Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal

Published on 02 December 2014. Downloaded by University of Zurich on 06/01/2015 11:14:10.

Cite this: DOI: 10.1039/c4ob02109f

An improved procedure to prepare 3-methyl-4-nitroalkylenethylisoxazoles and their reaction under catalytic enantioselective Michael addition with nitromethane†

Maria Moccia,* Robert J. Wells and Mauro. F. A. Adamo*

Received 3rd October 2014,
Accepted 2nd December 2014

DOI: 10.1039/c4ob02109f

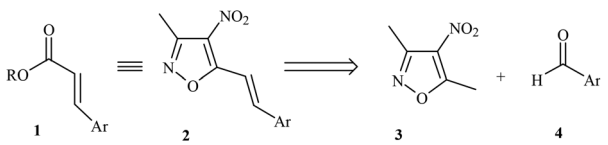
www.rsc.org/obc

Herein, we describe a short synthesis of 3-methyl-4-nitro-5-alkylethenyl isoxazoles and their reactivity as Michael acceptors. The title compounds reacted with nitromethane under phase-transfer catalysis to provide highly enantioenriched adducts (up to 93% ee) which were then converted to the corresponding γ-nitroacids.

Introduction

The isoxazole nucleus is an important pharmacophore in medicinal chemistry, due to its isosterism with an ester.[1] In addition isoxazoles could be employed as precursors to notable organic compounds such as 1,3-dicarbonyls,[2] hydroxyketones,[3] azirines,[4] enamines and β-hydroxynitriles.[5] In the recent past, we have developed several synthetic routes starting from aromatic styrylisoxazoles 2 (Scheme 1).[6–11] In compounds **2**, the 4-nitroisoxazole core activates the exocyclic alkene to react with soft nucleophiles. The 4-nitroisoxazole could be converted to a carboxylate *via* basic,[12] oxidative[13] and acidic[14] procedures which justified the definition of compounds **2** as a synthetic equivalent to cinnamates **1**.

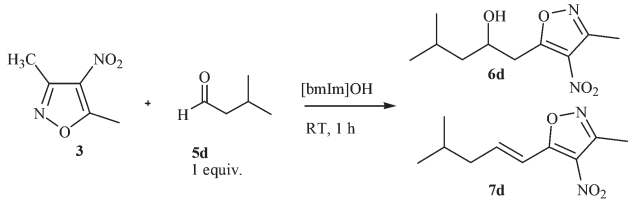
Following our reports, the synthetic relevance of compounds **2** has been recognized by other groups: Shibata reported the synthesis of trifluoromethylisoxazolines *via* addition of CF_3^- nucleophiles to compounds **2**;[15] Yuan reported a highly enantioselective thiolate addition to compounds **2** catalysed by bifunctional organocatalysts;[14] Rui Wang reported a highly enantioselective addition of unsaturated lactams to **2** catalysed by quinine-based thioureas.[16]



Scheme 1 Retrosynthetic analysis of 3-methyl-4-nitro-5-styrilisoxazoles **2**.

Centre for Synthesis and Chemical Biology (CSCB), Department of Pharmaceutical and Medicinal Chemistry, Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin 2, Ireland. E-mail: madamo@rcsi.ie, mariamoccia@rcsi.ie; Fax: (+353) 1 4022168

†Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and spectra of new compounds. See DOI: 10.1039/c4ob02109f



Scheme 2 Condensation of **3** and aliphatic aldehydes in [bmIm]-OH.

The preparation of aromatic compounds **2** proceeded *via* condensation of commercially available 3,5-dimethyl-4-nitroisoxazole **3** and aromatic or heteroaromatic aldehydes **4**.[17]

However, the same procedure failed when aliphatic aldehydes were employed.[6,18] Considering the growing interest in reagents **2**, we have recently reported a method to prepare aliphatic 5-ethenyl-4-nitroisoxazoles.[18] The synthesis involved four steps and allowed obtaining compounds **7** (Scheme 2) in high yields and exclusively as *E* stereoisomers.[18]

Results and discussion

With the intention of streamlining the preparation of compounds **7**, we reconsidered the condensation of commercially available **3** and aliphatic aldehydes **5a–i** under a new set of hitherto unexplored conditions. This study identified a two-step procedure that allowed condensation of commercially available 3,5-dimethyl-4-nitroisoxazole **3** and aliphatic aldehydes **5a–i** to alkylethenylisoxazole **7a–i** (Scheme 2). The

Published on 02 December 2014. Downloaded by University of Zurich on 06/01/2015 11:14:10.

synthetic relevance of compounds **7a–i** was then demonstrated by their reaction with nitromethane under phase transfer catalysis (PTC).[19] This reaction provided pharmaceutically relevant adducts **9a–i** in high enantiomeric excesses (Table 4).

