Synthesis, Structure, and Acylating Properties of 1-Aroyloxy-4,5-dimethyl-1,2,3-triazoles

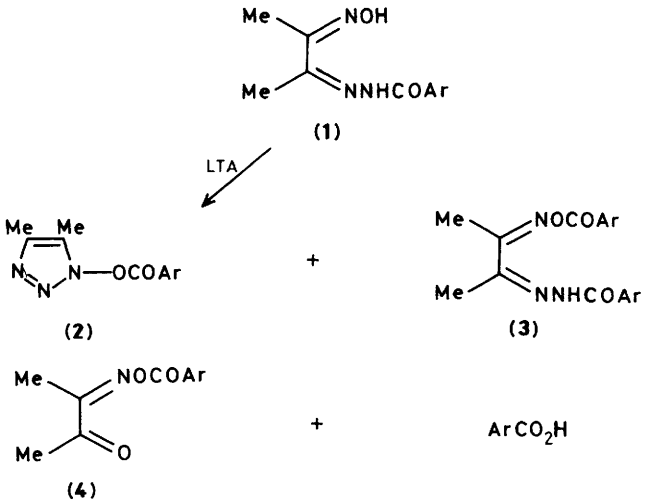
A. B. Theocharis, A. J. Maroulis, C. P. Hadjiantoniou-Maroulis, and N. E. Alexandrou *
Laboratory of Organic Chemistry, Aristotelian University of Thessaloniki, 540 06 Thessaloniki, Greece

Lead tetra-acetate oxidation of α-hydroxyimino aroylhydrazones of biacetyl (**1**) gives 1-aroyloxy-4,5-dimethyl-1,2,3-triazoles (**2**), the structures of which were confirmed by *X*-ray analysis. A mechanism for this reaction is discussed. The products (**2**) are effective aroylating agents for the amino function under mild conditions.

The lead tetra-acetate (LTA) oxidation of nitrogen heteroallylic systems of α-dicarbonyl compounds is a well established synthetic route to nitrogen heterocycles.[1] Until now these LTA oxidations were exclusively restricted to derivatives with the same heteroallylic group[1] (*i.e.* bishydrazones and dioximes *etc.*). As an extension to our studies,[2,3] we describe the oxidation of α-hydroxyimino aroylhydrazones of biacetyl (**1**) with LTA, to give triazoles as the main products. The oxidation of such compounds is to our knowledge unprecedented. The analogous α-hydroxyimino arylhydrazones of α-diketones give, upon oxidation,[4] 2-aryl-1,2,3-triazole 1-oxides and upon dehydration[5] 2-aryl-1,2,3-triazoles, whereas the α-hydroxyimino aroylhydrazones of 1,2-naphthoquinone yield upon cyclization naphtho-1,2,4-triazine 1-oxides.[6] Furthermore, the α-hydroxyimino semicarbazones react with thionyl chloride to give 2-carbamoyl-1,2,3-triazoles.[7]

The starting materials, α-hydroxyimino aroylhydrazones of biacetyl (**1a—e**), were prepared in high yields (75—90%) by the addition of equimolar amounts of the corresponding aroylhydrazines to methanolic solutions of biacetyl mono-oxime at room temperature.[8,†]

