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Mechanism of the replacement of phenolic hydroxyl by carbonyl on lead tetraacetate treatment of o-hydroxyaryl ketone acylhydrazones

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · AUGUST 1991

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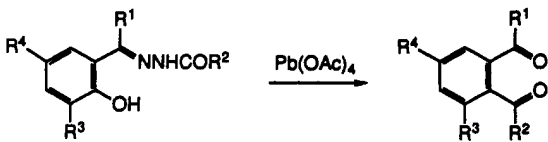
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- (9) (a) Gillis, B. T.; LaMontagne, M. P. *J. Org. Chem.* **1968**, *33*, 762-766. (b) Gillis, B. T.; LaMontagne, M. P. *Ibid.* **1968**, *33*, 1294-1295.
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Table I. Results of the Cross-Over Experiment

							
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 reported⁶ 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-diacetylbenzene 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.

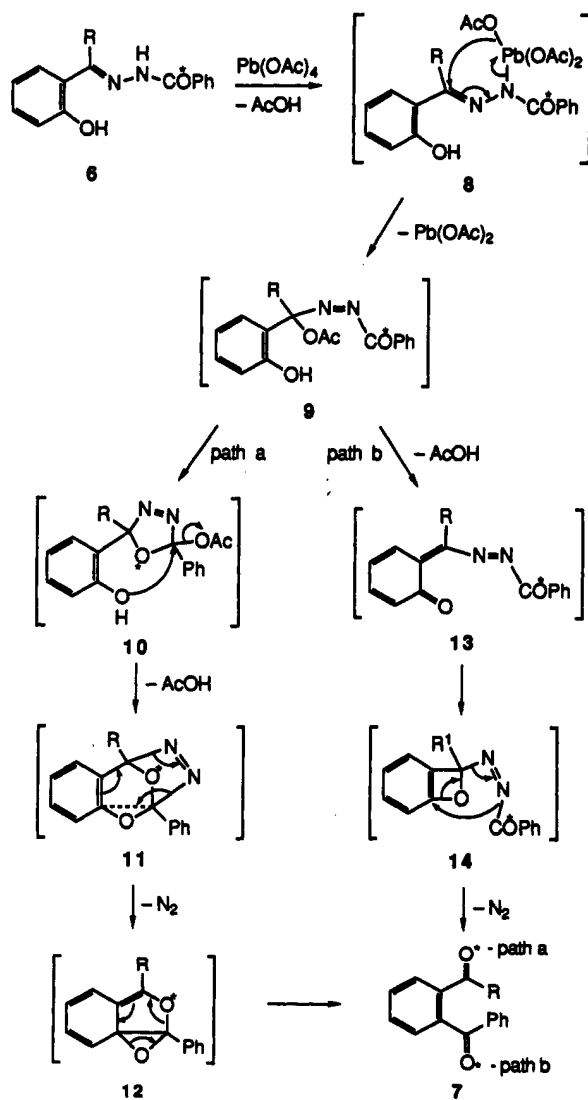
To differentiate between the two proposed routes, an oxygen-labeled benzoylhydrazone was prepared from benzoic-¹⁸O₂ acid. Treatment of 2-hydroxyacetophenone benzoyl-¹⁸O-hydrazone (15) with LTA resulted in incorporation of ¹⁸O at the acetyl position of the labeled 2-acetylbenzophenone (16) (see Scheme IV). This was clearly demonstrated in the mass spectrum of the 2-acetyl-¹⁸O-benzophenone (16) by observation of fragment ions at *m/z* 180, corresponding to a loss of labeled acetaldehyde (CH₃CH¹⁸O), and at *m/z* 105, corresponding to the fragment acylium ion PhC¹⁸O. 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-diacetylbenzene 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.

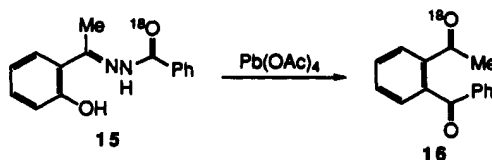
Experimental Section

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 $\text{DMSO}-d_6$. 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-Hydroxy-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 ($\text{DMSO}-d_6$) 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 ($\text{DMSO}-d_6$ - $\text{CF}_3\text{CO}_2\text{H}$) 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 $\text{C}_{10}\text{H}_8\text{Br}_2\text{N}_2\text{O}_2$: 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 $\text{C}_{10}\text{H}_8\text{Br}_2\text{O}_2$: 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- $^{18}\text{O}_2$ 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 ethereal 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- $^{18}\text{O}_2$ 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- $^{18}\text{O}_2$ 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 ($\text{M}^+ - \text{Me}$, 100), 181 ($\text{M}^+ - \text{C}^{18}\text{OMe}$, 7), 180 ($\text{M}^+ - \text{HC}^{18}\text{OMe}$, 17), 149 ($\text{M}^+ - \text{Ph}$, 24), 105 (PhCO , 22), 77 (Ph , 24); exact mass $\text{C}_{15}\text{H}_{12}\text{O}^{18}\text{O}$ requires 226.0880, found 226.0865; exact mass $\text{C}_{14}\text{H}_8\text{O}^{18}\text{O}$ requires 211.0645, found 211.0639; exact mass $\text{C}_{13}\text{H}_6\text{O}$ requires 180.0575, found 180.0568; exact mass $\text{C}_9\text{H}_7\text{O}^{18}\text{O}$ 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-hydroxy-3,5-dibromoacetophenone, 22362-66-9; acetic hydrazide, 1068-57-1; lead tetraacetate, 546-67-8; benzoic- $^{18}\text{O}_2$ 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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