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Rapid, Scalable Assembly of Stereochemically Rich, Mono- and Bicyclic Acyl Sultams

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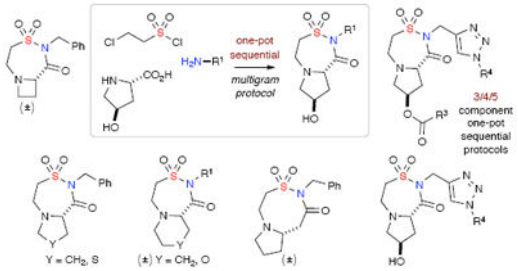
Abstract



A one-pot, sequential protocol is reported that involves complementary ambiphile pairing (CAP) of a vinyl sulfonamide with a variety of unprotected amino acids via aza-Michael addition and subsequent intramolecular amidation. The method generates diverse, sp^3-rich mono- and bicyclic acyl sultams in a highly scalable manner. Modular pairing of stereochemically rich building blocks allows quick access to all possible isomers. Extension to include one-pot, sequential 3-, 4- and 5-multicomponent protocols is also discussed.

Acyl sultams are unnatural compounds that possess unique physical and chemical properties rendering them attractive targets for probing biological systems. In this regard, a number of bioactive acyl sulfonamides/sultams have been reported that encompass a variety of activities, including antibacterial, anticancer, and antiinflammatory properties, as well as unique biological profiles in different cell assays as highlighted in Figure 1.[1] While the synthesis of acyl sulfonamides/benzofused sultams are well documented in the literature,[1] to the best of our knowledge reports of non-benzofused, 7-membered acyl sultams bearing stereogenic centers are relatively void in the literature. We herein report a complementary ambiphilic pairing (CAP) strategy, *vide infra*, employing vinyl sulfonamides and unprotected amino acids in a one-pot, sequential aza-Michael addition/intramolecular amidation reaction (formally a [4+3] heterocyclization) for the generation of skeletally and

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Supporting Information Available: Experimental details and spectral charactization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

stereochemically diverse, sp^3-rich [2] mono- and bicyclic acyl sultams. Extension of the method to include a one-pot, sequential 3-, 4- and 5-multicomponent protocols is also discussed.

The rapid generation of functionally diverse small molecule collections for high throughput screening, is an important aspect of modern drug discovery. In particular, the development of multicomponent, one-pot reaction strategies that allow for facile assembly of heterocyclic scaffolds, with minimum purification is particularly desirable. [3] Diversity-oriented synthesis (DOS) has emerged as a powerful strategy for systematically probing biological space aimed at uncovering novel leads. [4] Among several approaches, the build-couple-pair[5a] and functional group pairing[5b] strategies have featured prominently in advancing DOS. We recently reported the concepts of complementary ambiphile pairing (CAP)[6] and reaction pairing [7] as DOS strategies for the facile generation of diverse sultam scaffolds. In this regard, the complementary union of ambiphilic [8] synthons, in a formal [m+n] fashion ([4+3] and [4+4]), allows access to diverse cyclic heterocycles in a step-economical approach.[9] It was envisioned that the unification of CAP and multicomponent, one-pot protocols would provide a library amenable methodology to access the titled sp^3-rich[2] 7-membered acyl sultams.

The method was premised on the ambiphilic nature of both vinyl sulfonamides and amino acids. In this regard, the ambiphilic nature of vinyl sulfonamides were previously reported to readily undergo hetero-Michael additions as well as *N*-alkylations,[10] and participate in a [4+3] epoxide-opening/Michael protocol.[6a] Likewise, amino acids can be conceptually classified as ambiphilic synthons where they represent ideal starting materials as they allow for encoding stereochemical, skeletal and peripheral diversity. Furthermore, while aza-Michael addition of unprotected amino acids to acrylonitrile,[11] acrylate esters, [12] acrylaldehyde, [13] sulfones, [14] and vinylphosphoryl compounds[15] have been reported, to the best of our knowledge aza-Michael addition of unprotected amino acids to vinyl sulfonamides are absent in the literature.

