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Synthesis of Pyridodiazepinediones by Using the Ugi Multicomponent Reaction

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Benzodiazepines show a broad spectrum of biological activities. In an ongoing effort to extend molecular diversity in this type of systems, we developed a strategy for synthesizing 3,4-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepine-2,5-dione compounds starting from 2-hydroxynicotinic acid and by using an Ugi reaction as a key step in the synthesis. We opted to use 2-isocyanophenyl benzoate instead of Armstrong's convertible isocyanide in this multicomponent reaction.

Introduction

Benzodiazepines show a broad spectrum of biological activities.[1] They are widely used as antianxiety drugs that help to relieve nervousness, tension and other symptoms by slowing the central nervous system. Valium (Diazepam) and Xanax (Alprazolam) are two of the most used and best known benzodiazepines (Figure 1).

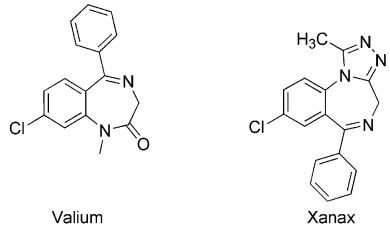

Figure 1. Valium and Xanax.

Results and Discussion

Large numbers of both natural and synthetic benzodiazepines have been reported. In an attempt to extend the molecular diversity in this type of systems, we developed a general strategy for preparing 3,4-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepine-2,5-dione compounds **1** (Figure 2), since only a few of these derivatives with a pyridine ring are known to date.[2]

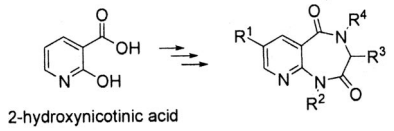

Figure 2. Conversion of 2-hydroxynicotinic acid to 3,4-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepine-2,5-dione compounds.

A high degree of functionalization was one of the goals we set ourselves when developing this synthesis, together with easy access of starting materials.

In our synthetic sequence the commercially available 2-hydroxynicotinic acid was converted to target compounds **1** (Figure 2) bearing various substituents R^1 to R^4 (see Table 1). The planned key step in the synthesis was an Ugi reaction,[3] which is widely used to synthesize benzodiazepine-type compounds.[4]

Table 1. Yields for Ugi and Suzuki reactions.

Product	Starting material	R^1	R^2	R^3	R^4	Yield [%]
1a	**2b**	Ph	Me	Pr	Bn	81
1b	**2c**	Ph	Bu	Pr	Bn	83
1c	**2f**	Ph	Bn	Pr	Bn	66
1d	**2f**	4-$MeOC_6H_4$	Bn	Pr	Bn	69
1e	**2f**	3-FC_6H_4	Bn	Pr	Bn	48
1f	**2f**	3-ClC_6H_4	Bn	Pr	Bn	61
1g	**2e**	3-$O_2NC_6H_4$	Bn	Ph	Bn	65
2a	**4a**	Br	H	Pr	Bn	22
2c	**4c**	Br	Bu	Pr	Bn	24
2d	**4c**	Br	Bu	Pr	Bu	28
2e	**4b**	Br	Bn	Ph	Bn	21
2f	**4b**	Br	Bn	Pr	Bn	48
2g	**4c**	Br	Bu	Ph	Bn	19

A general retrosynthetic analysis of the pyridodiazepinediones **1** is presented in Scheme 1. The R^1-substituted pyridodiazepinediones **1** could be prepared by a Suzuki cross-coupling reaction on bromo derivatives **2**. An Ugi multicomponent reaction on nicotinic acid derivatives **4** by using 2-isocyanophenyl benzoate as the isocyanide can yield in-

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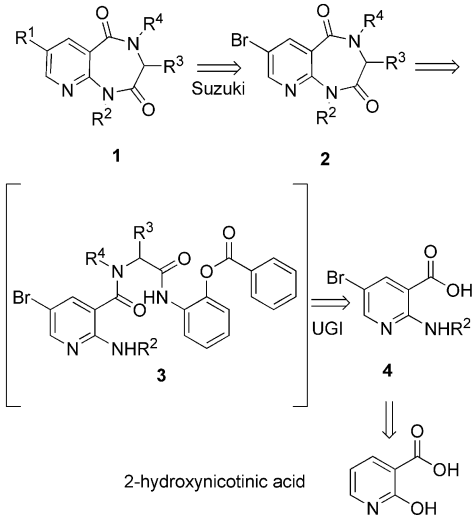
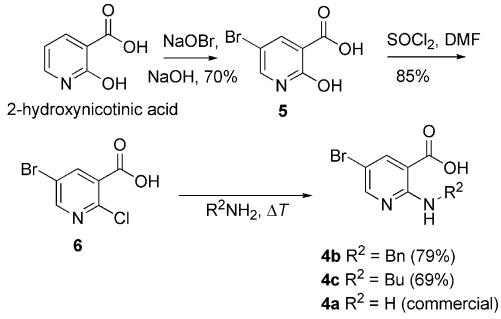
termediate **3**, which cyclises into the desired 3,4-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepine-2,5-dione core structure **2**. When R^2 in precursor **2** is a hydrogen atom, an extra substitution step is required to introduce the corresponding N-substituent. Compound **4** in turn can be prepared from 2-hydroxynicotinic acid in three steps.



