Oxidation of Bis-Arylacetylhydrazones of α-Dicarbonyl Compounds

J. Stephanidou-Stephanatou, E. Varella, E. D. Micromastoras and N. E. Alexandrou

Laboratory of Organic Chemistry, University of Thessaloniki, Thessaloniki, Greece

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Oxidation of the title compounds (IV) with lead tetraacetate gives, instead of the expected 1-(α-arylacetyloxyarylethyleneamino)-1,2,3-triazoles, the amides (V), 1-(*N*-arylacetylamino)-1,2,3-triazoles, as the main products in moderate yields. The reaction mechanism is discussed.

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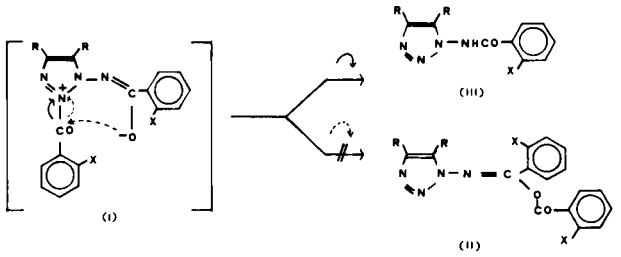
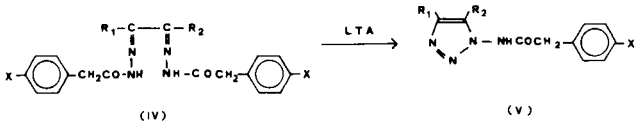
It has been shown (1) previously that in the oxidation of bis-aroylhydrazones of α-dicarbonyl compounds, there are two competing pathways, one leading to isoimides (II) and the other to amides (III). Thus, when the aryls in the hydrazone function are *o*-substituted, the formation of the corresponding amides predominates, since the carbonyl attack by the nucleophilic oxygen in the intermediate (I) (2,3) is sterically retarded.

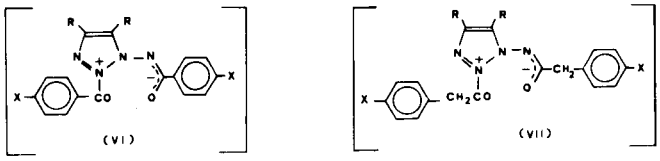


In the course of further work we have undertaken the preparation and oxidation with lead tetraacetate (LTA) of some bis-arylacetylhydrazones of α-dicarbonyl compounds (IV). We have found that the oxidation of IV follows an analogous pathway to that of *o*-substituted bis-hydrazones (1) with the formation of the corresponding 1-(*N*-arylacetylamino)-1,2,3-triazoles (V) without indication for the formation of triazolyl-isoimides.



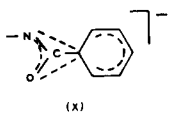
(a) $R_1 = R_2 = CH_3$, X = H
(b) $R_1 = R_2 = CH_3$, X = OCH_3
(c) $R_1 = R_2 = CH_3$, X = NO_2
(d) $R_1 = R_2 = C_6H_5$, X = H
(e) $R_1 = R_2 = C_6H_5$, X = OCH_3
(f) $R_1 = R_2 = C_6H_5$, X = NO_2
(g) $R_1 = C_6H_5$, R_2 = H, X = H
(h) $R_1 = C_6H_5$, $R_2 = CH_3$, X = H
(i) $R_1 = CH_3$, $R_2 = C_6H_5$, X = H

