

OXIDATION OF *N*-ACYL HYDRAZONES OF *o*-AMINOARYL KETONES:
SYNTHESIS OF 2-ACYLAMINOINDAZOLES [†]

Antigoni Kotali^{*a} and Philip A. Harris^b

^aLaboratory of Organic Chemistry, College of Engineering, University of Thessaloniki,
Thessaloniki, Gr-54006, Greece

^bBurroughs Wellcome Co., 3030 Cornwallis Road, Research Triangle Park, NC 27709, USA

Abstract - *Synthesis of 3-substituted-2-acylaminoindazoles via the lead tetraacetate oxidative cyclization of *N*-carbonylhydrazones of *o*-aminoarylketones is reported. A mechanism involving formation of organolead, azoacetate and *o*-quinonemethide imine intermediates is proposed. The formation of the indazole heterocycle was confirmed by an independent synthesis of 2-benzoylamino-3-phenylindazole.*

Lead tetraacetate (LTA) oxidation of organic nitrogen compounds has been widely used in organic synthesis and was the subject of a recent review.¹ In general, ketone hydrazones react with LTA to form azoacetates² ($R^1R^2C(OAc)-N=N-R^3$) which if unsubstituted ($R^3=H$) will lose acetic acid to give diazoalkanes,³ or alternatively, if derived from benzoylhydrazones ($R^3=COAr$), can cyclize to give 2-acetoxy- Δ^3 -1,3,4-oxadiazolines.⁴

In recent years we have focused on the reaction of *N*-acyl- and *N*-aroylhydrazones of *ortho* substituted aryl ketones with LTA. In this context, *o*-hydroxylaryl ketone monoacyl hydrazones undergo an unusual replacement

[†] Dedicated to Professor Alan R. Katritzky on the occasion of his sixty fifth birthday

of the phenolic hydroxyl with the acyl substituent to give 1,2-diacylbenzenes.⁵ Further extension of this reaction led to the synthesis of 1,2,3-triacylbenzenes from acyl hydrazones of 2,6-diacylcresols⁶ and ethyl *o*-benzoates from ethoxycarbonylhydrazones of *o*-hydroxyaryl ketones.⁷ Cross-over experiments demonstrate that the reaction is intramolecular and oxygen-labeling evidence suggests the formation of an intermediate 2-acetoxy- Δ^3 -1,3,4-oxadiazoline, followed by displacement of acetate by the phenoylic oxygen to give a 1,3-dioxane, elimination of nitrogen and rearrangement to the 1,2-diacylbenzene.⁸

In a continuation of our studies on acyl hydrazones of *ortho* substituted hydrazones and to compare the role of amino and hydroxyl groups at this position, we prepared the carbonyl hydrazones of *o*-aminoaryl ketones and examined their reactivity towards LTA. Hydrazones (3), readily obtained by treatment of *o*-aminoaryl ketones (1) with the corresponding acyl hydrazides (2), underwent rapid oxidative cyclization to give 2-acylaminoindazoles (7) in good yields (see Table).

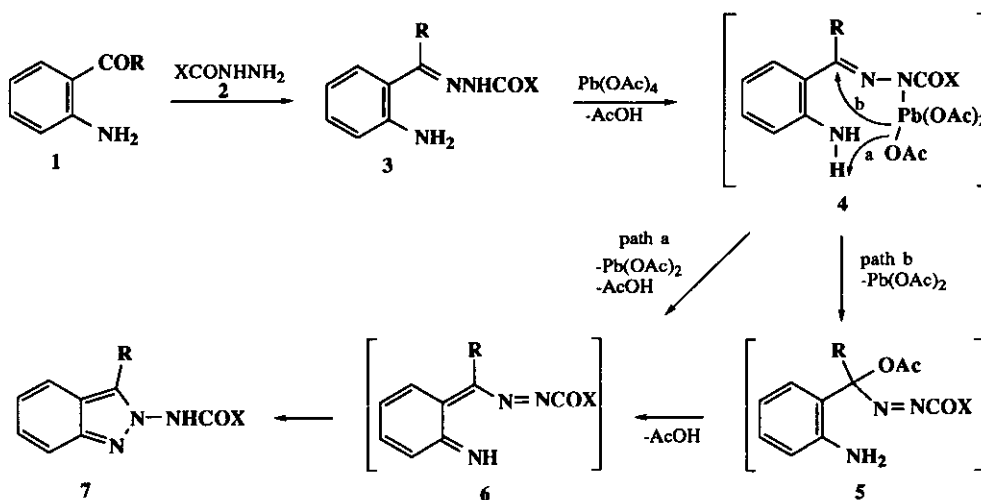
Table. Preparation of Carbonyl Hydrazones (3) and Indazoles (7).

