Heterocyclic Rearrangements. Synthesis of 1,2,4-Oxadiazolo[2,3-*a*]pyrimidinium Systems and Their Ring Opening into Pyrimidine *N*-Oxides

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The reaction of 3-amino-5-phenyl-(methyl-)-1,2,4-oxadiazole with acetylacetone or benzoylacetone in the presence of perchloric acid has been studied. Synthesis of 1,2,4-oxadiazolo[2,3-*a*]pyrimidinium perchlorates and their ring opening reaction into aminopyrimidine *N*-oxides is reported.

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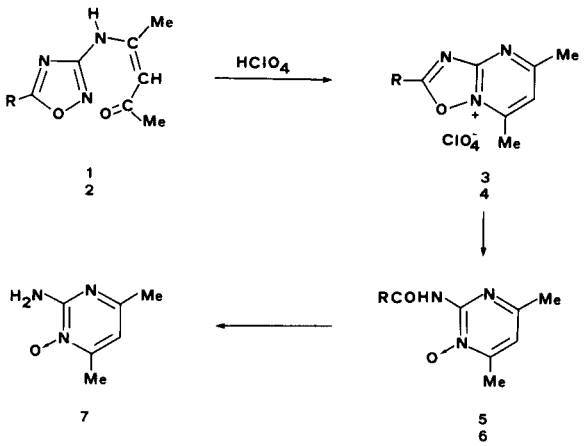
It is well known that α-aminoazoles react with β-diketones in the presence of perchloric acid to give azolopyrimidinium perchlorates. Ring opening reactions of these systems can involve either the azole or the pyrimidine moiety, depending on the nature of the azole ring, or substituents in both systems, as well as on the nature of the opening reagent which is employed [1].

The synthesis of 1,2,4-oxadiazolo[2,3-*a*]pyrimidinium perchlorate **3** has been reported [2] as a reaction of the 1,2,4-oxadiazole enaminoketone **1** with perchloric acid. Compound **3**, as soon as it was neutralized or on standing in acetonitrile/water, was shown to undergo hydrolytic ring opening of the 1,2,4-oxadiazole moiety to the benzoylaminopyrimidine *N*-oxide **5**. The enamino ketone **2**, under the same reaction conditions did not give the perchlorate **4**, nor the acetylamino derivative **6**, but the amino *N*-oxide **7** directly [2], thus showing the different stability of the 1,2,4-oxadiazole moiety in salts **3** and **4** [2,3].

Scheme 1



1 2 3 4 5 6 7

1,3,5: R = Ph
2,4,6: R = Me

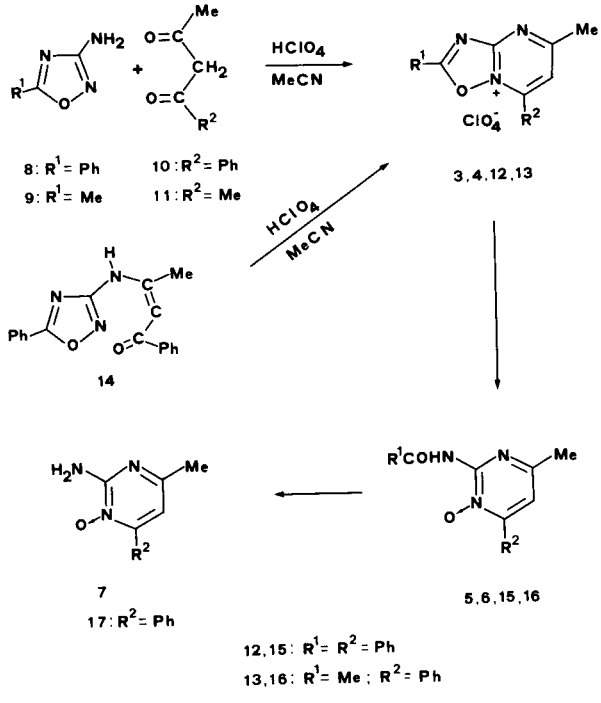
Our opinion is that the observed rearrangement could be viewed as an useful tool for the synthesis of aminopyrimidine *N*-oxides. In this connection we decided to investigate the straight reaction between 3-amino-1,2,4-oxadiazoles **8** and **9** and acetylacetone or benzoylacetone in the presence of perchloric acid.

On reacting compound **8** with acetylacetone or benzoylacetone in the presence of perchloric acid in acetonitrile as solvent at room temperature, we obtained perchlorates **3** and **12**, respectively. The regioisomer **12** was assumed on the basis of chemical evidences. In fact, as observed [2] for compound **3**, on standing in acetonitrile/water, compound **12** gave the benzoylamino *N*-oxide **15**, whose acid hydrolysis gave the aminopyrimidine *N*-oxide **17** [2]. Moreover, the regioisomer perchlorate **12** can be also obtained by reacting the regioisomer enamino ketone **14** [4] with perchloric acid in acetonitrile as solvent.

