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Practical route for N,O-heteroatom interchange in 3,5-disubstituted-4-nitroisoxazoles

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Abstract

Reaction of 3-methyl-4-nitro-5-alkylisoxazoles with hydroxylamine provides a practical means to interchange the N,O-heteroatoms on the isoxazole core thereby expanding the range of compounds obtainable from 3-methyl-4-nitro-5-styrylisoxazoles.

Keywords: Polyfunctional scaffolds; 4-Nitroisoxazole; Heteroatom interchange

1. Introduction

3-Methyl-4-nitro-5-styrylisoxazoles **1** represent a class of synthons that have been used for the preparation of several classes of compounds.[1–7] For example, we have shown that **1** could be employed for the preparation of spiroisoxazolines,[1,2] heteroarylpropionic acids,[3–5] 3-indolepropionic acids[6] and 3-arylglutaric acids.[7] Compounds **1** are easily accessible from the condensation of isoxazole **2** and an aromatic aldehyde **3**, which are commercially available materials (Fig. 1).

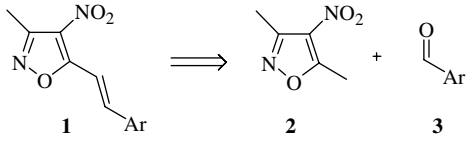
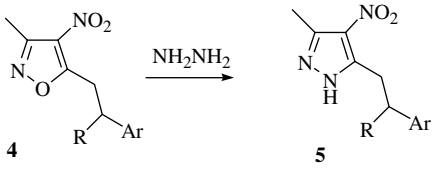


Fig. 1. Polyfunctional scaffold 5-styryl-4-nitroisoxazoles **1**.

As a part of our studies regarding the applications of **1** in synthesis (Scheme 1) we have revisited[4,5] a practical method to convert 4-nitroisoxazoles **4** into 4-nitropyrazoles **5**.[8] In this reaction, hydrazine attacks C-5 of the isoxazole, which is electrophilic by conjugation to the nitro group in C-4. This procedure involved refluxing 4-nitroisoxazoles **4** with a small excess of hydrazine (1.1 equiv) and furnished quantitative yields of 4-nitropyrazoles **5**.



Scheme 1. Conversion of 4-nitroisoxazoles into 4-nitropyrazoles.

Considering that hydroxylamine behaves primarily as an N-nucleophile, we speculated that its reaction with 3-methyl-4-nitroisoxazoles **6** would result in the formation of new regioisomeric isoxazoles **7**. This operation consists of a formal transposition of the C-3 and C-5 substituents (Scheme 2). The novel 5-methyl-4-nitroisoxazoles **7** could

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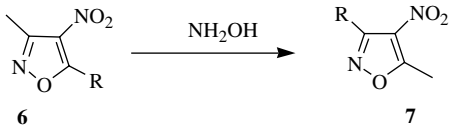


Scheme 2. A plan for heteroatom interchange in 4-nitroisoxazoles.

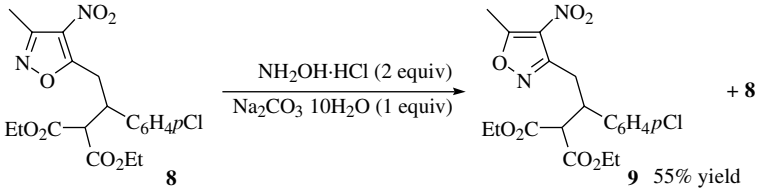
then be employed as starting materials in analogy to isoxazole **2**.

2. Results and discussion

Firstly, we reacted compound **8**[5] with 2 equiv of hydroxylamine hydrochloride and a base (Scheme 3). Analysis of the crude reaction mixture showed the presence of starting material **8** together with a new product in a 2:3 ratio. The new product was isolated in 55% yield using preparative TLC and characterised as the 5-methyl-4-nitroisoxazole **9**. Diagnostic for the assignment of compound **9** was the chemical shift of the C-5 methyl, which appeared at 2.77 ppm in the ^{1}H NMR spectrum.

