Preparation of a furfural-derived enantioenriched vinyloxazoline building block and exploring its reactivity

Madara Darzina[1,2], Anna Lielpetere[1] and Aigars Jirgensons[*1]

Full Research Paper

Address:
[1]Latvian Institute of Organic Synthesis Aizkraukles 21, Riga, LV-1006, Latvia and [2]Faculty of Natural Sciences and Technology, Riga Technical University, 3 P. Valdena Street, Riga LV-1048, Latvia

Email:
Aigars Jirgensons[*] - aigars@osi.lv

* Corresponding author

Abstract

N-Alloc-protected furfuryl amino alcohols derived from furfural and L- or D-valinol were subjected to Torii-type ester electrosynthesis to obtain the corresponding unsaturated esters. These served as key intermediates to prepare (*S*)- and (*R*)-enantioenriched unsaturated amides by *N*-Alloc deprotection which induced concomitant methoxymethyl group cleavage, *O*-to-*N* rearrangement, and isomerization of the double bond. An oxazoline ring formation in the resulting unsaturated amides provided the corresponding enantioenriched vinyloxazoline. The reactivity of the electron-deficient double bond in the vinyloxazoline was explored in several reactions. Out of these, the aza-Diels–Alder reaction with TsNCO was successful, leading to a highly diastereoselective formation of an oxazolo[3,2-*c*]pyrimidine derivative.

Introduction

The utilization of biomass as an alternative to fossil feedstock is central to circular economy for the production of value-added products [1-7]. Furfural [furan-2-carbaldehyde (**1**)], a platform compound derived from lignocellulosic biomass, has been utilized to obtain a range of versatile chemicals with applications to functional materials, pharmaceutically relevant compounds, and agrochemicals [8-17]. In our recent work, we have developed a Torii-type electrosynthesis of unsaturated esters **3a–c** starting from furfural (**1**) and amino alcohol conjugates **2a–c** [18]. The process involves an electrooxidative dialkoxyla-

tion of the furan ring providing spirocycles **4a–c** which undergo a further electrooxidative fragmentation to products **3a–c**. However, the further transformation of products **3a–c** was hampered by the problematic removal of the protecting groups (Ts, Boc, Ac) under the conditions compatible with the double bond and acetal functions. In this work, we present Torii-type electrosynthesis of ester **3d** (PG = Alloc) and its transformation to the enantioenriched vinyloxazoline building block **6**, which can be used for the asymmetric synthesis of complex molecules [19-24] (Scheme 1).

Scheme 1: Proposed approach for the preparation of vinyloxazoline **6**.
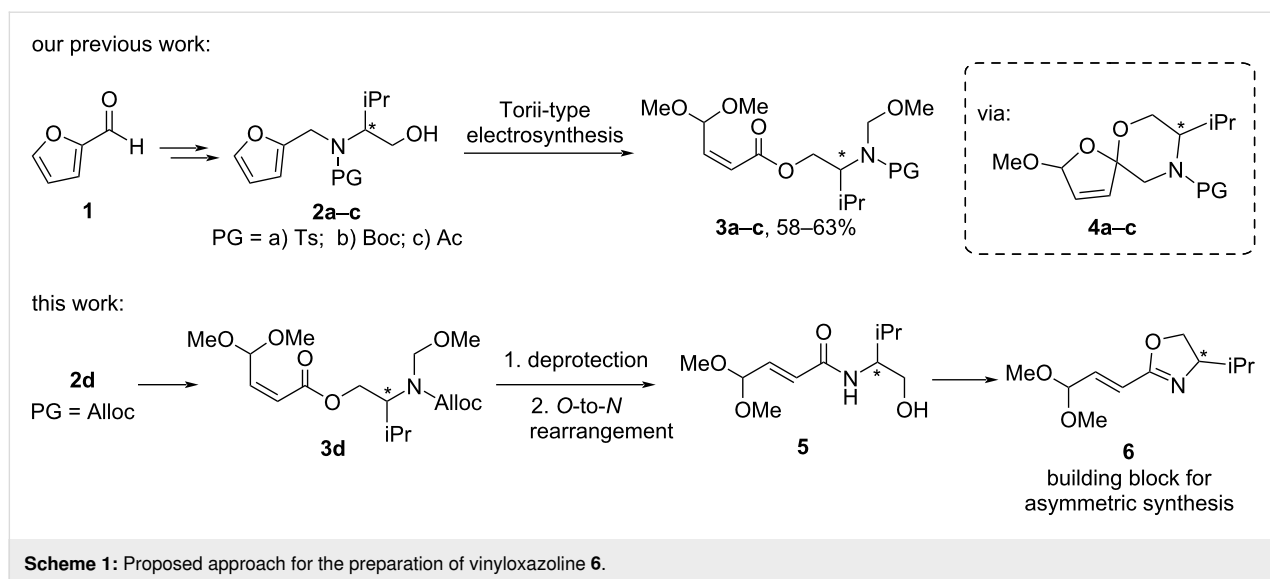
The proposed strategy relied on the *N*-deprotection of the intermediate ester **3d** inducing *O*-to-*N* rearrangement to form amide **5** as a precursor of vinyloxazoline **6**. For this purpose, Alloc (allyloxycarbonyl) turned out to be a suitable *N*-protecting group as it was compatible with the electrolysis conditions and its removal was compatible with the double bond and acetal functions in ester **3d** (see Supporting Information File 1 for attempts of other protecting groups such as Boc, Troc, and tfa). However, Pd-catalyzed *N*-Alloc deprotection induced isomerization of the double bond leading to the *trans*-isomer of amide **5**.

