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1,3,5-Trisubstituted 1,4-Diazepin-2-ones

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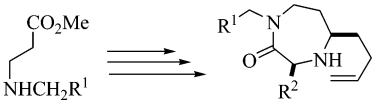
Received July 16, 2007



Six 1,3,5-trisubstituted 1,4-diazepin-2-ones were synthesized by a sequence featuring the cascade addition of vinyl Grignard to *N*-[Boc-aminoacyl]-*N*-alkyl-*β*-amino esters, followed by Boc group removal and annulation by a reductive amination. Relative to the parent sequence employing *N*-Boc-aminoacyl *β*-amino esters to make 3,5-disubstituted heterocycle, the additional *N*-alkyl substituent caused a noticeable acceleration and gave relatively higher yield in the 1,4-diazepin-2-one annulation.

Mimicry of peptide conformations by privileged organic structures has proven effective for identifying candidates for drug development.[1] For example, 1,4-diazepin-2-ones have been suggested to function as privileged structures in medicinal chemistry,[2] because the seven-member diazepinone ring may mimic *β*- and *γ*-turn secondary structures.[3,4] In X-ray structural analyses of 1,4-diazepinones,[5] the dihedral angle geometry of the α-amino acid moiety mimicked that of an ideal reverse *γ*-turn (Figure 1).[6] *γ*-Turn conformations have been suggested to be populated by many biologically active peptides.[7,8] Furthermore, biologically active 1,4-diazepinones include antagonists of the lymphocyte function-associated antigen-1/immunoglobulin superfamily ICAM-1 interaction,[9] the liposidomycin family of antibiotic inhibitors of bacterial peptidoglycan synthesis,[10] as well as anticonvulsants.[11] The development of methodology for the synthesis of 1,4-diazepin-2-ones is thus well merited with potential for creating new biologically active peptide mimics.

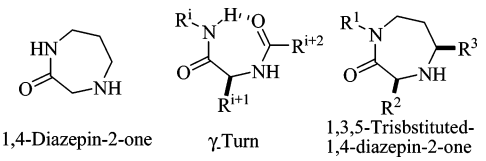


FIGURE 1. Structural relationship of *γ*-turns and 1,4-diazepin-2-ones.

The diazepinone ring has been typically formed from linear precursors by intramolecular reductive amination,[12] lactam formation,[13,14] and transamidation reactions.[15] For example, a library of 1,4-diazepinones was generated by a solid-phase reductive-amination approach.[16] A sequence employing Ugi multicomponent and Mitsunobu annulation reactions has also delivered libraries of 1,4-diazepin-1- and -5-ones.[17] We have reported the synthesis of enantiopure 3,5-disubstituted 1,4-diazepin-2-ones from inexpensive amino acids[5] by a process involving cascade addition of vinyl magnesium bromide to an α-aminoacyl *β*-amino ester to provide a *γ*,*δ*-unsaturated ketone intermediate.[18] Nitrogen deprotection and intramolecular reductive amination provided the 1,4-diazepinone.[5] In light of the relationship of 1,4-diazepin-2-ones and *γ*-turn conformations, the display of substituents on the 1-, 3-, and 5-positions of the heterocycle could respectively mimic the pharmacophores at the *i*, *i* + 1, and *i* + 2 residues in the *γ*-turn (Figure 1). Methodology for introducing substituents at the 3- and 5-positions was achieved by the employment of different α-amino acid starting materials and by the modification of the olefin of the *γ*,*δ*-unsaturated ketone, respectively.[5] Employing α-aminoacyl *β*-amino esters possessing *N*-alkyl substituents, we have now elaborated our synthesis methodology to introduce functionality at the N_1-position of the 1,4-diazepin-2-one. Moreover, the presence of the *N*-alkyl substituent was noted to accelerate ring closure in the reductive amination step and improve the yield of diazepinone.

