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Efficient Synthesis of 1,4-Thiazepanones and 1,4-Thiazepanes as 3D Fragments for Screening Libraries

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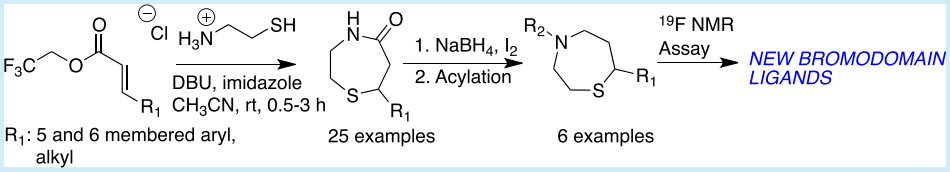

ABSTRACT: 1,4-Thiazepanes and 1,4-thiazepanones represent seven-membered ring systems with highly 3D character and are currently underrepresented in fragment screening libraries. A nuclear magnetic resonance (NMR) fragment screen identified 1,4-acylthiazepanes as new BET (bromodomain and extraterminal domain) bromodomain ligands; however, an efficient and readily diversified synthesis for library development has not been reported. Here we report a one-pot synthesis using α,β-unsaturated esters and 1,2-amino thiols to form 1,4-thiazepanones as precursors to 1,4-thiazepanes with high 3D character. This reaction proceeds in reasonable time (0.5−3 h) and in good yield and tolerates a broad scope of α,β-unsaturated esters. Several 1,4-thiazepanes were synthesized by a two-step transformation and were characterized as new BET bromodomain ligands using protein-observed ^{19}F NMR. This synthesis should provide ready access to diverse 3D fragments for screening libraries.

Fragment-based ligand discovery (FBLD) is an efficient approach for inhibitor discovery against difficult drug targets.[1] The premise of FBLD is a reduction of chemical space that is efficiently sampled through screening low-molecular weight molecules. Retrospective analyses identified a need for increasing the fragment library diversity.[2] Fragment libraries are largely composed of flat molecular scaffolds, with a high prevalence of aromatic rings.[3,4] Ring systems, such as saturated seven-membered rings, are underrepresented.[5] Fragments with increased 3D character have shown improved specificity in protein-binding assays, offering an additional metric for library design.[6] We recently screened a 3D-enriched library against the protein, BRD4,[7] an anticancer drug target.[8,9] One lead 3D fragment hit, **1a**, was an acylated 1,4-thiazepane. The structure−activity relationship (SAR) study was limited due to the lack of a robust and easily diversified synthetic route for creating a library of thiazepane molecules. To address this need, we report an optimized synthesis of 1,4-thiazepanes for fragment library development (Figure 1).

We sought to establish a high-yielding synthesis of 1,4-thiazepane and thiazepanones for BRD4 inhibitor development. Whereas multiple approaches have been described for forming benzothiazepinones,[10−13] which benefit from the rigidified amino thiols for optimizing cyclization, far fewer methods for non-ring-fused thiazepanones are reported (Figure 1, top). Tetrahydro-1,4-thiapyranones undergo Beckmann rearrangements[14,15] or Schmidt reactions.[16,17] These pathways yield the desired seven-membered rings, but access to starting materials for library synthesis and undesired regioisomer production[18] hinder their effectiveness. Conjugate additions into α,β-unsaturated lactones and lactams yield 1,4-thiazepanones, but these methods force hydroxyl or amino substituents in the seven-position, limiting the scope for product diversity.[19] Methyl-3-mercaptopropionate cyclizes using aziridine with sodium methoxide. This pathway requires several days and may not be compatible with base-sensitive functional groups.[20,21] Thiazepanones are also synthesized from cyclization with cysteamine or derivatives under basic conditions with α,β-unsaturated esters, taking 3−7 days and often resulting in low yield.[21−25] Our synthesis of **1a** using this approach gave similar yields (32%) and reaction time (3 days).[7] Here we develop cysteamine cyclization reactions with α,β-unsaturated esters to produce 1,4-thiazepanones in short (<3 h) reaction times (Figure 1, bottom). The significant improvement stems from the moderate reactivity of trifluoroethyl esters and milder reaction conditions to increase the substrate scope. Using our improved conditions, a broad scope of 1,4-thiazepanones is achieved, in many cases without chromatography. These

