Heterocyclic Rearrangements: Rearrangement of *N*-(1,2,4-Oxadiazol-3-yl)-β-enamino Ketones into Pyrimidine *N*-Oxides

Nicolò Vivona,* Silvestre Buscemi, Vincenzo Frenna, and Michele Ruccia
Institute of Organic Chemistry, University of Palermo, Via Archirafi 20, 90123 Palermo, Italy

The behaviour of *N*-(5-R-1,2,4-oxadiazol-3-yl)-β-enamino ketones towards rearrangement has been investigated. In the presence of anionic reagents in ethanol solution, they rearrange to pyrimidine *N*-oxides. The synthesis and hydrolytic ring opening of a [1,2,4]oxadiazolo[2,3-*a*]pyrimidinium system is also reported.

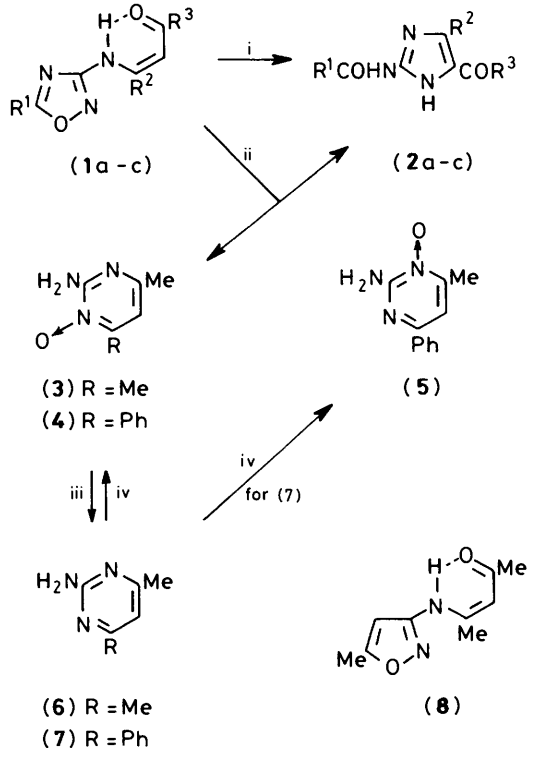
It is well known[1,2] that enamino ketones can act as polydentate nucleophiles, where the reactivity of nucleophilic sites is sensitive to factors such as the presence or the absence of a base, the nature of the base or the solvent used, or, in some instances, the geometry of the sequence.[2] Enamino ketones also have electrophilic sites which may react.

The enamino ketone side chain in (**1**) has two nucleophilic sites capable of attacking the nitrogen atom of the oxadiazole ring in a mononuclear heterocyclic rearrangement (m.h.r.) type reaction:[3] the central carbon as a carbanion and the carbonyl oxygen atom as an enolate. The ring nitrogen atom at position 2 can also act as a nucleophile towards the side chain carbonyl carbon atom.

In the course of our study[4] of m.h.r.s, we have already examined the reactivity of enamino ketones (**1**) towards anionic reagents in dimethylformamide solution.[5] Here, through a carbanionic species, the rearrangement gave the imidazoles (**2**) in good yields, in a m.h.r. involving C–N bond formation to form the new heterocyclic ring.† Considering the high tendency of the 1,2,4-oxadiazole ring to rearrange,[3c,6] as well as the predicted differences in reactivity of the enamino ketone sequence under different experimental conditions, we then studied the behaviour of enamino ketones (**1**) under experimental conditions different from those used for rearrangement into imidazoles. On refluxing with equimolar amounts of sodium ethoxide in ethanol, the enamino ketones (**1a**, **b**) gave 2-aminopyrimidine *N*-oxides (**3**)[7] and (**4**), respectively (70% yield). Small amounts of the 3-amino-1,2,4-oxadiazole deriving from side chain hydrolysis were also present, whereas no significant amounts of the corresponding imidazoles (**2**) were formed. The result of the rearrangement seems to be affected by the nature of the substituent on the 1,2,4-oxadiazole ring. In fact, the enamino ketone (**1c**), under similar experimental conditions, resulted mainly in hydrolysis of the side chain to give 3-amino-5-phenyl-1,2,4-oxadiazole. The aminopyrimidine *N*-oxide (**3**) was formed in *ca.* 15% yield, whilst (**2c**) (15%) was also present.

