Lead Tetraacetate Oxidation of Phenylhydrazones of 3-Benzoylazoles. Synthesis of Azoacetates and Their Conversion into Indazoles

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Lead tetraacetate (LTA) oxidation of *(E)*- and *(Z)*-phenylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole, 3-benzoyl-5-phenylisoxazole, and 3-benzoyl-4-methyl-1,2,5-oxadiazole has been studied. Conversion of azoacetate products into 3-(azol-3-yl)-substituted indazoles has been achieved by reacting them with aluminium chloride in benzene at room temperature.

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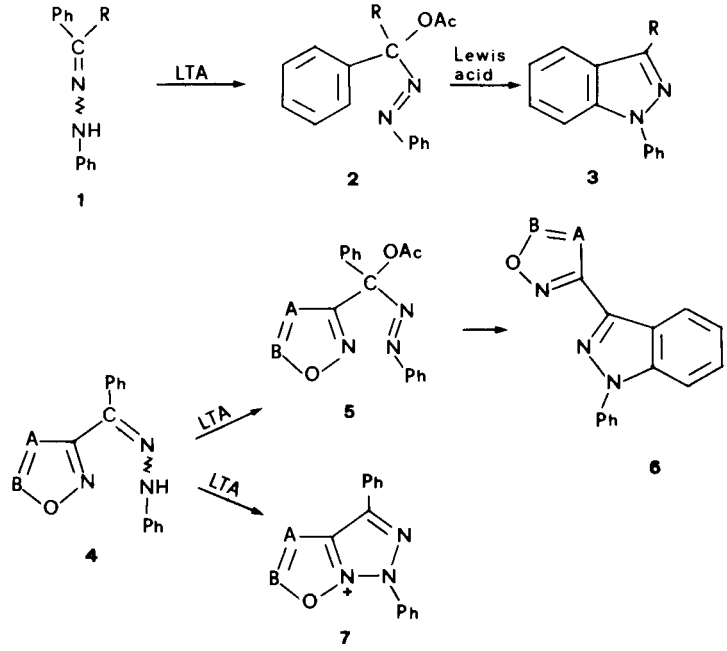
It is well known that LTA oxidation of ketone phenylhydrazones **1** gives azoacetates **2** [1]. In the case of phenyl ketone phenylhydrazones, azoacetate products, when reacted with Lewis acid, have furnished an useful tool of the synthesis of indazole derivatives **3** [2]. LTA oxidation of arylhydrazones of 2-benzoylpyridine, followed by Lewis acid treatment, gave low yields of indazole derivatives, and this result has been attributed to the occurrence of an intramolecular reaction in the oxidation process [3]. Moreover, LTA oxidation of the phenylhydrazone of 2-benzoylpyridine, followed by hydrogen chloride treatment, gave the 1,3-diphenyl-8-azaindazolium chloride [4].