In the case of the reaction between the 3-amino-5-methyl-1,2,4-oxadiazole (**9**) and acetylacetone, the perchlorate **4** was not obtained. However, dilution with water and neutralization of the reaction mixture with aqueous sodium hydrogen carbonate, gave the aminopyrimidine *N*-oxide **7** [2] directly. In the case of the reaction between compound **9** and benzoylacetone, the crude material which separated, after neutralization, gave a mixture of the aminopyrimidine *N*-oxide **17** [2] and its acetylamino derivative **16**. This latter compound has been also obtained through acetylation of **17** with acetic anhydride in benzene at room temperature. A pure sample of the perchlorate **13**, though in low yields, can be reached by working up the reaction mixture as reported in experimental section. Compound **13** did not show NH or C=O absorptions in the ir spectrum and, as expected, on standing in acetonitrile/water, gave the acetylaminopyrimidine *N*-oxide **16**.

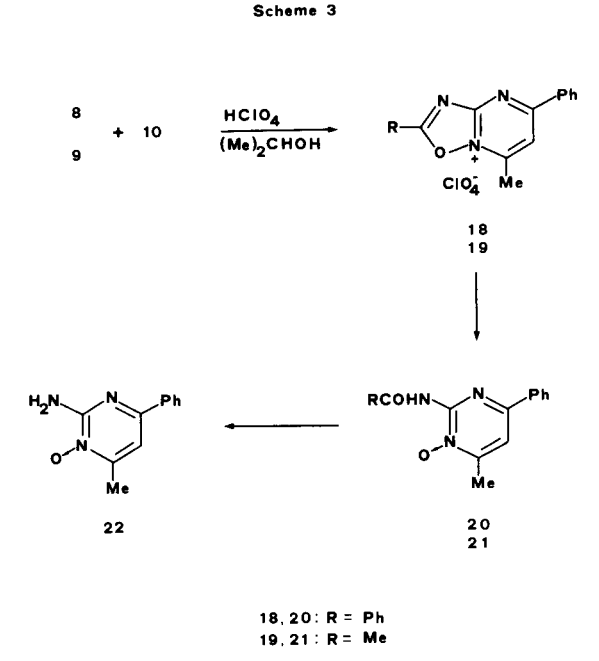
In order to get insight into the influence of the solvent in the regioisomers formation, we next explored the reaction between 3-amino-1,2,4-oxadiazoles and benzoylacetone in isopropyl alcohol as solvent. In this solvent, the aminooxadiazole **8** gave a mixture of both regioisomers **12**

Scheme 2



and **18**, this latter being the major component. In fact, hydrolytic cleavage of the crude perchlorate by allowing it to stand in acetonitrile/water, gave the benzoylamino *N*-oxide **15** (10%) and the isomer **20** (80%). Acid hydrolysis of **20** gave benzoic acid and the amino *N*-oxide **22** [2]. On the other hand, in the case of the reaction on compound **9**, no bicyclic perchlorate separated. Dilution with water and neutralization with sodium hydrogen carbonate of the reaction mixture, gave the aminopyrimidine *N*-oxide **22** and its acetylamino derivative **21**, together with some amounts of the amino *N*-oxide **17**. However, reaching compound **21** as well as the ratio between **22** and **17** seems to depend upon experimental conditions.

Scheme 3



EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus. The ir spectra (nujol) were determined with a Perkin Elmer 257 instrument, ^{1}H nmr spectra (60 MHz) with a Varian EM 360 spectrometer (tetramethylsilane as internal standard), and mass spectra with a JEOL JMS 01-SG-2 instrument. Dry column chromatography was performed on Riedel silica gel (0.063-0.2 mm) deactivated with water (15%), and Flash chromatography [5] on Merck silica gel (0.040-0.063 mm). Perchloric acid refers to the aqueous (70%) solution.

Reaction of 3-Aminooxadiazoles **8** and **9** with Benzoylacetone (**10**) or Acetylacetone (**11**) and Perchloric Acid in Acetonitrile. General Procedure.

To a mixture of compound **8** (3 mmoles) or **9** (5 mmoles) and equimolar amounts of benzoylacetone or acetylacetone in acetonitrile (3ml), perchloric acid (2 ml) was added. After standing (4 hours) at room temperature, the mixture was worked as below.

Reaction Between **8** and **10**.