Mass spectra of compounds (**3**) and (**4**), besides molecular ions, showed the ($M^+ - 16$) and ($M^+ - 17$) peaks, as expected for *N*-oxides carrying adjacent groups with hydrogen atoms.[8] Hydrogenolysis[9] of (**3**) and (**4**) in the presence of 10% palladium-on-charcoal gave the aminopyrimidines (**6**)[10] and (**7**)[11] respectively. *N*-Oxidation of (**6**) with hydrogen peroxide in acetic acid gave the expected *N*-oxide (**3**),[7] whereas *N*-oxidation of (**7**) gave the isomeric *N*-oxide (**5**),[12] as expected[13] on the basis of the course of *N*-oxidation of variously substituted pyrimidine derivatives (Scheme 1).

As to the formation of *N*-oxides from enamino ketones, one could tentatively suggest a rearrangement proceeding through the attack of an enolate anion on the ring nitrogen atom, followed by a [1,2] shift on the seven membered intermediate (**10**) and hydrolysis of the acylamino group. However, though open chain intermediates could not be excluded, an alternative pathway could be envisaged in a reaction proceeding through a bicyclic intermediate (**11**) arising from the ring nitrogen atom acting as a nucleophilic centre.

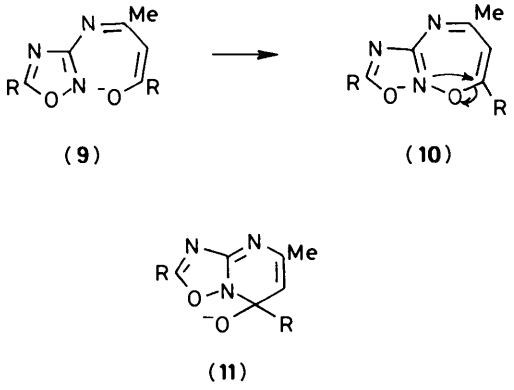


(**1**),(**2**) a; $R^1 = R^2 = R^3 = Me$
b; $R^1 = R^2 = Me$; $R^3 = Ph$
c; $R^1 = Ph$; $R^2 = R^3 = Me$
d; $R^1 = Me$; $R^2 = Ph$; $R^3 = OEt$

Scheme 1. *Reagents:* i, EtONa–DMF; ii, EtONa–EtOH; iii, H_2–Pd–C; iv, H_2O_2–AcOH

The enamino ester (**1d**) has been reported[5b] to rearrange into the imidazole (**2d**) when treated with sodium ethoxide in dimethylformamide. In this instance, reaction with sodium ethoxide in ethanol, gave rise to the imidazole (**2d**) (25%) and the *N*-hydroxypyrimidin-6-one (**13**)[14] (27%). Clearly, the

† For the influence of the enamino ketone moiety structure on the rearrangement into imidazoles, see M. Braun, G. Buchi, and D. F. Bushey, *J. Am. Chem. Soc.*, 1978, **100**, 4208.

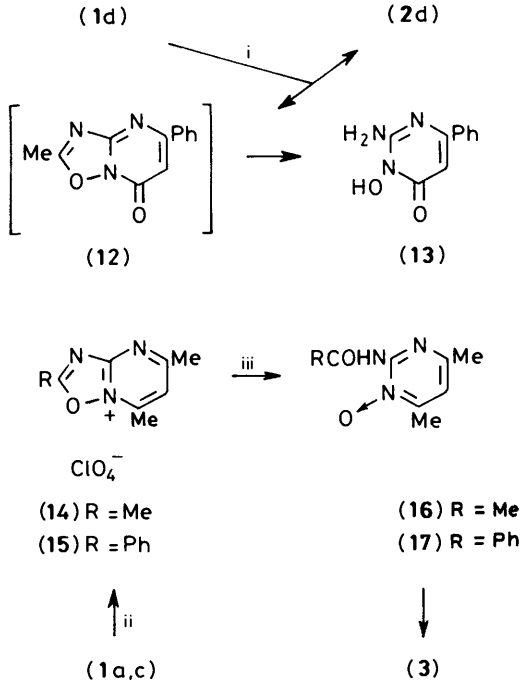


(9) (10) (11)

imidazole (**2d**) arises from a m.h.r. involving a carbanionic species, whereas the *N*-hydroxy compound (**13**) probably arises from the bicyclic intermediate (**12**).

The observed rearrangement shows a peculiar reactivity of the 1,2,4-oxadiazole ring. In fact, the same reaction on the isoxazole enamino ketone (**8**) resulted in complete hydrolysis of the side chain to the 3-aminoisoxazole derivative.

To gain insight into the possibility of the ring nitrogen atom acting as a nucleophile towards the enamino ketone sequence, and likewise into the behaviour of enamino ketones of other α-aminoazoles, we then looked at the synthesis of [1,2,4]-oxadiazolo[2,3-*a*]pyridinium salts. Ring opening reactions of the 1,2,4-oxadiazole moiety in salts (**14**) and (**15**) were also expected to give pyrimidine *N*-oxides.