The absence of isoimides in the oxidation products suggests a significant destabilization of the intermediate VII, by insertion of the methylene groups in the reacting system. The instability of the intermediate in this case cannot be attributed to a steric effect, as evidenced by inspection of stereomodels, or to the usual electronic effects. If we consider the two zwitterionic intermediates VI and VII derived from bis-aroylhydrazones and bis-arylacetylhydrazones respectively, it is observed that the inductive effect of the methylene groups in VII should be negligible and it is not possible to alter the reaction pathway. With respect to the resonance effect, the conjugation of the aryl and carbonyl group in VI stabilizes the cationic center by the resonance form VIII but destabilizes the anionic



center by the form IX. Therefore, the interuption of conjugation in VII should have an opposite effect. However, we propose that the difference in stability between the

intermediates VI and VII could be explained considering a nonbonded interaction (4) (homoconjugation) between the anion and the aryl group (X). It is evident that this interaction cannot be operative in VII, and consequently



the reaction path leading to amides will be the predominant one. Another factor which might prohibit the formation of isoimides is the possibility of enolization in the arylacetyl function which hinders the carbonyl attack by the anionic center. It should be noticed however, that the presence of the enol form, at least in the hydrazones (IV), must be negligible, as evidenced by nmr spectroscopy.

It is of interest to note that oxidation of bis-semicarbazones of α-dicarbonyl compounds gives analogously 1,2,3-triazolylureas (5), and oxidation of bis(toluene-*p*-sulphonyl)hydrazones of α-dicarbonyl compounds gives 1,2,3-triazolyl-sulphonamides (6).

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Table I

Analytical Data for the Bis-Arylacetylhydrazone (IV)

Compound No.	M.p. °C	Yield %	Ir (Nujol) cm^{-1}		Nmr (Deuteriochloroform + Trifluoroacetic Acid) (a)				Ms m/e (R.I. %)	Formula	Molecular Weight	Analysis % Calcd.			Found	
			ν NH	ν C=O	δ CH_3	δ CH_2	δ OCH_3	δ Aromatic Protons				C	H	N	C	H	N
IVa	279-281	82	3200	1655	2.23 [6] s	4.16 [4] s	—	7.37 [10] s	M: 350 (2) 259 (2) 231 (35) 203 (6) 118 (61) 91 (100) 68 (54)	$C_{20}H_{22}N_4O_2$	350.4	68.55	6.33	15.99	68.99	6.28	15.89
IVb	272-275	83	3190 3215	1650 1678	2.26 [6] s	4.15 [4] br s	3.90 [6] s	ν_A 6.99 [8] AB ν_B 7.29 system J_{AB} 8 Hz	M: 410 (23) 289 (3) 261 (16) 233 (3) 148 (57) 121 (100) 68 (10)	$C_{22}H_{26}N_4O_4$	410.5	64.37	6.39	13.65	64.34	6.36	13.55
IVc	298-300	80	3190	1660	2.08 2.25 [6] 2.55 three s (b)	3.92 [4] 4.28 two s (b)	—	ν_A 7.52 [8] AB ν_B 8.22 system (b) J_{AB} 9 Hz	M: 440 (<0.5) 276 (11) 220 (100) 163 (31) 137 (50)	$C_{20}H_{20}N_6O_6$	440.4	54.54	4.58	19.08	54.34	4.56	19.06
IVd	195-198	28	3195 3215	1670	—	3.60 [4] 3.65 two s (b)	—	6.90-7.70 [20] m (b)	M: 474 (0.5) 355 (4) 327 (10) 192 (30) 178 (16) 118 (30) 91 (100)	$C_{30}H_{26}N_4O_2$	474.5	75.93	5.52	11.81	75.95	5.47	11.66
IVd	207-211	6	3185	1660	—	3.57 [4] 3.66 two s (b)	—	6.55-7.75 [20] m (b)	M: 474 (<0.5) 355 (21) 327 (6) 192 (6) 178 (11) 118 (52) 91 (100)	$C_{30}H_{26}N_4O_2$	474.5	75.93	5.52	11.81	75.74	5.48	11.75
IVe	216-218 and 221-224	80	3195 3220	1670	—	3.60 [4] br s	3.78 [6] s	ν_A 6.78 [8] AB ν_B 6.92 system J_{AB} 5 Hz 7.10-7.80 [10] m	386 (0.5) M:-148 358 (2) 192 (11) 178 (30) 148 (23) 121 (100)	$C_{32}H_{26}N_4O_4$	534.6	71.89	5.66	10.48	71.93	5.60	9.99
IVf	259-260 and 269-270	78	3200	1670	—	3.83 [4] br s	—	ν_A 6.94 [8] AB ν_B 8.05 system J_{AB} 9 Hz 7.27-7.79 [10] m	(e)	$C_{30}H_{24}N_6O_6$	564.5	63.82	4.29	14.89	63.61	4.30	15.00
IVg	152-155 and 192-194	43	3200	1665	—	3.73 [4] br s	—	6.66-7.97 [16] m (c)	M: 398 (1) 279 (10) 251 (5) 118 (38) 116 (22) 91 (100)	$C_{24}H_{22}N_4O_2$	398.5	72.34	5.57	14.06	72.45	5.55	14.07
IVh	189-190	44	3185	1665	2.23 [3] s (b)	3.55 [2] s (d) 4.11 [2] s	—	6.70-7.70 [15] m (d)	M: 412 (1) 293 (9) 265 (6) 130 (29) 118 (43) 91 (100)	$C_{25}H_{24}N_4O_2$	412.5	72.79	5.87	13.58	73.00	6.00	13.68

