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A Novel Feature in Phenyliodine Diacetate Oxidation

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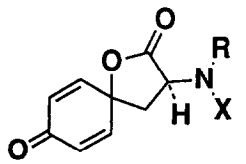
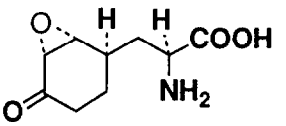
Summary: Phenyliodine diacetae (PIDA) oxidation of *N*-benzyl-*N*-benzyloxycarbonyltyrosine (**4a**) followed in one pot by quenching with aqueous sodium chloride or bromide solution gave the corresponding dihalodienone lactone (**5a or 5b**). With dihydrocinnamic acid similar feature of PIDA oxidation was obsearved. The plausible mechanism is also described.

Dienone lactones (**1**)[1] derived from L-tyrosine are regarded as a group of valuable compounds for synthesis of antibiotics, such as anticapsine (**2**)[2] and aranorosine (**3**)[3], in which synthetic approach to the latter *via* a dienone lactone (**1a**) has been recently reported by Rao et al.[4] On the other hand, transformation of *N*-protected L-tyrosines into the corresponding dienone lactones (**1**)[1] has been investigated using a variety of oxidants so far. Among the oxidants, phenyliodine(III) bis(trifluoroacetate) (PIFA) was presumed to be the most effective one. However, considering that PIFA is much more expensive than phenyliodine diacetate (PIDA), exploration of reaction conditions suitable for oxidation of tyrosine derivative (**4a**) with less effective PIDA was of necessary requirement. In the course of our studies for this purpose, we found formation of dihalogenated dienone lactones (**5**) by oxidation with PIDA, which is a novel feature. Here we wish to report a novel feature of the oxidation and its plausible mechanism.

Oxidation of **4a** with PIDA (1 eq.) in CH_3CN at room temperature gave a complex mixture. However, treatment with 3 eq. PIDA followed by decomposition of excess oxidant with aqueous sodium thiosulfate ($Na_2S_2O_3$) solution gave a dienone lactone (**1b**)[5] in 16% yield (entry 1 in Table). In addition, similar oxidation in higher diluted solution at lower temperature followed by quenching with saturated aqueous citric acid solution instead of aqueous $Na_2S_2O_3$ solution gave **1a** in improved yields. After several attempts amount of the oxidant was optimized to 3 equivalences. These results are summarized in Table. Interestingly, further examination of conditions brought to find an unexpected product (**5a**), whose spectral data [MS: m/z 427 (M^+-CO_2), 429 (M^++2-CO_2), 431 (M^++4-CO_2) (ratio of peaks; 1:0.64:0.09), IR($CHCl_3$, cm^{-1}): 1805(lactone νC=O), 1700(dienone and carbamate νC=O), ^{1}H-NMR($CDCl_3$): δ 6.84 (2H, m, olefinic H)] supported strongly



1a : R=H, X=$COCF_3$
1b : R=CH_2Ph,
X=$COOCH_2Ph$



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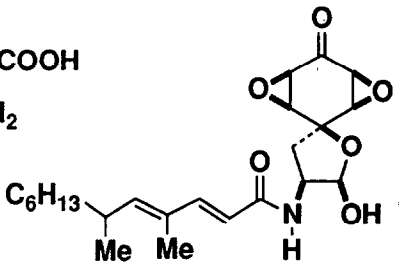

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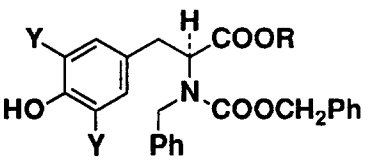
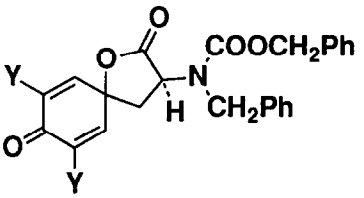
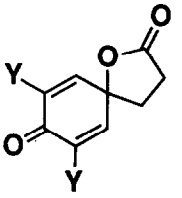


