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Oxidation of Hydrazones by Hypervalent Organoiodine Reagents: Regeneration of the Carbonyl Group and Facile Syntheses of α-Acetoxy and α-Alkoxy Azo Compounds

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Abstract: Various hydrazone derivatives of α-keto esters were prepared. The carbonyl group was readily regenerated in high yield from phenylhydrazones through oxidative hydrolysis using hypervalent organoiodine(III) reagents—either bis(trifluoroacetoxy)-iodobenzene (BTIB) in aqueous acetonitrile or hydroxy(tosyloxy)iodobenzene (HTIB) in chloroform. α-Acetoxy phenyl- or methylazo compounds were readily synthesized by oxidation of the corresponding hydrazones with iodobenzene diacetate (IBDA) in dichloromethane or acetic acid. α-Methoxy phenyl- or methylazo compounds were also prepared by oxidation of the hydrazones in methanol. The mechanisms of the oxidation reactions are discussed. Copyright © 1996 Elsevier Science Ltd

Protecting groups are important in organic synthesis. Among the many carbonyl protecting groups, hydrazones such as *N,N*-dimethylhydrazones, *p*-toluenesulfonylhydrazones, and 2,4-dinitrophenylhydrazones have been well studied.[1] *N,N*-Dimethylhydrazine has been used often in organic synthesis since many methods have been developed to regenerate the carbonyl group from dimethylhydrazones. Although *p*-toluenesulfonylhydrazones can be converted to the parent carbonyl group under a variety of conditions,[2] their applicability as protecting groups in organic synthesis has been limited largely by their instability to basic conditions.[3] It is more common for *p*-toluenesulfonylhydrazones to be used for other transformations, such as the preparation of diazo compounds or alkenes.[4]

Dedicated to the memory of Professor Gèza Zemplèn (1883-1956).

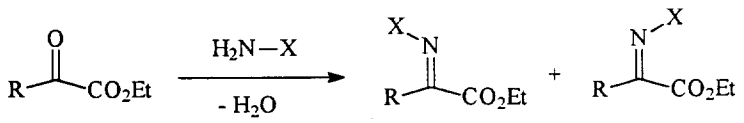
For more than a century, phenylhydrazine has played an important role in carbohydrate chemistry due to its tendency to form crystalline phenylhydrazones with simple carbohydrates.[5] The application of phenylhydrazones in organic synthesis has mainly been limited to the synthesis of indoles rather than protection of the carbonyl group because of the difficulty in the cleavage of the hydrazone.[6] Among the many oxidants developed, hypervalent organoiodine reagents are playing an increasingly important role in organic synthesis due to the mildness and versatility of the oxidation conditions.[7] In a short communication,[8] we have reported the facile regeneration of the carbonyl group from phenylhydrazone substrates by using commercially available hypervalent organoiodine reagents, such as [bis(trifluoroacetoxy)iodo]benzene (BTIB) or [hydroxy(tosyloxy)-iodo]benzene (HTIB, Koser's reagent), under mild conditions.

In an approach to the synthesis of 3-deoxy-D-*manno*-2-octulosonic acid (KDO), phenylhydrazine was chosen to protect the α-keto ester group.[9] It avoided the undesired β-elimination of the acetoxy group and facilitated the successful isolation of the KDO phenylhydrazone derivative. As models of KDO phenylhydrazone derivatives, several α-phenylhydrazono-esters were prepared and submitted to oxidation reactions. After screening many organic and inorganic oxidants, we have found that using iodobenzene diacetate (IBDA), the oxidation of phenylhydrazones can be readily controlled to form α-acetoxy phenylazo compounds under anhydrous conditions. Previously, this important class of compounds had only been obtained from the oxidation of phenylhydrazones by peracetic acid in low to moderate yields[10] or by the toxic reagents lead(IV) tetraacetate[11] and thallium(III) acetate.[12] The α-acetoxy phenylazo compounds can either be hydrolyzed to the corresponding α-hydroxy phenylazo compounds or, in some instances, be transformed to other important compounds, such as indazoles and pyrazoles.[13] The α-hydroxy phenylazo groups readily decompose to the carbonyl group. This allows the regeneration of the carbonyl group from phenylhydrazones to take place in a controlled fashion. Oxidation reactions of various hydrazones by hypervalent organoiodine reagents under different conditions will be presented. In addition, the reaction mechanisms will be discussed.

Preparation of hydrazone derivatives of α-keto-esters

Various α-hydrazono-esters were readily prepared from the parent α-keto esters (Scheme 1, Table 1). The phenylhydrazone derivatives **4**, **5**, and **6** of the three different α-keto esters, namely ethyl pyruvate **1**, ethyl benzoylformate **2**, and diethyl α-ketoglutarate **3**, were obtained in excellent yields with varying ratios of *E*- and *Z*-isomers (entries 1-3). The *E*-phenylhydrazone could be isomerized to the corresponding *Z*-isomer if desired.[14] As an example, *E*-**4** was partially isomerized into *Z*-**4** in 16% yield in acetic acid at 90°C. The assignment of the geometrical isomers was based on thin layer chromatography (TLC) and ^{1}H-NMR analysis. In general, the *Z*-phenylhydrazones of α-keto esters were less polar than the corresponding *E*-phenylhydrazones due to the existence of the intramolecular hydrogen bonding between the hydrazone N-H group and the adjacent carbonyl group. For the same reason, the N-H proton of *Z*-phenylhydrazones usually appeared at lower field in the NMR spectra. Most of the phenylhydrazone compounds were crystalline with the *E*-phenylhydrazones melting at higher temperatures than the corresponding *Z*-isomers. *N,N*-Dimethylhydrazone **7** was obtained as a single compound after flash chromatography, while **8** was obtained as an *E*- and *Z*-isomer mixture according to the literature method (entries 4, 5).[15a] The

methylhydrazone **9** and *t*-butylhydrazone **10** were obtained similarly by reaction of **2** with the corresponding methylhydrazine and *t*-butylhydrazine respectively (entries 6,7).



1 R = CH_3 *E*-isomer *Z*-isomer

2 R = Ph **4-11**

3 R = $EtO_2C(CH_2)_2$

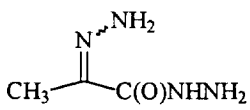
Scheme 1

Table 1. Preparation of the hydrazone derivatives of α-keto esters.