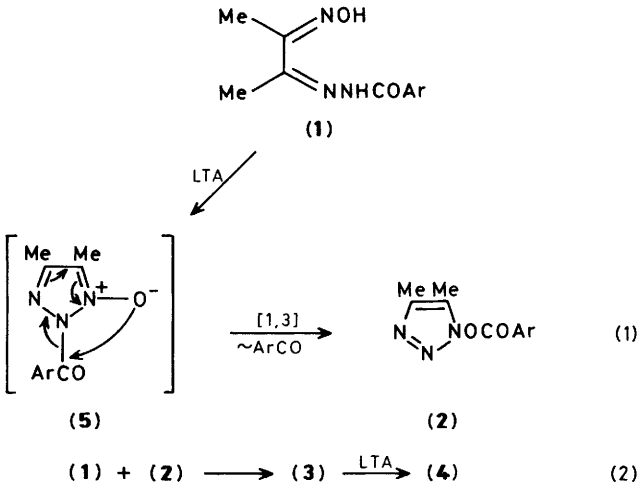
Oxidation of (**1**) in dry dichloromethane suspension with 1 equiv. of LTA at 0 °C gave 1-aroyloxy-4,5-dimethyl-1,2,3-triazoles (**2**) and *O*-aroyl α-hydroxyimino aroylhydrazones of biacetyl (**3**) (20% each) and also *O*-aroylbiacetyl mono-oxime (**4**) and the corresponding benzoic acids in lower yields (10%) (Scheme 1). However, when a solution of (**1**) in acetic acid–dichloromethane (1:2) was gradually added to a solution containing an excess of LTA in dichloromethane only product (**2**) was isolated in considerably higher yields (Table 1).



a; Ar = Ph
b; Ar = *p*-MeC_6H_4
c; Ar = *p*-ClC_6H_4
d; Ar = *p*-$O_2NC_6H_4$
e; Ar = *p*$MeOC_6H_4$

Scheme 1.

It is suggested that the reaction products, the 1-aroyloxy-4,5-dimethyl-1,2,3-triazoles (**2**) (Scheme 2), are formed by the oxidative cyclization of (**1**), *via* the 2-aroyl-1,2,3-triazole oxides (**5**) in agreement with previous reports[9] [equation (1)]. Although intramolecular [1,3]aroyl migration may account for the conversion of (**5**) into (**2**) an intermolecular aroyl transfer is also possible. Formation of (**3**) may result from aroylation of the starting material by the aroyloxytriazole (**2**) produced during the course of the reaction. The latter is supported by the fact that treatment of the starting material (**1**) with (**2**) in dichloromethane at 0 °C gave the product (**3**) in almost quantitative yield [equation (2)]. Further oxidation of (**3**) with LTA gives the *O*-aroylbiacetyl mono-oxime (**4**).



Scheme 2.

1-Aroyloxy-1,2,3-triazoles may, in principle, exist as any one of the three isomeric forms (**2**), (**5**), and (**6**) (Scheme 3). The isomerism between *N*- and *O*-acylated benzotriazol-1-ols has been extensively studied since the latter are considered important catalysts in stereoselective peptide synthesis.[10–15] In a recent study the *N*- *versus* *O*-substitution of alkoxycarbonyl-, acyl-, and sulphonate derivatives of benzotriazol-1-ol was also examined.[15]

The aroyl group position in the oxidation product of α-hydroxyimino aroylhydrazones of biacetyl, was established

† The preparation of (**1a**) has been reported by H. von Pechmann and W. Bauer, *Ber.*, 1909, **42**, 673. However, no details were given.

Table 1. Physical, spectral, and analytical data for 1-aroyloxy-4,5-dimethyl-1,2,3-triazoles (**2**) and *O*-aroyl-α-hydroxyiminoaroyl hydrazones of biacetyl[a]