Scheme 2. *Reagents:* i, EtONa–EtOH; ii, $HClO_4$; iii, H_2O–MeCN

Treatment of the enamino ketone (**1c**) in isopropyl alcohol with perchloric acid at room temperature, furnished the perchlorate (**15**), whose i.r. spectrum did not show NH or C=O absorptions, but a characteristic band at 1 090 cm^{-1} for a ClO_4 group.[15] The salt (**15**) was stable, but, as soon as it was neutralized, the 1,2,4-oxadiazole ring was cleaved to the benzoylaminopyrimidine *N*-oxide (**17**). However, a cleaner reaction to (**17**) was performed by allowing the salt (**15**) to stand in acetonitrile–water until dissolution was achieved. Acid hydrolysis of (**17**) gave (**3**) and benzoic acid (Scheme 2).

When the same reaction was tested on the enamino ketone (**1a**), we were unable to obtain the salt (**14**) or the acetylamino *N*-oxide (**16**). In fact, the reaction went directly to the amino *N*-oxide (**3**) as a perchlorate, thus showing that the 1,2,4-oxadiazole rings in (**14**) and (**15**) have different stabilities under the same reaction conditions.[14]

Experimental

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra (Nujol mulls) were determined with a Perkin-Elmer 257 instrument, ^1H n.m.r. spectra (60 MHz) with a Varian EM 360 spectrometer (tetramethylsilane as the internal standard), and mass spectra with a JEOL JMS 01-SG-2 instrument (75 eV). Light petroleum refers to that fraction boiling in the range 40—60 °C. The enamino ketones (**1a—c**) and the enamino ester (**1d**) were prepared according to the previously reported methods.[5b]

Reaction of the Enamino Ketones (**1a—c**) *and the Enamino Ester* (**1d**) *with Sodium Ethoxide.—General procedure.* A mixture of the enamino ketone or enamino ester (0.01 mol) and sodium ethoxide (0.012 mol) in absolute ethanol (40 ml) was refluxed for 3 h [7 h in the case of (**1c**)]. After this time, the solvent was removed and the residue worked up as below.

The enamino ketone (**1a**). The minimum amount of water was added and the insoluble material was filtered off to give the *amino pyrimidine* N-*oxide* (**3**) (70%), m.p. 254—255 °C (from ethanol) (lit.,[7] 252 °C); *m/z* 139 (M^+, 100), 123 (9), 122 (21), 98 (14), 95 (58), 81 (22), 67 (14), 54 (24), 43 (42), and 42 (57).

Refluxing compound (**1a**) (1.5 g) in ethanol (30 ml) containing aqueous potassium hydroxide (10%; 5 ml), for 3 h and work-up as before, also gave compound (**3**) (70%). Hydrogenation of (**3**) (0.5 g) in the Parr apparatus (at 45 lb in^{-2}; 1 h), in the presence of palladium-on-charcoal (10%; 0.5 g) gave a quantitative yield of (**6**), m.p. 152 °C (from water) (lit.,[10] 152—154 °C). *N*-Oxidation of (**6**) (1.5 g) was carried out in acetic acid (4 ml) with aqueous hydrogen peroxide (30%; 5 ml, in two portions) at 60—70 °C (5—6 h). The mixture was diluted with water and evaporated, and then treated with water and ethanol. After evaporation to remove the solvent and the acetic acid, and work-up with ethyl acetate to remove the starting material, compound (**3**) was obtained (60%).

The enamino ketone (**1b**). Water (50 ml) was added and the insoluble material was filtered off to give the *amino pyrimidine* N-*oxide* (**4**) (70%), m.p. 226—228 °C (from ethanol) (Found: C, 65.9; H, 5.5; N, 21.0. $C_{11}H_{11}N_3O$ requires C, 65.67; H, 5.51; N, 20.88%); $\nu_{max.}$ 3 300 and 3 120br (NH_2), and 1 185 cm^{-1} (N→O); δ[$(CD_3)_2SO$] 2.35 (3 H, s, Me), 7.0 (1 H, s, CH), and 7.30—8.0 (5 H, m, NH_2 and ArH), and 8.10—8.40 (2 H, m, ArH); *m/z* 201 (M^+, 100), 200 (25), 186 (16), 185 (14), 173 (24), 159 (60), 147 (35), 128 (20), 77 (45), 51 (35), and 43 (37).

