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Preparation of furfural derived enantioenriched vinyl oxazoline building block and exploring its reactivity

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Abstract

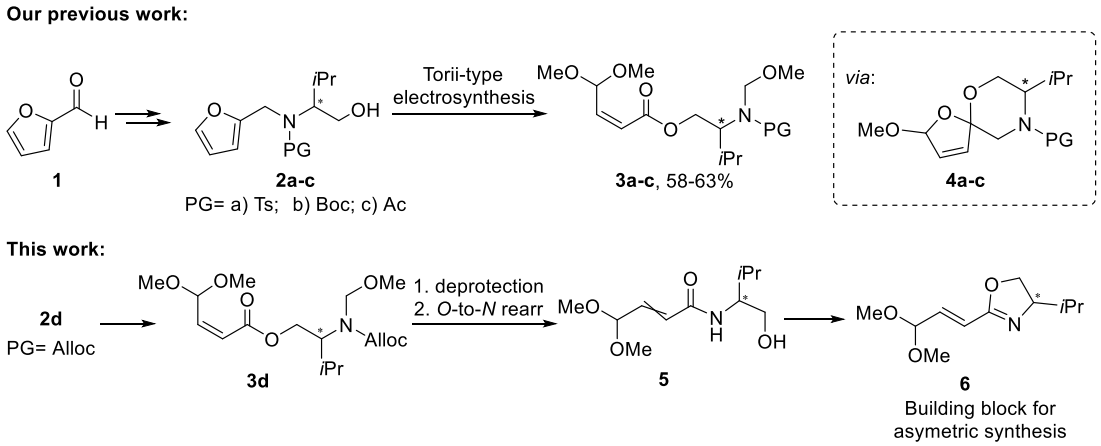
N-Alloc protected furfuryl amino alcohols derived from furfural and L- or D-valinol were subjected to Torii-type ester electrosynthesis to obtain the corresponding unsaturated esters. These served as key intermediates to prepare enantioenriched (*S*)- and *(R)*- unsaturated amides by *N*-Alloc deprotection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

Keywords

furfural; valinol; electrosynthesis; vinyl oxazoline; aza-Diels-Alder reaction

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 application 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 electrooxidative di-alkoxylation of furan ring providing spirocycles **4a-c** which undergo a further eletrooxidative fragmentation to products **3a-c**. In this work, we present Torii-type electrosynthesis of ester **3d** (PG = Alloc) and its transformation to the enantioenriched vinyl oxazoline building block **6,** which can be used for asymmetric synthesis of complex molecules (Scheme 1).

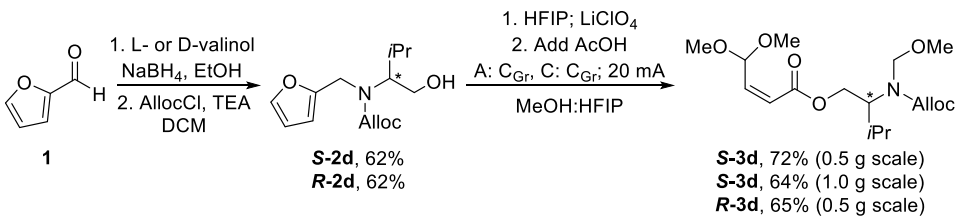


Scheme 1: Proposed approach for the preparation of vinyl oxazoline **6**.

The proposed strategy relied on *N*-deprotection of intermediate ester **3d** inducing *O*- to *N*- rearrangement to form amide **5** as a precursor of vinyl oxazoline **6**. For this purpose, Alloc (allyloxycarbonyl) was chosen as *N*-protecting group as the conditions for its deprotection could be compatible with double bond and dimethylacetal functions in ester **3d**. However, it was anticipated that Pd catalysed *N*-Alloc deprotection may induce full or partial isomerization of the double bond leading to either *cis*- and/or *trans*- isomer of amide **5**.