Hydrazone	Yield (%)	mp (°C)	Indazole	Yield (%)	mp (°C)
3a	88	184.5-185.5	7a	73	135.5-136.5
3b	67	136.5-137.0	7b	65	131.5-132.5
3c	86	215.5-217.0	7c	75	192.5-193.5
3d	69	225.0-226.0	7d	60	179.5-180.0
3e	95	138.0-139.0	7e	80	149.5-150.0
3f	89	122.5-123.5	7f	86	180.5-181.5

LTA oxidations of aromatic primary amines containing an unsaturated *ortho* substituent (N=O, N=N, C=O, N=CH) have previously been reported to undergo similar cyclizations leading to benzofurazan,^{9,10} benzotriazole,^{11,12} benzoxazole,¹³ and benzimidazole^{14,15} heterocycles, respectively. For the oxidative cyclization of *o*-aminoaryldazo compounds to the corresponding benzotriazoles, the presence of radical

intermediates has been proposed.¹¹ In general, LTA oxidations proceed by a variety of pathways including both ionic two-electron and free radical one-electron reductions of the metal. A plausible mechanism to explain the observed behavior of *N*-acyl hydrazones (3) towards LTA is outlined in Scheme 1.

Scheme 1



3-7	a	b	c	d	e	f
R	Me	Me	Me	Ph	Me	Me
X	Ph	Me		Ph	OEt	OBn

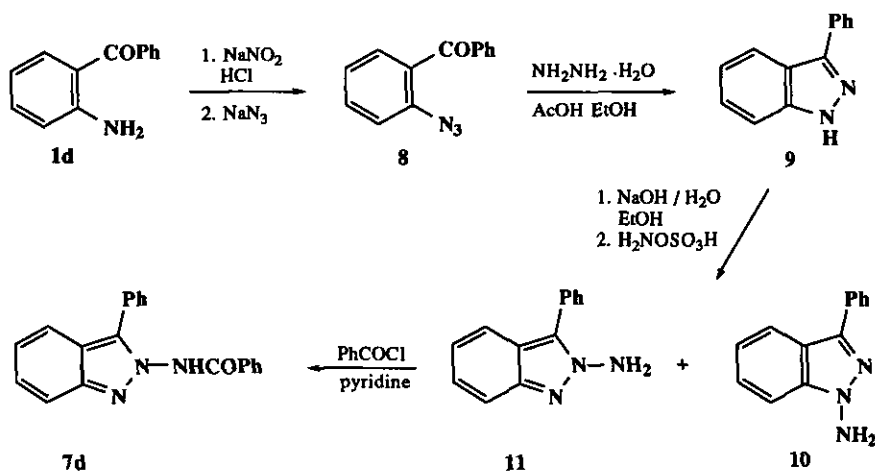
Rapid removal of the nitrogen hydrogen by an acetate ion generating the reactive *N*-metallo intermediate (4) is proposed as the first step. Elimination of lead(II) acetate and another molecule of acetic acid from 4, either directly by removal of an *ortho* amino hydrogen by acetate (path a) or *via* the azoacetate (5) through intramolecular redox with an acetoxy migration to the methine carbon (path b), would give the *o*-quinonemethide imine (6) that yields indazole (7) upon cyclization. The creation of the *N*-*N* bond as the last step of the ring

synthesis is common to indazoles as opposed to pyrazoles. A characteristic example is the dehydration of the oxime of *o*-aminoacetophenone with acetic anhydride which yields 1-acetyl-3-methylindazole.^{16,17}

The two step reaction sequence represents a simple and efficient route to 2-acylaminoindazoles. In a typical oxidation procedure, LTA is added to a solution of hydrazone (3) in dry tetrahydrofuran and the mixture is stirred at room temperature for 1 h. The crude product, obtained after filtration of lead(II) acetate and condensation of the filtrate, is purified either by recrystallization or column chromatography to give indazoles (7). Compounds (3) and (7) are all novel and were characterized by elemental analysis and by their ¹H and ¹³C nmr spectra.