4a : R=Y=H
4b : R=Me, Y=H
4c : R=Me, Y=Cl



5a : Y=Cl
5b : Y=Br



6a : Y=Cl
6b : Y=Br

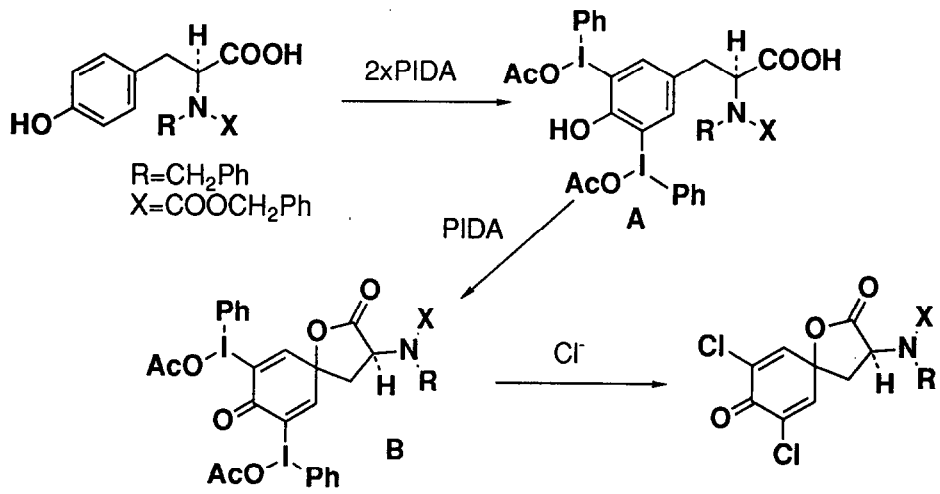
Table

Entry	Reagent	Eq.	Temp.	Solvent(ml[a])	Work-up[b]	Product(%)
1	PIDA	3	r.t.	CH_3CN(2)	A	**1b** (16)
2	PIDA	3	0°C	CH_3CN(2)	A	**1b** (28)
3	PIDA	3	0°C	CH_3CN(10)	A	**1b** (32)
4	PIDA	3	0°C	CH_3CN(10)	B	**1b** (41)
5	PIDA	3	0°C	CH_3CN(50)	B	**1b** (45)
6	PIDA	3	-5°C	CH_3CN(10)	B	**1b** (43)
7	PIDA	1.5	0°C	CH_3CN(10)	B	**1b** (30)
8	PIFA	1.1	r.t.	aq.CH_3CN[c](5)	H_2O	**1b** (63)
9	PIDA	3	-5°C	CH_3CN(10)	i)C,ii)B	**1b** (tr)[d]
						5a (74)
10	PIDA	3	-5°C	CH_3CN(10)	i)B,ii)C	**1b** (44)
						5a (tr)[d]
11	PIDA	3	-5°C	CH_3CN(10)	D	**5b** (79)

[a] Volume of solvent for 200 mg of starting **4a**. [b] A:sat.$Na_2S_2O_3$ aq. B:10% citric acid aq. C:sat. NaCl aq. D:10% NaBr aq. [c] CH_3CN-H_2O[6] [d] Trace

structure of dichlorodienone lactone (**5a**). Unexpected formation of **5a** was found to be attributable to the somewhat different work-up from that described above, in which brine was added into the reaction mixture before quenching with citric acid (entry 9). Work-up in inverse order gave the normal product (**1b**) (entry 10). While the dienone lactone (**1b**) was not chlorinated under the similar conditions to those described in entry 9, methyl ester (**4b**) was converted to the dichloro ester (**4c**) [MS, $M^+:M^+{+}2:M^+{+}4=9:6:1$] in 56% yield.

From above results a plausible mechanism could be depicted in Scheme. At first both ortho positions to hydroxyl group are attacked stepwise by PIDA to form an intermediate (**A**),[7] then oxidative lactonization occurs to give second intermediate (**B**), and finally hypervalent iodonium substituents would be displaced by chloride ion.[8] When aqueous sodium bromide solution instead of brine was used for work-up, the dibromo derivative (**5b**) was obtained (entry 11).



Scheme

With *p*-hydroxydihydrocinnamic acid, the novel reaction expectedly proceeded to afford known dihalodienone lactones (**6a**[9] and **6b**[10]) in the yields of 49% and 72%, respectively.[11] Thus, a novel feature in PIDA oxidation was found by changing the order in work-up and the present reaction is quite useful for one step synthesis of dihalodienone lactones from *p*-hydroxydihydrocinnamic acid derivatives. Application of the novel procedure to various phenolic systems and substitution[12] of the iodonium intermediary with other nucleophiles are now in progress.

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5. **1b**: mp 104-106°C. ^{1}H-NMR($CDCl_3$): δ 2.20, 2.51 (each 1H, *dd*, *J* =14.3 and 10Hz, CH_2CHN), 4.16 (1H, *t*, *J* =10Hz, CH_2CHN), 4.45, 4.80 (each 1H, *d*, *J* =15.7Hz, NCH_2Ph), 5.21 (2H, *s*, OCH_2Ph). IR($CHCl_3$, cm^{-1}): 1785 (lactone $_{\nu}C=O$), 1690, 1670 (carbamate and dienone $_{\nu}C=O$), MS (m/z): 403(M^+). Elemental analysis (%): *Calcd for* $C_{24}H_{21}NO_5$; C, 71.45; H, 5.25; N, 3.47. *Found.* C, 71.68; H, 5.41; N, 3.45. $[\alpha]_D^{25}$ -2.18($CHCl_3$, c=1). **4a**: mp 127-130°C. ^{1}H-NMR($CDCl_3$): δ 3.90 (2H, *s*, NCH_2Ph), 5.20 (2H, *s*, OCH_2Ph), 6.60, 6.80 (each 2H, *d*, *J* =8Hz, ArH). **5a**: an vicous oil. **5b**: mp 145-150°C. MS (m/z): 558(M^+), 560(M^++2), 562(M^++4) in the ratio of 1:2:1.
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