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# Synthesis of fused imidazo azepine derivatives by sequential van Leusen/enyne metathesis reactions

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**Abstract**—A facile synthesis of fused imidazo azepine derivatives by a van Leusen/intramolecular enyne metathesis synthetic sequence is reported. The two-step reaction sequence generates compounds of significant molecular complexity from simple starting materials in an expedient fashion with good overall yields.


Multicomponent reactions (MCRs) are widely employed for the construction of diversely functionalized molecules via simple one-step transformations.[1] Recently, isocyanide-based MCRs like the Passerini three-component and the Ugi four-component reactions have been combined with secondary transformations to produce even more functionalized and specialized heterocyclic molecules. Some examples of post-condensation reactions include Diels–Alder reactions, aminocyclizations, nucleophilic aromatic substitutions, lactonizations and ring-closing metathesis.[2] As part of our group's efforts to develop short and versatile routes to access novel heterocyclic structures, we have recently reported sequential Ugi/Heck,[3] Ugi/intramolecular nitrile oxide cycloaddition,[4] Ugi/intramolecular alkyne-azide cycloaddition[5] and Ugi/carbonylation intramolecular amidation[6] sequences.

The imidazole nucleus is present in a variety of natural products and medicinally relevant heterocycles[7] including antiviral and antibacterial agents.[8] It is in this context that we became interested in the van Leusen imidazole synthesis[9] as part of a program to identify and synthesize novel heterocyclic skeletons. We have recently reported on sequential van Leusen/ring-closing metathesis strategies to access novel bicyclic imidazoles.[10]

Herein, we report on our efforts on post-modifications of the van Leusen reaction using an enyne metathesis[11] as the ultimate step in our reaction sequence (Fig. 1). The

