



Sequential Reactions | Very Important Paper |

# Libraries of C-5 Substituted Imidazoles and Oxazoles by Sequential Van Leusen (VL)–Suzuki, VL–Heck and VL– Sonogashira in Imidazolium-ILs with Piperidine-Appended-IL as Base

Hemantkumar M. Savanur,<sup>[a]</sup> Rajesh G. Kalkhambkar,\*<sup>[a]</sup> and Kenneth K. Laali\*<sup>[b]</sup>

**Abstract:** Facile access to diverse C5-substituted imidazoles and oxazoles via sequential Van Leusen–Suzuki, Van Leusen– Heck, and Van Leusen–Sonogashira protocols, employing imidazolium-ILs as solvents along with piperidine-appended imidazolium [PAIM][NTf<sub>2</sub>] as task-specific basic IL has been demon-

#### Introduction

Imidazoles and oxazoles are highly important classes of heterocyclic compounds that are present in numerous bioactive natural products and are widely utilized as building blocks in medicinal chemistry and drug discovery.<sup>[1,2]</sup> Imidazolium salts in particular are widely employed as ionic liquids and have found wide application as solvents and catalysts.<sup>[3]</sup> It is therefore highly desirable to develop synthetic methods that provide facile access to diversely functionalized imidazoles and oxazoles that can serve as small molecule building blocks for further elaboration.

The Van Leusen tricomponent imidazole and oxazole syntheses are practical one-pot protocols that utilize the unique reactivity of tosylmethylisocyanide (Tos-MIC) to prepare imidazoles from aldimines and oxazoles from aldehydes.<sup>[4]</sup> Continuing developments in multi-component (MC) sequential reactions have created a new life for the van Leusen reaction, by combining this key reaction with other transformations such as cycloaddition,<sup>[5]</sup> C–H bond activation,<sup>[6]</sup> ring closing metathesis,<sup>[7]</sup> and other C–C bond forming reactions sequential reactions.<sup>[8–10]</sup>

We are aware of only one previous report in which [BMIM][Br] was used as solvent to prepare oxazoles by Van Leusen reaction using mono-substituted Tos-MICs along with base.<sup>[11]</sup> To the best of our knowledge IL-mediated MC-sequential methods involving the van Leusen reaction have not been reported.

 [a] Department of Chemistry, Karnatak University's Karnatak Science College, Dharwad Karnatak 580001, India
E-mail: rgkalkhambkar31@gmail.com

[b] Department of Chemistry, University of North Florida, 1 UNF Drive, Jacksonville, FL, 32224, USA E-mail: Kenneth.Laali@UNF.edu http://www.unf.edu/coas/chemistry/faculty/Kenneth\_Laali.aspx

 $\exists$  Supporting information and ORCID(s) from the author(s) for this article are

available on the WWW under https://doi.org/10.1002/ejoc.201800804.

as base,<sup>[13]</sup> we wish to report here a facile entry into diversely C-5 substituted imidazoles and oxazoles via sequential van Leusen–Suzuki, van Leusen–Heck, and van Leusen–Sonogashira protocols, employing imidazolium-ILs as solvent along with the piperidine-appended imidazolium-NTf<sub>2</sub><sup>[13]</sup> as task-specific basic IL, in one-pot high yielding reactions starting from readily available aldimines (for imidazole) or aldehydes (for oxazole) and tosylmethylisocyanide (Tos-MIC), under mild conditions. The potential for recycling and reuse of the IL solvent is also demonstrated, and scope of the method is highlighted by providing

scope of the method is supported 49 examples.

strated, in a high-yielding one-pot method, starting with readily

available aldimines (for imidazole) or aldehydes (for oxazole)

and tosylmethylisocyanide (Tos-MIC), under mild conditions

with potential for recycling and reuse of the IL solvent. The

In continuation of our work on developing synthetic methods in ILs as catalysts and solvents,<sup>[12]</sup> and in relation our recent

study on sequential reactions in ILs employing task-specific ILs

## **Results and Discussion**

49 examples.