Results and Discussion

The protected furfuryl amino alcohols *S*-**2d** and *R*-**2d** were prepared by reductive amination of furfural (**1**) with L- and D-valinol followed by *N*-protection with Alloc-Cl (Scheme 2). The amino alcohols *S*-**2d** and *R*-**2d** were then subjected to electrochemical oxidation in methanol in batch electrolysis conditions, providing unsaturated esters *S*-**3d** and *R*-**3d**, respectively (Scheme 2). The previously used one-reactor two-step conditions were found to be productive for the electrosynthesis of *S*-**3d**, requiring the addition of acetic acid for the intermediate spiroketal **4d** oxidation (Table 1, entry 1). We found that substrate *S*-**2d** can be transformed to ester *S*-**3d** in a single step with

a reduced amount of HFIP as the only additive (Table 1, entries 2 and 3). Given the high cost of HFIP, we examined if it could be replaced with other proton donors for the cathode reaction, and we found that acetic acid served well for this purpose (Table 1, entry 4). Using the reaction conditions with acetic acid as additive, the reaction could be performed also in a 0.5 g scale for the synthesis of both ester enantiomers *S*-**3d** and *R*-**3d** (Table 1, entries 5 and 6). In the absence of acetic acid or HFIP the electrochemical oxidation also provided the desired product **3d**, although in reduced yield (Table 1, entry 7). An increased amount of acetic acid (1 mL or ≈ 18 equiv) also reduced the yield (Table 1, entry 8). The attempt to use LiOAc as electrolyte instead of LiClO₄ was not successful as the reaction was stopped at the spirocycle **4d** formation stage (Table 1, entry 9).

The removal of the *N*-Alloc group in unsaturated ester *S*-**3d** was performed using a Pd catalyst and pyrrolidine as a nucleophile. The use of Pd(PPh₃)₄ as the catalyst led to a fast consumption of the starting material *S*-**3d** but provided a mixture of *cis*- and *trans*-amides *cis*-*S*-**5** and *trans*-*S*-**5** (Scheme 3). The use of PdCl₂(*S*-BINAP) complex as a precatalyst resulted in a longer reaction time and an exclusive formation of amide *trans*-*S*-**5** with isomerized double bond (Scheme 4). The amide *trans*-*R*-**5** was prepared analogously from ester *R*-**3d**.
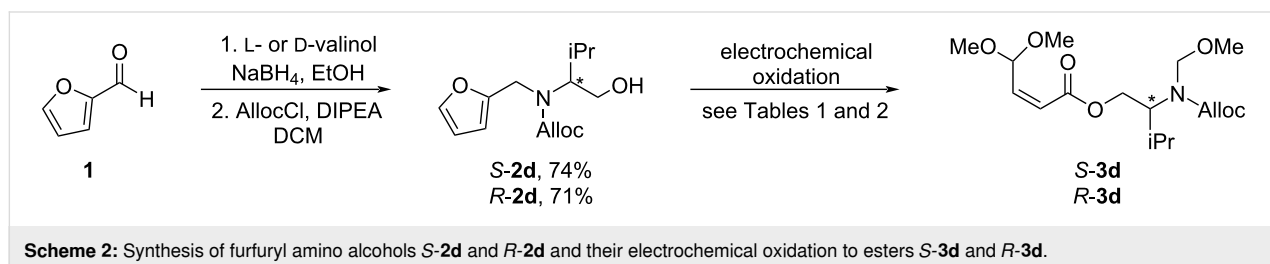

