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The preparation of 3-methyl-4-nitro-5-(2-alkylethenyl)isoxazoles

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Abstract: We report the first synthetic route to prepare 3-methyl-4-nitro-5-(2-alkylethenyl)isoxazoles in high yield and exclusively as *E*-diastereoisomers.

Keywords: Michael addition, 4-nitroisoxazoles, polyfunctional scaffolds, organocatalysis.

The isoxazole nucleus has been recognized as an important heterocycle in medicinal chemistry. Several reports have appeared describing the biological activity of isoxazoles as $GABA_A$ antagonists,[1] analgesics,[2] anti-inflammatory,[3] antimicrobial,[3] antifungal,[4] and anticancer agents,[5] as well as selective agonists of dopamine D_4 receptors.[6] For this reason the synthesis of novel compounds containing the isoxazole core is of interest for both the academic and industrial communities. The isoxazole nucleus is only poorly aromatic as it contains a weak nitrogen-oxygen bond, which is a potential site for ring cleavage. The limited aromaticity makes isoxazoles useful intermediates since they can be easily manipulated to obtain functionally complex derivatives, namely 1,3-dicarbonyls,[7] hydroxyketones,[8] azirines,[9] enamines and β-hydroxynitriles.[10] Moreover 4-nitroisoxazoles have been shown to undergo hydrolysis when treated with metal hydroxides, and for this reason, they can be considered as carboxylic acid equivalents.[11,12]

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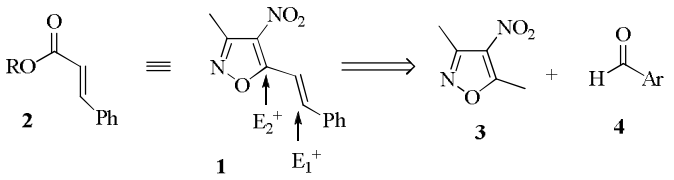
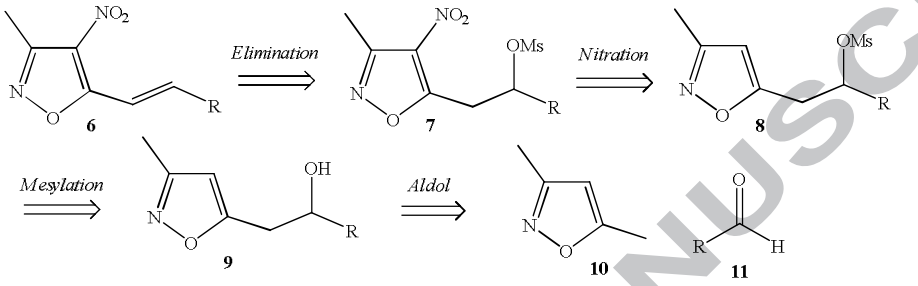


Scheme 1. 3-Methyl-4-nitro-5-styrylisoxazole (**1**) as a cinnamate equivalent

Our group has developed the synthesis of 3-methyl-4-nitro-5-styrylisoxazoles **1** and reported some of their synthetic applications (Scheme 1). Compounds **1** contain two electrophilic centres, each of which can selectively react. It has been shown that soft nucleophiles, such as enolates, are selective for the soft electrophilic centre E_1^+, whereas hard nucleophiles such as OH^- react exclusively at the hard electrophilic centre E_2^+.[12-14] We have shown that when reacted with an excess of NaOH, the 4-nitroisoxazol-5-yl core revealed a carboxylic acid,[12,13] for which reason compounds **1** should be considered as synthetic equivalents to cinnamate esters **2** (Scheme 1). The synthetic applications of 5-(2-arylethenyl)-4-nitroisoxazoles have been studied extensively in our laboratory.[16] It is noteworthy that the synthetic relevance of compounds **1** has been recognized by at least three other groups worldwide.[14,17,18] Shibata reported that the addition of CF_3^- nucleophiles to **1** occurred selectively at E_2 (Scheme 1), thus allowing an easy and efficient entry to important classes of trifluoromethylisoxazolines.[15] Yuan *et al.* have reported a highly enantioselective thiolate addition to compounds **1** that proceeded via bifunctional organocatalysis.[17] Also, Rui Wang reported a highly enantioselective addition of unsaturated lactams to **1** catalysed by quinine-based thioureas.[18]

