechanism this tendency is plausible. In a typical associative reaction mechanism a ligand exchange on the hypervalent iodine gives intermediate **A**.

After the key spirocyclization step with the esters carbonyl group acting as a nucleophile a carboxonium intermediate **B** can be formulated which needs to lose the alkyl group R either in an S_N1- or in an S_N2-type mechanism with the solvent or the counterion X^- as nucleophilic scavengers. In particular the S_N1-type pathway would be much more favourable for carbocation-stabilizing residues such as isopropyl or benzyl. The drop in yield for *t*Bu-ester **3e** might be the result of the steric demand of the *t*Bu-group making the nucleophilic attack of the ester more difficult. A radical mechanism *via* SET (single electron transfer) can be excluded since no phenol-centred radicals could be observed by ESR-spectroscopy. Since the acrylic double bonds in compounds **3a–e** are not directly involved in the spirolactonization we finally wondered whether a saturated derivative could be used for this reaction as well (Scheme 6). Thus we tested substrate **7** under our optimized reaction conditions. To our surprise we could not isolate the expected spirolactone **8**. Instead we observed the bis-(cyclohexa-2,5-dien-4-one) **9** as the only product in 61% yield.

The structure of **9** could be determined by multidimensional NMR-spectroscopy and was finally confirmed by single crystal X-ray diffraction (Fig. 2). However **9** is an exciting structure, since similar spirocyclohexadienones can undergo acid-mediated dienone-phenol rearrangements leading to highly interesting



Scheme 6 Unexpected formation of a bis(cyclohexa-2,5-dien-4-one) **9**.

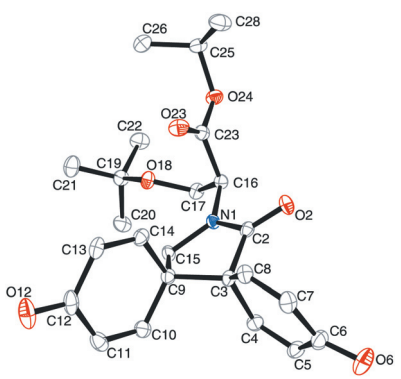


Fig. 2 Crystal structure of bis(cyclohexa-2,5-dien-4-one) **9**.

dibenzoazepinones.[15] The origin of the carbonyl group of the second spirocyclohexadienone-ring is unknown and part of current investigations.

Conclusions

In conclusion we have successfully developed a hypervalent iodine-mediated spirocyclization of 2-(4-hydroxybenzamido)-acrylates. We were able to observe the desired spirolactams in up to 52% yield. In fluorinated solvents high yields (up to 70%) of an unexpected δ-spirolactone could be observed *via* a very rare iodane-mediated oxidative 6-ring spirolactonization. Further synthetic studies, in particular towards the catalytic enantioselective reduction of the unsaturated spirolactams **4a–d**, are underway.

Acknowledgements

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