The investigation commenced with the Michael addition of *trans*-3-hydroxy-(L)-proline (**8a**) to *N*-propargylic vinyl sulfonamide in the presence of 0.2 equivalents of DBU. Initially, both MeOH and CH_3CN were probed as solvents with overnight stirring at 60 °C (Table 1, entry 2). However, these preliminary conditions failed to furnish the corresponding product. Changing the base to Et_3N generated the product in moderate yield, however, utilizing a 1:1 mixture of MeOH/H_2O as the solvent with Et_3N as base cleanly afforded the desired Michael adduct. The reaction mixture was concentrated to dryness, and subsequent resolvation of the reaction mixture with DMF and addition of EDC, HOBt and Et_3N with overnight stirring, afforded the desired bicyclic acyl sultam **10e** in 64% yield.

The substrate scope and the scalability of this protocol were next investigated (Table 1). The reaction was pleasingly found to work well with a variety of alkyl- and benzyl amine-derived vinyl sulfonamides to furnish the desired products in good to excellent yields on multigram scales. It is noteworthy that this one-pot protocol was shown to be scalable to produce 28 grams of **10e** (64% isolated yield). Also significant, is the ability to utilize a

hydroxy-functionalized amino acid without the need for any protection in the Michael addition step (Table 1).

This strategy was further extended to bicyclic acyl sultams using a variety of cyclic amino acids. Notable applications include a azetidine 2-carboxylic acid, (*R*)-thiazolidine-4-carboxylic acid, 2-(pyrrolidin-2-yl)acetic acid and morpholine 3-carboxylic acid to afford the 4,7-fused, 5,7-fused, 5,8-fused, and 6,7-fused bicyclic systems, respectively (Scheme 1).

Investigations were next focused on a modular approach using chiral amino ester-derived vinyl sulfonamides, as this would allow for the generation of stereochemically rich libraries[2] by a simple change in the amino acid/amino ester pair. Hence, (*L*)-alanine *tert*-butyl ester-derived vinyl sulfonamide was subjected to the established one-pot, CAP protocol employing (*D*)- and (*L*)-proline affording the acyl sultams (**18, 19**) without decomposition of the ester (Scheme 1). Use of the enantiomers of α-methylbenzylamine-derived vinyl sulfonamides, **20** and **21**, together with both *L-trans*- and *D-cis*-hydroxyproline in the aforementioned method, gratifyingly furnished a collection of four diastereoisomers in good yields without any signs of racemization (Scheme 2).

The methodology was further extended to acyclic amino acids with a variety of *N*-substituted vinyl sulfonamides utilizing the same protocol (Table 2). Amino acids bearing alkyl side chains (leucine, isoleucine, valine and alanine) gave good yields in a highly scalable manner. The reaction conditions also tolerated amino acids with nucleophilic side chains (trifunctional amino acids) such as tyrosine and cysteine, which reacted well albeit in lower yields.

We next set out to extend the method to a one-pot, sequential protocol by increasing the number of reactions that could be carried out before chromatographic intervention.[3a-d] Thus, 2-chloroethane sulfonyl chloride was sulfonylated with benzyl amine utilizing Et_3N (2.0 equiv) and upon completion of reaction, the mixture was concentrated to dryness. Subjection of the crude sulfonamide to the established one-pot, aza-Michael addition–intramolecular amidation with a variety of cyclic amino acids, furnished the desired products in 39–85% final isolated yields (Scheme 3). This one-pot, sequential 3-component protocol was also found to work with acyclic amino acids (DMF was the preferred solvent for cyclic amino acids, while $CHCl_3$ at 50 °C was used for acyclic amino acids) to furnish the corresponding acyl sultams in moderate to good overall yields.

