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Direct Lactone Formation by Using Hypervalent Iodine(III) Reagents with KBr via Selective C–H Abstraction Protocol

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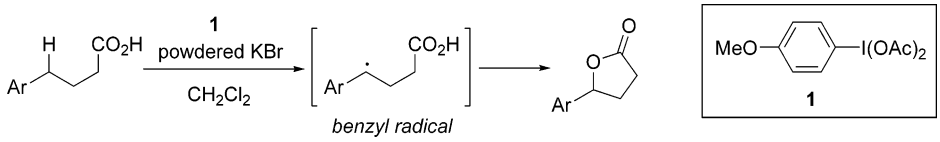
ABSTRACT



We have developed a new and reliable method for the direct construction of biologically important aryl lactones and phthalides from carboxylic and benzoic acids, using a combination of hypervalent iodine(III) reagents with KBr.

Lactones are the basic structural unit of natural products and are of great importance in the areas of pharmaceuticals, agrichemicals, flavor components, material, and polymer productions, and also are as well versatile building blocks for these applications.[1] In particular, certain aryl-substituted γ-lactones show a variety of significant biological behaviors.[2] One of the convenient and attractive routes for the synthesis of these lactones is the direct oxidative C−O coupling reaction starting from the corresponding carboxylic acids.[3,4] Despite the numerous efforts toward the realization of such processes, reported procedures using metal oxidants have limited applications because they typically need harsh reaction conditions, thus giving rise to serious problems in the product yield, undesired side reactions (decarboxylation, ring oxidation, ketone formation, etc.), and functional tolerance. To achieve the direct lactone synthesis, it is highly important to construct a mild and clean system enabling selective formation of benzyl radical **A** via sp^3 C−H abstraction, as the carbonyloxy radical **B** produced by the O−H activation is not productive due to the rapid decarboxylation of intermediate **B** (Scheme 1).[5] Herein, we would like to report the realization of a promising method for direct aryl lactone formation by using hypervalent iodine(III) reagents with the aid of KBr via the benzylic C−H bond abstraction strategy.

Recently, hypervalent iodine(III) reagents have gained much attention owing to their attractive features such as low toxicity, high stability, and reactivity similar to those of highly toxic heavy metal oxidants.[6] As a new direction of

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(4) γ-Lactone formation from aliphatic carboxylic acids having suitably activated benzyl positions: Jevric, M.; Taylor, D. K.; Greatrex, B. W.; Tiekink, E. R. T. *Tetrahedron* **2005**, *61*, 1885.

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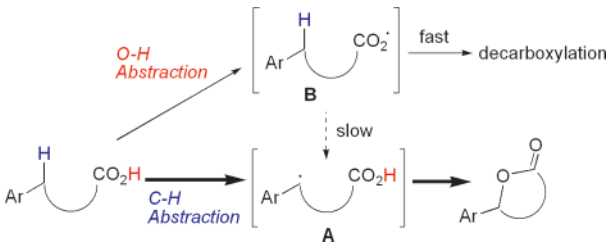
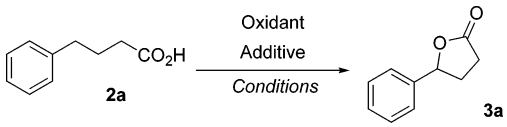
Scheme 1. Direct Formation of Aryl Lactones via the Selective C−H Abstraction



our ongoing study on hypervalent iodine(III) chemistry, we have decided to start our survey toward utilization of the reagents for mild and selective sp^3 C−H functionalization,[7] aiming at the synthesis of the important lactone compounds. Thus, initial investigation for the direct γ-lactone formation was carried out with simple carboxylic acid **2a**. Single use of hypervalent iodine(III) oxidants—specifically, $PhI(OAc)_2$ (PIDA) or $PhI(OCOCF_3)_2$ (PIFA)—did not give the lactone **3a** at all, and no conversion of **2a** was observed (Table 1, entry 1). Activation of PIDA and PIFA with a Lewis acid such as $BF_3{\cdot}Et_2O$ and TMSOTf did not afford any lactone **3a** either, and instead ring oxidation of **2a** occurred in these cases giving rise to complex product mixtures. We next tried to use other activation methods on the basis of our previous reports,[8] and thus the reaction of **2a** with PIDA in the presence of inorganic bromides[8,9a,b] was examined. Although the previous method itself did not induce selective formation of **3a**, use of KBr *in organic solvents* dramatically altered the situations; the reaction of **2a** with the combination of PIDA and finely powdered KBr in degassed dichloromethane afforded lactone **3a** in a good yield at room temperature (entry 2). It should be noted that the added KBr worked as a catalyst, since it is hardly soluble in CH_2Cl_2, and for the most part was present as the precipitate throughout the reaction. Indeed, catalytic use of KBr slightly affected the yield of **3a** (entry 3). Interestingly, only KBr was suitable as an effective bromide source,[10] and organic bromides,