α-Aminoacyl *β*-amino esters possessing *N*-alkyl substituents were prepared from the coupling of *N*-Boc-α-amino acids to *N*-alkyl *β*-amino esters. Methyl *N*-alkyl *β*-aminopropionate derivatives **2a**−**d** were made by reductive amination of the imine generated from methyl *β*-alaninate **1** and the respective aldehyde with sodium triacetoxy borohydride and 1% acetic acid in DMF.[19] *N*-Alkyl *β*-amino esters **2a**−**d** were then isolated by

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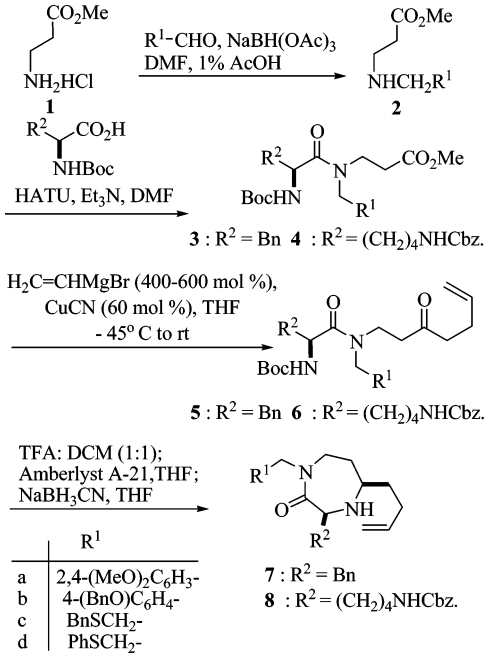
10.1021/jo701467d CCC: $37.00
Published on Web 10/10/2007

SCHEME 1. 1,3,5-Trisubstituted Diazepin-2-one Synthesis



chromatography on silica gel in 70−93% yields (Scheme 1). Some requisite aldehydes were obtained from commercial sources. Benzylthioacetaldehyde was prepared by oxidation of 2-benzylthioethanol.[20] Benzyl and phenylthioacetaldehydes were prepared by alkylation of the respective thiol with 3-bromo-1,1-dimethoxyethane, followed by acetal hydrolysis with 2 N HCl at 80 °C for 24 h.[21] 2,4-Dimethoxy- and 4-benzyloxybenzyl amino esters **2a** and **2b** exhibited identical spectra as previously described.[22,23]

Dipeptides **3a**−**d** and **4a**,**b** were respectively prepared by coupling either Boc-Phe or α-Boc-(ϵ-Cbz)-Lys to secondary amino esters **2** with HATU in DMF,[24] and isolated by silica gel chromatography in 55−90% yield. Lysine was employed because of the importance of constrained ϵ-amino alkyl amino acids,[25] and to examine the influence of a remote carbamate group on the synthesis method. Homoallylic ketones **5a**−**d** and **6a**,**b** were synthesized in 35−60% yields by respectively treating α-aminoacyl *β*-amino esters **3a**−**d** and **4a**,**b** with an excess of freshly prepared vinyl magnesium bromide in the presence of a catalytic amount of CuCN in THF at −45 °C followed by warming to rt.[18] Amides **3**−**6** were typically observed to exist as conformational isomers causing a doubling of NMR signals for the *cis* and *trans* isomers. Spectral data for the minor amide isomer are recorded with an asterisk in the Experimental Section.

Diazepinones **7a**−**d** and **8a**,**b** were respectively synthesized from *γ*,*δ*-unsaturated ketones **5a**−**d** and **6a**,**b** by Boc group removal with a 1:1 TFA:DCM solution, free-basing neutralization of the amine TFA salt with Amberlyste A-21 ion-exchange resin,[26] and reductive amination of the imine intermediate with sodium cyanoborohydride in THF (Scheme 1).

TABLE 1. Isolated Product Yields

% yields	a	b	c	d
amide				
3	77	82	90	77
4	55	63		
ketone				
5	66	50 (78)[a]	60	35
6	62	70		
diazepine				
7	68	85	65	66
8	71	78		

[a] Yield in parentheses accounts for recovered starting material.

