Synthesis of Fused Bicyclic Imidazoles by Sequential Van Leusen/Ring-Closing Metathesis Reactions
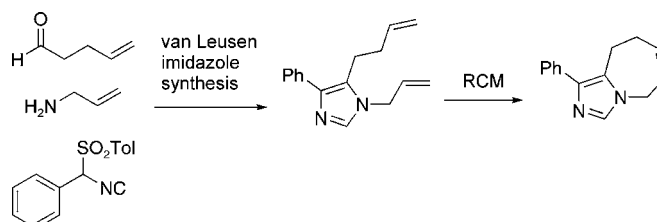
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ABSTRACT

A new strategy employing the van Leusen three-component reaction and the ring-closing metathesis reaction in a sequential fashion to access fused bicyclic imidazole rings is reported. The two-step sequence generated compounds of significant molecular complexity from simple starting materials in an expedient fashion with excellent yields.

Multicomponent reactions (MCRs) have been extensively investigated in organic and diversity-oriented synthesis mostly due to their ability to install complex molecular functionality in simple one-step transformations.[1] In recent years, isocyanide-based MCRs such as the Passerini three-component and the Ugi four-component reactions have been combined with postcondensation modifications that allow access to even more functionalized and specialized heterocyclic molecules. Some examples of postcondensation reactions include Diels−Alder reactions, amino cyclizations, nucleophilic aromatic substitutions, lactonizations, and ring-closing metathesis.[2] As part of our efforts to develop new routes to access novel heterocyclic structures, we have recently reported sequential Ugi/Heck,[3] Ugi/intramolecular nitrile oxide cycloaddition,[4] Ugi/intramolecular alkyne−azide

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cycloaddition,[5] and Ugi/carbonylation intramolecular amidation[6] sequences.

The imidazole nucleus is present in a variety of natural products and biologically important compounds and occupies an important position in medicinally relevant heterocyclic systems.[7] In particular, bicyclic imidazole nuclei are present in a number of bioactive molecules, including antiviral and antibacterial agents.[8] While a number of synthetic routes have been reported to access diversely substituted or bicyclic imidazole nuclei, some of these are circuitous and low-yielding and sometimes require preparation of synthetically challenging intermediates.[9] We became interested in the van Leusen imidazole synthesis[10] as part of a program to identify and synthesize novel heterocyclic skeletons that were primed to undergo further modification and derivatization to generate medicinally relevant, fused heterocyclic, bicyclic systems.

The van Leusen imidazole synthesis is a three-component reaction involving the cycloaddition of tosylmethyl isocyanides (TosMICs) with imines under mild reaction conditions (Figure 1). A variety of 1,4- and 4,5-disubstituted imidazoles
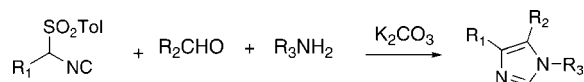

Figure 1. Van Leusen three-component reaction to imidazoles.

as well as 1,4,5-trisubstituted imidazoles can be readily synthesized by varying the aldehyde, amine and the TosMIC components. Furthermore, an efficient one-pot protocol to access polysubstituted imidazoles from aryl-substituted TosMIC reagents and imines generated in situ has been reported.[11] This report also demonstrated the functional groups that are tolerated by the van Leusen reaction, including chiral amines, aldehydes, and amino acids. Additionally, the availability of efficient routes to synthesize

substituted TosMIC reagents allows for the exploitation of versatile building blocks in the van Leusen reaction.[12]

Herein, we report on our efforts on postmodifications of the van Leusen reaction using a ring-closing metathesis as the ultimate step in our reaction sequence (Figure 2). The
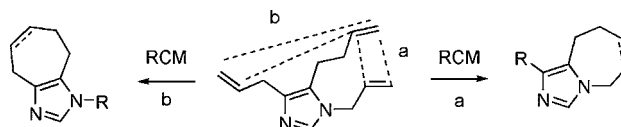

Figure 2. General strategy.

use of bifunctional starting materials with terminal olefinic bonds in the van Leusen reaction in combination with the RCM would allow access to novel fused imidazole scaffolds. We envisioned control of ring size and functional group features in the products based on the choice of the bifunctional starting materials. This concept has been previously reported in the context of Ugi and Passerini-type MCRs wherein alkene inputs were introduced into the reaction components and followed by a postcondensation RCM reaction to afford cyclic lactams.[2] Additionally, there has been one report of a facile synthesis of five- and six-membered bicyclic imidazoles via RCM of the alkene functionality on the imidazole core.[13] In this case, the authors generated the RCM precursor by a chemoselective metalation−electrophilic capture sequence.