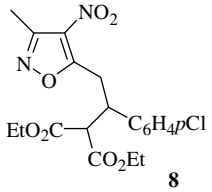
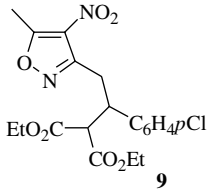
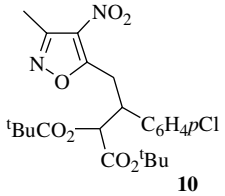
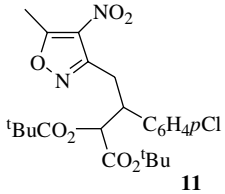
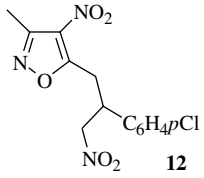
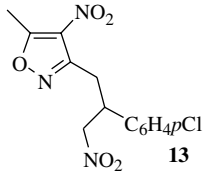
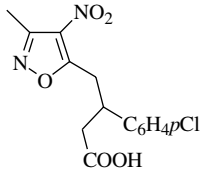
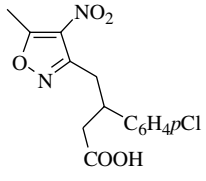
To explore the scope of this reaction, other isoxazoles were reacted under the same conditions (Table 1). Reaction of compounds **8**, **10**, **12** and **14** with 2 equiv of hydroxylamine hydrochloride and base furnished the isomeric isoxazoles **9**, **11**, **13** and **15** in good yields.

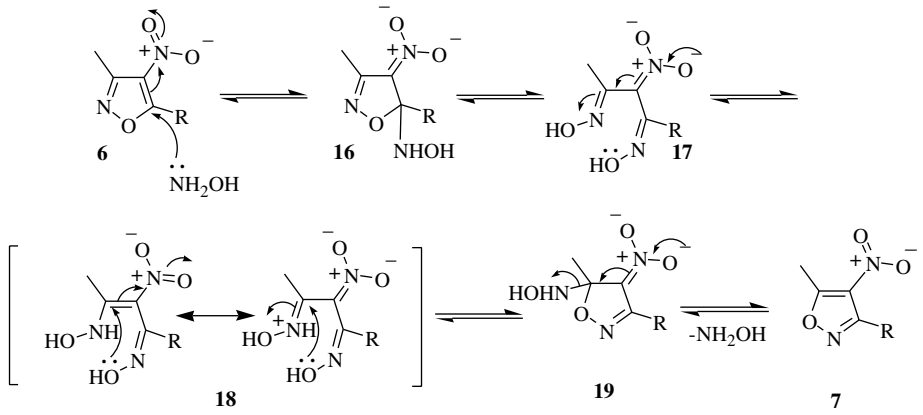
The following mechanism is proposed to explain the conversion of **8**, **10**, **12** and **14** to the corresponding **9**, **11**, **13** and **15** (Scheme 4). Preliminary addition of hydroxyl-



Scheme 3. Conversion of a 3-methyl-4-nitroisoxazole into a 5-methyl-4-nitroisoxazole.

Table 1
Conversion of 3-methylisoxazoles into 5-methylisoxazoles

Entry	Reactant	Product	Reactant:product in crude	Yield % of product
1	 **8**	 **9**	2:3	55
2	 **10**	 **11**	2:3	45
3	 **12**	 **13**	2:3	49
4	 **14**	 **15**	2:3	51

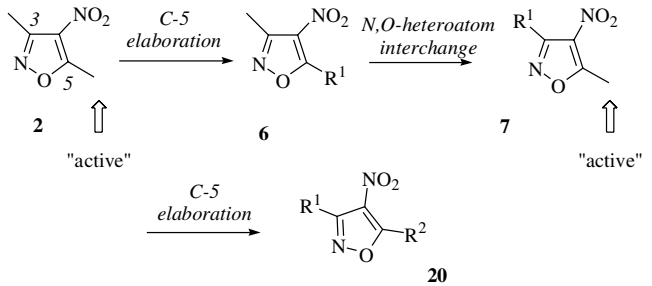


Scheme 4. Proposed mechanism for the conversion of isoxazole **6** into **7**.

