

François Chau, Jean-Claude Malanda and René Milcent*

 Laboratoire de Chimie Organique, Université Paris 7, 16 rue Henri-Huchard, 75018 Paris, France
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The 5-aryl(or methyl)-3-phenylcarbamoyl-1,3,4-oxadiazol-2(3*H*)-ones **2**, in the presence of sodium hydride in anhydrous dimethylformamide, were transformed into 1-benzamido(or acetamido)-3,5-diphenyl-1,3,5-triazine-2,4,6-trione derivatives **7** in poor yields. However, compounds **7** were obtained in better yields when the sodium salts of 5-aryl(or methyl)-1,3,4-oxadiazol-2(3*H*)-ones **1** were treated with two equivalents of aryl(or ethyl)isocyanates. Acidic hydrolysis of 1-acetamido-3,5-diphenyl-1,3,5-triazine-2,4,6-trione (**7i**) provided the corresponding free *N*-amino derivative **9**. Nitrous deamination of **9** gave the known 3,5-diphenyl-1,3,5-triazine-2,4,6-trione (**11**). This cyclic transformation is the first one to be reported providing 1,3,5-triazine-2,4,6-trione derivatives.

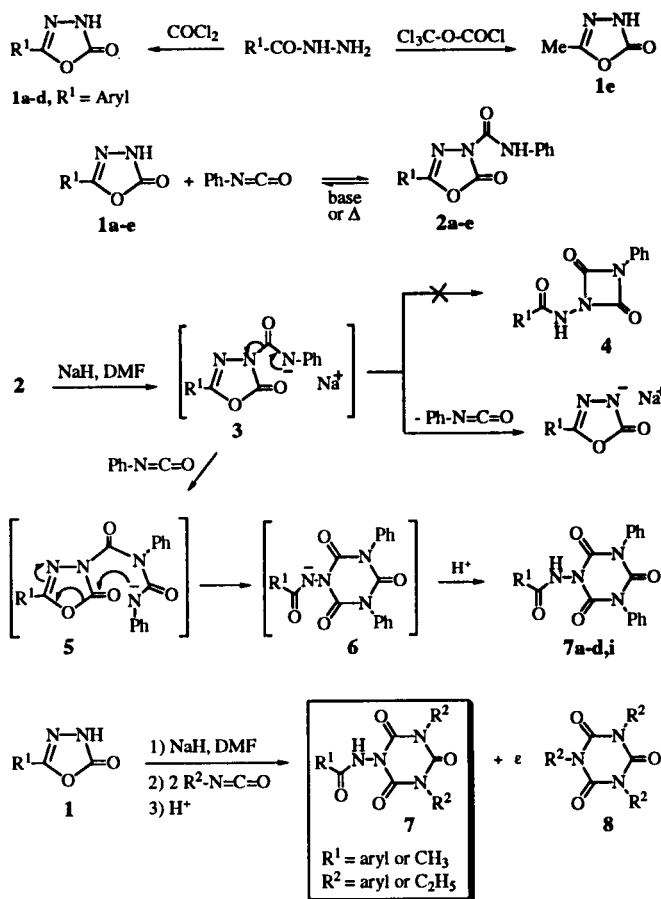
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After the study of several cyclic transformations of 1,3,4-oxadiazol-2(3*H*)-one derivatives **1** into various five or six-membered heterocycles [1], we have attempted to prepare by the same process four-membered heterocycles. With this aim, we have tried to obtain 1-benzamido(or acetamido)-3-phenylazetidine-2,4-dione derivatives **4** by cyclic transformation of the 5-aryl(or methyl)-3-phenylcarbamoyl-1,3,4-oxadiazol-2(3*H*)-ones **2** (Scheme 1).

Compounds **2a-e** were prepared in good yields by long treatment of 5-aryl(or methyl)-1,3,4-oxadiazol-2(3*H*)-ones **1a-e** with an excess of phenyl isocyanate in boiling benzene. They were unstable when they were heated in 1-butanol in the presence of triethylamine or pyridine, or at a temperature close to their melting point with formation of the corresponding oxadiazolone **1** and phenyl isocyanate. In spite of this observation, compounds **2** were reacted at 0° with sodium hydride in anhydrous dimethylformamide. Instead of the expected azetidediones **4**, the result of the cyclic transformation of anions **3** was the formation of 1-benzamido(or acetamido)-3,5-diphenyl-1,3,5-triazine-2,4,6-trione derivatives **7** which were isolated in poor yields in addition to oxadiazolones **1**. This result could be explained by the partial decomposition of anions **3** with elimination of phenyl isocyanate which reacted immediately with the remaining anions **3**. The new resulting intermediate anions **5** were transformed into anions **6** by an intramolecular reaction. Addition of acetic acid afforded triazinetriones **7**.

