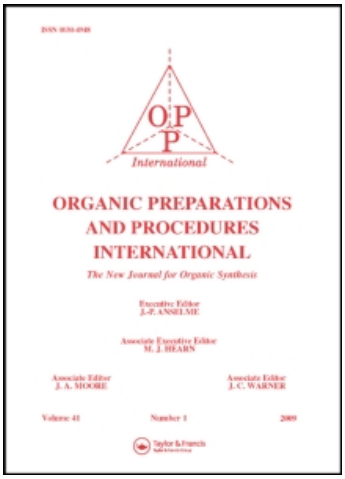

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF *o*-KETOARYL CARBOXYLIC ESTERS USING PHENYLIODOSO DIACETATE

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To cite this Article Kotali, Antigoni , Koulidis, Alexandros , Wang, Huey-Min and Chen, Ling-Ching(1996) 'SYNTHESIS OF *o*-KETOARYL CARBOXYLIC ESTERS USING PHENYLIODOSO DIACETATE', Organic Preparations and Procedures International, 28: 5, 622 — 627
To link to this Article: DOI: 10.1080/00304949609458576
URL: http://dx.doi.org/10.1080/00304949609458576

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SYNTHESIS OF *o*-KETOARYL CARBOXYLIC ESTERS USING PHENYLIODOSO DIACETATE

Submitted by (12/11/95)

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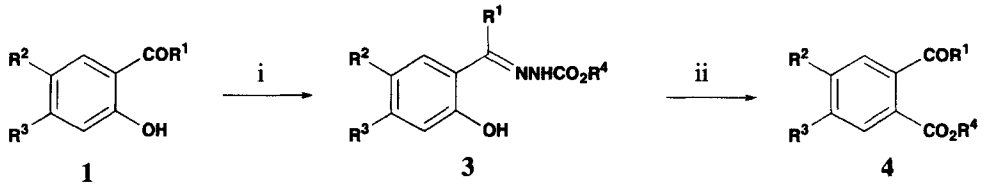
o-Hydroxyaryl ketones (**1**) are versatile synthons for heterocyclic synthesis due to the presence of phenolic hydroxy and acyl groups at adjacent positions on the benzene ring.[1] In addition to heterocyclic synthesis, the presence of these functional groups in close proximity can also result in novel rearrangements such as occurs on treatment of the monoacylhydrazones of *o*-hydroxyaryl ketones with lead tetraacetate (LTA) which results in replacement of the phenolic hydroxyl with an acyl group to give 1,2-diacylbenzenes.[2]

As a continuation of our interest in this rearrangement, we examined phenyliodoso diacetate (PID) as an alternative oxidative agent for the synthesis of *o*-ketoaryl esters (**4**,) from ethoxy- and benzyloxycarbonylhydrazones (**3**) of *o*-hydroxyaryl ketones. Since PID has similar reactivity to LTA[4] but is less toxic, its use as an alternative oxidant should be beneficial. Although it is a widely used oxidant in organic synthesis,[5] PID has been rarely used for oxidations of hydrazones in contrast to LTA.[6] Examples include conversion of benzophenone hydrazone to benzhydryl esters on treatment

with carboxylic acids in the presence of PID,[7] and the oxidation of *tert*-butoxycarbonylhydrazones of aromatic aldehydes to 1,3,4-oxadiazolin-2-ones.[8] Recently, PID was successfully employed as a substitute for LTA in the synthesis of 1,2-diacylbenzenes from *o*-hydroxyaryl ketone acylhydrazones,[9] 1,3-diacetyl-2,4-dibenzoylbenzene from the dibenzoylhydrazone of 2,4-diacetylresorcinol,[2c] as well as in the synthesis of 1,3,4-oxadiazoles from ketone acylhydrazones.[10] We now report the oxidation of *o*-hydroxyaryl ketone alkyloxycarbonylhydrazones using PID.



1 3 4

a) R^1 = Me, R^2 = R^3 = H, R^4 = Et b) R^1 = Me, R^2 = H, R^3 = OMe, R^4 = Et c) R^1 = Et, R^2 = R^3 = H, R^4 = Et
d) R^1 = R^2 = R^3 = H, R^4 = Et e) R^1 = Ph, R^2 = OMe, R^3 = H, R^4 = Et f) R^1 = R^2 = Me, R^3 = H, R^4 = Et
g) R^1 = R^2 = R^3 = Me, R^4 = Et h) R^1 = Me, R^2 = Cl, R^3 = H, R^4 = Et i) R^1 = Me, R^2 = Br, R^3 = H, R^4 = Et
j) R^1 = 2-OH-Ph, R^2 = R^3 = H, R^4 = Et k) R^1 = Me, R^2 = R^3 = H, R^4 = Bn l) R^1 = Et, R^2 = R^3 = H, R^4 = Bn

i) $NH_2NHCO_2R^4$ (2), EtOH, RT, 1-3 days ii) $PhI(OAc)_4$, CH_2Cl_2, RT, 2 hrs

Reaction of ethoxy- and benzyloxycarbonyl hydrazones **3** with two equivalents of PID in dichloromethane at room temperature gave the expected *o*-ketoaryl esters **4** after chromatographic purification. A comparison of the oxidants PID and LTA showed that yields of the *o*-ketoaryl esters **4** with PID were only slightly less than those obtained with LTA (Table 1).

