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Synthesis of Benzodiazepine β-Turn Mimetics by an Ugi 4CC/Staudinger/Aza-Wittig Sequence. Solving the Conformational Behavior of the Ugi 4CC Adducts

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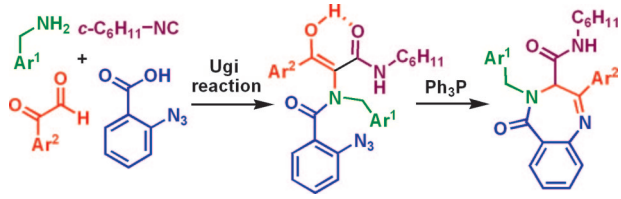

5-Oxobenzo[*e*][1,4]diazepine-3-carboxamides were synthesized by sequential Ugi reaction−Staudinger/aza-Wittig cyclization. The pseudopeptidic backbone of the new benzodiazepine derivatives superimposed well with type I, I′, II, and II′ β-turn motifs. The intermediate Ugi adducts were characterized as two conformers of the enol form by the correlation between ^{1}H NMR spectra and X-ray diffraction structures of model compounds.

The concept of privileged structures constitutes a fruitful approach to the discovery of novel biologically active molecules. Privileged structures are molecular scaffolds with versatile binding properties that are able to provide potent and selective ligands for different biological targets, also exhibiting good druglike properties.[1] Therefore, privileged structures have been successfully exploited for the discovery and optimization of novel bioactive molecules. Benzodiazepines were introduced into clinical practice for the treatment of anxiety and sleep disorders due to their specific interaction with the allosteric site to the benzodiazepine recognition site of the mammalian brain,[2] but the pharmacological spectrum of activity for benzodiazepine site ligands is much wider, being recognized as the first privileged structures as a result of their capability of acting as small-molecule inhibitors in protein−protein interactions.[3] Protein−protein interactions are ubiquitous, essential to almost all known biological processes, and offer attractive opportunities for the development of small molecules that mimic surfaces of protein-recognition motifs, acting as protein-complex antagonists. The interaction between the peptide ligands and their receptor targets commonly involves β-turn structures;[4] therefore, the synthesis of peptidomimetics capable of mimicking β-turn structures has gained high interest for the discovery of new therapeutic agents. Benzodiazepines have been proposed several times as β-turn mimetics,[5] but a landmark discovery in this field was asperlicin,[6] a benzodiazepine derivative from microbial fermentation that has been modified into a wide variety of benzodiazepine derivatives which act as selective antagonists of peptide hormone cholecystokinins CCK1 and CCK2.[7] All these derivatives have in common a voluminous polar group in the 3-position of the original 1,4-benzodiazepine-5-one moiety, a feature that could be easily accessed by a Ugi 4CC condensation, a useful reaction for the benzodiazepine synthesis.[3a,8] The 2-azidobenzoic acid[9] is a common starting material for the synthesis of benzodiazepines,[10] usually employed in aza-Wittig[6d,10a−c,11] or azide−alkyne cycloaddition[8i] schemes, which

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can be also combined with Ugi reactions.[8i,12] We have recently shown that the sequences of classical Ugi or Passerini isocyanide multicomponent reactions, followed by postcondensation transformations, constitute extremely powerful synthetic tools for the preparation of structurally diverse complex molecules, among them heterocyclic compounds with elaborate substitution patterns, constrained peptides, and peptide mimetics.[13] As a new contribution of this methodology, we want to report in this paper a new synthesis of β-turn mimetic 5-oxo-benzo[*e*][1,4]diazepine-3-carboxamides by the Ugi reaction between arylglyoxals, *para*-substituted benzylamines, cyclohexyl isocyanide, and 2-azidobenzoic acid, followed by a Staudinger/aza-Wittig cyclization of the Ugi products in the presence of triphenylphosphine.

