A Metathesis Approach to Aromatic Heterocycles

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The ring closing metathesis (RCM) reaction can be used to prepare substituted furans and pyrroles. By utilising a Pd-catalysed coupling reaction with methoxyallene, allylic alcohols and sulfonamides can be converted into substrates that are ideal precursors to ring closing metathesis. After the RCM reaction is complete, the addition of acid promotes an elimination of methanol to form the fully aromatised system. A range of different substitution patterns and functional groups are compatible with this sequence. Double allene coupling, RCM and elimination reactions are also possible and allow the formation of biaryl systems.

Introduction

The metathesis reaction has recently emerged as one of the most powerful methodologies for alkene formation and works particularly well in intramolecular coupling reactions to form cyclic olefins.[1] Notably, ring closing metathesis (RCM) is high yielding, easy to perform and tolerant of a wide variety of functional groups. Recently, Grubbs and others have introduced new classes of reactive catalysts,[1,2] which will perform RCM reactions on heavily functionalised substrates and which are even capable of synthesising tetra-substituted cyclic alkenes.[2a]

This project was designed to alter the application of the RCM reaction, from one that is capable of forming isolated alkenes to one, which provides intermediates at the correct oxidation state to prepare fully aromatised compounds (in this case heteroaromatic compounds). The use of RCM to form heteroaromatic compounds has only recently appeared in the literature[3–11] and given the central position of these compounds to medicinal chemistry another flexible approach was considered to be beneficial. (In some cases the formation of aromatic compounds from a RCM reaction was viewed as an undesirable degradation product following metathesis, see ref.[4,13b]) Therefore, our strategy was to construct the backbone of the target molecule by the formation of an X–Y bond (e.g. a carbon–heteroatom bond forming reaction to form **A**, Figure 1) followed by metathesis to form the ring-closed intermediate **B**. Elimination of the leaving group (LG) at this stage would provide a stable aromatic compound, hopefully in one pot (**A**→**C**). In this paper, we report the success of this strategy for the synthesis

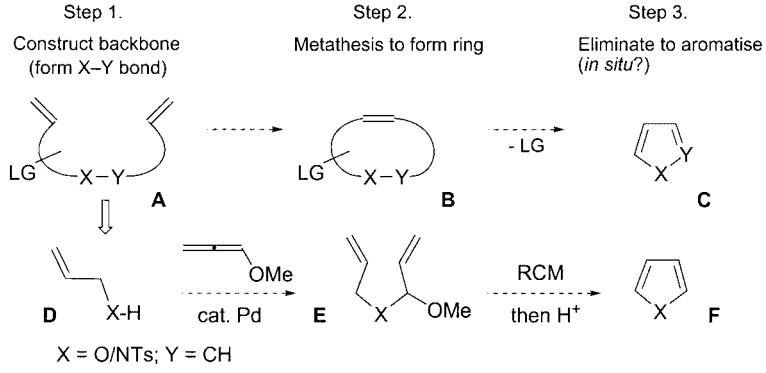

Figure 1. Gerneral strategy for formation of aromatic compounds.

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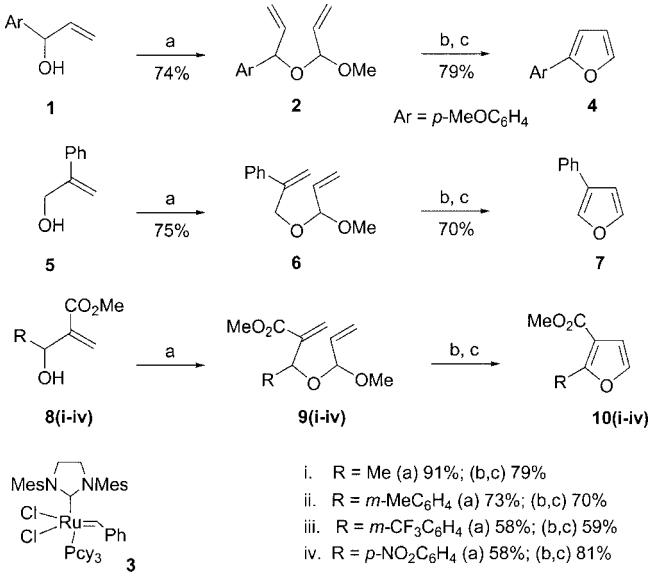
of substituted furans and pyrroles. Our approach to making the X–Y bond (i.e. **E**, Figure 1) relied upon the reaction of allylic alcohols and sulfonamides with methoxyallene[12] under Pd catalysis.[13] Subsequent RCM and then elimination of methanol was expected to form the aromatic compounds **F** directly.

Results and Discussion

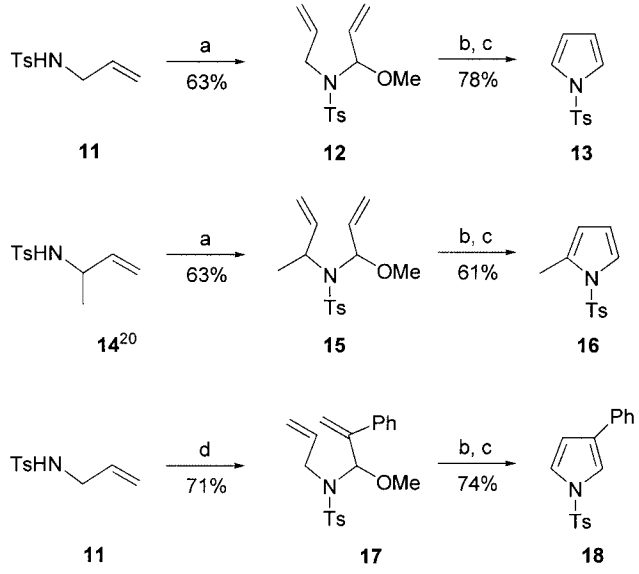
Initial synthetic studies focused on the formation of furans using the approach detailed in Figure 1. Thus, a range of differently substituted allylic alcohols (**1**,[14] **5**,[15] **8**[16]) were prepared by (short) routes described in the literature, Scheme 1. Each alcohol was subsequently reacted with methoxyallene under palladium(II) catalysis conditions to furnish a variety of unsymmetrical mixed acetals (**2**, **6**, **9**, as a mixture of stereoisomers where appropriate).