The solid was filtered off, worked up with hot benzene and filtered again, giving **12** (90%), mp 210-213°; ir: 1590 cm^{-1} (C=N) and 1090 cm^{-1} (ClO_4) [6]; nmr (DMSO-d_6): δ 2.45 (s, Me, 3H), 7.35 (s, CH, 1H), 7.45-8.10 (m, aromatic, 10H).

Anal. Calcd. for $C_{18}H_{14}ClN_3O_5$: C, 55.74; H, 3.61; N, 10.84. Found: C, 55.81; H, 3.60; N, 10.78.

Compound **12** (1 g) was allowed to stand in acetonitrile (10 ml) and water (2 ml) until dissolution (6 hours). Dilution with water and filtration gave **15** (85%), mp 157° (from ethanol); ir: 3240 cm^{-1} (NH), 1710 cm^{-1} (C=O), and 1260 cm^{-1} (N→O); nmr (deuteriochloroform): δ 2.60 (s, Me, 3H), 7.05 (s, CH, 1H), 7.40-8.15 (m, aromatic, 10H), and 11.50 (s, NH, 1H); ms: m/z 305 (M$^+$), 289, 288, 260, 169, 105, 77, 51.

Anal. Calcd. for $C_{18}H_{15}N_3O_2$: C, 70.80; H, 4.95; N, 13.76. Found: C, 70.95; H, 4.80; N, 13.85.

Acid hydrolysis of **15** in ethanol and concentrated hydrochloric acid on refluxing (3 hours), after working as usual, gave benzoic acid and **17** (90%), mp 226-228° (from ethanol), lit [2] mp 226-228°.

A solution of the enaminoketone **14** [4] (1 g) in acetonitrile (3 ml) and perchloric acid (2 ml) was kept at room temperature for 4 hours. The solid which separated was filtered off, taken up with hot benzene and filtered again, giving **12** (1.1 g) (90%), mp 210-213°.

Reaction Between **8** and **11**.

The solid was filtered off, worked up with hot benzene and filtered again, giving **3** (80%), mp 231°, lit [2] mp 231°.

Reaction Between **9** and **11**.

After dilution with water and neutralization with solid sodium hydrogen carbonate, the mixture was extracted with chloroform. Evaporation of the solvent gave **7** (80%), mp 254-255° (from ethanol), lit [2,7] mp 254-255°.

Reaction Between **9** and **10**.

The crude material which separated was filtered off (1 g) and then added to aqueous (7%) sodium hydrogen carbonate (30 ml). The mixture was stirred for 1 hour, extracted with chloroform which was dried and evaporated. Flash chromatography of the residue, on elution with ethyl acetate gave **16** (0.3 g) and then, on elution with ethyl acetate-ethanol (10:1) gave **17** (0.4 g). Compound **16** had mp 98° (from ethyl acetate-light pet-

roleum); ir: 3220 cm^{-1} (NH), 1685 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.45 and 2.50 (2 s, 2 Me, 6H), 6.95 (s, CH, 1H), 7.30-7.95 (m, aromatic, 5H), and 10.30 (s, NH, 1H); ms: m/z 243 (M^+), 227, 201, 185, 159, 147, 128.

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.20; H, 5.50; N, 17.10.

In the case that the reaction between **9** and **10** was interrupted after 30 minutes, the solid which was collected, after working up with benzene, gave a pure sample of **13** (10%), mp 205-210°; ir: 1590 cm^{-1} (C=N), and 1090 cm^{-1} (ClO_4); nmr (DMSO-d_6): δ 2.35 and 2.45 (2 s, 2 Me, 6H), 7.40-8.10 (m, aromatic, CH, 6H).

Anal. Calcd. for $C_{13}H_{12}ClN_3O_5$: C, 47.90; H, 3.69; N, 12.90. Found: C, 47.70; H, 3.50; N, 12.70.

Reaction Between **8** and **10** in Isopropyl Alcohol.

A mixture of compound **8** (0.5 g), equimolar amounts of **10**, isopropyl alcohol (3 ml) and perchloric acid (2 ml) was kept at room temperature for 4 hours. The crude material was collected, worked up with hot benzene and filtered again, giving a mixture of **12** and **18** (1.1 g). This mixture was allowed to stand in acetonitrile (10 ml) and water (2 ml) until dissolution. Dilution with water and filtration gave a mixture of **15** and **20** which was separated on flash chromatography. Elution with ethyl acetate gave **15** (10%) and then **20** (80%), mp 166-167° (from ethanol); ir: 3220 cm^{-1} (NH), 1700 cm^{-1} (C=O), and 1270 cm^{-1} (N→O); nmr (deuteriochloroform): δ 2.60 (s, Me, 3H), 7.35-8.20 (m, aromatic, CH, 11H), 11.15 (s, NH, 1H); ms: m/z 305 (M^+), 289, 288, 260, 169, 105.

