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Epoxidation of 3-methyl-4-*N*-acetyl-5-styrylisoxazoles

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Abstract—An efficient synthesis of novel isoxazoloepoxides is described. The title compounds were obtained in high yields and without the use of chromatography.

1. Introduction

The isoxazole nucleus has been recognised as an important heterocycle in medicinal chemistry.[1] Several reports have appeared describing the biological activity of isoxazoles as selective agonists of the dopamine D_4 receptor,[2] $GABA_A$ antagonists,[3] analgesics,[4] antiinflammatories,[4] antimicrobials,[5] antifungals,[5] COX-2 inhibitors,[6] antinociceptives[7] and anticancer agents.[8] For this reason the synthesis of novel compounds containing the isoxazole core is of interest for the academic and industrial communities.

3-Methyl-4-nitro-5-styrylisoxazoles **1** (Fig. 1) represent a class of polyfunctional scaffolds, which hold excellent potential for the generation of diversity.[9–15] Our approach to the development of multicomponent diversity oriented syntheses is based on the generation of building blocks containing several functionalities which can be reacted selectively.[9–15] For example, we have shown that **1** could be employed efficiently for the preparation of spiroisoxazolines,[9,10] heteroarylpropionic acids[11–14] or 3-indolepropionic acids.[15] In these syntheses, the two electrophilic centres present in **1** were reacted selectively and independently. Compounds **1** are easily accessible from the condensation of isoxazole **2** and an aromatic aldehyde **3**, which are commercially available materials.

As part of our ongoing studies on the generation of chemical diversity using polyfunctional scaffolds, we became interested in the preparation of epoxides **4** (Fig. 1). Similar to compounds **1**, epoxides **4** possess two electrophilic centres that can be reacted selectively. Epoxides are versatile synthons that can be regio- and stereoselectively ring opened when reacted with suitable nucleophiles. Additionally, several methods of asymmetric epoxidation of alkenes are available, which can be used to prepare **4** in enantiopure form.[16] Therefore, compounds **4** constitute a stereospecific version of scaffolds **1** that we hope to employ to generate diversity in stereoselective fashion. Considering that a 4-nitroisoxazole core represents a masked carboxylate[10–15] or a protected β-diketone,[1] it is easy to envisage the potential of compounds **4** in diversity oriented syntheses.

We started our investigation with the epoxidation of 3-methyl-4-nitro-5-styrylisoxazole **1a** (Scheme 1). This was a logical starting point as compounds **1** are accessible from commercially available materials (Fig. 1).

The oxidation of **1a** was attempted using several oxidation methods, which included uncatalysed processes, metal catalysed processes and organo catalytic procedures. Unfortunately, the preparation of **6** proved elusive. Compound **1a** was reacted with ^{t}BuOOH/Bu_4NBr; H_2O_2 in a basic medium (Et_3N or KOH); Bu_4NIO_4; *m*-CPBA; (Salen)Ru^{III}/^{t}BuOOH; (Salen)Cr^{II}/^{t}BuOOH; (Salen)Zn^{II}/^{t}BuOOH; (Salen)Mn^{II}/^{t}BuOOH; and dimethyldioxirane (DMD). However, compound **1a** was recovered quantitatively at the end of each experiment, showing a remarkable stability in the presence of oxidants. We concluded that the resistance to oxidation was due to conjugation of the exocyclic alkene in **1a** with

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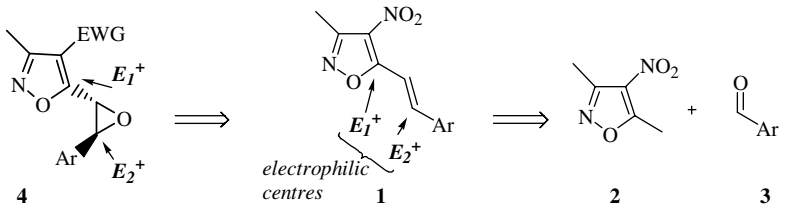
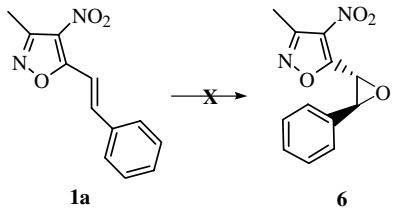


Figure 1. Two polyfunctional scaffolds: 5-styryl-4-nitroisoxazole **1** and isoxazoloepoxides **4**.