Scheme 1. Retrosynthetic analysis.

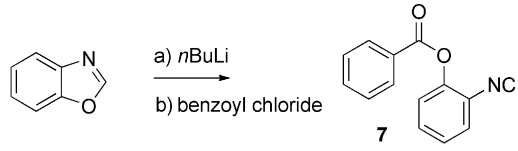
The first step in the synthesis is the bromination of 2-hydroxynicotinic acid,[5] which according to a literature procedure[5a] produced 5-bromo derivative **5** in yields of about 70% (Scheme 2). This halogen is needed for the final functionalization of the pyridine core.



Scheme 2. Synthesis of intermediates **4**; compound **4a** (R^2 = H) is commercially available.

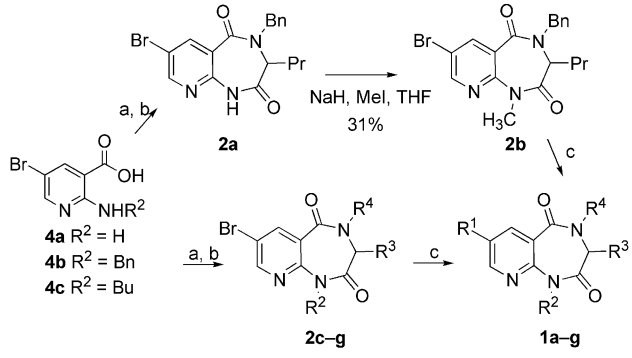
Substitution of the 2-hydroxy group in pyridine compound **5** by reaction with thionyl chloride afforded the corresponding 2-chloro derivative **6**.[5b,5c] Next, compound **6** was heated with benzylamine or butylamine to provide the corresponding 2-aminopyridine derivatives **4b** and **4c**. Compound **4a** with an unsubstituted 2-amino group is commercially available.

In the next step, a multicomponent Ugi reaction was applied to compounds **4b** and **4c** to introduce both R^3 and R^4 groups, and the resulting crude intermediates **3** are submitted to base-catalyzed ring closure. The Ugi reaction was carried out by using benzyl- or butylamine, respectively, as the amine component and benzaldehyde or butanal as the aldehyde component. For the desired cyclization step, a convertible isocyanide is required in the procedure. Normally, 1-isocyanocyclohexene (Armstrong's convertible isocyanide) is used for the synthesis of benzodiazepines.[6] However, due to reported synthetic and stability problems with this compound (also occurring in our hands), other classes of convertible isocyanides were also applied.[7] We finally opted to use 2-isocyanophenyl benzoate (**7**), which was prepared from benzoxazole according to the method reported by Pirrung and Ghorai (Scheme 3).[7b]



Scheme 3. Synthesis of 2-isocyanophenyl benzoate.

Intermediate **3**, the initial product of the Ugi reaction, could not be purified. Hence, the crude mixture was dried and heated with KO*t*Bu in dry THF[7a] to provide the pyridodiazepinedione core structure **2** (Scheme 4). The yields over the two steps were very moderate [due to side products and extensive chromatography (in some cases up to three purifications)]; however, it was possible to obtain the desired compounds in a pure form. The poor yield of the Ugi reaction is probably due to the use of **4** without a protective group, such as Boc or Fmoc.[8]



Scheme 4. (a) R^4NH_2, R_3CHO, MeOH, 2-isocyanophenyl benzoate; (b) KO*t*Bu, THF; (c) $R^1B(OH)_2$, 5 mol-% $Pd[P(Ph_3)]_4$, 2 N Na_2CO_3.

When R^2 is a butyl or benzyl group, only one extra step involving a Suzuki cross-coupling reaction was needed to yield the final products **1**. This conversion was achieved by heating a mixture of compound **2** with 1.1 equiv. of an arylboronic acid, a 2 M Na_2CO_3 solution and a catalytic amount of $[Pd(PPh_3)_4]$ at 80 °C in toluene. Products **1** were obtained in yields ranging from 48 to 83% (Scheme 4).

