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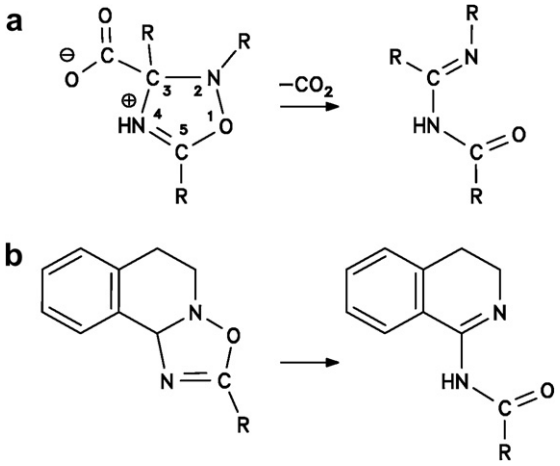
Keywords: 1,2,4-Oxadiazolines; Amidines; Ring opening; Rearrangement

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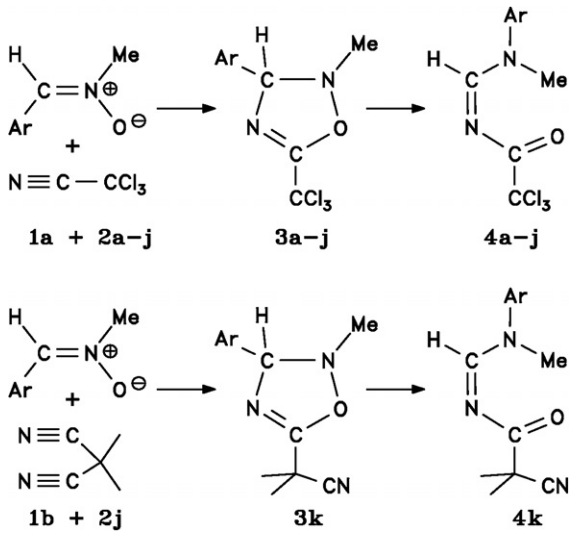
Formation of a related tautomeric rearrangement product has been observed in the coordination sphere of a platinum complex under an atmosphere of hydrogen.[12] In this case, the hydrogen attached to the amine nitrogen N2 and the electron lone pair of the imino N4 was blocked by coordination to the metal.

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.

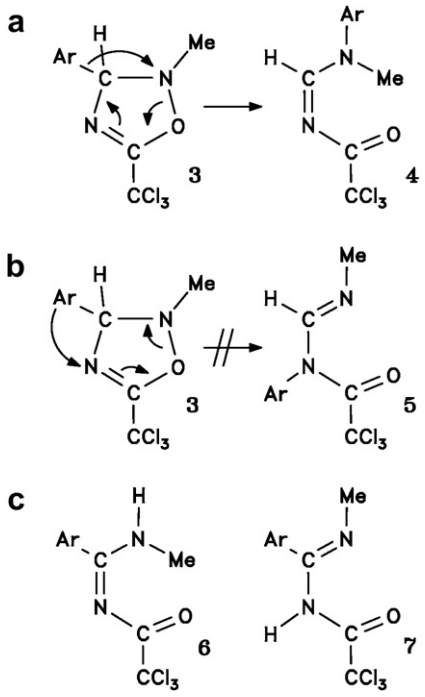
All the synthesised nitrones underwent facile cycloaddition with trichloroacetonitrile **1a** to provide 5-trichloromethyl-Δ^4-1,2,4-oxadiazolines.[15] The reaction of a chloroform solution of the most reactive nitrone **2j** (0.17 M) with a tenfold excess of **1a** at 60 °C was complete within approximately 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

