Synthesis of Sultams by Intramolecular Heck Reaction

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Dedicated to Professor Albert Heesing on the occasion of his 80th birthday

Abstract: A novel access to α-methylene-γ-sultams *via* the intramolecular Heck reaction of α-bromovinylsulfonamides derived from allylic amines is reported. These heterocycles are potent Michael acceptors towards sulfur nucleophiles.

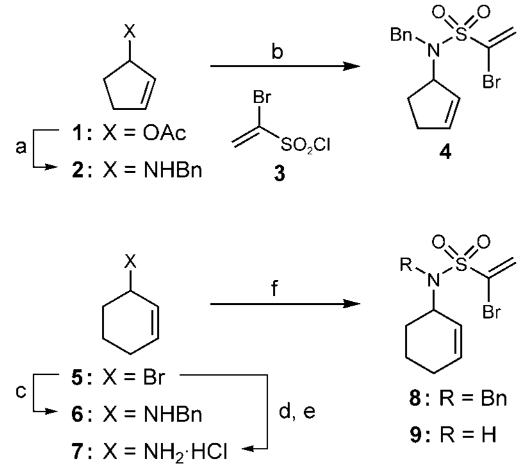
Keywords: cyclization; Heck reaction; homogeneous catalysis; Michael acceptors; sulfonamides; sultams

The sulfonamide group is one of the most important pharmacophores.[1] Likewise, sultams[2] are useful heterocycles for medicinal chemistry.[3] Among the methods that have recently emerged as powerful technologies for the generation of these cyclic sulfonamides are the intramolecular Diels–Alder reaction,[4] sulfonamide dianion alkylation,[5] radical cyclization,[6] and ring closing metathesis.[3a,7] As part of a program launched into the development of novel methods for the preparation of cyclic sulfonic acid derivatives, we have studied the intramolecular Heck reaction[8] in the synthesis of sultams. Here we report a concise access to α-methylene-γ-sultams[9] *via* the intramolecular Heck reaction of α-bromovinylsulfonamides which, in turn, are easily derived from allylic amines.

The synthesis of the sulfonamide substrates with cyclic and acyclic allyl amine moieties employed in this study is illustrated in Schemes 1 and 2. The sulfonyl chloride **3** was readily available from isethionic acid sodium salt by a known three-step sequence on a multi-gram scale.[10] Treatment of **3** with the cyclopentenyl- and cyclohexenylamines **2**, **6** and **7** furnished the desired sulfonamides **4**, **8** and **9** in high yields (Scheme 1).

The acyclic Heck substrates **12**, **15** and **19** were prepared in an analogous fashion (Scheme 2). A *trans* hydrosilylation[11] of propargylic amine **18** served as the key step in the diastereoselective synthesis of (*E*)-configurated substrate **19**.

For Heck cyclizations of the α-bromovinylsulfonamides we chose two established catalytic systems (Scheme 3). Besides standard conditions A, we also applied conditions B, which have recently been utilized for the synthesis of lactams *via* a tandem Heck-allylic substitution reaction.[12] However, next to formation of the expected α-methylene-γ-sultams, double bond migration by readdition of the palladium hydride species and occasionally also a complementary regioselectivity of carbopalladation (6-*endo* instead of 5-*exo*) was noticed under both conditions. Since these undesired features were especially pronounced for substrate **15**, we investigated the effect of silver and thallium additives[8] on the Heck cyclization of this bromovinylsulfonamide (Table 1).



Scheme 1. a) Bn-NH$_2$, 3 mol % [(C$_3$H$_5$-Pd)Cl]$_2$, 4.3 mol % TolBINAP, CH$_2$Cl$_2$, −20 °C, 67%; b) **3**, Et$_3$N, CH$_2$Cl$_2$, −78 °C, 89%; c) Bn-NH$_2$, K$_2$CO$_3$, MeCN, rt, 78%; d) NaN$_3$, H$_2$O, CCl$_4$, rt, 90%; e) LiAlH$_4$, Et$_2$O, reflux, then HCl gas, 64%; f) **3**, Et$_3$N, cat. DMAP, CH$_2$Cl$_2$, −78 °C, 77% **8**, 71% **9**. TolBINAP = 2,2′-bis(di-4-tolylphosphino)-1,1′-binaphthyl.