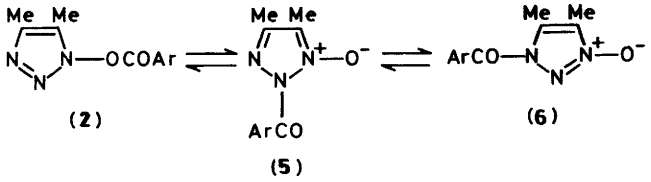
Compd.	Yield[b] (%)	M.p. (°C)	$\nu_{max.}$(Nujol)/cm^{-1} (C=O)	δ_H($CDCl_3$)[c]	Formula	Elemental analysis (%) Found (required) C	H	N
(**2a**)	9 (46)	Oil	1 785[d]	2.18 (3 H, s), 2.34 (3 H, s), 7.50—7.88 (3 H, m), 8.17—8.30 (2 H, dd)	$C_{11}H_{11}N_3O_2$	*e*, *f*		
(**2b**)	8 (35)	Oil	1 780[d]	2.18 (3 H, s), 2.33 (3 H, s), 2.50 (3 H, s), 7.48 (2 H, d, *J* 15 Hz), 8.22 (2 H, d, *J* 15 Hz)	$C_{12}H_{13}N_3O_2$	*f*, *g*		
(**2c**)	15 (38)	120—122	1 785	2.15 (3 H, s), 2.34 (3 H, s), 7.54 (2 H, d, *J* 16 Hz), 8.04 (2 H, d, *J* 16 Hz)	$C_{11}H_{10}N_3O_2Cl$ (251.55)	52.41 (52.47)	3.98 (4.01)	16.56 (16.70)
(**2d**)	9 (40)	164—166	1 795	2.25 (3 H, s), 2.37 (3 H, s), 8.45 (4 H, s)	$C_{11}H_{10}N_4O_4$ (262.10)	50.28 (50.36)	3.81 (3.85)	20.99 (21.38)
(**2e**)	23 (48)	129—130	1 775	2.20 (3 H, s), 2.35 (3 H, s), 4.05 (3 H, s), 7.02 (2 H, s, *J* 15 Hz), 8.12 (2 H, s, *J* 15 Hz)	$C_{12}H_{13}N_3O_3$ (247.12)	58.08 (58.27)	5.31 (5.30)	17.18 (17.00)
(**3a**)	29	198—199	1 750, 1 660	2.35 (3 H, s), 2.40 (3 H, s), 7.5—8.3 (10 H, m)	$C_{18}H_{17}N_3O_3$ (323.15)	66.84 (66.84)	5.18 (5.30)	13.07 (13.00)
(**3b**)	30	207—209	1 750, 1 680	2.32 (3 H, s), 2.40 (3 H, s), 2.43 (6 H, s), 7.2—8.1 (8 H, m)	$C_{20}H_{21}N_3O_3$ (351.18)	68.45 (68.34)	6.03 (6.03)	12.09 (11.96)
(**3c**)	17	190—192	1 750, 1 695	2.35 (6 H, s), 7.4—8.2 (8 H, m)	$C_{12}H_{15}N_3O_2Cl_2$ (376.04)	57.60 (57.44)	4.10 (4.02)	11.28 (11.17)
(**3d**)	15	189—190	1 780, 1 680	2.38 (3 H, s), 2.42 (3 H, s), 8.4—8.6 (8 H, m)	$C_{18}H_{15}N_5O_7$ (413.15)	52.16 (52.28)	3.62 (3.66)	17.02 (16.95)
(**3e**)	10	204—206	1 750, 1 650	2.40 (3 H, s), 2.58 (3 H, s), 3.90 (6 H, s), 7.0—8.4 (8 H, m)				

[a] Correct molecular ion peaks were observed in the mass spectra. [b] Values in parentheses represent the yields of the oxidation with excess LTA. [c] N.m.r. spectra of compounds (**3**) were recorded in $CDCl_3$–CF_3CO_2H solution. [d] Neat. [e] *m/z* 217 (M^+, 5%). [f] Oil not analysed. [g] *m/z* 231 (M^+, 6%).

Table 2. Reaction of 1-aroyloxytriazoles (**2**) with amines

Compd.	Ar	R	R′	Yield (%)[a]	Reaction time
(**7a**)	Ph	H	CH_2CO_2Et	(87)	1 min
(**7b**)	*p*-MeC_6H_4	H	CH_2CO_2Et	95	1 min
(**7c**)	*p*-ClC_6H_4	H	CH_2CO_2Et	(57)	10 min
(**7d**)	*p*-$O_2NC_6H_4$	H	CH_2CO_2Et	(65)	4 h
(**7e**)	*p*-$MeOC_6H_4$	H	CH_2CO_2Et	97	10 min
(**7f**)	*p*-$MeOC_6H_4$	H	Ph	92	24 h
(**7g**)	*p*-$MeOC_6H_4$	H	*p*-ClC_6H_4	81	4 h
(**7h**)	*p*-$MeOC_6H_4$	Me	Ph	66	48 h

[a] Values in parentheses represent the yields of the one-pot procedure and were based on the amount of the corresponding α-hydroxyimino aroylhydrazone (**1**).