To confirm the structure of the indazoles (7) and exclude the formation of the isomeric 2-acyl-1,2,3-benzotriazines by cyclization at the amido nitrogen, an independent synthesis of 7d was undertaken. This was achieved by synthesis and subsequent benzylation of 2-amino-3-phenylindazole (11), available as a minor product of the amination of 3-phenylindazole (9).¹⁸ The reaction sequence is shown in Scheme 2.

Scheme 2



o-Aminobenzophenone (1d) was converted *via* the corresponding diazonium salt to *o*-azidobenzophenone (8) on treatment with sodium azide. Subsequent cyclization of 8 to 3-phenylindazole (9) occurred by refluxing with hydrazine hydrate in acetic acid / ethanol. Amination of 3-phenylindazole (9) by treatment with hydroxylamine-*O*-sulfonic acid gave a 6:1 mixture of 1-amino-3-phenylindazole (10) and 2-amino-3-phenylindazole (11). After separation by column chromatography, 11 was benzylation to give 2-benzoylamino-3-phenylindazole (7d). All

spectral data and melting point of this compound corresponded to that obtained by LTA oxidation of **3d**.

In conclusion, the simple two-step synthesis of 3-substituted-2-acylaminoimidazoles described in this paper represents a useful entry to these relatively inaccessible heterocycles.

EXPERIMENTAL

Melting points were determined on a capillary tube apparatus and are uncorrected. ^1H and ^{13}C nmr spectra were recorded on a Varian VXR 200 or 300 MHz spectrometer using TMS as the internal standard (abbreviations used: s singlet; d doublet; t triplet; q quartet; m multiplet; br broad). Lead tetraacetate (95%), *o*-aminoacetophenone, *o*-aminobenzophenone, the acyl hydrazide and carbazates were all purchased from commercial suppliers (Aldrich, Inc. and Lancaster Synthesis, Inc.). Tetrahydrofuran was distilled from sodium prior to use.

A General Procedure for the Preparation of Carbonyl Hydrazones (3).

The *o*-aminoaryl ketone **1** (10 mmol) and hydrazide **2** (10 mmol) were refluxed in 2-propanol (50 ml) for 24 h. On allowing to cool the precipitated solid was filtered off to give the hydrazones (**3**) in good yields (see Table) which could be recrystallized to purity from alcohols. In the case of *o*-aminoacetophenone acetylhydrazone (**3b**) flash chromatography was required for purification (elution solvents : chloroform and then ethyl acetate).

***o*-Aminoacetophenone benzoylhydrazone (3a):** ^1H Nmr (DMSO- d_6) 2.39 (s, 3H), 6.55 (t, $J = 7.5$ Hz, 1H), 6.78 (d, $J = 7.8$ Hz, 1H), 7.07 (t, $J = 7.5$ Hz, 1H), 7.31 (s, 2H), 7.44 (d, $J = 7.8$ Hz, 1H), 7.52 (m, 3H), 7.92 (d, $J = 6.95$ Hz, 2H), 10.94 (s, 1H). ^{13}C Nmr (DMSO- d_6) 15.4, 114.9, 116.6, 118.0, 128.3, 128.8, 129.6, 130.1, 132.0, 134.1, 148.5, 157.9, 164.5. *Anal.* Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}$: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.07; H, 5.99; N, 16.63.

***o*-Aminoacetophenone acetylhydrazone (3b):** ^1H and ^{13}C Nmr data of **3b** showed the formation of the *cis* and *trans* isomers in a ratio of 1:4. ^1H Nmr (DMSO- d_6) 2.02 (s, 3H), 2.13 (s, 3H), 2.20 (s, 3H), 2.23 (s, 3H), 6.59 (m, 2H), 6.52 (m, 2H), 6.68 (m, 3H) 7.00 (m, 2H), 7.14 (s, 2H), 7.35 (m, 3H), 10.32 (s, 1H), 10.49 (s, 1H). ^{13}C Nmr (DMSO- d_6) 15.4, 16.2, 22.4, 115.45, 116.3, 117.1, 118.7, 120.0, 130.0, 130.2, 130.4, 148.15, 149.0, 152.0, 154.05, 167.2, 173.1. *Anal.* Calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.91; H, 6.83; N, 21.94.