Following the most common procedure, the corresponding benzylamine **1a**−**e** (1 equiv) was added to a solution of arylglyoxal **2a**−**h** (1 equiv) in methanol, and the mixture was stirred for 1 h.[14] Cyclohexyl isocyanide **3** (1 equiv) and 2-azidobenzoic acid[9] **4a** (1 equiv) were then added consecutively to the imine solution, and the mixture was stirred at room temperature for 1 h until complete precipitation of the Ugi adducts. The mixture was chilled, and the resulting solid products **5a**−**y** were then filtered, recrystallized, and characterized by the usual spectroscopic and analytical techniques. In turn, compounds **5a**−**y** (1 equiv) and triphenylphosphine (1.5 equiv) were stirred under nitrogen in toluene for 24 h at room temperature. Then the solvent was evaporated, and the residue was purified by column chromatography using mixtures of hexane and ethyl acetate as eluent. Solid products **6a**−**y** were obtained as colorless crystals and characterized by the usual spectroscopic and analytical techniques (Scheme 1 and Table 1). From them, compound **6f** was recrystallized in ethanol, giving suitable crystals for X-ray diffraction, confirming structure **6f** (Figure 1) as a racemic mixture. In the solid state, the seven-membered ring of the benzodiazepine system adopts a boat conformation, also found for other 3,4-dihydrobenzo[*e*][1,4]-diazepin-5-one examples.[15]

The crystal packing of **6f** is supported by intermolecular hydrogen bonds between the benzodiazepine carbonyl O[1] and the carboxamide hydrogen N[1]H of an adjacent molecule (Figure S1 in the Supporting Information). The all-trans conformation of the three substituents in the 2, 3, and 4 positions induces the carboxamide group in the 3-position to adopt a rigidified axial conformation that places the two pseudopeptidic carbonyl groups at a distance of 3.1 Å, similar to the distance

SCHEME 1

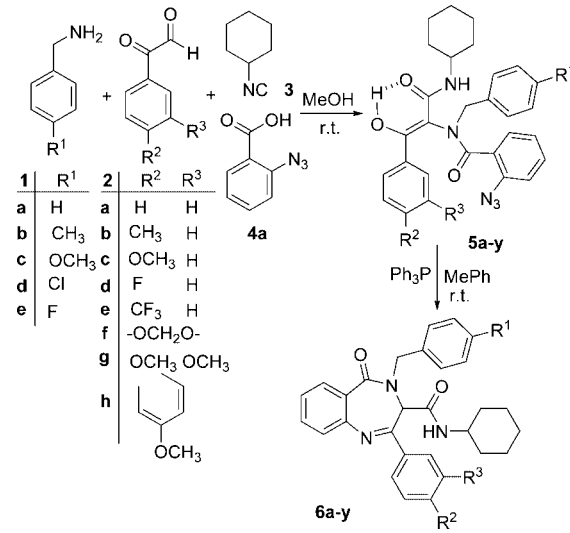
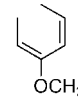


TABLE 1. Complete List of Reagents and Products of Scheme 1

Entry	R^1	R^2	R^3	**5** (%)	F_1/F_2	**6** (%)
a	H	H	H	59	65/35	71
b	H	CH_3	H	60	58/42	99
c	CH_3	H	H	53	67/33	99
d	CH_3	CH_3	H	60	58/42	95
e	CH_3	OCH_3	H	72	55/45	99
f	CH_3	F	H	50	70/30	83
g	CH_3	-OCH_2O-		59	67/33	90
h	CH_3	OCH_3	OCH_3	68	52/48	99
i	OCH_3	H	H	54	69/31	68
j	OCH_3	CH_3	H	53	58/42	99
k	OCH_3	OCH_3	H	50	55/45	91
l	OCH_3	F	H	45	70/30	96
m	OCH_3	-OCH_2O-		62	71/29	59
n	Cl	H	H	62	64/36	60
o	Cl	OCH_3	H	52	57/43	95
p	Cl	F	H	53	70/30	99
q	Cl	-OCH_2O-		46	67/33	91
r	F	H	H	57	70/30	99
s	F	CH_3	H	90	60/40	85
t	F	OCH_3	H	75	55/45	99
u	F	F	H	78	73/27	94
v	F	CF_3	H	56	80/20	88
w	F	-OCH_2O-		71	69/31	89
x	F	OCH_3	OCH_3	78	51/49	64
y	F			72	68/32	65

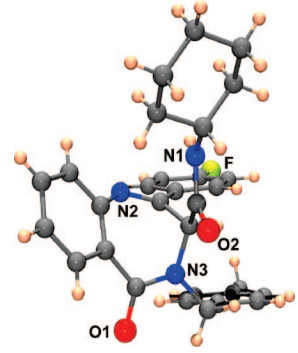


FIGURE 1. X-ray diffraction structure of **6f** (one enantiomer shown).