Scheme 3.

by an *X*-ray crystallographic analysis of compound (**2c**), the *N*- and *O*-acylated forms not being readily distinguished by spectral methods. For instance, carbonyl absorption in the i.r. spectra of *N*-acylated benzotriazol-1-ols[10,11,13] occurs at 1 730—1 750 cm^{-1} and at 1 795—1 840 cm^{-1} for *O*-acylated forms.[10–14] The corresponding absorption for compounds (**2**) was inconclusive, being observed at 1 775—1 795 cm^{-1} in both Nujol mull and dioxane solution. The ^{13}C n.m.r. spectrum of (**2e**) was similarly inconclusive with respect to the site of the acyl group since it showed a ^{13}C carbonyl shift at 165.4 p.p.m. This value lies between the reported carbonyl shifts for *O*- and

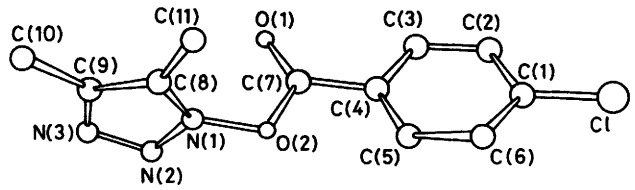


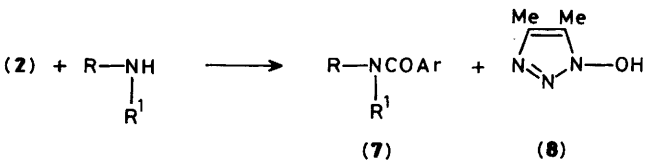
Figure 1. *X*-Ray crystal structure of compound (**2c**)

N-acyl benzotriazoles of 163.0 and 169.3 p.p.m. respectively.[16,17] The *X*-ray analysis confirmed[18] that the compounds (**2**) exist solely in the *O*-acylated form (Figure 1).

The high reactivity of the aroyloxytriazoles (**2**) towards the unchanged starting material (**1**) prompted us to investigate their use as amino-protection agents. The recent reports[19] concerning the acylating properties of the analogous 1-aroyloxybenzotriazoles are of special significance in this field. Using 1-aroyloxytriazoles (**2**) in dioxane solutions at room temperature, in the presence of a small amount of triethylamine, we converted a variety of amines and an α-amino acid ester into the corresponding anilides and amides (**7**) (Scheme 4, Table 2).

Use of the new acyl transfer agents offers the advantage of the very mild reaction conditions required as well as that of a simplified product isolation procedure resulting from the high water solubility of the by-product 4,5-dimethyl-1,2,3-triazol-1-ol (**8**).

Finally, although several fused benzotriazol-1-ols have been



Scheme 4.

reported, non-fused 1,2,3-triazol-1-ols, namely 1,2,3-triazol-1-ol[20] and the 4-pivaloyl-1,2,3-triazol-1-ol,[21] were only recently reported. The 4,5-dimethyl-1,2,3-triazol-1-ol (**8**) was isolated from the hydrolysis mixture of 1-aroyloxytriazole (**2**) after tedious attempts and identified by its spectral properties and elemental analysis.

