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Chemoselective Alkylation for Diversity-Oriented Synthesis of 1,3,4-Benzotriazepin-2-ones and Pyrrolo[1,2][1,3,4]benzotriazepin-6-ones, Potential Turn Surrogates

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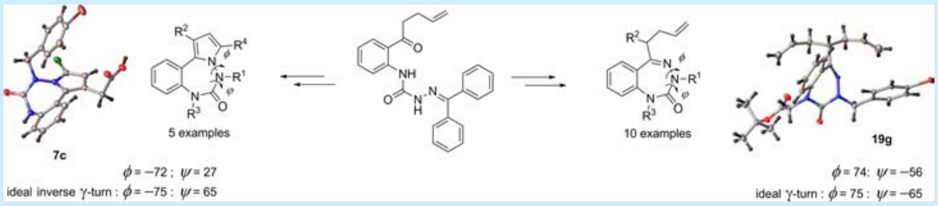
Ⓢ *Supporting Information*



ABSTRACT: 1,3,4-Benzotriazepin-2-ones garner interest for medicinal applications, in part due to their relationship with benzodiazepinones. Ten 1,3,4-benzotriazepin-2-ones **6** and **19** and six pyrrolo[1,2][1,3,4]benzotriazepin-6-ones **7** and **23** were prepared in four to seven steps and 4−60% overall yields by a divergent strategy from methyl anthranilate employing chemoselective alkylations of common linear and cyclic precursors to diversify three triazepinone ring positions (N1, N3, and C5). X-ray crystallography demonstrated that benzotriazepinone **19g** may serve as a γ-turn mimic.

1,4-Benzodiazepin-2-ones **1** are common targets because of their biological properties and medicinal applications,[1] which may be due in part to their potential to mimic peptide γ-turn secondary structures (Figure 1).[2−5] Although their aza counterparts have received relatively less attention, 1,3,4-benzotriazepin-2-ones **2** possess intriguing biological activity. For example, 5-cyclohexyl triazepinones **3** and **4** have, respectively, exhibited activity as a parathyroid hormone-1 receptor antagonist[6] and an orally active cholecystokinin-2 (CCK_2) antagonist (Figure 1).[7] 1,3,4-Benzotriazepin-2-ones have also been claimed to possess psychostimulant, antidepressant, anorexigenic, and antihypertensive properties.[8] Although relatively little is known about 1,3,4-triazepin-2-one conformation, similar to the amino acid component in 1,4-diazepin-2-ones,[9] the aza-phenylglycine residue of 7-chloro-3,5-diphenyl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-2-one **5** was observed by X-ray crystallography to adopt ϕ- and ψ-dihedral angle values close to those of the central residue of an ideal γ-turn.[10]

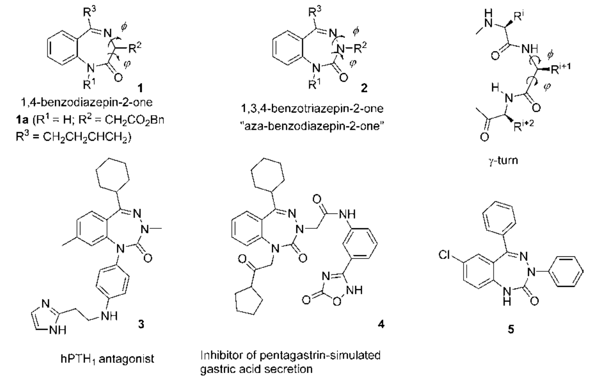


Figure 1. Representative benzodiazepin-2-one, benzotriazepin-2-ones, and γ-turn structures.

Since original syntheses from 2-aminobenzophenone,[4] 1,3,4-benzotriazepin-2-ones have been commonly prepared by cyclization of the corresponding hydrazone with a phosgene equivalent and by a one-pot annulation with a carbazate often at high temperature (e.g., 190 °C). Ring closure has also been achieved by palladium-catalyzed cyclization of aryl isocyanates and 2-haloaryl hydrazones under microwave irradiation[11] as well as condensation of anthranilic acid hydrazide with isatins, which provided the corresponding spiro[1,3,4-benzotriazepine-2,3′-indole]-2′,5(1*H*,1′*H*)-diones.[8] Benzotriazepinone skeletons have been alkylated on ring nitrogen and arylated at C5 using copper catalysis in solution[12] and on microelectrode arrays;[13] however, nitrogen protection has been essential for chemoselectivity.