At the onset, the potential to efficiently perform the van Leusen imidazole and oxazole reactions in [BMIM][X] with  $X = PF_6$  and  $BF_4$  as solvent with piperidine-appended imidazolium IL [PAIM][NTf<sub>2</sub>] as base was examined, by using *p*-bromo-benz-aldimines and benzaldehyde respectively, in one-pot reactions using Tos-MIC, and the reactions were monitored by TLC. The reactions went to completion at 60–70 °C typically after 5–6 hours (see exp. in SI file). The method also proved applicable when using *p*-bromo-furan-aldimine and *p*-bromo-furan-carboxaldehyde.

In the next phase, the feasibility to perform multi-component (MC) van Leusen imidazole–Suzuki and oxazole–Suzuki sequential reactions were examined by introducing  $Pd(OAc)_2$  and [PAIM][NTf<sub>2</sub>] along with various aryl/heteroaryl boronic acids into the same reaction tube with mild heating and TLC monitoring. The results are summarized in Table 1–Table 2 with 23 examples provided, and with isolated yields in the 70–80 % range





using fresh IL solvent, decreasing gradually when using recycled IL.

Table 1. The Van Leusen imidazole-Suzuki sequence.



[a] Recycled IL was used (1<sup>st</sup> time). [b] Recycled IL was used (2<sup>nd</sup> time). [c] Recycled IL was used (3<sup>rd</sup> time); \*Isolated yield of pure compounds.

Control experiments showed that it is possible to perform the reactions by using [PAIM][NTf<sub>2</sub>] alone, however this required a larger quantity of the basic-IL as it also acts as solvent for the reaction, and was not deemed economical, since the basic-IL is not recycled. Optimal results were achieved by a combined use of [BMIM][X] acting as solvent and [PAIM][NTf<sub>2</sub>] acting as a compatible base. Table 2. The Van Leusen oxazole-Suzuki sequence.



Entry No.	Van Leusen Product	Coupling Partner	Suzuki Reaction	IL	Time [h]	Yield [%]*
15	Br	B(OH) <sub>2</sub>	CO CN	[BMIM][PF6]	4	78
16	Br	B(OH) <sub>2</sub>	1000	[BMIM][PF6]	6	74 <sup>a</sup>
17	Br	B(OH) <sub>2</sub>	CO CN	[BMIM][PF6]	5	67 <sup>b</sup>
18	Br	B(OH) <sub>2</sub>		[BMIM][BF4]	5	73
19	Br	B(OH) <sub>2</sub>	TO OD	[BMIM][BF4]	7	60 <sup>b</sup>
20	Br	B(OH) <sub>2</sub>	() () ()	[BMIM][BF4]	7	54°
21	50 Br	B(OH) <sub>2</sub>	Jo Ss	[BMIM][PF6]	6	64 <sup>b</sup>
22	Br	B(OH) <sub>2</sub>	S C	[BMIM][BF4]	5	68
23	Br	B(OH) <sub>2</sub>	CS CN	[BMIM][BF4]	76	60 <sup>a</sup>

[a] Recycled IL was used (1<sup>st</sup> time). [b] <sup>b</sup>Recycled IL was used (2<sup>nd</sup> time). [c] <sup>c</sup>Recycled IL was used (3<sup>rd</sup> time); \*Isolated yield of pure compounds.

The efficacy to perform MC van Leusen imidazole–Heck and oxazole–Heck sequential reactions was examined next. For these reactions, following the completion of the van Leusen step, styrene or *p*-methyl-styrene was introduced along with Pd(OAc)<sub>2</sub> and [PAMI][NTf<sub>2</sub>] with no other additives with mild heating. Isolated yields using fresh IL solvent were in the 78–68 % range and decreasing gradually when recycled IL was employed. The results are summarized in Table 3–Table 4 with 17 examples provided.

