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One-pot enyne ring-closing metathesis–Diels–Alder reactions for the synthesis of polycyclic sulfamides

Joseph T. Hill-Cousins [a], Sofia S. Salim [a], Youssef M. Bakar [a], Richard K. Bellingham [b], Mark E. Light [a], Richard C.D. Brown [a,*]

[a] Department of Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, UK
[b] Synthetic Chemistry Department, Chemical Development, GlaxoSmithKline Pharmaceuticals, Old Powder Mills, Tonbridge, Kent TN11 9AN, UK

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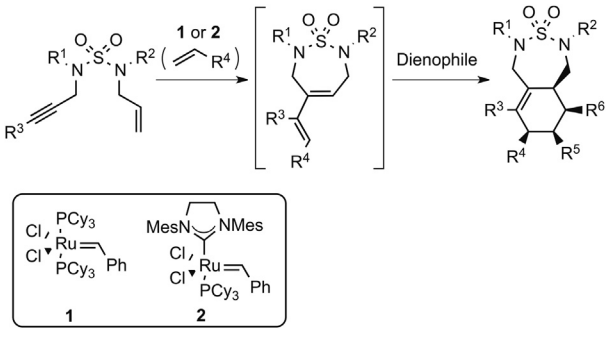
ABSTRACT

Ring-closing metathesis (RCM) and sequential $Yb(OTf)_3$ promoted Diels–Alder reactions of sulfamide-linked enynes proceeded selectively in one-pot to afford a series of bicyclic and tricyclic sulfamides. Excellent levels of diastereoselectivity are observed for the cycloaddition step, with only the *endo*-adducts being isolated. The protocol was further extended to incorporate a one-pot RCM–cross metathesis (CM)–Diels–Alder sequence, permitting rapid access to high levels of molecular complexity from simple and easily accessible precursors.

1. Introduction

Enyne metathesis has progressed significantly as a practical synthetic methodology since the advent of well-defined ruthenium based carbene catalysts that are tolerant of a wide variety of functionality.[1] Enyne ring-closing metathesis (RCM) is formally a cycloisomerisation process, thus providing an atom-efficient means for the synthesis of structurally diverse carbocycles and heterocycles and this strategy has attracted considerable interest in the context of target synthesis.[2] An additional appeal of enyne RCM lies in the potential for manipulation of the 1,3-diene products, particularly through the use of cycloaddition reactions, such as the Diels–Alder reaction to facilitate rapid access to bi- and tricyclic structures.[3] Hanson and co-workers recognised the benefit of ring-closing diene metathesis as a method to construct cyclic sulfamides, and applied this strategy in their synthesis of HIV protease inhibitor analogues.[4] We have previously reported strategies for the construction of cyclic sulfonamides[5] and sulfamides[6] using diene and enyne RCM, including a one-pot enyne RCM–cross metathesis (CM) protocol. Owing to the potential value of cyclic sulfamide scaffolds for the development of small-molecule therapeutics,[7] we were attracted to the concept of sequential and one-pot enyne RCM–cycloaddition and enyne RCM–CM–cycloaddition sequences to produce polycyclic sulfamides (Scheme 1). The results of our studies are described here.



Scheme 1. Enyne RCM(–CM–)cycloaddition sequence for the synthesis of polycyclic sulfamides.

2. Results and discussion

Sulfamide-linked enyne metathesis substrates were conveniently prepared from chlorosulfonyl isocyanate (**3**, Scheme 2).[4a,6b,8] Thus, sequential treatment of **3** with *t*-BuOH followed by *N*-allylbenzylamine or *N*-allylaniline gave *N*-Boc protected

* Corresponding author. E-mail addresses: rcb1@soton.ac.uk, R.C.Brown@soton.ac.uk (R.C.D. Brown).

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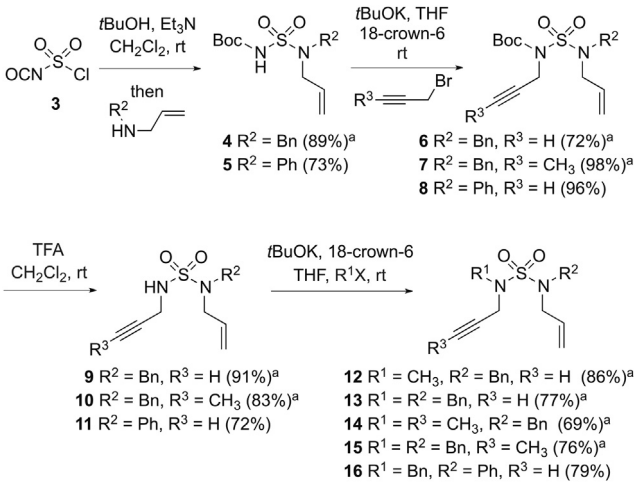
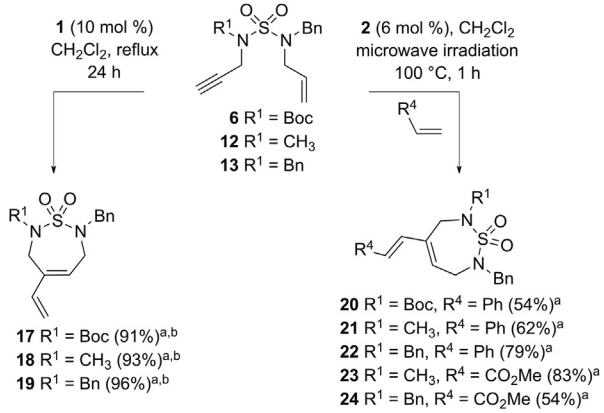
sulfamides **4** and **5** in 89 and 73% yields, respectively. *N*-Alkylation with either propargyl bromide or 1-bromo-2-butyne was carried out in the presence of *t*-BuOK and 18-crown-6 to afford enynes **6**–**8**, which underwent Boc cleavage in TFA to yield the deprotected sulfamides **9**–**11**. *N*-Alkylation of **9**–**11** under the basic conditions described above gave five additional sulfamide substrates **12**–**16** for enyne RCM studies.