Table 1. Influence of Oxidants and Additives



entry	oxidant[a]	additive[b]	conditions	time (h)	yield (%)[c]
1	PIDA or PIFA	none	CH_2Cl_2, rt	24	nr[d]
2	PIDA	KBr	CH_2Cl_2, rt	7	69
3	PIDA	KBr[e]	CH_2Cl_2, rt	24	65
4	PIDA	$Bu_4N^+Br^-$	CH_2Cl_2, rt	24	nd[f]
5	PIDA	TMSBr	CH_2Cl_2, rt	24	nd
6	PIFA	KBr	CH_2Cl_2, rt	24	<5[g]
7	HTIB	KBr	CH_2Cl_2, rt	20	25
8	DMP[h]	KBr	CH_2Cl_2, rt	24	39
9	**1**	KBr	CH_2Cl_2, rt	8	80 (91)[i]
10	DDQ[j]	none	benzene, 50 °C	24	nr
11	$NaBrO_3$	$NaHSO_3$[k]	AcOEt/H_2O (1/2), rt	18	15[l]

[a] 1.2 equiv of oxidants was used. [b] 1 equiv relative to **2a**. [c] Isolated yields based on **2a** used. [d] nr = no reaction. [e] 0.5 equiv. [f] nd = not detected. [g] Determined by ^1H NMR observation. [h] DMP = Dess−Martin periodinane. [i] Isolated yield based on consumed **2a**. [j] DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. [k] 1.2 equiv of $NaHSO_3$ was used. [l] 3-Benzoylpropionic acid was obtained as a major product.

$Bu_4N^+Br^-$ [9c,d] or TMSBr,[9e] did not give the desired **3a** (entries 4 and 5). In our screening of the oxidants, we have discovered an alternative appropriate oxidant, *p*-anisiodine-(III) diacetate **1**, having milder reactivity than PIDA (entries 6−9). As a comparison, we examined the oxidations using other types of organic or inorganic oxidants, i.e., DDQ[4] or $NaBrO_3$[11] with **2a**, but no reaction or undesired ketone formation[11b] was observed in these cases (entries 10 and 11).

Having established the optimum reaction conditions, we then investigated the influence of the nature of the starting carboxylic acids **2** on the reaction.[12] Accordingly, the γ-lactone forming reactions of para-substituted aryl butyric acids **2b**−**f** were examined (Table 2). As shown in entry 2, the presence of an electron donating group allowed the reaction to proceed to the formation of the corresponding γ-lactone **3b** in good yield. In contrast, the reaction

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(7) Benzylic azidation of phenyl ethers with phenyliodine bis(trifluoroacetate): Kita, Y.; Tohma, H.; Takada, T.; Mitoh, S.; Fujita, S.; Gyoten, M. *Synlett* **1994**, 427.

(8) Generation and detection of active iodine(III)−Br species in water by the combination of PIDA or iodosobenzene with KBr, see: (a) Tohma, H.; Takizawa, S.; Maegawa, T.; Kita, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 1306. (b) Tohma, H.; Maegawa, T.; Takizawa, S.; Kita, Y. *Adv. Synth. Catal.* **2002**, *344*, 328.

(9) Iodine(III) oxidations in the presence of bromide. LiBr or NaBr: (a) Braddock, D. C.; Cansell, G.; Hermitage, S. A. *Synlett* **2004**, 461. (b) Karade, N. N.; Shirodkar, S. G.; Dhoot, B. M.; Waghmare, P. B. *J. Chem. Res.* **2005**, 274. Ammonium bromide: (c) Hashem, M. A.; Jung, A.; Ries, M.; Kirschning, A. *Synlett* **1998**, 195. (d) Brunjes, M.; Sourkouni-Argirusi, G.; Kirschning, A. *Adv. Synth. Catal.* **2003**, *345*, 635. TMSBr: (e) Evans, P. A.; Brandt, T. A. *J. Org. Chem.* **1997**, *62*, 5321.

(10) In Group 1 alkali metal bromide, yield of **2a** decreased in order with KBr > NaBr ≫ LiBr. LiBr induced remarkable bromination at both aromatic and benzyl carbons.

