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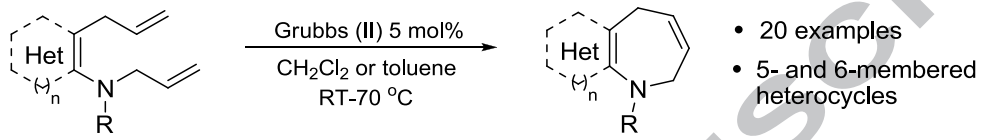

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A ring-closing metathesis approach to heterocycle-fused azepines

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ABSTRACT

Heterocycle-fused azepines, an important class of molecular scaffold, are readily synthesized through the ruthenium-catalyzed ring-closing metathesis reaction. Although benzo-fused azepines are well documented, heterocycle-fused examples are poorly developed. Herein, a range of five- and six-membered heterocycle-fused azepines are investigated, allowing access to a series of pharmaceutically interesting products.

Studies have identified a direct link between the degree of sp^3 saturation in a drug candidate molecule and its probability of clinical success.[1] With this in mind, we recently described a one-pot procedure for the synthesis of fused aza-indolines and aza-tetrahydroquinolines through an alkylation/ intramolecular cyclisation sequence with *N*-protected cyclic sulfamidates.[2] Although this allowed a range of partially saturated bicycles to be synthesized, larger ring systems (7- and above) were not accessible *via* this methodology. Medium-sized fused ring systems such as azepine derivatives are a particularly interesting structural motif, being found in a number of bioactive natural products and pharmaceuticals. Within this class, benzazepine derivatives have found use as vasopressin V_2 receptor antagonists (e.g. tolvaptan),[3] and in other disease areas.[4] Due to this widespread utility, benzazepine derivatives have attracted considerable attention from the synthetic community, with typical synthetic routes including ring expansion,[5] Dieckmann condensations[6] and intramolecular metal-catalyzed coupling reactions.[7]

A very useful method for synthesizing medium sized N-containing heterocycles is the ruthenium-catalyzed ring-closing metathesis reaction (RCM).[8] Since its inception, the RCM reaction has been widely used in the synthesis of benzo-fused azepines (7-) and azocines (8-).[9] However one area that has not been well researched is the synthesis of heterocycle-fused azepine ring systems, particularly those which contain key molecular recognition sites such as pyrimidines, pyridines and azoles[10] (Figure 1). Herein is described the synthesis of these useful building blocks through a ring-closing metathesis strategy, and the synthetic routes towards their RCM precursors.

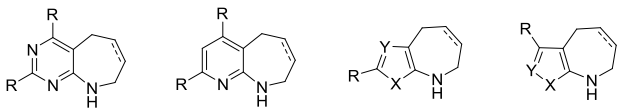
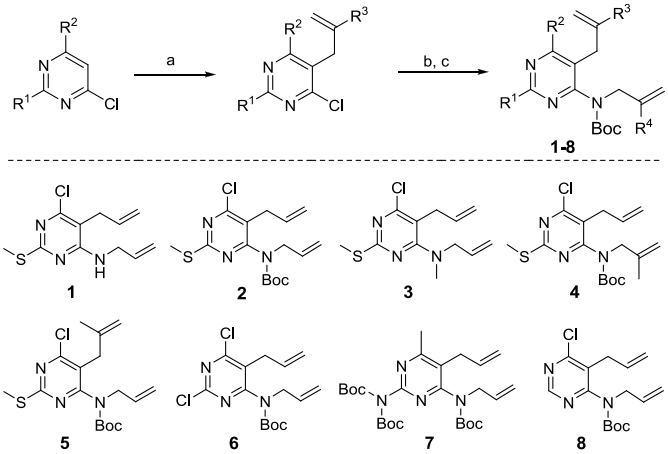


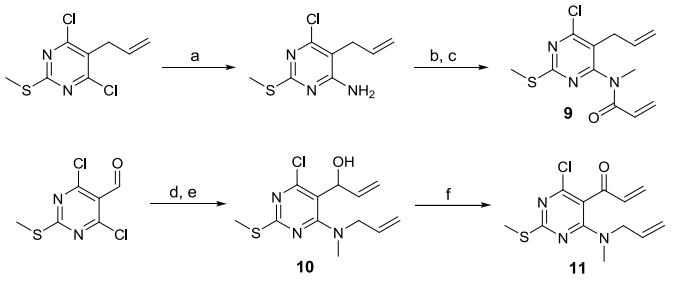
Figure 1. 5- and 6-membered heterocycle-fused azepine derivatives.