The preparation of aromatic compounds **1** proceeded *via* the condensation of commercially available 3,5-dimethyl-4-nitroisoxazole (**3**) and aromatic aldehydes **4**.[19] Compound **3** underwent efficient condensation with aromatic aldehydes **3**, but not with aliphatic aldehydes, [16f,19] for which reason the preparation of 5-(2-alkyethenyl)-4-nitroisoxazoles has not been reported. In view of the growing interest on reagents **1**, it would be desirable to provide a method to access the aliphatic series. Herein, we report the first synthesis of 3-methyl-4-nitro-5-(2-alkylethenyl)isoxazoles **6a-d** which complement compound **1** (Scheme 1). It was also decided to investigate strategies alternative to the condensation of **3** and an aliphatic aldehyde, since these are known to be restricted to aromatic aldehydes, α,β-unsaturated aldehydes[19] and cyclopropylcarboxaldehyde.[18] It is known that 3,5-dimethylisoxazole (**10**) (Scheme 2)

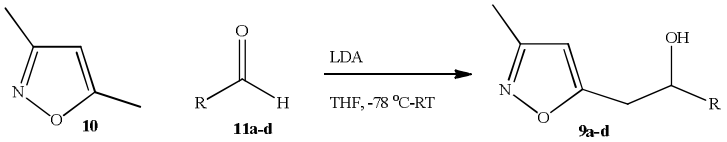
can be selectively deprotonated,[20] and its anion used as a nucleophile in reactions with classic electrophiles such as alkyl halides[21] and carbonyl compounds.[22] Butyllithium, or $NaNH_2/NH_3$ were equally good bases affording 5-methyl metallated **10**.[23] In this context, the aldol reaction of **10** and aldehydes **11** was identified as the C-C bond-forming step required to access products **6**. A retrosynthetic analysis identified mesylate **7** as a suitable starting material to prepare compounds **6.** In turn, compound **7** could be obtained from parent alcohol **9**, available via aldol reaction of **10** and **11** (Scheme 2).



Scheme 2. Retrosynthetic analysis of compounds **6**

Compound **10** could be easily prepared by condensation of acetylacetone and hydroxylamine.[19] The first step of this synthesis involved deprotonation of **10** to generate a C-5-methyl anion and its subsequent addition to aldehydes **11a-d** (Table 1). Aldehydes **11a-d** were selected for this study as representative examples of cyclic, acyclic and branched compounds. It was decided to employ lithium diisopropylamide (LDA) as the base and THF as the solvent. THF was a remarkably good solvent for 5-metallated **10**, which tended to crystallise out when generated in alkanes or in ethers. Compound **10** was treated with one equivalent of LDA to give a deep yellow solution, the colour of which was dissipated upon addition of one equivalent of aldehyde **11a-d**. At room temperature, this reaction gave the products **9a-d** in moderate yields, but contaminated by several side products, presumably arising from self-aldol condensation of **11a-d**. However, when the addition of the aldehyde to metallated **10** was carried out dropwise over the course of one hour at -78 ^{o}C, compounds **9a-d** were obtained in high isolated yields after column chromatography (Table 1).

Table 1. Synthesis of hydroxy isoxazoles **9a-d**



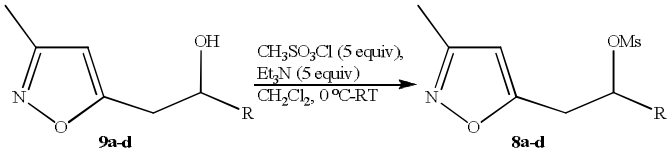
Entry	Aldehyde	R	Product	Yield (%)[a]
1	**11a**	cyclohexyl	**9a**	74
2	**11b**	$CH(CH_2CH_3)CH_2CH_2CH_2CH_3$	**9b**	55
3	**11c**	$CH_2CH(CH_3)_2$	**9c**	70
4	**11d**	$CH_2CH_2CH_2CH_2CH_2CH_3$	**9d**	64

[a] Isolated yields after flash chromatography eluting with 10% EtOAc in petroleum ether, followed by 20% EtOAc in petroleum ether.

