THE PREPARATION AND LEAD TETRAACETATE OXIDATION OF MIXED BISAROYL HYDRAZONES OF BIACETYL TO 1-(α-AROYLOXYARYLIDENEAMINO)-3,5-DIMETHYL-1,2,3-TRIAZOLES

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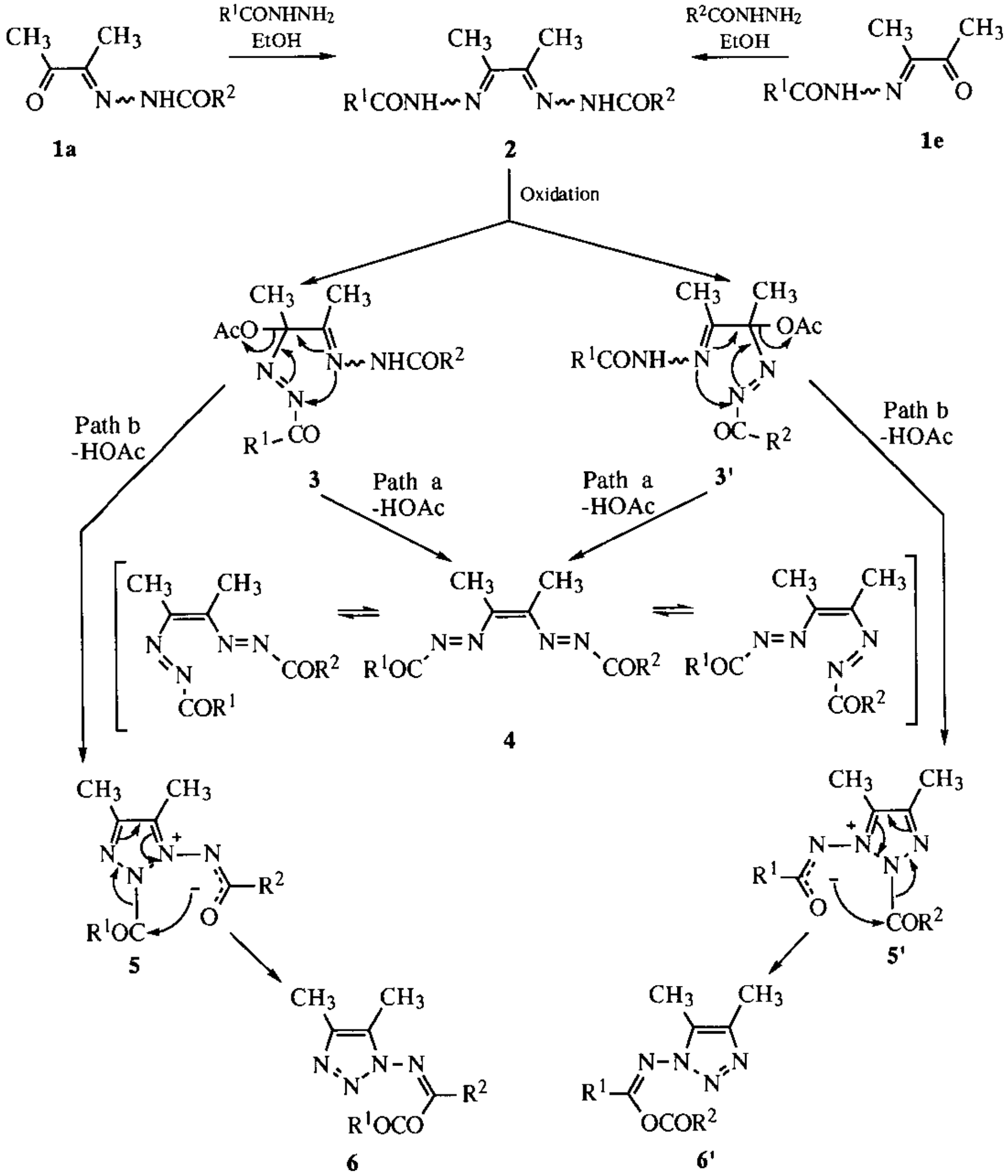
Abstract – The preparation and lead tetraacetate oxidation of the mixed aroyl hydrazones of biacetyl (**2**) to the pairs of isomeric 1-(α-aroyloxyarylideneamino)-3,5-dimethyl-1,2,3-triazoles (**6**) and (**6'**) is described. The product ratio of **6/6'** is evaluated in terms of the stability imparted to the zwiterionic intermediate (**5**) by the different substituents on the aroyl groups.