Studies began by investigating the synthesis of the required pyrimido-fused azepine precursors, as fused pyrimidines are known to be privileged scaffolds in medicinal chemistry. Treatment of the parent chloro-pyrimidines with TMPMgCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidine) at room temperature, followed by quenching with an allyl bromide gave the 5-allylated products.[11] For less electron rich pyrimidines such as 2,4,6-trichloropyrimidine and 4,6-dichloropyrimidine, the metallation was conducted at -78 °C with CuBr as an additive to minimize decomposition. Displacement of the chloride with allylamine or an allylamine derivative under microwave irradiation and subsequent *N*-Boc protection gave the required precursors **1-8** in good overall yields. Alternatively, the chloro-intermediates could be accessed by cyclisation of diethylallyl malonate with the appropriate amidine/urea/guanidine followed by chlorination with $POCl_3$ in MeCN (Scheme 1).



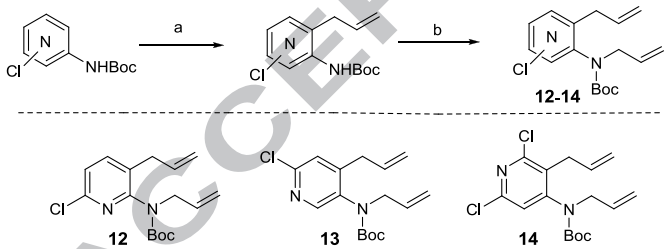
Scheme 1. *Reagents and conditions:* a) TMPMgCl·LiCl, THF, CH_2=CHR^3CH_2Br, RT or -78 °C. b) $NH_2CH_2CR^4$=CH_2, Et_3N, MeCN, 140 °C. c) Boc_2O, DMAP, MeCN, reflux.

A modified procedure was used for the synthesis of pyrimido-fused azepinone precursors: diplacement of the chloride with ammonia, followed by acylation and *N*-methylation gave acrylamide **9**, whereas Grignard addition to the allylation product (step d) of a commercially available 5-substituted aldehyde followed by oxidation of alcohol **10** with MnO_2[12] gave vinyl ketone **11** (Scheme 2).



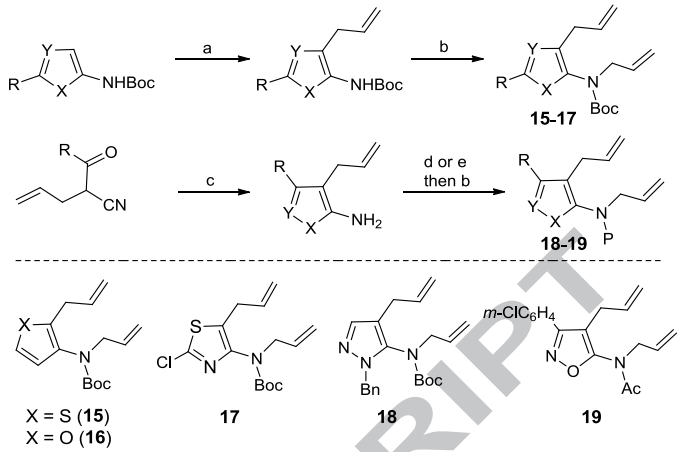
Scheme 2. *Reagents and conditions:* (a) NH_3/MeOH (7 M), 100 °C, 30 min. (b) NaHMDS, acryloyl chloride, THF, -78 °C. (c) NaH, MeI, DMF, -10 °C. (d) *N*-allylmethylamine, CH_2Cl_2. (e) vinylmagnesium chloride, THF, -78 °C. (f) MnO_2, CH_2Cl_2, reflux.