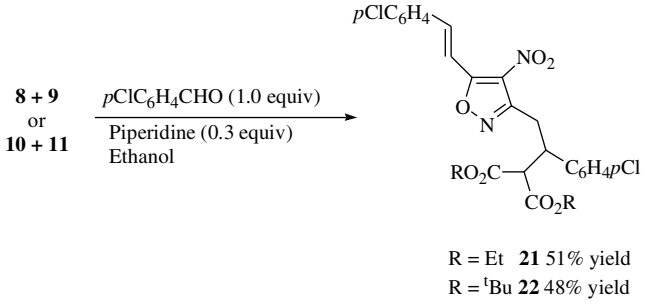
amine to isoxazole **6** would give **16** that would ring open to produce **17**. Subsequent rearrangement of **17** would give the stabilised iminium **18**, which could undergo an intramolecular cyclisation to furnish **19**. Finally, elimination of hydroxylamine from **19** would give inverted isoxazole **7**.

As would be expected on the basis of this mechanism, in which each step is an equilibrium, when compound **9** was reacted with hydroxylamine, a mixture of regioisomeric compounds **8** and **9** was obtained in the same 2:3 ratio (Scheme 2). Compound **9** is the major component due to its higher acidity compared to **8**, thus more of the anion of **9** is present in the basic media.

We envisaged a general strategy to prepare complex isoxazoles **20** from starting material **2** (Scheme 5). This plan involved a preliminary elaboration of the C-5 methyl to generate **6** followed by interchange of **6** to **7** and a final elaboration of **7** to **20**. Considering the versatility of 5-methyl-4-nitroisoxazoles[1–7] this strategy paves the way to the preparation of several complex isoxazoles in a regiocontrolled fashion. Thus the reactivity of the new isoxazoles **9** and **11** was examined by treating the regioisomeric mixtures **8**+**9** and **10**+**11** with *p*-chlorobenzaldehyde and base (Scheme 6). In both cases 5-styrylisoxazoles **21** and **22** were obtained in good yields together with unreacted **8** and **10**.



Scheme 5. A synthetic plan to prepare complex isoxazoles **20** from commercial isoxazole **2**.



Scheme 6. Preparation of 5-styrylisoxazoles **21** and **22**.

In conclusion, we have identified a simple strategy that has allowed an efficient construction of C-3 and C-5 substituents on 4-nitroisoxazoles. This methodology expands the range of products that can be obtained from 3,5-dimethyl-4-nitroisoxazole **2** and sets a general strategy for the preparation of complex isoxazoles using cheap and commercially available materials.

3. General procedure for the preparation of compounds 9, 11, 13 and 15 (Table 1)

A solution of hydroxylamine hydrochloride (0.350 g, 5 mmol), $Na_2CO_3{\cdot}10H_2O$ (0.720 g, 2.5 mmol) in water (5 mL) was added to a solution of **8**, **10**, **12** or **14** (2.4 mmol) in ethanol (10 mL). The reaction mixture was heated at reflux for 4 h, then allowed to reach room temperature, concentrated in vacuo and finally treated with dilute HCl. The colourless solid so obtained was filtered, dried, analysed by ^{1}H NMR and purified by preparative silica TLC (petroleum ether/ethyl acetate, 4:1).

3.1. 2-[1-(4-Chloro-phenyl)-2-(5-methyl-4-nitro-isoxazol-3-yl)-ethyl]-malonic acid diethyl ester **9**

Colourless solid, mp 83–84 °C (ethanol), ν_{max} (film)/cm^{-1}: 1743 (s), 1613 (m), 1510 (s), 1370 (m); δ_H (200 MHz, $CDCl_3$) 7.29–7.23 (4H, m, Ar), 4.24 (2H, q,