(11) (a) Hayat, S.; Atta-ur-Rahman; Choudhary, M. I.; Khan, K. M.; Bayer, E. *Tetrahedron Lett.* **2001**, *42*, 1647. (b) Kikuchi, D.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1998**, *63*, 6023.

(12) **Representative experimental procedure**: In a flame-dried two-necked round-bottomed flask, under nitrogen, the iodine(III) reagent **1** (211 mg, 0.6 mmol) was added to a stirred suspension of 4-pheyl butyric acid **2a** (82 mg, 0.5 mmol) and KBr (60 mg, 0.5 mmol) in dry CH_2Cl_2 (5 mL) then the mixture was vigorously stirred for 8 h at 30 °C. After checking the reaction completion by TLC, saturated aq $NaHCO_3$ was added to the mixture, which was then stirred for an additional 5 min. The organic layer was separated, washed with saturated aq $NaHCO_3$and dilute aq sodium thiosulfate, and dried over anhydrous Na_2SO_4. After removal of the solvents, the residue was subjected to silica gel column chromatography (eluents: *n*-hexane/AcOEt) to give the γ-phenyl γ-butyrolactone **3a** (65 mg, 80%) as a white powder. Unreacted **2a** (9.8 mg, 12%) was recovered from the combined aqueous phase by extraction of dichloromethane after acidifying the solution.

Table 2. Direct Aryl Lactone Forming Reaction from Aliphatic Carboxylic Acids **2** with Use of a Combination of **1** and KBr

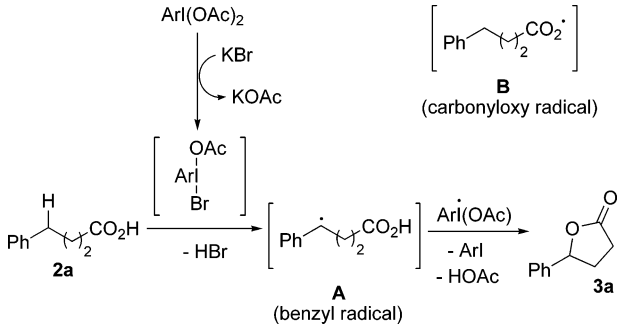
entry	carboxylic acid (**2**)	aryl lactone (**3**)	time (h)	yield (%)[a]
1	R = H (**2a**)	(**3a**)	8	80 (91)[b]
2	OMe (**2b**)	(**3b**)	8	71
3[c]	NO_2 (**2c**)	(**3c**)	18	47 (62)[b]
4	F (**2d**)	(**3d**)	24	73
5	Br (**2e**)	(**3e**)	18	61
6	Ph (**2f**)	(**3f**)	20	65
7[c]	(**2g**)	(**3g**)	15	85
8[c]	(**2h**)	(**3h**)	6	50[d]
9	(**2i**)	(**3i**)	24	65
10	(**2j**)	(**3j**)	24	21

[a] Isolated yields. [b] Yield based on consumed starting materials. [c] 1.2 equiv of PIDA was used. [d] The trans/cis ratio was estimated as 100/5 by ^{1}H NMR.

proceeded slowly in carboxylic acid **2c** bearing a nitro group, and a larger amount of starting **2c** was recovered than in the former two cases (entry 3). Reaction of **2d** and **2e** proceeded effectively, and the bromo group in the lactone **3e** would be helpful for further transformations (entries 4 and 5). Biaryl lactone[2a] **3f** and *gem*-diphenyl lactone **3g** were also obtained in similar ways (entries 6 and 7). We have examined the stereoselectivity of the reaction with β-substituted acid **2h**, giving *trans*-vicinal γ-lactone **3h** exclusively in 50% yield (entry 8). The product is known as a useful synthetic precursor for naturally occurring lactone neolignans.[13] Furthermore, larger ring lactones could be obtained (entries 9 and 10), even though the reaction proceeded less efficiently than the γ-lactone formation.

A possible explanation for the reaction mechanism of the direct lactone formation is exemplified with aliphatic carboxylic acid **2a** (Scheme 2). Initially, abstraction of the benzyl hydrogen atom occurred selectively by the action of the iodine(III) oxidants with KBr under the present mild conditions, and the benzyl radical **A** was successfully formed rather than the carbonyloxy radical **B**. The advantage of the

Scheme 2. A Possible Reaction Mechanism



hypervalent iodine(III) oxidants, which possess high reactivity under mild conditions (room temperature, nearly neutral conditions), is well utilized in this step. The resulting radical **A** then ensured the successive oxidative lactone forming step to give the observed product **3a**. Since only KBr was suitable here as the bromide source (Table 1), it is obvious that the generation of unique oxidation species was involved during the reaction by the combination of the iodine(III) reagents and KBr.[14] Therefore, from our previous observation,[8] we now consider that KBr might act as a generator of active iodine(III) oxidants containing a I(III)−Br bond,[15] although further studies on the detection of the species and the intermediates are needed to confirm this.