Next, the synthesis of pyrido-fused azepine precursors was investigated. As pyridines are generally more stable to organometallic reagents than pyrimidines, the required precursors could be synthesized by a directed *ortho*-metallation/allylation strategy.[13] Treatment of the NHBoc compounds with *n*-BuLi (2.25 equiv) in THF at -78 °C gave the *ortho*-lithiated species which were transmetallated with copper(I) bromide before quenching with allyl bromide. With this strategy and by judicious choice of the starting material, the relative positions of the *C*-allyl and *N*-allyl groups could be moved around the aryl ring. Interestingly, in the absence of copper, a significant amount of the *ortho*-brominated pyridines were isolated. The *N*-allyl moiety could then be introduced by alkylation with allyl bromide in DMF to give the pyridine substrates **12**-**14**. Double lithiation/allylation was also attempted, but no significant amounts of N-allylation were observed under these conditions (Scheme 3).



Scheme 3. *Reagents and conditions:* a) *n*-BuLi, CuBr, allyl bromide, THF, -78 °C. b) NaH, allyl bromide, DMF, 0 °C.

Finally, viable synthetic routes towards five-membered heterocycle-fused azepine precursors were investigated. As for pyridine-fused compounds, a directed metallation/allylation strategy could be used in most cases, giving access to thiophene-, furan- and thiazole-fused azepine precursors **15**-**17**. 1,2-Azoles such as pyrazoles and isoxazoles were not stable under these conditions, however the desired starting materials **18**-**19** could be constructed by an alternative approach involving acylation of 5-pentenenitrile, followed by addition of hydroxylamine hydrochloride or *N*-benzylhydrazine hydrochloride. The NH_2 products were then protected (in the case of isoxazole **19**, *N*-Boc protection was sluggish, so *N*-acylation was performed), and subsequently alkylated with NaH and allyl bromide in DMF (Scheme 4).



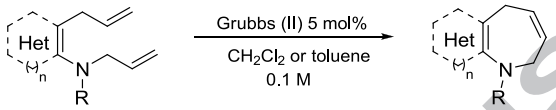
Scheme 4. *Reagents and conditions:* a) *n*-BuLi , allyl bromide, THF, -78 °C. b) NaH, allyl bromide, DMF, 0 °C. c) NaHDMS, HCO_2Et, THF, –78 °C then $BnNHNH_2$·HCl then d) Boc_2O, DMAP, MeCN, RT then b) for **18**; NaHDMS, *m*-$ClC_6H_4CO_2Et$, THF, –78 °C then NH_2OH·HCl then e) AcCl, pyridine, RT then b) for **19**.