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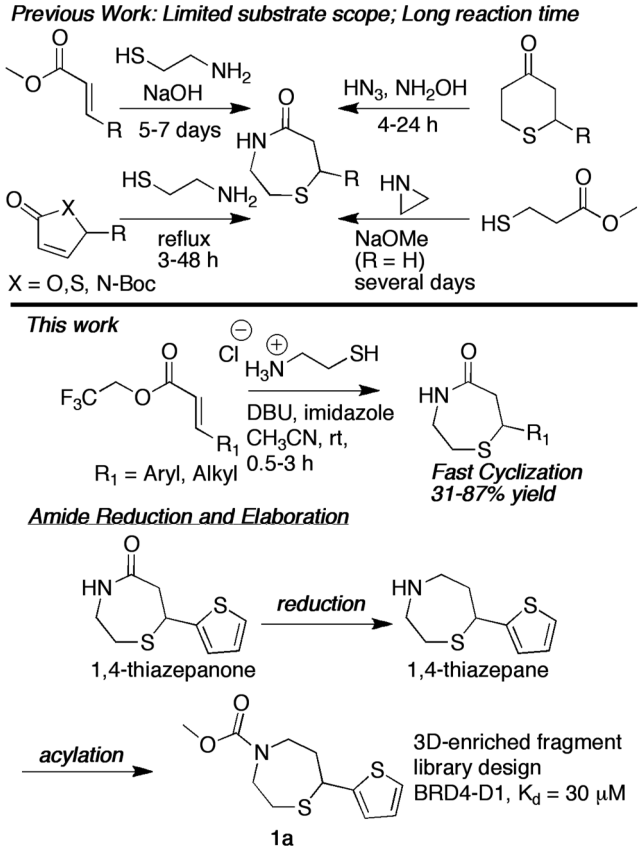


Figure 1. General scheme for 1,4-thiazepanone and 1,4-thiazepane synthesis.

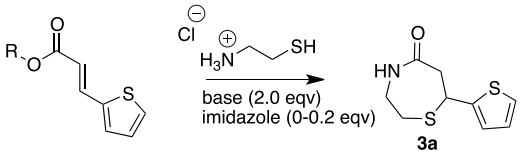
thiazepanones are subsequently reduced and functionalized to generate bromodomain ligands.

Our initial attempt to synthesize the 1,4-thiazepanone included a two-step reaction, creating an amide bond with aryl-substituted acrylic acids, followed by an intramolecular conjugate addition (Scheme S2). Here the conjugate addition step was not successful, presumably due to the reduced electrophilicity of the β-carbon. Conducting the conjugate addition first on 3-(2-thienyl)acrylic acid with *N*-Boc-cysteamine, followed by deprotection and intramolecular acylation to form **3a** led to a mixture of side products. We ultimately focused our attempts instead on a one-pot conjugate addition and acylation reaction (Figure 1).

The initial optimization of the tandem conjugate addition/cyclization reaction used the methyl ester of 3-(2-thienyl)-acrylic acid to favor conjugate addition prior to cyclization. A base screen showed DBU to yield the cyclized 1,4-thiazepanone, albeit in low yields (11%, Table 1). Other bases, DIEA, Et_3N, and NaOH, did not yield product. NaOH has been previously used; however, the reaction times took 5 days with modest yield.[24] Finally, we tested the effect of acyl transfer additives[26] and found 0.2 equiv of imidazole to increase the yield (53%, entry 5, Table 1). The reaction was further improved through solvent choice. Tetrahydrofuran and acetonitrile were well-suited for this reaction. Acetonitrile was optimal, as the reaction worked efficiently at ambient temperature (entry 9) and excluded the need for heating to solubilize reagents, as required for tetrahydrofuran.