Encouraged with the above results, efforts were focused toward the extension of the method to a one-pot, sequential, 4-component reaction protocol using variable pathways (Scheme 4). Thus, four reactions were setup using the one-pot sulfonylation–aza-Michael–intramolecular amidation sequence with propargyl amine and *trans*-3-hydroxy-(L)-proline. Upon completion of the four parallel procedures, a fourth component, cyclohexyl isocyanate, was added to the first crude reaction mixture to furnish the desired carbamate **28** in 37% yield after chromatography (78% avg/rxn). The second reaction mixture was concentrated to dryness, and a subsequent click reaction was carried out with the fourth component, 4-methylbenzyl azide, to generate the corresponding triazoylated thiadiazepin-1(2*H*)-one-3,3-dioxide **29** in 45% yield after chromatography (82% avg/rxn). To the third crude reaction, an

esterification was performed with the fourth component, 4-methyl benzoic acid, to afford the corresponding acyl sultam **30** in 42% yield after chromatography (81% avg/rxn).

Building upon these results, the highly functionalized sultam scaffold **31** was constructed via a one-pot, sequential, 5-component reaction sequence (Scheme 4). Thus, to the fourth reaction mixture, esterification with 4-methyl benzoic acid (fourth component), and subsequent click reaction with 4-methylbenzyl azide (fifth component) produced the desired triazolyl esterified [1,2,5]thiadiazepin-1(2*H*)-one-3,3-dioxide **31** in 35% yield (81% avg/rxn).