The general method to access the fused imidazoles is outlined in Scheme 1. Phenyl TosMIC was chosen as the

Scheme 1. General Method
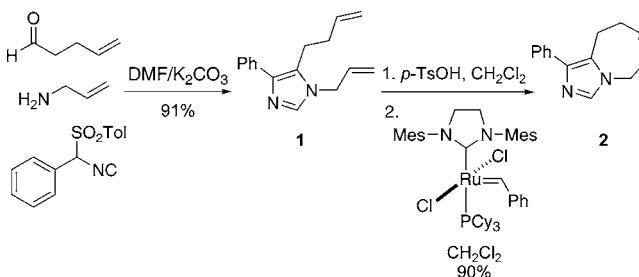
isocyanide component in the model van Leusen reaction system, as it had been previously reported to work well in this reaction.[11] Also, the best solvent/base combination for this reaction, DMF/K$_2$CO$_3$, was used. The reaction proceeded smoothly with the condensation of 4-pentenal with allylamine in DMF at room temperature to generate the imine in situ, which was followed by the addition of the TosMIC reagent

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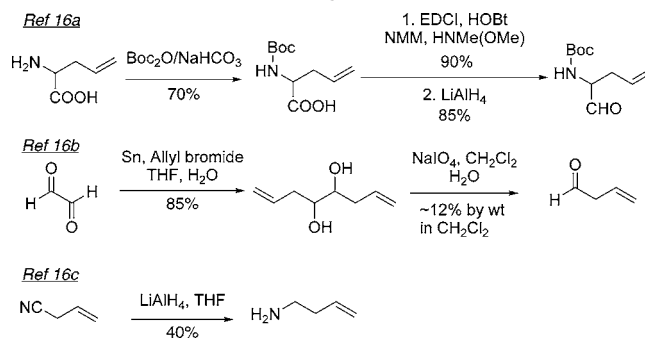
and base (K_2CO_3) to afford the van Leusen imidazole product **1** in 91% isolated yield. Substrate **1** had to be pretreated with 1 equiv of *p*-TsOH before subjecting it to the RCM.[14] The subsequent RCM reaction catalyzed by the second-generation Grubbs catalyst in refluxing CH_2Cl_2 cleanly afforded the fused bicyclic imidazole **2** in 90% yield.[15]

On the basis of the success of the model system, a series of products that could serve as precursors for the RCM were constructed in order to evaluate the scope of this reaction sequence. The results are outlined in Table 1.

Table 1. Results on the Van Leusen Imidazole Synthesis

$$R_1\text{-CH(SO}_2\text{Tol)(NC)} + R_2\text{-CHO} + R_3\text{-NH}_2 \xrightarrow{\text{DMF/K}_2\text{CO}_3} \text{imidazole}$$

entry	R_1	R_2-CHO	R_3-NH$_2$	van Leusen product (yield %)
1	Ph	but-3-enal	allylamine	(51)
2	Ph	BOC-NH-CH(CHO)-allyl	allylamine	(86)
3	Ph	pent-4-enal	2-methylallylamine	(92)
4	4-F-C$_6$H$_4$	BOC-NH-CH(CHO)-allyl	2-methylallylamine	(51)
5	Ph	pent-4-enal	but-3-enylamine	(92)
6	Ph	BOC-NH-CH(CHO)-but-3-enyl	but-3-enylamine	(53)
7	Ph	pent-4-enal	methyl 2-aminopent-4-enoate (CO$_2$Me)	(75)
8	but-3-enyl	pent-4-enal	BnNH$_2$	(32)

Scheme 2. General Synthetic Routes for the Preparation of the Starting Materials

Ref 16a

$$H_2N\text{-CH(COOH)-allyl} \xrightarrow[70\%]{\text{Boc}_2\text{O/NaHCO}_3} \text{Boc-HN-CH(COOH)-allyl} \xrightarrow[\substack{1.\ \text{EDCl, HOBt, NMM, HNMe(OMe)} \\ 90\% \\ 2.\ \text{LiAlH}_4 \\ 85\%}]{} \text{Boc-HN-CH(CHO)-allyl}$$

Ref 16b

$$\text{OHC-CHO} \xrightarrow[85\%]{\substack{\text{Sn, Allyl bromide} \\ \text{THF, H}_2\text{O}}} \text{CH}_2=\text{CH-CH}_2\text{-CH(OH)-CH(OH)-CH}_2\text{-CH=CH}_2 \xrightarrow[\substack{\sim 12\%\ \text{by wt} \\ \text{in CH}_2\text{Cl}_2}]{\substack{\text{NaIO}_4,\ \text{CH}_2\text{Cl}_2 \\ \text{H}_2\text{O}}} \text{but-3-enal}$$

Ref 16c

$$NC\text{-CH}_2\text{-CH=CH}_2 \xrightarrow[40\%]{\text{LiAlH}_4,\ \text{THF}} H_2N\text{-CH}_2\text{-CH}_2\text{-CH=CH}_2$$

One of the key features of this set was the variation in the chain length of substituents on the aldehyde and amine functionality. The imidazoles thus produced would serve as RCM substrates that provide products of varied ring size. Additionally, the scope of the reaction was expanded to secondary amino aldehydes and amino esters as building