Scheme 1. Epoxidation of 3-methyl-4-nitro-5-styrylisoxazole.

the nitro group. Therefore, it was decided to replace the nitro group with a milder electron withdrawing group. In our plan an electron withdrawing group was required to maintain C-5 of the isoxazole (E_1^+) activated towards nucleophilic addition. The *N*-acetoxy group was selected considering its ease of preparation from isoxazoles **1a**–**g**.

Compounds **1a**–**g** were submitted to reduction using $SnCl_2$, and amines **3a**–**g** were obtained in good yields. Subsequent acetylation of the amino group in **3a**–**g** furnished the desired *N*-acetylisoxazoles **4a**–**g**. These two steps could be performed in one-pot and **4a**–**g** were obtained without the need for isolating **3a**–**g** (Scheme 2, Table 1). Compounds **4a**–**g** were reacted with Oxone® and acetone, a standard procedure to generate dimethyldioxirane in situ.[16] We were delighted to observe that under these conditions, epoxidation of **4a**–**g** afforded **5a**–**g** in high yields (Table 2). Compounds **5a**–**g** were obtained sufficiently pure to be carried to the next transformation without the use of chromatography. We have also shown that synthons **5a**–**g** could be prepared from **1a**–**g** without purification of intermediates **3a**–**g** and **4a**–**g** (Scheme 3).

This rendered the synthesis of epoxides **5a**–**g** operationally simple. The electronic nature of the substituent on the aromatic group could be varied to include electron releasing and withdrawing groups without this being detrimental to the epoxidation yield (Scheme 3 and Table 2).

Table 1. One-pot preparation of **4a**–**g**

Entry	Compound	Ar	Yield[a] (%)
1	**4a**	Ph–	86
2	**4b**	*p*-CH_3–C_6H_4	87
3	**4c**	*p*-CH_3O–C_6H_4	76
4	**4d**	*p*-Cl–C_6H_4	81
5	**4e**	*p*-($NHCOCH_3$)–C_6H_4	63
6	**4f**	3,4-CH_3O–C_6H_3	72
7	**4g**	2,4,6-CH_3–C_6H_2	79

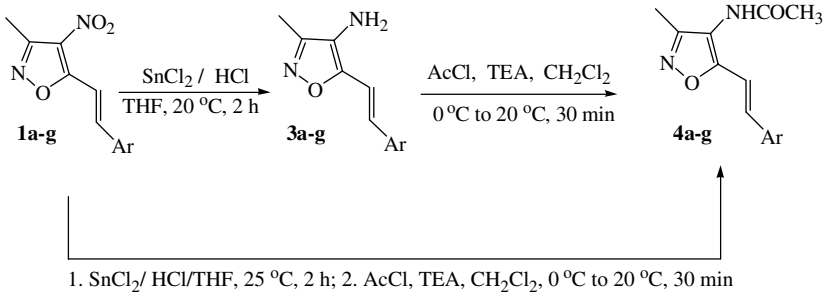
[a] Isolated yield after work up.

Given the presence of several functionalities in compounds **5a**–**g**, they constitute a class of ideal starting materials for further synthetic transformations. For example, the epoxide can be ring opened by a variety of nucleophiles and once the epoxide is reacted, the isoxazole ring could be elaborated to an isoxazoline, a carboxylate, a polyaminoalcohol, or an eneaminone. In conclusion, we have developed a synthetic method to prepare compounds **5a**–**g**, which were obtained in high yields and without the use of chromatography. Studies on the asymmetric epoxidation of **5a**–**g** and their

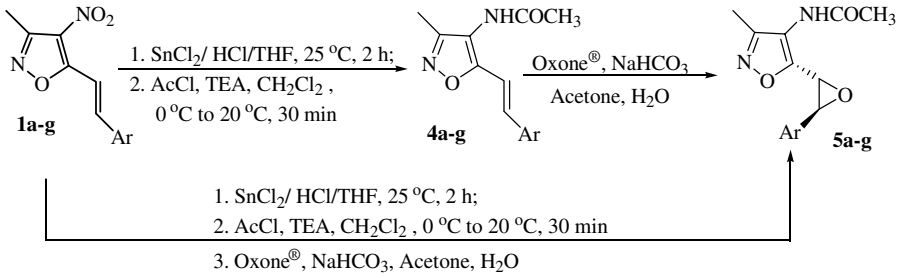
Table 2. Preparation of isoxazoloepoxides **5a**–**g**

Entry	Compound	Ar	Yield[a] (%)
1	**5a**	Ph–	95
2	**5b**	*p*-CH_3–C_6H_4	84
3	**5c**	*p*-CH_3O–C_6H_4	86
4	**5d**	*p*-Cl–C_6H_4	82
5	**5e**	*p*-($NHCOCH_3$)–C_6H_4	78
6	**5f**	3,4-CH_3O–C_6H_3	81
7	**5g**	2,4,6-CH_3–C_6H_2	82

[a] Isolated yield after work up.