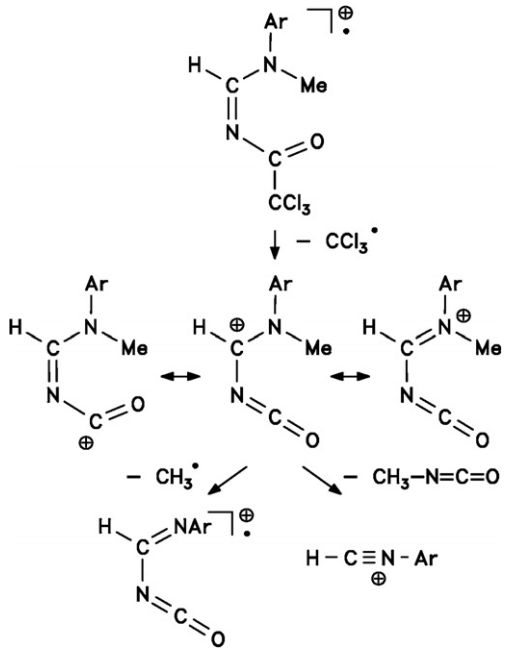
Table 1
Reaction conditions for the cycloaddition and rearrangement reactions

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.



Scheme 3. Proposed mechanism for the rearrangement of Δ^4-1,2,4-oxadiazolines into formamidine derivatives. Pathway (a) leads to the observed product, the alternative pathway (b) and the formation of products **6** and **7** were not observed.



Scheme 4. General EI mass fragmentation pattern of formamidines **4**.

appeared at 96 ppm in the typical range for trichloroacetyl groups, similar to trichloroacetamide (93.0 ppm) or trichloroacetyl chloride (94.1 ppm). ^{1}H and ^{13}C NMR data revealed the presence of an N–Me, an N–Ar, a C=O and an imino CH moiety. The latter appeared at a ^{13}C chemical shift of 163–166 ppm and was evident as a CH group in the DEPT spectrum. This correlated with a proton singlet at δ 8.3–8.7 in the ^{1}H, ^{13}C-HSQC, as one would expect for a N=CH group. The ^{1}H, ^{13}C-HSQC also showed that all the protons correlated to a carbon, excluding the possible presence of an NH group. The IR spectrum suggests the presence of a C=O and a C=N group, and confirmed the absence of an NH group. On the basis of these observations, structures **6** and **7** can be ruled out although their formation through an acid mediated process or rearrangement via H migration would have been plausible. The remaining two structures, **4** and **5**, can form via rearrangement of Δ^4-1,2,4-oxadiazolines as shown in Scheme 3. Both pathways involve an electrocyclic reaction with ring opening and aryl migration, but the direction of the electron flow is different. Consequently, pathway (a) involves aryl migration onto the amino nitrogen, whereas the alternative pathway (b) requires 1,2 aryl shift onto the imino N. The latter product is analogous to those described previously in the case of H-migration.[2,11]

On the basis of our NMR and mass spectrometry data, the product obtained in the experiment can be clearly identified as structure **4** whereas **5** can be ruled out. The typical MS fragmentation pattern is characterised by the loss of a CCl_3 radical from the molecular radical ion. The remaining amino substituted cyanate ion, which is usually the base peak in the spectrum, further decomposes via loss of a methyl radical from the amino nitrogen (−15 mass units, typically 2–5%), or under elimination of methylcyanate (−57 mass units, typically 30–35%). Only structure **4** is compatible with this type of fragmentation (see Scheme 4).

In the ^{1}H NMR, a strong NOE between the NMe and the aryl OMe or H in the *ortho* position was observed, in support of structure **4**. Accordingly, the HMBC spectrum displayed a strong cross peak for a long range correlation between the NMe protons and the *ipso*-carbon of the aryl substituent, suggesting that these two groups are bound to the same nitrogen. Additionally, DFT calculations (B3LYP/6-31G*) have been undertaken for the derivatives where Ar = Ph. These predicted that isomer **4** was 39.6 kcal/mol more stable than **5**.

The proposed reaction mechanism involves formation of a *Z*-configured product. Unfortunately, the stereochemistry cannot be determined from NOE measurements due to the lack of protons in the trichloroacetyl group. Compound **4k**, bearing a dimethylcyanomethyl moiety in the place of the CCl_3 group also did not display any NOE signals, which may be due to the compound adopting a preferred conformation where the dimethylcyanomethyl group points away from the NMeAr moiety, as depicted in Scheme 2. Attempts to determine the stereochemistry from the $^3J_{CH}$ coupling constant between the formamidine proton and the carbonyl carbon of the trichloroacetyl group were not fully conclusive due to the non-availability of the *E*-isomer for comparison. For compound **4j**, $^3J_{CH}$ was determined to be 6.3 Hz, which is in between the values for *Z*- or *E*-substituted propenoic acids ($^3J_{trans} = 10$ Hz, $^3J_{cis} = 5$ Hz),[18] and also significantly lower than the $^3J_{CH}$