The explanation of this reaction was confirmed when the sodium salts 5-aryl(or methyl)oxadiazolones **1** were treated at 0° in dimethylformamide with two equivalents of aryl(or ethyl) isocyanates, then heated at 80–100° for 30 minutes. Under these conditions, compounds **7** were obtained in good yields in addition to a small quantity of others triazinetriones **8** formed by the classical trimerization of isocyanate in basic media [2]. Compounds **7** and **8** were easily separated by their differences in solubility in chloroform. In these reactions, replacement of isocyanates by isothiocyanates gave no cyclic transformations.

Scheme 1

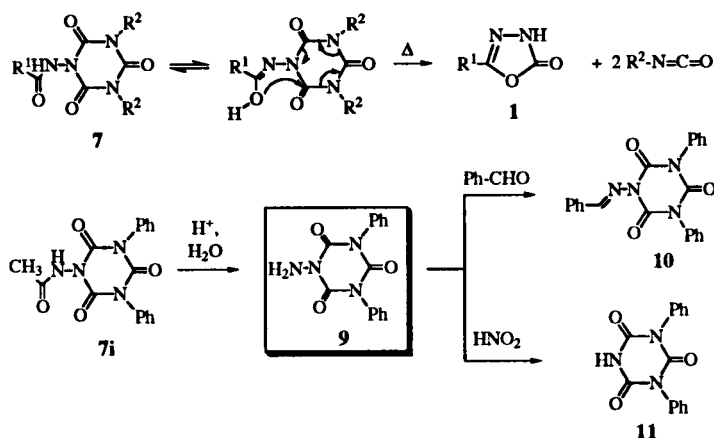


To our knowledge, this cyclic transformation providing to the 1,3,5-triazine-2,4,6-trione series is the first one to be reported.

Compounds **7** except for **7h,i** melted with strong decomposition above 310°. When heated in boiling dimethylformamide (bp 154°), these compounds were decomposed into oxadiazolones **1** and isocyanate according to the

reverse reaction of their formation (Scheme 2). In the presence of pyridine, this decomposition occurred in boiling 1-butanol. This reaction has some analogy with the observed transformation of others triazinetriones [3].

Scheme 2



Hydrolysis of 7i with boiling 10% hydrochloric acid occurred in a few minutes and gave 1-amino-3,5-diphenyl-1,3,5-triazine-2,4,6-trione (9) but the benzamido derivatives 7a-h were not hydrolyzed in this way. Elsewhere, hydrolysis of acetamido derivative 7i with sodium hydroxide solution proceeded to ring opening with formation of acyclic compounds.

Reaction of benzaldehyde with 9 in acetic acid gave the benzylidenamino derivative 10. Nitrous deamination of 9 gave 3,5-diphenyl-1,3,5-triazine-2,4,6-trione (11), identical to an authentic sample prepared by the literature method [4], by reacting phenyl isocyanate with potassium cyanate in dimethylformamide. This result confirmed the structure of new compounds 7a-i, 9 and 10.

Attempt to synthesize amino compound 9 from 11 by a classical method using hydroxylamine *O*-sulfonic acid [5] was unsuccessful.

Physicochemical data of new compounds 7 are listed in Table 1. Structural confirmation for the new products was provided by elemental analysis, ir and ¹H nmr spectra. Likewise, ¹³C nmr spectra of compounds 7a and 9 are provided in Figure 1.

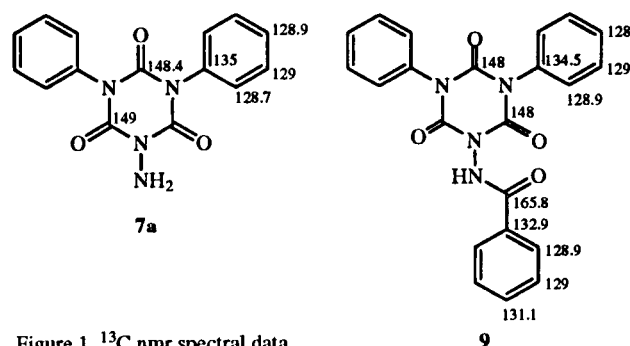
Figure 1. ¹³C nmr spectral data.

