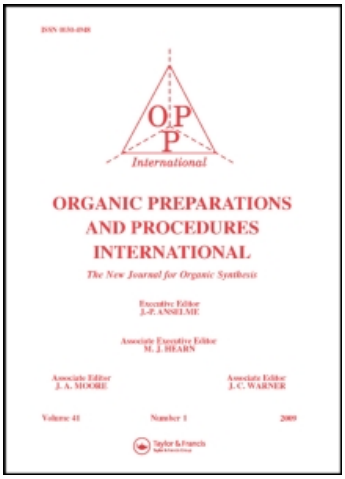

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A NOVEL AND FACILE SYNTHESIS OF *O*-ACYLBENZALDEHYDES

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A NOVEL AND FACILE SYNTHESIS OF *o*-ACYLBENZALDEHYDES

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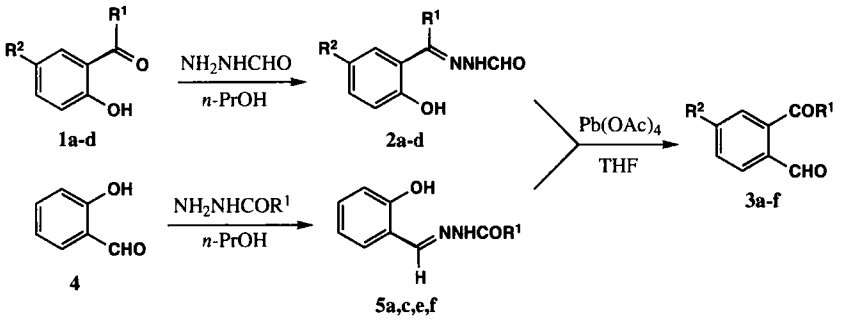
Several years ago, it was discovered in one of our laboratories that the oxidation of *N*-acylhydrazones of *o*-hydroxyaryl ketones with lead tetraacetate resulted in an unexpected replacement of the hydroxy group with the acyl group to yield *o*-diacylbenzenes.[1] The highly unusual nature of this transformation and its simplicity prompted us to investigate the scope[2-5] and the mechanistic pathway of the reaction.[6]

o-Acylbenzaldehydes are useful precursors for a number of heterocycles as demonstrated by their reaction with aliphatic diamines to give imidazo[2,1-a]isoindoles,[7] with iminophosphoranes to yield isoquinolines,[8] with isocyanates to afford phthalimidines,[9] and with nitromethane to give 2-nitro-1-hydroxyindenes.[10] However, no general method exists for their synthesis and a variety of routes have hitherto been employed including ozonolysis/reduction of naphthalenes to give *o*-phthalimides,[11] selenium dioxide oxidation of *o*-(hydroxymethyl)benzhydrol to prepare *o*-benzoylbenzaldehyde,[7] and ozonolysis of β-naphthol to *o*-acetyl-*cis*-cinnamic acid followed by permanganate oxidation to access *o*-acetylbenzaldehyde.[12] This paper reports that the lead tetraacetate mediated rearrangement can be extended to the formation of *o*-acylbenzaldehydes (**3**) either by migration of the formyl group from *N*-formylhydrazones (**2**) of *o*-hydroxyaryl ketones (**1**), or alternatively, by acyl group rearrangement of salicylaldehyde *N*-acylhydrazones (**5**) (**Scheme 1**).

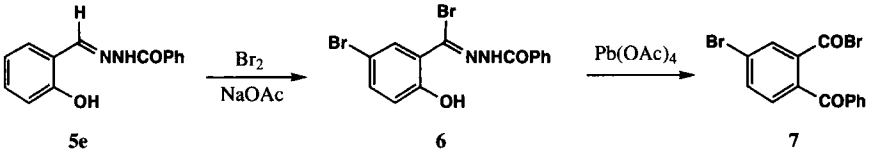
The first route involves initial conversion of *o*-hydroxyaryl ketones (**1**) to their *N*-formylhydrazones (**2a-d**), which upon LTA oxidation, loss of nitrogen and migration of the formyl group, give *o*-acylbenzaldehydes (**3a-d**) in 70-86% yields. The alternative path starts with salicylaldehyde (**4**) which was condensed with *N*-acylhydrazines to give acylhydrazones (**5a,c,e**), and subsequent LTA treatment results in acyl group migration to give *o*-acylbenzaldehydes (**3a,c,e**) in 77-82% yields, thus salicylaldehyde *N*-formylhydrazone (**5f**) on treatment with LTA afforded *o*-phthalaldehyde (**3f**) in 67% yield.