Diversity-oriented synthesis of 1,3,4-benzotriazepin-2-ones **6** has now been achieved by an approach that avoids nitrogen protection, toxic reagents, and harsh conditions to modify the N1, N3, and C5 positions. Moreover, pyrrolo[1,2][1,3,4]benzotriazepin-6-ones **7** have also been synthesized from common linear precursors prepared from 1-(2-aminophenyl)-pent-4-en-1-one **8**. This method enhances the utility of amino ketone **8**, which has been quantitatively synthesized by a copper-catalyzed cascade addition of vinyl Grignard reagent on methyl anthranilate[14,15] and used as valuable precursor to make

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substituted pyrroles **9**,[14] quinolines **10**,[15] pyrroloquinazolinones **11**,[14] 1,4-benzodiazepin-2-ones **12**,[5] and pyrrolobenzodiazepin-2-ones **13** (Figure 2).[5]

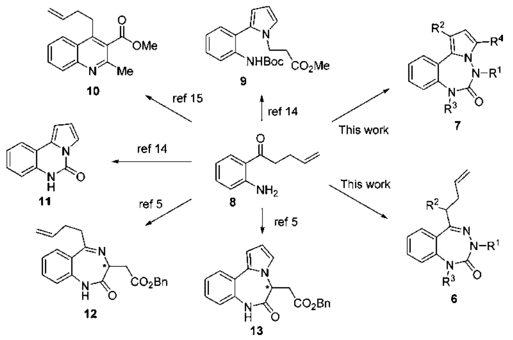


Figure 2. Amino ketone **8** as precursor for heterocycle synthesis.

Amino ketone **8** was acylated with activated carbazate **14**[16] in DCM in the presence of DIEA at room temperature to obtain the key precursor aza-glycinamide **15** in 71% yield on multigram scale (Scheme 1). Chemoselective alkylation of the semicarbazone nitrogen of aza-glycinamide **15** was achieved using conditions previously developed for sub-monomer aza-peptide synthesis.[17] Various aza-amino amide analogues **16a−h** were thus synthesized from **15** using tetraethylammonium hydroxide as base and a diverse set of alkyl halides in THF (Table 1).[18]

Scheme 1. Synthesis and Chemoselective Alkylations of Semicarbazone 15 and Ketone 16

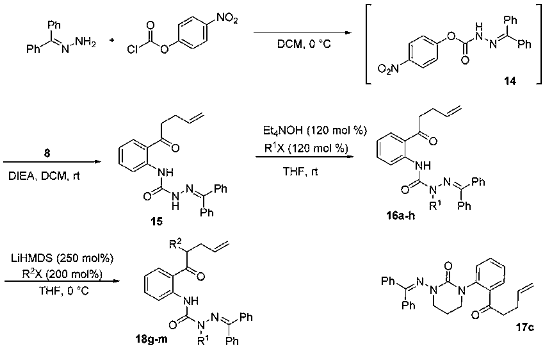


Table 1. *N*- and *C*-Alkylation Steps To Form 16 and 18

entry	R^{1}X (120 mol %)	yield **16** (%)	R^1	R^{2}X (200 mol %)	yield **18** (%)
a	CH$_3$I	100			
b	BrCH$_2$CCH	73			
c	Br(CH$_2$)$_3$Cl	79[a]			
d	Br(CH$_2$)$_4$Cl	88			
e	Br(CH$_2$)$_3$OR[b]	94			
f	BnBr	78			
g	BrCH$_2$C$_6$H$_{11}$	52[c]	C$_6$H$_{11}$CH$_2$	*p*-BrBnBr	72
h	*p*-BrBnBr	93	*p*-BrBn	BrCH$_2$CO$_2$Me	80
i			*p*-BrBn	BrCH$_2$CHCH$_2$	70
j			*p*-BrBn	BrCH$_2$CCH	68
k			*p*-BrBn	CH$_3$CH$_2$I	35
l			*p*-BrBn	CH$_3$I	47
m			*p*-BrBn	BrCH$_2$CO$_2$*t*Bu	73

[a]Et$_4$NOH (100 mol %) R^{1}X (150 mol %). [b]R = Si(Ph)$_2$*t*Bu. [c]Reflux.

