Mechanism of the Replacement of Phenolic Hydroxyl by Carbonyl on Lead Tetraacetate Treatment of *o*-Hydroxyaryl Ketone Acylhydrazones

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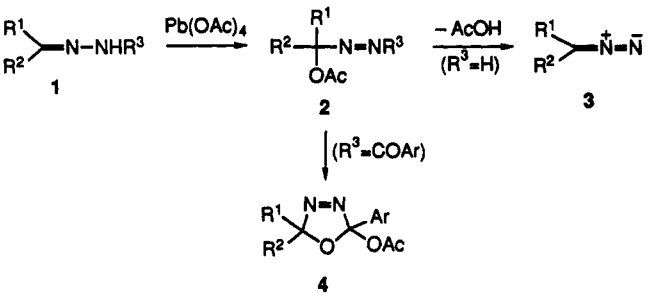
A mechanistic study has been carried out on the reaction of acylhydrazones of *o*-hydroxyaryl ketones **6** with lead tetraacetate, which gives 1,2-diacylbenzenes **7** by a novel overall replacement of phenolic hydroxyl with an acyl group. Cross-over experiments demonstrate that the reaction is intramolecular. Oxygen-labeling evidence suggests that following formation of the 1,3,4-oxadiazoline **10**, cyclization with loss of acetic acid leads to the tricyclic 1,3-dioxane **11**. Elimination of nitrogen leads to an intermediate **12**, which rearranges to the 1,2-diacylbenzene **7**.

The reactions of lead tetraacetate (LTA) with ketone hydrazones have been well-studied recently, and several reviews have discussed both mechanistic and synthetic aspects.[1-3] In general, acetoxylation of monosubstituted hydrazones **1** with LTA leads to the isolation of acetoxyazo compounds **2**.[4] Unsubstituted hydrazones undergo a dehydrogenation to give diazoalkanes **3**, presumably via initial acetoxylation followed by rapid loss of acetic acid. LTA oxidation of hydrazones derived from aromatic acyl hydrazides gives highly reactive azoacetates **2** (R^3 = COAr). These readily undergo cyclization to 1,3,4-oxadiazolines **4**, which yield epoxides with elimination of nitrogen on heating (Scheme I).[5]

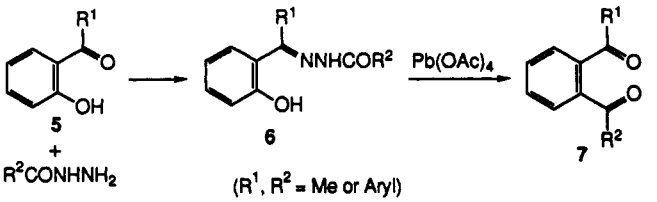
Recently, our attention has focused on the reactivity of LTA with *o*-hydroxyaryl ketone monoacylhydrazones **6**. Monoacylhydrazones of this type do not yield 1,3,4-oxadiazolines on treatment with LTA, but instead undergo a rearrangement resulting in an unusual replacement of the phenolic hydroxyl with the acyl substituent to give 1,2-diacylbenzenes **7**.[6] Further extension of this reaction led to the preparation of 1,2,3-triacylbenzenes from acylhydrazones of 2,6-diacylcresols[7] and *o*-ketoaryl esters from (ethoxycarbonyl)hydrazones of *o*-hydroxyaryl ketones.[8] No analogous transformations had been previously reported, and we now discuss a study of the mechanism of this novel reaction (Scheme II).

Cross-over experiments were carried out to determine whether the transfer of the acyl group occurs via an intramolecular or intermolecular mechanism (see Table I). LTA treatment of acylhydrazones **6a–6d** leads to the formation of the expected diacylbenzenes **7a–7d**. For the cross-over experiments, equimolar mixtures of two acylhydrazones (**6a** and **6c**, **6b** and **6d**) were allowed to react with LTA to give in each case only two products (**7a** and **7c**, **7b** and **7d**). The absence of any cross-over products indicates that an intramolecular rearrangement takes place as opposed to an intermolecular route involving formation of a free acylium ion.