The oxidation of bisacyl hydrazones of α-dicarbonyl compounds (**2**) ($R^1 = R^2$) is a general oxidative cyclization reaction which leads to 1-amino-1,2,3-triazole derivatives such as **6** ($R^1 = R^2$) and **7**.[1-6] The main oxidation products of bisaroyl hydrazones of α-dicarbonyl compounds in particular, in spite some early disputes,[7,8] are now generally considered as being 1-aroyloxylarylideneamino-1,2,3-triazoles (**6**, isoimides[1,4]). Although many aspects of the mechanism which leads to the isoimides (**6**) have been clarified over the past decades,[9,10] the course of the reaction under the influence of two different substituents on the aroyl group remained unexplored, mainly because of the difficulties encountered in the synthesis of mixed bisaroyl hydrazones (**2**) ($R^1 \neq R^2$).[2]

In the present work we report the synthesis and the oxidative cyclization of mixed bisaroyl hydrazones of biacetyl (**2**) with lead tetraacetate. Also, on the basis of product analysis, we draw conclusions relating to the oxidation mechanism.

The title mixed bisaroyl hydrazones of biacetyl (**2**) were prepared from the appropriate biacetyl monoaroyl hydrazone (**1**) and the corresponding aroyl hydrazine (Scheme 1). It was found that both the sequence of hydrazone formation (introduction of the appropriately substituted hydrazone moiety first) and the conditions of the condensation (i.e. composition of the solvent system and duration of heating) exerted great influence on the outcome of the reaction with respect to the homogeinity of the isolated products.

In the Table the results of both the synthesis of mixed bisaroyl hydrazones (**2**) and their oxidation are summarized.



a. $R^1 = 4\text{-}CH_3OC_6H_4$, $R^2 = C_6H_5$
b. $R^1 = 4\text{-}CH_3C_6H_4$, $R^2 = C_6H_5$
c. $R^1 = 4\text{-}ClC_6H_4$, $R^2 = C_6H_5$
d. $R^1 = 4\text{-}O_2NC_6H_4$, $R^2 = C_6H_5$
e. $R^1 = 4\text{-}CH_3OC_6H_4$, $R^2 = 4\text{-}O_2NC_6H_4$

Scheme 1

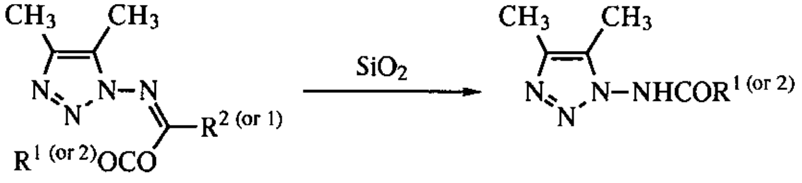
Table. Preparation and Oxidation of Mixed Bisaroyl Hydrazones (**2**) with Lead Tetraacetate [a].

	Isolated Yields (%)		
Entry	Hydrazone **2**	Isoimides (**6**+**6'**)	Ratio **6**/**6'** [b]
a	61	77	1.9
b	59	85	1.0
c	87	81	1.2
d	86	83	0.8
e	84	90	3.0

[a] Methylene chloride at room temperature.

[b] No product interconversion took place during the oxidation and the following work-up, as control experiments demonstrated.

Since the isoimides (**6**) are hydrolyzed to the corresponding 1-aroylamino-1,2,3-triazoles (**7**) (Scheme 2), when subjected to column chromatographic separation on silica gel, the mixture composition of the isomeric isoimides (**6**) and (**6'**) was determined by analyzing the ^{1}H NMR spectrum of the reaction mixture obtained after the oxidation procedure. The integration of the signals corresponding to the 5-methyl protons was primarily used. The assingment of the 5-methyl signals to the corresponding isoimides (**6** or **6'**) was aided by spiking the analysis mixture, after integration, with authentic samples of one of the isomeric isoimides which was prepared for this purpose following known literature procedures.[11,12]