Nitration at this stage might have induced dehydration[19] or formation of a nitrate ester, so it was decided to protect the alcohol as a mesylate, which would also allow elimination at a subsequent stage. Mesylation of **9a-d** was achieved by treating alcohols **9a-d** in CH_2Cl_2 with an excess (5 equivalents) of mesyl chloride and triethylamine at 0 °C. Under these conditions, compounds **9a-d** were completely converted in less than two hours, and the products **8a-d** were obtained in high yields (Table 2). Attempts were made to employ lower amounts of mesyl chloride and triethylamine, however these reactions gave incomplete conversions.

Having optimised the procedure to prepare compounds **8a-d**, we proceeded to study the aromatic nitration step. The classic method, involving treating **8a-d** with a mixture of concentrated sulfuric and nitric acids, was not attempted as it was anticipated that the strong acidity of this medium might promote a subsequent uncontrolled elimination leading to formation of **6** as an *E/Z* mixture. To avoid this potential risk, it was decided to perform the nitration using tetramethylammonium nitrate and trifluoromethanesulfonic (triflic) anhydride, which are mild and well known conditions employed to install an aromatic nitro group.

Table 2. Synthesis of mesylated isoxazoles **8a-d**

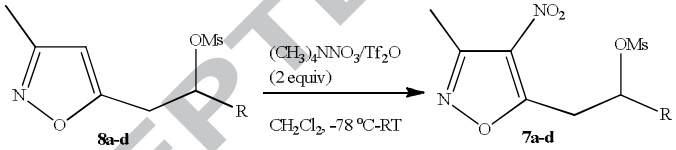


Entry	Alcohol	R	Product	Yield (%)[a]
1	**9a**	cyclohexyl	**8a**	82
2	**9b**	$CH(CH_2CH_3)CH_2CH_2CH_2CH_3$	**8b**	88
3	**9c**	$CH_2CH(CH_3)_2$	**8c**	85
4	**9d**	$CH_2CH_2CH_2CH_2CH_2CH_3$	**8d**	90

[a] Isolated yields after flash chromatography eluting with 2% MeOH in CH_2Cl_2.

Pleasingly, compounds **9a-d** underwent nitration at C-4 efficiently. Initial attempts were conducted using 1.05 equivalents of tetramethylammonium nitrate and triflic anhydride, however this only led to 50% conversion of the starting materials. This problem was overcome by using two equivalents of nitronium triflate which resulted in full conversions.

Table 3. Synthesis of 4-nitroisoxazoles **7a-d**



Entry	Mesylate	R	Product	Yield (%)[a]
1	**8a**	cyclohexyl	**7a**	79
2	**8b**	$CH(CH_2CH_3)CH_2CH_2CH_2CH_3$	**7b**	75
3	**8c**	$CH_2CH(CH_3)_2$	**7c**	70
4	**8d**	$CH_2CH_2CH_2CH_2CH_2CH_3$	**7d**	80

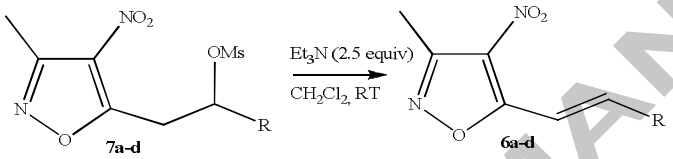
[a] Isolated yields after flash chromatography eluting with 10% EtOAc in petroleum ether, followed by 20% EtOAc in petroleum ether.

The addition of compounds **8a-d** to a premixed solution of tetramethylammonium nitrate and trifluoromethanesulfonic anhydride was carried out at -78 ^{o}C, the resulting

solution was left to warm to room temperature and then stirred for a further five hours. This procedure gave the desired 4-nitroisoxazoles **7a-d** in high isolated yields (Table 3). It was noted that when the additions were carried out at higher temperatures the yields decreased.

The final step involved a base-catalysed elimination to install the 5-ethenyl moiety. This step was realized by submitting compounds **7a-d** to mild basic conditions. The desired compounds **6a-d** were obtained by treating a solution of **7a-d** in CH_2Cl_2 with 2.5 equivalents of triethylamine (Table 4). These conditions ensured rapid conversions. Typically, the reactions were complete after one hour and the desired compounds **6a-d** were obtained as single *E*-diastereoisomers.