Entry	Substrate	X group	Product (yield, %)[a]	m.p. (°C)	^{1}H-NMR($CDCl_3$) (δ_{NH}, ppm)
1	**1**	NHPh	*E*-**4** (93)	116-117	7.9
			Z-**4** (trace)	30-31	12.1
2	**2**	NHPh	*E*-**5** (18)	117-118	8.1
			Z-**5** (72)	91-92	12.4
3	**3**	NHPh	*E*-**6** (73)	51-52	9.6
			Z-**6** (15)	39-40	12.1
4	**1**	NMe_2	**7** (90)[b]	oil	--
5	**2**	NMe_2	**8** (88, 2:1)[b]	oil	--
6	**2**	NHMe	**9** (77)[b]	oil	--
7	**2**	$NHBu^t$	**10** (84)[b]	oil	--
8	**2**	NH_2	**11**(97, *E*:*Z*=5:3)	oil	--

(a) Isolated yield. (b) The geometry of isomers was not determined.

Simple hydrazones are often prepared by the exchange reaction between hydrazine and the corresponding *N,N*-dimethylhydrazones due to the facile azine formation in direct reactions between hydrazine and carbonyl compounds.[15b] In the case of α-keto esters, the exchange method is not feasible because the ester group can be readily converted to hydrazide by free hydrazine. This took place in the reaction between **7** and hydrazine hydrate. Using two equivalents of hydrazine, the simple hydrazone hydrazide **12** was obtained as crystals quantitatively. When the reaction was carried out in $CDCl_3$ in an NMR tube, the quantitative release of dimethylhydrazine and ethanol was clearly observed in the ^{1}H-NMR spectrum. Using only one equivalent of hydrazine hydrate, the ^{1}H-NMR analysis showed a mixture containing the simple hydrazone hydrazide **12**, dimethylhydrazone hydrazide **13**, and the starting material **7** as the major components with trace amounts of the



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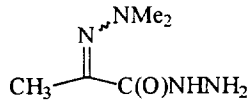

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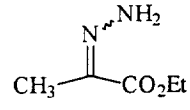

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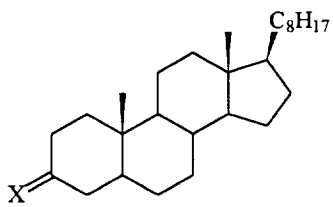
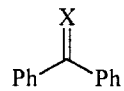


15 X=NNHPh
16 X=O



17 X=NNHPh
18 X=O

simple α-hydrazono-ester **14**. The hydrazine-acetic acid complex turned out to be a useful reagent for synthesis of simple hydrazones.[16] The reaction between **2** and hydrazine-acetic acid (1:1) complex in tetrahydrofuran gave the unsubstituted hydrazone ester **11** in an excellent yield (entry 8). No hydrazide was detected.

Besides the phenylhydrazones of α-keto esters, the simple ketone derivatives **15** and **17** were for comparison purposes also prepared from cholestanone **16** and benzophenone **18**.

Regeneration of the carbonyl group from hydrazones with BTIB or HTIB[8]

Two commercial hypervalent organoiodine(III) reagents were chosen for the regeneration of the carbonyl group from hydrazones. It was found that aqueous acetonitrile was a suitable solvent for the oxidation reaction by BTIB, while the oxidation with HTIB could be carried out in deuterated chloroform and the reaction followed by NMR spectroscopy. Presumably the transformation of the phenylhydrazone group into the carbonyl group involves the hydroxy phenylazo intermediate (*vide infra*). The BTIB oxidation reaction required water to hydrolyze the trifluoroacetoxy group of the reaction intermediate, but this was not necessary for the HTIB oxidation reaction because of the existence of the hydroxyl group in the reagent. The yields of the oxidative hydrolysis reactions are listed in Table 2.

Both the *E*- and *Z*-phenylhydrazono-esters **4**-**6** were transformed smoothly by using either reagent, BTIB (conditions A) or HTIB (conditions B), furnishing the corresponding α-keto esters **1**-**3** (entries 1-6). The BTIB oxidation of phenylhydrazone **4** was not carried out under aqueous conditions since the high volatility of the parent carbonyl compound **1** would result in a significant decrease of chemical yield (entries 1-2). The reaction under anhydrous condition did give the trifluoroacetoxy phenylazo compound **19g** in a good yield (*vide infra*).

The reaction with HTIB in $CDCl_3$ in an NMR tube usually required about 1.7 equivalents of reagent to force the reaction to completion. These methods were also successfully applied to the transformation of the simple ketone phenylhydrazones **15** and **17** to the parent ketones **16** and **18** (entries 7, 8). HTIB also oxidized

Table 2. Regeneration of the carbonyl group from hydrazones.

Entry	Substrate	Product	Yield (%)[b] (Conditions A)	Yield (%)[c] (Conditions B)
1	*E*-**4**	**1**	—	98
2	*Z*-**4**	**1**	—	98
3	*E*-**5**	**2**	82	98
4	*Z*-**5**	**2**	86	98
5	*E*-**6**	**3**	86	74[d]
6	*Z*-**6**	**3**	88	98
7	**15**	**16**	85	98
8	**17**	**18**	90	98
9	**7**	**1**	—	98
10	**8**[a]	**2**	—	98

Conditions A: 1.2 eq. $PhI(OCOCF_3)_2$, $MeCN/H_2O$ (5/1), 0°C.

Conditions B: 1.7 eq. PhI(OH)(OTs), $CDCl_3$, room temperature.

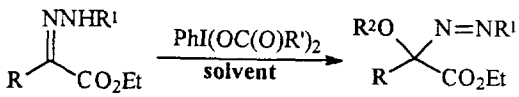
(a) A mixture of *E*- and *Z*-hydrazones was used; (b) Isolated yield; (c) Determined by ^{1}H-NMR; (d) 25 % of monoester $HO_2C(CH_2)_2COCO_2Et$ was observed.

dimethyl hydrazones **7** and **8** to give α-keto esters **1** and **2** quantitatively (entries 9, 10). The NMR spectra showed that the conversion of the dimethylhydrazones to the carbonyl group was very fast at room temperature. The high efficiency is comparable to that of reagents used before.[1a]

Synthesis of azo compounds from hydrazones by IBDA or BTIB

During the course of this work, the use of IBDA was reported for the oxidation of *N*-acyl hydrazones and tosylhydrazones.[2a, 17] *N*-Acylhydrazones were oxidized by IBDA in alcohol to form oxadiazole or oxadiazoline derivatives depending on whether ketone or aldehyde hydrazones were used. Oxidative hydrolysis of the tosylhydrazones could be accomplished by IBDA in aqueous acetonitrile. We attempted to use these conditions for the hydrolysis of the phenylhydrazone derivatives of α-keto-esters, but the reaction always gave a mixture containing α-keto-ester and a significant amount of the acetoxy phenylazo compound which could not be hydrolyzed under the oxidation reaction conditions. When water was excluded from the reaction system, using dichloromethane or acetic acid as solvent, oxidation of both *E*- and *Z*-phenylhydrazone derivatives of α-keto-esters with IBDA provided acetoxy phenylazo compounds **19a-c** in good isolated yields (Scheme 2, Table 3, entries 1-6). In a similar fashion, the α-acetoxy methylazo compound **19d** was obtained in the oxidation of **9** by IBDA in dichloromethane (entry 7). α-Methoxy azo compounds **19e,f** were also readily obtained from the oxidation of the phenylhydrazone **5** and methylhydrazone **9**, respectively using methanol as the solvent (entries 8, 9). Although dimethylhydrazone derivatives of α-ketoesters could be readily converted to carbonyl compounds by HTIB (*vide supra*), no reaction was observed between **8** and IBDA (entry 10). Using BTIB as the oxidant, the phenylhydrazone derivative **4** was readily converted to the α-trifluoroacetoxy phenylazo

compound **19g** (entry 11). It was isolated as a pale yellow oil and its structure was well established by IR and NMR spectroscopy. As expected, **19g** was not stable in air at room temperature. Presumably it is hydrolyzed by moisture in air to form **19h** which readily decomposes into the corresponding carbonyl compound.