In conclusion, we have developed a highly scalable, one-pot, CAP reaction employing vinyl sulfonamides and amino acids for the preparation of skeletally, stereochemically and peripherally diverse sp^3-rich sultam scaffolds containing an acylsulfonamide functionality. This approach was extended to various one-pot, sequential 3-, 4- and 5-component reaction protocols to afford thiadiazepin-1(2*H*)-one-3,3-dioxide scaffolds with high peripheral ligand diversity. Furthermore, the methodology is highly divergent and is eminently adaptable for the preparation of stereochemically-rich sultam libraries. Work in this regard is underway and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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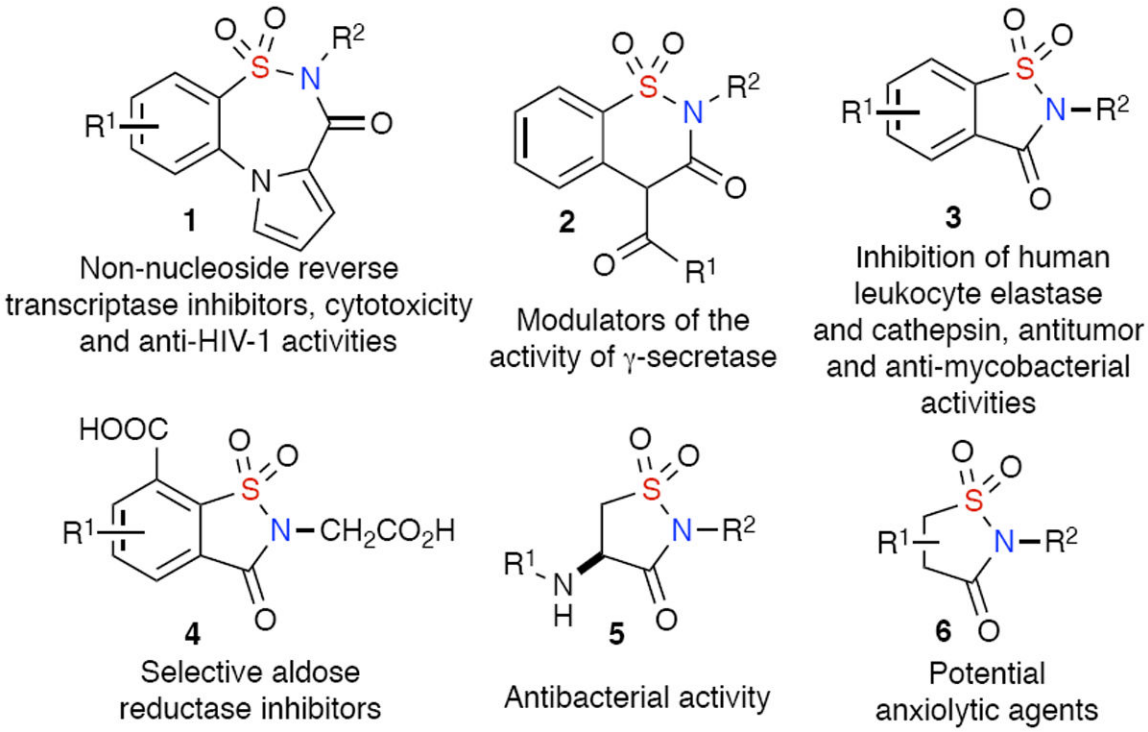
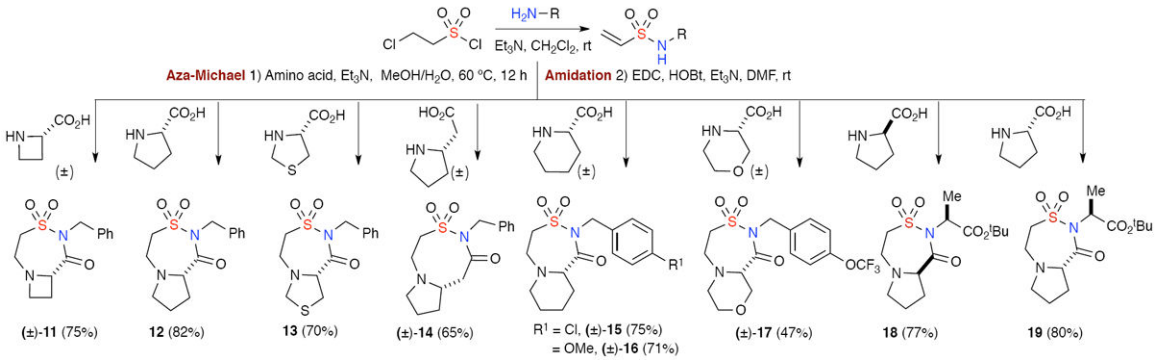
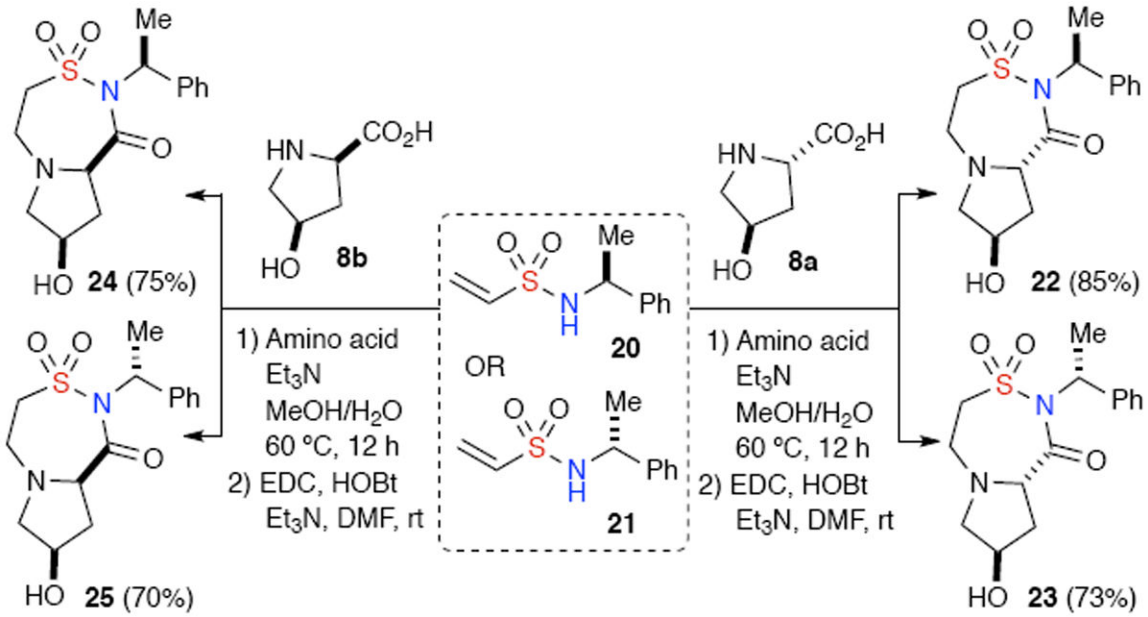


Figure 1.
Bioactive acyl sultams.