Finally, we sought to tune the electrophilicity of the α,β-unsaturated esters while favoring conjugate addition before

Table 1. Reaction Optimization with Solvent and Base[a]

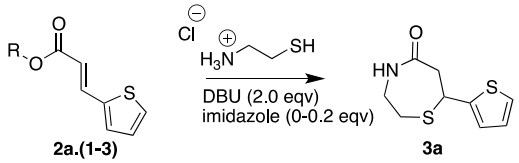


entry	base	time (h)	% yield	temp (°C)	imidazole	solvent
1	Et_3N	18	0	60	no	THF
2	DIEA	18	0	60	no	THF
3	NaOH	18	0	60	no	THF
4	DBU	18	11	60	no	THF
5	DBU	18	53	60	yes	THF
6	DBU	24	25	60	no	CH_3OH
7	DBU	18	27	60	no	DMF
8	DBU	18	53	60	yes	CH_3CN
9	DBU	18	56	rt	yes	CH_3CN

[a]Reactions performed with **2a.1** (1.0 equiv), cysteamine (1.2 equiv), base (2.0 equiv), and imidazole (0−20 mol %) in solvent (5 mL). Yields and temperature indicated.

acylation. We tested methyl (**2a.1**), 2,2,2-trifluoroethyl (**2a.2**), and hexafluoroisopropyl (**2a.3**) esters (Table 2).[27] Ester **2a.2** was the best-suited, yielding **3a** in higher yields (70%, entry 4, Table 2) and shorter reaction times (0.5 h) relative to the much slower methyl ester (56%, entry 1, 18 h). Under these conditions, alternative bases could be used but with reduced yield or extended reaction times. Unlike the methyl ester, the trifluoroethyl ester cyclization worked efficiently, forming thiazepanone **3a** without imidazole (71%, entry 5, Table 2).

Table 2. Optimization of Cyclization for 1,4-Thiazepanones[a]



entry	R	base	time (h)	% yield	imidazole
1	$-CH_3$ (**2a.1**)	DBU	18	56	yes
2	$-CH_2CF_3$ (**2a.2**)	DIEA	18	71	yes
3	$-CH_2CF_3$ (**2a.2**)	NaOH	18	22	yes
4	$-CH_2CF_3$ (**2a.2**)	DBU	0.5	70	yes
5	$-CH_2CF_3$ (**2a.2**)	DBU	0.5	71	no
6	$-CH(CF_3)_2$ (**2a.3**)	DBU	1	50	yes

[a]Reactions performed with ester (1 equiv), cysteamine (1.2 equiv), base (2 equiv), and imidazole (0−20 mol %) in CH_3CN (5 mL) at rt for 0.5−18 h. Yields are indicated.

Under these optimized conditions, we tested the order of the two-step reaction sequence. When the ester group was replaced by an amide via first acylating with cysteamine, the subsequent conjugate addition product was not formed using the optimized conditions. (Scheme S2).[28] This result is consistent with conjugate addition preceding cyclization when using the trifluoroethyl ester.

With a set of conditions in hand, we explored the reaction scope with respect to the α,β-unsaturated ester (Table 3). In the case of cinnamic esters, the syntheses worked efficiently. For para substitution, electron-donating and -withdrawing

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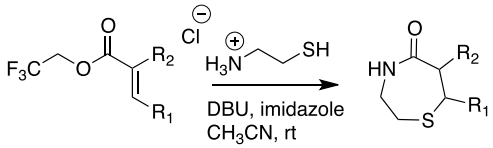
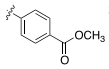
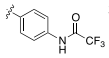
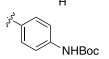
Table 3. Scope of Cyclization for 1,4-Thiazepanones[a]



compd	R_1	time	yield	compd	R_1	time	yield
3a		0.5 h	70%	3m		1 h	87%
3b		1 h	70%[b]	3n		1 h	81%
3c		3 h	69%	3o		1 h	77%
3d		1 h	0, 18%[c]	3p		1.5 h	56%
3e		1 h	0%	3q		1 h	84%
3f		2 h	78%	3r		1 h	56%
3g		1 h	82%	3s		3 h	62%[d]
3h		1 h	83%	3t		2 h	50%
3i		1 h	50%	3u		3 h	66%
3j		0.5 h	61%	3v		3 h	31%
3k		0.5 h	65%	3w		1 h	65%
3l		0.5 h	40%[b]				