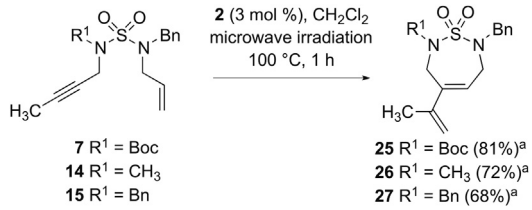


Scheme 2. Synthesis of sulfamide-linked enyne metathesis substrates. [a] Synthesis previously reported in Ref. 6b.

A useful selectivity was observed in enyne RCM experiments; treatment of enynes **6**, **12** and **13** with Grubbs' second generation catalyst (**2**) resulted in RCM–homo-CM products,[6b] whereas the corresponding reactions catalysed by Grubbs' first generation catalyst (**1**) favoured the products of formal cycloisomerisation, **17**–**19**, without significant CM (Scheme 3). The propensity for the initial enyne RCM products to undergo further metathesis in the presence of the second generation catalyst **2** was exploited to deliver a one-pot enyne RCM–CM process by including 2–3 equiv of a monosubstituted alkene in the reaction. As anticipated, sulfamides **20**–**24** were afforded in good yield, with excellent levels of *E*-selectivity (≥15:1 by ^{1}H NMR). The internal alkyne substrates **7**, **14** and **15** unsurprisingly displayed reduced reactivity towards metathesis, and RCM of these compounds using Grubbs I was impractically slow. However, rapid conversion to the cyclised dienes **25**–**27** was achieved using Grubbs II under microwave irradiation, without subsequent CM (Scheme 4).[6b]

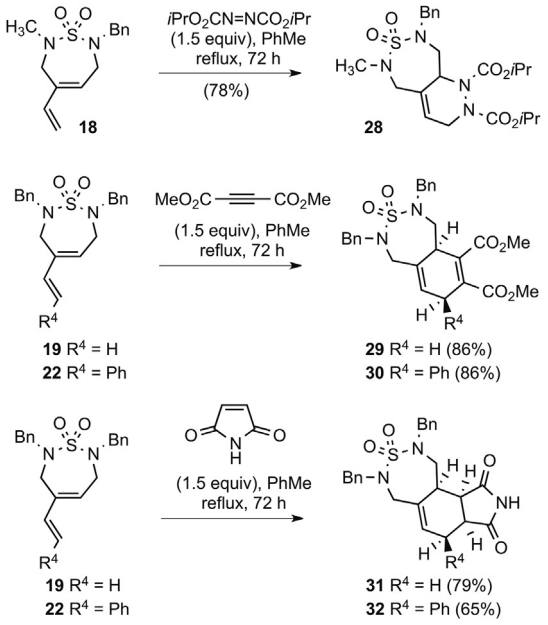


Scheme 3. Catalyst control in the metathesis reactions of sulfamide-linked enynes. [a] Synthesis previously reported in Ref. 6b. [b] **17**–**19** were previously isolated in lower yields (up to 8%, 60% and 63%, respectively) from mixtures with RCM–CM products obtained using Grubbs II catalyst.



Scheme 4. Enyne RCM reactions of sulfamides containing disubstituted alkynes. [a] Synthesis previously reported in Ref. 6b.

Having demonstrated that sulfamide-linked enynes were able to undergo RCM and RCM–CM reactions, we were intrigued by the prospect of further one-pot transformation through cycloaddition reactions of the 1,3-diene products. Towards this objective, an investigation of the Diels–Alder reactions of the isolated enyne RCM products **18**, **19** and **22** was conducted (Scheme 5),[9] using electron-deficient dienophiles (di-*iso*-propylazodicarboxylate (DIAD), dimethyl acetylenedicarboxylate (DMAD) and maleimide). The desired polycyclic sulfamides **28**–**32** were obtained in yields of 65–86%, although these thermal Diels–Alder reactions required 72 h heating at reflux in toluene to reach complete conversion.



Scheme 5. Diels–Alder reactions of isolated enyne RCM products.

Sulfamides **31** and **32** were isolated as single diastereoisomers, arising from *endo* selective addition of the dienophile.[12] The stereochemistry of sulfamide **32** was assigned using 2D ^{1}H NOESY NMR spectroscopy (Fig. 1). Additionally, sulfamide **30** was isolated as a single diastereoisomer. The stereochemistry of sulfamide **30** was assigned by analogy with **32**.

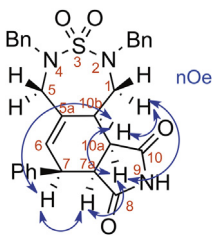


Fig. 1. Key cross-peaks in the 2D ^{1}H NOESY NMR spectrum of sulfamide **32**.