Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Ravindra Dere, Claudio Monasterolo, Maria Moccia, Mauro F. A. Adamo *

Centre for Synthesis and Chemical Biology (CSCB), Department of Pharmaceutical and Medicinal Chemistry, The Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin 2, Dublin, Ireland

ARTICLE INFO

Article history:
Received 30 September 2015
Revised 9 November 2015
Accepted 11 November 2015
Available online xxxx

Keywords:
Polyfunctional scaffolds
4-Nitroisoxazoles
Isoxazoles
Enamines

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

* Corresponding author. Tel.: +353 1 4022208; fax: +353 1 4022168.
E-mail address: madamo@rcsi.ie (M.F.A. Adamo).

http://dx.doi.org/10.1016/j.tetlet.2015.11.037
0040-4039/

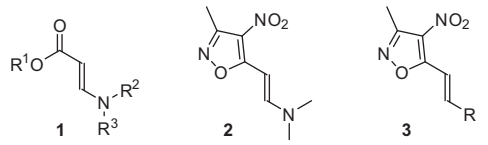


Figure 1. β-Enaminoesters **1**, dimethyl-[2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-amine **2**, and 3-methyl-4-nitro-5-styrylisoxazoles **3**.

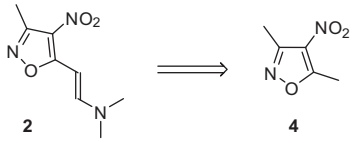
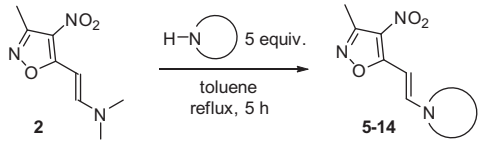


Figure 2. Retrosynthesis of dimethyl-[2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-amine **2**.

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**



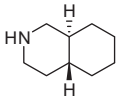
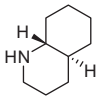
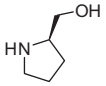
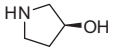
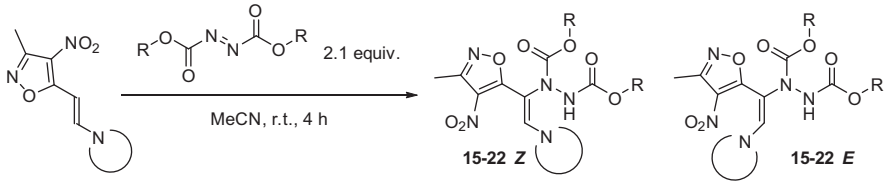
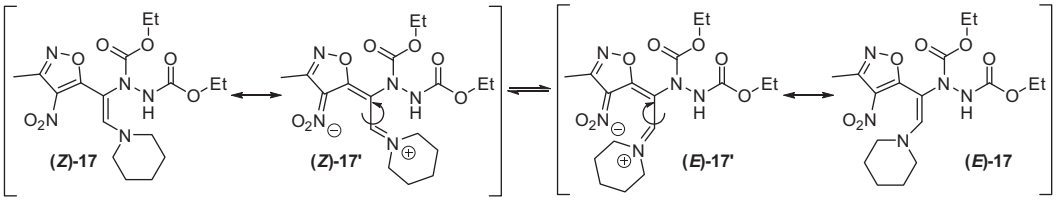
Entry	H–N	Product	Yield (%)
1		**5**	99
2		**6**	96
3		**7**	98
4		**8**	92
5		**9**	76
6		**10**	95
7		**11**	96
8		**12**	89
9		**13**	93
10		**14**	86

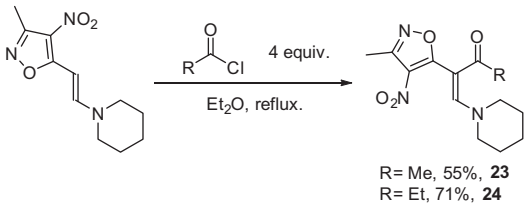
Table 2
Reaction of selected enamines with DEAD or DIAD



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



Scheme 1. Inter-conversion of (*Z*)-**17** to (*E*)-**17** in solution.



Scheme 2. Reaction of enamine **5** with acyl chlorides.