value of 12 Hz observed in purine derivatives.[19] However, our DFT calculations suggest that the H–C–N–C moiety in **4** is not fully planar, and the Karplus dependence of $^3J_{CH}$ on the dihedral angle predicts that any deviation from planarity should lower the coupling constant. In light of this a value of 6.3 Hz is acceptable for trans- but not a cis-coupling, thereby supporting the *Z*-configuration of **4**.

In conclusion, a new method is reported for the synthesis of *N*-acyl-formamidines from easily accessible starting materials such as nitrones and nitriles, by means of a 1,3-dipolar cycloaddition followed by a new type of rearrangement consisting of ring opening and a concomitant 1,2-aryl shift from the oxadiazoline carbon to the adjacent amino nitrogen.

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Supplementary data

Synthetic procedures and spectroscopic data of nitrones **2**, oxadiazolines **3** and formamidines **4** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.012.

References and notes

1. (a) Grigat, E.; Pütter, R.; Mühlbauer, E. *Chem. Ber.* **1965**, *98*, 3777; (b) Hedayatullah, M.; Iida, H.; Denivelle, L. *C. R. Hebd. Seances Acad. Sci. Ser. C* **1970**, *271*, 146.
2. (a) Rodríguez, H.; Pavez, H.; Márquez, A.; Navarrete, P. *Tetrahedron* **1983**, *39*, 23–27; (b) Pavez, H.; Márquez, A.; Navarrete, P.; Tzichinovsky, S.; Rodríguez , H. *Tetrahedron* **1987**, *43*, 2223.
3. Burger, K.; Einhellig, K.; Roth, W.-D.; Daltrozzo, E. *Chem. Ber.* **1977**, *110*, 605.
4. (a) Samuilov, Ya. D.; Solov'eva, S. E.; Konovalov, A. I. *Zh. Obshch. Khim.* **1980**, *50*, 138; see also *Russ. J. Gen. Chem.* **1980**, *50*, 117; (b) Hermkens, P. H. H.; van Maarseveen, J. H.; Kruse, C. G.; Scheeren, H. W. *Tetrahedron* **1988**, *44*, 6491; (c) Eberson, L.; McCullough, J. J.; Hartshorn, C. M.; Hartshorn, M. P. *J. Chem. Soc., Perkin Trans. 2* **1998**, 41.
5. Wagner, G.; Pombeiro, A. J. P.; Kukushkin, V. Yu. *J. Am. Chem. Soc.* **2000**, *122*, 3106.
6. (a) Wagner, G.; Haukka, M.; Fraústo da Silva, J. J. R.; Pombeiro, A. J. P.; Kukushkin, V. Yu. *Inorg. Chem.* **2001**, *40*, 264; (b) Desai, B.; Danks, T. N.; Wagner, G. *Dalton Trans.* **2004**, 166; (c) Coley, H. M.; Sarju, J.; Wagner, G. *J. Med. Chem.* **2008**, *51*, 135.
7. Wagner, G. *Inorg. Chim. Acta* **2004**, *357*, 1320.
8. Desai, B.; Danks, T. N.; Wagner, G. *J. Chem. Soc., Dalton Trans.* **2003**, 2544.
9. Wagner, G.; Haukka, M. *J. Chem. Soc., Dalton Trans.* **2001**, 2690.
10. Sang, H.; Janzen, E. G.; Poyer, J. L. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1183.
11. Plate, R.; Hermkens, P. H. H.; Smits, J. M. M.; Nivard, R. J. F.; Ottenheijm, H. C. J. *J. Org. Chem.* **1987**, *52*, 1047.
12. Charmier, M. A. J.; Haukka, M.; Pombeiro, A. J. L. *Dalton Trans.* **2004**, 2741.