Table 2. Results on the RCM Reaction Sequence

entry	van Leusen product	RCM product (yield %)
1	Ph-imidazole with diallyl	Ph fused bicyclic (86)
2	BOC-NH, Ph-imidazole	BOC-NH Ph fused bicyclic (80)
3	Ph-imidazole, Me	Ph fused bicyclic, Me (93)
4	F-C$_6$H$_4$, BOC-HN, Me	F-C$_6$H$_4$, BOC-HN, Me fused bicyclic (61)
5	Ph-imidazole	Ph fused bicyclic (39)
6	BOC-NH, Ph-imidazole	BOC-NH, Ph fused bicyclic (89)
7	Ph-imidazole, COOMe	Ph fused bicyclic, COOMe (53)
8	imidazole, N-Bn	fused bicyclic, N-Bn (73)

blocks alongside simple primary amines and aldehydes. These building blocks were either purchased from commercial vendors or prepared according to known procedures as illustrated in Scheme 2.[16]

All the van Leusen reactions proceeded without event to generate C1/C5-position RCM precursors in moderate to excellent yields (Table 1, entries 1−7). The reaction was then carried out in the context of generating RCM precursors with the alkene inputs at the C4/C5-position. To this end, allyl TosMIC[17] was used instead of phenyl TosMIC, which provided the desired compound, albeit in modest yields (Table 1, entry 8).

These imidazole products were then subjected to the RCM reaction using the optimized procedure outlined above (Table 2). A number of 5,6-, 5,7-, and 5,8-fused, bicyclic, func-

tionalized imidazoles were generated via this sequence of reactions. The initial example of a 5,8-fused bicyclic imidazole gave product in low yields (Table 2, entry 5). This was not entirely surprising, as the formation of eight-membered rings via the RCM methodology is considered significantly more difficult than the six- or seven-membered systems.[18] However, examples, which incorporated substituents on the alkene side chains α to the imidazole ring, gave RCM products in good to excellent yields (Table 2, entries 6 and 7). It is possible that the introduction of this α-group elicits just enough conformational cooperation from the uncyclized alkene side chains, predisposing them to ring closure.

In conclusion, we have demonstrated that the van Leusen imidazole reaction followed by the RCM reaction provides easy access to a variety of fused bicyclic imidazoles, a group of structures that represent useful scaffolds for lead generation. Other van Leusen postmodification reactions are currently in progress and will be reported in due course.

Supporting Information Available: Copies of ^{1}H NMR and MS spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) This treatment results in the formation of the imidazolium ion, preventing the lone pair of the imidazole nitrogen from inactivating the Grubbs catalyst. See ref 13. Our reaction failed to yield the RCM product in the absence of this pretreatment procedure.

(15) A representative procedure is demonstrated by the preparation of 1-phenyl-8,9-dihydro-5H-imidazo[1,5-a]azepine (**2**). To the 4-pentenal (252 mg, 3.0 mmol) in DMF (3 mL) was added allylamine (171 mg, 3.0 mmol), and the reaction mixture was stirred at room temperature for 2.5 h. This was followed by the addition of phenyl TosMIC (543 mg, 2.0 mmol) and K$_2$CO$_3$ (276 mg, 2.0 mmol), and the reaction mixture was allowed to stir for an additional 17 h at room temperature. The reaction was quenched by the addition of water. The aqueous layer was extracted with EtOAc, dried (anhydrous MgSO$_4$), concentrated, and purified by flash chromatography (97:2.5:0.5 CH$_2$Cl$_2$−CH$_3$OH−NH$_3$) to afford 433 mg (91%) of **1** as a clear oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.07 (m, 2H), 2.47−2.59 (m, 2H), 4.53 (m, 2H), 4.90−4.98 (m, 3H), 5.17 (m, 1H), 5.74 (m, 1H), 5.96 (m, 1H), 7.11−7.24 (m, 5H), 7.42 (s, 1H). MS (ESI): m/z 239 (M + H). To a solution of **1** (410 mg, 1.72 mmol) in CH$_2$Cl$_2$ (30 mL) was added p-TsOH (342 mg, 1.8 mmol), and the reaction mixture was heated at reflux for 30 min. The reaction was cooled to room temperature; the Grubbs catalyst (73 mg, 0.087 mmol) was added, and the reaction mixture was refluxed for an additional 30 min (TLC indicated disappearance of the starting material). The reaction was quenched by adding aqueous saturated K$_2$CO$_3$ and extracted with EtOAc. The organic layer was dried (anhydrous MgSO$_4$), concentrated, and purified by flash chromatography (97:2.5:0.5 CH$_2$Cl$_2$−CH$_3$OH−NH$_3$) to afford 327 mg (90%) of **2** as a light brown oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.19 (m, 2H), 2.88 (m, 2H), 4.58 (d, J = 6.0 Hz, 2H), 5.68 (m, 2H), 7.10−7.24 (m, 5H), 7.42 (s, 1H). MS (ESI): m/z 225 (M + H).

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