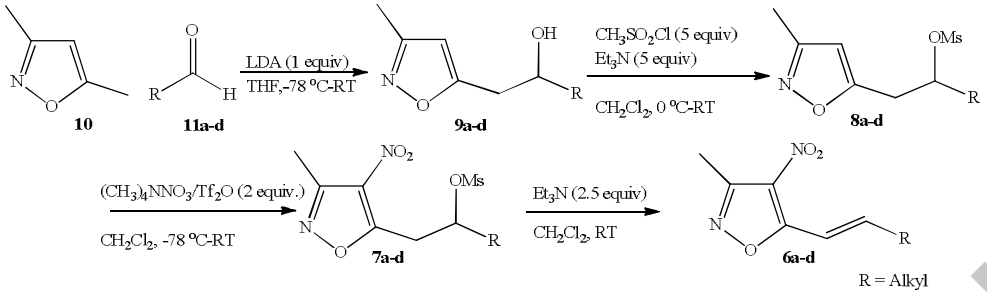
Table 4: Synthesis of aliphatic nitroisoxazoles **6a-d**



Entry	Substrate	R	Product	Yield (%)[a]
1	**7a**	cyclohexyl	**6a**	82
2	**7b**	$CH(CH_2CH_3)CH_2CH_2CH_2CH_3$	**6b**	88
3	**7c**	$CH_2CH(CH_3)_2$	**6c**	92
4	**7d**	$CH_2CH_2CH_2CH_2CH_2CH_3$	**6d**	89

[a] Isolated yields after flash chromatography eluting with CH_2Cl_2.

In conclusion, we have developed the first route to prepare 4-nitro-5-ethenylisoxazoles of the aliphatic series **6a-d** (Scheme 3). The synthesis started from the nucleophilic addition of 5-methyl metallated **10** to an aldehyde **11a-d**, which constitutes the key C-C bond forming reaction. Elaboration of the resulting alcohols **9a-d** through mesylation, subsequent nitration and base-promoted elimination gave the desired products **6a-d** in high isolated yields and exclusively as the *E*-diastereoisomers. Considering the demonstrated synthetic advantage of using 4-nitro-5-(2-alkylethenyl)isoxazoles as Michael acceptors,[12-16] and the growing interest of other research groups on reagents **1**, we believe this study will be of interest to those involved in the preparation of compounds for medicinal chemistry screening and in the development of novel organocatalytic enantioselective procedures.



Scheme 3. Synthetic route to aliphatic 4-nitro-5-alkylethenylisoxazoles **6a-d**

References and notes

1. Frølund, B.; Jørgensen, A. T.; Tagmose, L.; Stensbøl, T. B.; Vestergaard, H. T.; Engblom, C.; Kristiansen, U.; Sanchez, C.; Krogsgaard-Larsen, P.; Liljefors, T. *J. Med. Chem.* **2002**, *45*, 2454.
2. Raffa, D.; Daidone, G.; Maggio, B.; Cascioferro, S.; Plescia, F.; Schillaci, D. *Il Farmaco* **2004**, *59*, 451.
3. Velikorodov, A. V.; Sukhenko, L. T. *Pharm. Chem. J.* **2003**, *37*, 22-24.
4. Chevreuil, F.; Landreau, A.; Séraphin, D.; Larcher, G.; Mallet, S.; Bouchara, J. P.; Richomme, P. *J. Enzyme Inhib. Med. Chem.* **2007**, *5*, 563.
5. Kamal A, Bharathi E.V., Reddy J.S., Ramaiah M.J., Dastagiri D, Reddy M.K., Viswanath A., Reddy T.L., Shaik T.B., Pushpavalli S.N., Bhadra M.P. *Eur. J. Med. Chem.* **2011**, *46*, 691.
6. Sanner, M. A. *Expert Opin. Ther. Patents* **1998**, *8*, 383.
7. Barbero, A. N.; Pulido, F. J. *Synthesis* **2004**, 401.
8. Bode, J. W.; Carreira, E. M. *Org. Lett.* **2001**, *3,* 1587.
9. Nesi, R.; Giomi, D.; Turchi, S. *J. Org. Chem.* **1998**, *63*, 6050.
10. Nesi, R.; Turchi, S.; Giomi, D. *J. Org. Chem.* **1996**, *61*, 7933.
11. Adamo, M. F. A.; Duffy, E. F. *Org. Lett.* **2006**, *8*, 5157.
12. Adamo, M. F. A.; Konda, V. R.; Donati, D.; Sarti-Fantoni, P.; Torroba, T. *Tetrahedron* **2007**, *63*, 9741.
13. Adamo, M. F. A.; Konda, V. R. *Org. Lett.* **2007**, 9, 303-305.
14. Chimichi, S.; De Sio, F.; Donati, D.; Fina, G.; Pepino, R.; Sarti-Fantoni P. *Heterocycles*, **1983**, *20*, 26.