For **2a**, an extra step is needed, which involves methylation of the NH group by using NaH and MeI. In a final step, a Suzuki reaction is applied to **2b** to afford the tetrasubstituted pyridodiazepinedione structure **1a** (Scheme 4, Table 1).

Transparent plate crystals of **2a** were obtained. A small single crystal was measured by X-ray crystallography (Figure 3). The crystal structure clearly shows one conformation for compound **2a** with the propyl side chain dispositioned in an axial fashion.

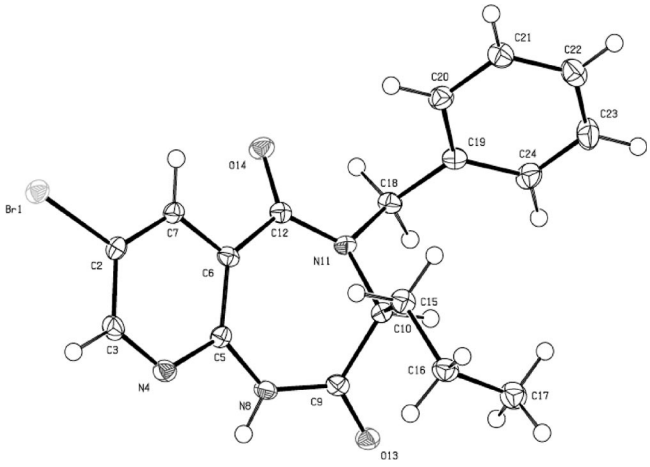


Figure 3. X-ray diffraction measurement of **2a**. CCDC-692196 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

The NMR spectra of the pyridodiazepinediones **1** and **2** revealed some interesting conformational characteristics, which were reported also for benzodiazepines.[7a] Indeed, except for **1g**, **2a** and **2e**, the spectra of compounds **1** and **2**, dissolved in $CDCl_3$ or [D_6]DMSO, at 298 K all exhibit split signal patterns. This finding reveals the existence of two conformers, which slowly interconvert on the NMR spectroscopic time scale. Cooling of compound **2a** below 270 K also results in a splitting of signals, again showing the existence of two interconverting conformers (Figure 4). However, even when cooling the 3-phenyl-substituted compound **2e** to 250 K, no separation of signals was observed.

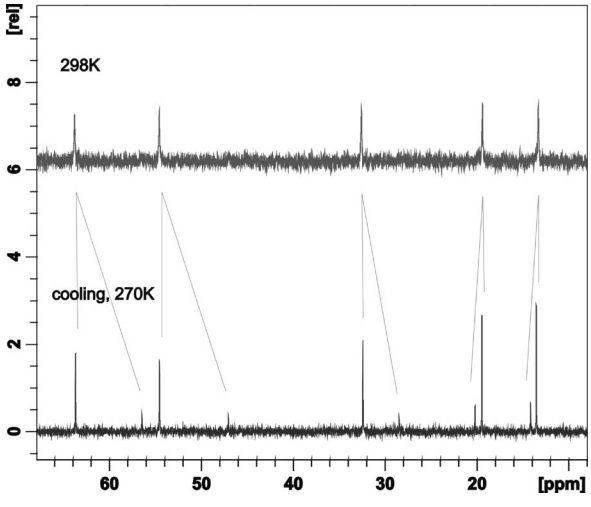


Figure 4. NMR spectroscopic variable-temperature experiment with compound **2a**.

From Hyperchem MM+ molecular mechanics and AM1 semiempirical calculations, it appears that compounds **1** and **2** can exist as two conformers, in which the 3-substituent has either an equatorial or axial orientation. In Figure 5, this is illustrated for the 3-Pr_{ax} and 3-Pr_{eq} conformers corresponding to the (3*S*) enantiomer of the 3-propyl-substituted compound **2f**. Interconversion of the two conformers, in which the two planar amide bonds remain fixed, can be effected by a coordinated rotation about the four single bonds of the seven-membered ring.

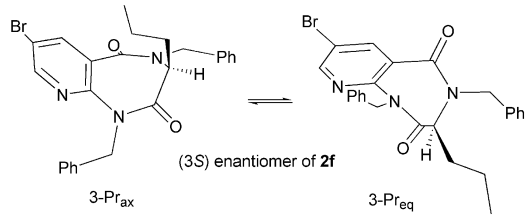


Figure 5. Conformational equilibrium for the (3*S*) enantiomer of **2f**.