Although reactive and primary alkyl halides reacted at room temperature to give **16** in >73% yields, cyclohexylmethyl bromide required heating at reflux to obtain **16g** in 52% yield. 1-Bromo-3-chloropropane (150 mol %) reacted with **15** and tetraethylammonium hydroxide (100 mol %) to give aza-chloropropylglycinamide **16c** in 79% yield with minimal amounts of cyclic urea **17c** from a second intramolecular alkylation of the aniline nitrogen.

Chemoselective alkylation of the ketone moiety of **16** without reaction on the aniline nitrogen was achieved using LiHMDS (250 mol %) to generate the dianion, which selectively reacted on carbon with various alkyl halides (200 mol %) in THF at 0 °C for 1 h to give branched ketones **18g−m** in 35−80% yields (Table 1). Selective alkylation of the ketone enolate may be due to the relative stability and hindered nature of the lithiated urea, which may interact respectively with the neighboring semicarbazone nitrogen and carbonyl oxygen in five and six membered ring chelates. Incomplete alkylation and difficulty in separating product from starting material may account for the lower yields using methyl and ethyl iodides.

Scheme 2. Cyclization of 16 and 18 and N1-Alkylation of 6

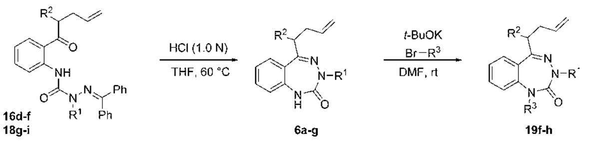


Table 2. 1,3,4-Benzotriazepin-2-ones 6 and 19

entry	yield **6** (%)	R^1	R^2	R^{3}Br	yield **19** (%)
a	99	(CH$_2$)$_4$Cl	H		
b	69	(CH$_2$)$_3$OH[a]	H		
c	40	*p*-BrBn	CH$_2$CO$_2$H[b]		
d	53[c]	*p*-BrBn	Me		
e	32	CH$_2$C$_6$H$_{11}$	*p*-BnBr		
f	90	Bn	H	CH$_2$CCH	85[d]
g	76	*p*-BrBn	CH$_2$CHCH$_2$	CH$_2$CO$_2$-*t*-Bu	100
h		*p*-BrBn	CH$_2$CHCH$_2$	CH$_2$CCH	100

[a]Alcohol from OTBDPS. [b]Acid from CO$_2$Me. [c]63% using EtOH. [d]Alkylation was performed in THF.

1,3,4-Benzotriazepin-2-ones **6a−f** were prepared in 32−99% yields from aza-amino amides **16** and **18** by semicarbazone cleavage and cyclization under acidic conditions using 1.0 N aq HCl in THF (Scheme 2, Table 2). Attempts to prepare benzotriazepinone from unsubstituted semicarbazone **15** were unsuccessful using similar conditions; instead, ions corresponding to oligomer were detected by HPLC−MS analysis of the reaction mixture. Semicarbazone alkylation may favor cyclization by lowering the barrier for urea isomerization to the required *E*-isomer.[19] α-Alkyl-branched ketones **18** reacted slower in the cyclization to **6**, likely because the neighboring ketone is engaged in a hydrogen bond with the aniline NH that disfavors the orientation for nucleophilic attack.[20] The favored hydrogen bonded conformer was illustrated in a comparison of **16h** and **18l** in deuterium exchange NMR experiments using MeOD-d_4 in CDCl$_3$. After 20 h, the amount of exchange of the aniline NH proton with deuterium was >95% for **16h** but <20% for **18l** under the same conditions. When EtOH was used to competitively hydrogen bond with ketone **18l** during the cyclization step, the reaction time was reduced and the yield increased: 22 h and 53% yield in THF versus 4 h and 63% yield in EtOH.

After cyclization, the aniline nitrogen of triazepinones **6** was chemoselectively alkylated using *t*-BuOK (120 mol %) and different alkyl bromides (120 mol %) to give the trisubstituted 1,3,4-benzotriazepin-2-ones **19** in 85−100% yields (Table 2). The installment of propargyl, bromoaryl, chloroalkyl, and carboxylate side chains has been demonstrated with particular interest to further diversify the 1,3,4-benzotriazepin-2-one scaffolds by future employment of such functional groups in orthogonal chemistry, e.g., CuAAC,[21] cross-coupling,[22] nucleophilic displacement,[23] and amide bond forming reactions, respectively. Such chemistry is being explored presently and will be reported in due time.