Table II

Analytical Data for the 1-(*N*-Arylacetylamino)-1,2,3-triazoles (V)
Obtained from the Oxidation of the Bis-Arylacetylhydrazones (IV)

Compound No.	M.p. °C	Yield %	Ir (Nujol) cm^{-1} ν NH	ν C=O	Nmr (Deuteriochloroform) δ CH$_3$	δ CH$_2$	δ OCH$_3$	δ Aromatic Protons	Ms m/e (R.I. %)	Formula	Molecular Weight	Calcd. C	Calcd. H	Analysis % Found N	Found C	Found H	Found N
Va	163-165	23	3190	1680	1.94 [3] s 212 [3] s	3.65 [2] s	—	7.28 [5] s	M$^+$ 230 (2.5) 202 (25) 118 (15) 91 (100) 68 (26)	$C_{12}H_{14}N_4O$	230.3	62.59	6.13	24.33	62.39	6.09	23.93
Vb	98-99	25	3215	1685	1.92 [3] s 212 [3] s	3.55 [2] s	3.72 [3] s —	ν_A 6.79 [4] AB ν_B 7.17 system J_{AB} 9 Hz	M$^+$ 260 (7) 232 (29) 148 (10) 121 (100) 69 (35)	$C_{12}H_{16}N_4O_2$	260.3	59.98	6.20	21.53	59.92	6.26	21.48
Vc	212-214	80	3190	1700	2.18 [3] s (a) 2.37 [3] s	3.90 [2] s (a)	—	ν_A 7.52 [4] AB ν_B 8.17 system (a) J_{AB} 9 Hz	M$^+$ 275 (c) 247 (36) 163 (26) 136 (66) 68 (100)	$C_{12}H_{13}N_5O_3$	275.3	52.36	4.76	25.45	52.34	4.96	25.35
Vd	218-219	27	3195	1680	—	3.70 [2] s (a)	—	6.90-7.55 [15] m (a)	M$^+$ 354 (<0.5) 326 (20) 192 (35) 118 (21) 103 (79) 91 (100)	$C_{22}H_{18}N_4O$	354.4	74.55	5.12	15.81	74.65	5.18	15.80
Ve	188-189	74	3245	1685	—	3.52 [2] s	3.73 [3] s	ν_A 6.73 [4] AB ν_B 6.95 system J_{AB} 9 Hz 7.15-7.60 [10] m	M$^+$ 384 (0.5) 356 (47) 192 (20) 148 (47) 121 (88) 103 (100)	$C_{23}H_{20}N_4O_2$	384.4	71.86	5.24	14.58	72.01	5.29	14.59
Vf	217-219	55	3185	1685	—	3.86 [2] s (a)	—	7.17-8.30 [14] m (a)	M$^+$ 399 (<0.5) 371 (3.5) 192 (12) 163 (6) 136 (5) 103 (100)	$C_{22}H_{17}N_5O_3$	399.4	66.15	4.29	17.54	66.25	4.32	17.64
Vg	219-220	16	1680	3140		3.90 [2] s (a)	—	7.20-7.80 [11] m (a,b)	M$^+$ 278 (1) 250 (31) 118 (17) 117 (61) 103 (43) 91 (100)	$C_{16}H_{14}N_4O$	278.3	69.05	5.07	20.13	68.68	5.13	20.24
Vh	142-143	16	1705	3170	2.17 [3] s	3.72 [2] s	—	7.10-7.70 [10] m	M$^+$ 292 (1) 264 (24) 130 (36) 118 (22) 91 (100)	$C_{17}H_{16}N_4O$	292.3	69.84	5.52	19.17	69.85	5.52	19.21
Vi	140-141	10	1675	3190	2.33 [3] s	3.64 [2] s	—	7.05-7.55 [10] m	M$^+$ 292 (2) 264 (66) 130 (70) 118 (17) 104 (39) 91 (100)	$C_{17}H_{16}N_4O$	292.3	69.84	5.52	19.17	69.39	5.57	19.29

