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A thermal fragmentation of 1,2,4-oxadiazole-4-oxides to nitriles and nitrosocarbonyls[†]

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Abstract

1,2,4-Oxadiazole-4-oxides undergo clean thermal cleavage in refluxing chlorobenzene or xylene to nitriles and nitrosocarbonyl intermediates, which are either trapped with suitable olefins to afford ene adducts or dimerize and rearrange to anhydrides. © 2000 Elsevier Science Ltd. All rights reserved.

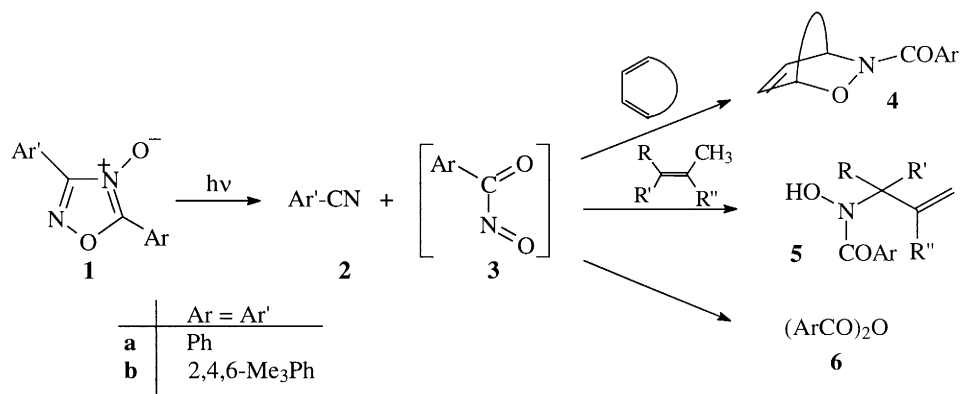
Keywords: ene reactions; nitroso compounds.

We have recently reported that 1,2,4-oxadiazole-4-oxides **1** undergo a clean photochemical cleavage¹ to nitriles **2** and nitrosocarbonyls **3**, highly reactive intermediates² which can be quantitatively trapped with dienes or alkenes to afford the hetero Diels–Alder (HDA) adducts **4** or the ene adducts **5** (Scheme 1). The HDA³ and ene⁴ reactions of nitrosocarbonyls have recently acquired a broad synthetic significance because of the easy manipulation of both the HDA and ene adducts, allowing the introduction of functionality into the diene and ene components. The photochemical cleavage of 1,2,4-oxadiazole-4-oxides offers a very mild entry to the nitrosocarbonyls, which are usually generated by oxidation of hydroxamic acids^{2,3,5} or nitrile oxides⁶ or by thermal cycloreversion of their HDA adducts.^{2,4}

In spite of its photochemical lability the 3,5-diphenyl-1,2,4-oxadiazole-4-oxide **1a** proved to be thermally stable and could be recovered unchanged after 2 h in boiling benzene or toluene. However, when we recently dealt with the dimesityl derivative **1b**, readily available by the BF₃-catalyzed dimerization of mesitronitrile oxide,⁷ the thermal instability of the 1,2,4-oxadiazole-4-oxides became manifest. The dimesityl derivative **1b** did not undergo the usual⁸ deoxygenation to 1,2,4-oxadiazole with trimethyl phosphite in refluxing benzene, presumably because of the bulky substituents around the oxygen. When we tested the stability of **1b** in refluxing toluene for 2 h, we found that a smooth fragmentation had taken place affording a 2:1 mixture of mesitronitrile **2b** and the mesitoic anhydride **6b**. The fragmentation of **1b** also takes place in refluxing benzene, albeit more slowly (24 h).

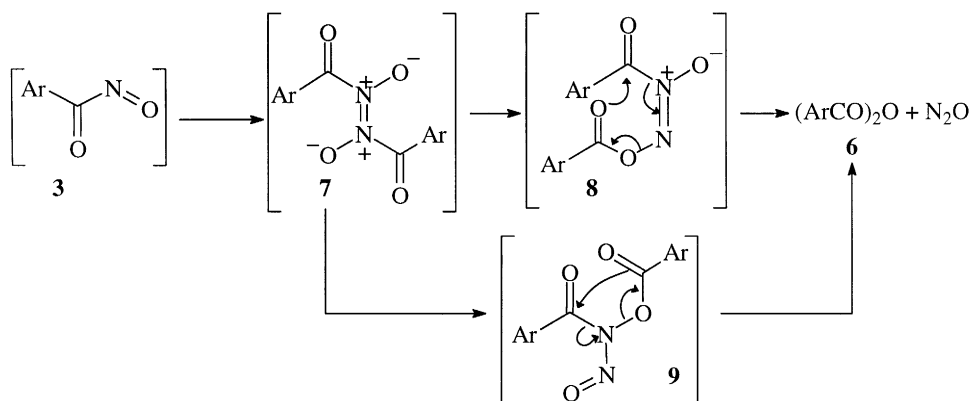
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[†] Dedicated to Prof. Rolf Huisgen on the occasion of his 80th birthday.



Scheme 1.