Pyrrolo[1,2][1,4]benzodiazepin-6-ones have garnered interest because of their biological and medicinal relevance. For example, pyrrolobenzodiazepinone (*S*)-**20b** has exhibited activity as a non-nucleoside HIV-1 reverse transcriptase inhibitor (Figure 3).[24] To the best of our knowledge, the aza-variant of this ring system has never been reported. Pyrrolobenzotriazepinones **7** were thus pursued to further demonstrate the utility of the alkene function. Olefins **16** and **18**, respectively, were oxidized using Lemieux−Johnson conditions to give aldehydes **22a−d** in 76−84% yields.[25] Aldehydes **22** were then treated with 1.0 N aq HCl in THF at 60 °C to affect semicarbazone cleavage and intramolecular Paal−Knorr condensation. Pyrrolo[1,2][1,3,4]-benzotriazepin-6-ones **7** were isolated in 23−67% yields by column chromatography. The sterically hindered semicarbazone **22d** gave pyrrole **7e** in 30% yield along with a side product in 23% yield having a molecular ion and spectral properties consistent with imine dimer **21** (Figure 3). Chloropyrrole **7c** was isolated in 23% yield from **22c** using the acidic cyclization conditions and characterized by its four molecular ions corresponding to the bromine and chlorine isotopes and the pyrrole proton singlet in the NMR spectrum. X-ray analysis of **7c** confirmed the structural assignment. Alternatively, by conducting the Paal−Knorr reaction in MeOH in the dark, pyrrolobenzotriazepinone **7d** was isolated in 52% yield.

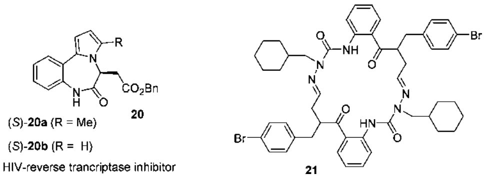
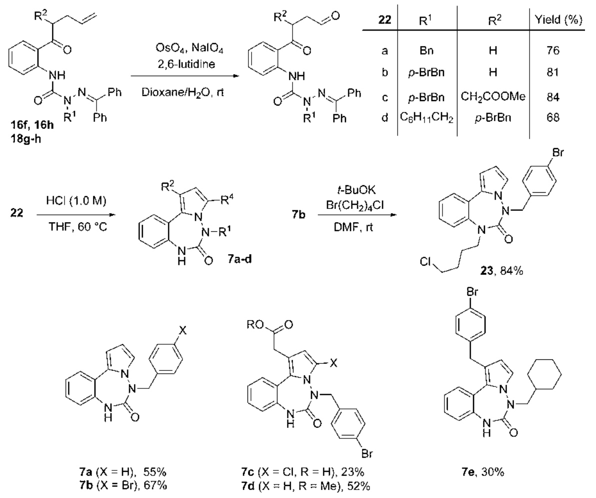


Figure 3. Pyrrolobenzodiazepinone **20** and macrocyle **21**.

To demonstrate the potential to further diversify pyrrolo-[1,2][1,3,4]benzotriazepin-6-one **7**, analogous conditions were employed as described above for the alkylation of triazepinone **6**. The aniline nitrogen of pyrrolobenzotriazepinone **7b** was thus alkylated with potassium *tert*-butoxide and 1-bromo-4-chlorobutane in 84% yield (Scheme 3).

Crystals of 1,3,4-benzotriazepin-2-one **19g** and the pyrrolo-[1,2][1,3,4]benzotriazepin-6-one **7c** were grown by slow diffusion of *n*-hexane into samples in EtOAc and subjected to X-ray structural analysis (Figure 4). Substitution of the diazepinone amino acid component by an aza-residue in triazepinone CCK antagonists has previously been used to amplify selectivity for the CCK$_2$ over CCK$_1$ receptors.[6] Better accommodation by the CCK$_2$ receptor of the achiral triazepinone may be due to the aza-residue exhibiting adaptive chirality[26] or a relatively flat geometry.

