The Lead Tetraacetate Oxidation of Bisacylhydrazones of α-Diketones: A Scope Re-assesment

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Oxidation of the title compounds yields, besides the reported isoimides **3** and/or the amides **4**, also the imides **5**. The observed product dichotomy is considered as the result of an intramolecular nucleophilic attack on the aroyl group, of the pressumed zwitterionic intermediate **2**, by *O* or *N* present in the ambident *N*-aroylimine site of **2**. The results of AM1 calculations agree with the product studies and both permit the formulation of a set of rules correlating structure and selectivity.

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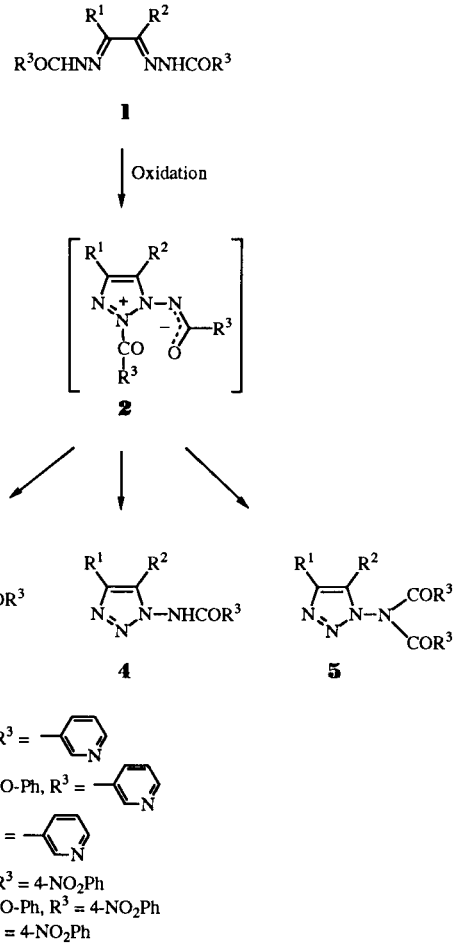
The oxidation of bisacylhydrazones of 1,2-dicarbonyl compounds **1** (R^3 = Ar) with a variety of oxidants has been known to yield generally either 1-(α-aroyloxyarylideneamino)-1,2,3-triazoles (isoimides, **3**) or 1-aroylamino-1,2,3-triazoles (amides, **4**) [1-5] (Scheme 1). On the other hand, the isomeric to isoimides **3**, 1-(*N,N*-bisaroylamino)-1,2,3-triazoles (imides, **5**) were never found amongst the oxidation products.

Scheme 1



The oxidative cyclization presumably proceeds *via* the zwitterionic intermediate **2** in favor of which we have recently provided evidence [6]. The transformation of intermediate **2** to products **3** or **5** can be viewed as an intramolecular nucleophilic attack of its acyl group by *O* or *N* respectively present in the ambient *N*-acylimine site, while the formation of **4** is the result of an intermolecular nucleophilic capture.

When considering the transformations **2** → **3**, **2** → **4** and **2** → **5** from the foregoing point of view, we saw no apparent reason for the reported limitation of the reaction scope to the production of only **3** and **4**. In fact we believed that by selecting conditions which are known to favor attack by the softer site of an ambident nucleophile [7], we could isolate from the oxidation mixture the hitherto unobtainable triazole imides **5**. Our attempts were therefore focused towards the synthesis and oxidation of bisacylhydrazones **1** with strong electron withdrawing substituent R^3 such as nicotinyl, **1a-c**, or 4-nitrophenyl, **1d-f**, which, by destabilizing the positive charge on the carbonyl carbon, would make the nucleophilic attack (stage **2** → **3** or **5**) less charge controlled, and therefore more favorable for the production of **5** [8]. The results of these oxidations are summarized in Table 1.

