

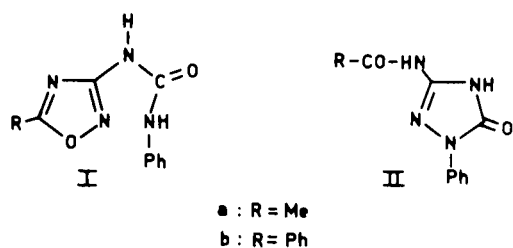
Rearrangements in the 1,2,4-Oxadiazole Series. IV.
Conversion of *N*-(1,2,4-Oxadiazol-3-yl)-*N'*-arylformamidines into
3-Acylamino-1-aryl-1,2,4-triazoles.

M. Ruccia, N. Vivona and G. Cusmano

Istituto di Chimica Organica-Facoltà di Scienze-dell'Università,
Via Archirafi 20, Palermo, Italy, 90123

Received October 14, 1970

Monocyclic rearrangement of 3-substituted-1,2,4-oxadiazoles have been investigated in our previous papers (1,2,3). Recently (3) we reported that *N*-(5-R-1,2,4-oxadiazol-3-yl)-*N'*-phenylureas (Ia and Ib), undergo a base-induced rearrangement into 3-acylamino-1-phenyl-1,2,4-triazolin-5-one (IIa and IIb), on refluxing for 90 minutes with aqueous potassium hydroxide in ethanolic solution, while the same ureas (Ia and Ib) are recovered unchanged after heating at their m.p. for 30 minutes.

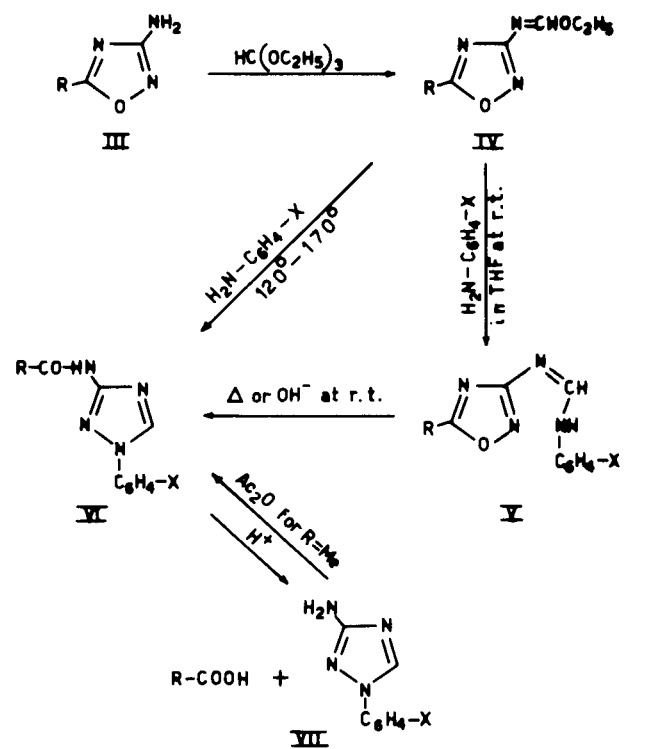


It has been emphasized that this rearrangement, which leads to the synthesis of a 1,2,4-triazole ring from an 1,2,4-oxadiazole system, is the first example of this type. Therefore, in order to develop our studies concerning monocyclic rearrangements of 3-substituted 1,2,4-oxadiazoles (influence of side-chain structure) and to perform further reactions leading to the 1,2,4-triazole ring system, our attention has been now directed to *N*-(5-R-1,2,4-oxadiazol-3-yl)-*N'*-arylformamidines (V) that carry, as the side-chain, a -N=CH-NH- group in place of the -NH-CO-NH- group in I. Thus the formamidines (V) should make available a direct synthesis of 1,2,4-triazoles (VI) instead of 1,2,4-triazolin-5-ones (II).

Refluxing 5-methyl- and 5-phenyl-3-amino-1,2,4-oxadiazoles (IIIa and IIIb) with $\text{CH}(\text{OC}_2\text{H}_5)_3$, gave the ethoxyformylamino derivatives, IVa and IVb, respectively. The latter compounds with aniline, *p*-toluidine or *p*-nitro-aniline in THF solution at room temperature, gave the related amidino compounds (Va-f). Heating for 30 minutes at 140-170° or upon standing with 10% aqueous sodium hydroxide in ethanolic solution at room temperature converted compounds Va-f into the related 3-acetamido- and 3-benz-

amido-1-aryl-1,2,4-triazoles (VIa-f). It was also possible to obtain VIa-f directly from the ethoxyformylamino derivatives (IVa and IVb) by action of aniline, *p*-toluidine or *p*-nitroaniline at 120-170° without solvent, probably through the intermediate formation of V. Acid hydrolysis of VIa-f gave acetic or benzoic acid and 3-amino-1-aryl-1,2,4-triazoles [VIIa (4), VIIb (5) and VIIc], thus supporting the assigned structures which were also confirmed by analytical and spectroscopic data.