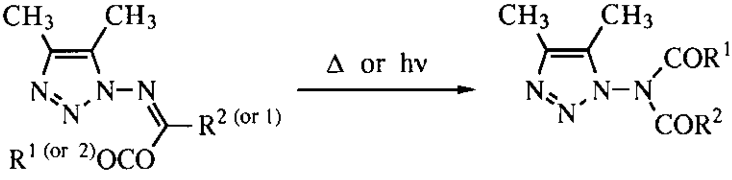
6 (or **6'**)

7

Scheme 2

Inspection of Scheme 1, which is based on literature propositions regarding the mechanism of the oxidation reaction,[2,4,10] reveals that the relative stability and ease of formation of the presumed intermediates (**5**) and (**5'**) controls the ratio of **6**/**6'**. This holds true both in the direct formation of **5** from **3** and in the formation of **5** *via* the bisazoethylene compound (**4**). Consequently one would expect electron donating substituents on the aroyl group attached to the triazole ring to stabilize intermediate (**5**), while electron withdrawing substituents stabilize the same intermediate when attached to the aryl group of the ambident site. The results depicted in the Table are consistent with the above analysis. The lowest and highest ratios **6**/**6'** are realized during the oxidation of **2d** (R^1= 4-$O_2NC_6H_4$, R^2= C_6H_5) and **2e** (R^1= 4-$CH_3OC_6H_4$, R^2= 4-$O_2NC_6H_4$) respectively (Table). However, the oxidation of **2b** (R^1= 4-$CH_3C_6H_4$, R^2= C_6H_5) and **2c** (R^1= 4-ClC_6H_4, R^2= C_6H_5) deviates from this general trend. It is likely that free radicals are precursors of a fraction of the products (**6**) and (**6'**).[13] With polar substituents this fraction seems to be small and the oxidation reaction follows basically an anionic pathway, while in the presence of relatively non-polar substituents the free-radical pathway gains significance. The unsatisfactory fit of the ratios **6b/6′b** and **6c/6′c** to the general trend possibly reflects the change in emphasis from an ionic to a radical mechanism.

In conclusion, the experimental conditions described here for the synthesis of mixed bisaroyl hydrazones of biacetyl lead generally to good yields for these compounds. The presence of the two different substituents could be used to "fine tune" the formation of analytically usefull metal complexes which hydrazones and in particular aroyl hydrazones are known to form.[14] On the other hand, the synthetic utility of the oxidative cyclization of mixed hydrazones remains important despite the fact that it leads to mixtures of the isoimides (**6**) and (**6'**), since it is easy in principle to convert both isoimides, thermally or photochemically to the same imide (**8**) (Scheme 3).[11,12,15] The latter have been shown to be effective photoinitiators for the polymerization of methyl methacrylate.[16]



6 (or **6'**)

8

Scheme 3

EXPERIMENTAL

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded for Nujol mulls on a Perkin-Elmer 297 or 257 spectrophotometer calibrated with the 1602 cm^{-1} absorption of polystyrene. Proton NMR spectra were obtained in deuteriochloroform solution with TMS as internal standard, using a Bruker AW 80 or a Bruker AM 300 instrument. The MS were recorded from a VG Tritech TS-250 spectrometer and elemental microanalyses were performed with a Perkin-Elmer 240 B analyzer. The reactions were monitored by TLC using pre-coated 0.25-mm Merck silica gel 60 F_{254} plates, and the spots were visualized under UV light. All solvents were purchased from Fluka and were purified according to established procedures.[17]

Aroyl hydrazones of biacetyl (**1a**)),[18], and (**1e**) were prepared as described in the appropriate section (preparation of aroyl hydrazones (**1**) and were identified from their IR and NMR spectra, melting points and analyses. The reference compounds 1-(α-aroyloxyarylideneamino)-4,5-dimethyl-1,2,3-triazoles (**6a-e**) and (**6'a-e**) were prepared by addition of aroyl chloride to the sodium salt of the appropriate 1-aroylamino-4,5-dimethyl-1,2,3-triazoles at -50 to -110 °C.[11,12] The oxidation of the mixed bisaroyl hydrazones (**2**) with lead tetraacetate is described bellow.

General Procedure for the Preparation of Biacetyl Monoaroyl Hydrazones (1).