13. Tyrrell, E.; Allen, J.; Jones, K.; Beauchet, R. *Synthesis* **2005**, 2393.
14. Bjorgo, J.; Boyd, D. R.; Neill, D. C.; Jennings, W. B. *J. Chem. Soc., Perkin Trans. 1* **1977**, 254.
15. *General procedure for the synthesis of 3-(2,4,6-trimethoxyphenyl)-2-methyl-5-trichloromethyl-Δ^4-1,2,4-oxadiazoline* (**3j**): A 10-fold excess of trichloroacetonitrile (100 μl, 144.4 mg, 1 mmol) was added to a solution of nitrone **2j** (0.1 mmol) in $CDCl_3$ (0.5 ml). The reaction mixture was stirred at 60 °C and the progress of the reaction was monitored by ^{1}H NMR at regular time intervals. The cycloaddition was completed within 1 h. The crude product was used for the subsequent reactions without further purification. GC-TOF MS: 225 $[M-CCl_3CN\ (nitrone)]^+$ (11%), 209 $[nitrone-O]^+$ (6%), 208 $[nitrone-OH]^+$ (8%), 194 $[nitrone-OMe]^+$ (38%), 179 $[nitrone-NMeOH]^+$ (100%). IR (neat film, selected bands), cm^{-1}: 3004, 2962 and 2941 m ν(C–H), 2842 m ν(C–H of OMe), 1670 s ν(C=N), 1610 m ν(C=C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 2.95 (s, br s, 3H, NMe) 3.78 (s, 3H, OMe), 3.79 (s, 6H, 2 × OMe), 6.10 (s, 2H, aryl-H), 6.36 (s, br s, 1H, N–CH–N). ^{13}C NMR (125.8 MHz, $CDCl_3$), δ (ppm): 48.4 (CH_3, NMe), 55.5 (CH_3, OMe), 56.0 (CH_3, 2 × OMe), 85.8 (C_q, CCl_3), 87.6 (CH, N–CH–N), 91.1 (aryl CH), 106.5, 159.1 and 162.3 (aryl C_q), 160.1 (C_q, C=N).
16. (a) Wagner, G. *Chem. Eur. J.* **2003**, *9*, 1503; (b) Wagner, G.; Danks, T. N.; Desai, B. *Tetrahedron* **2008**, *64*, 477.
17. *General procedure for the synthesis of N-(2,4,6-trimethoxyphenyl)-N-methyl-N′-(trichloroacetyl)-formamidine* (**4j**): The crude Δ^4-1,2,4-oxadiazoline **3j** (0.1 mmol) in $CDCl_3$ (0.5 ml) or, alternatively, a solution of nitrone **2j** (0.1 mmol) and trichloroacetonitrile (10 μl, 14.44 mg, 0.1 mmol) in $CDCl_3$ (0.5 ml) was heated to 60 °C and the reaction was periodically monitored by ^{1}H NMR spectroscopy. The cycloaddition to the Δ^4-1,2,4-oxadiazoline and the subsequent rearrangement into the formamidine derivative was complete after 12 h. The product was purified by chromatography (SiO_2/CH_2Cl_2) and obtained as a colourless solid. Yield 82%. Elemental Anal. Calcd for $C_{13}H_{15}Cl_3N_2O_4$: C, 42.24; H, 4.09; N, 7.58. Found: C, 42.38; H, 3.87; N, 7.58. GC-TOF MS: 368, 370, 372 $[M]^+$ (1%, 1%, 0.3%), 337, 339, 341 $[M-OMe]^+$ (3%, 3%, 0.8%), 251 $[M-CCl_3]^+$ (100%), 236 $[M-CCl_3-Me]^+$ (4%), 194 $[M-CCl_3-MeNCO]^+$ (31%). Mp 124–126 °C.
18. Keah, H. H.; Rae, I. D. *Aust. J. Chem.* **1993**, *46*, 1413.
19. (a) Sečkářová, P.; Marek, R.; Maliňáková, K.; Kolehmainen, E.; Hocková, D.; Hocek, M.; Sklenář, V. *Tetrahedron Lett.* **2004**, *45*, 6259; (b) Hocková, D.; Buděšínský, M.; Marek, R.; Marek, J.; Holý, A. *Eur. J. Org. Chem.* **1999**, *10*, 2675.