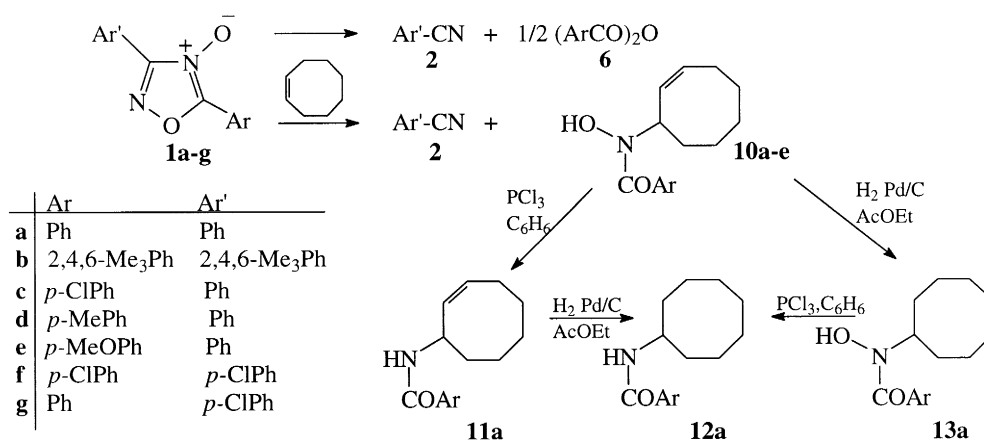
The formation of the anhydride **6b** suggests the intermediacy of the nitrosocarbonyl **3b** in the thermal cleavage, since anhydrides **6** are the typical products of the decay of nitrosocarbonyls, when generated thermally in the absence of trapping agents, e.g. in the thermolysis of the HDA adducts to 9,10-dimethyl anthracene.^{2,9} A reasonable mechanism^{6,9} for their formation involves the dimerization of the nitrosocarbonyl to the azo *N,N*-dioxide **7**, a 1,2 shift of the acyl group to the acyloxy azo *N*-oxide **8** or a 1,3 acyl shift to the *N*-nitroso *O*-benzoyl benzhydroxamic acid **9**, and final collapse to the anhydride **6** with loss of nitrous oxide (Scheme 2). Indeed, on performing the thermolysis of **1b** in benzene, in the presence of 10 equiv. of tetramethylethylene, we obtained a 1:1 mixture of mesitonitrile and the known⁶ ene adduct **5b** (R,R',R''=CH₃).



Scheme 2.

Fragmentation of the 3,5-diphenyl-1,2,4-oxadiazole-4-oxide **1a** takes place similarly but under more vigorous conditions. On refluxing in chlorobenzene (bp 132°C) or xylene for 4 h, **1a** afforded a 2:1 mixture of benzonitrile and benzoic anhydride while in the presence of a suitable ene component, cyclooctene (bp 145°C, 10 equiv.), afforded instead a 1:1 mixture of benzonitrile **2a** and the nitrosocarbonyl ene adduct **10a** (Scheme 3). The latter is identical to a sample prepared by generating the nitrosocarbonyl according to the nitrile oxide route⁶ and its structure can be proved by comparison of the spectroscopic data¹⁰ as well as on the ready deoxygenation (PCl₃, benzene, rt, 8 h, 83%) to **11a**, mp 151–152°C, and its further conversion by catalytic hydrogenation (Pd/C 10%, AcOEt, rt, 95%) to *N*-cyclooctylbenzamide **12a**, mp 112–113°C, identical to an authentic specimen¹¹ obtained from benzoylation of cyclooctyl

amine. Alternatively, the ene adduct **10a** afforded on hydrogenation the *N*-cyclooctyl benzhydroxamic acid **13a** (86%), mp 84–85°C, which was then deoxygenated to **12a** (91%).



Scheme 3.

A few other 1,2,4-oxadiazole-4-oxides **1c-g**, with the same or different aryl substituents in positions 3 and 5 on the heterocyclic ring, easily available by cycloaddition of nitrile oxides to amidoximes,⁸ behaved similarly. Refluxing in chlorobenzene for 4 h afforded a mixture of nitriles and anhydrides while in the presence of 10 equiv. cyclooctene the nitriles and the ene adducts **10a-e** were formed (Table 1).

Table 1
Ene adducts **10a-e** by thermolysis of 3,5-diaryl-1,2,4-oxadiazole-4-oxides **1** in chlorobenzene (4 h)

10	Ar	mp °C, Solvent[a]	Yield % [b]	ν_{OH} , $\nu_{\text{C=O}}$ (cm ⁻¹)
a	Ph	102-4, B/L	81, (77)[c]	3126, 1604
b	2,4,6,-Me ₃ Ph	205-6, E	(73)[d]	2920, 1615
c	<i>p</i> -ClPh	153-4, B/L	87, (74)[e]	3000, 1588
d	<i>p</i> -MePh	110-1, B/L	83	3250, 1614
e	<i>p</i> -MeOPh	112-3, B/L	76	3131, 1614

[a]. B, Benzene; E, Ethanol; L, Ligroin; [b]. Isolated by crystallization or column chromatography of the residues of 3-phenyl-5-aryl-1,2,4-oxadiazole-4-oxides **1a,c-e**, unless otherwise stated; [c]. From **1g**;

[d]. From **1b** in refluxing toluene, 2 h; [e]. From **1f**.

The isomeric 1,2,5-oxadiazole 5-oxides (furoxans) undergo cleavage under significantly harsher conditions (>200°C) and afford nitriles and nitrile oxides, which may be trapped with suitable dipolarophiles or isomerize to isocyanates.¹² With bulky substituents the fragmentation is, however, more facile.¹³ The relatively easy cleavage of the 3,5-dimesityl-1,2,4-oxadiazole-4-oxide **1b** could be similarly ascribed to an increase of strain due to the *o,o'*-phenyl substituents.

The 3,5-diphenyl-1,2,4-oxadiazole-4-oxide **1a** was first described by Wieland in 1906¹⁴ and has attracted some attention in connection with the acid- and base-catalyzed dimerizations of nitrile oxides.¹⁵ Its chemistry remained, however, essentially unexplored. The results discussed here and the ones previously reported¹ show that these heterocycles undergo a clean thermal or photochemical cleavage and are ideal precursors of nitrosocarbonyls, a class of fleeting intermediates which are awaiting detection.

Acknowledgements

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