Compounds **15**–**22** (Table 2) could not be separated as single (*E*) or (*Z*) diastereoisomers by column chromatography. However, it was possible to crystallize compound (*Z*)-**17** and obtain a single crystal X-ray diffraction measurement thereby confirming its structure (Fig. 3).[20] Interestingly, a pure sample of (*Z*)-**17** established equilibrium with its (*E*) form, rapidly forming a 1:1 *E*/*Z* mixture in solution. It is possible that the electron withdrawing character of the hydrazine moiety in compound **17** favored resonance structure (*Z*)-**17**′, thereby allowing rotation along the enamine bond and consequent (*Z*) to (*E*) inter-conversion (Scheme 1).

The reactivity of compound **5** was further investigated by its reaction with acetyl chloride and propionyl chloride (Scheme 2). Hence, a solution of compound **5** was treated with acyl chloride and the resulting mixture heated at reflux for 4 h. These reactions provided the corresponding ketones **23** and **24** in 55% and 71% yields, respectively. Interestingly, compounds **22** and **23** were solely obtained as the (*E*)-isomers, thus demonstrating the capability of the 1-[2-(3-methyl-4-nitro-isoxazol-5-yl)-vinyl]-amines to react with carbon electrophiles in a stereoselective fashion. The structure of compound **23** was confirmed by single crystal X-ray diffraction (Fig. 4).[21]

Once it was established that compound **5** reacted as an enamine, we studied its reaction with the electrophilic halogenating reagent *N*-chlorosuccinimide (NCS). Hence, compound **5** was reacted with NCS in an attempt to prepare compound **25**

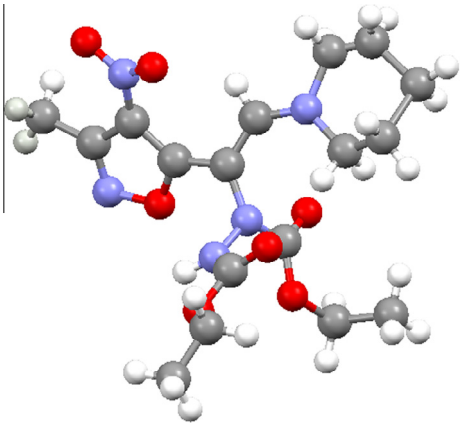


Figure 3. X-ray diagram of compound (*Z*)-**17**.

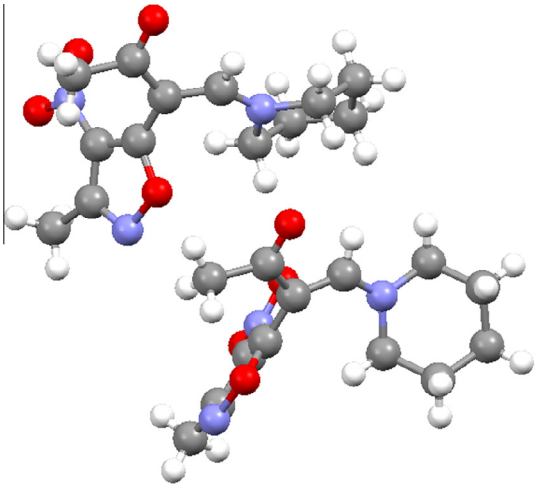
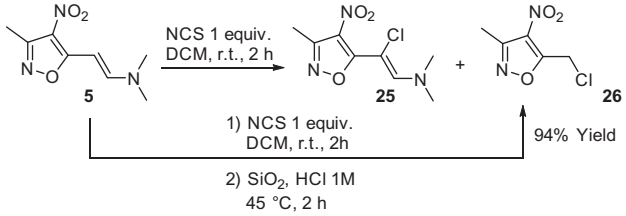


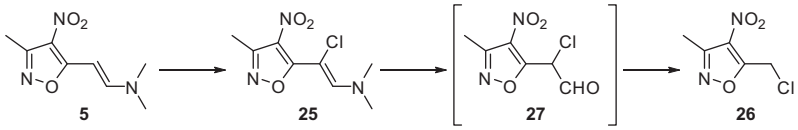
Figure 4. X-ray diagram of compound **23**.



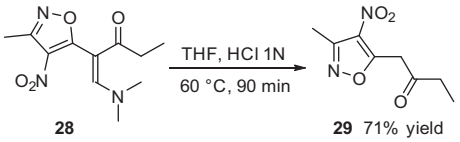
Scheme 3. Reaction of enamine **5** with *N*-chloro succinimide.