Scheme 2. Stepwise and one-pot syntheses of isoxazoles **4a**–**g**.



Scheme 3. Epoxidation of 3-methyl-4-*N*-acetyl-5-styryl isoxazoles.

use for the preparation of polyhydroxylated synthons are in progress.

2. General procedure for the preparation of compounds 4 (Table 1)

To a solution of 3-methyl-4-nitro-5-styrylisoxazole **1a** (0.46 g, 2 mmol) in THF was added $SnCl_2{\cdot}2H_2O$ (1.35 g, 6 mmol) followed by dropwise addition of conc. HCl (4 mL). The reaction mixture was stirred at room temperature for 2 h, then poured into a cold solution of 10% NaOH (40 mL) and extracted with ethyl acetate (2×20 mL). The combined organic layer was dried and concentrated in vacuo, then treated with H_2O (50 mL) and extracted with CH_2Cl_2 (2×15 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and cooled to 0–5 °C. Next, acetyl chloride (0.23 mL) and triethylamine (0.45 mL) were added dropwise, the reaction mixture was allowed to reach room temperature and then stirred for 30 min. After this time, the reaction was diluted with CH_2Cl_2 (30 mL), washed with water, then brine, dried over Na_2SO_4, filtered and finally concentrated to obtain title compound **4a** as a colourless solid (0.415 g, 86% yield).

N-(3-Methyl-5-styryl-isoxazol-4-yl)-acetamide **4a**: δ_H (400 MHz, $CDCl_3$) 7.40–7.38 (2H, m, Ar-H), 7.30–7.29 (3H, m, Ar-H), 7.24 (1H, br s, NH), 7.17–7.16 (1H, m, CH), 6.70 (1H, d, $J = 16$, CH), 2.12 (6H, s, $COCH_3$, CH_3): δ_c (100.6 MHz) 169.6, 161.2, 158.4, 135.5, 134.5, 129.0, 128.8, 127.4, 113.7, 111.0, 23.1, 9.8; HRMS found: $[M^+]$ 242.1045, $C_{14}H_{14}N_2O_2$ requires 242.1055; *m/z*: 242 (100%, M^+).

3. General one-pot procedure for the preparation of compounds 5 (Table 2)

To a solution of *N*-(3-methyl-5-styryl-isoxazol-4-yl)-acetamide, **4a** (0.516 g, 2 mmol) in acetone (50 mL) was added water (25 mL) followed by $NaHCO_3$ (1 g, 12 mmol, 6 equiv). The reaction mixture was cooled to 5 °C and then added to a solution of Oxone® (1.89 g, 3 mmol, 1.5 equiv) in water (25 mL) maintaining the temperature at 5–10 °C. The reaction mixture was stirred for 2 h at 5–10 °C, then brought to room temperature and stirred for a further 10 h. After this time, the inorganic salts were removed by filtration, the liquid phase concentrated in vacuo, and the residue taken up in chloroform (10 mL). The chloroform layer was washed with brine, dried over Na_2SO_4 and finally evaporated to give pure **5a** (0.490 g, 95% yield) as a colourless oil.

N-[3-Methyl-5-(3-phenyl-oxiranyl)-isoxazol-4-yl]-acetamide **5a**: δ_H (400 MHz, $CDCl_3$) 7.31–7.22 (5H, m, Ar-H), 4.32–4.31 (1H, d, $J = 2$ Hz, O–CH), 3.92 (1H, d, $J = 2$ Hz, O–CH), 2.14 (3H, s, $COCH_3$), 2.07 (3H, s, CH_3); δ_c (100.6 MHz) 169.4, 158.8, 158.2, 135.1, 128.8, 128.7, 125.6, 116.6, 59.3, 54.1, 23.0, 10.0; HRMS found: $[M^+]$ 258.1031, $C_{14}H_{14}N_2O_3$ requires 258.1004; *m/z*: 258 (100%, M^+).

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