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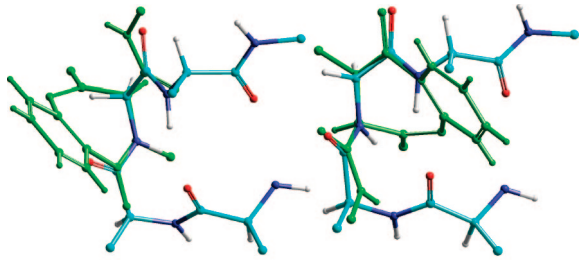

FIGURE 2. Two modes of superimposition of **6f** (one enantiomer, green) to a type I′ β-turn motif (lateral chains of both structures were not shown). (A) Parallel superimposition of the peptide backbone of both structures. (B) Antiparallel superimposition by fitting of the carbonyl groups.

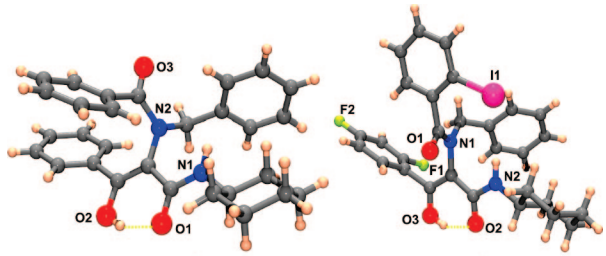

FIGURE 3. X-ray diffraction structures of **5za** and **5zd** (one independent molecule).

found in most β-turn motifs (3.2−3.3 Å).[16] To find out how well the benzodiazepine ring of **6f** mimics a β-turn, we superimposed the β-turn mimetic backbone part from both enantiomers found in the crystal cell of **6f** with different crystallographic β-turn protein examples, by fitting the two carbonyl groups from **6f** to the two central amino acid backbones from every selected β-turn motif. Thus, δ antigen, having a type I β-turn, LDL receptor module 5, having a type II β-turn, acetyl-CoA carboxylase, having a type I′ β-turn, and erabutoxin B, having a type II′ β-turn, were used.[17] This revealed that the backbone of the β-turn in every enantiomer of **6f** superimposed well with the two central amino acid backbone of type-I, I′, II, and II′ β-turn motifs (Figure 2 and Figures S2−S4 in the Supporting Information) by performing a parallel or, alternatively, an antiparallel superimposition of the peptide chains from both structures until perfect fitting of all four carbonyl groups. Both modes of approach, each having some electrostatic or steric advantages, may be useful for new drug design, in combination with the easy availability of the synthetic approach and the large scope of the reaction.

Previous α-amido-β-ketoamides, obtained by Ugi reactions, existed as mixtures of keto and enol forms.[18] In our case, the Ugi products **5a**−**y** were obtained exclusively as mixtures of two different enol forms with no trace of the keto tautomer, on the basis of NMR spectra in $CDCl_3$. This fact had no consequence on their reactivity with triphenylphosphine but complicated the spectral assignment by NMR because of the

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SCHEME 2

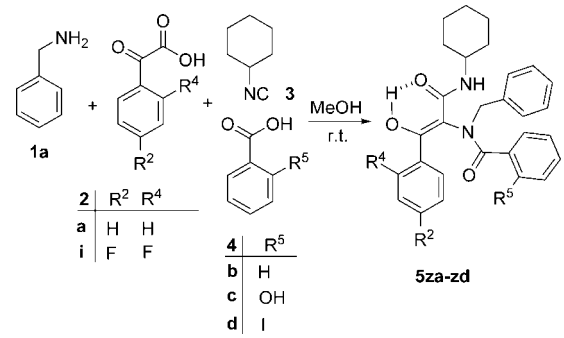

TABLE 2. Complete List of Reagents and Products of Scheme 2

entry	R^2	R^4	R^5	**5** (%)	E_1/E_2
za	H	H	H	69	<1/99
zb	H	H	OH	83	<1/99
zc	H	H	I	74	70/30
zd	F	F	I	71	90/10