a) R^1 = Me, R^2 = H b) R^1 = Et, R^2 = H c) R^1 = *o*-OH-C_6H_4, R^2 = H
d) R^1 = Ph, R^2 = Me e) R^1 = Ph, R^2 = H f) R^1 = R^2 = H

Scheme 1

To further explore the rearrangement and its compatibility with other functionalities, salicylaldehyde *N*-benzoylhydrazone (**5e**) was brominated to give 5-bromo-2-hydroxybenzoylbromide *N*-benzoylhydrazone (**6**). Oxidation of **6** with LTA yielded the expected 5-bromo-2-benzoylbenzoylbromide **7** in 75% yield (**Scheme 2**). This result indicates that *N*-benzoyl or *N*-acylhydrazones of *o*-hydroxybenzoyl bromide are precursors to *o*-benzoyl and *o*-acylbenzoyl bromides for which only one prior preparative procedure is available.[13]



Scheme 2

Mechanistically the LTA reaction would be expected to follow the pathway previously proposed for the general rearrangement.[6] All new compounds were fully characterized by their spectroscopic and analytical data which are presented in Tables 1 and 2.

In conclusion, an efficient two-step preparation of *o*-acylbenzaldehydes was presented from readily available starting materials involving LTA rearrangement of either *N*-formylhydrazones of *o*-hydroxyaryl ketones or *N*-acylhydrazones of salicylaldehyde.

EXPERIMENTAL SECTION

^1H and ^{13}C NMR spectra were recorded on a Varian Unity Plus 300 or 400 MHz spectrometer. Mass spectra were obtained on a Micromass Platform II spectrometer. Microelemental analyses were carried out by Atlantic Microlab Inc., Norcross, GA. Melting points were uncorrected. Hydrazones **5a** (Sigma-Aldrich Library of Rare Chemicals), **5c** (Frinton Labs), **5e** (Lancaster Synthesis Inc.) and *o*-phthalaldehyde **3f** (Aldrich Chemical Co.) are commercially available while hydrazone **5f**[14] and *o*-acylbenzaldehydes **3a**,[12] **3d**,[15] and **3e**[7] have been reported previously.

TABLE 1. Analytical and Mass Spectrometry Data of New Compounds

Cmpd	mp. (°C)	Elemental Analysis Calcd (Found) C	H	N	ES-MS *m/z*
2a	208-209	60.66 (60.60)	5.65 (5.65)	15.72 (15.84)	379 (2M+Na), 201 (M+2Na)
2b	174-175	62.48 (62.28)	6.29 (6.26)	14.57 (14.62)	215 (M+Na), 193 (M+1), 178, 176
2c	250-251	65.62 (65.80)	4.72 (4.80)	10.93 (10.91)	279 (M+Na), 257 (M+1)
2d	286-287	70.85 (71.08)	5.55 (5.65)	11.01 (11.05)	255 (M+1)
3b	semi-solid	74.05 (74.16)	6.21 (6.30)		163 (M+1), 162 (M), 148, 133
3c	semi-solid	74.33 (74.40)	4.55 (4.47)		227 (M+1), 226, 225, 209, 133
6	188-190	42.24 (42.37)	2.53 (2.51)	7.04 (7.05)	421 (M^++23), 398(M^+)
7	thick oil	45.69 (45.49)	2.19 (2.21)		391 (M^++23), 368 (M^+)[a]

a) HR-MS Molecular Mass Calculated : 368.0240. Found : 368.0241.

General Procedure for the Preparation of Hydrazones 2 and 5.- The *o*-hydroxyaryl ketone (**1**) or salicylaldehyde (**4**) (10 mmol) and the appropriate acyl- or formylhydrazide (10 mmol) were refluxed in 1-propanol (50 mL) for 24 h. The precipitated solid was collected to give the pure hydrazone **2** or **5**: **2a** (71%), **2b** (68%), **2c** (72%), **2d** (87%), **5a** (99%), **5c** (92%), **5e** (95%), **5f** (95%).