The amino compounds (VIIa-c) with acetic anhydride



III and IV a: R = Me
b: R = Ph

V and VI a: R = Me; X = H
b: R = Ph; X = H
c: R = Me; X = *p*-Me
d: R = Ph; X = *p*-Me
e: R = Me; X = *p*-NO₂
f: R = Ph; X = *p*-NO₂

VII a: X = H
b: X = *p*-Me
c: X = *p*-NO₂

TABLE

Physical data related to compounds (V)				Physical data related to compounds (VI)			
No.	m.p. °C	λ_{\max} (log ϵ) nm	$\nu_{\text{N}=\text{CH}}$ cm ⁻¹	No.	m.p. °C	λ_{\max} (log ϵ) nm	$\nu_{\text{C}=\text{O}}$ cm ⁻¹
Va	140	275 (4.36)	1664	VIa	168 (b)	251 (4.05)	1689
Vb	144	274 (4.51)	1656	VIb	172 (c)	255 (4.27)	1695
Vc	(a)	279 (4.39)	1656	VIc	216 (c)	254 (4.16)	1698
Vd	(a)	275 (4.50)	1653	VI d	212 (c)	257 (4.29)	1689
Ve	(a)	236 (3.93); 338 (4.32)	1653	VIe	287 (d)	305 (4.15)	1718
Vf	(a)	245 (4.30); 338 (4.34)	1650	VI f	276 (c)	305 (4.27)	1653

(a) There is no m.p. because of rearrangement on heating; apparent m.ps. coincide with those of related compounds (VI). (b) From AcOEt. (c) From ethanol. (d) From acetic acid. (e) deuteriochloroform solutions. (f) DMSO-d₆ solutions.

2.40 (s, 3 COCH₃); 7.26-7.80 (m, 5 ArH); 8.47 (s, 1 Heter.H); 9.88 (s, 1 NH) (c)

7.20-7.98 (m, 10 ArH); 8.0 (s, 1 Heter.H); 10.7 (s, 1 NH) (e)

2.41 (s, 6 CH₃, COCH₃); 7.0-7.6 (m, 4 ArH); 8.37 (s, 1 Heter.H); 8.72 (s, 1 NH) (e)

2.40 (s, 3 CH₃); 7.15-8.10 (m, 9 ArH); 8.16 (s, 1 Heter.H); 10.05 (s, 1 NH) (e)

2.13 (s, 3 COCH₃); 7.98-8.50 (m, 4 ArH); 9.37 (s, 1 Heter.H); 10.72 (s, 1 NH) (f)

7.46-8.52 (m, 9 ArH); 9.48 (s, 1 Heter.H); 11.16 (s, 1 NH) (f)

gave the acetyl derivatives (VIa, VIc and VIe). A mono-acetyl derivative of VIIa had been described by Cuneo (4) as 2-acetyl-3-imino-1-phenyl-1,2,4-triazolin. This structure, however, must be considered incorrect since Cuneo's acetyl derivative was proved to be identical with our acetylamino-1-phenyl-1,2,4-triazole (VIa) obtained by rearrangement of Va thus confirming the structure.

The successful rearrangement of V into VI by heating or by action of aqueous alkali at room temperature indicates that compounds I and V behave differently towards this type of reaction. In our opinion, this different behavior, other factors being equal, must be related to the different structures of the side chain involved in the rearrangement reactions.

Research is in progress in an attempt to elucidate the detailed mechanism (6) of this type of rearrangement and therefore to determine the dependence upon structural (electronic or steric) factors.

EXPERIMENTAL

Satisfactory elemental analyses were obtained for all new compounds. All melting points (Kofler) are uncorrected; IR (nujol mull): Perkin-Elmer Infracord 137 spectrophotometer; UV (ethanol solution): Beckmann DB (with recorder) spectrophotometer; NMR: Jeol C-60H spectrometer (TMS as internal reference).

3-Ethoxyformylamino-5-methyl-1,2,4-oxadiazole (IVa).