***o*-Aminoacetophenone *o*-hydroxybenzoylhydrazone (3c):** ^1H Nmr (DMSO- d_6) 2.28 (s, 3H), 6.61 (t, $J = 7.5$ Hz, 1H), 6.79 (d, $J = 7.5$ Hz, 1H), 7.15 (m, 4H), 7.42 (m, 3H), 8.08 (d, $J = 7.5$, 1H), 11.39 (s, 1H). ^{13}C Nmr (DMSO- d_6) 14.2, 108.0, 114.6, 116.3, 116.9, 117.4, 117.6, 119.7, 129.1, 129.8, 130.4, 133.5, 148.1, 156.9, 162.3. *Anal.* Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.81; H, 5.62; N, 15.65.

***o*-Aminobenzophenone benzoylhydrazone (3d):** ^1H Nmr (DMSO- d_6) 6.40-7.75 (m, 15H), 8.02 (d, $J = 7.5$ Hz, 1H), 10.48 (br, 1H). ^{13}C Nmr (DMSO- d_6) 114.2, 115.8, 116.1, 116.9, 127.1, 127.4, 127.7, 127.8, 128.3, 128.4, 128.7, 129.3, 129.4, 129.6, 130.9, 131.4, 131.8, 133.5, 145.3, 165.8. *Anal.* Calcd for $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}$: C, 76.17; H, 5.43; N, 13.32. Found: C, 76.18; H, 5.48; N, 13.35.

***o*-Aminoacetophenone ethoxycarbonylhydrazone (3e):** ^1H Nmr (CDCl_3) 1.25 (t, $J = 7$ Hz, 3H), 2.15 (s, 3H), 4.21 (q, $J = 7$ Hz, 2H), 6.72 (q, $J = 8.4$ Hz, 3H), 7.01 (t, $J = 7$ Hz, 1H), 7.29 (d, $J = 6.9$ Hz, 2H), 8.69 (s, 1H). ^{13}C Nmr (DMSO- d_6) 14.4, 14.6, 60.7, 114.5, 116.0, 117.9, 128.7, 129.1, 147.6, 154.5. *Anal.* Calcd for $\text{C}_{11}\text{H}_{15}\text{N}_3\text{O}_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.64; H, 6.83; N, 18.97.

***o*-Aminoacetophenone benzyloxycarbonylhydrazone (3f):** ^1H Nmr (DMSO- d_6) 2.20 (s, 3H), 5.20 (s, 2H), 6.51 (t, $J = 5$ Hz, 1H), 6.70 (d, $J = 5$ Hz, 1H), 7.01 (m, 3H), 7.48 (m, 6H), 10.37 (s, 1H). ^{13}C Nmr (DMSO- d_6) 15.6, 67.3, 115.6, 117.15, 118.9, 129.2, 129.4, 129.6, 129.85, 130.3, 137.7, 148.8, 155.5. *Anal.* Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.73; H, 6.12; N, 14.85.

A General Procedure for the Preparation of Indazoles 7.

Hydrazone (3) (5 mmol) was dissolved in dry tetrahydrofuran (30 ml) and LTA (2.56 g, 5.5 mmol) was gradually added. The mixture was stirred under nitrogen at room temperature for 1 h. After evaporation of the solvent, the obtained residue was treated with dichloromethane (50 ml). The insoluble white solid was filtered off and washed with dichloromethane (2 x 25ml). The dichloromethane solutions were combined and evaporated to give a light brown solid which was recrystallized either by toluene / hexane (for **7a**, **7b** and **7d**) or by toluene (for **7e** and **7f**). In the case of **7c**, an oil was obtained which was subjected to column chromatography (silica gel 70-230 ASTM) eluted with hexane / ether 1:1 to give the indazole (**7c**) (see Table).

2-Benzoylamino-3-methylindazole (7a): ^1H Nmr (CDCl_3) 2.35 (s, 3H), 6.88 (m, 1H), 7.11-7.43 (m, 6H), 7.86 (d, $J = 7.5$ Hz, 2H), 11.99 (br, 1H). ^{13}C Nmr (CDCl_3) 9.3, 116.0, 119.5, 120.4, 121.0, 127.5, 127.9, 128.0, 128.6, 130.8, 132.7, 134.1, 145.6, 166.0. *Anal.* Calcd for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.57; H, 5.24; N, 16.69.

2-Acetylamino-3-methylindazole (7b): ^1H Nmr ($\text{DMSO}-d_6$) 2.10 (s, 3H), 2.43 (s, 3H), 7.00 (t, $J = 7.5$ Hz, 1H), 7.24 (t, $J = 7.65$ Hz, 1H), 7.48 (d, $J = 8.6$ Hz, 1H), 7.65 (d, $J = 8.6$ Hz, 1H), 11.98 (br, 1H). ^{13}C Nmr ($\text{DMSO}-d_6$) 10.3, 21.7, 117.9, 120.0, 121.5, 121.6, 127.5, 133.1, 146.0, 169.6. *Anal.* Calcd for $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.57; H, 5.92; N, 22.26.

