Pergamon

Tetrahedron Letters 41 (2000) 3681–3685

TETRAHEDRON LETTERS

Solid-phase synthesis of cyclic sulfonamides employing a ring-closing metathesis–cleavage strategy

Richard C. D. Brown,[a,*] José L. Castro [b] and Jean-Dominique Moriggi [a]

[a] *Department of Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, UK*
[b] *Merck Sharp & Dohme Research Laboratories, Terlings Park, Harlow CM20 2QR, UK*

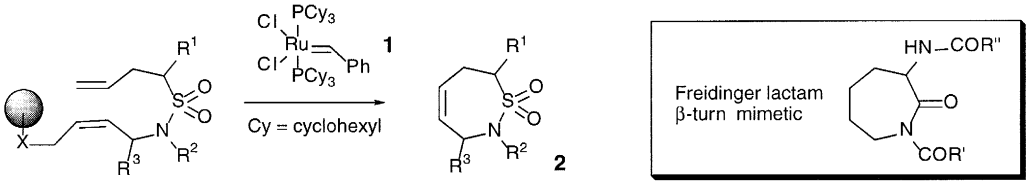
Received 9 February 2000; accepted 13 March 2000

Abstract

Ring-closing olefin metathesis using the Grubbs catalyst was applied to the cyclisative release of resin-bound sulfonamides. Flexible linkers apparently facilitated the cyclisation–cleavage, allowing a number of novel cyclic sulfonamides to be prepared in good yields using catalytic amounts of the Grubbs catalyst.

Keywords: ring-closing metathesis; solid-phase synthesis; sulfonamides; linkers.

The solid-phase synthesis of small molecules has been under intensive study over the past several years and is now widely used in industrial and academic research laboratories.[1–3] Most solid-phase syntheses rely on the presence of a polar functional group within the target as a means of attachment to the solid-support. In some cases, the presence of polar functional groups may impose an undesirable constraint on the product structure, or using that position as a point of attachment may block it from further manipulation. In order to increase the scope of solid-phase synthesis, considerable effort has been devoted towards the development of so-called 'traceless linkers' as well as nucleophilic and cyclisation–cleavage strategies (Scheme 1).[4,5]



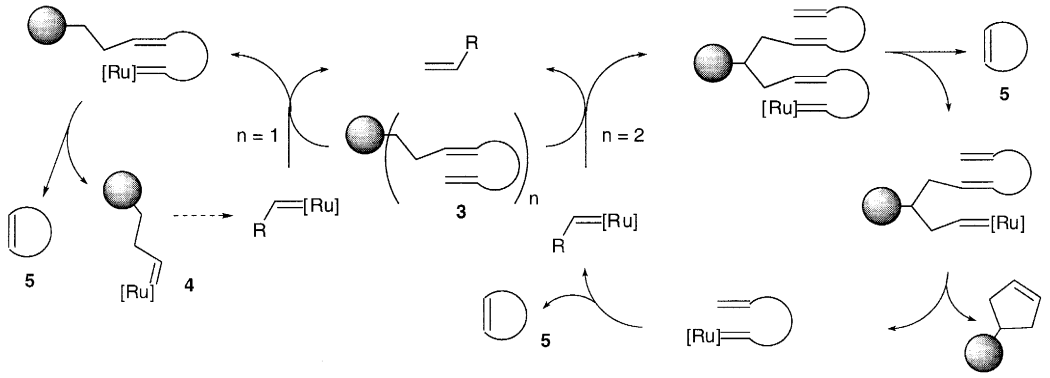
Scheme 1. Cyclisation–cleavage approach to the synthesis of cyclic sulfonamides

Seven-membered ring-containing cyclic sulfonamides have attracted considerable interest as analogs of known biologically active nitrogen-containing heterocycles, with examples of HIV protease

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

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00442-1

inhibitors,[6] bile acid uptake inhibitors,[7] and herbicides[8] having been reported. The idea that cyclic sulfonamides **2** might also constitute the basis for libraries of novel peptidomimetics led us to consider a solid-phase approach to their synthesis.[9] We were attracted to the idea of using a ring-closing metathesis reaction to cleave the desired products from the resin,[10–13] allowing elaboration of the central scaffold at two or more positions. However, for this approach to be viable the cyclisation–cleavage reaction would need to proceed efficiently using catalytic quantities of the Grubbs ruthenium complex **1**. Other research groups have found that in order to obtain efficient cyclisation–cleavage either flexible linkers,[13] or an olefin additive was required.[11] These findings have been explained by the breakdown of the catalytic cycle caused by the formation of resin-bound ruthenium alkylidene complexes **4** which are either slow or unreactive as metathesis catalysts due to site isolation effects within the resin (Scheme 2). We decided to investigate an alternative strategy to improve the catalytic efficiency of the cyclisation–cleavage reaction by employing a double-armed linker **3** (*n*=2).[14]