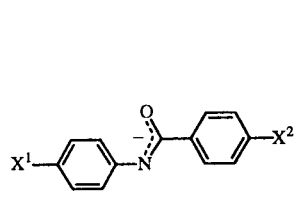
Table 1

Oxidation of Bisacylhydrazones **1** with LTA

Hydrazone	Solvent	Isolated Yields % [a] Isoimide	Amide	Imide	O/N [b]
1		**3**	**4**	**5**	
a	CH_2Cl_2	80	3	–	
b	CH_2Cl_2	73	–	–	
c	C_6H_6	39	–	11	3.5
c	CH_2Cl_2	48	–	32	1.5
c	CH_3CN	8	–	35	0.2
d	CH_2Cl_2	76	–	6	
e	CH_2Cl_2	66	–	–	
f	CH_2Cl_2	31	40	–	

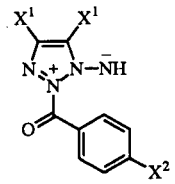
[a] No product interconversion or removal took place during the oxidation and the following work-up, as control experiments demonstrated. [b] % Yield of **3**/% Yield of **5**.

Scheme 2



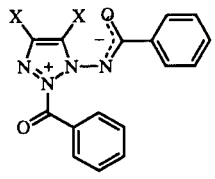
6

X^1 = H, CH_3, Cl, NO_2, CH_3O
X^2 = H, CH_3, Cl, NO_2, CH_3O



7

X^1 = CH_3
X^2 = H, CH_3, Cl, NO_2



8

X = CH_3, Ph, 4-CH_3O-Ph

Benzil hydrazones **1c** and **1f** yielded upon oxidation fair yields of imide **5c** and amide **4f** respectively in addition to isoimides **3c** and **3f**. Products **5c** and **4f**, although different structurally, both owe their formation to the diminished nucleophilicity of the *O* atom in intermediate **2** and consequently are produced at the expense of isoimide **3**. While *N* attack is realized with **2c** and must be favorable with **4f** as well, it is prohibited, apparently for steric reasons introduced by the *p*-NO_2 group, in the latter. The intermolecular capture of the aroyl group therefore in **2f** led to the amide **4f**.

Another important aspect, gleaned from the results of Table 1, is that however important the influence of the substituents in the acyl moiety might be, it can totally be offset by appropriate selection of the substituents R^1. In particular by increasing the electron donating ability of the latter (*i.e.* on going from **1c** → **1b** → **1a**) *O* attack is favored while *N* as such is totally suppressed.

Although difficult to rationalize at this stage solvent seems to have a profound effect on the outcome of the oxidation reaction. Polar aprotic solvents tend to favor *N* attack while non polar ones promote *O* attack (Table 1).

Motivated by the need to establish a set of simple rules governing the outcome of this synthetically useful [5] and general reaction we executed a series of AM1 calculations [9] related to the product dichotomy which results from the ambident nature of the presumed zwitterionic intermediate **2**.

The calculations were carried out assuming planarity of the triazole and phenyl rings present, as well as strict tetrahedral environment around the sp^3 carbon atoms. Due to the complexity of the target systems and aiming at the best possible generalization of the final results, we studied a series of model compounds gradually building up intermediate **2** (Scheme 2) from smaller fragments containing the same ambident site.

In the first step, model compounds **6** were studied at their optimized geometries. The effect of substituents X^2 on both the atomic charges and the energies of the "active" orbitals of the ambident nucleophilic site is negligible. The nature of the FMOs is not affected by the X^1 substituents either, except in the case of X^1 = NO_2, where both *O* and *N* net charges are lowered (*i.e. O* from −0.490 to −0.448 e, and *N* from −0.430 to −0.410 e, relative to the unsubstituted model). A localization performed reveals that the n_o orbital is always lower in energy than the n_N one, the energy difference depending on the nature of the substituent X^1 and falling in the sequence $CH_3 \cong H > Cl > NO_2$. In view of these results, models **7** were constructed in order to look at the effect of the substituted triazole in **2**. The MOs of the models were studied and were found practically insensitive to the substituents X^2, except in the case of X^2 = NO_2, where the HOMO of the system is mainly localized on the N-NH^- region.