While all additives employed caused a remarkable enhancement in selectivity, use of thallium acetate turned out to give the best result with efficient formation of α-methylene-γ-sultam **20a** featuring a 1,4-diene partial structure as the sole product after a short reaction time. This optimized protocol was highly successful for a completely selective Heck cyclization of the other *N*-benzyl substrates as well (Table 2). Just like (*Z*)-isomer

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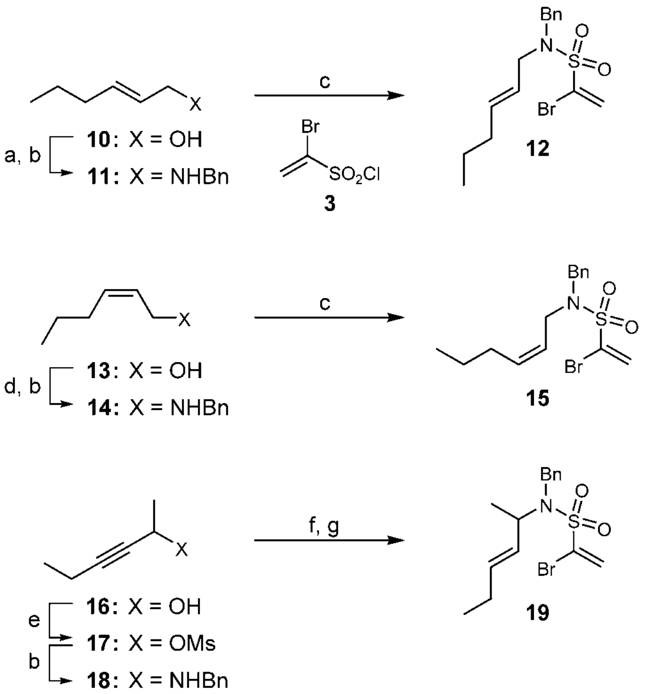


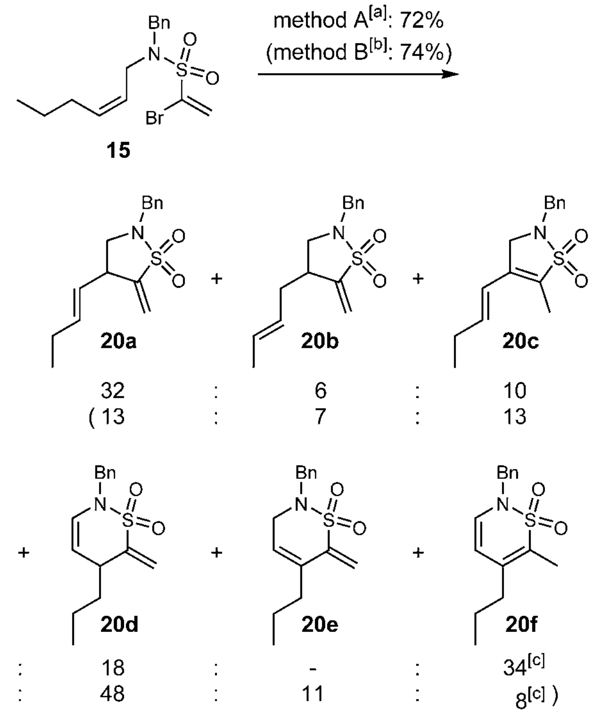
Scheme 2. a) MsCl, Et_3N, THF, 0 °C, 94%; b) Bn-NH_2, 80 °C, 55% **11**, 73% **14**, 72% **18**; c) **3**, Et_3N, cat. DMAP, CH_2Cl_2, −78 °C, 79% **12**, 70% **15**; d) MsCl, Et_3N, Et_2O, rt, 100%; e) MsCl, Et_3N, CH_2Cl_2, −78 °C, 100%; f) $(EtO)_3SiH$, 3 mol % $[Cp^*Ru(MeCN)_3]PF_6$, CH_2Cl_2, 0 °C → rt, then 10 mol % CuI, Bu_4NF, THF, rt, 56%; g) **3**, Et_3N, CH_2Cl_2, −78 °C, 87%. Cp* = pentamethylcyclopentadienyl.