Only one diastereoisomer was observed by LCMS analysis of diazepinones **7a**,**b**,**d** and **8a**,**b**; diazepinone **7b** was observed to consist of a 30:1 mixture of diastereoisomers measured by HPLC. The *cis* relative configuration of the newly formed chiral center in diazepinones **7a**−**d** and **8a**,**b** was initially assigned based on our previous study,[5] and confirmed by a NOESY experiment on **7b**, which indicated strong NOE between the C_3 and C_5 protons.

In our previous synthesis of 3,5-disubstituted 1,4-diazepin-2-ones from α-aminoacyl *β*-amino esters, the final amine deprotection/free-basing neutralization/reductive amination sequence gave at best 50% overall yield.[5] Improved overall yield was obtained from performing this sequence on tertiary amides **5** and **6** to form 1,3,5-trisubstituted 1,4-diazepin-2-ones **7** and **8**. For example, a 45% augmentation in overall yield was obtained from performing the Boc removal/reductive amination sequence on *N*-(4-benzyloxylbenzyl) amide **5b** instead of the corresponding secondary amide. The increase in yield was accompanied by a noticeable acceleration in the reductive-amination step, which had usually occurred in 3 to 7 days in the absence of the *N*-alkyl substituent.[5] In the presence of *N*-alkyl substituent, the reductive amination was typically complete after 24 h. The steric effects of *N*-alkylation likely destabilized the *trans* and augmented the population of the *cis* amide isomer, which was necessary for ring formation.[27,28] Tertiary amides exhibited multiple signals indicative of *cis* and *trans* isomers under slow isomerization on the NMR time scale. In addition, the trisubstituted diazepinones **7** and **8** were less polar than their disubstituted counterparts and easier to purify by silica gel chromatography, which may also account for the better yields in the annulation sequence.

The removal of the 1-position substituent was explored by using trisubstituted diazepinone **7** as an alternative strategy for making 3,5-disubstituted diazepinone **10** (Scheme 2). The presence of olefin and secondary amine groups in diazepinones **7c** and **7d** prevented attempts to remove the mercaptoethyl moieties by oxidation of the sulfur to the sulfone,[29−31] followed

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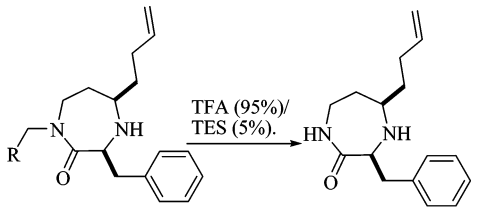
SCHEME 2. 4-Benzyloxybenzylamide Cleavage under Acidic Conditions



7b : R = 4-BnO-C_6H_4-
9 : R = 4-HO-C_6H_4-

10

by β-elimination. Employing diazepinone **7b**, oxidative conditions[32,33] failed similarly to remove the 4-benzyloxybenzyl group and gave back starting material at rt. By using CAN in acetonitrile:water at 100 °C, trace amounts of diazepinone **10** and 1-hydroxybenzyl diazepinone **9** were detected by LCMS analysis; however, decomposition ensued on prolonged exposure of **7b** to these conditions. Alternatively, deprotection of the 4-benzyloxybenzyl group was successful under acidic conditions. Employing a 95:5 TFA/triethylsilane (TES)[34] mixture at rt for 1 day gave some diazepinone **10** and its 1-hydroxybenzyl counterpart **9**. After heating at 80 °C for 3 d, and purification by chromatography, diazepinones **9** and **10** were isolated in 25% and 70% yields.