During our studies on the preparation of compounds **7**, Reddy reported a fast preparation of **2** (yields of 85–92% in 10–15 minutes) that occurred at room temperature. The new procedure involved the use of 1-butyl-3-methylimidazolium hydroxide [bmIm]-OH as the media.[20] The fast rates described by Reddy prompted us to react **3** and **5d** (Scheme 2) in [bmIm]-OH.

Hence, equimolar amounts of 3,5-dimethyl-4-nitroisoxazole **3** and isovaleraldehyde **5d** were taken in IL [bmIm]-OH and the reaction mixture was stirred at room temperature for 1 h. This reaction provided 20% of compound **7d** and 32% of alcohol **6d**. Increase of temperature, reaction time or reactant concentration did not prove useful and **7d** was obtained in yields not greater than 20–25%.

The unprecedented reaction of **3** and aliphatic **5d** in IL [bmIm]-OH was explained considering quantitative formation of deprotonated **3** which is very stable in a polar solvent. The high concentration of deprotonated **3** was responsible for the generation of compounds **6d** and **7d**. In order to prove this, we have designed a new protocol in which compound **3** was first reacted with 1 equiv. of NaOH in a mixture of 9 : 1 of ethanol–water and then the resulting metallated-**3** quenched with isovaleraldehyde **5d**.

This new protocol provided about 50% of compounds **6d** and **7d** in 1 : 1 ratio, proving therefore that the amount of ionized **3** was crucial to ensure progress of the desired aldol reaction.

Further improvements were logically achieved by (a) reduction of NaOH base to 0.2 equiv., to decrease aldehyde self-condensation; (b) replacement of ethanol with methanol to increase the amount of isoxazole **3** in solution; (c) addition of THF as a co-solvent to favor the formation of a homogeneous phase.

Delightfully, under this set of optimized conditions, the reaction of **3** and aldehydes **5a–i** proceeded to completion and alcohols **6a–i** were obtained in high isolated yields (Table 1).

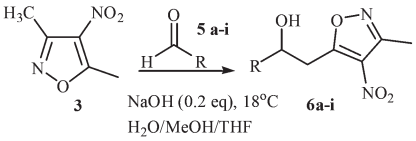
Compounds **6a–i** were then treated with a small excess of methane sulfonyl chloride (1.2 equiv.) and an excess of triethylamine (2 equiv.), providing the corresponding alkenes **7a–i** in good to excellent yields (Table 2). Significantly, only the *E*-alkene was observed.

This two steps procedure was run under a milder set of conditions (NaOH in H_2O/MeOH) compared to those previously reported (LDA in THF)[18] and expanded significantly the scope of alkenes **7** that could be prepared. The reactivity of compounds **7a–i** was then tested in the Michael reaction with nitromethane. We initially treated a solution of **7d** in toluene (0.1 M) with nitromethane (5 equiv.), solid K_2CO_3 (5 equiv.), a suitable combination of bases and solvents already reported by us,[6] with a range of *cinchonidine*-derived phase transfer catalysts (Table 3).

The use of catalysts **8** and **8.2** at room temperature provided compound **9d** in 86% ee (Table 3, entries 1 and 5). The reaction carried out at lower temperature (−30 °C) afforded **9d** in a decreased enantiomeric excess (Table 3, entry 3). The use of commercially available catalyst **8.3** provided the desired product **9d** in a lower 74% at 0 °C (Table 3, entry 7). Similarly, catalysts **8.4** and **8.5** gave **9d** in reduced enantioselectivity (Table 3, entries 8 and 9). Final optimisation involved the use of 10 mol% of catalyst and diluting the reaction from 0.1 M to 0.03 M, which enhanced the ee. Hence, the optimised set of conditions required the use of 10 mol% of catalyst **8** at 0 °C, solid K_2CO_3 as the base, a concentration of reagents of 0.03 M (Table 3, entry 4). Importantly, the use of pseudoenantiomeric catalysts allowed obtaining *ent*-**9d** in similarly high ee (Table 3, entries 2 and 6).