4-**6**, **8**, **9** (R'=CH_3, CF_3) **19a-i**

19a-i	R	R^1	R^2
a	Me	Ph	Ac
b	Ph	Ph	Ac
c	$EtO_2C(CH_2)_2$	Ph	Ac
d	Ph	Me	Ac
e	Ph	Ph	Me
f	Ph	Me	Me
g	Me	Ph	CF_3CO
h	Me	Ph	H
i	Ph	Bu^t	Ac

Scheme 2

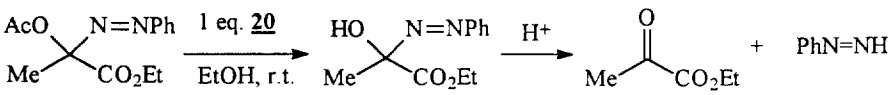
Table 3. Oxidation of Hydrazones by IBDA or BTIB.

Entry	Substrate	Oxidant	Solvent	Product	Yield (%)[b]
1	*E*-**4**	IBDA	CH_2Cl_2	**19a**	97
2	*Z*-**4**	IBDA	CH_2Cl_2	**19a**	93
3	*E*-**5**	IBDA	CH_2Cl_2	**19b**	85
4	*Z*-**5**	IBDA	CH_2Cl_2	**19b**	86
5	*E*-**6**	IBDA	CH_2Cl_2	**19c**	90
6	*Z*-**6**	IBDA	CH_2Cl_2	**19c**	85
7	**9**	IBDA	CH_2Cl_2	**19d**	82
8	*E*-**5**	IBDA	MeOH	**19e**	90
9	**9**	IBDA	MeOH	**19f**	88
10	**8**[a]	IBDA	CH_2Cl_2	no reaction	—
11	*E*-**4**	BTIB	MeCN	**19g**	82

(a) A mixture of *E*- and *Z*-hydrazones was used. (b) Isolated yield.

All of the azo compounds in Table 3 show two characteristic absorptions in their UV spectra, which are at 240-280 nm (ε_{max} ~10,000) and 340~410 nm (ε_{max} ~200) (see Experimental part). The α-acetoxy phenylazo compounds are the intermediates in the synthesis of pyrazoles from phenylhydrazones.[13] Lead(IV) tetraacetate, thallium(III) acetate, and peracetic acid were among the few reagents reported for this interesting transformation.[10-12] A recent review highlighted the parallel nature and synthetic utility of thallium(III) and organoiodine(III) reagents in the oxidative rearrangement of alkyl aryl ketones to α-arylalkanoates or acids.[18] The present article provides an excellent example of the similarity between these two reagents and the lead(IV) compound. The easily handled organoiodine(III) reagents provide a useful alternative to the toxic lead(IV) and thallium(III) derivatives.

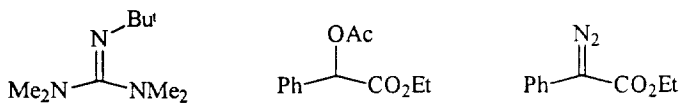
To prove the assumption that the α-hydroxy phenylazo compound was the intermediate in the oxidative hydrolysis of phenyl hydrazones,[19] **19h** was prepared independently by ethanolysis of **19a** in the presence of 2-*t*-butyl-1,1,3,3-tetramethyl guanidine base **20**[20] (Scheme 3). This reaction gave **19h** as a pale yellow oil in 86% yield. The structure was confirmed by IR and NMR analysis. Reacetylation of **19h** by acetic anhydride in the presence of pyridine and 4-dimethylamino pyridine(DMAP) regenerated the parent compound **19a** in 72% yield. This further proved the structure of the α-hydroxy phenylazo intermediate **19h**. The stability of the hydroxy phenylazo compound was studied by NMR spectroscopy. In $CDCl_3$, **19h** decomposed at the room



19a **19h** **1**

Scheme 3

temperature to give **1**. Benzene was formed as a byproduct. In contrast, the decomposition in CD_3OD was very slow under argon or oxygen even at 60°C. The solvent effect might be due to the existence of a trace of HCl in $CDCl_3$, which catalyzed the elimination of the phenylazo group to form phenyl diazene. It is well known that phenyl diazene readily decomposes by a radical pathway to form benzene as a product.[21]



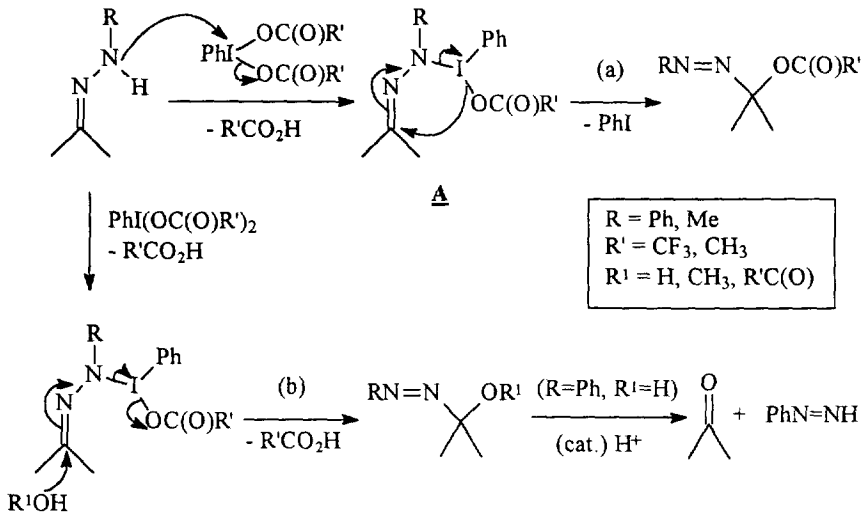
20 **21** **22**

Oxidation of simple hydrazones and *t*-butylhydrazones

When the simple hydrazone **11**, or *t*-butylhydrazone **10**, were submitted to oxidation using IBDA as the oxidant, ethyl *O*-acetylmandelate **21** was obtained as the major product.[22] In the case of the oxidation of *t*-butylhydrazone **10** in acetic acid, the α-acetoxy *t*-butylazo compound **19i** (Scheme 2) was also detected as a minor product.