In a subsequent study, the van Leusen imidazole–Sonogashira and oxazole–Sonogashira sequential reactions were performed by introducing substituted alkynes along with 6 mol-% Pd(OAc)<sub>2</sub> and with Cul as additive. The reactions went to completion after overnight stirring and mild heating. Average isolated yields were in 70–60 % range and again lower yields were obtained by using recycled IL. The results are gathered in Table 5–Table 6 with 12 examples provided.

To get a sense for the limits of recovery and reuse of the IL solvent, one reaction was selected from each category and was repeated in  $[BMIM][BF_4]$  and  $[BMIM][PF_6]$  up to five times to compare isolated yields. The results are presented in graphical form in the SI file. The data show a relatively consistent trend of decreasing yields by about 10 % after each cycle. For some





Table 3. The Van Leusen imidazole-Heck sequence.



[a] Recycled IL was used  $(1^{st}$  time). [b] Recycled IL was used  $(2^{nd}$  time). [c] Recycled IL was used  $(3^{rd}$  time); \*Isolated yield of pure compounds.

Table 4. The Van Leusen oxazole-Heck sequence.



[a] Recycled IL was used (1<sup>st</sup> time). [b] Recycled IL was used (2<sup>nd</sup> time); \*Isolated yield of pure compounds.

Table 5. The Van Leusen imidazole-Sonogashira sequence.



[a] Recycled IL was used (1<sup>st</sup> time). [b] Recycled IL was used (2<sup>nd</sup> time); \*Isolated yield of pure compounds.

Table 6. The Van Leusen oxazole-Sonogashira sequence.



[a] Recycled IL was used (1<sup>st</sup> time). [b] Recycled IL was used (2<sup>nd</sup> time). \*Isolated yield of pure compounds.





of the transformations  $[BMIM][PF_6]$  appears more resilient and would be the preferred IL solvent.

In summary, we have demonstrated the potential for sequential Van Leusen imidazole and oxazole with Suzuki, Heck, and Sonogashira coupling protocols, employing imidazolium-ILs as solvent along with [PAIM][NTf<sub>2</sub>] as task-specific basic IL, starting with readily available aldimines (for imidazole) or aldehydes (for oxazole) and tosylmethylisocyanide (Tos-MIC) under mild conditions and highlighted the scope of these sequential reactions with 49 examples. We also demonstrated the possibility to recycle and reuse the IL solvent for a limited number of cycles.

**Supporting Information** (see footnote on the first page of this article): Synthetic procedures, IL recycling feasibility studies, analytical data for isolated compounds, and NMR spectroscopic data

### Acknowledgments

Authors at Karnatak University thank the University Scientific and Instrument Center, KUD for IR, GC, GC-MS, <sup>1</sup>H and <sup>13</sup>C NMR, and the NMR Research Centre at Indian Institute of Science Bangalore for <sup>1</sup>H and <sup>13</sup>C NMR Spectra. They also acknowledge financial assistance by Department of Science and Technology, Science and Engineering Research Board New Delhi (DST-SERB) Project No. SB/FT/CS-175/2013. K. K. L. thanks University of North Florida for the outstanding faculty scholarship and presidential professorship awards, as well as faculty scholarship and UNF Foundation Board grants.