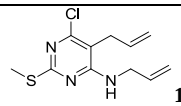
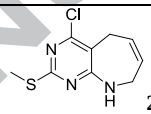
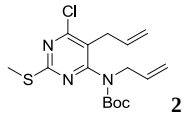
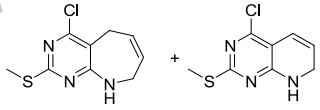
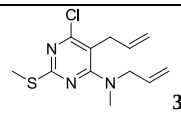
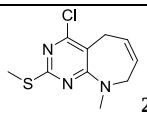
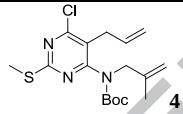
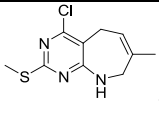
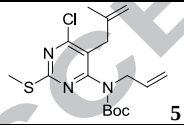
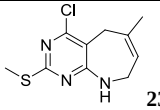
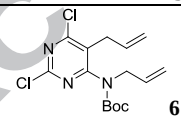
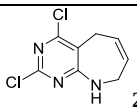
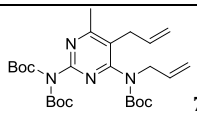
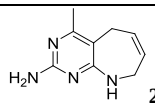
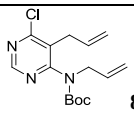
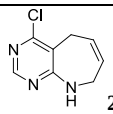
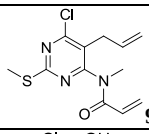
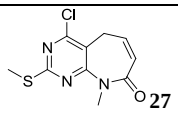
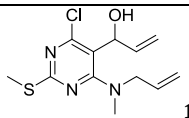
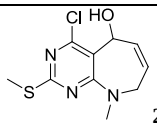
With the desired azepine precursors in hand, their suitability in RCM reactions was investigated (Table 1). Treatment of unprotected pyrimidine **1** with 5 mol% Grubbs (II) catalyst in a solution of either CH_2Cl_2 or toluene only gave traces of the RCM azepine product **20**, even at elevated temperatures or in the presence of an acid co-catalyst. This was slightly surprising since RCM reactions are known on substrates containing NH functionality,[9a] leading us to postulate that the free amino-pyrimidine may be ligating the catalyst. Pleasingly, the *N*-Boc protected precursor **2** did react smoothly in the RCM, giving the azepine derivative in good yield after stirring for 16 hours at room temperature in CH_2Cl_2, or for 1 hour at reflux in CH_2Cl_2. Interestingly, a small amount (up to 5%) of the piperidine product (presumably formed from isomerisation of the *C*-allyl prior to cyclisation) had also formed in the reaction. The two products were inseparable by chromatography, but could be easily separated once the *N*-Boc had been cleaved with TFA in CH_2Cl_2, allowing access to pyrido-fused azepine **20** in good overall yield from **2**. Separation difficulties as a result of piperidine formation was sometimes seen in other pyrimidine and pyridine-fused ring-closed products (but not the azole-fused products), thus the *N*-Boc cleavage was routinely telescoped with the RCM reaction to give the NH products directly. No intermolecular reaction products were seen in the ring-closing metathesis, so all the reactions were carried out at moderate dilution (0.1 M). The *N*-Boc group could be replaced with an *N*-Me **3** giving the azepine product **21** in high yield. This again points to the NH- aminopyrimidine being the cause of the sluggish reaction with **1**. *N*- and *C*-methylallyl precursors **4** and **5** were both well tolerated in the RCM, giving the 7-methylated and 6-methylated pyridoazepines **22** and **23**, respectively, in good yields. In these cases, the RCM reaction was sluggish at room temperature, and required heating to reflux in CH_2Cl_2 to furnish the products efficiently, with no observable isomerisation of the alkene. Various orthogonally reactive substituents including chloro-, amino- and methyl could be appended to the pyrimidines, with compounds **6**-**8** all reacting smoothly to give the azepine derivatives **24**-**26** in good yields after *N*-Boc cleavage.

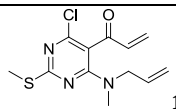
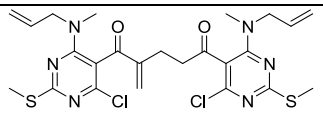
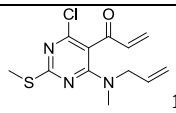
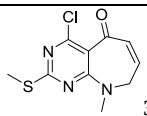
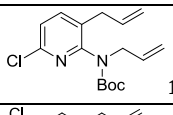
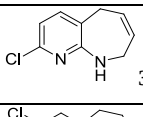
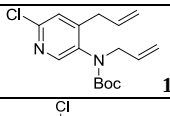
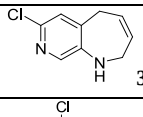
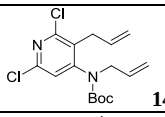
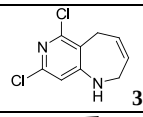
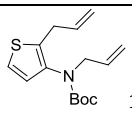
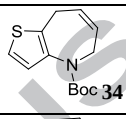
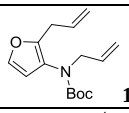
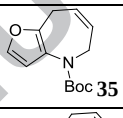
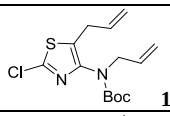
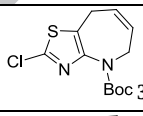
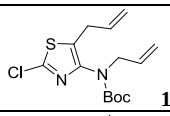
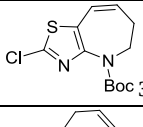
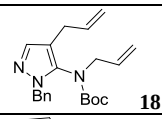
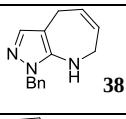
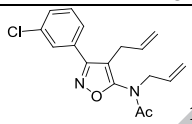
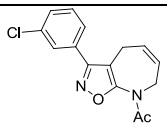
N-Me acrylamide **9** was also successful in the RCM reaction, giving the azepin-8-one **27** in a pleasing 84% yield. Again in this case, the free NH precursor was not well tolerated. Alcohol **10** worked well in the RCM reaction, giving hydroxy-azepine **28** in 85% yield. Interestingly however, the vinyl ketone **11**[14] gave only traces of the RCM product with 5 mol% of Grubbs (II) catalyst. Instead, the major product was the Morita Baylis-Hilman type adduct **29**. Aromatic vinyl ketones are known to undergo Baylis-