Scheme 2. Cyclisation–cleavage on single- and double-armed linkers: possible catalytic pathways

In order to determine if a double-armed linker would offer any advantage in the cyclisation–cleavage reaction the analogous single-armed and double-armed metathesis substrates **10** and **13** were prepared (Scheme 3). Starting with allylic chloride **6**[15] standard malonate alkylation and Krapcho dealkoxycarbonylation reactions gave ester **7** which was reduced to the corresponding primary alcohol **8**. Acylation of **8** and removal of the THP protecting group allowed coupling with the *N*-Boc sulfonamide **14**[16–18] using a Mitsunobu reaction. Finally, careful removal of the acetate group[†] afforded the desired allylic alcohol **9**. The single-armed alcohol **12** was assembled using a similar approach and the synthesis of resins **10** and **13** was completed by carbodiimide coupling of the alcohols **9** and **12** to a carboxyethylpolystyrene resin which we prepared from Merrifield resin in three steps.[19]

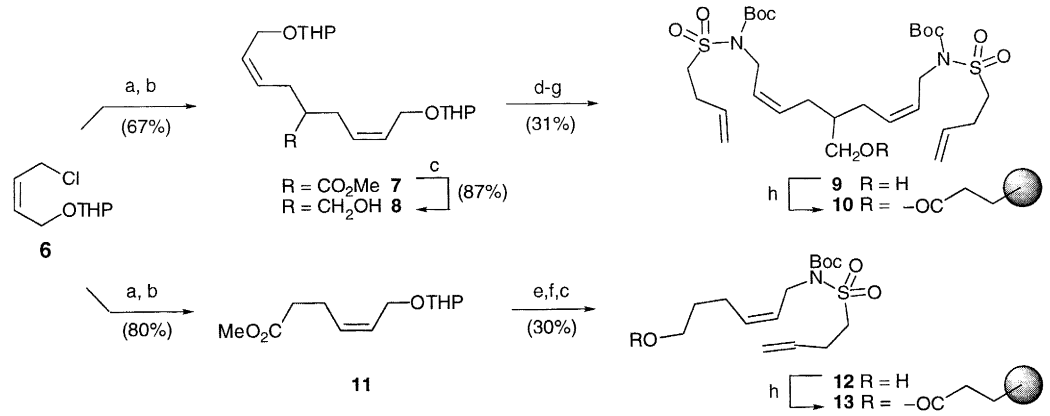
A third metathesis substrate[‡,§] **15** was prepared by Mitsunobu coupling[10,20] of sulfonamide **14** directly to an allylic alcohol resin **16** (Scheme 4).[21]

The efficiency of ring-closing metathesis–cleavage for the substrates **10**, **13** and **15** was investigated under a range of different conditions (Scheme 5, Table 1). Interestingly, the substrate **15** with a relatively inflexible linker gave very low yields of the cyclic sulfonamide **18**, whereas the more flexible substrates **10** and **13** afforded **18** in good yield with 2.5–5 mol% of catalyst **1**. No benefit was seen by the addition

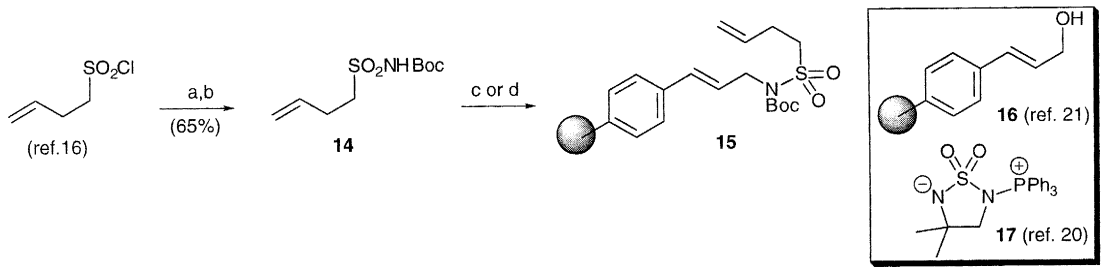
† Care was required as the *N*-sulfonylcarbamate was also labile under the basic conditions of the transesterification reaction.