Scheme I



Scheme II



LTA oxidations proceed by a variety of pathways including both ionic two-electron and free-radical one-electron reductions of the metal. Iminoxy radicals have been detected in reactions of LTA with oximes, and a free-radical mechanism was originally invoked[4,9] for LTA–ketohydrazone reactions involving abstraction of the hydrazino hydrogen atom by an acetate radical followed by attack at the carbon atom by $^{\bullet}Pb(OAc)_3$. However, ESR studies on solutions of hydrazones and LTA failed to detect the presence of radicals.[10] Further kinetic studies[11,12] indicate that the rate-determining step of the oxidation probably involves displacement of an acetate anion from LTA by the NH-nitrogen, followed by intramolecular uptake of an acetoxy group at the hydrazone carbon of the organolead intermediate. We examined the reaction of 2-hydroxyacetophenone benzoylhydrazone (**6a**) with LTA to give 2-acetylbenzophenone (**7a**) for a CIDNP phenomenon. The reaction was fast and the NMR spectrum taken within seconds after the addition of LTA showed that the formation of the product was almost complete, but no

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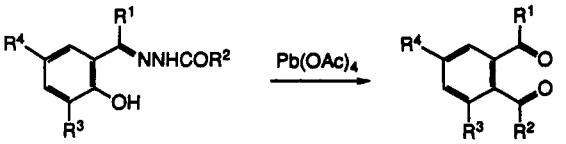
Table I. Results of the Cross-Over Experiment



reactants 6	mp (°C) (lit.[6] mp)	R^1	R^2	R^3	R^4	products 7	mp (°C) (lit.[6] mp)
6a	185.5–186.5 (164–165)[a]	Me	Ph	H	H	7a	96–97 (96–97)
6b	176–178 (176–177)	Me	Me	H	H	7b	38–39 (38–39)
6c	187–189	Me	Me	Br	Br	7c	180–181
6d	245–246 (246–247)	Me	Ph	Br	Br	7d	175–177 (175–176)
6a + 6c		Me, Me	Ph, Me	H, Br	H, Br	7a + 7c	
6b + 6d		Me, Me	Me, Ph	H, Br	H, Br	7b + 7d	

[a] Mp for this hydrazone was earlier reported[6] using an instrument later found to be inaccurate.

CIDNP effect was observed. This observation is consistent with a polar mechanism. The reaction of LTA with acylhydrazone **6a** was repeated in the presence of triethylamine so that no external acetic acid could exist. No change in reactivity was observed, indicating that the reaction is not acid-catalyzed.

It seems probable that the reaction initially proceeds as expected for a substituted hydrazone with formation of the organolead intermediate **8**, followed by intramolecular acetoxy migration to the hydrazone carbon, giving the azoacetate **9** (see Scheme III). Two possible reaction pathways for the azoacetate **9** are initiated by either (path a) formation of the 1,3,4-oxadiazoline **10** followed by loss of acetic acid to give the tricyclic 1,3-dioxane **11** or (path b) initial loss of acetic acid to give the quinone methide **13** and cyclization to the benzoxetane **14**. The two pathways differ in the origin of the two oxygens of the 1,2-diacylbenzene **7**. Path a results in a migration of the original benzoyl oxygen to the hydrazone carbon, whereas in path b the benzoyl oxygen is retained.