(Schemes 3 and 4). Compound **5** was completely converted to the desired compound **25**, which, however, could not be purified as it rapidly decomposed on silica gel to provide a mixture of **25** and 5-chloromethyl-4-nitroisoxazole **26**. Evidence for the formation of compound **25** was obtained by ^{1}H NMR analysis of the crude reaction mixture. Inspired by this finding, we optimized a procedure which allowed the conversion of compounds **5**–**26** in high yield. Hence, **5** was first submitted to chlorination to give **25**, followed by treatment of the reaction mixture with silica gel and hydrochloric acid to provide **26** in 94% isolated yield. It should be noted that attempts to prepare alkyl chloride **26** via the chlorination of commercially available 3,5,dimethyl-4-nitroisoxazole **4** led to complex mixtures of mono-, di-, and tri-chloromethyl compounds. Hence, the method described constitutes an excellent method to prepare monochloride **26** in high yields.

Evidence for the formation of compounds **25** and **26** indicated a mechanism in which compound **25** underwent acid mediated hydrolysis, presumably to form aldehyde **27**. This, in turn, underwent acid catalyzed decarbonylation to provide compound **26**. It is likely that the ability of the 4-nitroisoxazole to stabilize carboanions favored the observed decarbonylation. A similar behavior has



Scheme 4. Proposed mechanism for the formation of compound **26**.



Scheme 5. Preparation of ketone **29**.

been observed for the acidic hydrolysis of compound **28** (Scheme 5) which gave β-ketoester equivalent **29** in 71% yields.

In conclusion, we have studied the reactivity of compound **2**. This study has provided a general method for the preparation of compound **2** congeners thus allowing the generation of a family of related products **5**–**14**. Selected compounds from **5** to **14** were shown to react with -*N* and -*C* electrophiles generating aza-substituted enamines and ketones in high yields. It was also shown that electrophilic chlorination of compound **5** provided an efficient method to prepare monochloromethyl isoxazoles. This study will be of interest for those involved in the preparation of chemical libraries and for the preparation of natural products and drug discovery.

Acknowledgements

We thank the Irish Research Council for a grant to C.M., Enterprise Ireland for a grant to R.D. and Fondazione CON IL SUD for a grant to M.M.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.11.037.