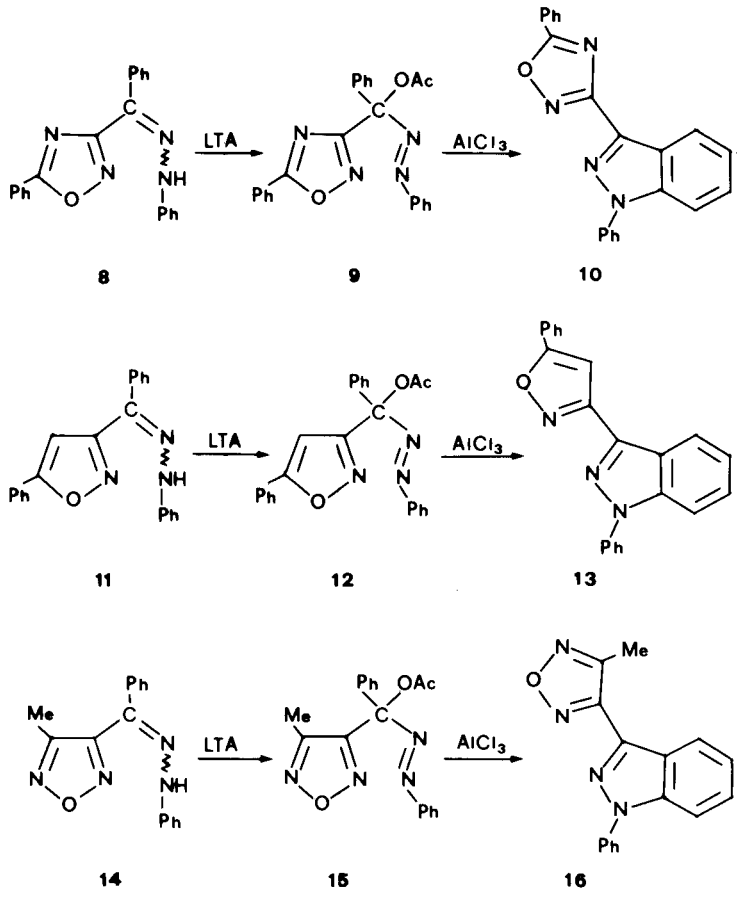
To our knowledge, there is no report about LTA oxidation of phenylhydrazones of 3-acylazoles of the type **4**, from which azoacetates **5** would be expected, as well as triazolium salts of the type **7** or their ring opened products. In connection with our research concerning heterocyclic rearrangements of azole derivatives, and with the aim of synthetizing indazoles of the type **6**, we planned to investigate LTA oxidation of both *(E)*- and *(Z)*-phenylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole **8**, 3-benzoyl-5-phenylisoxazole **11**, and 3-benzoyl-4-methyl-1,2,5-oxadiazole **14**.

Synthesis and characterization of *(E)*- and *(Z)*-phenylhydrazones **8** [5] and **11** [6] have been previously described. As for 3-benzoyl-4-methyl-1,2,5-oxadiazole, Ponzio reported [7] the synthesis of two phenylhydrazone isomers, namely, an α-isomer (mp 101°) and a β one (mp 213°). Spectroscopic evidences (uv and nmr) allowed us to assign the *Z* and *E* structure, **14Z** and **14E**, respectively. Isomer **14Z** is yellow [uv-visible spectrum in ethanol: λ max 240 nm (log ϵ, 4.20), 350 nm (4.18)], whereas isomer **14E** is colourless [λ max 235 (3.99), 335 (4.24)]. The nmr spectrum of **14Z** in deuteriochloroform shows the NH proton at δ 9.55,

SCHEME 1



SCHEME 2



whereas in the case of **14E**, the NH proton resonates at δ 8.10. In DMSO, the NH proton resonates at δ 9.95 and 9.70, respectively. As for the methyl protons, in **14Z** they resonate at δ 2.05, whereas in **14E** they resonate at δ 2.75, as a consequence of the different effect of the phenyl ring and/or the exocyclic C=N bond in the two isomers.

Oxidation reactions were performed in acetic acid or in anhydrous benzene as solvent, but a cleaner reaction was found in the last solvent at room temperature. Starting from *(E)*-phenylhydrazones as well as from the *(Z)*- ones, we obtained the same oxidation product, to which we assign the azoacetate structure **9** (70%), **12** (90%), and **15** (90%). The nmr spectra, besides other signals, showed the resonance of methyl protons in the range of δ 2.30-2.40, ir spectra showed the characteristic absorption band at 1750-1765 cm^{-1} for *O*-acetyl group, and uv spectra showed a low intensity band at 395 nm characteristic for a Ph-N=N- group [1a]. In the oxidation reactions, performed in our experimental conditions, we were not able to take compounds deriving from a triazolium structure of the type **7** [8].

We next explored the reactivity of azoacetates towards a Lewis acid which should have formed an electrophilic sequence available to an attack by the phenyl ring as well as by the azole ring through its nitrogen atom. It is well known [3], however, that azoacetates deriving from the arylhydrazones of 3-benzoyl(or 4-benzoyl)pyridine, or of 2-benzoylthiophene, give pyridylindazoles or thienopyrazoles, respectively, accordingly with the different reactivity towards aromatic electrophilic substitution. In our case, only the indazolic cyclization would be expected, unless the ring opening of the azole nucleus containing a weak O-N bond could furnish a driving force in a reaction of the type **5** to **7**.