large number of peaks found in the spectra and introduced uncertainty in the structure because of the various types of enol forms that can exist from the **5a**−**y** structures. COSY, HMQC, and HMBC experiments on a representative example **5t** (see the Supporting Information) permitted the complete assignation of peaks to every one of the two enol forms but did not afford the final enol structures. We noticed that the nature of R^1 did not affect the E_1/E_2 proportion, but electron attractor substituents in R^2 favor a higher abundance of the E_1 form better than electron donor substituents in R^2/R^3 favor the E_2 form. In this way, a CF_3 group in R^2 gave an E_1/E_2 proportion of 80/20 between both enols **5v**. The ^{1}H NMR spectrum of this compound **5v** showed two characteristic enolic OH signals at δ 15.6 and 15.2, whose integration permitted determination of the E_1/E_2 proportion (Figure S5 in the Supporting Information). The CH of the keto form, which should appear at δ 6.0 in ^{1}H NMR and δ 65 in ^{13}C NMR, was not observed. The benzylic CH_2 appeared as two pairs of doublets; for E_1, the doublets appeared centered at δ 4.03 and 3.94, but for E_2 the CH_2 doublets appeared at δ 5.73 and 3.85, separated by roughly 2 ppm, a very uncommon feature. These differences should correspond to two benzyl groups surrounded by different environments, and this characteristic permitted assignement of E_1/E_2 mixtures of conformers. In addition, the ^{13}C NMR of **5v** showed two peaks at the enolic double bond region, as well as two differently heighted benzylic methylene and cyclohexyl methyne carbon signals (Figure S6 in the Supporting Information). Careful crystallization of **5a**−**y** samples did not get crystals suitable for X-ray diffraction. In order to properly describe the structure of **5a**−**y** we performed some additional Ugi reactions between benzylamine **1a**, arylglyoxals **2a** and **2i**, and unsubstituted or ortho-substituted benzoic acids **4b**−**d** to get samples of every type of enol (Scheme 2 and Table 2).

Compounds **5za**−**zb**, corresponding to a single enol E_1 from their ^{1}H NMR spectra in $CDCl_3$, and **5zd**, which was shown to be a preferred enol E_2 by NMR ($CDCl_3$), were repeatedly recrystallized in *i*-PrOH (**5za**−**zb**) or EtOH (**5zd**), from which single-crystal X-ray diffraction structures of the major conformers were obtained (Figure 3 and Figure S7 in the Supporting Information). Structure **5za**, where there is no ortho substitution at the benzoyl moiety, showed a six-center quasi-cyclic enol supported by a hydrogen bond between O1 and the hydrogen

from the enol O2. The benzamide moiety, containing atoms O3 and N2, was located orthogonally to the quasicyclic enol, placing the carbonyl group at the top of the plane but pointing to the opposite direction of both the enol and the carboxamide carbonyl groups. The conformation is similar to a known example.[18] This conformation places the benzyl group *syn* to the carbonyl group; therefore, every benzylic proton undergoes a different environment, giving rise to ^{1}H NMR doublets centered at δ 5.83 and 3.94 in $CDCl_3$ and δ 5.41 and 4.38 in CD_3OD, proving that this is the preferred conformation independently of the solvent. Thus, the conformer E_2 is assigned to this conformation.