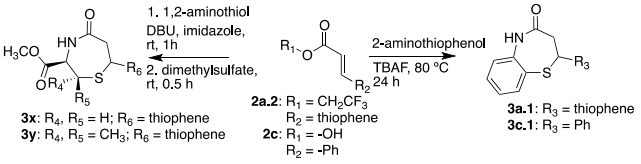
[a]Reactions performed with ester (1.0 equiv), cysteamine (1.2 equiv), base (2 equiv), and imidazole (0−20 mol %) in CH_3CN (5 mL) at rt, 0.5−3 h. Yields indicated. [b]Product obtained using methyl ester and no imidazole. [c]No imidazole was added. [d]Product isolated as a diastereomeric mixture; $R_2 = CH_3$

groups led to isolated yields of 50−83% for **3f**−**k**. For *p*-nitro groups, reduced yields and increased side products were obtained. The yield of **3l** could be improved to 40% by excluding the acyl transfer catalyst or by using the less reactive methyl ester. Ortho- and meta-substituted cinnamic esters provided modest to high yields of 50−87% (e.g., **3m**−**o**) and trisubstituted α,β-unsaturated esters **3p** and **3s**. High-yielding reactions (i.e., **3f**, **3g**, **3h**, **3j**, **3m**, and **3n**) did not require chromatographic purification. A few reactions showed modest conversion of 50% (**3i** and the disubstituted aryl ether **3t**) primarily due to unreacted cinnamic ester, even after several hours of reaction. For the heterocyclic substituent nitrofuryl-containing **3d**, the reaction did not form the major product. Alternatively, **3d** was obtained using the less reactive methyl ester but in low yield. Imidazole-containing ester was nonreactive toward these conditions to form **3e**, indicating sensitivity toward more electron-deficient heterocycles. α,β-Unsaturated esters substituted without aromatic groups are also substrates and yield **3q** and **3r** in comparable yield.

Finally, we tested polar and acid- and base-sensitive functional groups. Thiazepanones with acid- or base-labile protecting groups, Boc and trifluoroacetamide, respectively, also formed (**3w**, **3v**). A methyl ester was also tolerated (**3u**). In contrast, previously reported protocols using either strongly basic or acidic conditions provide limited access to these acid- or base-labile functional groups.[20−25]

We next tested the generality of this reaction using cysteine, penicillamine, and 1,4-aminothiophenol (Table 4).[22] For

Table 4. Cyclization with Different 1,2-Aminothiols[a]



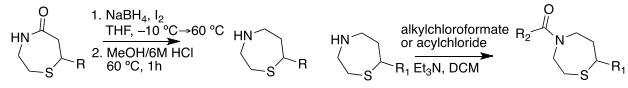
entry	compd	1,2-aminothiol	base/catalyst	time (h)	% yield
1	**3x**	L-cysteine	DBU	18	67[b]
2	**3y**	L-penicillamine	DBU	18	62[b]
3	**3a.1**	2-aminothiophenol	DBU	18	0[c]
4	**3c.1**	2-aminothiophenol	TBAF	24	65[d]

[a]For **3x** and **3y**, reactions were performed with 1.0 equiv of ester, 1,2-aminothiol (1.2 equiv), base (2 equiv), dimethylsulfate (1.5 equiv), and imidazole (0−20 mol %) in CH_3CN (5 mL). For **3c.1**, the reaction was performed with cinnamic acid (1 equiv), 2-aminothiophenol (2 equiv), and TBAF (0.1 equiv) at 80 °C for 24 h. Yields indicated. [b]Obtained as a mixture of diastereomers. [c]Predominant disulfide formation under optimized conditions. [d]Synthesized using the previously reported protocol.[29]

cysteine derivatives, the free carboxylic acid was converted to a methyl ester prior to isolation to yield **3x** and **3y**. A moderate to high degree of diastereoselectivity was observed (i.e., **3x**, dr = 2.3:1; **3y**, dr = >95:1). Additionally, we reacted 2-aminothiophenol with either a trifluoroethyl or a methyl ester of cinnamic acids. The reaction was unsuccessful with predominant disulfide formation. Alternately, compound **3c.1** was synthesized via a reported protocol using TBAF as a catalyst under neat conditions.[29] In our hands, these conditions were not compatible with the synthesis of non-ring-fused 1,4-thiazepanones, demonstrating the complementary nature of both methods.