The same result was obtained by using aqueous 10% potassium hydroxide in ethanol. Hydrogenation of (**4**) as before gave (**7**) quantitatively, m.p. 175 °C (lit.,[11] 173 °C). *N*-Oxidation of compound (**7**) as before gave the *amino pyrimidine* N-*oxide* (**5**) (45%), m.p. 230—232 °C (from ethanol) (lit.,[12] 231—233 °C) [No trace amounts of the isomer (**4**) were present].

The enamino ketone (**1c**). The residue was taken up with water (50 ml) and aqueous sodium hydroxide (10%; 20 ml) and filtered. The insoluble material was 3-amino-5-phenyl-1,2,4-oxadiazole (55%). Neutralization of the alkaline solution with acetic acid, and extraction with chloroform gave a residue which was chromatographed [Riedel silica gel (0.065—0.2 mm)

deactivated with water (15%)]. Elution with light petroleum–ethyl acetate (5:1) gave the *imidazole* (**2c**) (15%), m.p. 221 °C (from ethanol–water) (lit.,[5b] 221 °C). Elution with ethyl acetate and then with ethyl acetate–ethanol (1:1) gave the *N*-oxide (**3**) (15%).

The enamino ester (**1d**). Water (50 ml) was added to the residue and the alkaline solution was extracted with ether which was discarded. Neutralization with acetic acid gave a crude material which was treated with boiling ethanol and filtered. The insoluble fraction was the *N*-hydroxypyrimidin-6-one (**13**) (27%), m.p. 292 °C (from ethanol) (lit.,[14] 292 °C). Concentration of the ethanol gave the *imidazole* (**2d**) (25%), m.p. 155 °C (from ethanol) (lit.,[5b] 155 °C).

The enamino ketone (**8**). This compound was prepared by adopting the procedure described for other enamino ketones. Compound (**8**) had m.p. 65 °C[16] (from light petroleum) (Found: C, 59.9; H, 6.8; N, 15.6. $C_9H_{12}N_2O_2$ requires C, 59.98; H, 6.71; N, 15.55%); δ[$(CD_3)_2CO$] 2.05, 2.25, 2.35 (9 H, 3 s, 3 × Me), 5.40, 6.10 (2 H, 2 s, 2 × CH), and 12.65 (1 H, s, NH).

On reaction with sodium ethoxide as in the general procedure, compound (**8**) gave 3-amino-5-methylisoxazole quantitatively. On reaction with sodium ethoxide in dimethylformamide, compound (**8**) did not rearrange to the corresponding imidazole.

Reaction of the Enaminoketone (**1c**) *with Perchloric Acid.*—To a suspension of (**1c**) (1 g) in isopropyl alcohol (10 ml) aqueous perchloric acid was added (70%; 2 ml). After standing for 1 h at room temperature, the solid was filtered off to give 5,7-*dimethyl*-2-*phenyl*[1,2,4]*oxadiazolo*[2,3-a]*pyrimidinium perchlorate* (**15**) (1 g), m.p. 231 °C (decomp.) (Found: C, 47.7; H, 3.5; N, 12.7. $C_{13}H_{12}ClN_3O_5$ requires C, 47.89; H, 3.68; N, 12.89%); $\nu_{max.}$ 1 090 cm^{-1} (ClO_4).

A mixture of compound (**15**) (0.5 g), acetonitrile (8 ml), and water (2 ml) was kept at room temperature until dissolution was complete (3 h). After dilution with water and neutralization with aqueous sodium hydrogen carbonate, the mixture was extracted with chloroform, dried, and evaporated to afford the *benzoylamino* N-*oxide* (**17**) (0.35 g), m.p. 165 °C (from isopropyl alcohol–light petroleum) (Found: C, 64.2; H, 5.4; N, 17.2. $C_{13}H_{13}N_3O_2$ requires C, 64.18; H, 5.39; N, 17.28%); $\nu_{max.}$ 3 300 (NH), 1 730 (CO), and 1 260 cm^{-1} (N→O); δ($CDCl_3$) 2.52 (6 H, s, 2 × Me), 6.90 (1 H, s, CH), 7.40—8.20 (5 H, m, Ph), and 11.20 (1H, s, NH); *m/z* 243 (M^+, 23), 227 (1), 226 (2), 105 (100), 77 (87), and 51 (28).

Reaction of the Enamino Ketone (**1a**) *with Perchloric Acid.*—To a solution of compound (**1a**) (1 g) in isopropyl alcohol (5 ml) was added perchloric acid (1.5 ml) and the mixture was kept at room temperature for 2 h. On cooling, the perchlorate of (**3**) separated (1 g), m.p. 210—215 °C (decomp.). This salt was added to aqueous sodium hydrogen carbonate (7%; 20 ml). Extraction with chloroform gave the amino *N*-oxide (**3**) (80%).