TABLE 1. Preparation of Hydrazones **3** and *o*-Ketoesters **4**[a]

Cmpd	m.p.(°C)	Yield (%)[lit.]	Cmpd[b]	Yield (%) LTA[lit.]	Yield (%) PID
3a	144[2d]	75[2d]	**4a**	87[2d]	80
3b	160-162[2d]	79[2d]	**4b**	76[2d]	65
3c	140[2d]	83[2d]	**4c**	90[2d]	83
3d	229[2d]	98[2d]	**4d**	60[2d]	72
3e	183-185[2d]	76[2d]	**4e**	71[2d]	61
3f	132-133	82	**4f**	c	80
3g	185-186	79	**4g**	c	91
3h	178	75	**4h**	c	81
3i	185-186	77	**4i**	c	83
3j	168-169	78	**4j**	70	66
3k	124-125	81	**4k**	76	70
3l	117-118	80	**4l**	76	72

a) All melting points are uncorrected. b) Esters **4** are all oils. c) The preparation of esters **4f-4i** was attempted only by PID oxidation.

Novel compounds **3f-3l** and **4f-4l** were characterized by their ^{1}H NMR spectra and confirmed by elemental analysis for the hydrazones and exact molecular weight for the esters (Tables 2 and 3). Representative IR as well as ^{13}C NMR and MS spectra are presented in Tables 4 and 5. Known compounds were identified by comparison of their spectral data with those reported in the literature.[2d] The reaction probably proceeds *via* an analogous acetoxy azoacyl intermediate to the one postulated by us for the LTA conversion of *o*-hydroxyaryl ketone acylhydrazones to 1,2-diacylbenzenes.[11]

TABLE 2. Analytical Data of Hydrazones **3** and *o*-Ketoesters **4**

Cmpd	Elemental Analysis (Found)			Cmpd	Elemental Analysis (Found)	
	C	H	N		C	H
3f	61.00	6.82	11.86	**4f**	69.88	6.84
	(61.02)	(6.82)	(11.93)		(69.66)	(6.79)
3g	62.38	7.25	11.9	**4g**	70.89	7.32
	(62.15)	(7.21)	(11.14)		(70.65)	(7.25)
3h [a)]	51.46	5.10	10.91	**4h** [b)]	58.29	4.89
	(51.31)	(5.17)	(10.87)		(58.54)	(4.76)
3i	43.87	4.35	9.30	**4i** [c)]	48.73	4.09
	(43.77)	(4.37)	(9.28)		(48.71)	(4.21)
3j	63.97	5.37	9.33	**4j**	71.10	5.22
	(64.15)	(5.47)	(9.43)		(71.25)	(5.15)
3k	67.57	5.67	9.86	**4k**	75.57	5.55
	(67.76)	(5.84)	(9.95)		(75.68)	(5.56)
3l	68.42	6.08	9.39	**4l**	76.11	6.01
	(68.67)	(5.90)	(9.40)		(76.18)	(5.92)

a) Calcd for Cl, 13.81. Found: 13.72. b) Calcd for Cl, 15.64. Found : 15.51 c) HR-MS Molecular Mass Calcd: 269.9891. Found: 269.9890

EXPERIMENTAL SECTION

Melting points are uncorrected. The IR spectra were recorded on a Schimadzu IR-27G spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded either on a Varian Gemini-200 or Varian Unity Plus 300 or 400 MHz. MS were obtained either on a JEOL JMS D-300 or Kratos MS-50. The microelemental analyses were carried out either on a Heraeus CHN-O Rapid or Tacussel Coulomax 78 or by Atlantic Microlab Inc., Norcross, GA.

General Procedure for the Preparation of Hydrazones 3a-3l.- The carbonyl compounds **1a-1l** (10 mmol) and the corresponding hydrazide **2** (10 mmol) were stirred at room temperature in ethanol (50 mL) for 1-3 days. The precipitateds solid were collected, washed with ethanol and dried to give the pure hydrazones **3a-3l**.

