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Reversal of Regiochemistry in the Synthesis of Isoxazoles by Nitrile Oxide Cycloadditions

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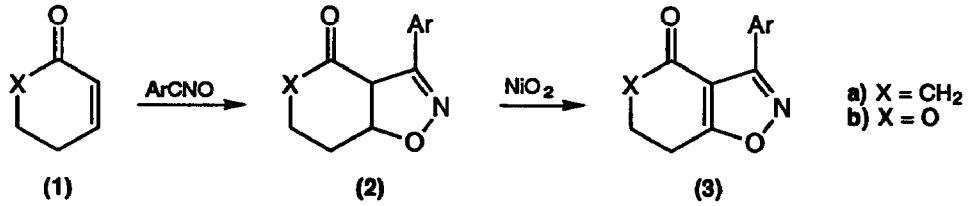
Abstract: The isoxazolines **2a**, **2b** and **8** obtained from nitrile oxide cycloadditions to cyclohex-2-enone **1a** and its analogues **1b** and **7** reacted with nickel peroxide to give the isoxazoles **3a**, **3b** and **9**. In contrast, the corresponding 2-bromocyclohex-2-enones **4a**, **4b** and **10**, prepared by bromination of the corresponding alkenes **1a**, **1b** and **7**, underwent nitrile oxide cycloadditions to afford the regioisomeric isoxazoles **6a**, **6b** and **12**, respectively.

Isoxazoles can be obtained by cycloaddition of nitrile oxides with alkynes or by dehydrogenation of the corresponding Δ^2-isoxazolines.[1] The latter method is particularly useful in ring systems where the alkynes are inaccessible. Using this approach we prepared the isoxazoline **2a** by reaction of 2,6-dichlorobenzonitrile oxide with cyclohex-2-enone **1a**.[2] The isoxazoline **2a** did not react with DDQ[3] or chloranil[4] under standard conditions used to dehydrogenate Δ^2-isoxazolines. However, nickel peroxide was found to be a mild and effective reagent for the preparation of the isoxazole **3a**[5] (Scheme 1).



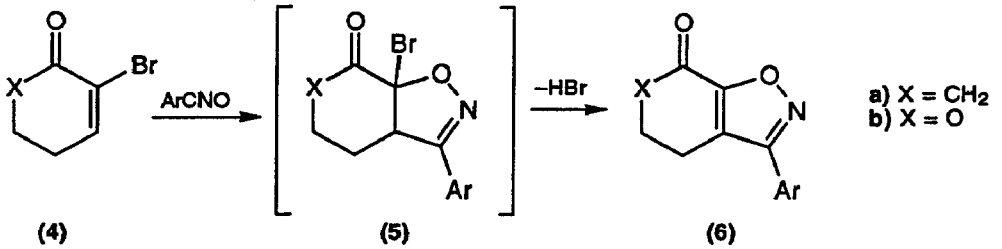
(1) (2) (3)

Scheme 1

The nitrile oxide cycloaddition to give the isoxazoline **2a** was regiospecific and the regiochemistry may be attributed to the electronic effect of the carbonyl substituent.[1] In order to obtain the regioisomeric isoxazole **6a** it was necessary to reverse the regiochemistry of the cycloaddition. We now report that the introduction of an α-bromo substituent on the alkene **1a** achieves this reversal. The regiocontrolled synthesis of each of the isoxazoles **3a**, **3b** and **9**, and **6a**, **6b** and **12** demonstrates the synthetic utility of this finding.

By a modification of Posner's method,[6] reaction of the alkene **1a** with bromine in dichloromethane at room temperature, followed by addition of triethylamine, gave the crystalline bromide **4a**.[7] Cycloaddition of

2,6-dichlorobenzonitrile oxide with this bromide **4a** led directly, and regiospecifically, to the isoxazole **6a**, the regioisomer of **3a**. Presumably the reaction proceeds through the cycloadduct **5a** which undergoes spontaneous dehydrobromination (Scheme 2).



Scheme 2

The structures of the isoxazoles **3a** and **6a** were confirmed by X-ray crystallographic analysis[8,9] (Figure 1) (See Table 1 for selected physical and spectroscopic data of key compounds).