The scope of the reaction was shown by reacting alkylethenylisoxazoles **7a–i** with nitromethane under the catalysis of **8**

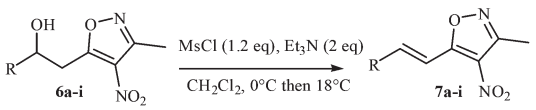
Table 1 Synthesis of hydroxyl isoxazoles



Entry[a]	Ald.	R group	*T* [h]	Prod.	Yields[b] [%]
1	**5a**	CH_2CH_3	36	**6a**	90
2	**5b**	$CH_2CH_2CH_3$	36	**6b**	88
3	**5c**	$(CH_2)_3CH_3$	36	**6c**	88
4	**5d**	$CH_2CH(CH_3)_2$	36	**6d**	92
5	**5e**	$(CH_2)_4CH_3$	48	**6e**	87
6	**5f**	$(CH_2)_5CH_3$	48	**6f**	88
7	**5g**	$(CH_2)_6CH_3$	48	**6g**	85
8	**5h**	$(CH_2)_7CH_3$	60	**6h**	84
9	**5i**	$(CH_2)_8CH_3$	60	**6i**	84

[a] Reaction conditions: 3,5-dimethyl-4-nitroisoxazole **3** (5 mmol), H_2O/MeOH/THF, NaOH (0.2 mmol), aldehydes **5a–i** (6 mmol), 18 °C. [b] Isolated yields after flash column chromatography.

Table 2 Synthesis of alkenethyl isoxazoles[a]



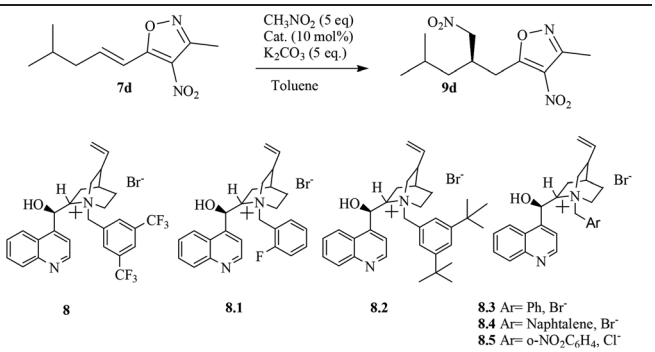
Entry	R	Prod.	Yield[b] [%]
1	CH_2CH_3	**7a**	98
2	$CH_2CH_2CH_3$	**7b**	96
3	$(CH_2)_3CH_3$	**7c**	97
4	$CH_2CH(CH_3)_2$	**7d**	95
5	$(CH_2)_4CH_3$	**7e**	96
6	$(CH_2)_5CH_3$	**7f**	94
7	$(CH_2)_6CH_3$	**7g**	90
8	$(CH_2)_7CH_3$	**7h**	88
9	$(CH_2)_8CH_3$	**7i**	88

[a] Reaction conditions: **6a–i** (1 mmol), CH_2Cl_2 (7mL), MsCl (1.2 mmol), Et_3N (2 mmol), 0 °C then 18 °C. [b] Isolated yields after flash column chromatography.

This journal is © The Royal Society of Chemistry 2014

Published on 02 December 2014. Downloaded by University of Zurich on 06/01/2015 11:14:10.

Table 3 Representative results of the screening of cinchonidine-derived catalysts **8–8.5**

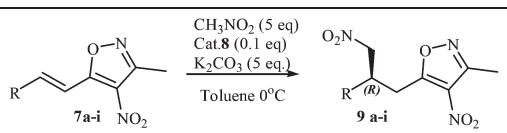


Entry[a]	Cat.	Temp [°C]	*T* [h]	Conv.[b] [%]	ee[c] [%]
1	**8**	RT	1.5	98	86
2	**8**	0	3	98	87(72)[d]
3	**8**	−30	18	87	82
4	**8.1**	0	18	98	73
5	**8.2**	RT	0.25	92	86
6	**8.2**	0	1.5	92	86(85)[d]
7	**8.3**	0	18	98	74
8	**8.4**	0	48	98	78
9	**8.5**	0	24	98	53

[a] Reaction conditions: alkenethylisoxazole **7d** (0.1 mmol), toluene (1.0 mL), cat. **8–8.5** (10 mol%), nitromethane (0.5 mmol), K_2CO_3 (0.5 mmol). [b] Conversion was determined by ^{1}H NMR analysis. [c] The enantiomeric excess (ee) of the product was determined by chiral stationary phase HPLC. [d] In parentheses the ee of *ent*-**9d** obtained using the pseudoenantiomeric catalysts **8** and **8.2**.