Scheme 2: Synthesis of furfuryl amino alcohols *S*-**2d** and *R*-**2d** and their electrochemical oxidation to esters *S*-**3d** and *R*-**3d**.

Table 1: Electrochemical oxidation of protected amino alcohol **2d** to ester **3d**.

Entry	Conditions[a]	Yield of **3d**
1[b]	1st step: MeOH/HFIP (10:4 mL), LiClO$_4$ (1 equiv), 2.0 F; 2nd step: add AcOH (4 equiv), 3.5 F	72% (*S*-**3d**)
2	single step: MeOH/HFIP (13:1 mL), LiClO$_4$ (1 equiv), 5.5 F	71% (*S*-**3d**)
3	single step: MeOH/HFIP (13.5:0.5 mL), LiClO$_4$ (1 equiv), 5.5 F	70% (*S*-**3d**)
4	single step: MeOH (14 mL), AcOH (3 equiv), LiClO$_4$ (1 equiv), 5.5 F	72% (*S*-**3d**)
5[b]	single step: MeOH (14 mL), AcOH (3 equiv), LiClO$_4$ (0.5 equiv), 5.5 F	68%[c] (*S*-**3d**)
6[b]	single step: MeOH (14 mL), AcOH (3 equiv), LiClO$_4$ (0.5 equiv), 5.5 F	68% (*R*-**3d**)
7	single step: MeOH (14 mL), LiClO$_4$ (1 equiv), 5.5 F	60% (*S*-**3d**)
8	single step: MeOH/AcOH (13:1 mL), LiClO$_4$ (1 equiv), 5.5 F	55% (*S*-**3d**)
9	single step: MeOH (14 mL), AcOH (3 equiv), LiOAc (1 equiv), 5.5 F	0%[d] (*S*-**3d**)

[a]Scale: 1 mmol. [b]Scale: 2 mmol. [c]Faradaic efficiency 49.5%; cell productivity 0.09 mmol/h. [d]Major product is spirocycle **4d** (PG = Alloc).
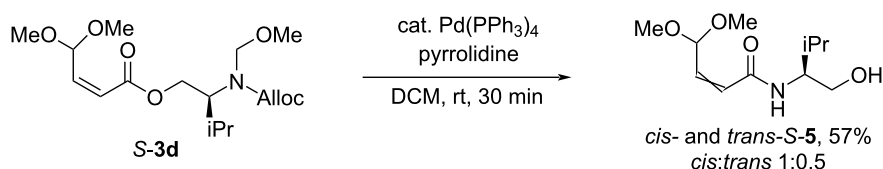

Scheme 3: Cleavage of the *N*-Alloc group leading to a mixture of isomers *cis-S*-**5** and *trans-S*-**5**.
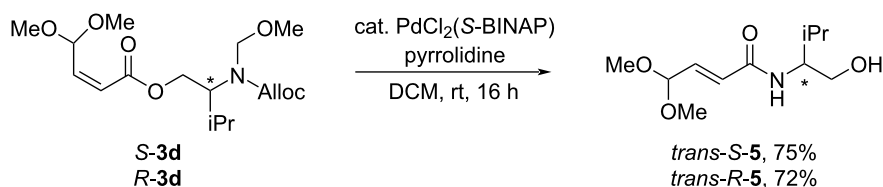
Scheme 4: Cleavage of the *N*-Alloc group with PdCl$_2$(*S*-BINAP) leading to *trans-S*-**5** and *trans-R*-**5**.

