Organic synthesis using a hypervalent iodine reagent: unexpected and novel domino reaction leading to spiro cyclohexadienone lactones†

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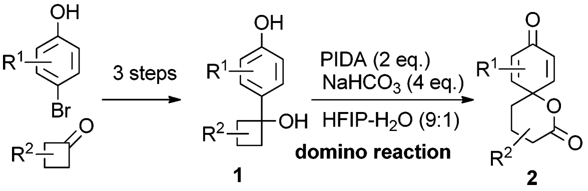
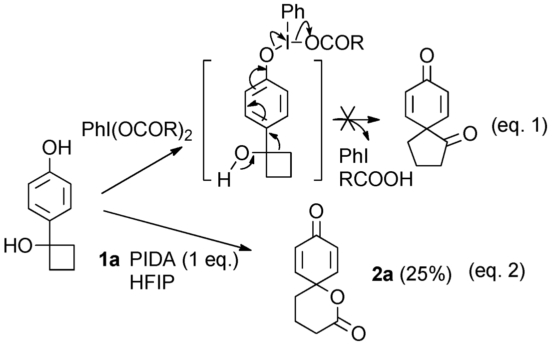
The reaction of 1-(*p*-hydroxyaryl)cyclobutanols and phenyl iodide(III) diacetate in hexafluoroisopropanol and water produced spiro cyclohexadienone lactones *via* a domino reaction.

Hypervalent iodine reagents are widely recognized as non-toxic oxidizing agents for use in the place of highly toxic heavy metal oxidizing reagents, and many such oxidation methods have been developed.[1] We have also been developing many synthetic reactions using hypervalent iodine reagents.[2] As a part of our studies into the use of hypervalent iodine reagents, we found that the reaction of phenol compounds with benzylic *tert*-alcohol and phenyliodine diacetate (PIDA) produced a novel one-pot transformation to afford spiro cyclohexadienone lactones in good yields (Scheme 1). We now describe the study of this novel domino transformation.

Since phenols having a *p*-substituent with a nucleophilic function, such as hydroxyl or carboxylic acid groups, are known to produce spiro cyclohexadienones on reaction with hypervalent iodine reagents, such as phenyliodine bistrifluoroacetate (PIFA) or PIDA,[3] we theorized that the treatment of phenol compounds with a benzylic *tert*-alcohol would afford the spiro cyclohexadienone ketone through a rearrangement reaction (Scheme 2, eqn (1)). **1a** was then prepared in a three-step sequence from *p*-bromophenol and cyclobutanone: (1) *tert*-butyldimethylsilylation of *p*-bromophenol, (2) condensation of the lithio compound, obtained by the treatment of *p*-bromophenol-TBDMS ether with n-BuLi, and cyclobutanone, and (3) desilylation of the coupling product. Next, the reaction of the phenol **1a** and 1 equivalent of PIFA or PIDA in just-purchased hexafluoroisopropanol (HFIP) was carried out. As a result, although a complex mixture was obtained in the case of PIFA, the reaction with PIDA gave the spiro[5.5]dienone lactone **2a**, but in low yield (Scheme 2, eqn (2)).[4,5] This was an unexpected and unprecedented result. We then studied this reaction in detail (Table 1). As a hypervalent iodine reagent, PIDA was much better than PIFA (entry 2 *vs.* entry 1). As a reaction solvent, HFIP–H_2O (9 : 1) was the solvent of choice (entry 4 *vs.* entries 2, 3, and 9). This transformation needed 2 equivalents of PIDA (entries 5, 7, 8 *vs.* entries 4, 6). The addition of $NaHCO_3$ as an additive improved the yield of **2a** (entries 7 and 8 *vs.* entry 5). The optimized conditions were the reaction with **1a**, PIDA (2 eq.), $NaHCO_3$ (4 eq.) in HFIP–H_2O (9 : 1), and **2a** was obtained in 75% yield (entry 8).



