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Synthesis of 5-trichloromethyl-Δ^4-1,2,4-oxadiazolines and their rearrangement into formamidine derivatives

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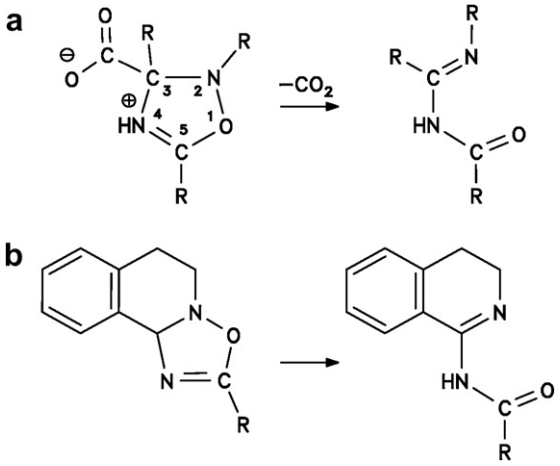
Abstract

A series of 5-trichloro-Δ^4-1,2,4-oxadiazolines have been synthesised by 1,3-dipolar cycloaddition of nitrones to trichloroacetonitrile. These oxadiazolines rearrange into formamidine derivatives, via ring opening and a 1,2-aryl shift from carbon to the adjacent amino nitrogen. Both cycloaddition and rearrangement are facilitated when electron deficient nitriles and electron rich nitrones are used.

Keywords: 1,2,4-Oxadiazolines; Amidines; Ring opening; Rearrangement

Δ^4-1,2,4-Oxadiazolines are a comparatively rare class of heterocycles, and to date, only a small number of derivatives have been described in the literature. The first reported Δ^4-1,2,4-oxadiazolines were made by the cycloaddition of nitrones to organic cyanates,[1] or by the reaction of nitrosobenzene with Δ^2-oxazolin-5-ones[2] or nitrile ylides.[3] The latter method usually produces mixtures of the Δ^3- and Δ^4-1,2,4-oxadiazolines, among other products. The most general synthetic method involves the cycloaddition of nitrones to electron deficient nitriles.[4] Aliphatic and aromatic nitriles can be activated by coordination to a suitable transition metal, for example, platinum(IV),[5] platinum(II)[6] and palladium(II)[7] centres. This technique also allows for chemoselective activation of nitriles in the presence of a more reactive C=C bond.[8] Moreover, a stereoselective synthesis in the coordination sphere of a chiral Pt(II) complex has been developed, leading to enantiomerically enriched Δ^4-1,2,4-oxadiazolines.[9]

Comparatively little is known about the reactivity and general properties of Δ^4-1,2,4-oxadiazolines. The poor stability of this type of compounds has occasionally been mentioned,[10] but not much effort seems to have been made to analyse the products formed. Δ^4-1,2,4-Oxadiazolines bearing a carboxylate at C3 on the ring undergo ring opening and decarboxylation to form *N*-acyl-formamidines,[2] as shown in Scheme 1. Similarly, a ring-opening H-migration reaction of Δ^4-1,2,4-oxadiazolines has been reported.[11]



Scheme 1. Rearrangements of Δ^4-1,2,4-oxadiazolines reported in the literature: (a) ring opening and decarboxylation;[2] (b) ring opening and H-migration.[11]

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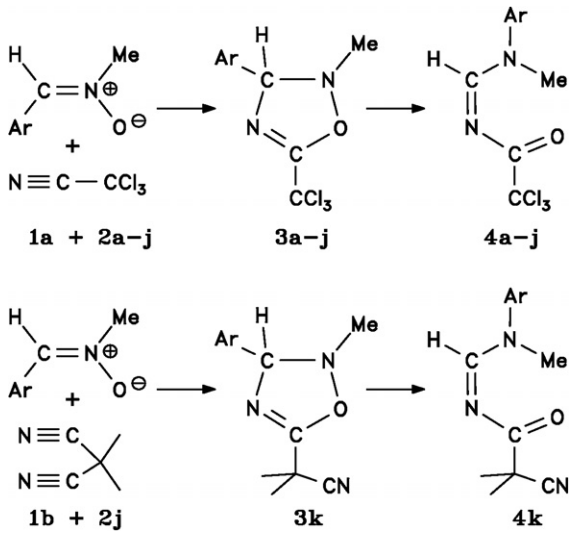
Formation of a related tautomeric rearrangement product has been observed in the coordination sphere of a platinum complex under an atmosphere of hydrogen.[12] In this case, the hydrogen attached to the amine nitrogen N2 and the electron lone pair of the imino N4 was blocked by coordination to the metal.