(Table 4). The results collected pointed out: (a) compounds containing either short (**7a**,**7b**) or long chains (**7h**,**7i**) were equally good substrates and the corresponding compounds **9a,b** and **9h,i** were obtained in good yields and in up to 93% ee; (b) importantly, it was verified that at least compounds **9a,c,d,e,f,i** could be obtained in a preparative scale (Table 4) without loss of yield or enantioselectivity. The absolute configuration of compounds **9a–i** obtained was determined to be *R* by comparison of optical rotation and HPLC data of compounds **10d** and *ent*-**10d** with published data.[21]

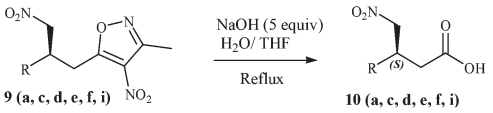
Table 4 Enantioselective addition of nitromethane to alkenethenyl-isoxazoles **7a–i** under the catalysis of **8**



Entry[a]	R	Prod.	Yield[b] [%]	ee[c] [%]
1	CH_2CH_3	**9a**[d]	91	93
2	$CH_2CH_2CH_3$	**9b**[d]	91	87
3	$(CH_2)_3CH_3$	**9c**	90	88
4	$CH_2CH(CH_3)_2$	**9d**[d]	90	89
5	$(CH_2)_4CH_3$	**9e**[d]	91	88
6	$(CH_2)_5CH_3$	**9f**[d]	90	86
7	$(CH_2)_6CH_3$	**9g**	99	83
8	$(CH_2)_7CH_3$	**9h**	89	87
9	$(CH_2)_8CH_3$	**9i**[d]	89	85

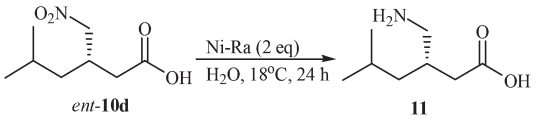
[a] Reaction condition: styrylisoxazoles **7a–i** (0.2 mmol), toluene (6.7 mL), cat. **8** (0.02 mmol), CH_3NO_2 (1 mmol), K_2CO_3 (1 mmol). [b] Isolated yields after flash column chromatography. [c] The enantiomeric excess (ee) of the product was determined by chiral stationary phase HPLC. [d] Reaction performed on a 5.0 mmol scale.

Table 5 Synthesis of aliphatic γ-nitro acids[a]



Entry	R	Prod.	Yield[b] [%]
1	CH_2CH_3	**10a**	92
2	$(CH_2)_3CH_3$	**10c**	90
3	$CH_2CH(CH_3)_2$	**10d**	94
4	$(CH_2)_4CH_3$	**10e**	88
5	$(CH_2)_5CH_3$	**10f**	87
6	$(CH_2)_8CH_3$	**10i**	87

[a] Reaction conditions: compounds **9** (0.25 mmol), THF (0.5 mL), aqueous NaOH (1.25 mmol), reflux. [b] Isolated yields after flash column chromatography.



Scheme 3 Preparation of enantioenriched (*S*)-Pregabalin **11**.

The carboxylic acid functionality was then unveiled from Michael adducts **9a,b,d,e,f,i** (Table 5) which were efficiently converted into the corresponding γ-nitro acids **10a,b,d,e,f,i** in high yields (87%–94%).