Scheme 3. Synthesis and Alkylation of Pyrrolo[1,2][1,3,4]benzotriazepin-6-ones



22	R^1	R^2	Yield (%)
a	Bn	H	76
b	*p*-BrBn	H	81
c	*p*-BrBn	CH$_2$COOMe	84
d	C$_6$H$_{11}$CH$_2$	*p*-BrBn	68

23, 84%

7a (X = H), 55%
7b (X = Br), 67%

7c (X = Cl, R = H), 23%
7d (X = H, R = Me), 52%

7e, 30%

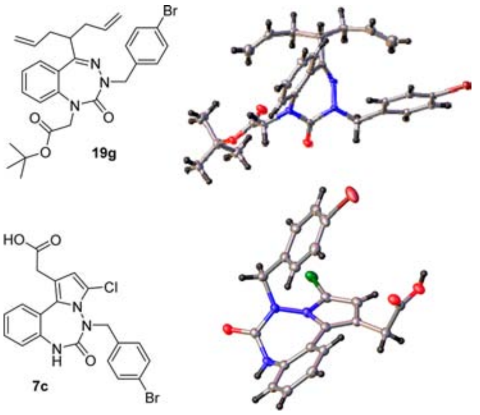


Figure 4. X-ray crystal structures of **19g** and **7c**.

Employing X-ray data to probe the differences of their geometry a comparison of *ϕ*- and *ψ*-dihedral angle values has been made using tri- and disubstituted 1,3,4-benzotriazepin-2-ones **19g** and **5**, benzodiazepinones *R*- and *S*-**1a**, pyrrolobenzodi- and triazepinones **20a** and **7c**, as well as the central residues of ideal normal and inverse *γ*-turns (Figure 4, Table 3).[27] The addition of an N1 substituent on benzotriazepinone **5** had limited influence on the dihedral angles relative to its disubstituted counterpart **19g**. In comparison to the relatively

Table 3. Crystal Analyses with *ϕ* and *ψ* Dihedral Angles Compared with Ideal *γ*-Turn

type of turn	*ϕ*	*ψ*	ref
γ-turn	75	−65	27
Inverse *γ*-turn	−75	65	27
R-**1a**	75	−68	5
S-**1a**	−72	69	5
R-**20a**	−61	57	5
S-**20a**	61	−57	5
5	75	−57	10
19g	74	−56	
7c	−72	27	

similar dihedral angles of benzodiazepinone **1a** and ideal γ-turns ($\phi = 75° \pm 3$, and $\psi = -65° \pm 3$), benzotriazepinones **5** and **19g** deviated more significantly about the ψ torsion angle ($\phi = 75° \pm 1$, and $\psi = -65° \pm 9$). Pyrrolobenzotriazepinone **7c** exhibited a ϕ torsion angle ($-75° \pm 3$) that was more similar to that of an ideal inverse γ-turn than the value in pyrrolobenzodiazepinone *R*-**20a** ($-75° \pm 14$); however, the ψ-torsion angle of **7c** differed by 40° away from that of an ideal inverse γ-turn, significantly more than that of its pyrrolobenzodiazepinone counterpart **20a** ($65° \pm 8$). The dihedral angle values of the aza-amino acid residue in **7c** appear to be more closely related to that of the $i + 2$ residue of a type II′ β-turn ($\phi = -80° \pm 8$, and $\psi = 0° \pm 27$). The aza-amino acid residue nitrogen in the triazepinones adopted nonplanar configurations existing out of the plane formed by its three neighboring atoms by ±0.361(1) Å for benzotriazepinone **19g** and ±0.015(2) Å for pyrrolobenzotriazepinone **7c**. For comparison, the deviation from planarity of the corresponding α-carbons of (*R*)-**1a**, (*S*)-**1a**, and **20a** were, respectively, +0.497(2), −0.500(3), and ±0.441 Å and illustrate that triazepinones **19g** and **7c** are chiral albeit flatter than their diazepinone counterparts.

In conclusion, chemoselective alkylation was key for conception of efficient diversity oriented strategies to make 1,3,4-benzotriazepin-2-one and pyrrolo[1,2][1,3,4]-benzotriazepin-6-one analogues. Without nitrogen protection under relatively mild conditions, benzotriazepinones were made in four to seven steps and 4−60% yields from methyl anthranilate. Using groups suitable for further functionalization, a set of scaffolds was synthesized and shown by X-ray analysis to have potential for γ-turn mimicry. Biological activity of triazepinone library members is under investigation and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03046.

X-ray crystallographic data for **19g** and **7c** (CIF)
Experimental details and spectroscopic characterization for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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