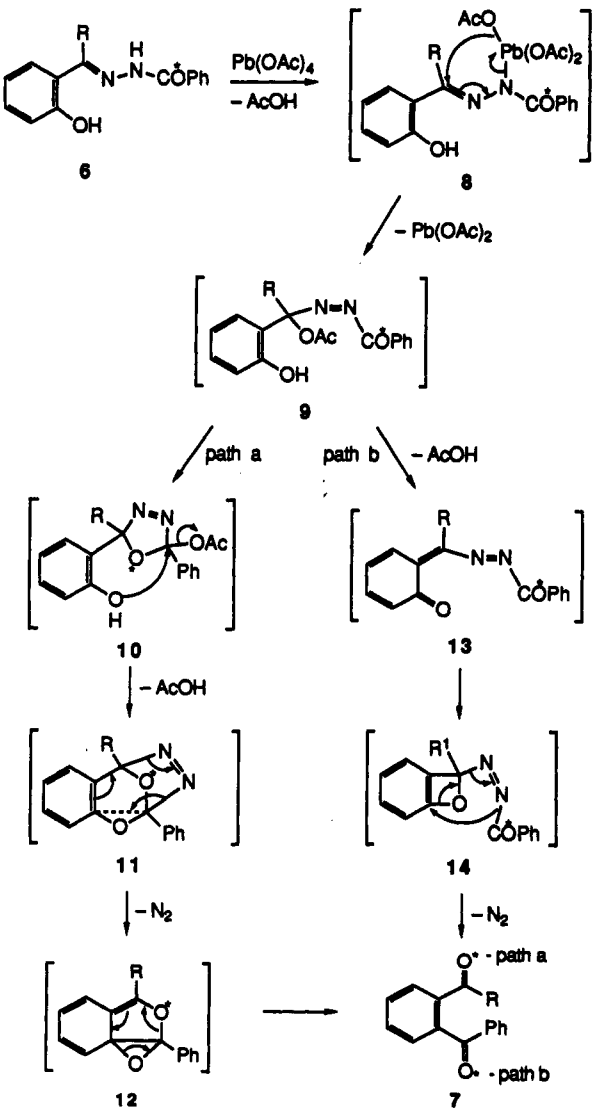
To differentiate between the two proposed routes, an oxygen-labeled benzoylhydrazone was prepared from benzoic-$^{18}O_2$ acid. Treatment of 2-hydroxyacetophenone benzoyl-^{18}O-hydrazone (**15**) with LTA resulted in incorporation of ^{18}O at the acetyl position of the labeled 2-acetylbenzophenone (**16**) (see Scheme IV). This was clearly demonstrated in the mass spectrum of the 2-acetyl-^{18}O-benzophenone (**16**) by observation of fragment ions at m/z 180, corresponding to a loss of labeled acetaldehyde ($CH_3CH^{18}O$), and at m/z 105, corresponding to the fragment acylium ion $PhC^{16}O$. The fragment ions at m/z 180 and 105 are also seen in the mass spectrum of the unlabeled diketone **7a** as would be expected. On the basis of this result, we suggest the reaction mechanism proceeds via path a involving formation of the 1,3,4-oxadiazoline **10** followed by cyclization and loss of acetic acid to give 1,3-dioxane **11**. Elimination of nitrogen with formation of epoxide then give intermediate **12**, which undergoes electrocyclic rearrangement to form the 1,2-diacylbenzene **7**.

In summary, we have shown that this novel replacement of phenolic hydroxyl by a migrating acyl group occurs by an intramolecular reaction. The striking feature of the replacement is the resulting transfer of oxygen from the acyl group to the hydrazone carbon, which suggests the formation of 1,3,4-oxadiazoline **10** and 1,3-dioxane **11** as key intermediates of the reaction.

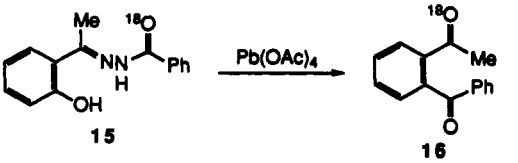
Experimental Section

Melting points were recorded on a hot-stage microscope and are uncorrected. ^1H NMR spectra were recorded at 300 MHz with

Scheme III



Scheme IV



TMS as an internal reference. ^{13}C NMR spectra were recorded at 75 MHz and are referenced either to the 77.0 ppm resonance of $CDCl_3$ or the 39.5 ppm resonance of DMSO-d_6. Mass spectra were recorded at 70 eV.