2-(*o*-Hydroxybenzoyl)amino-3-methylindazole (7c): ^1H Nmr (CDCl_3) 2.53 (s, 3H), 7.00 (m, 3H), 7.27 (m, 1H), 7.43 (m, 1H), 7.56 (m, 2H), 8.00 (d, $J = 7.8$ Hz, 1H), 11.08 (br, 1H). ^{13}C Nmr (CDCl_3) 8.7, 112.6, 116.5, 117.2, 118.6, 118.7, 119.6, 120.3, 126.3, 127.9, 132.3, 134.4, 145.3, 159.9, 168.1. *Anal.* Calcd for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.32; H, 4.89; N, 15.76.

2-Benzoylamino-3-phenylindazole (7d): ^1H Nmr (CDCl_3) 7.11 (t, $J = 7.2$ Hz, 1H), 7.32 (m, 5H), 7.63 (m, 3H), 7.82 (d, $J = 7.4$ Hz, 2H), 12.28 (br, 1H). ^{13}C Nmr (CDCl_3) 116.8, 119.4, 120.8, 122.5, 127.5, 127.9, 128.0, 128.5, 128.8, 129.0, 129.2, 130.9, 132.5, 145.9, 166.1. *Anal.* Calcd for $\text{C}_{20}\text{H}_{15}\text{N}_3\text{O}$: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.74; H, 4.84; N, 13.39.

2-Ethoxycarbonylamino-3-methylindazole (7e): ^1H Nmr ($\text{DMSO}-d_6$) 1.23 (br, 3H),* 2.48 (s, 3H), 4.15 (br, 2H),* 6.99 (t, $J = 7.9$ Hz, 1H), 7.18 (t, $J = 7.8$ Hz, 1H), 7.48 (d, $J = 8.7$ Hz, 1H), 7.67 (d, $J = 8.6$ Hz, 1H), 11.50 (br, 1H). ^{13}C Nmr ($\text{DMSO}-d_6$) 9.3, 14.7, 62.1, 117.1, 119.2, 120.8, 120.9, 126.8, 132.5, 145.1, 155.4. *Anal.* Calcd for $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.27; H, 5.99; N, 19.14.

*The ethyl group displays broad peaks due to restricted rotation.

2-Benzoyloxycarbonylamino-3-methylindazole (7f): ^1H Nmr ($\text{DMSO}-d_6$) 2.47 (s, 3H), 5.21 (s, 2H), 7.01 (t, $J = 7.5$ Hz, 1H), 7.25 (t, $J = 7.5$ Hz, 1H), 7.40 (m, 5H), 7.51 (d, $J = 8.6$ Hz, 1H), 7.69 (d, $J = 8.4$ Hz, 1H), 11.67 (br, 1H). ^{13}C Nmr ($\text{DMSO}-d_6$) 9.3, 67.4, 117.2, 119.2, 120.9, 126.95, 128.3, 128.5, 128.6, 128.7, 128.85, 129.0, 132.55, 136.2, 145.2, 155.3. *Anal.* Calcd for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.23; H, 5.36; N, 14.97.

Independent Synthesis of 2-Benzoylamino-3-phenylindazole (7d).

Following a previous report,¹⁸ 2-amino-3-phenylindazole (**11**) (mp 79.5-81.5°C; lit.,¹⁸ mp 80.5-81.5°C) was prepared and separated from its isomer, 1-amino-3-phenylindazole (**10**) (mp 112.5-113°C; lit.,¹⁸ mp 112-113°C), by flash chromatography (hexane / ether). 2-Amino-3-phenylindazole (**11**) (1.05 g, 5 mmol) was then dissolved in anhydrous pyridine (10 ml) and benzoyl chloride (0.8 ml, 7 mmol) was added under stirring in an ice bath. Stirring was continued overnight at room temperature. The mixture was poured into ice and extracted with dichloromethane (2 x 50 ml). The extract was washed with 1.0 N hydrochloric acid (30 ml) and water (30 ml), dried with MgSO₄, and concentrated under reduced pressure. The residue was purified by recrystallization from a toluene / hexane mixture to give 2-benzoylamino-3-phenylindazole (**7d**) (mp 170.5-172°C), in 68 % yield.

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