Anal. Calcd. for $C_{18}H_{15}N_3O_2$: C, 70.80; H, 4.95; N, 13.76. Found: C, 70.70; H, 4.80; N, 13.70.

Acid hydrolysis of **20** in ethanol and concentrated hydrochloric acid, on refluxing (4 hours), after working as usual, gave benzoic acid and **22** (90%), mp 230-232° (from ethanol), lit [2,8] mp 230-232°.

In the case that the reaction between **8** and **10** was interrupted after 2 hours the separated solid, after working up with benzene, gave a pure sample of **18** (40%), mp 265°; ir: 1090 cm^{-1} (ClO_4); nmr (DMSO-d_6): δ 2.50 (s, Me, 3H), 7.35-8.20 (m, aromatic, CH, 11H).

Anal. Calcd. for $C_{18}H_{14}ClN_3O_5$: C, 55.74; H, 3.61; N, 10.84. Found: C, 55.47; H, 3.82; N, 11.09.

Reaction Between **9** and **10** in Isopropyl Alcohol.

A mixture of compound **9** (0.5 g), equimolar amounts of **10**, isopropyl alcohol (3 ml) and perchloric acid (2 ml) was kept at room temperature for 4 hours. After dilution with water and neutralization with solid sodium hydrogen carbonate, the mixture was extracted with chloroform which was dried and evaporated and the residue was chromatographed on Flash silica gel. Elution with ethyl acetate gave **21** (0.27 g), **17** (0.1 g), and then **22** (0.4 g). Compound **21** had mp 166-167° (from ethanol); ir: 3270 cm^{-1} (NH), 1690 cm^{-1} (C=O), and 1280 cm^{-1} (N→O); nmr (deuteriochloroform): δ 2.55 and 2.60 (2 s, 2 Me, 6H), 7.30-8.05 (m, aromatic, CH, 6H), and 10.15 (s, NH, 1H); ms: m/z 243 (M^+), 227, 201, 185, 142.

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.30; H, 5.30; N, 17.35.

On performing the same reaction under refluxing (2 minutes), after working as usual, gave **17** (0.2 g) and **22** (0.6 g).

Acetylation of **17** and **22**.

A solution of **17** or **22** (0.5 g) in anhydrous benzene (35 ml) and acetic anhydride (0.3 ml) was kept at room temperature for 3-4 days. After evaporation of the solvent, the residue was purified by chromatography (in the case of the reaction on **17**), or by crystallization from ethanol (in the case of the reaction on **22**). One obtains, respectively, compound **16** (40%), mp 98°, and compound **21** (90%), mp 166-167°.

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REFERENCES

[1a] G. Zvilichovsky and M. David, *J. Org. Chem.*, **48**, 575 (1983); [b] I. P. Bachkovskii and V. A. Chuiguk, *Khim. Geterotsikl. Soedin.* **11**, 1493 (1975); *Chem. Abstr.*, **84**, 74214d (1976); [c] V. A. Chuiguk and P. D. Medik, *Khim. Geterotsikl. Soedin.*, **14**, 1422 (1978); *Chem. Abstr.*, **90**, 38869m (1979); [d] I. P. Bachovskii, A. P. Mikhaylovskii, and V. A. Tchuyguk, *Ukr. Khim. Zhur.*, **46**, 637 (1980); *Chem. Abstr.*, **93**, 168222t (1980).

[2] N. Vivona, S. Buscemi, V. Frenna, and M. Ruccia, *J. Chem. Soc., Perkin Trans. I*, 17 (1986).

[3] N. Vivona and G. Cusmano, *Heterocycles*, **6**, 107 (1977).

[4a] M. Ruccia, N. Vivona, and. G. Cusmano, *Tetrahedron Letters*, 4959 (1972); [b] *Tetrahedron*, **30**, 3859 (1974).

[5] W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).

[6] C. G. Newton, W. D. Ollis, and D. E. Wright, *J. Chem. Soc. Perkin Trans. I*, 69 (1984).

[7] V. F. Sedova, T. Yu. Mustafina, and V. P. Mamaev, *Khim. Geterotsikl. Soedin.*, **17**, 1515 (1981); *Chem. Abstr.*, **96**, 85504 (1982).

[8] V. F. Sedova, T. Yu. Mustafina, V. P. Krivopalov, and V. P. Mamaev, *Khim. Geterotsikl. Soedin.*, **19**, 102 (1983); *Chem. Abstr.*, **98**, 198138r (1983).