(a) Nmr solvent: deuteriochloroform containing a few drops of trifluoroacetic acid. (b) CH proton also included. (c) Negligible intensity.

The hydrazone IVd was obtained in two stereochemical forms (m.p. 195-198° and 207-211°) but both of them gave, on oxidation, the same amide Vd in different yields (39%, 13%). On the other hand, oxidation of the hydrazone IVh gave the isomeric amides Vh and Vi. The structural assignment of these products was based on their hydrolysis to the corresponding amino-1,2,3-triazoles. Thus, the product Vh, m.p. 142-143°, gave upon acid hydrolysis, 1-amino-4-phenyl-5-methyl-1,2,3-triazole, m.p. 140-142° (5,7), whereas the product Vi, m.p. 140-141°, gave 1-amino-4-methyl-5-phenyl-1,2,3-triazole, m.p. 69-71° (7).

The amides V show in the mass spectra, similar fragmentation pattern with the isoimides (8). Thus, the low intensity peak of the molecular ion is followed by the more intensive peak ($M^{+\cdot}$)-28. Other prominent peaks are those corresponding to the ions $ArCHC\overset{+\cdot}{O}$ or $ArCH_2\overset{+}{C}O$, Ar-C=C-Ar, $ArC\equiv C\overset{+\cdot}{Ar}$ and $Ar\overset{+}{C}H_2$, which usually appears as the base peak in the spectra. It should be mentioned that the isomeric amides Vh and Vi gave almost the same spectrum, the only difference being in the relative intensity of some ions (Figures 1 and 2). The identification of these two isomers by the mass spectra is problematic.

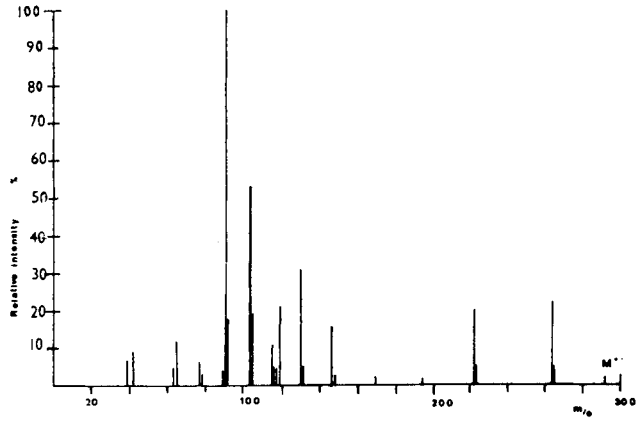

Figure 1: Mass spectrum of 1-(*N*-phenacetylamino)-4-phenyl-5-methyl-1,2,3-triazole (Vh).