Mechanistic considerations

Based on the above results, the following mechanisms are proposed for the oxidation of phenylhydrazones by BTIB and IBDA (Scheme 4). The so-called ligand exchange through electrophilic attack of the organoiodine(III) moiety on the NH group of the phenylhydrazone with loss of a carboxylic acid molecule, initiates the oxidation reaction.[23] The formation of the phenylazo compound could take place by intramolecular rearrangement of intermediate **A** with reductive elimination of an iodobenzene molecule (pathway (a)), or by attack of another nucleophile (pathway (b)). Pathways (a) and (b) are competitive. This

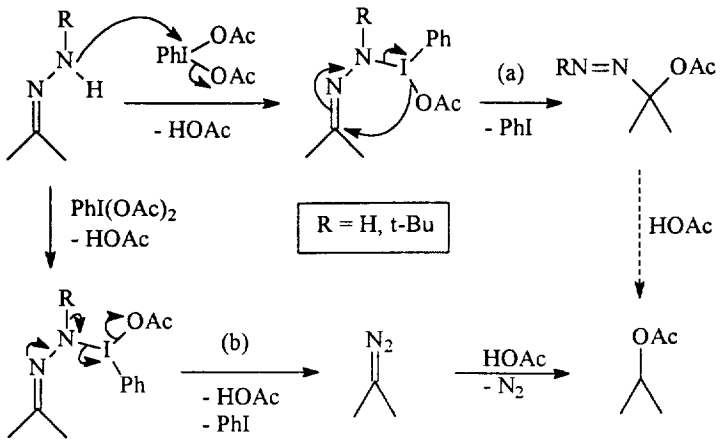


Scheme 4

was supported by the synthesis of the α-methoxy phenylazo compounds **19e,f** when methanol was used as the solvent. As mentioned before, the oxidation of phenylhydrazones by IBDA in aqueous acetonitrile gave a mixture of α-acetoxy phenylazo compounds and the parent carbonyl compound. The carbonyl compound is formed *via* the α-hydroxy phenylazo compound. The blank experiment showed that the α-acetoxy phenylazo compound is not the precursor of the α-hydroxy phenylazo compound, although it can be converted to the α-hydroxy phenylazo compound by base catalyzed ethanolysis. These results suggest the α-hydroxy phenylazo adduct is the common intermediate in the oxidative hydrolysis of phenylhydrazones.

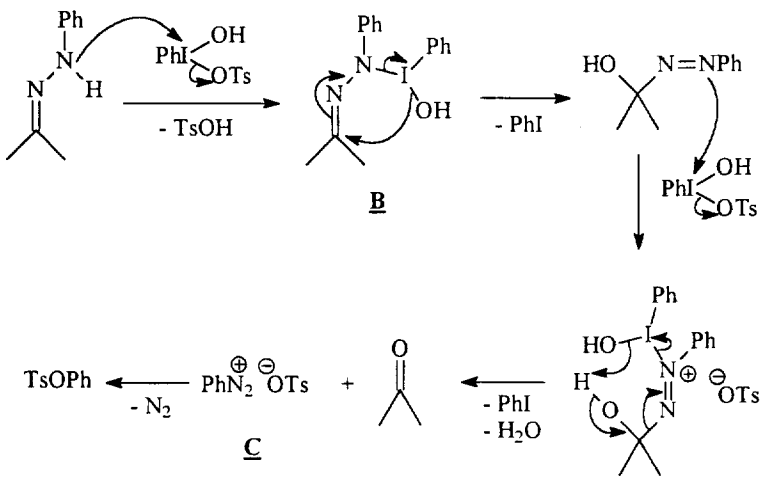
When the simple hydrazone **11** and *t*-butylhydrazone **10** were oxidized by IBDA, the corresponding azo compounds could be formed in a similar fashion (Scheme 5, pathway (a)). The azo compounds might decompose to give **21** in the presence of acetic acid. For simple hydrazone **11**, it is more likely that **21** is generated via the corresponding diazo intermediate (pathway (b)). In fact, when **11** was treated with IBDA in $CDCl_3$, diazo compound **22** was observed quantitatively by comparing its ^{1}H-NMR spectrum with that of an authentic sample.[4a] The preparation of diazo compounds from oxidation of simple hydrazones by lead(IV) tetraacetate[16] or manganese dioxide has been described.[24] Futhermore, the reaction of diazo compounds with acetic acid to give the corresponding acetoxy compounds is well known.[24a]

Considering that the oxidation by HTIB under anhydrous condition usually needs about two equivalents of the oxidant, a plausible mechanism is proposed as Scheme 6. The electrophilic attack of iodine(III) on the NH group of hydrazone with loss of *p*-toluenesulfonic acid gives the unstable species **B** which readily undergoes rearrangement to form an α-hydroxy phenylazo compound and iodobenzene. Another molecule of iodine(III) reagent attacks the azo group to initiate the decomposition of the α-hydroxy phenylazo intermediate. The decomposition reaction gives α-keto ester with formation of iodobenzene, water, and



Scheme 5

benzenediazonium salt C. C decomposes to phenyl tosylate (TsOPh) with loss of nitrogen. To prove this proposed mechanism, a preparative experiment was carried out on substrate 4. TsOPh was indeed obtained as



Scheme 6

the major component of the products after column chromatography. The NMR and GC-MS spectra of the isolated product were identical to those of an authentic sample prepared from a reaction between p-toluenesulfonyl chloride and phenol.[25] As a reference, the formation of aryl triflates from solvolysis of aryl diazonium salts in trifluoromethanesulfonic acid has been documented.[26] In fact, the NMR tube reaction

between **4** and HTIB in $CDCl_3$ did show the formation of **19h** (CH_3 at 1.87 ppm) which completely decomposed to form **1** in several hours at room temperature. The reactions between **4**, **5**, or **6** and HTIB all showed the gradual formation of phenyl tosylate during the decomposition of the oxidation adduct. Furthermore, no benzene could be observed in these reactions although it was the major byproduct in the decomposition reaction of **19h** in $CDCl_3$. These suggest that the hydroxy phenylazo intermediate does not decompose to the carbonyl compounds directly, but instead is activated by another molecule of the oxidant.