Finally models **8** were examined, in order to investigate the electronic effects originating from the substituents at positions 4 and 5 of the triazole ring. Regarding the net atomic charges on *O* and *N*, it seems that methyl substitution slightly favors nucleophilic attack by *N* (q_N/q_O = 1.16) while phenyl or 4-methoxyphenyl strongly favor *O* attack (q_N/q_O = 0.21 and 0.25 respectively). The same trend could be implied with respect to the concomitant *N vs. O* attack were the reaction (**2** → **3** or **5**) charge controlled. Since this contrasted the experimental evidence, attention was drawn to the MOs of the systems which were mainly localized on the ambident site. The localization of these MOs in the methyl compound **8** (X = CH_3) is much more prevalent than in the phenyl **8** (X = Ph) or 4-methoxyphenyl **8** (X = 4-CH_3O-Ph). Taking into consideration the value c_N/c_O, *i.e.* the contribution of *N* and *O* in the specific MO, an enhanced *N* nucleophilicity is predicted for the phenyl substituted compound (c_N/c_O = 2.42), and a more balanced (c_N/c_O = 1.25) for the methyl, whereas an enhanced *O* nucleophilicity is expected for the 4-methoxyphenyl compound (c_N/c_O = 0.68), in perfect agreement with the results presented in Table 1.

In conclusion, the oxidation of the title compounds can, in principle, yield three different products: the isoimide **3**, the imide **5** and the amide **4**. Products **3** and **5** are the results of the bidentate nature of the presumed intermediate **2** and are formed in an intramolecular reaction. Product **4** is obtained when either *O* or *N* attack is hindered

[10] for steric reasons. When planning a synthesis, it is of interest to note that formation of isoimide **3** is favored by the use of: *a.* Electron donating substituents on both the acyl group and on the methine carbon atom and *b.* Non polar aprotic solvents. The opposite conditions are expected to favor formation of imide **5**.

EXPERIMENTAL

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded for Nujol mulls on a Perkin-Elmer 297 or 257 spectrometer 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 instrument. The mass spectra were recorded from a VG Tritech TS-250 spectrometer and elemental microanalyses were performed with a Perkin-Elmer 240B 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 used were purchased from Fluka and were purified according to established procedures [11].

Compounds **1d** [12], **3d** [13], **5d** [13], **1f** [14] and **3f** [14] were identified from their reported mp's and spectra. Bisacylhydrazones **1** were prepared by refluxing the diketone with the corresponding hydrazide in ethanol solution [13]. Unless otherwise specified, further purification was achieved by repeated washings with hot ethanol. In the case of **1b** and **1e** the condensation was achieved by heating the homogenized mixture of the starting materials for 0.5 hour at 150°.

Biacetyl Bisnicotinoylhydrazone (**1a**).

The yield of **1a** was 64%, pale yellow crystals, mp 283-285°; ir (Nujol): 3190, 3090, 1680, 1591, 1462, 1155, 694, cm^{-1}; ms: m/z (relative intensity) 324 ($M^{+\cdot}$, 8), 218 (56), 203 (14), 123 (14), 106 (100), 78 (77), 68 (48).

Anal. Calcd. for $C_{16}H_{16}N_6O_2$ (324.34): C, 59.25; H, 4.97; N, 25.21. Found: C, 58.98; H, 4.89; N, 25.36.

4,4'-Dimethoxybenzil Bisnicotinoylhydrazone (**1b**).

The yield of **1b** was 67%, pale yellow crystals, mp 233-234°; ir (Nujol): 3155, 1638, 1588, 1512, 1033, 835, cm^{-1}; ms: m/z (relative intensity) 507 ($M^{+\cdot}$-1, 13), 374 (16), 270 (64), 252 (100), 134 (44), 106 (82), 78 (78).

Anal. Calcd. for $C_{28}H_{24}N_6O_4$ (508.52): C, 66.13; H, 4.76; N, 16.53. Found: C, 66.20; H, 4.85; N, 16.43.

Benzil Bisnicotinoylhydrazone (**1c**).

The yield of **1c** was 59%, pale yellow crystals, mp 228-231° (ethanol): ir (Nujol): 3392, 3200, 1675, 1594, 1282, 1140, 732, cm^{-1}; ms: m/z (relative intensity) 447 ($M^{+\cdot}$-1, 8), 210 (54), 192 (40), 165 (34), 132 (32), 106 (100), 78 (94).

Anal. Calcd. for $C_{26}H_{20}N_6O_2$ (448.47): C, 69.63; H, 4.50; N, 18.74. Found: C, 69.78; H, 4.66; N, 18.87.