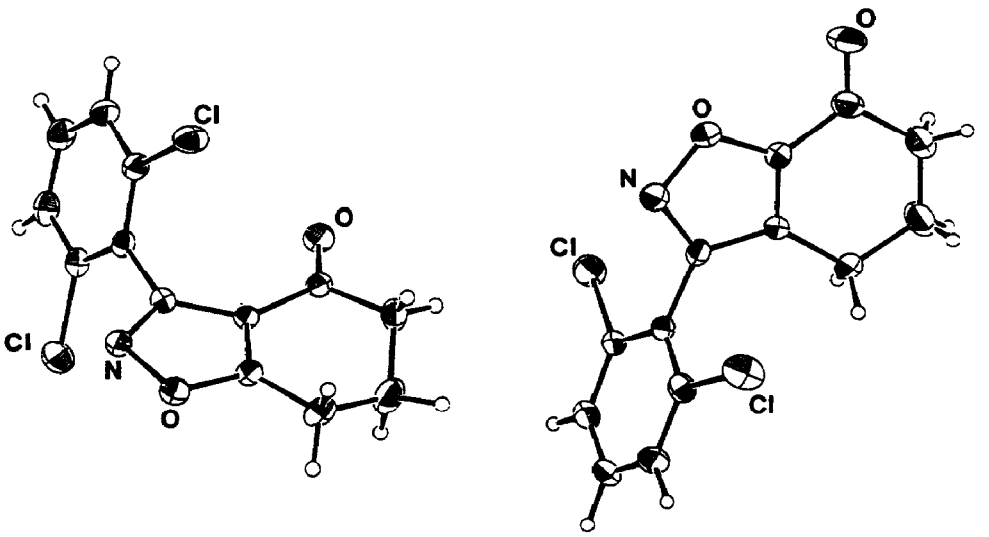


Figure 1. Molecular structures of **3a** and **6a**

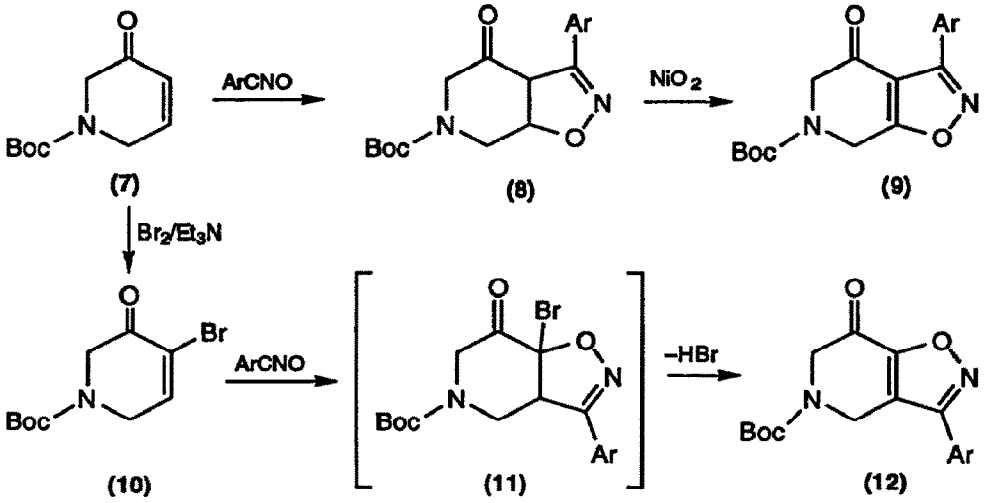
Presumably the steric influence of the bromo substituent of the alkene **4a** directs the regiochemistry of the cycloaddition of this compound, the reverse to that observed with the enone **1a**.

In further examples of this novel methodology (Schemes 1-3), the dihydropyranone **1b** and the dihydropyridinone **7**[10] underwent regiospecific cycloaddition to give the corresponding isoxazolines **2b** and **8**. Nickel peroxide again proved an effective dehydrogenating agent to convert the isoxazolines **2b** and **8** to the isoxazoles **3b** and **9**, respectively. Bromination[6] of the alkenes **1b** and **7** afforded the corresponding bromoalkenes **4b** and **10**. Each of these underwent regiospecific nitrile oxide cycloaddition to give the corresponding cycloadducts **5b** and **11**. The unisolated cycloadducts underwent spontaneous dehydrobromination to give the isoxazoles **6b** and **12**, which are regioisomers of the isoxazoles **3b** and **9** respectively.