General Procedure for the Preparation of *o*-Acyl Benzaldehydes 3.- Hydrazone **2** or **5** (5 mmol) was dissolved in THF (30 mL) and LTA (5 mmol) was gradually added. The mixture was stirred at room temperature for 2 h. After evaporation of the solvent, the mixture was subjected to column chromatography (silica gel 70-230 mesh, pet. ether/ chloroform 1/1) to give the pure *o*-acylbenzaldehyde **3**: **3a** (70% from **2a**, 82% from **5a**), **3b** (86%), **3c** (80% from **2c**, 80% from **5c**), **3d** (78%), **3e** (77%), **3f** (67%).

Preparation of 5-Bromo-2-hydroxybenzoyl Bromide *N*-Benzoylhydrazone (6).- Hydrazone **5e** (0.96 g, 4 mmol) and anhydrous sodium acetate (2.4 g, 29 mmol) were dissolved in acetic acid (10 mL) and a solution of bromine (0.41 mL, 8 mmol) in acetic acid (5 mL) was gradually added. The mixture was stirred at room temperature for 2 h. After addition of water (150 mL) the mixture was filtered. The solid was washed initially with 5% sodium carbonate solution and subsequently with water. Recrystallization from 2-propanol gave hydrazone **6** (1.07 g, 67% yield).

Preparation of (5-Bromo-2-benzoyl)benzoyl Bromide (7).- Hydrazone **6** (0.4 g, 1 mmol) was dissolved in THF (30 mL) and LTA (0.66 g, 1.5 mmol) was gradually added. The mixture was stirred

at room temperature for 2 h. After evaporation of the solvent the mixture was subjected to column chromatography (silica gel 70-230 mesh, pet. ether/chloroform 1/1) to give the pure benzoyl bromide **7** (0.28 g, 75% yield).

TABLE 2. ^{1}H NMR and ^{13}C NMR Data for New Compounds

Cmpd	^{1}H NMR[a] (δ)	^{13}C NMR[a] (δ)
2a	2.30 (s, 3H), 6.80-6.90 (m, 2H), 7.20-7.60 (m, 2H), 8.19 (s, 1H), 11.40 (s, 1H), 12.90 (s, 1H)	13.8, 117.6, 119.0, 128.9, 131.1, 131.7, 157.8, 165.9, 168.5
2b	1.14 (t, 3H), 3.30 (q, 2H), 6.90-8.25 (s, 1H), 11.48 (s, 1H), 13.09 (s, 1H)	11.4, 19.6, 119.2, 119.6, 120.5, 131.7, 157.9, 160.5, 173.4
2c	6.73-7.47 (m, 8H), 9.89 (s, 1H), 10.65 (s, 1H), 12.05 (s, 1H), 12.79 (s, 1H)	116.9, 117.5, 119.0, 119.1, 119.7, 121.1, 129.8, 130.4, 131.6, 131.9, 158.9, 159.4, 160.3, 165.2
2d	2.13 (s, 3H), 6.80-7.10 (m, 3H), 7.30 (m, 2H), 7.64 (m, 3H), 11.71 (s, 1H)	20.4, 117.6, 127.9, 128.3, 129.3, 129.4, 131.9, 134.5, 152.4, 158.3, 158.4, 164.2, 168.7, 171.5
3b	1.18 (t, 3H), 3.33 (q, 2H), 6.96-6.99 (m, 2H), 7.39-7.43 (m, 1H), 7.76-7.78 (m, 1H), 13.00 (s, 1H)	11.9, 21.7, 117.9, 118.2, 119.6, 129.8, 133.3, 168.5, 173.3
3c	7.41-7.49 (m, 1H), 7.52-7.69 (m, 2H), 7.71-7.75 (m, 2H), 8.00-8.09 (m, 1H), 8.74-8.76 (m, 2H), 9.97 (s, 1H)	119.8, 119.9, 120.3, 128.0, 130.1, 131.0, 133.1, 134.1, 135.4, 137.8, 140.0, 162.5, 190.0, 202.1
6	7.54 (m, 3H), 7.89 (m, 2H), 7.93 (m, 2H), 8.50 (s, 1H), 12.5 (s, 1H), 12.7 (s, 1H)	110.7, 111.6, 121.3, 128.1, 128.2, 129.0, 132.5, 132.6, 132.7, 135.9, 147.5, 154.1, 163.4
7	7.52 (m, 3H), 7.64 (m, 1H), 7.80 (m, 2H), 8.10 (m, 2H)	121.5, 124.0, 128.2, 129.2, 129.3, 130.2, 132.8, 134.3, 136.0, 136.8, 140.3, 140.4, 187.8, 194.0

a) DMSO-d_6 for compounds **2,6** and $CDCl_3$ for **3,7**.

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