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A concise synthesis of β-lactam–sulfonamide hybrids

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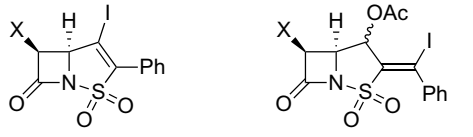
Dedicated to Professor Achim Mehlhorn on the occasion of his 65th birthday

Abstract—Using ring closing metathesis (RCM) as the key operation, a rapid access to β-lactams fused to a sultam moiety of variable ring size was developed from low cost, commercially available starting materials. An efficient RCM of 4-vinyl-azetidin-2-ones to give 1-aza-bicyclo[4.2.0]oct-4-en-8-ones is also reported.

Seventy-five years after Sir Alexander Fleming's discovery of penicillin, β-lactams continue to be one of the most important classes of antibacterial agents.[1] However, many bacteria have developed effective defense mechanisms against commonly used β-lactams such as penicillins and cephalosporins.[2] One approach to combat bacterial resistance is the search for novel bioactive substances based on the azetidin-2-one core.[3] Turos and co-workers reported a range of nonconventionally fused β-lactams including the *N*-sulfonyl compounds **1a**,**b**[4a] and **2a**,**b**[4b] by blending classical β-lactam antibiotic partial structures from monobactams and carbapenems or clavulanic acids, respectively (Fig. 1). A sequence involving [2+2] ketene–imine cycloaddition, halogen-promoted cyclization of alkynyl *N*-methylthio β-lactams and oxidation was used for the synthesis of these compounds.[5]

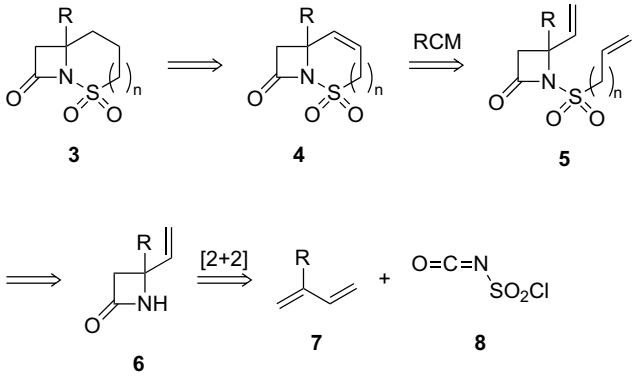


1a: X = OMe **2a**: X = OMe
1b: X = *N*-phthalimidyl **2b**: X = *N*-phthalimidyl

Figure 1. Carbapenem–monobactam hybrids **1a**,**b** and clavulanic acid–monobactam hybrids **2a**,**b**.

As part of a program initiated to develop novel methods for the preparation and synthetic elaboration of sultones and sultams,[6] we have devised a complementary access to the structurally related heterobicyclic compounds **3**, which can be viewed as β-lactam–sulfonamide hybrids (Scheme 1). Similar to the β-lactam function, the sulfonamide functional group stands out as one of the most important pharmacophores.[7] Recently, cyclic sulfonamides (sultams) have been shown to be highly useful heterocycles for medicinal chemistry as well.[8,9] Our approach to hybrids **3** uses [2+2] olefin–isocyanate cycloaddition,[10] ring closing metathesis (RCM),[11,12] and hydrogenation to rapidly arrive at the designed targets with variable ring size of the sultam moiety. Moreover, the presence of the olefin in unsaturated intermediates **4** offers further options for straightforward modification.

β-Lactams **6a**,**b** synthesized by cycloaddition of chlorosulfonyl isocyanate (**8**)[13] with 1,3-butadiene (**7a**) and



Scheme 1. Synthetic strategy for β-lactam–sulfonamide hybrids **3**.

Keywords: Cycloaddition; Ring closing metathesis; β-lactams; Sultams.
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† X-Ray diffraction analysis.

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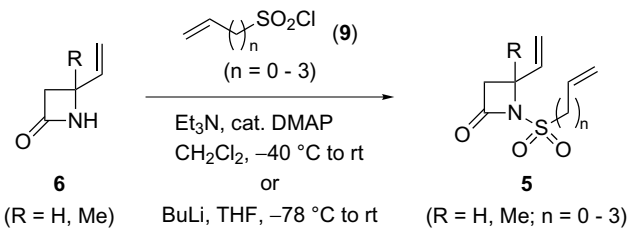


Scheme 2.