1,4-Diazepin-2-ones with substituents at the 1-, 3-, and 5-positions of the heterocycle have been synthesized by an effective method featuring the copper-catalyzed cascade addition of vinyl Grignard reagent to *N*-alkyl *N*-Boc-α-aminoacyl β-amino esters **3a**−**d** and **4a**,**b**. Trisubstituted diazepinones **7a**−**d** and **8a**,**b** were respectively synthesized from phenylalanine and lysine to provide diversity at the 3-position. Furthermore, a variety of 1-position substituents were introduced by reductive aminations of different aldehydes onto the β-amino ester precursor. A cursory study of the removal of the 1-position thioethyl and benzyl amide substituents demonstrated that the 4-benzyloxybenzyl group may be cleaved under acid conditions to provide an alternative route to 3,5-disubstituted 1,4-diazepin-2-ones. A study to extend this approach for generating a library of diazepinones is currently in progress in our laboratory.

Experimental Section

General Protocol 2, Synthesis of Tertiary Amides 3a−d and 4a,b. *N*-Boc-α-Amino acid (*N*-(Boc)Phe or *N*-(Boc)-ϵ-(Cbz)Lys, 2.2 mmol) and HATU (2.2 mmol) were placed in a 100-mL round-bottomed flask, dissolved in DMF (0.4 M), cooled to 0 °C, treated with DIEA (4.4 mmol), stirred for 10 min under argon, and treated with a solution of secondary amine **2** (2 mmol) in DMF (0.8 M). The reaction mixture was stirred overnight at room temperature. The solvent was concentrated on a rotary evaporator, and the reduced volume was partitioned between an aqueous HCl solution (10%, 50 mL) and ether (50 mL). The aqueous phase was separated and extracted with ether (3 × 20 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 30 mL) and brine (2 × 50 mL), dried over magnesium sulfate, filtered, and evaporated to a residue, which was purified on silica gel by using the specified solvent as eluant to afford respectively tertiary amide **3a**−**d**, **4a**, or **4b**.

(2*S*)-Methyl *N*-(2,4-dimethoxybenzyl)-*N*-[(Boc)phenylalaninyl]-β-alaninate (3a). A colorless oil was prepared from amine **2a** (2 mmol, 0.506 g) according to the general protocol 2 and isolated in 77% yield after purification on silica gel eluting with 40% EtOAc in hexane (R_f 0.4, 40% EtOAc in hexane). ^{1}H NMR (1.6:1 isomer ratio, 400 MHz, CD_3OD) δ 1.39 (s, 9H), 1.4* (s, 9H), 2.4* (m, 2H), 2.45 (m, 2H), 2.90−2.93 (m, 2H), 2.95−2.95* (m, 2H), 3.42−3.50 (m, 3H), 3.59* (s, 3H), 3.60 (s, 3H), 3.74 (s, 6H), 3.78* (s, 6H), 4.24−4.70 (m, 2H), 5.0 (br d, 1H), 6.41−7.20 (m, 8H). ^{13}C NMR (2:1 isomer ratio, 100 MHz, CD_3OD) δ 172.4*, 172.0, 171.9, 171.3*, 160.7, 160.2*, 158.2, 158.1*, 155.6*, 155.2, 136.7*, 136.5, 129.5, 129.3, 128.9, 126.2, 126.0*, 116.4*, 115.8, 103.9*, 103.8, 97.9, 97.4*, 78.8, 78.7, 54.2, 51.7, 46.7, 42.6*, 42.2*, 41.4, 38.8*, 38.2, 32.2, 31.1, 27.1. $[\alpha]^{20}_D$ −7.1 (*c* 0.008 M, $CHCl_3$). HRMS (EI) *m*/*z* 523.2425 $[M + Na]^+$; calcd for $C_{27}H_{36}N_2O_7Na$ 523.2429.