TABLE 3. ^{1}H NMR Data of Hydrazones **3** and *o*-Ketoesters **4**[a]

Cmpd	Chemical Shifts (δ), J (Hz)
3f	1.37 (t, 3H, J = 7.1), 2.26 (s, 3H), 2.30 (s, 3H), 4.34 (q, 2H, J = 7.1), 6.90 (d, 1H, J = 8.3), 7.09 (dd, 1H, J = 2.1 and 8.3), 7.21 (d, 1H, J = 2.1), 7.98 (br s, 1H), 12.17 (s, 1H)
3g	1.37 (t, 3H, J = 7.1), 2.21 (s, 3H), 2.24 (s, 3H), 4.33 (q, 2H, J = 7.1), 6.80 (s, 1H), 7.14 (s, 1H), 7.86 (br s, 1H), 12.11 (s, 1H)
3h	1.37 (t, 3H, J = 7.1), 2.25 (s, 3H), 4.35 (q, 2H, J = 7.1), 6.94 (d, 1H, J = 8.7), 7.24 (dd, 1H, J = 2.5 and 8.7), 7.38 (d, 1H, J = 2.5), 8.19 (br s, 1H), 12.37 (s, 1H)
3i	1.38 (t, 3H, J = 7.1), 2.25 (s, 3H), 4.35 (q, 2H, J = 7.1), 6.89 (d, 1H, J = 8.7), 7.34 (dd, 1H, J = 2.3 and 8.7Hz), 7.51 (d, 1H, J = 2.3), 8.08 (br s, 1H), 12.38(s, 1H)
3j	1.28 (t, 3H), 4.20 (q, 4H), 6.72-6.99 (m, 1H), 7.01-7.13 (m, 8H), 7.26-7.39 (m, 2H), 7.42-7.45 (m, 2H), 9.96 (s, 1H), 12.72 (s, 2H)
3k	1.11 (t, 3H, Me), 2.87 (q, 2H), 5.30 (s, 1H), 6.91-6.95 (m, 2H), 7.28-7.39 (m, 1H), 7.41-7.53 (m, 5H), 7.59-7.61 (m, 1H), 11.10 (s, 1H), 13.04 (s, 1H)
3l	1.24 (t, 3H), 3.50 (q, 2H), 6.83-7.18 (m, 4H), 7.21-7.38 (m, 4H)
4f	1.37 (t, 3H, J = 7.1), 2.42 (s, 3H), 2.52 (s, 3H), 4.35 (q, 2H, J = 7.1), 7.15 (d, 1H, J = 1.7), 7.29 (dd, 1H, *J* = 1.7), 7.81 (d, 1H, J = 7.9)
4g	1.37 (t, 3H, J = 7.1), 2.32 (s, 3H), 2 34 (s, 3H), 2.51 (s, 3H), 4.35 (q, 2H, J = 7.1), 7.17 (s, 1H), 7.62 (s, 1H)
4h	1.37 (t, 3H, J = 7.1), 2.53 (s, 3H), 4.36 (q, 2H, J = 7.1), 7.33 (d, 1H, J = 2.1), 7.46 (dd, 1H, J = 2.1 and 8.4), 7.86 (d, 1H, J = 8.4)
4i	1.37 (t, 3H, J = 7.1), 2.53 (s, 3H), 4.36 (q, 2H, J = 7.1), 7.63 (dd, 1H, J = 1.9 and 8.3), 7.78 (d, 1H, J = 8.3)
4j	1.24 (t, 3H), 3.50 (q, 2H), 6.83-7.18 (m, 4H), 7.21-7.38 (m, 4H)
4k	2.35 (s, 3H), 5.35 (s, 2H), 7.2-7.6 (m, 9H)
4l	1.13 (s, 3H), 2.99 (q, 2H), 5.33 (s, 2H), 7.0-7.8 (m, 9H)

a) DMSO for compounds **3** and $CDCl_3$ for compounds **4**.

TABLE 4. IR Data of Hydrazones **3** and *o*-Ketoesters **4**

Cmpd	IR [a] $(cm)^{-1}$	Cmpd	IR [a] $(cm)^{-1}$
3f	3210, 1705	**4f**	1720, 1685
3g	3240, 1690	**4g**	1720, 1685
3h	3300, 1730	**4h**	1720, 1680
3i	3240, 1700	**4i**	1720, 1680

a) KBr for compounds **3** and neat for compounds **4**.

General Procedure for the Preparation of *o*-Ketoaryl Esters 4a-4l. To a solution of hydrazone **3** (5 mmol) in dichloromethane (30 mL) was gradually added as a solid PID (10 mmol) over 5 min. The mixture was stirred at room temperature for 2 hours. After evaporation of the solvent, the mixture was subjected to column chromatography (silica gel 70-230 mesh, pet. ether/chloroform, 1/1).

