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A NEW SYNTHESIS OF 1,2,4-OXADIAZOLES

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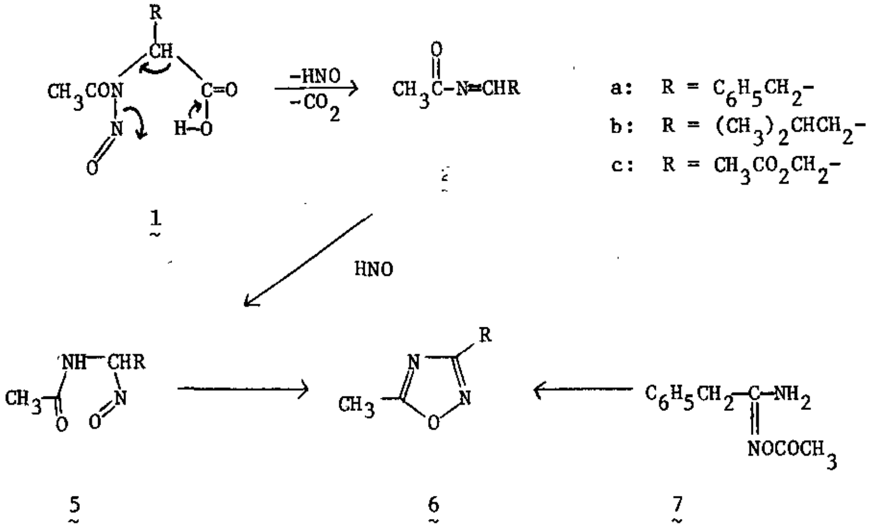
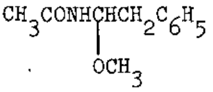
Irradiation of N-nitroso-N-acyl-α-amino acids under weakly basic condition led to the formation of substituted 1,2,4-oxadiazoles in competition with slow basic decompositions of nitrosamides. The cyclization was shown to occur from the C-nitroso compound 5 but not from its tautomeric oxime 8.

Nitrosamides are versatile compounds for synthesis but labile to heat, irradiation, acids and bases.[1] We have reported[2] that N-acyl-N-nitroso-α-amino acids are photodecomposed in neutral solvent, such as alcohols, ether, and acetonitrile, to give the corresponding N-acylimides (e.g. 2) as the primary product by simultaneous decarboxylation and elimination of HNO. As N-acylimides are susceptible to nucleophilic attack, products arising from additions of nucleophiles are isolated, e.g., photolysis of N-nitroso-N-acetyl-D,L-phenylalanine (1a) in mehanol gives N-acetyl-2-phenyl-1-methoxyethylamine (3a) and N-acetyl-β-styrylamine (4a). Reinvestigation with careful work-up of the crude product afforded a small amount of 3-benzyl-5-methyl-1,2,4-oxadiazole (6a); i.r. 1585, 1520, 1500, 1455, 1360, 735, and 700 cm^{-1}; ^{1}H.n.m.r. τ 2.75 (5H), 5.98 (s, 2H), 7.52 (s, 3H); ^{13}C.n.m.r. 11.7 (q), 31.6 (t), 168.6 (t), 175.8 (q), 134.8 (s), 126.3 (d), 127.9 (d), 128.2 (d); found C (68.95), H (5.87), N (16.29). The structure 6a was authenticated with an independent synthesis by heating the *O*-acetylamidoxime 7 (i.r. 1740 cm^{-1}) in water.[3]