$J = 7$ Hz, CH_2O), 4.19–4.03 (1H, m, CHAr), 3.97 (2H, q, $J = 7$ Hz, CH_2O), 3.79 (1H, d, $J = 10$ Hz, $CHCO_2Et$), 3.45 (2H, d, $J = 7$ Hz, CH_2), 2.77 (3H, s, CH_3), 1.31 (3H, t, $J = 7$ Hz, CH_2CH_3), 1.04 (3H, t, $J = 7$ Hz, CH_2CH_3); δ_C (80 MHz) 172.0, 168.1, 167.6, 156.6, 138.2, 133.8, 129.9, 62.4, 62.1, 58.2, 42.3, 30.8, 14.5, 14.4, 14.2; Anal. Calcd for $C_{19}H_{21}ClN_2O_7$: C, 53.72; H, 4.98; N, 6.60. Found C, 53.38; H, 5.08; N, 6.27; MS (EI): m/z 424 (100%, M^+).

4. Synthesis of compounds 21 and 22

Piperidine (25 mg, 0.3 mmol) and a 2:3 mixture of compounds **8**+**9** or **10**+**11** (2 mmol) were added to a solution of *p*-chlorobenzaldehyde (170 mg, 1.0 mmol) in ethanol (20 mL). The reaction mixture was heated at reflux for 1 h, then the solvent was removed in vacuo. The crude material so obtained was purified by flash chromatography eluting with petroleum ether (40–70)/ethyl acetate 11:1 to give **21** or **22** as yellow solids.

4.1. 2-(1-(4-Chloro-phenyl)-2-{5-[2-(4-chloro-phenyl)-vinyl]-4-nitro-isoxazol-3-yl}-ethyl)-malonic acid diethyl ester **21**

Yellow solid, mp 130–131 °C (ethanol), ν_{max} (film)/cm^{-1}: 1751 (s), 1718 (s), 1628 (m), 1556 (s), 1365 (m); δ_H (200 MHz, $CDCl_3$) 7.69–7.23 (10H, m, Ar and CH=CH), 4.29 (2H, q, $J = 7$ Hz, CH_2O), 4.11 (1H, m, CHAr), 4.02 (2H, q, $J = 7$ Hz, CH_2O), 3.86 (1H, d, $J = 10$ Hz, $CHCO$), 3.53 (2H, $J = 7$ Hz, CH_2), 1.36 (3H, t, $J = 7$ Hz, CH_2CH_3), 1.05 (3H, t, $J = 7$ Hz, CH_2CH_3); δ_C (80 MHz) 168.1, 167.6, 167.5, 157.2, 147.2, 138.3, 137.8, 133.7, 133.2, 130.2, 130.0, 129.9, 129.1, 111.7, 62.5, 62.0, 58.3, 42.4, 31.0, 14.6, 14.2; Anal. Calcd for $C_{26}H_{24}Cl_2N_2O_7$: C, 57.05; H, 4.42; N, 5.12. Found C, 57.12; H, 4.39; N, 5.11; MS (EI): m/z 547 (90%, MH^+).

4.2. 2-(1-(4-Chloro-phenyl)-2-{5-[2-(4-chloro-phenyl)-vinyl]-4-nitro-isoxazol-3-yl}-ethyl)-malonic acid dibutyl ester **22**

Yellow solid, mp 185–186 °C (ethanol), ν_{max} (film)/cm^{-1}: 1745 (s), 1726 (s), 1610 (m), 1554 (s), 1375 (m); δ_H (200 MHz, $CDCl_3$) 7.71–7.17 (10H, m, Ar and CH=CH), 3.97 (1H, m, CHAr), 3.61 (1H, d, $J = 10$ Hz, $CHCO$), 3.43 (2H, $J = 7$ Hz, CH_2), 1.46 (9H, s, $(CH_3)_3C$), 1.20 (9H, s, $(CH_3)_3C$); δ_C (80 MHz) 167.3, 167.1, 157.2, 141.7, 138.6, 137.4, 133.3, 133.1, 130.3, 129.8, 129.7, 128.7, 111.6, 66.0, 64.6, 59.8, 41.9, 31.4, 28.1, 27.8; Anal. Calcd for $C_{30}H_{32}Cl_2N_2O_7$: C, 59.71; H, 5.34; N, 4.64. Found C, 59.78; H, 5.69; N, 4.98; MS (EI): m/z 529 (90%, M^+).

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