Thus, Alloc was validated as non-expensive and relatively small *N*-protecting group, removal of which is compatible with double bond and acetal function of amides *S*-**5** and *R*-**5**. The removal of the Pd catalyst at laboratory scale was done by chromatography. For large scale synthesis, Pd scavengers have to be considered at the work-up.

Unsaturated amides *trans-S*-**5** and *trans-R*-**5** were transformed to oxazolines *S*-**6** and *R*-**6** in good yields by mesylation of the hydroxy group (Scheme 5). Having both enantiomers in hand, the enantiomeric excess of oxazolines *S*-**6** and *R*-**6** was determined by chiral HPLC. This confirmed that no erosion of enantiomeric purity had happened during the deprotection stage.

Scheme 5: Cyclization of amides *trans-S*-**5** and *trans-R*-**5** to oxazolines *S*-**6** and *R*-**6**.

With the enantioenriched vinyloxazoline *S*-**6** in hand, we explored the reaction scope involving its electron-deficient double bond. Unfortunately, the olefin appeared unreactive or gave a mixture of products in copper-catalyzed 1,4-addition of phenylmagnesium bromide, Giese reaction with 2-iodopropane, Simmons–Smith or Johnson–Corey–Chaykovsky cyclopropanation, hydroboration reaction with 9-BBN, and Diels–Alders reaction with Danishevsky diene. Gratifyingly, it was found that vinyloxazoline *S*-**6** is a good substrate for an aza-Diels–Alder reaction with tosylisocyanate (TsNCO) providing the oxazolo[3,2-*c*]pyrimidine derivative **7** as the only detectable diastereomer (Scheme 6) [22-24]. Oxazolo[3,2-*c*]pyrimidines are substructures in several pharmaceutically relevant compounds such as potent gonadotropin-releasing hormone receptor antagonists with potential application as anticancer drugs [25] and as nucleoside analogs with antiviral potency [26].

Scheme 6: aza-Diels–Alder reaction of vinyloxazoline *S*-**6** with TsNCO.
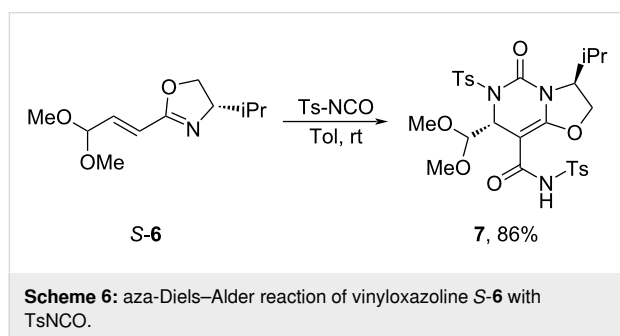
According to the reaction mechanism proposed by Elliott et al., the aza-Diels–Alder reaction of vinyloxazoline *S*-**6** with TsNCO is a step-wise process [22]. The first step involves addition of the oxazoline nitrogen to TsNCO leading to a zwitterionic intermediate **A**, which undergoes 1,4-conjugate addition forming a cyclic intermediate **B**. Subsequently, the electron-rich double bond in intermediate **B** reacts with a second equivalent of TsNCO to form oxazolo[3,2-*c*]pyrimidine derivative **7** (Scheme 7).

The highly diastereoselective formation of product **7** can be explained based on the theoretical calculations by Elliott et al. of aza-Diels–Alder reaction of vinyloxazoline with TsNCO [19].

According to their investigations, the aza-nucleophile attack to the double bond in intermediate **A** is kinetically preferred from the face forming the *R*-configured carbon of the C–N bond as a result of a minimized steric interaction of the oxygen in zwitterion with iPr substituent of oxazoline.

Conclusion
Unsaturated ester obtained by Torii-type ester electrosynthesis from the conjugate of two biobased starting materials furfural and valinol serves as an intermediate to prepare an enantioenriched vinyl oxazoline **6** with atom economy 24.5% over 5 steps (>75% average per step). The electrochemical oxidation of *N*-Alloc can be performed as a single step operation in MeOH with acetic acid as an additive. This is a step toward the large scale synthesis of enantioenriched vinyloxazolines **6** from biomass-derived furfural, however, several challenges remain such as replacing LiClO$_4$ as electrolyte at the oxidation step and avoiding chromatography for purification. Further scale-up could be achieved by switching to flow conditions, or designing a continuous tank reactor [27].