To a hot solution of aroylhydrazine (20 mmol) in ethanol (~30 mL) biacetyl (25 mmol) was added. The mixture was refluxed for ~1 h and after cooling, was suction filtered to yield the crude monoaroyl hydrazone (**1**). Further purification was achieved by recrystallization from ethanol.

*Biacetyl mono-4-Methoxybenzoyl Hydrazone (**1e**)*

This compound was obtained as pale yellow crystalls in 82% yield, mp 158.5 - 159.5 °; IR (nujol): 3230, 1692, 1655, 1605, 1258, 1175, 1028, 845 cm^{-1}; ^{1}H NMR (300 MHz): δ 7.79 (d, J=8.5 Hz, 2H, aromatic *m*- to CH_3O), 6.84 (d, J=8.5 Hz, 2H, aromatic *o*- to CH_3O), 3.82 (s, 3H, CH_3O), 2.04 (s, 3H, CH_3C=N-); MS: m/z 235 (M+1$^+$, 15.7), 191 (25.2), 135 (100), 107 (32.2), 92 (81.4); Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.56; H, 6.17; N, 12.02.

*General Procedure for the Preparation of Biacetyl Mixed Bisaroyl hydrazones (**2**).*

To a hot, clear (freshly filtered) solution of biacetyl monoaroyl hydrazone (**1**) (10 mmol) in ~60 mL of ethanol, aroyl hydrazine (12 mmol) in ~10 mL of ethanol was added. The mixture was refluxed until a considerable amount of the product (~50% of the total yield) precipitated (~0.5 h) and then filtered *in vacuo* while hot. The crude product was filtered and purified by repeated washings with boiling ethanol. The filtrate upon further refluxing gave additional crops of product of lower purity.

*Biacetyl α-Benzoylhydrazino 4-Methoxybenzoyl Hydrazone (**2a**)*

This compound was obtained as colorless crystalls in 61% yield, mp 298 - 300 °; IR (nujol): 3256, 1658, 1642, 1274, 1184, 1016, 842, 758 cm^{-1}; MS: m/z 352 (M$^+$, 1), 135 (99), 105 (48), 92 (84), 77 (100); Anal. Calcd for $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.72; N, 15.90. Found: C, 64.63; H, 5.63; N, 15.97.

*Biacetyl α-Benzoylhydrazino 4-Methylbenzoyl Hydrazone (**2b**)*

This compound was obtained as colorless crystalls in 59% yield, mp 277 - 280 °; IR (nujol): 3294, 1650, 1520, 1270, 1130, 846, 749 cm^{-1}; MS: m/z 232 (30), 120 (80), 106 (57), 92 (100), 77 (60); Anal. Calcd for $C_{19}H_{20}N_4O_2$: C, 67.84; H, 5.99; N, 16.66. Found: C, 67.83; H, 5.90; N, 16.76.

*Biacetyl α-Benzoylhydrazino 4-Chlorobenzoyl Hydrazone (**2c**)*

This compound was obtained as colorless crystalls in 87% yield, mp 282 - 284 °; IR (nujol): 3256, 1658, 1642, 1274, 1184, 1016, 842, 758 cm^{-1}; MS: m/z 352 (M$^+$, 1), 135 (99), 105 (48), 92 (84), 77 (100); Anal. Calcd for $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.72; N, 15.90. Found: C, 64.63; H, 5.63; N, 15.97.

*General Procedure for the Lead Tetraacetate Oxidation of Mixed Bisaroyl Hydrazones (**2**), to 1-(α-Aroyloxyarylideneamino)-1,2,3-triazoles (**6**).*

To a stirred solution of **2** (2 mmol) in methylene chloride (20 mL), lead tetraacetate (1.06 g, 2.4 mmol) dissolved in the same solvent (20 mL) was added. The slight excess of the oxidant was checked throughout the experiment by the use of potassium iodide-starch paper and maintained, if necessary, by the addition of extra amounts of lead tetraacetate. When all the starting material was consumed the mixture was filtered and the filtrate was washed successively with aqueous sodium thiosulfate and saturated sodium carbonate. The solution after drying with anhydrous sodium sulfate was evaporated under reduced pressure and the residue was used for proton NMR analysis.

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