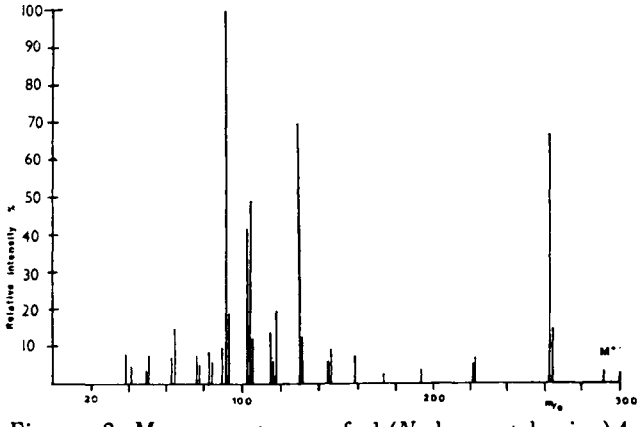

Figure 2: Mass spectrum of 1-(*N*-phenacetylamino)-4-methyl-5-phenyl-1,2,3-triazole (Vi).

EXPERIMENTAL

All melting points are uncorrected and they are obtained with a Kofler hot stage apparatus. Ir spectra were obtained with a Perkin-Elmer Model 257, whereas nmr spectra reported in δ units with a Varian Associates A-60A spectrometer with TMS as internal reference. The mass spectra were obtained with a Hitachi-Perkin-Elmer Model RMU-6L spectrometer with ionization energy 70eV. Analyses were performed with a Perkin-Elmer Model 240 CHN Analyser.

Preparation of Bis-Arylacetylhydrazones of α-Dicarbonyl Compounds (IV).

According to a general procedure (1), the bis-hydrazones were obtained by heating 1 mole of the α-dicarbonyl compound with 2.2 moles of the corresponding hydrazide in *n*-butyl alcohol for 8 hours. The products were pruified by washing repeatedly with hot ethyl acetate and *n*-butyl alcohol (Table I).

Oxidation of Bis-Arylacetylhydrazones with Lead Tetraacetate.

A general procedure (1) is described. To a suspension of 0.02 mole of bis-hydrazone in 40 ml. of methylene chloride, a solution of 0.04 moles of lead tetraacetate in 40 ml. of methylene chloride was added and the mixture was stirred at room temperature for 8 hours. The methylene chloride solution was treated with water and filtered. The organic layer was washed with sodium carbonate solution and water, and then dried. The oil which was left behind was subjected to column chromatography on silica gel (petroleum ether acetate 3:1) and the 1-(*N*-arylacetylamino)-1,2,3-triazoles were isolated and recrystallized from ethanol (Table II). The corresponding ethyl phenylacetates and phenylacetic acids were also isolated moving in the column faster than the triazoles. Their m.p.'s and ir spectra were identical with those described in the literature.

Hydrolysis of 1-(*N*-Phenacetylamino)-4-phenyl-5-methyl-1,2,3-triazole (Vh) and 1-(*N*-Phenacetylamino)-4-methyl-5-phenyl-1,2,3-triazole (Vi).

The phenacetylamino-1,2,3-triazole Vh or Vi (150 mg.) and concentrated hydrochloric acid (20 ml.) were refluxed for 6 hours. The reaction mixture was neutralized with dilute sodium hydroxide solution and extracted with chloroform. Evaporation of the solvent afforded crude 1-amino-1,2,3-triazole in 90% yield; the product was recrystallised from a mixture of petroleum ether/chloroform. Phenacetylamino-1,2,3-triazole (Vh) gave 1-amino-4-phenyl-5-methyl-1,2,3-triazole (5,7), m.p. 140-142°, whereas phenacetylamino-1,2,3-triazole (Vi) gave 1-amino-4-methyl-5-phenyl-1,2,3-triazole, (7), m.p. 69-71°.

Acknowledgment.

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