Table 1
3,5-Disubstituted 1-Acylamino-1,3,5-triazine-2,4,6-triones 7

7	R ¹	R ²	Yield % [a]	Mp °C	Formula (mo.wt)	Analysis, %			IR ν cm ⁻¹	¹ H NMR [b] δ ppm
						Calcd./Found C	H	N		
a	Ph	Ph	68 (B) 48 (A)	[c, d]	C ₂₂ H ₁₆ N ₄ O ₄ (400.38)	65.99 66.03	4.03 4.04	13.99 14.03	3270, 1690 (b), 1590	7.4-7.95 (m, 15H), 11.4 (s, 1H)
b	4-MePh	Ph	51 (B) 27 (A)	[c, e]	C ₂₃ H ₁₈ N ₄ O ₄ (414.40)	66.66 66.65	4.38 4.38	13.52 13.57	3260, 1680 (b), 1600	2.4 (s, 3H), 7.2-7.8 (m, 14H), 11.4 (s, 1H)
c	4-MeOPh	Ph	53 (B) 30 (A)	[c, d]	C ₂₃ H ₁₈ N ₄ O ₅ (430.40)	64.18 64.15	4.22 4.15	13.02 12.91	3280, 1705 (b), 1670 (b), 1600	3.8 (s, 3H), 7.1 and 7.95 (2d, 4H), 7.5 (m, 10H), 11.4 (s, 1H)
d	4-ClPh	Ph	57 (B) 17 (A)	[c, e]	C ₂₂ H ₁₅ ClN ₄ O ₄ (434.82)	60.77 60.75	3.48 3.43	12.89 12.85	3280, 1710 (b), 1675 (b), 1590	7.4-7.6 (m, 10H), 7.65 and 7.95 (2d, 4H), 11.6 (s, 1H)
e	Ph	4-MePh	74 (B)	[c, e]	C ₂₄ H ₂₀ N ₄ O ₄ (428.43)	67.28 67.38	4.71 4.69	13.08 13.17	3280, 1715 (b), 1680 (b), 1590	2.3 (s, 6H), 7.3-8 (m, 13H), 11.4 (s, 1H)
f	4-MePh	4-MePh	62 (B)	[c, e]	C ₂₅ H ₂₂ N ₄ O ₄ (442.45)	67.86 67.98	5.01 5.03	12.66 12.63	3280, 1715 (b), 1680 (b), 1600	2.3 (s, 9H), 7.3 (m, 10H), 7.8 (d, 2H), 11.4 (s, 1H)
g	4-MeOPh	4-MePh	63 (B)	[c, e]	C ₂₅ H ₂₂ N ₄ O ₅ (458.45)	65.49 65.63	4.84 4.82	12.22 12.17	3300, 1715 (b), 1680 (b), 1600	2.3 (s, 6H), 3.75 (s, 3H), 7.1 and 7.9 (2d, 4H), 7.3 (m, 8H), 11.3 (s, 1H)
h	Ph	Et	15 (B)	170 [f]	C ₁₄ H ₁₆ N ₄ O ₄ (304.30)	55.26 55.32	5.30 5.27	18.41 18.51	3290, 1720 (b), 1685 (b), 1590	1.1 (t, 6H), 3.85 (q, 4H), 7.5-8.0 (m, 5H), 11.4 (s, 1H)
i	Me	Ph	65 (B)	246 [g]	C ₁₇ H ₁₄ N ₄ O ₄ ·C ₃ H ₈ O (398.40) [h]	60.29 60.33	5.56 5.51	14.06 14.05	3300, 1700 (b), 1680 (b), 1590	2 (s, 3H), 7.5 (m, 10H), 10.8 (s, 1H)

[a] Non optimized yields with methods A or B. [b] In DMSO-d₆. [c] Melted with strong decomposition from 310°. [d] Acetonitrile. [e] 1-Butanol. [f] Ethyl acetate. [g] 1-Propanol. [h] Calculated with 1 mole of 1-propanol.

EXPERIMENTAL

Melting points were determined on a Büchi 510 oil heated apparatus and are uncorrected. The ir spectra were recorded on a Perkin Elmer 1310 spectrophotometer as potassium bromide disks. The ^1H and ^{13}C nmr spectra were run on a Bruker 200 MHz spectrometer and are reported as δ values (ppm) relative to tetramethylsilane as an internal standard.