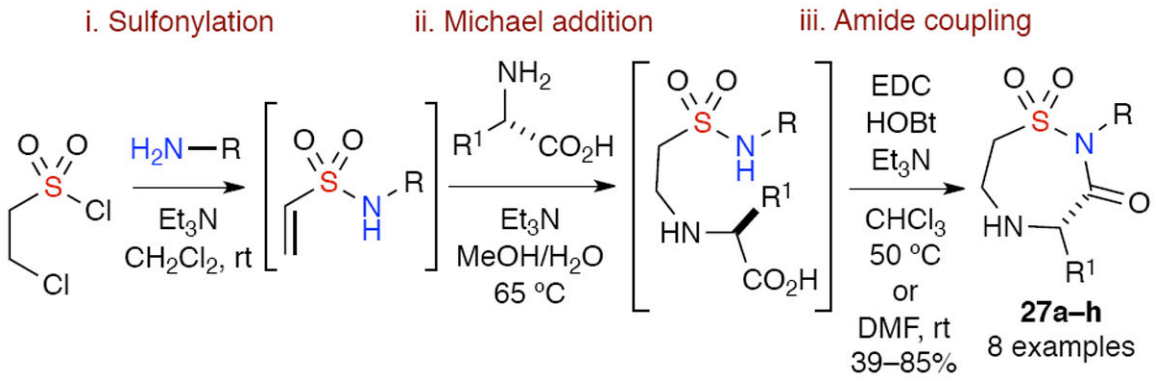


Scheme 1.

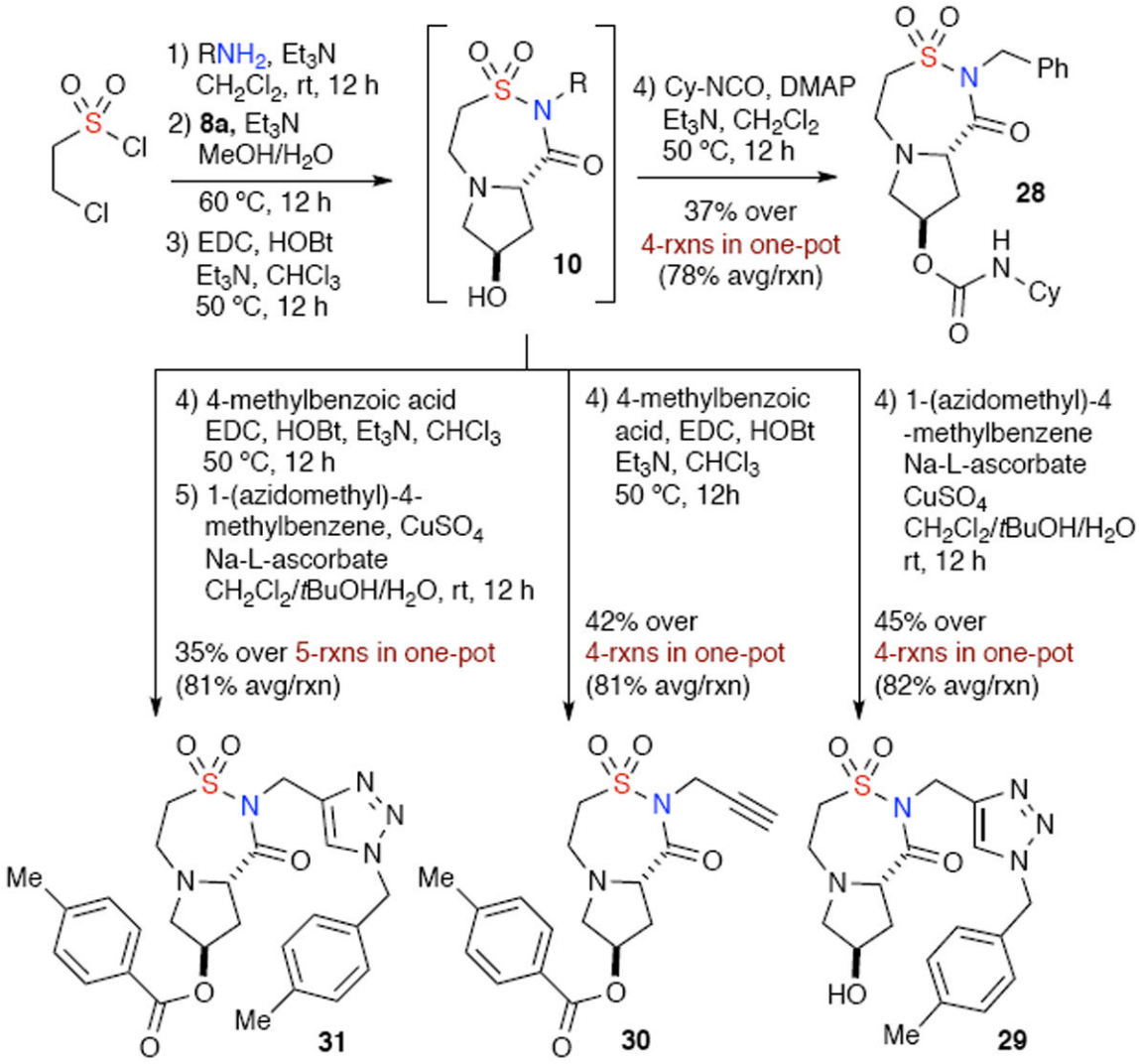
One-pot, sequential [4+3] CAP strategy to generate bicyclic sultams with an array of cyclic amino acids.