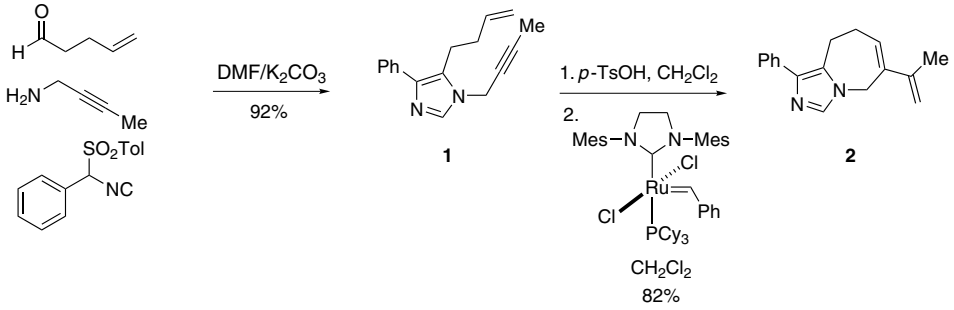


**Figure 1.** General strategy.

*Keywords*: Multicomponent reactions; van Leusen; Enyne metathesis.
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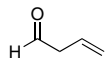
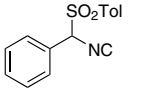
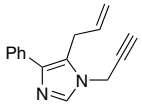
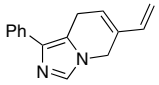
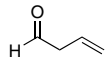
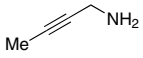
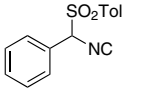
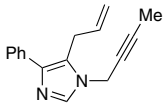
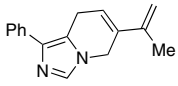
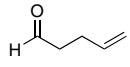
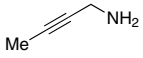
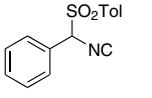
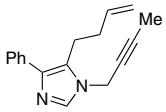
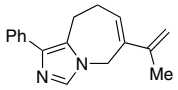
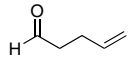
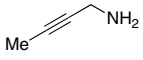
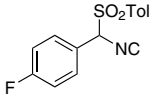
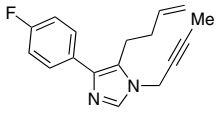
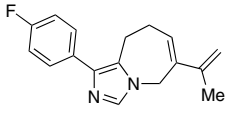
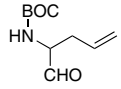
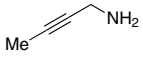
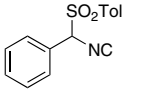
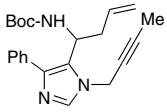
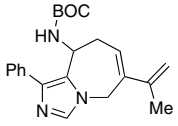
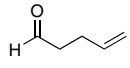
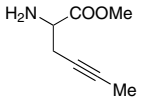
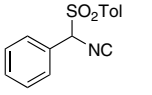
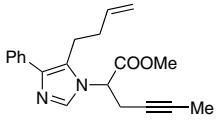
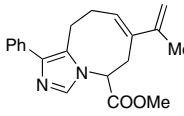
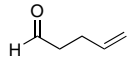
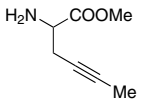
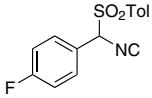
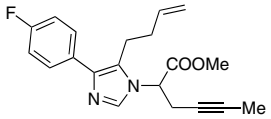
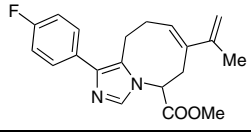
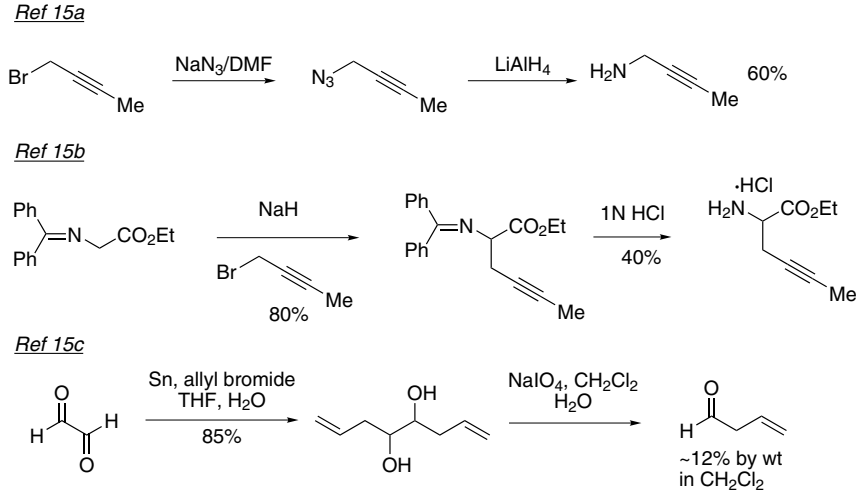
use of an alkene functionality on the aldehyde and an alkyne functionality on the amine provides bifunctional starting materials for the van Leusen reaction resulting in substrate **1**. Subsequent cyclization via the intramolecular enyne metathesis results in the formation of the cyclized product **2** containing a diene functionality.

The condensation of 4-pentenal with but-2-yn-1-amine in DMF at room temperature generates the imine in situ, which is followed by the addition of phenyl TosMIC and base ($K_2CO_3$) to afford the van Leusen imidazole product **1** in 92% yield. As with the alkene metathesis post-modification, the imidazole was pretreated with an equivalent of *p*-TsOH before subjecting it to the enyne ring closure.[12] The subsequent reaction catalyzed by the second-generation Grubbs catalyst (10 mol %) in refluxing $CH_2Cl_2$ gave the fused bicyclic imidazole **2** in 82% yield.[13]

**Table 1.** Products obtained from the van Leusen/enyne metathesis reaction sequence

| Entry | Aldehyde | Amine | TosMIC | van Leusen product | Yield (%) | Enyne product | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 |  |  |  |  | 48 |  | <5 |
| 2 |  |  |  |  | 45 |  | 54 |
| 3 |  |  |  |  | 92 |  | 82 |
| 4 |  |  |  |  | 87 |  | 71 |
| 5 |  |  |  |  | 53 |  | 64 |
| 6 |  |  |  |  | 87 |  | 63 |
| 7 |  |  |  |  | 86 |  | 54 |