Indazolic cyclization was generally achieved by treating azoacetates with a Lewis acid, such as boron trifluoride-ether complex or aluminium chloride in aprotic solvents. We found that, when added as a benzene solution to a suspension of aluminium chloride in benzene at room temperature, azoacetates **9**, **12**, and **15** smoothly gave indazoles **10**, **13** and **16**, respectively. In the case of the reaction on azoacetates **12** and **15**, indazoles **13** and **16** were obtained in nearly quantitative yield. In the case of the reaction on the azoacetate **9**, a lower yield of the indazole **10** was obtained. However, by performing the reaction in a very dilute benzene solution, yield of **10** goes to 60%.

Structure of indazoles **10, 13**, and **16** were assigned on the basis of their formation, analytical data and spectroscopic evidences. The nmr spectra showed all foreseen signals and mass spectra presented characteristic fragmentation patterns for azole derivatives [9].

Obtainement of indazoles **10, 13** and **16**, characterized by the presence of an azole substituent, constitutes an useful tool for the synthesis of indazole derivatives variously substituted in the 3 position, since the azole rings are known to behave as synthons for heterocyclic synthesis through ring rearrangements.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus. The ir spectra (nujol) were determined with a Perkin Elmer 257 instrument, uv spectra (ethanol) with a Zeiss PMQ II spectrophotometer, ^{1}H nmr spectra (60 MHz) (deuteriochloroform) with a Varian EM 360 spectrometer (tetramethylsilane as internal standard), and mass spectra with a JEOL JMS 01-SG-2 instrument (75 eV). Dry column chromatography was performed on a Riedel silica gel column (0.063-0.2 mm) deactivated with water (15%). Light petroleum refers to that fraction boiling in the range 40-60°.

(E)- and *(Z)*-phenylhydrazones **8** [5] and **11** [6] were prepared as previously reported. From 3-benzoyl-4-methyl-1,2,5-oxadiazole we prepared the two phenylhydrazone isomers. Thus, to a solution of the ketone (2 g) in ethanol (20 ml) containing acetic acid (6 ml) phenylhydrazine (3 ml) was added and the mixture was heated in a water bath for 20 minutes. After standing 5 hours at room temperature, the precipitate was filtered off giving the *(E)*-phenylhydrazone **14E** (0.6 g). Dilution of the mother liquor with the minimum of water and filtration gave the *(Z)*-phenylhydrazone **14Z** (1.2 g).

(E)-Phenylhydrazone **14E**.

This compound had mp 214° (from ethanol), lit [7] mp 213°; uv: λ max (log ε) 235 nm (3.99), 335 (4.24); ir: 3300 cm^{-1} (NH); nmr: δ 2.75 (s, Me, 3H), 7.0-8.0 (m, aromatic, 10H), 8.10 (s, NH, 1H).

(Z)-Phenylhydrazone **14Z**.

This compound had mp 105° (from benzene-light petroleum), lit [7] mp 101°; uv: λ max (log ε) 240 nm (4.20), 350 (4.18); ir: 3320 cm^{-1} (NH); nmr: δ 2.05 (s, Me, 3H), 7.5-8.5 (m, aromatic, 10H), 9.55 (s, NH, 1H).

Lead Tetraacetate Oxidation. General Procedure for Azoacetates.

To a stirred solution of *(E)*- or *(Z)*-phenylhydrazone (4 mmoles) in anhydrous benzene (200 ml) lead tetraacetate (6 mmoles) was added in three portions. The mixture was stirred at room temperature until tlc analysis revealed the disappearance of the starting phenylhydrazone (about 30 minutes). At the end of the reaction, water (300 ml) was added and the mixture was extracted three times with benzene. The benzene layer was washed successively with water, dilute sodium hydrogen carbonate until free of acetic acid, with water again, and then dried over sodium sulfate. The benzene was removed under reduced pressure and the product isolated.

Azoacetate **9**.

The crude material as above was chromatographed with light petroleum-ethyl acetate (20:1), giving the azoacetate **9** (70%), mp 112-114° (from ethyl acetate-light petroleum); uv: λ max (log ε) 260 nm (4.49), 395 (2.47); ir: 1765 cm^{-1} (C=O); nmr: δ 2.45 (s, Me, 3H), 7.30-8.40 (m, aromatic, 15H).