Several attempts were made to explore enantioenriched vinyloxazoline **6** as a chiral building block. While additions to the double bond were not successful, vinyloxazoline **6** was found to be a competent substrate for the aza-Diels–Alder reaction in with TsNCO to give oxazolo[3,2-*c*]pyrimidine derivative **7** as a single diastereomer.
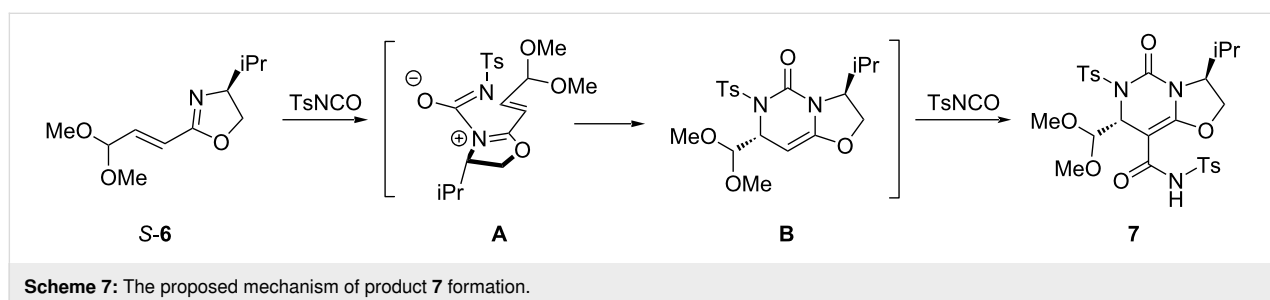
Supporting Information

Supporting Information File 1
Experimental procedures, characterization data and copies of NMR spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-21-136-S1.pdf]

Funding

Scheme 7: The proposed mechanism of product **7** formation.

Author Contributions

Madara Darzina: investigation; writing – original draft. Anna Lielpetere: investigation; writing – original draft. Aigars Jirgensons: conceptualization; funding acquisition; project administration; writing – original draft; writing – review & editing.

ORCID® iDs

Anna Lielpetere - https://orcid.org/0000-0002-4727-0935
Aigars Jirgensons - https://orcid.org/0000-0002-8937-8792

Data Availability Statement

All data that supports the findings of this study is available in the published article and/or the supporting information of this article.

Preprint

A non-peer-reviewed version of this article has been previously published as a preprint: https://doi.org/10.3762/bxiv.2025.35.v1