References and notes

1. (a)*The Chemistry of Enamines*; Rappoport, Z., Ed.; John Wiley & Sons: New York, 1994; (b) Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Palmieri, G.; Petrini, M. *J. Org. Chem.* **1994**, *59*, 5328; (c) Potin, D.; Dumas, F.; D'Angelo, J. *J. Am. Chem. Soc.* **1990**, *112*, 3483; (d) Beholz, L. G.; Benovsky, P.; Ward, D. L.; Barta, N. S.; Stille, J. R. *J. Org. Chem.* **1997**, *62*, 1033; (e) David, O.; Blot, J.; Bellec, C.; Fargeau-Bellassoued, M. C.; Haviari, G.; Célérier, J. P.; Lhommet, G.; Gramain, J. C.; Gardette, D. *J. Org. Chem.* **1999**, *64*, 3122; (f) Murai, K.; Hayashi, S.; Takaichi, N.; Kita, Y.; Fujioka, H. *J. Org. Chem.* **2009**, *74*, 1418; (g) Barta, N. S.; Brode, A.; Stille, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 6201.
2. (a) Alan, C.; Spivey, A. C.; Srikaran, R.; Diaper, C. M.; David, J.; Turner, D. *Org. Biomol. Chem.* **2003**, *2*, 1638; (b) Hassneen, H. M.; Abdallah, T. A. *Molecules* **2003**, *8*, 333; (c) Lourdusamy, E.; Yao, L.; Park, C. M. *Angew. Chem.* **2010**, *122*, 8135.
3. Appelbaum, F. C.; Hunter, P. A. *Int. J. Antimicrob. Agents* **2000**, *16*, 5.
4. Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Lett.* **2007**, *9*, 3283.
5. Heravi, M. M.; Jaddi, Z. S.; Oskooie, H. A.; Khaleghi, S.; Ghassemzadeh, M. *J. Chem. Res.* **2005**, *9*, 578.
6. Boger, D. L.; Ishizaki, T.; Wysocki, J. R. J.; Munk, S. A.; Kitos, P. A.; Suntomwat, O. *J. Am. Chem. Soc.* **1989**, *111*, 6461.
7. (a) Martin, D. F.; Janusonis, G. A.; Martin, B. B. *J. Am. Chem. Soc.* **1961**, *83*, 73; (b) Baraldi, P. G.; Simoni, D.; Manfredini, S. *Synthesis* **1983**, 902; (c) Lin, J.; Zhang, L. F. *Monatsh. Chem.* **2007**, *138*, 77.
8. Kurtz, A. N.; Billups, W. E.; Greenlee, R. B.; Hamil, H. F.; Pace, W. T. *J. Org. Chem.* **1965**, *30*, 3141.
9. (a) Hannick, S. M.; Kishi, Y. *J. Org. Chem.* **1983**, *48*, 3833; (b) Lee, A. S.-Y.; Cheng, R.-Y. *Tetrahedron Lett.* **1997**, *38*, 443.
10. (a) Fukuyama, T.; Yung, Y. M. *Tetrahedron Lett.* **1981**, *22*, 3759; (b) Jiang, N.; Qu, Z.; Wang, J. *Org. Lett.* **2001**, *3*, 2989.
11. Ke, Y.-Y.; Li, Y.-J.; Jia, J.-H.; Sheng, W.-J.; Han, L.; Gao, J.-R. *Tetrahedron Lett.* **2009**, *50*, 1389.
12. Vetelino, M. G.; Coe, J. W. *Tetrahedron Lett.* **1994**, *35*, 219.
13. (a) Adamo, M. F. A.; Sarti-Fantoni, P.; Chimichi, S.; Sandrelli, A. *Tetrahedron Lett.* **2010**, *51*, 6310; (b) Adamo, M. F. A.; Duffy, E. F.; Konda, V. R.; Murphy, F. *Heterocycles* **2007**, *71*, 1173; (c) Adamo, M. F. A.; Duffy, E. F. *Org. Lett.* **2006**, *8*, 5157; (d) Adamo, M. F. A.; Suresh, S.; Piras, L. *Tetrahedron* **2009**, *65*, 5402; (e) Adamo, M. F. A.; Chimichi, S.; De Sio, F.; Donati, D.; Sarti-Fantoni, P. *Tetrahedron Lett.* **2002**, *43*, 4157; (f) Adamo, M. F. A.; Donati, D.; Duffy, E. F.; Sarti-Fantoni, P. *J. Org. Chem.* **2005**, *70*, 8395; (g) Adamo, M. F. A.; Duffy, E. F.; Donati, D.; Sarti-Fantoni, P. *Tetrahedron* **2007**, *63*, 2047; (h) Adamo, M. F. A.; Duffy, E. F.; Donati, D.; Sarti-Fantoni, P. *Tetrahedron* **2007**, *63*, 2684; (k) Adamo, M. F. A.; Konda, V. R. *Org. Lett.* **2007**, *9*, 303; (i) Salazar Illera, D.; Suresh, S.; Moccia, M.; Bellini, G.; Saviano, M.; Adamo, M. F. A. *Tetrahedron Lett.* **1808**, *2012*, 53; (l) Fini, F.; Nagabelli, M.; Adamo, M. F. A. *Adv. Synth. Catal.* **2010**, *352*, 3163; (m) Bruschi, S.; Moccia, M.; Adamo, M. F. A. *Tetrahedron Lett.* **2011**, 3602.
14. (a) Baschieri, A.; Bernardi, L.; Ricci, A.; Suresh, S.; Adamo, M. F. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9342; (b) Wells, R.; Moccia, M.; Adamo, M. F. A. *Org. Biomol. Chem.* **2015**, *13*, 2192.
15. Del Fiandra, C.; Piras, L.; Fini, F.; Disetti, P.; Moccia, M.; Adamo, M. F. A. *Chem. Commun.* **2012**, 3863.
16. Adamo, M. F. A.; Disetti, P.; Moccia, M.; Salazar-Illera, D.; Suresh, S. *Org. Biomol. Chem.* **2015**, *13*, 10609.
17. Wells, R.; Moccia, M.; Adamo, M. F. A. *Tetrahedron Lett.* **2014**, *55*, 803.
18. Moccia, M.; Cortigiani, M.; Monasterolo, C.; Torri, F.; Del Fiandra, C.; Fuller, G.; Kelly, B.; Adamo, M. F. A. *Org. Process Res. Dev.* **2015**, *19*, 1274.
19. (a) Pei, Q.-L.; Sun, H.-W.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2011**, *76*, 7849; (b) Zhang, J.; Liu, X.; Ma, X.; Wang, R. *Chem. Commun.* **2013**, 9329; (c) Kawai, H.; Tachi, K.; Tokunaga, E.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 7803.
20. CCDC repository No. CCDC 953776.
21. CCDC repository No. CCDC 953777.