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Preparation and reactivity of [2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-amines

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ABSTRACT

Herein, we report our investigation into the reactivity of 5-enamino-4-nitroisoxazoles. This study revealed that the title compounds, in spite of conjugation to the 4-nitroisoxazole, displayed similar reactivity to enamines, reacting with electrophiles to form new C–C, C–N, and C–Cl bonds.

β-Enaminoesters **1** are a class of key intermediates in organic synthesis,[1] employed as starting materials for the preparation of many types of heterocyclic moieties[2] or as precursors for a variety of biologically active compounds including antibacterial,[3] anticonvulsant,[4] anti-inflammatory,[5] and antitumor agents (Fig. 1).[6] Several procedures have been described for their preparation: direct condensation of amines and β-ketoesters followed by Lewis acid catalysis,[7] addition of amines to alkynes,[8] addition of ester enolates to nitriles,[9] addition of ester enolates to tosyl imines,[10] and the Reformatsky reaction of zinc ester enolates with dialkylformamides.[11]

It has been shown that 3,5-dimethyl-4-nitroisoxazole **4** reacts with dimethylformamide to give the expected condensation product **2** as a single diastereoisomer (Fig. 2).[12] This procedure has allowed the preparation of compound **2** in high yields using an operatively simple procedure. In addition, being a solid, compound **2** was obtained in pure form by crystallization.

Our group has developed the synthesis of 3-methyl-4-nitro-5-styrylisoxazoles **3** and demonstrated this class of compounds to be excellent Michael acceptors, capable of reacting with many soft nucleophiles to provide the corresponding 1,6 addition products in high yields.[13] Crucial to the observed behavior is the conjugation of the 5-ethenyl electrophile with the 4-nitro group. Compounds **3** were found to react under phase transfer catalysis providing the corresponding nitroadducts,[14] cyclopropanes,[15] and pyrrolidines[16] in high enantiomeric excess. Recently, compounds **3** were employed as a key synthon in the development of a novel process to manufacture γ-aminoacids[17] and in particular the Active Pharmaceutical Ingredient (*S*)-Pregabalin.[18] Following our reports,[14–18] other groups have used compounds **3** to develop organocatalytic asymmetric procedures confirming, therefore, the high synthetic value of these reagents.[19]

Compound **2** bears a structural similarity to enamines **1** which are known to behave as nucleophilic species. However, compound **2** also contains the 4-nitroisoxazole core which is known to render conjugated alkenes highly electrophilic. Therefore, at least in principle, compound **2** could be considered as either an electrophilic or a nucleophilic synthon. In order to establish its chemical nature, we have carried out a study in which compound **2** was reacted with nucleophiles and electrophiles. This study showed that compound **2** behaved exclusively as an activated enamine, in spite of the counter effect exerted by the conjugated nitro group.

At the onset, we screened **2** against common nucleophiles including soft enolizable nitroalkanes, alkylmalonates, indoles, bisulfite, and *S*-nucleophiles. These reactions were carried out under Lewis acid and basic catalysis. In all experiments, unreacted compound **2** was recovered, even after prolonged heating. The reaction of compound **2** with harder nucleophiles such as Grignard reagents, *n*BuLi or copper organometal species furnished a complex reaction mixture. This was explained by considering the electrophilicity of the isoxazole C-5, which likely reacted with the nucleophiles leading to formation of an unstable isoxazoline that underwent uncontrolled fragmentation. Surprisingly, the reaction

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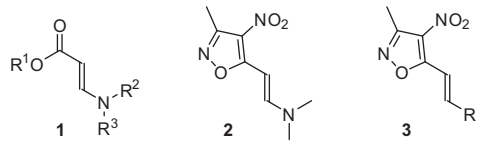


Figure 1. β-Enaminoesters **1**, dimethyl-[2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-amine **2**, and 3-methyl-4-nitro-5-styrylisoxazoles **3**.

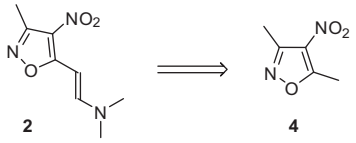
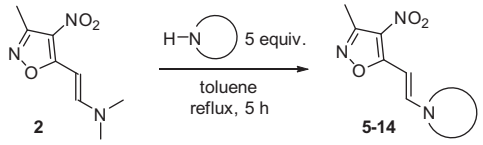


Figure 2. Retrosynthesis of dimethyl-[2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-amine **2**.

of **2** with amine nucleophiles occurred easily, generating the corresponding *N*-substituted products in high yields (Table 1). The reactions were conducted by heating **2** in toluene at reflux for 5 h with 5 equiv of the cyclic amine. This procedure furnished the desired enamines **5**–**14** in 76–99% yields as single (*E*)-isomers (Table 1). The ease of purification of compounds **5**–**14**, which only involved evaporation of the reaction mixture under reduced pressure, ensured that the desired compounds **5**–**14** were obtained in high yields.

The reactivity of enamines selected from compounds **5**–**14** with electrophiles was investigated (Table 2) by the reaction with *N*-electrophiles diethyl azodicarboxylate (DEAD) and diisopropyl azodicarboxylate (DIAD). Delightfully, these reactions progressed to full conversion, providing the desired products in high isolated yields and as a near 1:1 mixture of (*E*) and (*Z*) isomers. It was noteworthy that an increase of the steric hindrance of the cyclic amine lead to a small change in the *E*/*Z* ratio from 1:1 to 4:6, presumably favouring the (*Z*) isomer (Table 2, entries 5, 7, and 8).

Table 1
Synthesis of 1-[2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-amines **5**–**14**



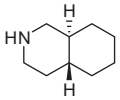
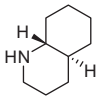
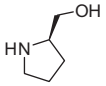
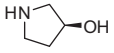
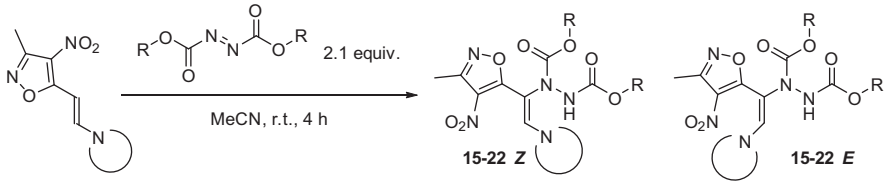
Entry	H–N	Product	Yield (%)
1		**5**	99
2		**6**	96
3		**7**	98
4		**8**	92
5		**9**	76
6		**10**	95
7		**11**	96
8		**12**	89
9		**13**	93
10		**14**	86

Table 2
Reaction of selected enamines with DEAD or DIAD



Entry	H–N	R	Product	Yield (%)	(*E*/*Z*) ratio
1	$-NEt_2$	–Et	**15**	75	1:1
2		–Et	**16**	88	1:1
3		–Et	**17**	89	1:1
4		–Et	**18**	84	1:1
5		–Et	**19**	84	4:6
6	$-NEt_2$	–*i*Pr	**20**	92	1:1
7		–*i*Pr	**21**	89	4:6
8		–*i*Pr	**22**	79	4:6