**Scheme 1.** General synthetic routes for the preparation of the starting materials.

Aldehyde and amine components of varying chain length were used in the van Leusen reaction to provide the corresponding C1/C5-substituted metathesis precursors. These were subjected to the intramolecular enyne metathesis sequence to provide products of varied ring size (Table 1). A diverse set of 5,6- 5,7- and 5,8-fused bicyclic functionalized imidazoles was generated via this reaction sequence. With terminal alkynes low yields of the metathesis product was observed (Table 1, entry 1).[14] In addition to simple primary amines and aldehydes, secondary amino aldehydes and amino esters were used as building blocks to provide another functional group for further elaboration of the skeleton (Table 1, entries 4–6). The requisite building blocks were purchased from commercial sources or prepared according to known procedures as illustrated in Scheme 1.[15] Finally, the availability of efficient routes to synthesize substituted TosMIC reagents provides another site of diversity in the three-component reaction.[16] In conclusion, we have demonstrated that by incorporating alkene–alkyne inputs in the van Leusen reaction, followed by an enyne metathesis reaction a variety of fused bicyclic imidazoles can be readily generated. Each of the bicyclic scaffolds generated by this reaction sequence had the diene functionality, which could then serve as a site for further diversification. Elaboration of the bicyclic dienes via cycloaddition reactions and other van Leusen post-modification reactions are currently in progress and will be reported in due course.

## Acknowledgement

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12. This treatment results in the formation of the imidazolium ion, preventing the lone pair of the imidazole nitrogen from inactivating the Grubbs catalyst. See reference: Chen, Y.; Dias, H. V. R.; Lovely, C. J. *Tetrahedron Lett.* **2003**, *44*, 1379–1382. Our reaction failed to yield the enyne product in the absence of this pretreatment procedure.
13. A representative procedure is demonstrated by the preparation of 6-isopropenyl-1-phenyl-8,9-dihydro-5*H*-imidazo[1,5-*a*]azepine (**2**). To the 4-pentenal (126 mg, 1.5 mmol) in DMF (2 mL) was added but-2-yn-1-amine (138 mg, 2.0 mmol) and the reaction mixture was stirred at rt for 2.5 h. This was followed by the addition of phenyl TosMIC (271 mg, 1.0 mmol) and $K_2CO_3$ (138 mg, 2.0 mmol) and the reaction mixture was allowed to stir for an additional 17 h at rt. The reaction was quenched by the addition of water. The aqueous layer was extracted with EtOAc, dried (anhyd $MgSO_4$) concentrated and purified by flash chromatography (97–2.5–0.5: $CH_2Cl_2$–$CH_3OH$–$NH_3$) to afford 230 mg (92%) of **1** as a clear oil. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.84 (t, $J = 3.0$ Hz, 3H), 2.38 (m, 2H), 2.92 (m, 2H), 4.59 (m, 2H), 5.05 (m, 2H), 5.85 (m, 1H), 7.22–7.42 (m, 3H), 7.65 (m, 3H); MS (ESI): *m/z* 251 (M+H). To a solution of **1** (190 mg, 0.76 mmol) in

$CH_2Cl_2$ (20 mL) was added *p*-TsOH (145 mg, 0.76 mmol) and the reaction mixture was heated at reflux for 30 min. The reaction was cooled to rt and the Grubbs catalyst (65 mg, 0.076 mmol) was added and the reaction mixture was refluxed for an additional 2 h (TLC indicated disappearance of the starting material). The reaction was quenched by adding aq satd $K_2CO_3$ and extracted with EtOAc. The organic layer was dried (anhyd $MgSO_4$), concentrated and purified by flash chromatography (97–2.5–0.5: $CH_2Cl_2$–$CH_3OH$–$NH_3$) to afford 155 mg (82%) of **2** as a light brown oil. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.93 (s, 3H), 2.59 (m, 2H), 3.17 (d, $J = 6.0$ Hz, 2H), 4.83 (s, 2H), 5.02 (d, $J = 9.0$ Hz, 2H), 5.95 (t, $J = 3.0$ Hz, 1H), 7.25 (m, 1H), 7.38 (m, 2H), 7.46 (s, 1H), 7.62 (d, $J = 6.0$ Hz, 2H); MS (ESI): $m/z$ 251 (M+H).

14. The use of ethylene gas is reported to give improved yields in the enyne metathesis of terminal alkynes. See reference: Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082–6083. We did not try the enyne metathesis of terminal alkynes using ethylene gas.
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