Scheme 1



Scheme 2

Scheme 3 shows the reaction of the **1a** derivative, **1a-Me**, whose benzylic *tert*-alcohol was protected as a methyl ether. In this case, the spirolactone **2a** was also obtained, although its yield was slightly low. This result means that the contribution of the benzylic alcohol to this transformation does not occur during the initiation step of the reaction.

To clarify the reaction mechanism, the reaction of **1a** to **2a** was carried out in the same manner except for the H_2O (Scheme 4). In this case, ^{18}O labeled water was used in place of H_2O, and ^{18}O-introduced spirolactone **2a**[^{18}O] and ^{16}O-introduced spirolactone **2a**[^{16}O] were obtained in 83% yield in the ratio of 2 to 1. ^{16}O must be derived from $H_2{}^{16}O$ formed by the reaction of AcOH from PIDA and $NaHCO_3$. The formation of **2a**[^{18}O] meant that one of the two oxygen atoms of the lactone moiety came from water. $LiAlH_4$ reduction of the mixture of **2a**[^{18}O] and **2a**[^{16}O] gave a mixture of **3**[^{18}O], whose oxygen atom of the primary alcohol is the ^{18}O labeled one, and **3**[^{16}O], whose oxygen atom of the primary alcohol is the normal one, in the ratio of 1 to 2 in a total 71% yield. That

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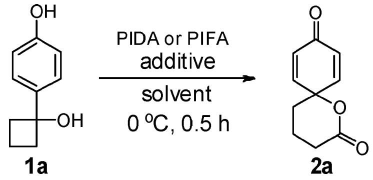
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for the compounds. See DOI: 10.1039/b925687c

Table 1 Optimization of the reaction conditions to spiro[5.5]lactone **2a**



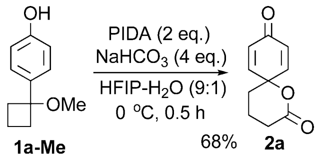
Entry	PIDA or PIFA	Solvent	Additive	Yield (%)
1	PIFA (1 eq.)	HFIP	—	Decomp.
2	PIDA (1 eq.)	HFIP	—	27 (20[a])
3	PIDA (1 eq.)	CH_3CN	—	0 (61[a])
4	PIDA (1 eq.)	HFIP–H_2O (9 : 1)	—	24 (42[a])
5	PIDA (2 eq.)	HFIP–H_2O (9 : 1)	—	61
6	PIDA (1 eq.)	HFIP–H_2O (9 : 1)	$NaHCO_3$ (2 eq.)	35 (41[a])
7	PIDA (2 eq.)	HFIP–H_2O (9 : 1)	$NaHCO_3$ (2 eq.)	63
8	PIDA (2 eq.)	HFIP–H_2O (9 : 1)	$NaHCO_3$ (4 eq.)	75
9	PIDA (2 eq.)	CH_3CN–H_2O (9 : 1)	—	16
10	PIDA (2 eq.)	CH_3CN–H_2O (9 : 1)	$NaHCO_3$ (4 eq.)	13

[a] Recovered SM.

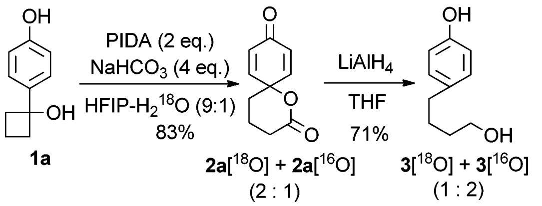
meant that the carbonyl oxygen atom was composed of ^{18}O and ^{16}O in the ratio of 1 to 2.