Hydrazones **6a,b,d** and 1,2-diacylbenzenes **7a,b,d** were previously reported by us.[6]

2-Hydroxy-3,5-dibromoacetophenone Acetylhydrazone (6c). 2-Hydroxyl-3,5-dibromoacetophenone (1.0 g, 3.4 mmol) and acetic hydrazide (0.25 g, 3.4 mmol) were refluxed in 1-propanol (25 mL) for 20 h. The reaction was cooled to 25 °C; the product was filtered off, washed with cold 1-propanol (5 mL), and dried to yield 1.04 g (87%) of the hydrazone **6c**: mp 187–189 °C (ethanol–$CHCl_3$); ^1H NMR (DMSO-d_6) δ 2.11 (s, 3 H), 2.38 (s, 3 H), 3.35 (br s, 1 H), 7.72 (s, 1 H), 7.78 (s, 1 H), 11.2 (s, 1 H); ^{13}C NMR (DMSO-d_6-CF_3CO_2H) δ 21.8, 28.6, 113.7, 124.3, 136.0, 144.8, 160.8, 175.7, 208.8; MS m/z (rel intensity) 350 (M^+, 45), 307 (21), 292 (17), 290 (58), 247 (44), 204 (52), 43 (100). Anal. Calcd for $C_{10}H_{10}Br_2N_2O_2$: C, 34.31; H, 2.88; N, 8.00. Found: C, 34.09; H, 2.82; N, 7.87.

2-Acetyl-3,5-dibromoacetophenone (7c). To a solution of the hydrazone **6c** (0.75 g, 2.1 mmol) in THF (15 mL) stirred at room temperature was slowly added lead tetraacetate (1.1 g, 2.5 mmol) during which time a mild effervescence was observed. After being stirred for 2 h, the reaction mixture was filtered and the filtrate concentrated in vacuo to leave an oily residue that crystallized on trituration in petroleum ether–chloroform to give 0.54 g (80%) of the diacylbenzene **7c**: mp 180–181 °C; ^1H NMR ($CDCl_3$) δ 2.54 (s, 3 H), 2.59 (s, 3 H), 7.93 (d, 1 H, J = 2.4 Hz), 7.94 (d, 1 H, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 26.9, 30.5, 119.6, 122.7, 131.7, 137.2, 139.1, 142.5, 195.9, 202.1; MS m/z (rel intensity) 320 (M^+, 65), 305 (48), 277 (53), 262 (37), 261 (34), 247 (100). Anal. Calcd for $C_{10}H_8Br_2O_2$: C, 37.53; H, 2.52. Found: C, 37.35; H, 2.44.

General Procedure for the Cross-Over Experiments. Equimolar amounts of two hydrazones **6** (2.5 mmol of each) were dissolved in THF (30 mL), and lead tetraacetate (2.4 g, 5.5 mmol) was slowly added. After being stirred for 2 h, the solution was filtered to remove the lead diacetate byproduct and the filtrate concentrated to give an oily mixture of the two diketones **7**, which was analyzed by GC and NMR spectrometry (see Table I).

Benzoic-$^{18}O_2$ Acid. Gaseous $C^{18}O_2$ (500 mL, 22.3 mmol) contained in a sealed round-bottom flask was frozen in liquid nitrogen for 30 min. To the flask was injected freshly prepared Grignard reagent from bromobenzene (4.37 g, 27.8 mmol) and magnesium turnings (0.92 g, 38.0 mmol) in THF (20 mL). The flask was maintained in liquid nitrogen for a further 15 min, after which time it was gradually allowed to warm to room temperature and shaken occasionally for 1 h. The seal was broken, ether (50 mL) added, and the mixture decomposed with ice and dilute hydrochloric acid (25 mL). The benzoic acid was extracted from the etheral layer with sodium carbonate solution (30 mL). After being washed with ether (20 mL), the basic solution was acidified with hydrochloric acid and extracted with ether (50 mL), which on drying and evaporation gave 2.3 g (82%) of benzoic-$^{18}O_2$ acid; mp 123–124 °C, sufficiently pure for the next stage.