Results and Discussion

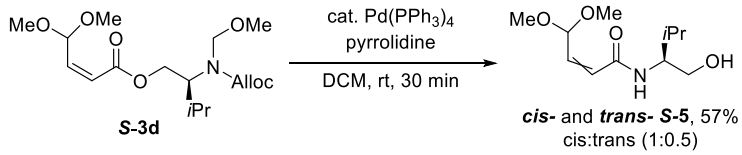
The protected furfuryl amino alcohols ***S*-2d** and ***R*-2d** were prepared by reductive amination of furfural (**1**) with L- and D-valinol followed by *N*-protection with Alloc-Cl (Scheme 2). The amino alcohols ***S*-2d** and ***R*-2d** were subjected to electrochemical oxidation in methanol in batch electrolysis conditions, providing unsaturated esters ***S*-3d** and ***R*-2d** respectively (Scheme 2). One-reactor two-step conditions were found the best for batch electrosynthesis, requiring the addition of acetic acid for the intermediate spiroketal **4d** oxidation. The electrolysis could be successfully performed in 0.5 gram (2 mmol) and gram scale (4 mmol).



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

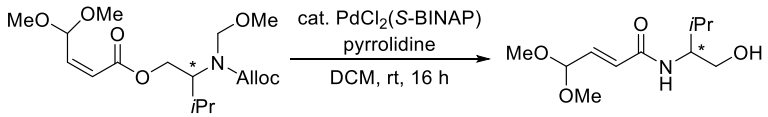
The deprotection of *N*-Alloc group in unsaturated ester ***S*-3d** was performed using Pd catalyst and pyrrolidine as a nucleophile. The use of $Pd(PPh_3)_4$ as

the catalyst led to fast consumption of 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 $PdCl_2$(*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). Amide ***trans*-*R*-5** was prepared analogously from ester ***R*-3d**.



***S*-3d**

Scheme 3: Cleavage of *N*-Alloc group leading to mixture of isomers ***cis*-*S*-5** and ***trans*-*S*-5**.

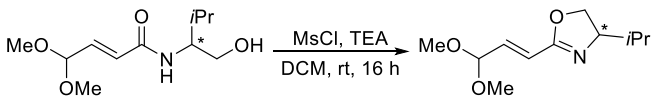


***S*-3d**
***R*-3d**

***trans*-*S*-5**, 75%
***trans*-*R*-5**, 72%

Scheme 4: Cleavage of *N*-Alloc group with $PdCl_2$(*S*-BINAP) leading to ***trans*-*S*-5** and ***trans*-*R*-5**.

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 hydroxyl group (Scheme 5). Having both enantiomers in hand, an enatiomeric 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.



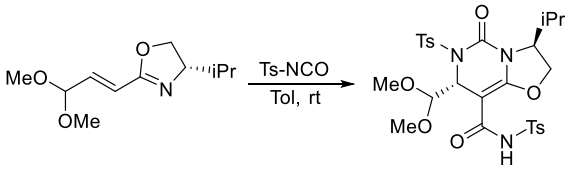
***trans*-*S*-5**
***trans*-*R*-5**

***S*-6**, yield 75%, ee 99%
***R*-6**, yield 70%, ee 97%

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

With enatioenriched vinyl oxazoline ***S*-6** in hand, we explored the reaction scope involving its electron deficient double bond. Unfortunately, the olefin

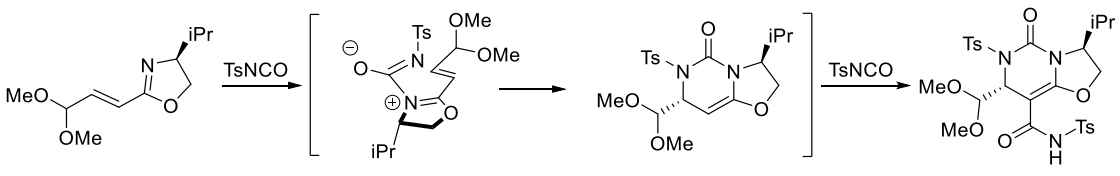
appeared unreactive or gave a mixture of products in copper catalysed 1,4-addition of phenyl magnesium bromide, Giese reaction with 2-iodopropane, Simons–Smith or Johnson–Corey–Chaykovsky cyclopropanation, hydroboration reaction with 9-BBN and Diels-Alders reaction with Danishevsky diene. Gratifyingly, it was found that vinyl oxazoline ***S*-6** is a good substrate for aza-Diels-Alder reaction with tosylisocyanate (TsNCO) providing the oxazolo[3,2-c]pyrimidine derivative **7** as the only detectable diasteromer (Scheme 6).[19,20,21]



***S*-6** **7**, 86%

Scheme 6: aza-Diels-Alder reaction vinyl oxazoline ***S*-6** with TsNCO.