General Protocol 3, Synthesis of Ketones 5a−d and 6a,b. A suspension of CuCN (0.3 mmol, 60 mol %) in THF (2 mL of THF per 1 mmol of CuCN) was cooled to −45 °C, treated with vinyl magnesium bromide (3 mmol, 600 mol %, 1 M) over 10 min, stirred for 1 h, treated with a solution of the corresponding ester **3a**−**d**, **4a**, or **4b** (0.5 mmol, 100 mol %) in THF (0.1 M), stirred for 2 h at −45 °C, and warmed to room temperature for an additional 30 min. The reaction mixture was cooled to 0 °C, treated with a saturated ammonium chloride solution (30 mL), and shaken vigorously for 20 min. The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 50 mL) or EtOAc. The combined extracts were washed with saturated sodium bicarbonate solution (50 mL), pH 6.8 phosphate buffer (50 mL), and brine (2 × 50 mL), dried over magnesium sulfate, and concentrated under vacuum. The crude product was purified by column chromatography with an eluant of EtOAc in hexane as specified for each compound. Evaporation of the collected fractions afforded the respective ketone **5a**−**d**, **6a**, or **6b.**

(2*S*)-*N*′-(2,4-Dimethoxybenzyl)-*N*′-1-(3-oxohept-6-enyl)-*N*-(Boc)phenylalaninamide (5a). A colorless oil was prepared from ester **3a** (0.5 mmol, 0.25 g) according to the general protocol 3, purified on silica gel eluting with 30% EtOAc:hexane (R_f 0.2, 30% EtOAc:hexane), and isolated in 66% yield: ^{1}H NMR (1.3:1 isomer ratio, 400 MHz, CD_3OD) δ 1.39 (s, 9H), 1.42* (s, 9H), 2.16−2.53 (m, 6H), 2.89−2.92 (m, 2H), 3.33−3.41 (m, 2H), 3.42−3.76* (m, 2H), 3.77 (s, 6H), 4.86 (s, 2H), 4.93−5.03 (m, 3H), 5.76−5.80 (m, 1H), 6.41−7.23 (m, 8H). ^{13}C NMR (2:1 isomer ratio, 100 MHz, CD_3OD) δ 210.0, 209.2*, 173.7*, 173.2, 161.9, 161.4*, 159.4, 159.2*, 156.8, 156.5*, 137.9, 137.8*, 130.5, 130.4*, 130.2, 130.1*, 129.8, 129.0, 128.9, 127.4, 127.2, 117.6, 117.0, 115.1, 99.0*, 98.6, 80.0*, 79.9, 55.4*, 55.3, 47.6, 42.5, 42.2, 41.9, 41.6, 40.7, 39.9*, 28.2, 28.1*. $[\alpha]^{20}_D$ −7.82 (*c* 0.011 M, $CHCl_3$). HRMS (EI) *m*/*z* 525.2957 $[M + H]^+$; calcd for $C_{30}H_{40}N_2O_6$ 525.2959.

General Protocol 4, Synthesis of 1,3,5-Trisubstituted 1,4-Diazepinones 7a−d and 8a,b. Ketone **5a**−**d**, **6a**, or **6b** (0.095 mmol, 100 mol %) was dissolved in a 1:1 TFA/DCM solution (4 mL), stirred for 10 min, and evaporated to a residue. The residue was dissolved in THF (5 × 10^{-3} M), treated with supported free tertiary amine Amberlyste A-21 resin (1.9 mmol, 2000 mol %, prewashed with methanol, THF, DCM, and dried under high vaccum for 2 h), stirred for 2 h, filtered, and treated with a sodium cyanoborohydride solution in THF (0.475 mmol, 500 mol %, 1 M). The reaction mixture was stirred overnight under argon atmosphere. After completion of the reaction was indicated by TLC, the solvent was concentrated on a rotary evaporator, and the remainder was partitioned between a saturated $NaHCO_3$ solution (20 mL) and ethyl acetate (20 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 10 mL). The

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combined organic phase was dried over magnesium sulfate, filtered, and evaporated to a residue, which was purified further as specified below.