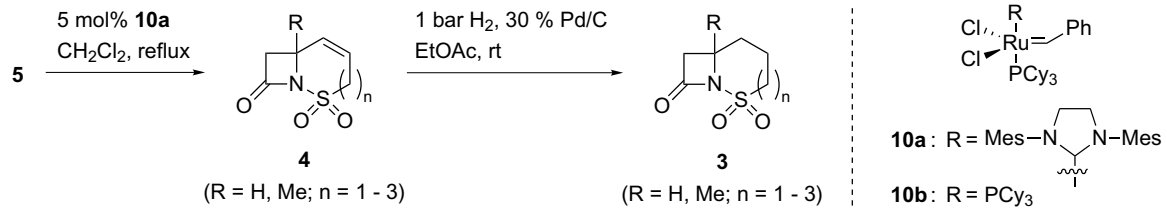
Table 1. Preparation of *N*-sulfonyl β-lactams **5**

6	R	9	*n*	5	Method[a]	Yield 5 (%)[b]
a	H	**a**	0	**a**	A	64
b	Me	**a**	0	**b**	A	30
a	H	**b**	1	**c**	B	80
b	Me	**b**	1	**d**	B	46
a	H	**c**	2	**e**	B	73
b	Me	**c**	2	**f**	B	84
a	H	**d**	3	**g**	B	68
b	Me	**d**	3	**h**	B	67

[a] Method A: Et_3N, 10 mol% DMAP, CH_2Cl_2, −40 °C to rt, 2 h. Method B: **6**+BuLi, THF, −78 °C then **9**, −78 °C to rt, 16 h.
[b] Isolated yield after flash chromatography.

isoprene (**7b**) according to a published procedure[10] were converted to *N*-sulfonyl derivatives **5** with olefinic sulfonyl chlorides **9a–d** (Scheme 2, Table 1). Vinylsulfonyl chloride (**9a**) can be readily derived from commercially available 2-chloroethanesulfonyl chloride via dehydrohalogenation,[14] while building blocks **9b–d** are easily secured in two steps from the corresponding olefinic bromides.[15] For preparation of *N*-vinylsulfonyl imides **5a**,**b**, triethylamine proved to be a suitable base, whereas for all other RCM substrates **5**, deprotonation of **6** with butyllithium prior to coupling with sulfonyl chlorides **9b–d** turned out to give higher yields.

The generation of bicyclic and tricyclic β-lactam arrays by ring closing metathesis of dienes and enynes has received considerable attention in recent years.[16–20] Since RCM of 4-vinyl-azetidin-2-ones bearing an alkene containing substituent on nitrogen has met with no success so far,[16] we were not too surprised about the complete failure of a first attempted RCM of *N*-sulfonyl β-lactams **5a**,**b** with Grubbs' second generation catalyst **10a**[21] to give the carbapenem–monobactam hybrids **4a**,**b** (Scheme 3, Table 2). However, much to our delight, subjecting the homologs **5c–h** to standard RCM conditions[22] resulted in the smooth



Scheme 3.

Table 2. Synthesis of β-lactam–sulfonamide hybrids **3** by RCM of dienes **5** and subsequent hydrogenation

5	*t* (min)[a]	4	Yield 4 (%)[b]	3	Yield 3 (%)[b]
a	60	**4a**: R = H	0	—	—
b	60	**4b:** R = Me	0	—	—
c	30	**4c:** R = H	56	**3c:** R = H	82
d	30	**4d:** R = Me	82	**3d:** R = Me	97
e	15	**4e:** R = H	98	**3e:** R = H	99
f	15	**4f:** R = Me	97	**3f:** R = Me	100
g	90	**4g:** R = H	28	**3g:** R = H	90
h	90	**4h:** R = Me	63	**3h:** R = Me	92

[a] Reaction time for the RCM step.
[b] Isolated yield after flash chromatography.

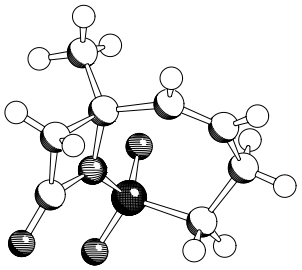


Figure 2. Crystal structure of unsaturated sultam **4f**.[23,24]

formation of the desired heterobicycles **4c**–**h** as crystalline materials. Unsaturated ε-sultam **4f** provided suitable crystals for X-ray diffraction analysis that unequivocally confirmed its structure, which features an sp^2 hybridized nitrogen atom (sum of angles around N = 359.1°) and a C(O)–N bond length of 1.393 Å (Fig. 2).[23,24] The best yields were obtained for the seven-membered annelated sultams **4e**,**f** independent of the substituent R at the 4-position of the azetidin-2-one core. While the six- and eight-membered sultams **4d**,**h** with R = Me were isolated in good yields as well, cyclization to furnish the hydrogen substituted counterparts **4c**,**g** was somewhat less productive. Given the high efficacy in generation of **4e**, this latter reactivity difference is not readily understood, but may be attributed to the conformational requirements imposed by the azetidin-2-one template.

With respect to the unsuccessful RCM to give the α,β-unsaturated γ-sultams **4a**,**b**, enhanced ring strain of the bicyclic products (and the corresponding transition states leading to **4a**,**b**) might be an impeding factor. Notably, a similar reactivity trend was also evident from RCM studies with *N*-homoallyl and *N*-allyl substituted β-lactams **11a**,**b** and **13a**,**b**, respectively (Scheme 4). Using Grubbs' first generation catalyst **10b**, no RCM has been achieved with **11a** or **13a**.[16b] In contrast, treatment of *N*-homoallyl substrates **11a**,**b** with 5 mol% of **10a** allowed the smooth formation of both six-membered olefins **12a**,**b** in good to excellent yields within 30 min, which highlights the superior performance of this catalyst.