Benzoic-^{18}O Hydrazide. Prepared by the method of Rabini and Vita.[13] Benzoic-$^{18}O_2$ acid (1.0 g, 7.9 mmol) was placed in a three-necked flask equipped with a thermometer and a Dean-Stark apparatus, followed by 1-butanol (3 mL), hydrazine monohydrate (0.57 mL, 1.1 mmol), and 0.2 g of alumina (80–200 mesh, activity 1, neutral). The mixture was refluxed for 6 h with the gradual addition of toluene (1 mL) during the course of the reaction. The reaction mixture was filtered while hot, the alumina washed with hot 1-butanol (1 mL), and the butanol evaporated to yield 0.89 g (82%) of benzoic-^{18}O hydrazide sufficiently pure for the next stage: mp 106–113 °C (lit.[13] mp 115–117 °C for ^{16}O derivative); MS m/z (rel intensity) 138 (M^+, 23), 107 (100), 77 (95), 51 (43).

2-Hydroxyacetophenone Benzoyl-^{18}O-hydrazone (15). Benzoic-^{18}O hydrazide (0.85 g, 6.2 mmol) and 2-hydroxyacetophenone (0.84 g, 6.2 mmol) were refluxed in 1-propanol (25 mL) for 20 h. On being cooled, 1.24 g (78%) of the labeled acylhydrazone **15** crystallized and was filtered off, sufficiently pure for the next stage: mp 184.5–185.5 °C (mp 185.5–186.5 °C for ^{16}O derivative **6a**); MS m/z (rel intensity) 256 (M^+, 15), 241 (10), 107 (100), 77 (39).

2-Acetyl-^{18}O-benzophenone (16). The labeled hydrazone **15** (0.75 g, 3 mmol) was stirred at room temperature in THF (15 mL), and lead tetraacetate (1.56 g, 3.5 mmol) was added. After being stirred for 2 h, the reaction mixture was filtered and the filtrate concentrated in vacuo to give 0.65 g (98%) of the labeled diacylbenzene **16**: mp 90–97 °C (lit.[6] mp 96–97 °C for ^{16}O derivative **7a**); MS m/z (rel intensity) 226 (M^+, 11), 211 (M^+ – Me, 100), 181 (M^+ – $C^{18}OMe$, 7), 180 (M^+ – $HC^{18}OMe$, 17), 149 (M^+ – Ph, 24), 105 (PhCO, 22), 77 (Ph, 24); exact mass $C_{15}H_{12}O^{18}O$ requires 226.0880, found 226.0865; exact mass $C_{14}H_9O^{18}O$ requires 211.0645, found 211.0639; exact mass $C_{13}H_8O$ requires 180.0575, found 180.0568; exact mass $C_9H_7O^{18}O$ requires 149.0489, found 149.0468.

Registry No. **6a**, 22233-86-9; **6b**, 10003-76-6; **6c**, 134627-33-1; **6d**, 114070-34-7; **7a**, 18019-57-3; **7b**, 704-00-7; **7c**, 134627-34-2; **7d**, 114070-39-2; **15**, 134627-35-3; **16**, 134627-36-4; 2-hydroxyl-3,5-dibromoacetophenone, 22362-66-9; acetic hydrazide, 1068-57-1; lead tetraacetate, 546-67-8; benzoic-$^{18}O_2$ acid, 17217-84-4; benzoic-^{18}O hydrazide, 21048-32-8; 2-hydroxyacetophenone, 118-93-4.

Supplementary Material Available: MS spectra for compounds **7a** and **16** (2 pages). Ordering information is given on any current masthead page.

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