15. Kawai, H.; Tachi, K.; Tokunaga, E.; Shiro, M.; Shibata, N. *Angew. Chem. Int. Ed.,* **2011**, 50 , 7803.

16. (a) Adamo, M. F. A. PCT Int. Appl. (2013), WO 2013076225 A1 20130530; (b) Del Fiandra, C.; Piras, L.; Fini, F.; Disetti, P.; Moccia, M.; Adamo, M. F. A. *Chem. Commun.* **2012**, *48*, 3863. (c) Salazar Illera, D.; Suresh, S.; Moccia, M.; Bellini, G.; Saviano, M.; Adamo, M. F. A. *Tetrahedron Lett.* **2012**, *53*, 1808; (d) Bruschi, S.; Moccia M.; Adamo, M. F. A. *Tetrahedron Lett*, **2011**, *52*, 3602; (e) Dorschner, K. V.; Toomey, D.; Brennan, M. P.; Heinemann, T.; Duffy, F. J.; Nolan, K. B.; Cox, D.; Adamo, M. F. A.; Chubb A. J. *J. Chem. Inf. Model.* **2011**, *51,* 986; (f) Adamo, M. F. A.; Sarti-Fantoni, P.; Chimichi, S.; Sandrelli, A. *Tetrahedron Lett.*, **2010**, *51*, 6310; (g) Baschieri, A.; Bernardi, L.; Ricci, A.; Suresh, S.; Adamo, M. F. A. *Angew. Chem. Int. Ed.* **2009**, 9342; (h) Adamo, M. F. A.; Bruschi, S.; Suresh, S.; Piras, L. *Tetrahedron Lett.,* **2008**, *49,* 7406; (i) Adamo, M. F. A.; Konda, V. R. *Tetrahedron Lett.,* **2008**, *49*, 6224; (k) Adamo, M. F. A.; Nagabelli, M. *Org. Lett.*, **2008**, *10*, 1807; (l) Adamo, M. F. A.; Donati, D.; Sarti-Fantoni, P.; Buccioni A. *Tetrahedron Lett.,* **2008**, *49,* 941**;** (m) Adamo, M. F. A.; Nagabelli, M. *Tetrahedron Lett.*, **2007**, 4703; (n) Adamo, M. F. A.; Donati, D.; Duffy, E. F.; Sarti-Fantoni, P. *Tetrahedron*, **2007**, *63*, 2684; (o) Adamo, M. F. A.; Donati, D.; Duffy, E. F.; Sarti-Fantoni, P. *Tetrahedron*, **2007**, *63*, 2047**;** (p) Adamo, M. F. A.; Donati, D.; Duffy, E. F.; Sarti-Fantoni P. *J. Org. Chem*., **2005**, *70*, 8395; (q) Adamo, M. F. A.; Chimichi, S.; De Sio, F.; Donati, D.; Sarti-Fantoni P. *Tetrahedron Lett.*, **2002**, 4157.

17. Pei, Q. L.; Sun, H. W.; Wu, Z. J.; Zhang, X. M.; Yuan, W. C. *J. Org. Chem.* **2011**, *76*, 7849.

18. Zhang, J.; Liu, X.; Ma, X.; Wang, R. *Chem Commun.* **2013**, *49*, DOI 10.1039/c3cc44059a.

19. Adamo, M. F. A.; Duffy, E. F.; Konda, V. R.; Murphy, F. *Heterocycles*, **2007**, *71*, 1173.

20. Deprotonation of C-5 is 280-fold faster than at C-3; see Kashima, C.; Yamamoto, Y.; Tsuda, Y.; Omote, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1047.

21. Micetich, R. G.; *Can J. Chem*. **1970**, *48*, 2006.

22. Kashima, C.; Uemori, M.; Tsuda, Y.; Omote, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2254.

23. Kashima, C. *Heterocycles*, **1979**, *12*, 1343.

Graphical abstract

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