References

1. Corma, A.; Iborra, S.; Velty, A. *Chem. Rev.* **2007,** *107,* 2411–2502. doi:10.1021/cr050989d
2. Li, H.; Guo, H.; Fang, Z.; Aida, T. M.; Smith, R. L. *Green Chem.* **2020,** *22,* 582–611. doi:10.1039/c9gc03655e
3. He, J.; Chen, L.; Liu, S.; Song, K.; Yang, S.; Riisager, A. *Green Chem.* **2020,** *22,* 6714–6747. doi:10.1039/d0gc01869d
4. Hommes, A.; Heeres, H. J.; Yue, J. *ChemCatChem* **2019,** *11,* 4671–4708. doi:10.1002/cctc.201900807
5. Iglesias, J.; Martínez-Salazar, I.; Maireles-Torres, P.; Martin Alonso, D.; Mariscal, R.; López Granados, M. *Chem. Soc. Rev.* **2020,** *49,* 5704–5771. doi:10.1039/d0cs00177e
6. Sun, Z.; Barta, K. *Chem. Commun.* **2018,** *54,* 7725–7745. doi:10.1039/c8cc02937g
7. Li, X.-L.; Zhang, K.; Jiang, J.-L.; Zhu, R.; Wu, W.-P.; Deng, J.; Fu, Y. *Green Chem.* **2018,** *20,* 362–368. doi:10.1039/c7gc03125d
8. Liu, X.; Li, Y.; Deng, J.; Fu, Y. *Green Chem.* **2019,** *21,* 4532–4540. doi:10.1039/c9gc01767d
9. Song, S.; Fung Kin Yuen, V.; Di, L.; Sun, Q.; Zhou, K.; Yan, N. *Angew. Chem., Int. Ed.* **2020,** *59,* 19846–19850. doi:10.1002/anie.202006315
10. Scodeller, I.; Mansouri, S.; Morvan, D.; Muller, E.; de Oliveira Vigier, K.; Wischert, R.; Jérôme, F. *Angew. Chem., Int. Ed.* **2018,** *57,* 10510–10514. doi:10.1002/anie.201803828
11. Mariscal, R.; Maireles-Torres, P.; Ojeda, M.; Sádaba, I.; López Granados, M. *Energy Environ. Sci.* **2016,** *9,* 1144–1189. doi:10.1039/c5ee02666k
12. Lange, J.-P.; Wadman, S. H. *ChemSusChem* **2020,** *13,* 5329–5337. doi:10.1002/cssc.202001376
13. Kuznetsov, A.; Kumar, G.; Ardagh, M. A.; Tsapatsis, M.; Zhang, Q.; Dauenhauer, P. J. *ACS Sustainable Chem. Eng.* **2020,** *8,* 3273–3282. doi:10.1021/acssuschemeng.9b06881
14. Li, X.; Jia, P.; Wang, T. *ACS Catal.* **2016,** *6,* 7621–7640. doi:10.1021/acscatal.6b01838
15. Li, M.; Dong, X.; Zhang, N.; Jérôme, F.; Gu, Y. *Green Chem.* **2019,** *21,* 4650–4655. doi:10.1039/c9gc02206f
16. Simeonov, S. P.; Ravutsov, M. A.; Mihovilovic, M. D. *ChemSusChem* **2019,** *12,* 2748–2754. doi:10.1002/cssc.201900601
17. Babij, N. R.; Choy, N.; Cismesia, M. A.; Couling, D. J.; Hough, N. M.; Johnson, P. L.; Klosin, J.; Li, X.; Lu, Y.; McCusker, E. O.; Meyer, K. G.; Renga, J. M.; Rogers, R. B.; Stockman, K. E.; Webb, N. J.; Whiteker, G. T.; Zhu, Y. *Green Chem.* **2020,** *22,* 6047–6054. doi:10.1039/d0gc02063j
18. Darzina, M.; Lielpetere, A.; Jirgensons, A. *Eur. J. Org. Chem.* **2021,** 4224–4228. doi:10.1002/ejoc.202100605
19. Barluenga, J.; Suárez-Sobrino, A. L.; Tomás, M.; García-Granda, S.; Santiago-García, R. *J. Am. Chem. Soc.* **2001,** *123,* 10494–10501. doi:10.1021/ja010719m
20. Mitsui, K.; Sato, T.; Urabe, H.; Sato, F. *Angew. Chem., Int. Ed.* **2004,** *43,* 490–492. doi:10.1002/anie.200352769
21. Meyers, A. I.; Stoianova, D. *J. Org. Chem.* **1997,** *62,* 5219–5221. doi:10.1021/jo970429h
22. Elliott, M. C.; Kruiswijk, E.; Willock, D. J. *Tetrahedron Lett.* **1998,** *39,* 8911–8914. doi:10.1016/s0040-4039(98)01949-2
23. Elliott, M. C.; Kruiswijk, E. *J. Chem. Soc., Perkin Trans. 1* **1999,** 3157–3166. doi:10.1039/a905700e
24. Elliott, M. C.; Kruiswijk, E. *Chem. Commun.* **1997,** 2311–2312. doi:10.1039/a705571d
25. Pontillo, J.; Chen, C. *Bioorg. Med. Chem. Lett.* **2005,** *15,* 1407–1411. doi:10.1016/j.bmcl.2005.01.009
26. Folkers, G.; Junginger, G.; Müller, C. E.; Schloz, U.; Eger, K. *Arch. Pharm. (Weinheim, Ger.)* **1989,** *322,* 119–123. doi:10.1002/ardp.19893220213
27. Lehnherr, D.; Chen, L. *Org. Process Res. Dev.* **2024,** *28,* 338–366. doi:10.1021/acs.oprd.3c00340