From the results in Schemes 3 and 4, a plausible reaction mechanism is depicted as follows (Scheme 5). Firstly, the iodo complex **i** is formed by the reaction of **1a** and 1 equivalent of PIDA. The elimination of PhI and AcOH and the rearrangement reaction then converted **i** to the intermediate **ii** corresponding to the spiro cyclohexadienone ketone compound in Scheme 2. For our reaction conditions, water is included in the reaction vessel, and C–C bond cleavage and aromatization occurs to afford the phenolic carboxylic acid by nucleophilic attack of the water.[6] The reaction with one more PIDA then gives the final spiro cyclohexadienone lactone **2a** *via* the intermediate **iii**. During this reaction process, 2 equivalents of PIDA are necessary and 4 equivalents of AcOH were released. This was the reason why the addition of 4 equivalents of $NaHCO_3$ gave better results by neutralizing the acidity in the reaction vessel.

The effect of the substituent on the aromatic ring was next examined (Table 2). The result of **1a** with no substituent is used as a reference (entry 1). *ortho*-Substituted phenols **1b–d** produced the corresponding spirolactones in good yields (entries 2–4). It is noteworthy that the *o*,*o*′-disubstituted one **1d** gave the product in good yield (entry 4). Even the reaction of the *m*-substituted phenol **1e** gave the product **2e** with a slightly lower yield (entry 5) (maybe, the *m*-substituent might hinder the transformations from **ii** to **2a** in Scheme 5).



Scheme 3

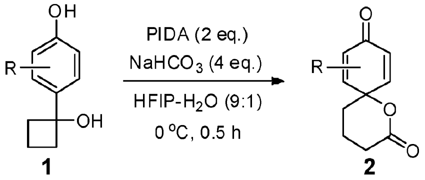


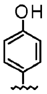
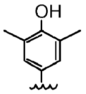
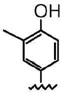
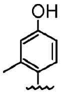
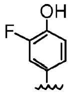
Scheme 4

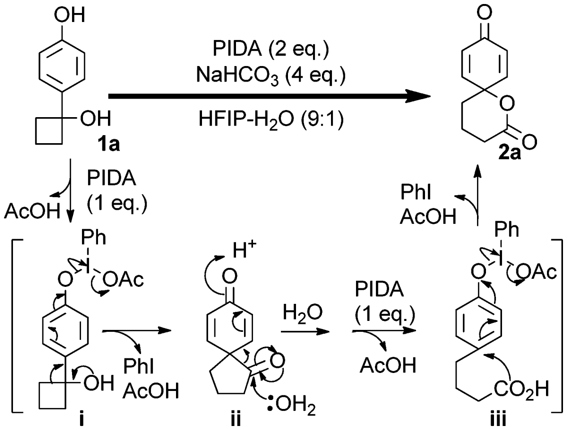
We next examined the selectivity of the rearrangement depending on the substituents (methyl or isopropyl) next to the hydroxyl group on the cyclobutane ring. (Scheme 6). In both cases, a good selectivity was observed. **4a** containing a methyl group produced **5a** and **6a** in the ratio of 5 to 1, and **4b** having an isopropyl group afforded **5b** and **6b** in the ratio of 6.7 to 1.

In conclusion, we have succeeded in developing a novel transformation of phenols with a benzylic *tert*-alcohol and proved its reaction mechanism. The one-pot four-step transformation was as follows: (1) oxidation of the phenolic hydroxyl group forming a carbocation at the *p*-position, (2)

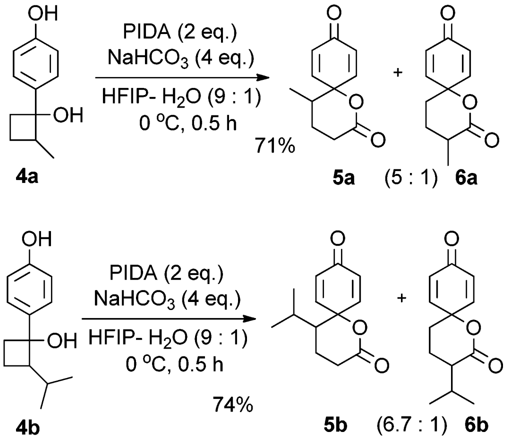
Table 2 Synthesis of spiro[5.5]lactone compounds