Conclusions

Various hydrazone derivatives of α-keto esters have been prepared. Phenylhydrazones could be oxidatively hydrolyzed to the parent carbonyl compound by hypervalent organoiodine reagent BTIB in aqueous acetonitrile or HTIB in chloroform. This makes phenylhydrazones a practical protecting group for carbonyl compounds in organic synthesis. On the other hand, α-acetoxy, hydroxy, or methoxy azo compounds could also be readily synthesized from phenylhydrazones and methylhydrazones using IBDA as the oxidant. This interesting transformation strongly supports the parallel nature and synthetic utility of organoiodine(III), thallium(III), and lead(IV) reagents.

EXPERIMENTAL SECTION

General methods and starting materials.

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 881 infrared spectrophotometer. UV spectra were recorded on a Beckman DU®-7 spectrometer. ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) spectra were determined with Me_4Si as internal standard on Varian Gemini-200 or Varian XL-200E spectrometers. GC-MS data were obtained on a Hewlett-Packard 5890 GC-MS system equipped with a Hewlett-Packard 5971 mass selective detector. TLC analysis was performed on thin layer analytical plates $60F_{254}$ (Merck). Column chromatography was carried out on silica gel 60 (0.040-0.063 mm). Microanalyses were performed by Atlantic Microlab, Inc. Starting compounds **16**[27] and **20**[20] were synthesized according to the literature method. **3**[28] was synthesized by the usual esterification of α-ketoglutaric acid in EtOH in the presence of catalytic amount of sulfuric acid. Other reference compounds and starting materials were purchased from Aldrich Chemical Co. Inc., Milwaukee, Wisconsin, or Fluka Chemika-BioChemika, Buchs, Switzerland. Solvents were used either as purchased or dried and purified by standard methodology under dry nitrogen. Extracts were dried over anhydrous magnesium sulfate.

General procedure for the syntheses of α-(phenylhydrazono)-esters (4-6).

To a solution of an α-keto ester (20 mmol) in dichloromethane (15 mL), phenylhydrazine (2.16 g, 20 mmol) was added at room temperature under argon. The mixture was stirred overnight and the solution was then evaporated. The mixture was purified by column chromatography.

Ethyl α-(*E*-phenylhydrazono)-propionate (*E*-4): The title compound was obtained as pale yellow crystals (3.83 g, 93%), m.p. 116-117°C (benzene), [lit.[14], 116-117°C]. IR ($CHCl_3$): 3356, 1692, 1602, 1579 cm^{-1}. ^{1}H-NMR ($CDCl_3$) (δ, ppm): 1.37 (3H, t, J = 7.1 Hz), 2.10 (3H, s), 4.32 (2H, q, J = 7.1 Hz), 6.69 (1H, dt, J = 6.8 and 11.5 Hz), 7.15-7.35 (4H, m), 7.88 (1H, brs). ^{13}C-NMR ($CDCl_3$) (δ, ppm): 10.2, 14.2, 61.1, 113.9, 121.9, 129.2, 132.3, 143.2, 165.2. A trace amount of *Z*-isomer was also obtained.

Isomerization of *E*-4 to *Z*-4: A solution of the *E*-hydrazone **4** (618 mg, 3 mmol) in acetic acid (3 mL) was heated with stirring at 90°C under argon overnight. After evaporation of the acetic acid under reduced

pressure, the residue was purified by column chromatography (hexanes-Et_2O, 4:1). The *Z*-isomer **4** was obtained as pale yellow crystals (99 mg, 16%). The unchanged *E*-**4** was recovered (439 mg, 71 %). *Z*-**4**: m.p. 30-31°C [lit.[12], 31.7-32.2°C]. IR ($CHCl_3$): 3270, 1672, 1600, 1548 cm^{-1}. ^{1}H-NMR ($CDCl_3$) (δ, ppm): 1.32 (3H, t, *J* = 7.1 Hz), 2.14 (3H, s), 4.24 (2H, q, *J* = 7.1 Hz), 6.90 (1H, dt, *J* = 7.1 and 1.4 Hz), 7.10-7.35 (4H, m), 12.10 (1H, brs). ^{13}C-NMR ($CDCl_3$) (δ, ppm): 14.1, 19.4, 60.5, 113.3, 121.5, 125.2, 129.2, 143.5, 163.8. MS *m/z* 206 (M^+, 86), 132 (75), 91 (100), 65 (35).

Ethyl α-(phenylhydrazono)-benzeneacetate (5): The title compound was obtained as a 4:1 mixture of *Z*- and *E*-isomers. The mixture was separated by column chromatography (hexanes-Et_2O, 3:1) *E*-**5** was obtained as colorless crystals (966 mg, 18%), m.p. 117-118°C (benzene). Anal. calcd. for $C_{16}H_{16}N_2O_2$: C(71.60); H(6.01); N(10.44). Found: C(71.48); H(6.07); N(10.39). IR ($CHCl_3$): 3320, 1720, 1599 cm^{-1}. ^{1}H-NMR ($CDCl_3$) (δ, ppm): 1.38 (3H, t, *J* = 7.1 Hz), 4.34 (2H, q, *J* = 7.1 Hz), 6.96 (1H, m), 7.10-7.40 (9H, m), 8.14 (1H, s). ^{13}C-NMR ($CDCl_3$) (δ, ppm): 14.2, 61.1, 113.9, 122.1, 128.9, 129.1, 129.3, 129.4, 129.8, 134.3, 142.6, 164.4. MS *m/z* 268 (M^+, 90), 221 (16), 194 (100), 91 (85), 77 (18), 65 (33). *Z*-**5** was obtained as yellow crystals (3.86g, 72 %), m.p. 91-92°C (hexanes). [lit.[29] m.p. 94°C (hexane)]. Anal. calcd. for $C_{16}H_{16}N_2O_2$: C(71.60); H(6.01); N(10.44). Found: C(71.53); H(6.09); N(10.48). IR ($CHCl_3$): 3249, 1670, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) (δ, ppm): 1.37 (3H, t, *J* = 7.1 Hz), 4.36 (2H, q, *J* = 7.1), 7.00 (1H, m), 7.20-7.50 (7H, m), 7.66 (2H, m), 12.43 (1H, brs). ^{13}C-NMR ($CDCl_3$) (δ, ppm): 13.8, 60.6, 113.9, 122.1, 127.2, 127.5, 128.3, 128.7, 129.0, 129.1, 136.2, 142.9, 163.4.