5-Aryl-1,3,4-oxadiazol-2(3H)-ones 1a-d.

These compounds were prepared by reacting phosgene with the corresponding aroylhydrazines by the method of Dornow and Bruncken [6].

5-Methyl-1,3,4-oxadiazol-2(3H)-one (1e).

To a solution of acetylhydrazine (37 g, 0.5 mole) in anhydrous ethyl acetate (400 ml) was added slowly at 0° with stirring trichloromethyl chloroformate (99 g, 0.5 mole). The mixture was heated at reflux for 3 hours until hydrogen chloride evolution has ceased. After cooling to 25° , petroleum ether (300 ml) was added. The precipitate was filtered, dried and recrystallized from toluene giving 40 g (80%) of 1e, mp 112° , lit [6] mp 112° .

5-Aryl(or Methyl)-3-phenylcarbamoyl-1,3,4-oxadiazol-2(3H)-ones 2.

A mixture of oxadiazolone 1 (10 mmoles), phenyl isocyanate (3.6 g, 30 mmoles) and anhydrous benzene (5 ml) was heated at reflux for 8 hours. After cooling and addition of petroleum ether (20 ml), compound 2 precipitated. It was filtered and recrystallized from a suitable solvent.

5-Phenyl-3-phenylcarbamoyl-1,3,4-oxadiazol-2(3H)-one (2a).

This compound was recrystallized from toluene giving 2.3 g (82%), mp 155° ; ir: 3260, 1775, 1730, 1590 cm^{-1} ; ^1H nmr (DMSO- d_6): δ 7-8 (m, 10H), 9.7 (s, 1H).

Anal. Calcd. for $\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_3$ (281.26): C, 64.05; H, 3.94; N, 14.94. Found: C, 63.88; H, 3.91; N, 14.99.

5-(4-Methylphenyl)-3-phenylcarbamoyl-1,3,4-oxadiazol-2(3H)-one (2b).

This compound was recrystallized from ethanol or toluene giving 2.2 g (75%), mp 182° dec; ir: 3260, 1760, 1740, 1605 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 2.4 (s, 3H), 7.00-8.05 (m, 9H), 9.25 (s, 1H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_3$ (295.29): C, 65.08; H, 4.44; N, 14.23. Found: C, 65.17; H, 4.43; N, 14.22.

5-(4-Methoxyphenyl)-3-phenylcarbamoyl-1,3,4-oxadiazol-2(3H)-one (2c).

This compound was recrystallized from toluene giving 2.2 g (71%), mp 156° ; ir: 3260, 1760, 1740, 1595 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 3.85 (s, 3H), 6.95-8.00 (m, 9H), 9.1 (s, 1H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_4$ (311.29): C, 61.73; H, 4.21; N, 13.50. Found: C, 61.58; H, 4.24; N, 13.60.

5-(4-Chlorophenyl)-3-phenylcarbamoyl-1,3,4-oxadiazol-2(3H)-one (2d).

This compound was recrystallized from acetonitrile giving 2.3 g (73%), mp 180° dec; ir: 3280, 1770, 1740, 1600 cm^{-1} ; ^1H nmr (DMSO- d_6): δ 7.00-8.05 (m, 9H), 9.75 (s, 1H).

Anal. Calcd. for $\text{C}_{15}\text{H}_9\text{ClN}_3\text{O}_3$ (315.70): C, 57.06; H, 3.19; N, 13.31. Found: C, 57.20; H, 3.22; N, 13.25.

5-Methyl-3-phenylcarbamoyl-1,3,4-oxadiazol-2(3H)-one (2e).

This compound was recrystallized from ethanol giving 2 g (91%), mp 124° ; ir: 3290, 1770, 1730, 1655, 1600 cm^{-1} ; ^1H nmr (DMSO- d_6): δ 2.35 (s, 3H), 7.0-7.8 (m, 5H), 9.8 (s, 1H).

Anal. Calcd. for $\text{C}_{10}\text{H}_9\text{N}_3\text{O}_3$ (219.19): C, 54.79; H, 4.14; N, 19.17. Found: C, 54.88; H, 4.15; N, 19.24.

1-Acylamino-3,5-diaryl(or Diethyl)-1,3,5-triazine-2,4,6-triones 7.