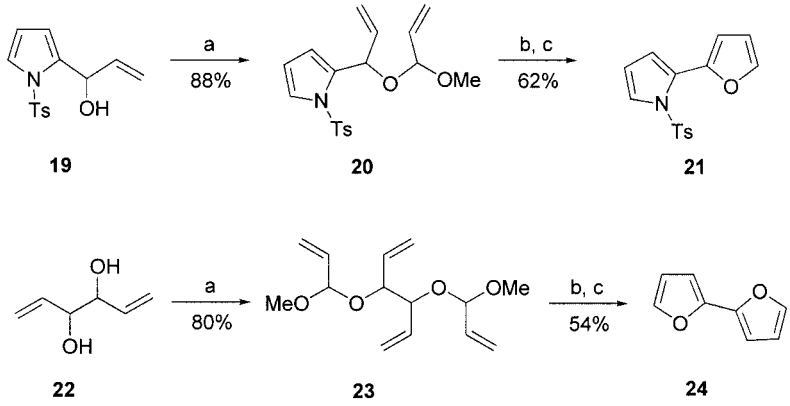
Scheme 1. a) Methoxyallene, 5% $Pd(OAc)_2$, 5% dppp, Et_3N, MeCN, Δ; b) 10% **3**, CH_2Cl_2, Δ; c) TFA.

The key C–C bond forming metathesis reaction was performed on these mixed acetals using Grubbs catalyst **3** and, in each case, the expected unsaturated five-membered ring compounds were obtained. The RCM reactions proceeded smoothly, and it was discovered that the aromatisation of these heterocycles could be performed in the same reaction pot as the metathesis reaction, simply by adding acid. For example, **2** → **4** proceeded in 90% yield in a one-pot process. However, the main drawback with this approach is that the nonpolar aromatic products were often contaminated with (nonpolar) phosphane residues from the metathesis catalyst. Therefore, we adopted a protocol whereby the metathesis reaction was quenched, the (more polar) dihydrofuran product purified by chromatography and then aromatised separately by reaction with acid. Using this methodology, a range of differently substituted furans **4, 7, 10** were prepared in good yield, Scheme 1. The tolerance of aryl, alkyl and carbonyl functional groups to this sequence is noteworthy.

The possibility of forming pyrroles by this route (Scheme 2) was also examined. The strategy followed similar lines to that described above and was also successful in



Scheme 2. a) Methoxyallene, 5% $Pd(OAc)_2$, 5% dppp, Et_3N, MeCN, Δ; b) 10% **3**, CH_2Cl_2, Δ; c) TFA; d) methoxyallene, 5% $Pd(PPh_3)_4$, PhI, $C_6H_5CH_3$.



Scheme 3. a) Methoxyallene, 5% $Pd(OAc)_2$, 5% dppp, Et_3N, MeCN, Δ; b) 10% **3**, CH_2Cl_2, Δ; c) TFA.

allowing the preparation of 2- and 3-substituted pyrroles (**16**, **18**). The addition of a phenyl group at the C-3 position is particularly noteworthy (see **18**), as this group derives from the coupling of sulfonamide **11**[17] with methoxyallene in the presence of Pd^0 and iodobenzene. Therefore, the aryl group is inserted onto the allene as part of the coupling process.[18,19] This approach is potentially valuable because it increases the complexity of any target prepared by this route (**18**), without adding any extra steps in the preparation of the metathesis precursor.

Finally, the extension of this strategy towards the synthesis of some linked biaryl compounds was attempted (Scheme 3). Consequently, allylic alcohol **19**[21] was subjected to the allene coupling and then the RCM/aromatisation protocol to furnish the pyrrole-furan biaryl **21** in good yield. Then it was discovered that biaryl compounds could be prepared by a double coupling, RCM/aromatisation process. Hence, the commercially available diol **22** was subjected to reaction with methoxyallene under standard conditions, followed by double RCM on acetal **23** and treatment of the product with acid. Pleasingly, the bisfuran **24** was produced in good yield for the overall sequence. The selectivity observed during RCM for formation of five-membered rings, at the expense of other-sized rings, is precedented in metathesis chemistry.[4] Such a double RCM approach holds many opportunities for the rapid construction of polyaryl compounds.

To conclude, we have reported a novel and versatile approach to the synthesis of furans and pyrroles that uses metathesis as a key C–C bond forming reaction. The flexibility that this methodology holds for the formation of poly-substituted aromatic compounds and the tolerance of many functional groups to this sequence bodes well for future studies.[22]

Acknowledgments

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[22] Supporting information which describes experimental procedures and spectroscopic data for key compounds for this article is available on the WWW under http://www.eurjoc.org or from the author:

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