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

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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 azoacetates[2] ($R^1R^2C(OAc)$-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-diacylcresols[6] 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).

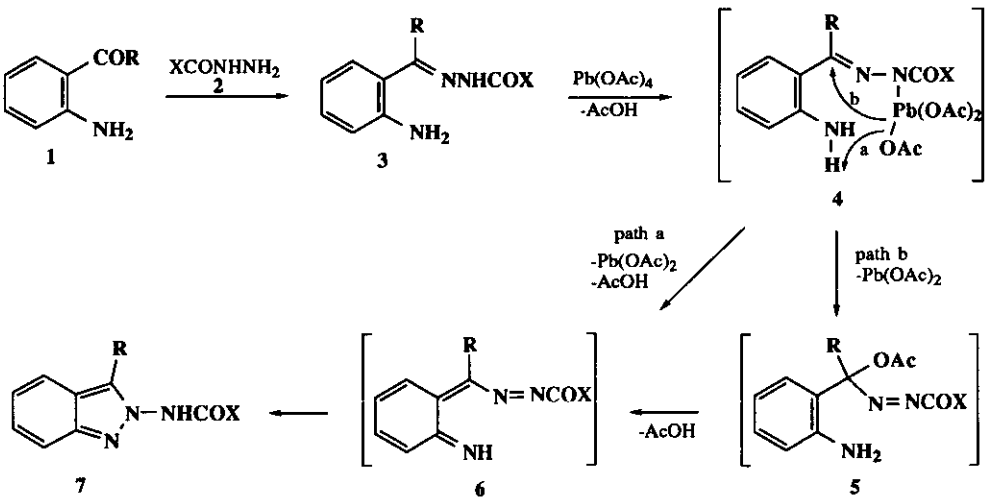
Table. Preparation of Carbonyl Hydrazones (3) and Indazoles (7).

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*-aminoarylazo 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

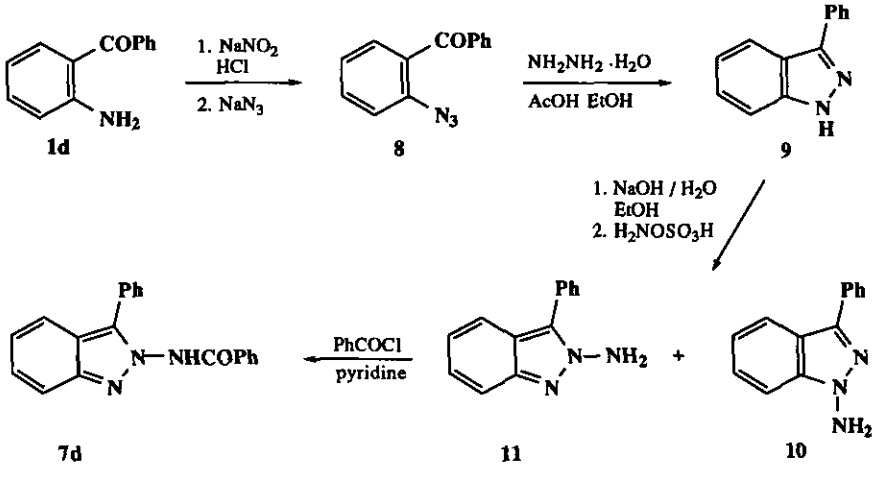
Rapid removal of the nitrogen hydrogen by an acetate ion generating the reactive *N*-metallo intermediate (**4**) is proposed as the first step. Elimination of lead(II) acetate and another molecule of acetic acid from **4**, either directly by removal of an *ortho* amino hydrogen by acetate (path a) 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 ^{1}H and ^{13}C 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 benzoylation 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 benzoylated to give 2-benzoylamino-3-phenyindazole (**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-acylaminoimadazoles 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. ^{1}H 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): ^{1}H 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 $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.07; H, 5.99; N, 16.63.

***o*-Aminoacetophenone acetylhydrazone (3b)**: ^{1}H and ^{13}C Nmr data of **3b** showed the formation of the *cis* and *trans* isomers in a ratio of 1:4. ^{1}H 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 $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.91; H, 6.83; N, 21.94.

***o*-Aminoacetophenone *o*-hydroxybenzoylhydrazone (3c)**: ^{1}H 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 $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.81; H, 5.62; N, 15.65.

***o*-Aminobenzophenone benzoylhydrazone (3d)**: ^{1}H 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 $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32. Found: C, 76.18; H, 5.48; N, 13.35.

***o*-Aminoacetophenone ethoxycarbonylhydrazone (3e)**: ^{1}H 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 $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.64; H, 6.83; N, 18.97.

***o*-Aminoacetophenone benzyloxycarbonylhydrazone (3f)**: ^{1}H 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 $C_{15}H_{15}N_3O_2$: 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): ^{1}H 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 $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.57; H, 5.24; N, 16.69.

2-Acetylamino-3-methylindazole (7b): ^{1}H Nmr (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 (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 $C_{10}H_{11}N_3O$: 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): ^{1}H 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 $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.32; H, 4.89; N, 15.76.

2-Benzoylamino-3-phenylindazole (7d): ^{1}H 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 $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.74; H, 4.84; N, 13.39.

2-Ethoxycarbonylamino-3-methylindazole (7e): ^{1}H Nmr (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 (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 $C_{11}H_{13}N_3O_2$: 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-Benzyloxycarbonylamino-3-methylindazole (7f): ^{1}H Nmr (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 (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 $C_{16}H_{15}N_3O_2$: 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 $MgSO_4$, 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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