Table 1. Effect of silver and thallium salts on the Heck cyclization of α-bromovinylsulfonamide **15**.[a]

Additive	t [h]	Sultams[b]	
Ag_3PO_4	29	**20a** (58%)	**20b** (10%)
Ag_2CO_3	48	**20a** (25%)	
Tl_2CO_3[c]	14	**20a** (52%)	**20c** (5%)
TlOAc[d]	2.5	**20a** (73%)	

[a] Conditions: 10 mol % $Pd(OAc)_2$, 11 mol % $P(o\text{-}Tol)_3$, 2 equivs. of silver or thallium salt, MeCN, reflux.
[b] Isolated yield after chromatographic separation.
[c] In addition, 21% of the starting material was recovered.
[d] In addition, 8% of the starting material was recovered.

15, (*E*)-sulfonamide **12** cleanly provided sultam **20a** exclusively. Whereas the cyclic olefins **4** and **8** only led to the *cis*-fused bicyclic sultams **21** and **22**, respectively, which was unambiguously proven by X-ray diffraction analysis (Figure 1),[13] (*E*)-sulfonamide **19** with alkyl branching α to nitrogen solely gave rise to the *trans*-dialkyl-substituted product **24**. In contrast to the *N*-benzyl substrates, transformation of sulfonamide **9** with an unprotected NH group to give sultam **23** was not accomplished under these conditions even after a prolonged reaction time.

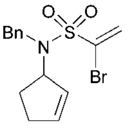
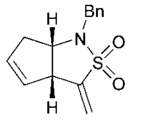
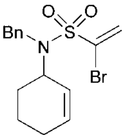
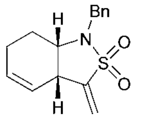
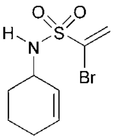
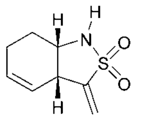
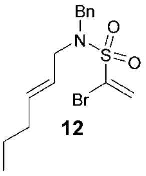
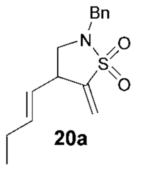
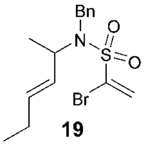
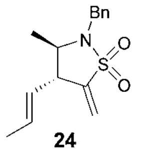


Scheme 3. Intramolecular Heck reactions of vinylsulfonamide **15**.
[a] 5 Mol % $Pd(PPh_3)_4$, 2 equivs. Et_3N, MeCN, reflux, reaction time: 2 h.
[b] 5 Mol % $Pd(OAc)_2$, 11 mol % $P(o\text{-}Tol)_3$, 2 equivs. Bu_4NCl, 2 equivs. Na_2CO_3, MeCN, reflux, reaction time: 1 h. *o*-Tol = 2-methylphenyl.
[c] Ratios determined by GC integration.

α-Methylene-γ-sultams are structurally similar to α-methylene-γ-butyrolactones, which display a wide range of interesting biological activities.[15] Moreover, several vinylsulfonamides have proven to be potent cysteine protease inhibitors.[16] Inspired by recent work of Roush with vinylsulfonyl compounds,[17] we investigated the reactivity of bicyclic α-methylene-γ-sultams **21** and **22** as Michael acceptors towards the sulfur nucleophiles **25** and **26** (Scheme 4). At room temperature, a smooth base-assisted conjugate addition of thiophenol **25** as well as aliphatic thiol **26** occurred to give adducts **27**–**30** in excellent yields as diastereomeric mixtures. The diastereomeric ratios listed in Scheme 4 were determined by ^1H NMR integration, and 2D-NMR analyses revealed the thermodynamically more stable adducts bearing the thiomethyl substituent on the convex face of the bicyclic scaffold to be the major products.