Hilman type dimerisation reactions with a range of nucleophilic catalysts including DABCO, phosphines and phosphine ligated metal complexes.[14] Anticipating that a dissociated tricyclohexyl phosphine ligand present in the Grubbs (II) catalyst might be promoting this unwanted pathway, the same reaction was attempted using the Hoveyda-Grubbs (II) catalyst, which does not contain any phosphine ligands. Gratifyingly, treatment of vinyl ketone **11** with 5 mol% of Hoveyda-Grubbs (II) catalyst in CH_2Cl_2 gave solely the azepin-5-one product **30** in 82% yield after heating to reflux for 4 hours. Pyridines **12**-**14** worked well in the RCM reaction, giving pyrido-fused azepines **31**-**33** in good yields (77-85%). Pleasingly, the five-membered heterocycles were also good substrates in the RCM reaction. Thiophene **15** reacted smoothly at RT to give the azepine **34** in good yield, however the NH compound, after *N*-Boc cleavage, was found to be somewhat unstable as the free-base, so the product was stored as the *N*-Boc protected form. Furan-fused azepine **35**, formed rapidly at RT (85%, ^{1}H NMR yield of the crude product after stirring for 1 hour), but was found to be unstable. Even the *N*-Boc protected product **35** was prone to isomerisation and decomposition on silica gel. Thiazole **17** did not react at room temperature, but formed azepine **36** in good yield after heating to 70 ^{o}C in toluene for 3 hours. Further heating the RCM reaction with thiazole **17** to reflux in toluene gave the isomerised alkene **37** in 83% yield after 4 hours, allowing both isomers of the product to be readily obtained from the same starting material simply by conducting the reaction at different temperatures. 1,2-Azoles **18** and **19** both worked well in the RCM reaction giving the pyrazole- and isoxazole-fused azepine derivatives **38** and **39** respectively, in high yields.

Table 1 Scope of the RCM reaction



Entry	Starting Material	Conditions	Time (h)	Product	Yield (%)[a]
1	 **1**	CH_2Cl_2, RT	16	 **20**	<5
2	 **2**	CH_2Cl_2, RT then TFA, CH_2Cl_2, RT	16	 **20** + **20b**	**20**: 85 **20b**: <5
		CH_2Cl_2, 45 ^{o}C then TFA, CH_2Cl_2, RT	1		**20**: 83
3	 **3**	CH_2Cl_2, 45 ^{o}C	1	 **21**	89
4	 **4**	CH_2Cl_2, 45 ^{o}C then TFA, CH_2Cl_2, RT	1	 **22**	83
5	 **5**	CH_2Cl_2, 45 ^{o}C then TFA, CH_2Cl_2, RT	2	 **23**	91
6	 **6**	CH_2Cl_2, 45 ^{o}C then TFA, CH_2Cl_2, RT	2	 **24**	88
7	 **7**	CH_2Cl_2, 45 ^{o}C then TFA, CH_2Cl_2, RT	1	 **25**	86
8	 **8**	CH_2Cl_2, 45 ^{o}C then TFA, CH_2Cl_2, RT	1	 **26**	92
9	 **9**	toluene 70 ^{o}C	3	 **27**	84
10	 **10**	CH_2Cl_2 45 ^{o}C	1	 **28**	85