‡ Use of the ylide **17** as the source of activation was found to provide an experimentally convenient alternative to the more coventional Mitsunobu conditions, provided a double coupling was employed.

§ Successful immobilisation of the sulfonamide on the solid-phase was demonstrated by strong bands in the on-bead IR spectra of the resins **10**, **13** and **15** at around 1730 (CO), 1340 (SO_2) and 1160cm^{-1} (SO_2).

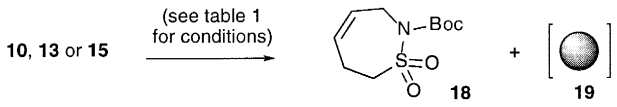


Scheme 3. *Reagents and conditions*: (a) dimethyl malonate, NaH/DMF; (b) KOAc, 140°C/DMSO; (c) $LiAlH_4/Et_2O$; (d) Ac_2O, EtN^iPr_2, $DMAP/CH_2Cl_2$; (e) *p*-TSA/MeOH; (f) DEAD, PPh_3, $CH_2{=}CH{-}(CH_2)_2SO_2NHBoc$ (**14**)/THF; (g) K_2CO_3/MeOH; (h) 2-carboxyethylpolystyrene (1.0 mmol/g), DIC, DMAP (1 equiv.)/CH_2Cl_2



Scheme 4. *Reagents and conditions*: (a) NH_4OH/H_2O; (b) Boc_2O, DMAP, Et_3N/CH_2Cl_2; (c) **16**, PPh_3, DEAD/THF; (d) **16**, **17**/THF

of an olefin co-factor to any of the reactions we examined, in fact the yields were actually lower and the purity of the crude product was reduced. The resins **19** collected after the cyclisation–cleavage reactions were coloured, and on-bead IR indicated that some residual sulfonamide groups remained. Resubmission of the resins **19** (entries 4–6, Table 1) to the metathesis conditions produced small additional amounts of the cyclic sulfonamide **18**. The same coloured resins **19** were also active metathesis catalysts for the dimerisation of 1-octene,[22] although surprisingly, no additional cyclic sulfonamide **18** was released from the resin **19** in these reactions.



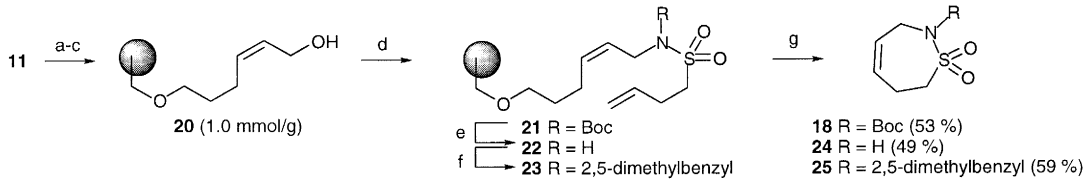
Scheme 5. Cyclisation–cleavage reactions performed on resins **10**, **13** and **15**

Having established that efficient cyclisation–cleavage of sulfonamide **18** could be achieved using a flexible single-armed linker, and that the more elaborate double-armed linker was not necessary, we embarked on the synthesis of *N*-substituted cyclic sulfonamides (Scheme 6). The approach was broadly the same as that described above with the exception that the linker was attached to Merrifield resin by an ether bond, allowing alkylation of the immobilised sulfonamide **22** under basic conditions.[23] Three cyclic products **18**, **24** and **25** were prepared in good yield using only 5 mol% of the ruthenium catalyst **1**.

Table 1
Results from cyclisation–cleavage reactions[a]

Entry	Resin	Amount of catalyst **1** (mol%)[b]	co-factor[c]	Yield of **18** (%)[d-e]
1	**10**	2.5	✗	66
2	**13**	2.5	✗	61
3	**10**	2.5	✓	53
4	**10**	5	✗	61 (7)
5	**13**	5	✗	43 (7)
6	**10**	5	✓	38 (4)
7	**10**	50	✗	41
8	**13**	50	✗	55
9	**15**	10	✗	Not observed
10	**15**	10	✓	Trace

[a] Reactions were carried out in dry CH_2Cl_2 at reflux under an atmosphere of argon for 14 hours.
[b] Quantities are calculated on the basis of the measured loading of allylic alcohol resin **16** (2.0 mmol/g) and the theoretical loadings of resins **10** (0.76 mmol/g) and **13** (1.24 mmol/g) calculated from a loading of 2-carboxyethylpolystyrene (1.0 mmol/g). Nitrogen and sulfur analysis of resins **10** and **13** gave loadings of 0.76 and 1.16 mmol/g respectively.
[c] One equivalent of 1-octene was used as the olefin co-factor where indicated.
[d] Yields refer to purified material. All compounds displayed spectroscopic data consistent with the proposed structure.
[e] The yield in parentheses is the amount of additional product released upon resubmission to the metathesis conditions.