4,4'-Dimethoxybenzil Bis-4-nitrobenzoylhydrazone (**1e**).

The yield of **1e** was 57%, pale yellow crystals, mp 266-268°; ir (Nujol): 3135, 1650, 1600, 1512, 1253, 1032, 718, cm^{-1}; ms: m/z (relative intensity) 297 (4), 252 (40), 238 (100), 223 (42), 150 (63), 135 (40), 104 (43).

Anal. Calcd. for $C_{30}H_{24}N_6O_8$ (596.54): C, 60.40; H, 4.06; N, 14.09. Found: C, 60.63; H, 3.95; N, 13.83.

Lead Tetraacetate Oxidation of Benzil Bisnicotinoylhydrazone (**1c**) in Methylene Chloride, to 1-(α-Nicotinoyloxynicotinylideneamino)-4,5-diphenyl-1,2,3-triazole (**3c**) and to 1-(*N,N*-Bisnicotinoylamino)-4,5-diphenyl-1,2,3-triazole (**5c**).

To a stirred suspension of **1c** (1.12 g, 2.5 mmoles) in methylene chloride (50 ml), lead tetraacetate (1.6 g, 3.0 mmoles) 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 additon of extra amounts of lead tetraacetate. After the starting material was consumed (usually after 1-2 hours) workup of the mixture involved filtration of the (mostly) insoluble Pb(II) salts, extraction of the filtrate with sodium thiosulphate, washing with sodium bicarbonate and water, and evaporation of the solvent from the dried solution in order to get the crude reaction mixture. Treatment of the mixture with diethyl ether followed by filtration gave 0.54 g (48%) of **3c** as the insoluble solid, while evaporation of the filtrate left 0.36 g (32%) of **5c**. The products were further purified by recrystallization in order to obtain samples for elemental analyses and spectra.

According to the general procedure described above all bisacylhydrazones **1** were oxidized. Product yields are reported in Table 1.

1-(α-Nicotinoyloxynicotinylideneamino)-4,5-dimethyl-1,2,3-triazole (**3a**).

This compound was obtained as colorless crystals, mp 114-116° (methanol); ir (Nujol): 1755, 1632, 1600, 1266, 1062, 1014, 716, cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.22 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 7.07-7.70 (m, 1H), 8.11-8.58 (m, 1H), 8.63-9.02 (bs, 1H), 9.11-9.45 (bs, 1H); ms: m/z (relative intensity) 323 ($M^{+\cdot}+1$, 32), 294 (26), 106 (100), 78 (65), 68 (29), 51 (30).

Anal. Calcd. for $C_{16}H_{14}N_6O_2$ (322.32): C, 59.62; H, 4.38; N, 26.07. Found: C, 59.65; N, 4.26; N, 26.02.

1-(α-Nicotinoyloxynicotinylideneamino-4,5-bis(4-methoxyphenyl)-1,2,3-triazole (**3b**).

This compound was obtained as colorless crystals, mp 159-160° (ethyl acetate); ir (Nujol): 1760, 1588, 1250, 1072, 1015, 841, 723 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.77 (s, 3H, CH_3O), 3.89 (s, 3H, CH_3O), 6.56-9.56 (m, 16H, aromatic); ms: m/z (relative intensity) 478 ($M^{+\cdot}$-N_2, 13), 372 (11), 281 (12), 252 (54), 135 (100), 106 (88), 78 (52).

Anal. Calcd. for $C_{28}H_{22}N_6O_4$ (506.50): C, 66.39; H, 4.38; N, 16.59. Found: C, 66.20; H, 4.40; N, 16.38.

1-(α-Nicotinoyloxynicotinylideneamino)-4,5-diphenyl-1,2,3-triazole (**3c**).

This compound was obtained as colorless crystals, mp 161-162° (ethyl acetate); ir (Nujol): 1760, 1637, 1589, 1251, 1072, 1001, 695, cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.97-9.54 (m, 18H, aromatic); ms: m/z (relative intensity) 478 ($M^{+\cdot}+1$, <1), 418 ($M^{+\cdot}$-N_2, 7), 312 (4), 192 (33), 178 (15), 165 (12), 106 (100), 78 (63).