Experimental

M.p.s were determined using a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded for Nujol mulls or liquid films on a Perkin-Elmer 297 spectrometer. ^{1}H N.m.r. spectra were recorded on a Varian A-60A or Bruker AW 80 instrument; unless otherwise stated, samples were dissolved in deuteriochloroform with tetramethylsilane as internal standard. ^{13}C N.m.r. spectra were recorded on a Varian CFT-20 spectrometer. The mass spectra were obtained using a Hitachi-Perkin-Elmer RMU-6L spectrometer and elemental microanalyses were performed with a Perkin-Elmer 240 B analyser. Column chromatography on silica gel was performed using Merck Kieselgel GF_{254}. Preparative thin layer chromatography (p.t.l.c.) was performed on plates coated with the same material. Light petroleum refers to the fraction b.p. 40—60 °C.

Oxidation of α-Hydroxyimino Aroylhydrazones of Biacetyl with 1 Equiv. of LTA: General Procedure.—A stirred suspension of compound (**1**) (6 mmol) in dry dichloromethane (30 ml) was cooled at 0 °C and a solution of LTA (6.6 mmol) in the same solvent was added dropwise. The additional mixture was stirred at 0 °C for an additional 15–30 min until the reaction was essentially complete (t.l.c.). The excess of LTA was then reduced by aqueous sodium thiosulphate (10%). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure at room temperature. The residual light yellow oil crystallized with time or upon addition of diethyl ether and was recrystallized from a chloroform–light petroleum to give compound (**3**). The mother liquor was concentrated and the resulting oily matter was column chromatographed with benzene–acetone (9:1) as eluant. The following compounds were obtained. *O*-Aroylbiacetyl mono-oxime (**4**) (identified by comparison of its i.r. spectrum with that of an authentic sample prepared by a standard method), 1-aroyloxy-4,5-dimethyltriazole (**2**) (yields are given in Table 1), and arenoic acid.

Oxidation of α-hydroxyimino Aroylhydrazones of Biacetyl with Excess of LTA: General Procedure.—A solution of (**1**) (1 mmol) in acetic acid–dichloromethane (1:5, 30 ml) was added over 20 min to a stirred solution of LTA (4 mmol) in dry dichloromethane (30 ml). The solution was stirred at 0 °C for 30 min and then aqueous sodium thiosulphate (10%) was added. The organic layer was separated, washed with brine, dried, and evaporated. The resulting residue was either chromatographed, (**2a**) and (**2b**), or recrystallized from the appropriate solvent (**2c**—**e**) (Table 1).

Aminolysis of 1-Aroyloxy-4,5-dimethyl-1,2,3-triazoles: General Procedure.—The aroylations were effected by treatment of the corresponding amine with an equimolar amount (1—2 mmol) of 1-aroyloxy-4,5-dimethyl-1,2,3-triazole (**2**) in the presence of triethylamine (1—2 drops) in either dioxane or THF (5—10 ml) at room temperature. The reaction mixture was stirred for the appropriate time (see Table 2) and then diethyl ether (60 ml) was added. The ethereal layer was washed with hydrochloric acid (2M), aqueous sodium hydrogen carbonate (5%), and water, dried, and evaporated under reduced pressure. The amides thus obtained were chromatographically pure and identified by comparison of their m.p.s and i.r. spectra with those of authentic samples prepared by known procedures. The best way we found to shorten the experimental procedure and to increase the overall yield of amide was to perform the oxidation, and the protection of the amino group without isolation of the intermediate aroyloxytriazole (**2**).

4,5-*Dimethyl*-1,2,3-*triazol*-1-*ol* (**8**).—1-Aroyloxy-4,5-dimethyl-1,2,3-triazole (**2a**), (**2c**), or (**2e**) (1 mmol) was dissolved in 5% aqueous sodium hydroxide (5 ml) and after 10 min the mixture was acidified with hydrochloric acid (2M). The water was azeotropically removed with benzene under reduced pressure and the dry residue extracted with chloroform. The organic layer was dried and concentrated and the residue was chromatographed (p.t.l.c.; eluant ethyl acetate). Compound (**8**) was recovered from the silica gel by multiple extraction with acetonitrile (total yield 45%), m.p. 110—112 °C ($CHCl_3$–light petroleum). $\nu_{max.}$(Nujol or KBr), 3 300br, 2 400br, 1 900br, and 1 620s cm^{-1}; δ_H($CDCl_3$) 2.20 (3 H, s, Me), 2.31 (3 H, s, Me), and 16.87 (1 H, s, OH); *m/z* 113 (M^+, 5%), 97, 85, 69, and 68 (Found: C, 42.05; H, 6.1; N, 37.05. Calc. for C, 42.45; H, 6.24; N, 37.16%).