Finally, the unsaturated sultams **4c**–**h** were hydrogenated[25] in ethyl acetate to give the β-lactam–sulfonamide hybrids **3c**–**h** (Scheme 3, Table 2). A proper choice of solvent was crucial to the success of this transformation, since first experiments in methanol were found to be detrimental.

In summary, we have established a simple protocol for the rapid production of potentially pharmacologically interesting,[26] nonconventionally fused β-lactams using a cycloaddition–RCM strategy. Further functionalization of the unsaturated sultams **4**, as well as investigations on the pharmacological properties of the novel heterocycles described in this letter will be reported as results unfold.

Acknowledgements

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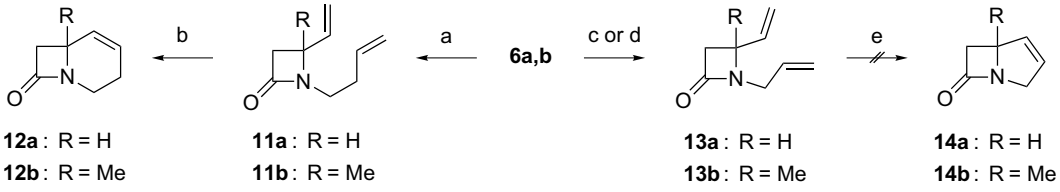

Scheme 4. Reagents and conditions: (a) aq KOH, cat. Bu_4NHSO_4, 4-bromo-but-1-ene, cat. NaI, THF, rt, 35% **11a** from **6a**, 55% **11b** from **6b**; (b) 5 mol% **10a**, CH_2Cl_2, reflux, 81% **12a** from **11a**, 100% **12b** from **11b**; (c) (i) BuLi, THF, −78 °C, (ii) allyl bromide, −78 °C to rt, 32% **13a** from **6a**; (d) (i) NaH, THF, 0 °C, (ii) allyl bromide, 0 °C to rt, 90% **13b** from **6b**; (e) 25 mol% **10a**, CH_2Cl_2, reflux.

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22. Typical procedure for RCM of dienes **5**: Under argon atmosphere, a three-necked flask was charged with a solution of *N*-sulfonyl β-lactam **5f** (62 mg, 0.27 mmol) in dichloromethane (27 mL). Grubbs catalyst **10a** (11.5 mg, 0.014 mmol, 5 mol %) was added in one portion under reflux, the mixture was stirred for 30 min at reflux, and the solvent was concentrated in vacuo. Purification by flash chromatography on silica gel (diethyl ether) gave **4f** (52.7 mg, 97%) as a white solid; IR (neat) 1785 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.67 (s, 3H), 2.55–2.69 (m, 2H) 3.04 (AB pattern, $J = 15.6$ Hz, $\Delta\delta = 19.9$ Hz, 2H), 3.29–3.39 (m, 2 H), 5.70–5.80 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.8 (t), 24.9 (q), 52.2 (t), 53.9 (t), 61.6 (s), 125.6 (d), 135.2 (d), 162.5 (s); MS (LC–MS, ESI) m/z: 219 (100) [$M+NH_4^+$]. Anal. Calcd for $C_8H_{11}NO_3S$: C, 47.75; H, 5.51; N, 6.96; S, 15.93. Found: C, 47.80; H, 5.71; N, 6.83; S, 15.45.
23. Crystallographic data (excluding stucture factors) for the structure **4f** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary material publication no CCDC 228439. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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25. Typical procedure for hydrogenation of unsaturated sultams **4**: Sultam **4f** (20.4 mg, 0.101 mmol) was dissolved in ethyl acetate (3 mL). Pd/C (7 mg, 30%) was added, and hydrogen was passed through the rapidly stirred solution for 2 h. The resulting mixture was filtered through a short plug of silica gel by elution with ethyl acetate. Subsequent removal of the solvent afforded pure **3f** (20.5 mg, 100%) as a white solid; IR (neat) 1787 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.35–1.41 (m, 1H), 1.64 (s, 3H), 1.81–1.84 (m, 1H), 1.98–2.02 (m, 1H), 2.09–2.14 (m, 1H), 2.20 (dd, $J = 7.5$ Hz, $J = 14.8$ Hz, 1H), 2.92 (AB pattern, $J = 16.2$ Hz, $\Delta\delta = 29.6$ Hz, 2H), 3.20 (ddd, $J = 3.7$ Hz, $J = 13.3$ Hz, $J = 14.7$ Hz, 1H) 3.32 (ddd, $J = 3.5$ Hz, $J = 3.5$ Hz, $J = 14.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.9 (t), 24.3 (t), 27.1 (q), 39.0 (t), 48.0 (t), 53.1 (t), 60.5 (s), 165.3 (s); MS (LC–MS, ESI) m/z: 226 (14) [$M+Na^+$]. Anal. Calcd for $C_8H_{13}NO_3S$: C, 47.27; H, 6.45; N, 6.89; S, 15.78. Found: C, 47.55; H, 6.56; N, 6.55; S, 15.92.
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