The existence of two conformers was confirmed by 2D NMR spectroscopic experiments (ratio ca. 1.1:1). The Hyperchem AM1 calculations for compound **2f** (Figure 6) indeed revealed about equal energies for the 3-Pr_{ax} and 3-Pr_{eq} conformers, whereas a somewhat larger energy difference was calculated for compound **2e**, favouring the 3-Ph_{ax} conformer.

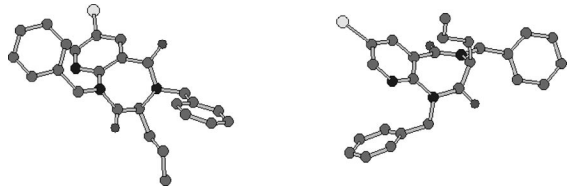


Figure 6. Hyperchem presentation for the 3-Pr_{eq} and 3-Pr_{ax} conformers of the (3*S*) enantiomers of **2f**.

Heating of a solution of compound **2f** in $CDCl_3$ did not produce changes in the ^1H NMR spectrum. However, when the sample was dissolved in [D_6]DMSO, changes were observed starting from 333 K. Coalescence of all proton signals occurred at 353 K. This is illustrated (Figure 7) for the methyl group located in the propyl side chain of **2f**.

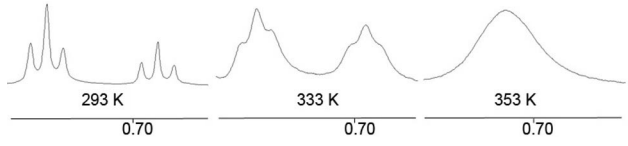


Figure 7. Proton signal observed for the methyl group located in the propyl side chain of **2f** at different temperatures.

Conclusions

The synthesis of 3,4-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepine-2,5-dione compounds **1** has been reported. By using the Ugi reaction as a key step, structural variation was achieved

at three positions, that is, 1, 3 and 4. A fourth variation was accomplished by a Suzuki cross-coupling reaction on the 7-bromo position of precursor **2**. The NMR spectra of compounds **1** and **2** revealed the existence of a slow equilibrium between two conformers with equatorial and axial orientation of the 3-substituent.

Experimental Section

General: NMR spectra were recorded with a Bruker Avance 300 (300 MHz), a Bruker Avance 400 (400 MHz) or a Bruker Avance 600 II+ (600 MHz) spectrometer. HPLC was performed with a Waters Delta 600 analytical/preparative HPLC system equipped with a Waters 996 PDA detector (Alltech C18 Prevail column, 5 μm, 22 × 150 mm and Phenomenex Luna C18 column, 5 μm, 21.2 × 150 mm). Melting points (uncorrected) were recorded with a Reichert-Jung Thermovar or an Electrothermal 9200 melting point apparatus.

General Procedures. Ugi Reaction: The aldehyde (1 equiv.) and the amine (1.25 equiv.) were dissolved in methanol. This solution was stirred at room temperature under argon for 1 h until the imine had formed (checked by mass spectrometry). Then, the starting material and the isocyanide (1 equiv.) were added. The mixture was stirred until the reaction was complete (TLC monitoring). **Suzuki Reaction:** $[Pd(PPh_3)_4]$ (5 mol-%) and degassed 2 N Na_2CO_3 solution (6.8 equiv.) were added to a mixture of starting material and boronic acid (1.1 equiv.) in toluene (degassed). The mixture was stirred under argon at 80 °C until disappearance of the starting material according to TLC. The solution was concentrated under reduced pressure. Water was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). After drying the pooled CH_2Cl_2 layers with $MgSO_4$ and concentration under reduced pressure, the residue was purified by column chromatography.