References

1 R. N. Butler, in 'Synthetic Reagents,' ed. J. P. Pizey, Wiley, New York, 1977, vol. 3, ch. 4; R. N. Butler, *Chem. Rev.*, 1984, **84**, 249.
2 S. Lefkopoulou, J. Stephanidou-Stephanatou, C. Tsoleridis, and N. Alexandrou, *Helv. Chim. Acta*, 1985, **68**, 1748; E. Malamidou-Xenikaki and N. Alexandrou, *Tetrahedron Lett.*, 1982, **23**, 3957.
3 A. J. Maroulis and C. P. Hadjiantoniou-Maroulis, *J. Heterocycl. Chem.*, 1986, **21**, 1653.
4 M. Begtrup and J. Holm, *J. Chem. Soc., Perkin Trans. 1*, 1981, 503; K. Kiouplidis, Ph.D. Thesis, University of Zurich, 1980.
5 R. F. Coles and C. S. Hamilton, *J. Am. Chem. Soc.*, 1946, **68**, 1799.
6 F. J. Lalor and F. L. Scott, *J. Chem. Soc. C*, 1969, 1034.
7 D. M. Patel, M. M. Patel, and M. R. Patel, *J. Indian Chem. Soc.*, 1985, **62**, 604.
8 A. B. Theocharis, Ph.D. Thesis, University of Thessaloniki, 1988.
9 R. Huisgen and V. Weberndorfer, *Chem. Ber.*, 1967, **100**, 71.
10 W. Koning and R. Geiger, *Chem. Ber.*, 1970, **103**, 788.
11 K. Horiki, *Tetrahedron Lett.*, 1977, 1897.
12 D. G. McCarthy, A. F. Hegarty, and B. J. Hathaway, *J. Chem. Soc., Perkin Trans. 2*, 1977, 224.
13 S. Nagarajan, S. R. Wilson, and K. L. Rinehart, Jr., *J. Org. Chem.*, 1985, **50**, 2174.
14 K. Barlos, D. Papaioannou, S. Voliotis, R. Prewo, and J. H. Bieri, *J. Org. Chem.*, 1985, **50**, 696.
15 J. Singh, R. Fox, M. Wong, T. P. Kissick, J. L. Moniot, J. Z. Gougoutas, M. F. Malley, and O. Kocy, *J. Org. Chem.*, 1988, **53**, 205.
16 A. Fruchier, J. Elguero, A. F. Hegarty, and D. G. McCarthy, *Org. Magn. Reson.*, 1980, **13**, 339.
17 M. Begtrup, R. M. Claramunt, and J. Elguero, *J. Chem. Soc., Perkin Trans. 2*, 1978, 99.
18 C. A. Kavounis, A. P. Bozopoulos, C. J. Cheer, P. J. Rentzeperis, and A. B. Theocharis, *Acta Crystallogr., Sect. C*, 1988, **44**, 1063.
19 S. Kim and H. Chang, *J. Chem. Soc., Chem. Commun.*, 1983, 1357; J. Takeda, K. Tsuboyama, M. Hoshino, M. Kishino, and H. Ogura, *Synthesis*, 1987, 557.
20 C. Guimon, S. Khayar, G. Pfister-Guillouzo, and M. Begtrup, *Spectrosc. Lett.*, 1987, **20**, 105.
21 G. L'abbé, F. Godts, and S. Toppet, *Tetrahedron Lett.*, 1983, **24**, 3149.

Received 28*th June* 1988; *Paper* 8/02569J