In summary, we have developed a novel access to structurally intriguing sultams of high Michael acceptor reactivity *via* an intramolecular Heck reaction. Testing the α-methylene-γ-sultams as potential cysteine protease inhibitors is planned and will be reported as results unfold.

Table 2. Intramolecular Heck reactions of further α-bromovinylsulfonamides to give sultams.[a]

Vinylsulfonamide	Time	Sultam[b]	Yield [%]
 **4**	5 h	 **21**	64[c]
 **8**	3.5 h	 **22**	72
 **9**	5 d	 **23**	–[d]
 **12**	6 h	 **20a**	75
 **19**	5 h	 **24**	74

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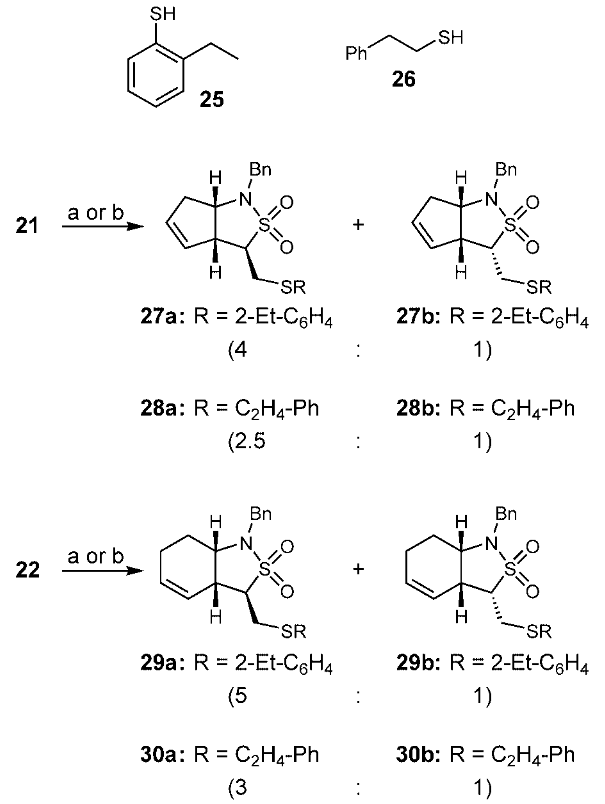
[a] Conditions: 10 mol % $Pd(OAc)_2$, 11 mol % $P(o\text{-}Tol)_3$, 2 equivs. TlOAc, MeCN, reflux.

[b] Isolated yield after chromatographic separation.

[c] In addition, 10% of the starting material was recovered.

[d] No conversion.



Scheme 4. a) **25**, Et_3N, MeOH, rt, 100% **27**, 100% **29**; b) **26**, Et_3N, MeOH, rt, 88% **28**, 92% **30**.

Experimental Section

Optimum Procedure for the Preparation of α-Bromovinylsulfonamides

1-Bromoethenesulfonyl chloride (**3**; 1.2 mmol, 1.2 equivs.) was added dropwise to a solution of the allylic amine (1.0 mmol)