Representative Experimental Procedure for 4-Benzyl-7-bromo-3-propyl-3,4-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepine-2,5-dione (2a; R^1 = Br, R^2 = H, R^3 = Pr, R^4 = Bn): The Ugi product was synthesized according to the general procedure for Ugi reactions by using butanal (0.21 mL), benzylamine (0.31 mL), 2-amino-5-bromonicotinic acid (500 mg, 2.3 mmol) and 2-isocyanophenyl benzoate (0.51 g). After addition of **4a** and the isocyanide to the imine, the mixture was stirred for 2 h. After this time, the mixture was concentrated under reduced pressure and dried under vacuum. Subsequently, dry THF and KO*t*Bu (0.517 g, 2 equiv.) were added to the crude product. The solution was then refluxed for 16 h, after which time the THF was removed under reduced pressure. The residue was purified by column chromatography (silica gel, heptane/EtOAc, 80:20). A last purification was performed by HPLC (60 → 100 MeOH/water + 1% HCO_2H; 20 min; flow rate 0.2 mL/min). Yield: 22%. M.p. 176.1–176.9 °C. IR (KBr): $\tilde{\nu}$ = 1676 (s, CO amide), 1632 (s, CO amide) cm^{-1}. Compound **2a** appears as a single conformer at 298 K. ^1H NMR (600 MHz, $CDCl_3$): δ = 9.46 (br. s, 1 H), 8.61 (s, 1 H), 8.54 (s, 1 H), 7.36–7.32 (m, 5 H), 4.92 (d, 1 H), 4.77 (d, 1 H), 4.12 (br. s, 1 H), 1.50–1.43 (m, 1 H), 1.28–1.21 (m, 1 H), 1.20–1.09 (m, 2 H), 0.70 (br. s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.6 (C), 163.6 (C), 152.8 (CH), 146.2 (C), 143.7 (CH), 136.0 (C), 129.0 (CH), 128.8 (CH), 128.4 (CH), 122.2 (C), 115.3 (C), 63.9 (CH), 54.7 (CH_2), 32.7 (CH_2), 19.5 (CH_2), 13.4 (CH_3) ppm. EIMS: *m*/*z* (%) = 387 (100) $[M]^+$, 345 (7) $[M - C_3H_6]^+$, 296 (37) $[M - C_7H_7]^+$. HRMS: calcd. for $C_{18}H_{18}BrN_3O_2$ 387.0582; found 387.0586.

Representative Experimental Procedure for 4-Benzyl-1-butyl-7-phenyl-3-propyl-3,4-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepine-2,5-dione (1b; R^1 = Ph, R^2 = Bu, R^3 = Pr, R^4 = Bn): See the general procedure for the Suzuki reaction: **2b** (61 mg, 0.14 mmol), phenylboronic acid (50 mg), Na_2CO_3 solution (1.0 mL). Column chromatography: silica gel; (1) 100 DCM → MeOH/DCM, 1:99; (2) EtOAc/heptane, 10:90. A final purification was performed by HPLC (80 → 100 MeOH/water + 1% HCO_2H; 20 min; flow rate 0.2 mL/min). Yield: 83%. Oil. IR (NaCl): $\tilde{\nu}$ = 1686 (s, CO amide), 1643 (s, CO amide), 1600 (s, phenyl) cm^{-1}. Compound **1b** exists in 2 conformations in a ratio of 1:1 at 298 K. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.81 [t (2 × d), J_{meta} = 3 Hz, 2 H, CH], 8.51 + 8.49 [2 × (d, J_{meta} = 3 Hz, 1 H, CH)], 7.68 (m, *J* = 7 Hz, 4 H, CH), 7.50 (m, *J* = 7 Hz, 4 H, CH), 7.44–7.26 (m, 12 H, H arom), 4.99 (d, *J* = 14 Hz, 1 H, CH_2), 4.84–4.74 (m, 3 H, CH_2), 4.28–4.19 + 4.14–4.05 (m, 6 H, CH + CH_2), 2.27–2.19 (m, 1 H, CH_2), 1.79–1.70 (m, 1 H, CH_2), 1.69–1.00 (m, 14 H, CH_2), 0.90–0.83 [quint (2 × t), 9 H, CH_3 + CH_3], 0.65 (t, *J* = 7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3 + 168.3 (C), 167.7 + 165.2 (C), 150.0 + 149.1 (C), 149.5 + 149.2 (CH), 138.3 + 138.2 (CH), 137.7 + 136.3 + 136.2 + 136.1 (C_{ipso}), 133.8 + 133.4 (C), 129.6 + 129.4 (2) + 128.9 (2) + 128.6 (2) + 128.2 + 127.9 + 127.6 + 127.0 (2, C arom), 124.7 + 124.3 (C), 65.3 + 57.0 (CH), 54.2 + 46.6 (CH_2), 45.8 + 45.0 (CH_2), 32.5 + 29.3 (CH_2), 30.5 + 30.3 (CH_2), 20.2 + 20.1 (2) + 19.7 (CH_2 + CH_2), 14.0 + 13.9 (2) + 13.4 (CH_3 + CH_3) ppm. EIMS: *m*/*z* (%) = 441 (94) $[M]^+$, 398 (5) $[M - C_3H_7]^+$, 385 (10) $[M - C_4H_8]^+$, 350 (10) $[M - C_7H_7]^+$. HRMS: calcd. for $C_{28}H_{31}N_3O_2$ 441.2416; found 441.2426.

Supporting Information (see footnote on the first page of this article): X-ray data of **2a**, experimental procedures and full spectroscopic data for all new compounds.

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