To produce 1,4-thiazepanes for bromodomain inhibition experiments, the 1,4-thiazepanones **3a**, **3c**, **3g**, and **3h** were reduced using sodium borohydride/iodine (Table 5) or borane

Table 5. Synthesis of 1,4-Thiazepanes[a]



compd	R	yield (%)	compd	R_1	R_2	yield (%)
4a		80	1a		-OMe	49
4c		85	5a		-CH_2CH_3	63
4g		89	6a		-$OCH_2CH_2CH_3$	49
4h		54	7a		-OCHCH=CH_2	86
			1g		-OMe	47
			1h		-OMe	51

[a]Reduction conditions: thiazepanone (1.0 equiv), $NaBH_4$ (5 equiv), iodine (2 equiv) in THF (5 mL). Carbamoylation and acylation conditions: amine (1 equiv), triethylamine (1.2 to 1.5 equiv), and electrophile (1.2 to 1.5 equiv) for 0.5 to 2 h, rt. Yields indicated.

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dimethylsulfide[28] to the corresponding 1,4-thiazepanes **4a**, **4c**, **4g**, and **4h** and converted to carbamates or amides (Table 5 and Table S1).[28] Using this approach, we significantly improved the prior synthesis of parent compound **1a** over the reported synthesis.[7] The current methodology should be preferable for the synthesis of 1,4-thiazepanes to other approaches with an improvement in time, yield, and scope.

With several 1,4-thiazepanes and thiazepanones in hand, we tested for BRD4-D1 binding. These molecules possess a significant 3D character with a plane-of-best fit of 0.84 to 1.0 and 0.61 to 1.1, respectively (Table S2),[31] above the threshold of 0.25 for describing a 3D fragment.[6] We used ^{19}F NMR to quantify ligand binding to fluorinated BRD4-D1 by measuring a change in chemical shift of a fluorinated tryptophan (W81) resonance located in the protein binding site (Figure 2B).[30]

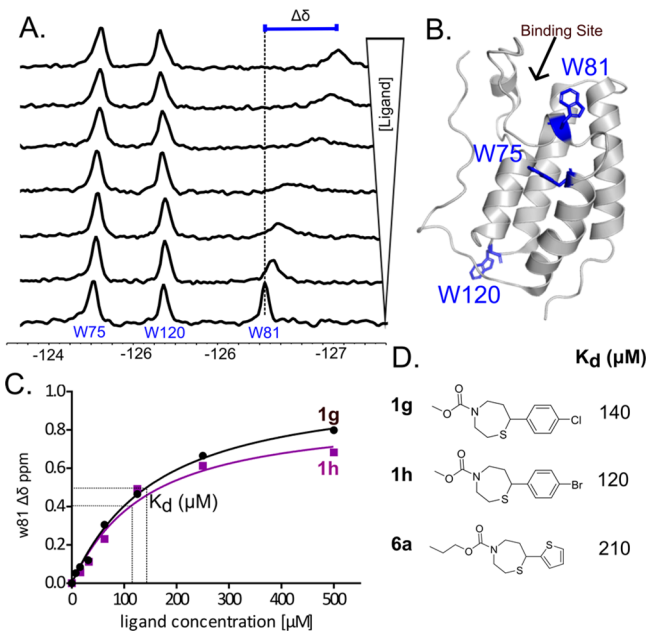

Figure 2. (A) Fluorine NMR titration. (B) BRD4-D1 with the 5-fluorotrytophans labeled in blue (PDB ID: 3MXF). (C) Binding isotherm of **1g** (black circles) and **1h** (purple squares). (D) Structure and corresponding ligand affinities.

We tested 11 compounds at a single concentration, including six thiazepanones and five thiazepanes. Thiazepanes **1g**, **1h**, and **6a** induced a significant chemical shift and were titrated to obtain a K_d value of 120−210 μM (Figure 2 and Figures S1 and S2), demonstrating good affinity. These titration experiments also demonstrate the good water solubility of the thiazepane scaffold.

In conclusion, we report the efficient synthesis of 1,4-thiazepane and 1,4-thiazepanones with an improved substrate scope. Several thiazepanes maintain affinity for BRD4. Ready access to this scaffold will increase the diversity of 3D fragment screening libraries. The versatility of this short approach will be used for library generation for screening against diverse proteins and for improving binding efficiency to BRD4.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01230.

Full experimental details and spectral characterization data (PDF)

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Author Contributions

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Notes

The authors declare the following competing financial interest(s): We have submitted a provisional patent on this work: Pomerantz, W. C. K.; Johnson, J.; Kirberger, S. E.; Pandey, A. Improved Synthesis of Substituted 1,4-Thiazepan-5-ones. UMN Provisional Patent 2020-042, filed 2019.

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