These intriguing observations prompted us to undertake the present study on the reaction of electron rich nitrones with trichloroacetonitrile (see Scheme 2 and Table 1) in the course of which we discovered a new type of rearrangement of Δ^4-1,2,4-oxadiazolines where ring opening is accompanied by a highly selective 1,2 aryl shift from the oxadiazoline C3 to the adjacent *amine* nitrogen N2, rather than the imino nitrogen N4. In the course of the reaction, no competing H migration was observed.

Nitrones **2a–j** were synthesised by the condensation of the corresponding aldehydes with *N*-methyl-hydroxylamine under the standard conditions.[13] As expected for acyclic aldonitrones,[14] the *Z*-configured products were obtained exclusively, except for the 2,6-dimethoxy- and 2,4,6-trimethoxy-derivatives (**2e** and **2j**) where a small amount of the *E*-configured nitrone could be detected in the NMR.



Scheme 2. Synthesis of the Δ^4-1,2,4-oxadiazolines studied in this work and their thermal rearrangement into formamidine derivatives.

All the synthesised nitrones underwent facile cycloaddition with trichloroacetonitrile **1a** to provide 5-trichloromethyl-Δ^4-1,2,4-oxadiazolines.[15] The reaction of a chloroform solution of the most reactive nitrone **2j** (0.17 M) with a tenfold excess of **1a** at 60 °C was complete within approximately 1 h, but reactions with less activated nitrones required 3–5 h under the same conditions. In the case of nitrones **2e** and **2j**, the *E*-isomer reacted slightly faster than the *Z*-isomer but, as expected, Δ^4-1,2,4-oxadiazolines **3e** and **3j**, respectively, were obtained. The reaction of nitrone **2j** with the less electron deficient dimethylmalononitrile **1b** was slow and required 4 days to complete. These trends are in good agreement with published kinetic data of similar reactions,[4b,c] and show that the cycloaddition is of 'normal electron demand'.[16] All the spectroscopic data of oxadiazolines **3** agreed well with those reported previously for 5-trichloromethyl-oxadiazolines,[4b,c] including the characteristic broad NMe and N–CH–N signals in the ^{1}H and ^{13}C NMR, which are due to nitrogen inversion taking place in the NMR dynamic range at room temperature. The chemical shift of the CCl_3 carbon (85 ppm) is similar to that in trichloroacetic anhydride (87.9 ppm) but significantly higher than in trichloroacetonitrile (70.1 ppm). Under GC–MS conditions, all the oxadiazolines underwent retro-cycloaddition, as previously observed for similar compounds.[4b,c,10]

Under prolonged reaction times the oxadiazolines rearranged into new products.[17] This reaction is facilitated when the substituent at C5 of the oxadiazoline is electron deficient and the migrating aryl group is electron rich, hence Δ^4-1,2,4-oxadiazolines that form easily are also fast to rearrange. The elemental analysis and spectroscopic data revealed the new product to be an isomer of the parent oxadiazoline for which structures **4** to **7** are possible (see Scheme 3). The ^{13}C NMR signal of the CCl_3 moiety

Table 1
Reaction conditions for the cycloaddition and rearrangement reactions

Nitrone		Δ^4-1,2,4-Oxadiazoline			Formamidine		
No.	Ar	No.	Conditions	Yield	No.	Conditions	Yield
2a	2-Methoxyphenyl	**3a**	60 °C, 5 h	(a)	**4a**	60 °C, 8 d	(b)
2b	2,3-Dimethoxyphenyl	**3b**	60 °C, 4 h	(a)	**4b**	60 °C, 8 d	(b)
2c	2,4-Dimethoxyphenyl	**3c**	60 °C, 3 h	(a)	**4c**	60 °C, 3 d	80%
2d	2,5-Dimethoxyphenyl	**3d**	60 °C, 4 h	(a)	**4d**	60 °C, 8 d	(b)
2e	2,6-Dimethoxyphenyl	**3e**	60 °C, 3 h	(a)	**4e**	60 °C, 8 d	78%
2f	3,4-Dimethoxyphenyl	**3f**	60 °C, 4 h	(a)	**4f**	60 °C, 4 d	44%
2g	2,3,4-Trimethoxyphenyl	**3g**	60 °C, 3 h	(a)	**4g**	60 °C, 8 d	(b)
2h	3,4,5-Trimethoxyphenyl	**3h**	60 °C, 4 h	(a)	**4h**	60 °C, 8 d	(b)
2i	2,4,5-Trimethoxyphenyl	**3i**	60 °C, 3 h	(a)	**4i**	60 °C, 2 d	79%
2j	2,4,6-Trimethoxyphenyl	**3j**	60 °C, 1 h	(a)	**4j**	60 °C, 12 h	82%
2j	2,4,6-Trimethoxyphenyl	**3k**	60 °C, 4 d	(a)	**4k**	60 °C, 70 d	66%

(a): NMR yields are nearly quantitative.
(b): NMR yields 15–25%, the rearrangement is accompanied by side reactions.