Scheme 6. *Reagents and conditions*: (a) $LiAlH_4/Et_2O$; (b) NaH, Merrifield resin (2.3 mmol/g)/DMF; (c) MeOH, *p*-TSA; (d) **14**, PPh_3, DEAD/THF; (e) TFA/CH_2Cl_2; (f) $ArCH_2Cl$, KO^tBu/THF; (g) **1** (5 mol%)/CH_2Cl_2, reflux

In conclusion, several novel cyclic sulfonamides have been prepared using a solid-phase cyclisation–cleavage approach. Flexible linkers were required in order to obtain an efficient release using only 2.5–5 mol% of the Grubbs catalyst **1**. Our future work will focus upon extending this solid-phase approach to the synthesis of more substituted cyclic sulfonamides.

Acknowledgements

The authors would like to thank Merck Sharp & Dohme for an unrestricted grant (J.-D.M.) and generously providing the Mitsunobu coupling reagent **17**, and The Royal Society for a University Research Fellowship (R.C.D.B.). We would also like to acknowledge the use of the EPSRC funded Chemical database Service at Daresbury.[24]

References

1. Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995,** *51*, 8135.
2. Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555.
3. Brown, R. C. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293.
4. James, I. W. *Tetrahedron* **1999**, *55*, 4855.
5. van Maarseveen, J. H. *Combinatorial Chemistry and High Throughput Screening* **1998**, *1*, 185.
6. Lam, P. Y.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; De Lucca, G. V.; Rodgers, J. D. US Patent 5,610,294, 1997.
7. Handlon, A. L.; Hodgson, G. L.; Hyman, C. E.; Clifton, E. WO Patent 9838182, 1998.
8. Makino, K.; Sato, T.; Morimoto, K.; Akiyama, S.; Suzuki, H.; Suzuki, K.; Nawamaki, T.; Watanabe, S. EP Patent 342456, 1989.
9. The synthesis of some closely related cyclic sulfonamides have recently been reported: Hanson, P. R.; Probst, D. A.; Robinson, R. E.; Yau, M. *Tetrahedron Lett.* **1999**, *40*, 4761.
10. Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron* **1999**, *55*, 8189.
11. Veerman, J. J. N.; van Maarseveen, J. H.; Visser, G. M.; Kruse, C. G.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **1998**, 2583.
12. Nicolaou, K. C.; Hepworth, D.; King, N. P.; Finlay, M. R. V. *Pure Appl. Chem.* **1999**, *71*, 989.
13. Pernerstorfer, J.; Schuster, M.; Blechert, S. *Chem. Commun.* **1997**, 1949.
14. For related linkers used for the metathesis cleavage of acyclic olefins, see: Peters, J. U.; Blechert, S. *Synlett* **1997**, 348; Knerr, L.; Schmidt, R. R. *Synlett* **1999**, 1802.
15. Deslongchamps, P.; Lamothe, S.; Lin, H. *Can. J. Chem.* **1987**, *65*, 1298.
16. King, J. F.; Harding, R. D. K. *J. Am. Chem. Soc.* **1976**, *98*, 3312.
17. Tsuri, T.; Haga, N.; Matsui, T.; Kamata, S.; Kakushi, H.; Uchida, K. *Chem. Pharm. Bull.* **1992**, *40*, 75.
18. Neustadt, B. R. *Tetrahedron Lett.* **1994**, *35*, 379.
19. Brown, R. C. D.; Fisher, M. *Chem. Commun.* **1999**, 1547.
20. Castro, J. L.; Matassa, V. G.; Ball, R. G. *J. Org. Chem.* **1994**, *59*, 2289.
21. Frechet, J. M.; Schuerch, C. *J. Am. Chem. Soc.* **1971**, *93*, 492.
22. Ahmed, M.; Barrett, A. G. M.; Braddock, D. C.; Cramp, S. M.; Procopiou, P. A. *Tetrahedron Lett.* **1999**, *40*, 8657.
23. Beaver, K. A.; Siegmund, A. C.; Spear, K. L. *Tetrahedron Lett.* **1996**, *37*, 1145.
24. Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746.