a: R = $C_6H_5CH_2$-
b: R = $(CH_3)_2CHCH_2$-
c: R = $CH_3CO_2CH_2$-



$CH_3CONHCH(OCH_3)CH_2C_6H_5$

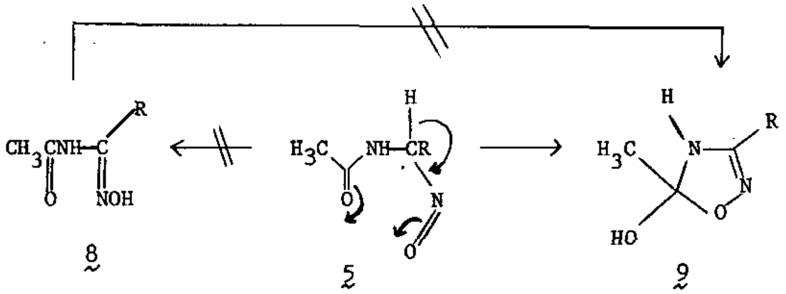
3a

$CH_3CONHCH{=}CHC_6H_5$

4a

Photolysis of 1a in methanol at 0° in the presence of two equivalents of triethylamine afforded oxadiazole 6a in 64% and a small amount of 3a. Similar photolysis in acetronitrile cleanly converted 1a to 6a; distillation of the crude oil gave 6a in a 63% isolated yield. Photolysis of *N*-nitroso-*N*-acetyl-*D*,*L*-leucine (1b) in acetonitrile in the presence of triethylamine (2 equivalent) gave minor amounts of other products and fairly volatile oxadiazole 6b; 21% isolated yield; i.r. 1590, 1390, 1360, 790 cm^{-1}; n.m.r. τ 7.42 (d, J = 7 Hz, 2H), 7.42 (s, 3H), 7.88 (nonet, J = 7 Hz, 1H), 9.01 (d, J = 6, 6H). However, under similar conditions N-nitroso-N,O-diacetyl-D,L-serine (1c) was photodecomposed to give a mixture from which oxadiazole 6c was isolated in 12%; i.r. 1750, 1590, 1220, 1040 cm^{-1}; ^{1}H.n.m.r. τ 4.82 (s, 2H), 7.40 (s, 3H), 7.85 (s, 3H); ^{13}C.n.m.r. 13.6 (q), 20.6 (q), 56.7 (t), 165.0 (s), 168.6 (t), 175.3 (q).

Dependent on structures, nitrosamides derived from α-amino acids have varied stability toward heating and bases. For example, N-nitroso-N-benzoyl-D,L-phenylalanine (1a, where $CH_3CO=C_6H_5CO$) in acetonitrile decomposed extensively on addition of triethylamine at 0°; photolysis of this solution afforded only 5% of 3-benzyl-5-phenyl-1,2,4-oxadiazole (6a, where $CH_3=C_6H_5$). Nitrosamide 1a in methanol or acetonile exhibits absorption maxima at about 400 nm. When two equivalents of triethylamine were added, the solution immediately developed an intense absorption at 340 nm. in addition to those peaks of 1a at ca. 400 nm. This solution was irradiated immediately to give the above results but it was fairly stable at 0° in the dark. Therefore, the photochemical formations of oxadiazoles 6 compete with basic decomposition (dark reactions) of 1. It was demonstrated that the photolytic oxadiazole formation was favored in solutions containing at least two mole equivalents of a weak base; e.g., photolysis of 1a in acetonitrile containing 0.75, 1.5 and 2 mole equivalents of triethylamine gave 6a in 27, 41 and 63%, respectively. However,



in aqueous or THF solution, 1a was rapidly decomposed in the dark on addition of sodium carbonate.

The requirement of a weak base is assumed to convert [HNO] to a more nucleophilic $[ON^-]$ ion which adds to *N*-acylimides **2** to form the C-nitroso intermediates **5**. Cyclization must have taken place directly from **5** leading to **6** under the conditions since the oxime **8**, synthesised independently from $C_6H_5CH_2C(Cl)=NOH$ and $CH_3CONH^-Na^+$, does not react to give **6** under comparable conditions. Intermediacy of such diacylamidoximes has been proposed previously.[4,5] While this oxime **8** can arise from tautomerization of **5**, it is not isolated in our reaction.

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