Method A. Reaction of Sodium Hydride with Compounds 2.

A solution of 2 (5 mmoles) in anhydrous dimethylformamide (10 ml) was added slowly at 0° to a stirred suspension of sodium hydride (0.12 g, 5 mmoles) in the same solvent (10 ml). When hydrogen gas evolution has ceased, the mixture was heated at 60 - 80° for 30 minutes, then cooled at 20° and poured onto ice-water (100 ml). The precipitate was collected, dried and washed with ethyl acetate (20 ml), then treated with chloroform (10 ml). The insoluble product was compound 7. It was recrystallized from a suitable solvent (Table 1).

Method B. Reaction of Isocyanates with the Sodium Salts of Oxadiazolones 1.

A solution of 1 (40 mmoles) in anhydrous dimethylformamide (25 ml) was added slowly at 0° to a stirred suspension of sodium hydride (0.96 g, 40 mmoles) in the same solvent (20 ml). (Beware! With 1e, formation of foam; use of a large Erlenmeyer Flask is recommended). When hydrogen gas evolution has ceased, the stirred mixture was heated at 40 - 60° for 15 minutes (90 minutes for 1e), then cooled at 0° and isocyanate (90 mmoles) was added dropwise. The mixture was heated at 80 - 100° for 30 minutes. The solvent was evaporated under reduced pressure and the resulting crop was treated at 0° with a mixture of 1-propanol (30 ml) and acetic acid (2 ml). The mixture was stirred for 30 minutes. A white compound precipitated. It was filtered and dried, then treated with chloroform (30 ml). The resulting mixture was allowed to stand at room temperature for 2 hours. Compound 7 was filtered and the chloroform filtrate was evaporated. The resulting crop was treated a second time at 0° with chloroform (10 ml). The insoluble recovered solid was triazine 7. Both fractions of 7 were recrystallized from a suitable solvent (Table 1).

1-Amino-3,5-diphenyl-1,3,5-triazine-2,4,6-trione (9).

A stirred suspension of 7i (2.5 g, 7.5 mmoles) in 50 ml of hydrochloric acid solution (10% w/w) was heated at reflux. After 15-20 minutes, the solid was solubilized, then 10 minutes later a white solid precipitated. After 15 minutes, the mixture was cooled to 10° and the precipitated solid was filtrated, dried, then recrystallized from 1-butanol giving 1.9 g of 9 (86%), mp 234° ; ir: 3300, 3190, 1765, 1690 (b) cm^{-1} ; ^1H nmr (DMSO- d_6): δ 4.75 (bs, 2H), 7.4 (m, 10H).

Anal. Calcd. for $\text{C}_{15}\text{H}_{12}\text{N}_4\text{O}_3$ (296.27): C, 60.81; H, 4.08; N, 18.91. Found: C, 60.79; H, 4.04; N, 18.87.

1-Benzylidenamino-3,5-diphenyl-2,4,6-trione (10).

A solution of 9 (0.59 g, 2 mmoles) and benzaldehyde (0.21 g, 2 mmoles) in acetic acid (5 ml) was heated under reflux for 20 minutes. The solvent was evaporated under reduced pressure. The resulting solid was recrystallized from 1-propanol giving 0.7 g of 10 (91%), mp 248° ; ir: 1765, 1715 (b), 1685 (b) cm^{-1} ; ^1H nmr (DMSO- d_6): δ 7.4-8.1 (m, 15H), 8.9 (s, 1H).

Anal. Calcd. for $C_{22}H_{16}N_4O_3$ (384.38): C, 68.74; H, 4.20; N, 14.58. Found: C, 68.60; H, 4.19; N, 14.64.

3,5-Diphenyl-1,3,5-triazine-2,4,6-trione (**11**) from Compound **9**.

To a solution of **9** (0.59 g, 2 mmol) in acetic acid (10 ml) and commercial concentrated hydrochloric acid (0.25 ml) was added dropwise at 0–5° a solution of sodium nitrite (0.15 g, 2.2 mmol) in water (1.5 ml). After 10 minutes, the mixture was evaporated under reduced pressure. The resulting crop was treated with water (10 ml) and the solid was filtered, dried, then recrystallized from ethanol giving 0.5 g of **11** (89%), mp 266° identical with an authentic sample (mp 265–266°) prepared by reaction of phenyl isocyanate with potassium cyanate [4].

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