Acknowledgements

We thank the M.P.I. (Rome) for support.

References

1 L. Kozerski, *Tetrahedron*, 1976, **32**, 1299; L. Kozerski and E. Czerwinska, *Tetrahedron*, 1977, **33**, 1365.
2 A. I. Meyers, A. H. Reine, and R. Gault, *J. Org. Chem.*, 1969, **34**, 698.
3 (*a*) A. J. Boulton, A. R. Katritzky, and A. M. Hamid, *J. Chem. Soc. C*, 1967, 2005; (*b*) A. J. Boulton, 'Lectures in Heterocyclic Chemistry,' Hetero Corporation, Provo, 1973; (*c*) M. Ruccia, N. Vivona, and D. Spinelli, *Adv. Heterocycl. Chem.*, 1981, **29**, 141.
4 N. Vivona, G. Macaluso, G. Cusmano, and V. Frenna, *J. Chem. Soc., Perkin Trans. 1*, 1982, 165; N. Vivona, G. Macaluso, and V. Frenna, *J. Chem. Soc., Perkin Trans. 1*, 1983, 483; N. Vivona, G. Macaluso, V. Frenna, and M. Ruccia, *J. Heterocycl. Chem.*, 1983, **20**, 931; V. Frenna, N. Vivona, G. Consiglio, and D. Spinelli, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1199; V. Frenna, N. Vivona, A. Caronia, G. Consiglio, and D. Spinelli, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1203; V. Frenna, N. Vivona, G. Consiglio, and D. Spinelli, *J. Chem. Soc., Perkin Trans. 2*, 1984, 541; V. Frenna, N. Vivona, A. Caronia, G. Consiglio, and D. Spinelli, *J. Chem. Soc., Perkin Trans. 2*, 1984, 785; N. Vivona, V. Frenna, S. Buscemi, and M. Ruccia, *J. Heterocycl. Chem.*, 1985, **22**, 97; N. Vivona, S. Buscemi, V. Frenna, M. Ruccia, and M. Condò, *J. Chem. Res.*, 1985, (*S*) 190; (*M*), 2184—2197.
5 (*a*) M. Ruccia, N. Vivona, and G. Cusmano, *Tetrahedron Lett.*, 1972, 4959; (*b*) *Tetrahedron*, 1974, **30**, 3859.
6 L. B. Clapp, *Adv. Heterocycl. Chem.*, 1976, **20**, 65.
7 V. F. Sedova, T. Yu. Mustafina, and V. P. Mamaev, *Khim. Geterotsikl. Soedin.*, 1981, 1515 (*Chem. Abstr.*, 1982, **96**, 85504x).
8 T. A. Bryce and J. R. Maxwell, *J. Chem. Soc., Chem. Commun.*, 1965, 206; A. Tatematsu, H. Yoshizumi, E. Hayashi, and H. Nakata, *Tetrahedron Lett.*, 1967, 2985; Q. N. Porter and J. Baldas, 'Mass Spectrometry of Heterocyclic Compounds,' eds. A. Weissberger and E. C. Taylor, Wiley-Interscience, 1971.
9 A. Metallidis, A. Sotiriadis, and D. Theodoropoulos, *J. Heterocycl. Chem.*, 1975, **12**, 359; L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Am. Chem. Soc.*, 1960, **82**, 475.
10 C. A. C. Haley and P. Maitland, *J. Chem. Soc.*, 1951, 3155; T. F. Scholz and G. M. Smith, U.S.P., 1953 (*Chem. Abstr.*, 1954, **48**, 12184g).
11 P. N. Evans, *J. Prakt. Chem.*, 1893, **48**, 489.
12 V. F. Sedova, T. Yu. Mustafina, V. P. Krivopalov, and V. P. Mamaev, *Khim. Geterotsikl. Soedin.*, 1983, 102 (*Chem. Abstr.*, 1983, **98**, 198138r).
13 T. Sakamoto, S. Niitsuma, M. Mizugaki, and H. Yamanaka, *Chem. Pharm. Bull. Jpn.*, 1979, **27**, 2653.
14 N. Vivona and G. Cusmano, *Heterocycles*, 1977, **6**, 107.
15 C. G. Newton, W. D. Ollis, and D. E. Wright, *J. Chem. Soc., Perkin Trans. 1*, 1984, 69.
16 V. A. Chuiguk and N. A. Parkhomenko, *Ubr. Khim. Zh.*, (*Russ. Ed.*), 1976, **42**, 261 (*Chem. Abstr.*, 1976, **85**, 21276).

Received 6th March 1985; *Paper* 5/381