11	 **11**	CH_2Cl_2 RT	16	 **29**	46
12[b]	 **11**	CH_2Cl_2 45 °C	4	 **30**	82
13	 **12**	CH_2Cl_2, 45 °C then TFA, CH_2Cl_2, RT	24	 **31**	77
14	 **13**	CH_2Cl_2, 45 °C then TFA, CH_2Cl_2, RT	1	 **32**	82
15	 **14**	CH_2Cl_2, 45 °C then TFA, CH_2Cl_2, RT	1	 **33**	85
16	 **15**	CH_2Cl_2 RT	2	 **34**	80
17	 **16**	CH_2Cl_2 RT	2	 **35**	(85) <5[c]
18	 **17**	toluene 70 °C	3	 **36**	81
19	 **17**	toluene 110 °C	4	 **37**	83
20	 **18**	CH_2Cl_2, RT then TFA, CH_2Cl_2, RT	2	 **38**	80
21	 **19**	CH_2Cl_2 RT	2	 **39**	93

[a] Isolated yields after column chromatography. [b] 5 mol% Hoveyda-Grubbs (II) used as the catalyst. [c] Value in parenthesis is the crude ^{1}H NMR yield. The product could not be readily isolated on silica gel.

In conclusion, the ruthenium-catalysed ring-closing metathesis is shown to be an extremely useful reaction in the synthesis of heterocycle-fused azepine and azepinone derivatives.[15] The products formed have multiple handles for further elaboration and constitute exceptionally versatile fragment-sized building blocks. As such, this transformation and the synthetic routes towards the required starting materials should be of interest to the synthetic community in general, and particularly in medicinal chemistry campaigns.

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15. Representative procedure for the synthesis of **20**: Grubbs 2nd generation catalyst (63.6 mg, 0.075 mmol, 5 mol%) was added to a solution of *tert*-butyl allyl[5-allyl-6-chloro-2-(methylthio) pyrimidin-4-yl]carbamate (**2**) (532.7 mg, 1.50 mmol) in anhydrous CH_2Cl_2 (15 mL) at room temperature. The mixture was heated at reflux for 2 h. After cooling to room temperature, TFA (5 mL) was added and the mixture was stirred for a further 30 min before the volatiles were removed under vacuum. The residue was dissolved in CH_2Cl_2 (15 mL) and washed with sat. $NaHCO_3$ solution (15 mL), then dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography (heptane/EtOAc, 9:1 to 3:1) to give 4-chloro-2-(methylthio)-8,9-dihydro-5*H*-pyrimido[4,5-*b*]azepine **20** as a colourless solid (283.2 mg, 83%). M.p. 129-130 ^oC; ν_{max} (cm^{-1}) 3425 (br), 3287 (m), 1580 (s), 1525 (s), 1386 (m), 1335 (m), 1302 (m), 1260 (m), 1100 (w); ^1H NMR [400 MHz, $CDCl_3$] 6.16 (dt, 1 H, *J* = 6.9, 9.6 Hz, CH), 6.00 (dt, 1 H, *J* = 6.8, 9.7 Hz, CH), 6.00 (br s, 1 H, NH), 4.00 (dd, 2 H, *J* = 5.0, 6.7 Hz, CH_2), 3.57 (d, 2 H, *J* = 6.9 Hz, CH_2), 2.44 (s, 3 H, CH_3); ^{13}C NMR [100 MHz, $CDCl_3$] 168.24, 163.25, 157.58, 131.64, 127.33, 106.58, 39.67, 25.22, 13.95; *m/z* (ES) 228 ($[M+H]^+$, 100); HRMS (EI) *m/z* $[M+H]^+$ calcd for $C_9H_{11}N_3ClS$: 228.03567; found; 228.03555,