This transformation required treatment with 1 M aqueous NaOH in THF. The ee reflected the values of the starting materials thus demonstrating the stereochemical stability of compounds under the conditions adopted.[6] The γ-nitroacids obtained are important intermediates as precursors of γ-amino acids.[5,7,16] This has been demonstrated by reducing γ-nitroacid *ent*-**10d** to enantioenriched (*S*)-Pregabalin **11** (Scheme 3), using a literature procedure.[22]

Conclusions

In conclusion, we have developed a new short synthesis of *E*-alkenylethyl isoxazoles, the aliphatic version of a popular class of Michael acceptors. Similarly to their aromatic analogues **2**, compounds **7** reacted promptly under phase transfer catalysis providing highly enantioenriched nitromethane adducts. This study delivers to the scientific community a novel enantioselective strategy for the synthesis of aliphatic γ-nitroacids and confirms 4-nitro-5-alkethenylisoxazoles as a useful synthon for organic synthesis.

Published on 02 December 2014. Downloaded by University of Zurich on 06/01/2015 11:14:10.

Notes and references

1 D. Xiao, X. Zhu, Y. Yu, N. Shao, J. Wu, K. D. McCormick, P. Dhondi, J. Qin, R. Mazzola, H. Tang, A. Rao, P. Siliphaivanh, H. Qiu, X. Yang, M. Rivelli, C. G. Garlisi, S. Eckel, G. Mukhopadhyay, C. Correll, D. Rindgen, R. Aslanian and A. Palani, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 1615.
2 A. Barbero and F. J. Pulido, *Synthesis*, 2004, 401.
3 J. W. Bode and E. M. Carreira, *Org. Lett.*, 2001, **3**, 1587.
4 R. Nesi, D. Giomi and S. Turchi, *J. Org. Chem.*, 1998, **63**, 6050.
5 R. Nesi, S. Turchi and D. Giomi, *J. Org. Chem.*, 1996, **61**, 7933.
6 A. Baschieri, L. Bernardi, A. Ricci, S. Suresh and M. F. A. Adamo, *Angew. Chem., Int. Ed.*, 2009, **48**, 9342.
7 M. F. A. Adamo, E. F. Duffy, D. Donati and P. Sarti-Fantoni, *Tetrahedron*, 2007, **63**, 2684.
8 M. F. A. Adamo and V. R. Konda, *Org. Lett.*, 2007, **9**, 303.
9 F. Fini, M. Nagabelli and M. F. A. Adamo, *Adv. Synth. Catal.*, 2010, **352**, 3163.
10 S. Bruschi, M. Moccia and M. F. A. Adamo, *Tetrahedron Lett.*, 2011, **52**, 3602.
11 M. F. A. Adamo, D. Donati, E. F. Duffy and P. Sarti-Fantoni, *J. Org. Chem.*, 2005, **70**, 8395.
12 M. F. A. Adamo, P. Sarti-Fantoni, S. Chimichi and A. Sandrelli, *Tetrahedron Lett.*, 2010, **51**, 6310.
13 C. Del Fiandra, L. Piras, F. Fini, P. Disetti, M. Moccia and M. F. A. Adamo, *Chem. Commun.*, 2012, **48**, 4215.
14 Q. L. Pei, H. W. Sun, Z. J. Wu, X.-M. Zhang and W. C. Yuan, *J. Org. Chem.*, 2011, **76**, 7849.
15 H. Kawai, K. Tachi, E. Tokunaga, M. Shiro and N. Shibata, *Angew. Chem., Int. Ed.*, 2011, **50**, 7803.
16 J. Zhang, X. Liu, X. Ma and R. Wang, *Chem. Commun.*, 2013, **49**, 9329.
17 M. F. A. Adamo, E. F. Duffy, V. R. Konda and F. Murphy, *Heterocycles*, 2007, **71**, 1173.
18 R. Wells, M. Moccia and M. F. A. Adamo, *Tetrahedron Lett.*, 2014, **55**, 803.
19 *Asymmetric Phase Transfer Catalysis*, ed. K. Maruoka, Wiley-VCH, Weinheim, 2008.
20 E. Rajanarendar, S. Raju, A. Siva, S. R. Reddy, K. G. Reddy and M. N. Reddy, *Chem. Pharm. Bull.*, 2010, **58**, 833.
21 H. Gotoh, H. Ishikawa and Y. Hayashi, *Org. Lett.*, 2007, **9**(25), 5307.
22 F. Berti, F. Felluga, C. Forzato, G. Furlan, P. Nitti, G. Pitacco and E. Valentin, *Tetrahedron: Asymmetry*, 2008, **19**, 945; M. F. A. Adamo, *PCT Int. App*, WO 2013076225 A1 20130530, 2013.

 This journal is © The Royal Society of Chemistry 2014