Anal. Calcd. for $C_{23}H_{18}N_4O_3$: C, 69.33; H, 4.55; N, 14.06. Found: C, 69.50; H, 4.70; N, 14.20.

Azoacetate **12**.

The crude material was taken up with ethanol and filtered, giving pure **12** (90%), mp 136-138° (from ethanol); uv: λ max (log ε) 271 nm (4.48), 395 (2.41); ir: 1755 cm^{-1} (C=O); nmr: δ 2.30 (s, Me, 3H), 6.95 (s, CH, 1H), 7.35-8.20 (m, aromatic, 15H).

Anal. Calcd. for $C_{24}H_{19}N_3O_3$: C, 72.53; H, 4.82; N, 10.57. Found: C, 72.65; H, 4.90; N, 10.50.

Azoacetate **15**.

The crude material was taken up with ethanol and filtered, giving pure **15** (90%), mp 85° (from ethanol); uv: λ max (log ε) 280 nm (4.10), 390 (2.36); ir: 1750 cm^{-1} (C=O); nmr: δ 2.30 and 2.35 (2 singlets, 2 × Me, 6H), 7.40-8.20 (m, aromatic, 10H).

Anal. Calcd. for $C_{18}H_{16}N_4O_3$: C, 64.27; H, 4.80; N, 16.66. Found: C, 64.40; H, 4.90; N, 16.50.

1-Phenyl-3-(5-phenyl-1,2,4-oxadiazol-3-yl)indazole (**10**).

To a well stirred suspension of aluminium chloride (1.3 g) in anhydrous benzene (300 ml) at room temperature, a solution of the azoacetate **9** (0.3 g) in benzene (200 ml) was added over two hours. At the end of the reaction the mixture was poured into water. The benzene solution was separated, washed successively with water and dilute sodium hydrogen carbonate, and then dried over sodium sulfate and evaporated. Chromatography of the crude residue with light petroleum-ethyl acetate (20:1) gave 0.15 g (60%) of the indazole **10**, mp 170° (from ethanol); uv: λ max (log ε) 250 nm (4.54), 314 (4.26); nmr: δ 7.4-8.7 (m, aromatic); ms: m/z (abundance) 338 (M$^+$, 100), 235 (58), 105 (36), 77 (94), 51 (37).

Anal. Calcd. for $C_{21}H_{14}N_4O$: C, 74.54; H, 4.17; N, 16.56. Found: C, 74.65; H, 4.30; N, 16.70.

1-Phenyl-3-(5-phenylisoxazol-3-yl)indazole (**13**).

To a well stirred suspension of aluminium chloride (0.4 g) in anhydrous benzene (70 ml) at room temperature, a solution of the azoacetate **12** (0.5 g) in benzene (30 ml) was added over 30 minutes. At the end of the reaction, the previous procedure was followed, and the residue from benzene was taken up with light petroleum and filtered, giving 0.4 g (94%) of the indazole **13**, mp 116° (from ethanol); uv: λ max (log ε) 252 nm (4.51), 313 (4.31); nmr: δ 7.4 (s, CH, 1H), 7.50-8.70 (m, aromatic, 14H); ms: m/z (abundance) 337 (M$^+$, 17), 235 (5), 105 (43), 77 (100), 51 (65).

Anal. Calcd. for $C_{22}H_{15}N_3O$: C, 78.32; H, 4.48; N, 12.46. Found: C, 78.20; H, 4.55; N, 12.50.

1-Phenyl-3-(4-methyl-1,2,5-oxadiazol-3-yl)indazole (**16**).

This compound was obtained by the procedure adopted for **13**. Starting from 0.5 g of the azoacetate **15** and 0.4 g of aluminium chloride, we obtained 0.4 g (97%) of the indazole **16**, mp 148° (from ethanol); uv: λ max (log ε) 248 nm (4.30), 314 nm (4.21); nmr: δ 2.8 (s, Me, 3H), 7.50-8.70 (m, aromatic, 9H); ms: m/z (abundance), 276 (M$^+$, 86), 235 (100), 219 (35), 192 (18), 77 (60), 51 (44).

Anal. Calcd. for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.70; H, 4.30; N, 20.40.

Acknowledgements.

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