The reaction involving benzyl radical intermediates is also applicable to the 2-alkyl benzoic acid derivatives, leading to phthalides **4**.[16,17] Selected examples of the substrates are presented in Figure 1. It became clear that not only primary

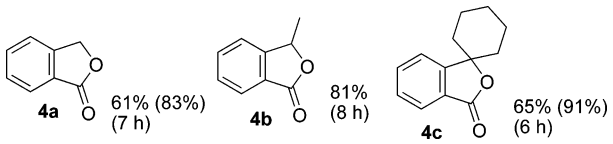


Figure 1. Phthalide formation from 2-alkyl benzoic acids (conversion yields are shown in the parentheses).

and secondary alkyl C−H groups, but also the tertiary C−H group was not controversial. In fact, even formation of the rigid spirocyclic **4c** was obtained in 65% yield (91% relative

(13) (a) Pohmakotr, M.; Pinsa, A.; Mophuang, T.; Tuchinda, P.; Prabpai, S.; Kongsaeree, P.; Reutrakul, V. *J. Org. Chem.* **2006**, *71*, 386. (b) Yamauchi, S.; Hayashi, Y.; Nakashima, Y.; Kirikihira, T.; Yamada, K.; Masuda, T. *J. Nat. Prod.* **2005**, *68*, 1459. (c) Brown, R. C. D.; Bataille, C. J. R.; Bruton, G.; Hinks, J. D.; Swain, N. A. *J. Org. Chem.* **2001**, *66*, 6719. (d) Yoda, H.; Kimura, K.; Takabe, K. *Synlett* **2001**, 400. (e) Yoshida, S.; Ogiku, T.; Ohmizu, H.; Iwasaki, T. *Tetrahedron Lett.* **1995**, *36*, 1459.

(14) It was reported that other bromides such as $Bu_4N^+Br^-$ and TMSBr produce hypobromite or the bromate(I) complex and molecular bromine, respectively. See, refs 9c−e.

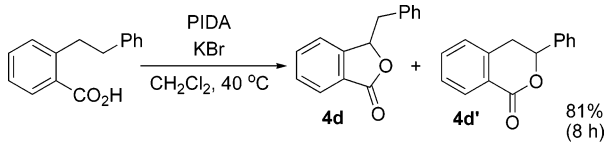
(15) Isolation of cyclic I(III)−Br compounds and their use as radical initiators: Amey, R. L.; Martin, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 3060.

(16) Direct phthalide formation with metal oxidants: (a) Lee, J. M.; Chang, S. *Tetrahedron Lett.* **2006**, *47*, 1375 and references cited therein. (b) Creighton, A. M.; Jackman, L. M. *J. Chem. Soc.* **1960**, 3138. (c) Mahmoodi, N. O.; Salehpour, M. *J. Heterocycl. Chem.* **2003**, *40*, 875.

(17) Phthalide formation with hypervalent iodine(III) reagents under UV irradiation was reported with few example of substrates; however, the procedure was not applicable to aliphatic carboxylic acids because of the rapid decarboxylation: (a) Togo, H.; Muraki, T.; Yokoyama, M. *Tetrahedron Lett.* **1995**, *36*, 7089. (b) Muraki, T.; Togo, H.; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1713.

to the consumed starting material). Six-membered isocoumarin derivative **4d′** was formed over phthalide **4d** from 2-phenethylbenzoic acid, which reflects the formation of another benzyl radical at the more reactive pendent phenyl group (Scheme 3).

Scheme 3. Product Selectivity in 2-Phenethylbenzoic Acid



(**4d**: **4d'** = 22 : 78)

In summary, we have developed the mild and clean direct oxidative C−H lactonization of both the aliphatic carboxylic and benzoic acids based on the selective benzylic C−H abstraction strategy, leading to biologically important aryl lactones and phthalides, using a combination of hypervalent iodine(III) reagents with KBr.

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Supporting Information Available: Experimental procedures and detailed spectroscopic data containing ^{1}H and ^{13}C NMR of all lactone products. This material is available free of charge via the Internet at http://pubs.acs.org.

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