Entry	Substrate	Product	Yield (%)	Entry	Substrate	Product	Yield (%)
1	1a 	2a	75	4	1d 	2d	77
2	1b 	2b	76	5	1e 	2e	54
3	1c 	2c	64				



Scheme 5



Scheme 6

rearrangement reaction producing a spiro diene dione compound, (3) water attack on the ketone affording a carboxylic phenol, and (4) intramolecular cyclization giving the spiro cyclodienone lactone, proceeding in a domino manner. This new information adds a new aspect to reactions using hypervalent iodine reagents.

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Notes and references

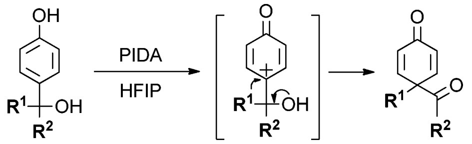
1 For recent reviews by other groups, see: (*a*) P. J. Stang and V. V. Zhdankin, *Chem. Rev.*, 1996, **96**, 1123–1178; (*b*) V. V. Zhdankin and P. J. Stang, *Chem. Rev.*, 2002, **102**, 2523–2584; (*c*) T. Wirth, *Angew. Chem., Int. Ed.*, 2005, **44**, 3656–3665.

2 For reviews by our group, see: (*a*) Y. Kita, H. Tohma and T. Yakura, *Trends Org. Chem.*, 1992, 113–128; (*b*) Y. Kita, T. Takada and H. Tohma, *Pure Appl. Chem.*, 1996, **68**, 627–630; (*c*) H. Tohma and Y. Kita, *J. Synth. Org. Chem. Jpn.*, 2004, **62**, 116–127; (*d*) Y. Harayama and Y. Kita, *Curr. Org. Chem.*, 2005, **9**, 1567; (*e*) T. Dohi and Y. Kita, *Chem. Commun.*, 2009, 2073–2085.

3 Y. Kita, H. Tohma, K. Kikuchi, M. Inagaki and T. Yakura, *J. Org. Chem.*, 1991, **56**, 435–438.

4 We have already developed the rearrangement reaction of epoxy acylates *via* carbocation species. For our recent papers, see: (*a*) Y. Kita, J. Futamura, Y. Ohba, Y. Sawama, J. K. Ganesh and H. Fujioka, *J. Org. Chem.*, 2003, **68**, 5917–5924; (*b*) H. Fujioka, Y. Yoshida and Y. Kita, *J. Synth. Org. Chem. Jpn.*, 2003, **61**, 133–143; (*c*) Y. Kita, J. Futamura, Y. Ohba, Y. Sawama, J. K. Ganesh and H. Fujioka, *Tetrahedron Lett.*, 2003, **44**, 411–413; (*d*) Y. Kita, S. Matsuda, R. Inoguchi, J. K. Ganesh and H. Fujioka, *J. Org. Chem.*, 2006, **71**, 5159–5157 and references cited therein.

5 Quite recently, the reaction of phenols, with benzylic alcohol, and PIDA in HFIP was reported (K. M. Guerard, C. Chapelle, M.-A. Giroux, C. Sabot, M.-A. Beaulieu, N. Achache and S. Canesi, *Org. Lett.*, 2009, **11**, 4756–4759). Guerard *et al.* used only the phenols with the acyclic benzylic alcohol, and produced keto dienones, which correspond to our intermediates **ii** in Scheme 5 (see the lower part of the scheme). The difference in the reaction might be due to the HFIP purity. In our case, we used the commercially available HFIP without distillation, and maybe a small amount of H_2O might be included in it.



6 The cleavage of spiro cyclohexadienone ketones giving phenolic carboxylic acids is well established. See: L. B. Jackson and A. J. Waring, *J. Chem. Soc., Perkin Trans. 2*, 1990, 907–913.