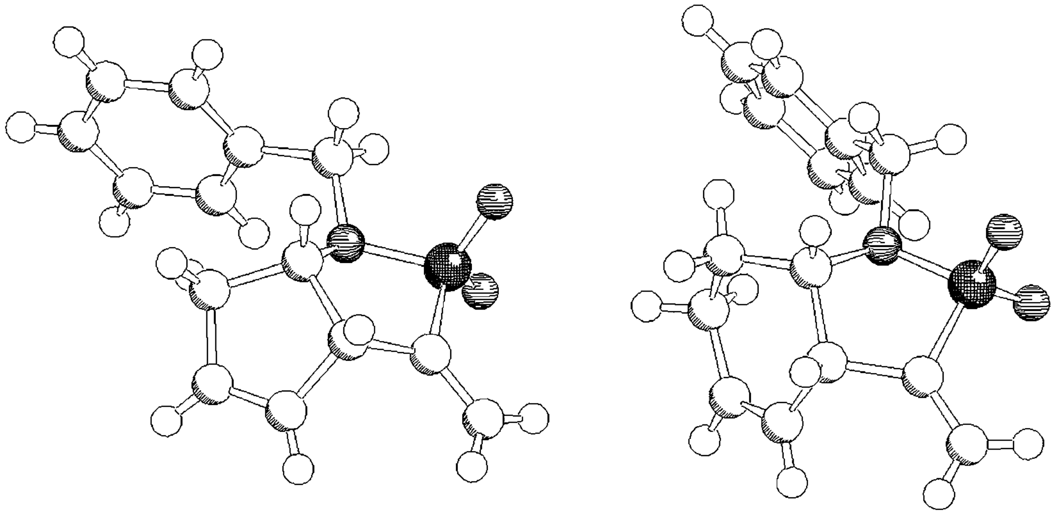


Figure 1. Crystal structures of sultams **21** (left) and **22** (right).[13,14]

and Et_3N (1.2 mmol, 1.2 equivs.) in CH_2Cl_2 (10 mL) at −78 °C under an argon atmosphere. After stirring for 1 h at −78 °C, the reaction mixture was filtered through a plug of silica gel and washed with additional diethyl ether. The filtrate was concentrated under vacuum, and the crude product was purified by flash chromatography.

Heck Cyclization of 15 with $Pd(PPh_3)_4$ (Scheme 3, Method A)

To a suspension of $Pd(PPh_3)_4$ (0.0125 mmol, 5 mol %) and Et_3N (0.5 mmol, 2 equivs.) in dry CH_3CN (10 mL) was added the α-bromovinylsulfonamide (0.25 mmol) under an argon atmosphere. After heating under reflux for 2 h, the mixture was filtered through a plug of silica gel and washed with diethyl ether. The filtrate was concentrated under vacuum, and the residual brown oil was purified by flash chromatography on silica gel.

Heck Cyclization of 15 with $Pd(OAc)_2$ (Scheme 3, Method B)

The α-bromovinylsulfonamide (0.25 mmol) was added to a suspension of $Pd(OAc)_2$ (0.0125 mmol, 5 mol %), P(*o*-Tol)$_3$ (0.0275 mmol, 11 mol %), Bu_4NCl (0.5 mmol, 2 equivs.) and Na_2CO_3 (0.5 mmol, 2 equivs.) in dry CH_3CN (5 mL) under an argon atmosphere. After refluxing for 1 h, the mixture was filtered through a plug of silica gel. The filtrate was concentrated under vacuum, and the oily residue was purified by flash chromatography on silica gel.

General Procedure for Heck Cyclization in the Presence of a Silver or Thallium Salt

To a stirred suspension of $Pd(OAc)_2$ (0.02 mmol, 10 mol %), P(*o*-Tol)$_3$ (0.022 mmol, 11 mol %), and a silver or thallium salt (0.4 mmol, 2 equivs.) in dry CH_3CN (2 mL) was added the α-bromovinylsulfonamide (0.2 mmol) under an argon atmosphere. After refluxing for the time listed in Tables 1 and 2, the mixture was filtered through a plug of silica gel. Following removal of the solvent under vacuum, the oily residue was purified by flash chromatography on silica gel.

General Procedure for Michael Addition of Thiols to α-Methylene-γ-sultams

To a solution of the α-methylene-γ-sultam (0.15 mmol) in dry MeOH (1 mL) was added the thiol (0.75 mmol, 5 equivs.) followed by a dropwise addition of Et_3N (0.3 mmol, 2 equivs.). After stirring the mixture at room temperature for 8–24 h, the solvent was removed under vacuum, and the crude product was purified by flash chromatography.

Acknowledgements

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[13] Crystallographic data (excluding structure factors) for the structures **21** and **22** reported in this paper have been deposited with the Cambridge Crystallographic

Data Centre as supplementary publications no. CCDC-235625 (**21**) and CCDC-262746 (**22**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.)+44 1223/336–033; e-mail: deposit@ccdc.cam.ac.uk].

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