Phenylhydrazone derivatives of diethyl α-keto-glutarate (6): The title compound was obtained as a 5:1 mixture of *E*- and *Z*-isomers. The isomers were separated by column chromatography (hexanes-Et_2O, 3:1). *E*-**6** was isolated as yellow crystals (4.23g, 73%), m.p. 51-52°C (hexanes). Anal. calcd. for $C_{15}H_{20}N_2O_4$: C(61.62); H(6.90); N(9.59). Found: C(61.56); H(6.93); N(9.60). IR ($CHCl_3$): 3273, 1720, 1600, 1547, 1498 cm^{-1}. ^{1}H-NMR ($CDCl_3$) (δ, ppm): 1.25 (3H, t, *J* = 7.2 Hz), 1.39 (3H, t, *J* = 7.2 Hz), 2.68 (2H, m), 2.88 (2H, m), 4.15 (2H, q, *J* = 7.2 Hz), 4.31 (2H, q, *J* = 7.2 Hz), 6.97 (1H, tt, *J* = 6.7 and 1.8 Hz), 7.30-7.40 (4H, m), 9.62 (1H, brs). ^{13}C-NMR ($CDCl_3$) (δ, ppm): 14.3, 14.4, 19.8, 31.5, 61.4, 61.7, 114.0, 121.8, 129.2, 134.5, 143.7, 163.4, 175.2. MS *m/z* 292 (M^+,72), 218 (34), 173 (28), 145 (28), 119 (28), 125 (17), 91 (100), 65 (67). *Z*-**6** was obtained as pale yellow crystals (846 mg, 15%), m.p. 39-40°C (hexanes). Anal. calcd. for $C_{15}H_{20}N_2O_4$: C(61.62); H(6.90); N(9.59). Found: C(61.57); H(6.96); N(9.62). IR ($CHCl_3$): 3269,1716, 1599, 1499 cm^{-1}. ^{1}H-NMR ($CDCl_3$) (δ, ppm): 1.26 (3H, t, *J* = 7.2 Hz), 1.34 (3H, t, *J* = 7.2 Hz), 2.65 (2H, brt, *J* = 6.7 Hz), 2.85 (2H, brt, *J* = 6.7 Hz), 4.14 (2H, q, *J* = 7.2 Hz), 4.25 (2H, q, *J* = 7.2 Hz), 6.97 (1H, tt, *J* = 7.2 and 1.3 Hz), 7.14 (2H, brt, *J* = 7.2 Hz), 7.26 (2H, brt, *J* = 7.2 Hz), 12.06 (1H, brs). ^{13}C-NMR ($CDCl_3$) (δ, ppm): 14.0, 14.1, 27.4, 31.0, 60.2, 60.6, 113.4, 121.6, 126.1, 129.1, 143.5, 163.3, 173.2.

General Procedure for the Preparation of *N,N*-Dimethylhydrazones (7, 8).

To a solution of the α-keto ester **1** or **2** (4 mmol) in CH_2Cl_2 (5 mL), 1,1-dimethylhydrazine (360 mg, 6 mmol) was added at room temperature under argon. The mixture was warmed from room temperature to 70°C with stirring for ovenight. When the reaction was finished by TLC or GC-MS, the solution was evaporated and the residue was purified by column chromatography.

Ethyl α-(*N,N*-dimethylhydrazono)-propionate (7):[15a] pale yellow oil (570 mg, 90%). IR (neat): 2981, 1707, 1577 cm^{-1}. ^{1}H-NMR ($CDCl_3$) (δ, ppm): 1.34 (3H, t, J = 7.1 Hz), 2.13 (3H, s), 2.85 (6H, s), 4.30 (2H, q, J = 7.1 Hz).^{13}C-NMR ($CDCl_3$) (δ, ppm): 14.1, 15.6, 46.8, 61.4, 145.5, 165.2. MS m/z 158 (M^+, 100), 116 (35), 88 (17), 85 (42).

Ethyl α-(*N,N*-dimethylhydrazono)-benzeneacetate (8): a mixture of two isomers (2:1) (775 mg, 88%). Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C(65.43); H(7.32); N(12.72). Found: C(65.33); H(7.28); N(12.66). IR (neat): 2980, 1720, 1551 cm^{-1}. ^{1}H-NMR ($CDCl_3$) (δ, ppm): 1.29 (3H, t, *J* = 7.1 Hz), 1.38 (1H, t, *J* = 7.1 Hz),

2.83 (2H, s), 2.87 (4H, s), 4.25 (4/3H, q, J = 7.1 Hz), 4.40 (2/3H, q, J = 7.1 Hz), 7.20-7.40 (5H, m). ^{13}C-NMR ($CDCl_3$) (δ, ppm): 14.1, 14.3, 46.9, 61.0, 61.2, 126.2, 127.5, 127.9, 128.3, 128.4, 129.3, 130.0, 130.5, 134.0, 135.5, 166.0, 166.2. MS *m/z* 220 (M^+, 81), 178 (45), 147 (85), 104 (100), 77 (34).

Ethyl α-(methylhydrazono)-benzeneacetate (9).

To a solution of acetic acid (264 mg, 4.4 mmol), and methyl hydrazine (203 mg, 4.4 mmol) in tetrahydrofuran (5 mL), **2** (356 mg, 2 mmol) was added at room temperature under argon. The mixture was stirred overnight and then diluted with dichloromethane. The solution was washed with an aqueous sodium bicarbonate solution and water, dried and evaporated. The residue was purified by column chromatography (hexanes-Et_2O, 4:1 to 2:1 gradient) to give the methylhydrazone **9** as a pale yellow oil (317 mg, 77%). This compound is slowly oxidized by air at room temperature. IR ($CHCl_3$): 3260, 1666, 1596 cm^{-1}. ^{1}H-NMR ($CDCl_3$) (δ, ppm): 1.32 (3H, t, J = 7.1 Hz), 3.32 (3H, s), 4.27 (2H, q, J = 7.1 Hz), 7.25-7.40 (3H, m), 7.52 (2H, m). ^{13}C-NMR ($CDCl_3$) (δ, ppm): 14.1, 38.5, 50.1, 125.3, 126.7, 127.6, 128.1, 137.1, 163.7. MS *m/z* 206 (M^+, 81), 159 (39), 132 (100), 104 (88), 77 (55).

Ethyl α-(*t*-butylhydrazono)-benzeneacetate (10).

To a solution of **2** (1.78g, 10 mmol) and triethylamine (2.02 g, 20 mmol) in tetrahydrofuran (15 mL), *t*-butylhydrazine hydrochloride (2.49g, 20 mmol) was added at 0°C under argon. The mixture was then stirred at room temperature for 48 hours. The solution was evaporated and the residue was diluted with dichloromethane. The dichloromethane solution was then washed twice with water, dried and evaporated. The residue was purified by column chromatography (hexanes-diethyl ether, 3:1). Hydrazone **10** was obtained as a colorless oil (2.08g, 84%). Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C(67.71); H(8.12); N(11.28). Found: C(67.46); H(8.03); N(11.03). IR (neat): 3243, 3056, 1663, 1598 and 1508 cm.$^{-1}$ ^{1}H-NMR ($CDCl_3$) (δ, ppm): 1.32 (9H, s), 1.32 (3H, t, J = 7.6 Hz), 4.26 (2H, q, J = 7.6 Hz), 7.23-7.40 (3H, m), 7.57 (2H, m). ^{13}C-NMR ($CDCl_3$) (δ, ppm): 14.3, 28.8, 55.1, 60.1, 126.4, 127.6, 128.1, 137.7, 163.7. MS *m/z:* 248 (M^+, 66.8), 233 (100), 159 (42.6), 119 (50.1), 104 (26), 77 (38.2).