Structure **5zd**, where there is a voluminous iodine atom at the ortho position on the benzoyl moiety, showed a similar six-center quasicyclic enol supported by a hydrogen bond between O3 and the hydrogen from the enol O2. An additional hydrogen bond between the benzamide carbonyl group and the hydroxyl group of a molecule of ethanol, the solvent of crystallization, was also found. The benzamide moiety, containing atoms O1 and N1, was located orthogonally to the quasicyclic enol, placing the carbonyl group at the top of the plane, but this time pointing in the same direction of both the enol and the carboxamide carbonyl groups. This conformation places the benzyl group anti to the neighbor carbonyl group; therefore, the environment of every benzylic proton becomes more uniform, giving rise to ^{1}H NMR doublets centered at δ 4.21 and 3.72 in both $CDCl_3$ (for the main conformer) and CD_3OD, proving that this is the preferred conformation independently of the solvent. Thus, the conformer E_1 is assigned to this conformation. Therefore, the two conformations depended strongly on the aryl substitution and the presence of hydrogen bonds (for an additional case **5zb**, see the Supporting Information) The behavior of these compounds is quite unusual but is well described by the correlation between the crystal conformation and the ^{1}H NMR signals of the benzyl methylene protons in the syn (E_2) or anti (E_1) position with respect to the carbonyl oxygen, giving the assignation of conformational structures in Tables 1 and 2.

In conclusion, we have reported a new synthesis of 5-oxo-benzo[*e*][1,4]diazepine-3-carboxamides by a Ugi 4CC/Staudinger/aza-Wittig sequence of reactions. The intermediate Ugi adducts have been characterized as two opposite conformers of the enol form, on the basis of the correlation between the ^{1}H NMR spectra and the X-ray diffraction structures of selected model compounds. The pseudopeptidic backbone of the new benzodiazepine derivatives superimposed well with type-I, I′, II, and II″ β-turn motifs which, in combination to the easy availability of the synthetic approach and the large scope of the reaction, makes it useful for new drug design.

Experimental Section

Synthesis of 6a. 1a (132 mg, 1.23 mmol) was added to **2a** (165 mg, 1.23 mmol) in MeOH (10 mL), the solution was stirred for 1 h at rt, **3** (134 mg, 1.23 mmol) and **4a** (201 mg, 1.23 mmol) were added, and the mixture was stirred for 1 day. Workup of the solid gave **5a**: 360 mg, 59%; colorless crystals (iPrOH/iPr_2O); mp 169−170 °C. Then, PPh_3 (157 mg, 0.6 mmol) was added under N_2 to a solution of **5a** (198 mg, 0.4 mmol) in toluene (10 mL); and the mixture was stirred for 24 h at rt. Workup and chromatography (hexane/AcOEt) gave **6a**: 128 mg, 71%; colorless crystals (hexane/AcOEt); mp 168−169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, J = 1.5 Hz, J = 7.9 Hz, 1H), 7.72−7.69 (m, 2H), 7.45−7.16 (m, 11H), 5.22 (s, 1H), 5.15 (d, J = 14.3 Hz, 1H), 5.03 (d, J = 8.4 Hz, 1H), 4.43 (d, J = 14.3 Hz, 1H), 3.16−3.06 (m, 1H), 1.38−0.89 (m, 8H), 0.50−0.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 164.5, 164.4, 146.2, 137.8, 136.4, 132.0, 131.0, 130.6, 129.2, 128.9, 128.7, 128.5, 127.5, 127.1, 126.1, 125.8, 59.2, 52.7, 47.9, 32.2, 32.0, 25.1, 24.5, 24.3; IR (KBr) $\tilde{\nu}$ 3297, 1652; EIMS *m*/*z* 451 (M^+, 8), 326 (100); HRMS (EI) calcd for $C_{29}H_{29}N_3O_2$ 451.2260, found 451.2260. Anal. Calcd for $C_{29}H_{29}N_3O_2$: C, 77.13; H, 6.47; N, 9.31. Found: C, 76.98; H, 6.59; N, 9.41.

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Supporting Information Available: Crystal packing of **6f**, superimposition images of **6f** to type I, II, and II′ β-turn motifs, and the commented X-ray diffraction structure of **5zb**. General procedures, spectral and analytical data, crystal structure determinations, and spectra of all new compounds. Crystallographic information files (CIF) of compounds **6f**, **5za**, **5zb**, and **5zd** (CCDC 710906-710909). Superimposition models of **6f** to type I, I′, II, and II′ β-turn motifs. This material is available free of charge via the Internet at http://pubs.acs.org.

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