According to the reaction mechanism proposed by Elliott *et al*, the aza-Diels-Alder reaction of vinyl oxazoline ***S*-6** with TsNCO is a step-wise process.[19] The first step involves addition of 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**.



***S*-6** **A** **B** **7**

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

Highly diastereoselective product **7** formation can be explained based on the theoretical calculations by Elliott *et al* of aza-Diels Alder reaction of vinyl oxazoline with TsNCO.[19] According to their investigations, aza-nucleophile attack to double bond in intermediate **A** is kinetically preferred from the face forming R-configured carbon of C-N bond as a result of minimized steric interaction of the oxygen in zwitterion with *i*-Pr 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**. Enantioenriched vinyl oxazoline **6** was found to be competent substrate for aza-Diels-Alder reaction in with TsNCO to give oxazolo[3,2-c]pyrimidine derivative **7** as a single diastereomer.

Supporting Information

Experimental procedures, characterization data and copies of NMR spectra.

Funding

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References

1. Corma Canos, A.; Iborra, S.; Velty, A. *Chem. Rev.,* **2007,** *107*, 2411-2502.

2. Li, H.; Guo, H.; Fang, Z.; Aida, T. M.; Smith, R. L. *Green Chem.,* **2020,** *22*, 582-611.

3. He, J.; Chen, L.; Liu, S.; Song, K.; Yang, S.; Riisager, A. *Green Chem.,* **2020,** *22*, 6714-6747.

4. Hommes, A.; Heeres, H. J.; Yue, J. *ChemCatChem,* **2019,** *11*, 4671-4708.

5. Iglesias, J.; Martínez-Salazar, I.; Maireles-Torres, P.; Martin Alonso, D.; Mariscal, R.; López Granados, M. *Chem. Soc. Rev.,* **2020,** *49*, 5704-5771.

6. Sun, Z.; Barta, K. *Chem. Comm.,* **2018,** *54*, 7725-7745.

7. Li, X.-L.; Zhang, K.; Jiang, J.-L.; Zhu, R.; Wu, W.-P.; Deng, J.; Fu, Y. *Green Chem.,* **2018,** *20*, 362-368.

8. Liu, X.; Li, Y.; Deng, J.; Fu, Y. *Green Chem.,* **2019,** *21*, 4532-4540.

9. Song, S.; Fung Kin Yuen, V.; Di, L.; Sun, Q.; Zhou, K.; Yan, N. *Angew. Chem. Int. Ed.,* **2020,** *59*, 19846-19850.

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.

11. Mariscal, R.; Maireles-Torres, P.; Ojeda, M.; Sádaba, I.; López Granados, M. *Energy Environ. Sci.,* **2016,** *9*, 1144-1189.

12. Lange, J.-P.; Wadman, S. H. *ChemSusChem,* **2020,** *13*, 5329-5337.

13. Kuznetsov, A.; Kumar, G.; Ardagh, M. A.; Tsapatsis, M.; Zhang, Q.; Dauenhauer, P. J. *ACS Sustain. Chem. Eng.,* **2020,** *8*, 3273-3282.

14. Li, X.; Jia, P.; Wang, T. *ACS Catalysis,* **2016,** *6*, 7621-7640.

15. Li, M.; Dong, X.; Zhang, N.; Jérôme, F.; Gu, Y.*Green Chem.* **2019,** *21*, 4650-4655.

16. Simeonov, S. P.; Ravutsov, M. A.; Mihovilovic, M. D. *ChemSusChem,* **2019,** *12*, 2748-2754.

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.

18. Darzina, M.; Lielpetere, A.; Jirgensons, A. *Eur. J. Org. Chem.* **2021,** *2021*, 4224-4228.

19. Elliott, M. C.; Kruiswijk, E.; Willock, D. J. *Tetrahedron Lett.,* **1998,** *39*, 8911-8914.

20. Elliott, M. C.; Kruiswijk, E. *J. Chem. Soc., Perkin Trans 1,* **1999**, 3157-3166.

21. Elliott, M. C.; Kruiswijk, E. *Chem. Comm.,* **1997**, 2311-2312.