Scheme 2.
Generation of stereochemical diversity.



Scheme 3.
One-pot, sequential 3-component protocol.

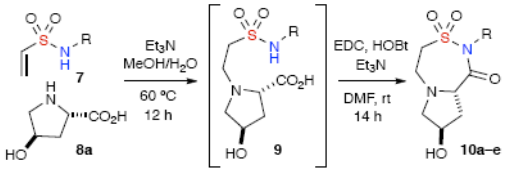


Scheme 4.

One-pot, sequential 4/5-component reaction to stereochemically-rich sultams.

Table 1

Scope and scale-up.



entry	R	scale	10	yield %[a]
1	Bn	0.2 g	NR	0[b]
2	propargyl	0.2 g	NR	0[b]
3	*n*-butyl	2 g	**10a**	67[c]
4	4-OMe-Bn	1 g	**10b**	72[c]
5	allyl	12 g	**10c**	86[c]
6	Bn	12 g	**10d**	76[c]
7	propargyl	28 g	**10e**	64[c]

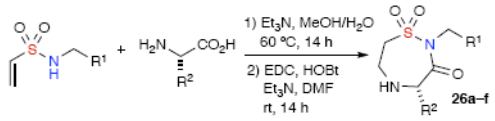
[a] Final isolated yield after flash chromatography.

[b] Conditions: DBU (0.2 equiv) in MeOH or DBU (0.2 equiv) in MeCN.

[c] **Aza-Michael: 8a** (1.0 equiv), Et_3N (3.0 equiv), $MeOH/H_2O$ (0.5 M, 1:1), 60 °C, 12 h. **Amidation:** EDC (2.0 equiv), HOBt (0.2 equiv), Et_3N (2.0 equiv), DMF (0.05 M), rt, 14 h.

Table 2

Substrate scope - acyclic amino acids.



entry	R^1	R^2	26	yield %[a]
1	Ph	^{i}Bu	**26a**	63
2	4-F-Ph	*sec*-Bu	**26b**	65
3	4-F-Ph	^{i}Pr	**26c**	67
4	4-Cl-Ph	Me	**26d**	65
5	$(CH_2)_6CH_3$	CH_2SH	**26e**	33
6	Ph	(4-OH)-Bn	**26f**	41

[a]Final isolated yield after flash chromatography.