Table 1. Selected physical and spectral data of key compounds

No.*	Yield%	M.p. (°C)	^{1}H n.m.r. δ ($CDCl_3$)
2a	40	150-1	1.7-2.7, m, 6H; 4.53, d, *J* 11.0 Hz, 1H; 5.26, dt, *J* 4.5, 11.0 Hz, 1H; 7.3-7.4, m, 3H
2b	64	159-62	2.26, m, 2H; 4.46, m, 1H; 4.69, ddd, *J* 3.0, 11.0, 11.0 Hz, 1H; 4.47, d, *J* 11.0 Hz, 1H; 5.32, m, 1H; 7.3-7.4, m, 3H
3a	65	166-9	2.31, m, *J* 6.0 Hz, 2H; 2.56, t, *J* 6.0 Hz, 2H; 3.14, t, *J* 6.0 Hz, 2H; 7.4-7.5, m, 3H
3b	69	175-7	3.34, t, *J* 6.5 Hz, 2H; 4.69, t, *J* 6.5 Hz, 2H; 7.4-7.5, m, 3H
4b	75	32-4	2.57, dt, *J* 4.5, 6.0 Hz, 2H; 4.49, t, *J* 6.0 Hz, 2H; 7.30, t, *J* 4.5 Hz, 1H
6a	53	109-11	2.24, m, *J* 6.0 Hz, 2H; 2.63, t, *J* 6.0 Hz, 2H; 2.73, t, *J* 6.0 Hz, 2H; 7.4-7.5, m, 3H
6b	50	106-7	2.89, t, *J* 6.0 Hz, 2H; 4.68, t, *J* 6.0 Hz, 2H; 7.4-7.5, m, 3H
7	56	oil	1.40, s, 9H; 4.05, s, 2H; 4.15, t, *J* 5.2 Hz, 2H; 6.10, dt, *J* 10.3, 5.2 Hz, 1H; 7.0, br, 1H
8	43	gum	1.52, s, 9H; 3.59, dd, *J* 15.1, 3.7 Hz, 1H; 3.90, d, *J* 19.0 Hz, 1H; 4.22, dd, *J* 15.1, 3.7 Hz, 1H; 4.53, m, 1H; 4.57, d, *J* 11.2 Hz, 1H; 5.26, dt, 11.2, 3.7 Hz, 1H; 7.25-7.45, m, 3H
9	87	75-78	1.52, s, 9H; 4.22, s, 2H; 5.00, s, 2H; 7.43, m, 3H
10	42	oil	1.48, s, 9H; 4.31, s, 4H; 7.42, m, 1H
12	25	foam	1.45, s, 9H; 4.38, s, 2H; 4.58, s, 2H; 7.45, m, 3H

* All new compounds gave satisfactory elemental analysis and spectral data



Scheme 3

In conclusion nickel peroxide has been shown to be a new reagent for the conversion of Δ^2-isoxazolines to isoxazoles, and α-bromination of cyclohex-2-enone and its analogues has been used to reverse the regiochemistry of cycloadditions with nitrile oxides providing direct regiocontrolled access to isoxazoles.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. Easton, C. J.; Hughes, C. M.; Savage, G. P.; Simpson, G. W. Adv. Heterocycl. Chem. 1994, 60, in press.
2. General procedure for nitrile oxide cycloadditions: A solution of 2,6-dichlorobenzohydroximoyl chloride (Dondoni, A.; Pedulli, G. F. *J. Org. Chem.* **1972**, *37*, 3564) (5 mmol) in THF (5 ml) was added dropwise to a solution of the enone (5 mmol) and triethylamine (5.5 mmol) in THF (8 ml) at room temperature. The solution was stirred at room temperature for 1 h, heated to reflux for 3 hrs, concentrated and the residue taken up in chloroform (20 ml). The solution was washed with water (3x10 ml), dried ($MgSO_4$) and concentrated under reduced pressure. Crystalline products were recrystallized from ethyl acetate/light petroleum.
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4. a) De Micheli, C.; Gandalfi, R.; Grünanger, P. *Tetrahedron*, **1974**, *30*, 3765; b) Akhrem, A. A.; Lakhvich, F. A.; Khripach, V. A.; Klebanovich, I. B.; *Tetrahedron Lett.* **1976**, *44*, 3983.
5. A suspension of nickel peroxide (Nakagawa, K.; Onoue, H.; Nakata, T. *J. Org. Chem.* **1962**, *27*, 1597) (11 mmol) in a solution of the isoxazoline (0.4 mmol) in benzene (10 ml) was stirred at reflux, under nitrogen, for 14 hrs, then cooled, filtered, and the filtrate was concentrated under reduced pressure to give the isoxazole, which was recrystallized from ethyl acetate/light petroleum (see also: Evans, D. L.; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, A. L., Jr.; Meyers, A. I. *J. Org. Chem.* **1979**, *44*, 497).
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7. Lie, R.; Undheim, K. *J. Chem. Soc. Perkin Trans. I*, **1973**, 2049.
8. Molecular structure of **3a**: monoclinic, $P2_1/c$, a = 10.065(2), b = 12.924(2), c = 10.369(2) Å, β = 107.99(1)°, Z = 4, R = 0.071 for 1172 observed data. Structural data have been submitted for publication in *Z. Krist.*
9. Molecular structure of **6a**: mono Cc, a = 21.688(4), b = 7.804(2), c = 14.921(2) Å, β = 103.14(1)°, Z = 8, R = 0.037 for 1515 observed data; absolute structure determined. Structural data have been submitted for publication in *Z. Krist.*
10. Prepared as follows: ethyl 3-hydroxy-1,2,3,6-tetrahydropyridine-1-carboxylate (Imanishi, T.; Shin, H.; Hanaoka, M.; Momose, T.; Imanishi, I. *Chem. Pharm. Bull.* **1982**, *30*, 3617) was treated with sodium hydroxide in ethanol to afford the parent amine. This amine reacted with di-*tert*-butyl dicarbonate and triethylamine in dichloromethane to give the N-Boc protected compound which was then oxidised with PCC in chloroform to give **7**.

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