Anal. Calcd. for $C_{26}H_{18}N_6O_2$ (446.45): C, 69.94; H, 4.06; N, 18.83. Found: C, 70.00; H, 3.89; N, 18.81.

1-(α-4-Nitrobenzoyloxy-4-nitrobenzylideneamino-4,5-bis(4-methoxyphenyl)-1,2,3-triazole (**3e**).

This compound was obtained as mustard yellow crystals, mp 157-158° (ethyl acetate); ir (Nujol): 1765, 1605, 1525, 1254, 1177, 1060, 840, cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.77 (s, 3H, CH_3O), 3.89 (s, 3H, CH_3O), 6.65-8.65 (m, 16H, aromatic); ms: m/z (relative intensity) 402 (2), 252 (24), 238 (38), 223 (21), 150 (100), 135 (58), 104 (39).

Anal. Calcd. for $C_{30}H_{22}N_6O_8$ (594.52): C, 60.60; H, 3.73; N, 14.14. Found: C, 60.28; H, 3.62; N, 14.28.

1-(*N*-Nicotinoylamino)-4,5-dimethyl-1,2,3-triazole (**4a**).

This compound was obtained as pale yellow crystals, mp 71-72° (ethanol); ir (Nujol): 3485, 1675, 1590, 1300, 909, 814, 709, cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.13 (s, 6H, CH_3), 6.90-7.70 (m, 2H, H-5, H-6), 8.35 (d, J = 8.0 Hz, 1H, H-4), 8.73 (d, J = 4.0 Hz, 1H, H-2); ms: m/z (relative intensity) 218 ($M^{+\cdot}+1$, 95), 189 ($M^{+\cdot}-N_2$, 24), 122 (16), 106 (100), 78 (57), 68 (65), 42 (49).

Anal. Calcd. for $C_{10}H_{11}N_5O$ (217.23): C, 55.29; H, 5.10; N, 32.24. Found: C, 55.19; H, 5.24; N, 32.10.

1-(*N,N*-bisnicotinoylamino)-4,5-diphenyl-1,2,3-triazole (**5c**).

This compound was obtained as colorless crystals, mp 176-177° (ethanol); ir (Nujol): 1705, 1584, 1529, 1280, 1150, 961, 706, cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.00-8.20 (m, 14H, aromatic), 8.64 (d, J = 5.0 Hz, 2H, H-4), 8.85 (d, J = 8.0 Hz, 2H, H-2); ms: m/z (relative intensity) 446 ($M^{+\cdot}$, 7), 340 (2), 106 (14), 105 (100), 78 (14), 77 (22), 51 (3).

Anal. Calcd. for $C_{26}H_{18}N_6O_2$ (446.45): C, 69.94; H, 4.06; N, 18.83. Found: C, 69.88; H, 3.88; N, 18.90.

Hydrolysis of 1-(α-4-Nitrobenzoyloxy-4-nitrobenzylideneamino)-4,5-diphenyl-1,2,3-triazole (**3f**) to 1-(*N*-4-Nitrobenzoylamino)-4,5-diphenyl-1,2,3-triazole (**4f**).

To 5 ml of 1 *M* aqueous solution of potassium hydroxide 1 ml of methanol and 85 mg (0.16 mmole) of **3f** were added. After the isoimide **3f** was dissolved the yellow solution was filtered and the filtrate acidified with glacial acetic acid. The precipitate formed upon acidification was filtered at the pump and after recrystallization from ethanol gave 20 mg (16%) of **4f**, as colorless crystals, mp 222-224°; ir (Nujol): 3122, 1713, 1522, 1261, 824, 755, 692, cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.97-7.65 (m, 10H, aromatic, 4-Ph, 5-Ph), 7.78-8.41 (m, 4H, aromatic, 4-NO_2Ph); ms: m/z (relative intensity) 224 (1), 181 (77), 150 (100), 120 (20), 104 (55), 92 (26), 76 (45).

Anal. Calcd. for $C_{21}H_{15}N_5O_3$ (385.37): C, 65.45; H, 3.92; N, 18.17. Found: C, 65.39; H, 4.06; N, 18.06.

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