Ethyl α-(hydrazono)-benzeneacetate (11).[16]

To a solution of **2** (712 mg, 4 mmol) in tetrahydrofuran (5 mL), hydrazine acetate (405 mg, 4.4 mmol) was added at room temperature under argon. The mixture was stirred at room temperature overnight. It was then diluted with dichloromethane, washed with aqueous saturated sodium bicarbonate solution and water, dried, and evaporated. The residue was purified on a column chromatography (hexanes-diethyl ether, 3:1). A mixture of the corresponding *E*- and *Z*-**11** (5:3) was obtained as a pale yellow oil (737 mg, 97%). IR ($CHCl_3$): 3428 , 3290, 1685 and 1560 cm.$^{-1}$ ^{1}H-NMR ($CDCl_3$) (δ, ppm): 1.32 (9/8H, t, J = 7.1 Hz), 1.34 (15/8H, t, J = 7.1 Hz), 4.29 (10/8H, q, J = 7.1 Hz), 4.30 (6/8H, q, J = 7.1 Hz), 7.20-7.60 (5H, m). ^{13}C-NMR ($CDCl_3$) (δ, ppm): 13.8, 14.0, 60.2, 60.8, 127.0, 127.3, 127.4, 127.8, 128.5, 128.7, 128.8, 129.4, 130.2, 136.3, 136.4, 162.5, 164.2. MS *m/z*: 192 (M^+, 40.6), 145 (15), 119(100), 77 (69.9).

α-(Hydrazono)-propionic acid hydrazide (12).

To a solution of **7** (10 mmol) in THF (2 mL) was added hydrazine hydrate (20 mmol) at room temperature. After stirred at room temperature for 2.5 hours, evaporation of the reaction mixture yielded pure form of hydrazone hydrazide **12** (98%) as colorless crystals, m.p.: 149-150°C (methanol). Anal. Calcd. for $C_3H_8N_4O$: C(31.03); H(6.94); N(48.25). Found: C(31.08); H(6.99); N(48.23). IR(nujol): 3340, 3295, 3187, 1640, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$/DMSO-d_6) (δ,ppm) : 1.94 (s, 3H), 3.9 (brs, 2H), 6.0 (brs, 2H), 8.1 (brs, 1H). ^{13}C-NMR ($CDCl_3$/DMSO-d_6) (δ,ppm): 7.7, 137.1, 164.8.

General procedure for the oxidative hydrolysis of hydrazones 5, 6, 15, and 17 with BTIB.

To a solution of the appropriate hydrazone (1 mmol) in acetonitrile (3 mL) and water (0.5 mL), BTIB (516 mg, 1.2 mmol) was added at 0°C under argon. After stirred for 30 minutes, the mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate solution and water, dried, and evaporated. The

residue was purified by column chromatography (hexanes-Et_2O, 4:1 to 1:3). The yields are in Table 2. The regenerated ketones were identified by comparison of their NMR (^1H and ^{13}C) and infrared spectra with those of the authentic samples.

General procedure for the oxidation of hydrazones 4-8, 15, and 17 with HTIB.

To a solution of hydrazone (0.1 mmol) in $CDCl_3$ (0.3 mL), HTIB (67 mg, 0.17 mmol) was added at room temperature. The reaction was followed by ^1H-NMR spectroscopy until the conversion was complete. The reactions are usually very fast, but the rate depends on the substrates. The yields of the resulting keto esters were determined by ^1H-NMR (Table 2).

General procedure for the synthesis of α-(acetoxy)-phenylazo compounds (19a-d).

To a solution of the appropriate hydrazone (1 mmol) in dichloromethane (5 mL), IBDA (1.1 mmol, 354 mg) was added at room temperature under argon. The mixture was stirred for two hours and then diluted with dichloromethane. The dichloromethane solution was washed with saturated sodium bicarbonate solution and water, dried, and evaporated. The residue was purified by column chromatography (hexanes-Et_2O, 4:1 to 1:3).

19a: yellow oil (97% yield). Anal. calcd. for $C_{13}H_{16}N_2O_4$: C(59.08); H(6.05); N(10.60). Found: C(59.35); H(6.13); N(10.66). IR ($CHCl_3$): 1741 cm^{-1}. UV($CHCl_3$): 276 nm (log ε 3.95), 399 nm (log ε 2.30). ^1H-NMR ($CDCl_3$) (δ, ppm): 1.28 (3H, t, J = 7.1 Hz), 1.81 (3H, s), 2.22 (3H, s), 4.28 (2H, q, J = 7.1 Hz), 7.46 (3H, m), 7.75 (2H, m). ^{13}C-NMR ($CDCl_3$) (δ, ppm): 14.0, 20.8, 21.5, 62.0, 98.9, 122.9, 129.0, 131.7, 151.0, 167.8, 169.1.

19b:[13] yellow oil (86% yield). Anal. calcd. for $C_{18}H_{18}N_2O_4$: C(66.24); H(5.56); N(8.59). Found: C(66.12); H(5.57); N(8.61). IR ($CHCl_3$): 1742, 1596 cm^{-1}. UV($CHCl_3$): 275 nm (log ε 4.08), 394 nm (log ε 2.45). ^1H-NMR ($CDCl_3$) (δ, ppm): 1.29 (3H, t, J =7.1), 2.35 (3H, s), 4.20-4.50 (2H, m), 7.44 (6H, m), 7.80 (4H, m). ^{13}C-NMR ($CDCl_3$) (δ, ppm): 13.9, 20.6, 62.3, 98.6, 123.2, 126.2, 128.6, 128.9, 129.2, 131.5, 135.0, 150.8, 167.7, 168.6.

19c: yellow oil (90% yield). Anal. Calcd. for $C_{17}H_{22}N_2O_6$: C(58.27); H(6.33); N(8.00). Found: C(58.13); H(6.47); N(7.83). IR ($CHCl_3$): 1740, 1515 cm^{-1}. UV($CHCl_3$): 274 nm (log ε 3.97), 394 nm (log ε 2.38). ^1H-NMR ($CDCl_3$) (δ, ppm): 1.21 (3H, t, J = 7.2 Hz), 1.32 (3H, t, J = 7.2 Hz), 2.22 (3H, s), 2.30-2.38 (4H, m), 4.08 (2H, q, J = 7.2 Hz), 4.32 (2H, q, J = 7.2 Hz), 7.48 (3H, m), 7.80 (2H, m). ^{13}C-NMR ($CDCl_3$) (δ, ppm): 14.1, 14.6 20.6, 27.6, 30.9, 60.7, 62.2, 98.7, 123.1, 129.0, 131.7, 150.8, 165.7, 167.6, 172.1.