**Keywords:** Synthetic methods · C-C coupling · Domino reactions · Ionic liquids

- Selected reviews on imidazoles: a) L. Zhang, X.-M. Peng, G. L. V. Damu, R.-X. Geng, C.-H. Zhou, Med. Res. Rev. 2014, 34, 340–437; b) P. Gupta, J. K. Gupta, Int. J. Modern. Chem. 2015, 7, 60–80; c) K. Shalini, P. K. Sharma, N. Kumar, Der Chemica Sinica 2010, 1, 36–47; d) A. Sharma, V. Kumar, R. Kharb, S. Kumar, P. C. Sharma, D. P. Pathak, Curr. Pharm. Des. 2016, 22, 3265–3301; e) Y.-L. Fan, X.-H. Jin, Z.-P. Huang, H.-F. Yu, Z.-G. Zeng, T. Gao, L.-S. Feng, Eur. J. Med. Chem. 2018, 150, 347–365.
- [2] Selected reviews on oxazoles: a) H. Zhang, Z. Zhao, C. Zhao, *Eur. J. Med. Chem.* 2018, 144, 444–492; b) D. Zhang, J. Guo, M. Zhang, X. Liu, M. Ba, X. Tao, L. Yu, Y. Guo, J. Dai, *J. Nat. Prod.* 2017, 80, 3241–3246; c) H. Zhou, J. Cheng, Z.-S. Wang, F. Chen, X. Liu, *Curr. Top. Med. Chem.* 2016, 16, 3582–3589; d) L. Swellmeen, *Der Pharma Chemica* 2016, 8, 269–286.
- [3] Selected reviews: a) J. P. Hallett, T. Welton, Chem. Rev. 2011, 111, 3508–3576; b) C. Chiappe, S. Rajamani, Eur. J. Org. Chem. 2011, 5517–5539; c) H. Olivier-Bourbigou, L. Magna, D. Morvan, Appl. Catal. A 2010, 373, 1–56; d) H. Olivier-Bourbigou, L. Magna, J. Mol. Catal. A 2002, 182–183, 419–437; e) T. L. Greaves, C. J. Drummond, Chem. Rev. 2008, 108, 206–237; f) J. Pavlinac, M. Zupan, K. K. Laali, S. Stavber, Tetrahedron 2009, 65, 5625–5662; g) M. A. P. Martins, C. P. Frizzo, D. N. Moreira, N. Zanatta, H. G. Bonacorso, Chem. Rev. 2008, 108, 2015–2050.
- [4] D. van Leusen, A. M. van Leusen in Synthetic Uses of Tosylmethyl Isocyanide (TOSMIC) in Organic Reactions (Ed.: L. E. Overman), Wiley, Hoboken, New Jersey, 2004, pp. 417–666.
- [5] V. Gracias, D. Darczak, A. F. Gasiecki, S. W. Djuric, *Tetrahedron Lett.* 2005, 46, 9053–9056.
- [6] a) X. Beebe, V. Gracias, S. W. Djuric, *Tetrahedron Lett.* 2006, 47, 3225–3228; b) V. Gracias, A. F. Gasiecki, T. G. Pagano, S. W. Djuric, *Tetrahedron Lett.* 2006, 47, 8873–8876.
- [7] V. Gracias, A. F. Gasiecki, S. W. Djuric, Org. Lett. 2005, 7, 3183-3186.
- [8] F. De Moliner, C. Hulme, Tetrahedron Lett. 2012, 53, 5787-5790.
- [9] T. Yoshizumi, T. Satoh, K. Hirano, D. Matsuo, A. Orita, J. Otera, M. Miura, *Tetrahedron Lett.* 2009, 50, 3273–3276.
- [10] J. Maiti, S. Biswas, R. Das, Asian J. Chem. 2016, 28, 1519–1522.
- [11] B. Wu, J. Wen, Z. Zhang, J. Li, Y.-Z. Xiang, X.-Q. Yu, Synlett 2009, 500–504.
- [12] K. K. Laali, ARKIVOC **2016**, *i*, 150–171.
- [13] H. M. Savanur, R. G. Kalkhambkar, K. K. Laali, Appl. Catal. A 2017, 543, 150–161.

Received: May 24, 2018





#### Sequential Reactions

VIP

Ð

H. M. Savanur, R. G. Kalkhambkar,\* K. K. Laali\* ...... 1–5

Libraries of C-5 Substituted Imidazoles and Oxazoles by Sequential Van Leusen (VL)–Suzuki, VL–Heck and VL–Sonogashira in Imidazolium-ILs with Piperidine-Appended-IL as Base



By sequencing the Van Leusen imidazole and oxazole syntheses with Suzuki, Heck and Sonogashira reactions, diverse libraries of C5-functionalized imidazoles and oxazoles were synthesized in one-pot reactions employing [BMIM][X] as a solvent and [PAIM]-[NTf<sub>2</sub>] as a base.

# DOI: 10.1002/ejoc.201800804