TABLE 5. ^{13}C NMR and MS Data of Hydrazones **3** and *o*-Ketoesters **4**

Cmpd	Chemical Shifts (δ)[a]	EI-MS *m/z* (%)
3j	14.4, 61.3, 116.5, 117.0, 117.2, 118.4, 119.5, 129.5, 130.5, 131.2, 152.6, 153.5, 154.7, 158.2	300 (100), 284 (5), 283 (18), 254 (13), 227 (30), 212 (28), 211 (30), 210 (11), 197 (20), 93 (57)
3k	13.5, 66.6, 117.1, 118.5, 119.5, 128.0, 128.2, 128.5, 130.7, 136.2, 154.0, 158.3	284 (88), 265 (5), 264 (37), 149 (30), 134 (25), 133 (35), 132 (29), 91 (100), 77 (63)
3l	11.0, 19.0, 66.7, 117.4, 118.1, 118.5, 127.7, 128.2, 128.5, 130.6, 136.2, 154.0, 157.3, 158.8	298 (75), 282 (40), 281 (3), 163 (37), 147 (42), 146 (33), 91 (100), 77 (72)
4j	15.2, 65.2, 117.1, 119.9, 122.4, 123.6, 126.6, 128.6, 129.3, 129.4, 129.8, 129.9, 131.9, 149.2, 153.4, 155.9	270 (100), 177 (54), 149 (48), 121 (39), 93 (76), 77 (69)
4k	28.9, 66.8, 118.6, 122.8, 123.0, 125.3, 128.5, 128.7, 130.0, 131.4, 134.3, 137.0, 160.1, 199.1	254 (60), 211 (41), 210 (37), 135 (28), 119 (36), 91 (100), 77 (60), 43 (88)
4l	13.9, 35.8, 66.7, 118.7, 121.1, 129.7, 129.9, 130.1, 131.4, 132.3, 132.9, 133.5, 160.5, 199.0	268 (68), 224 (36), 148 (27), 135 (33), 133 (42), 91 (100), 77 (57), 57 (72)

a) DMSO for the compounds **3** and $CDCl_3$ for the compounds **4**.

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SYNTHESIS OF 7-HYDROXY-4-(ω-CARBOXYALKYL)COUMARINS AND 7-(DIMETHYLAMINO)-4-(ω-CARBOXYALKYL)COUMARINS

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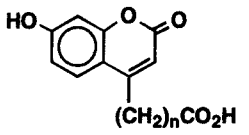
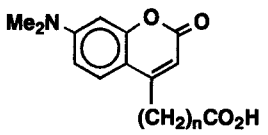
Although coumarin itself has a very low fluorescence quantum yield, its 7-hydroxy and 7-dimethylamino derivatives (**1** and **2**) are highly fluorescent and have been widely used as molecular probes[1,2] and enzyme substrates.[3] Additionally, fluorescent coumarins have been used to prepare bioconjugates of proteins[4] and nucleic acids.[5] We were interested in exploring the impact of the linker used in such bioconjugations on the performance of these two classes of compounds with particular attention to the solubility and quantum yield of the derived bioconjugates. Thus, we required a series of 7-hydroxy and 7-dimethylamino-4-(ω-carboxyalkyl)coumarins in which the linker varied in length. Commercially available 7-hydroxy and 7-dimethylamino-4-(ω-carboxyalkyl)coumarins were limited to



1



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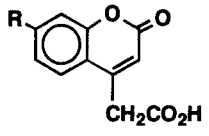

3

a) n = 2 b) n = 3 c) n = 4 d) n = 5 e) n = 6 f) n = 7 g) n = 8 a) R = OH b) R = NMe_2

the acetic acid congeners (**3a** and **3b**). The literature revealed few additional examples. Chaterjee[6] reported the preparation of 7-methoxy-4-(3-carboxypropyl)coumarin *via* a modified Pechman condensation. 7-Hydroxy-4-(2-carboxyethyl)coumarin was prepared by alkylation of ethyl malonate with 7-methoxy-4-(bromomethyl)coumarin, followed by decarboxylation and 7-demethylation.[7] 7-Hydroxy-4-(2-carboethoxyethyl)coumarin was prepared by the direct condensation of ethyl 5-oxo-4-oxaspiro[2,3]hexane-1-carboxylate with resorcinol in ethanolic HCl.[8] The latter method proceeded by the *in situ* generation of the diethyl β-oxoadipate required for the Pechman condensation.[9,10] Indeed, the Pechman condensation seemed to be the most general method for the