(3*S*,5*S*)-3-Benzyl-5-but-3-enyl-1-(2,4-dimethoxybenzyl)[1,4]-diazepin-2-one (7a). A colorless oil was prepared from ketone **5a** (0.095 mmol, 0.05 g) according to the general protocol 4, purified on silica gel eluting with 20% EtOAc:hexane (R_f 0.22, 20% EtOAc:hexane), and isolated in 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18−1.34 (m, 3H), 1.62 (m, 1H), 1.78 (m, 2H), 2.50 (m, 1H), 2.83−2.89 (q, J = 8, 1H), 3.28−3.33 (m, 2H), 3.57−3.60 (m, 2H), 3.81 (s, 6H), 4.51−4.68 (q, J = 16, 2H), 4.7−4.84 (m, 2H), 5.56−5.57 (m 1H), 6.46−6.49 (m, 2H), 7.25−7.35 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 159.8, 158.1, 138.9, 137.5, 130.8, 129.0, 128.1, 126.0, 118.0, 114.4, 103.9, 97.9, 60.6, 59.8, 55.0, 55.9, 46.9, 45.2, 37.8, 35.7, 35.3, 29.4. $[\alpha]^{20}_D$ −7.6 (*c* 0.018, $CHCl_3$). HRMS (EI) *m*/*z* 409.2491 $[M + H]^+$; calcd for $C_{25}H_{32}N_2O_3$ 409.2486.

(3*S*,5*S*)-3-Benzyl-5-(but-3-enyl)-1,4-diazepin-2-one (10) and 3-Benzyl-5-(but-3-enyl)-1-(4-hydroxybenzyl)-1,4-diazepin-2-one (9). 4-Benzyloxybenzyl amide **7b** (12 mg, 0.026 mmol) was placed into a 10-mL three-necked flask, equipped with a water condenser, treated with 3 mL of a mixture of TFA/TES (95:5), and heated with an oil bath to a bath temperature of 80 °C for 72 h. The progress of the reaction was followed by LCMS analysis, by removing aliquots from the mixture and injecting directly onto a Gemini column (C18 110 A, 50 × 4.60 mm, 5 μm) with an eluant of 20−80% acetonitrile:H_2O buffered with 0.1% TFA. After 72 h, a 75:25 ratio was observed of two peaks eluting at retention times of 3.49 and 4.24 min corresponding to 3,5-disubstituted diazepinone **10** and 4-hydroxybenzylamide **9**. The solution was cooled to room temperature, and concentrated under vacuum to a residue, which was purified on silica gel with 50% EtOAc:hexane as eluent, to afford diazepinone **9** (2.4 mg, 25% yield) as a colorless oil: R_f 0.25 (50% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29−1.47 (m, 2H), 1.6−1.93 (m, 4H), 2.02−2.22 (m, 4H), 3.20−3.24 (br d, 1H), 3.75−3.82 (br q, 1H), 4.50−4.62 (m, 2 H), 5.02−5.10 (m, 2H), 5.75−5.83 (m, 1H), 6.70−7.39 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 165.7, 156.5, 135.8, 135.6, 129.0, 128.8, 127.8, 126.5, 126.2, 114.8, 114.6, 60.4, 58.6, 43.9, 34.7, 32.0, 30.1, 28.6. HRMS (EI) *m*/*z* 365.2228 $[M + H^+$; calcd for $C_{23}H_{28}N_2O_{23}$ 365.2224]. $[\alpha]^{20}_D$ −7.0 (c 0.014, $CHCl_3$). Second to elute was diazepinone **10**[5] on changing the solvent system to 5% methanol in DCM. After evaporation of the combined collected fractions, the residue was dissolved in 10% HCl solution followed by freeze drying to afford diazepinone **10**[5] (5.0 mg, 70% yield): mp 138−140 °C; R_f 0.32 (5% MeOH/DCM), $[\alpha]^{20}_D$ −35.0 (*c* 0.008, DMF). HRMS (EI) *m*/*z* 259.1808 $[M + H]^+$; calcd for $C_{16}H_{23}N_2O$ 259.1804. Lit.[5] mp 138−140 °C; $[\alpha]^{20}_D$ −35.6 (*c* 0.008, DMF).

Acknowledgment. The authors gratefully acknowledge financial support from the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Fonds Québécois de la Recherche sur la Nature et les Technologies (FQRNT).

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

JO701467D