A mixture of IIIa (3 g.) and ethyl orthoformate (8 ml.) was refluxed for 8 hours. After cooling, the reaction mixture was treated with petroleum ether and filtered from starting material. Removal of the solvent left 2.5 g. of IVa (m.p. 38-40°, from petroleum ether) after cooling in ice-bath.

3-Ethoxyformylamino-5-phenyl-1,2,4-oxadiazole (IVb).

A mixture of IIIb (3 g.) and ethyl orthoformate (5 ml.) was heated at 150° for 3 hours. After cooling, the reaction mixture was taken up with ethanol and filtered from starting material. Addition of water to the ethanol solution yielded 2.5 g. of IVb, m.p. 95-98°.

N-(5-R-1,2,4-Oxadiazol-3-yl)-*N'*-arylformamidines (Va-f).

General Procedure.

A solution of equimolar amounts of IV (5 mmoles) and of the suitable amino compound in dry THF (15 ml.) was kept at room temperature for 1 or 2 days. The resulting precipitate was filtered and washed with THF. Compounds (V) thus obtained were considered to have a good degree of purity (7); yields, 40-50%. Physical data are reported in the table.

3-Acylamino-1-aryl-1,2,4-triazoles (VIa-f).

General Procedures.

(A) After heating V (1 g.) for 30 minutes at 140° (for Va and Vb) or at 160-170° for Vc-f, the resulting solid was crystallized from a suitable solvent; yields, 70%.

(B) As a typical procedure, the conversion of Va was carried out as follows: Va (0.5 g.) in ethanol (10 ml.) was treated with aqueous sodium hydroxide 10% (1 ml.). After several hours at room temperature, water (20 ml.) was added and solution acidified with acetic acid. Product VIa so obtained (50%) was proven to be identical with the sample prepared by method A.

(C) A mixture of equimolar amounts of IV (1 g.) and the amino compounds was heated for 30 minutes at 120° (for IVa and IVb) or at 160-170° (for IVc-f). The resulting solid was taken up with ethanol, filtered and crystallized from suitable solvent. Compounds (VIa-f) so obtained (60-70% yield) were proven to be identical with the samples prepared by methods A and B. Physical data for (VIa-f) are reported in the table.

Acid Hydrolysis of 3-Acylamino-1-aryl-1,2,4-triazoles (VIa-f).

General Procedure.

An ethanol solution (20 ml.) of VI (5 mmoles) and concentrated hydrochloric acid (4 ml.) was refluxed for 4 hours (8 hours for VIe and VIf); removal of the solvent, addition of water (30 ml.) and sodium hydroxide (10%) afforded the amino compounds (VIIa-c). Compounds VIIa and VIIb were proven to be identical in every respect (m.p., m.m.p. and IR spectrum) with samples prepared as described in literature (4 and 5) (VIIc): m.p. 294° (water-ethanol 1:1); IR 3390, 3289 cm^{-1} (NH_2); NMR (DMSO- d_6) 6.0 δ (s, 2H, NH_2), 7.85-8.40 δ (m, 4ArH), 9.10 δ (s, 1 Heter. H). Upon acid hydrolysis of VIb, VIc and VIf benzoic acid was collected as follows: after removal of the amino compounds, the alkaline solution was refluxed 30 minutes, acidified and extracted with ether which after evaporation, gave benzoic acid.

Reaction of 3-Amino-1-aryl-1,2,4-triazoles (VIIa-c) with Acetic Anhydride.

General Procedure.

Compound VII (1 g.) was dissolved in acetic anhydride (10 ml.) and refluxed for 5 minutes (for VIIa with stirring 10 minutes at room temperature), after addition of water, VIa, VIc and VIe were obtained and shown to be identical with previous samples.

REFERENCES

- (1) M. Ruccia and D. Spinelli, *Gazz. Chim. Ital.*, **89**, 1654 (1959).
- (2) M. Ruccia and N. Vivona, *Ann. Chim. (Rome)*, **57**, 680 (1967).
- (3) M. Ruccia and N. Vivona, *Chem. Commun.*, 866 (1970).
- (4) C. Cuneo, *Gazz. Chim. Ital.*, **29**, 1, 12 (1899).
- (5) C. Cuneo, *ibid.*, **29**, 1, 89 (1899).
- (6) A mechanism for a similar reaction has been proposed by H. Kano and E. Yamazaki, *Tetrahedron*, **20**, 159, 461 (1964).
- (7) In some cases, attempts to crystallize compounds V afforded the related compounds VI.