19d: colorless crystals (82% yield), m.p. 61-62°C. Anal. calcd. for $C_{13}H_{16}N_2O_4$: C(59.08); H(6.10); N(10.60). Found: C(59.17); H(6.13); N(10.68). IR ($CHCl_3$): 2930, 1727, 1451 cm^{-1}. UV($CHCl_3$): 240 nm (log ε 3.13), 340 nm (log ε 1.82). ^1H-NMR ($CDCl_3$) (δ, ppm): 1.25 (3H, t, J = 7.3), 2.25 (3H, s), 3.90 (3H, s), 4.30 (2H, m), 7.36-7.38 (3H, m), 7.60-7.70 (2H, m). ^{13}C-NMR ($CDCl_3$) (δ, ppm): 13.8, 20.4, 56.2, 62.1, 98.0, 125.8, 128.4, 129.1, 134.5, 167.4, 168.4.

General procedure for the synthesis of α-(methoxy)-phenylazo compounds (19e,f).

IBDA (338 mg, 1.05 mmol) was dissolved in methanol (20 mL) at room temperature under argon. The appropriate hydrazone (1 mmol) was added to the solution at room temperature and the reaction mixture was then stirred for three hours. The solution was evaporated and the residue was diluted with dichloromethane. The dichloromethane solution was then washed with an aqueous saturated sodium bicarbonate solution and water, dried, and evaporated. The residue was purified by column chromatography (hexanes-Et_2O, 4:1 to 1:3).

19e: orange crystals (90% yield), m.p. 58-59.5°C. Anal. calcd. for $C_{17}H_{18}N_2O_3$: C(68.43); H(6.08); N(9.39). Found: C(68.37); H(6.10); N(9.40). IR ($CHCl_3$): 1740, 1448 cm^{-1}. UV($CHCl_3$): 276 nm (log ε 4.05), 411 nm (log ε 2.24). ^1H-NMR ($CDCl_3$) (δ, ppm): 1.19 (3H, t, J = 6.9 Hz), 3.50 (3H, s), 4.22 (2H, q, J = 6.9 Hz), 7.30-7.50 (6H, m), 7.60 (2H, m), 7.81 (2H, m). ^{13}C-NMR ($CDCl_3$) (δ, ppm): 14.0, 53.4, 61.7, 100.3, 122.8, 127.3, 128.2, 128.7, 128.9, 131.4, 136.7, 151.3, 168.6.

19f: colorless oil (88% yield). Anal. calcd. for $C_{12}H_{16}N_2O_3$: C(60.99); H(6.82); N(11.86). Found: C(61.06); H(6.81); N(11.79). IR ($CHCl_3$): 1740, 1448 cm^{-1}. UV($CHCl_3$): 244 nm (log ε 3.14), 347 nm (log ε

1.86). ^{1}H-NMR ($CDCl_3$) (δ, ppm): 1.17 (3H, t, J = 7.1 Hz), 3.41 (3H, s), 3.95 (3H, s), 4.19 (2H, q, J = 7.1 Hz), 7.30-7.40 (3H, m), 7.48-7.55 (2H, m). ^{13}C-NMR ($CDCl_3$) (δ, ppm): 13.9, 53.4, 57.3, 61.7, 100.1, 127.0, 128.1, 128.7, 136.2, 168.4.

General procedure for the oxidation of hydrazones 16e or 16f with iodobenzene diacetate.

To a solution of the corresponding hydrazone **16e** (0.5 mmol) in acetic acid (2 mL), iodobenzene diacetate (177 mg, 0.55 mmol) was added at room temperature. The mixture was stirred for 15 hours and the solution was evaporated. The residue was purified by column chromatography (hexanes-diethyl ether, 5:1 to 2:1). The acetoxy ester **24**[22] was obtained as a colorless oil (96 mg, 86%). IR (neat): 1736, 1587 and 1444 cm.$^{-1}$ ^{1}H-NMR ($CDCl_3$) (δ, ppm): 1.20 (3H, t, J = 7.3 Hz), 2.17 (3H, s), 4.16 (2H, m), 5.89 (1H, s), 7.35-7.46 (5H, m). ^{13}C-NMR ($CDCl_3$) (δ, ppm): 13.9, 20.6, 61.6, 74.5, 127.6, 128.7, 129.1, 133.8, 168.8, 170.3.

α-(Trifluoroacetoxy)-phenylazo compound (19g).

To a solution of hydrazone *E*-**4** (412 mg, 2 mmol) in dichloromethane (3 mL), BTIB (860 mg, 2 mmol) was added at 0°C under argon. The mixture was stirred for one hour at 0°C. The solution was evaporated and the residue was quickly purified by chromatography (hexanes-Et_2O, 3:1). The title compound was obtained as a yellow oil (512 mg, 82%). The azo compound slowly decomposed at room temperature. **19g**: IR ($CHCl_3$): 1794, 1751, 1515 cm^{-1}. ^{1}H-NMR ($CDCl_3$) (δ, ppm): 1.30 (3H, t, J = 7.1), 1.95 (3H, s), 4.33 (2H, q, J = 7.1), 7.48 (3H, m), 7.80 (2H, m). ^{13}C-NMR ($CDCl_3$) (δ, ppm): 13.8, 21.8, 63.0, 101.3, 123.3, 129.2, 132.4, 150.4, 166.2.

α-(Hydroxy)-phenylazo compound (19h)

To a solution of the acetoxy azo compound **19a** (264 mg, 1 mmol) in ethanol (3 mL), **20** (171 mg, 1 mmol) was added at room temperature under argon. The reaction mixture was stirred for one hour and diluted with dichloromethane. The solution was then washed with 5% hydrochloric acid and water at 0°C, dried , and evaporated under reduced pressure below 35°C. The hydroxyazo compound **19h** was obtained as a pale yellow oil (190 mg, 86%). This compound slowly decomposed at room temperature. It was used for the next reaction without further purification. IR ($CHCl_3$): 3364, 1739, 1445 cm^{-1}. UV ($CHCl_3$) (λ_{max}, nm): 376 nm (log ε 2.26) and 276 nm (log ε 4.03). ^{1}H-NMR ($CDCl_3$) (δ, ppm): 1.32 (3H, t, J = 7.1 Hz), 1.90 (3H, s), 4.28 (2H, q, J = 7.1 Hz), 7.53 (3H, m), 7.84 (2H, m). ^{13}C-NMR ($CDCl_3$) (δ, ppm): 14.1, 22.6, 62.2, 96.0, 123.2, 129.2, 131.9, 149.7, 169.8.

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