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Expedient One-Pot Synthesis of Novel Chiral 2-Substituted 5-Phenyl-1,4-benzodiazepine Scaffolds from Amino Acid-Derived Amino Nitriles

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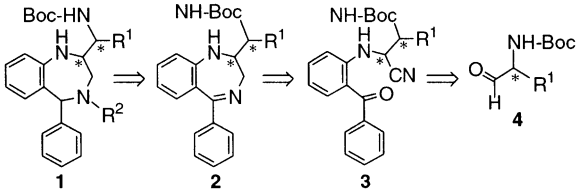
Abstract: An efficient and stereocontrolled synthesis of phenylalanine- and tryptophan-derived 5-phenyl-1,4-benzodiazepines is described. This new methodology involves, as a key step, the synthesis of 5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepines by a one-pot cyano reduction and reductive cyclization of the appropriate amino nitrile, which were obtained via a modified Strecker reaction of N-protected α-amino aldehydes with 2-aminobenzophenone and trimethylsilyl cyanide. The subsequent reduction of these 2,3-dihydro-1*H*-1,4-benzodiazepines, followed by regioselective alkylation or acylation at position 4, led to 2,4-disubstituted-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine.

Because of the wide range of biological activities displayed by benzodiazepine-derived compounds, benzodiazepine scaffolds are considered among the most important privileged structures for drug discovery.[1] Particularly, 5-aryl-1,4-benzodiazepine templates are recurrent structures in anxiolytics, hypnotics and anticonvulsants,[2] anti-HIV agents,[3] and antiarrhythmics.[4] Furthermore, diverse 1,4-benzodiazepine derivatives have also been used as constrained dipeptide mimics or nonpeptide scaffolds in the search of peptidomimetics either as enzyme inhibitors[5] or as ligands of diverse G-protein coupled receptors[6] such as cholecystokinin, fibrinogen, integrin, vasopressin, oxytocin, bradykinin, or *k*-opioid receptors.

In the context of our current interest in methodologies for generating peptidomimetics, particularly directed toward the search of new cholecystokinin receptor ligands, we envisioned a versatile access to novel chiral 2-substituted 5-phenyl-1,4-benzodiazepine derivatives **1** and **2**, from amino acid-derived amino nitriles **3**, as shown in the retrosynthetic Scheme 1. This strategy would involve the synthesis of the 2,3-dihydro-1*H*-1,4-benzodiazepines **2**, by cyano reduction and reductive cyclization of amino nitriles **3**, which could be prepared by adapting our methodology for the synthesis of Ψ[CH(CN)NH]pseudopeptides from α-amino aldehydes.[7−10] The reduction of **2**, followed by functionalization at position 4, would give access to the 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine derivatives **1**. We have studied and reported herein the applicability of retrosynthetic Scheme 1 to the preparation of phenylalanine- and tryptophan-derived 1,4-benzodiazepines.

SCHEME 1. Retrosynthesis of 5-Phenyl-1,4-benzodiazepine Derivatives



Initially, the synthesis of the starting amino nitriles **7a** and **7b**, by a modified Strecker reaction of 2-aminobenzophenone (**5**) with the N-protected α-amino aldehydes *N*-Boc-L-Phe-H (**4a**) or *N*-Boc-L-Trp-H (**4b**) and trimethylsilyl cyanide (TMSCN) (Scheme 2), was attempted by applying the reaction conditions developed for the synthesis of Ψ[CH(CN)NH]pseudopeptides,[7] which involved reaction of an α-amino aldehyde with an amino acid in the presence of $ZnCl_2$ at −20 °C for 1 h, followed by in situ reaction with TMSCN for 24 h at 0 °C. However, under these conditions, amino nitriles **7a**,**b**

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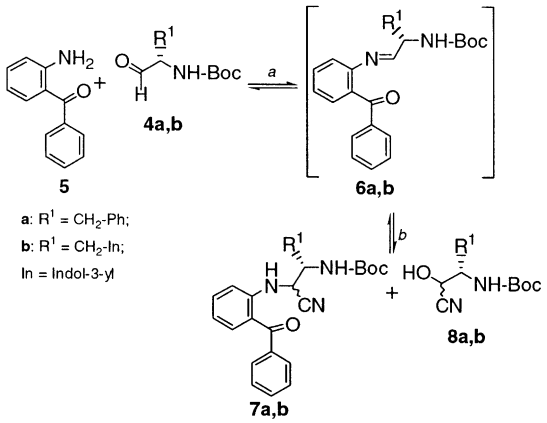
SCHEME 2. Synthesis of Amino Acid-Derived Amino Nitriles 7a and 7b[a]



[a] Reagents: (a) $ZnCl_2$, MeOH; (b) TMSCN, MeOH.

TABLE 1. Influence of Temperature and Time of Reaction of 4a with 5, Previous to the Addition of TMSCN, on the Yield of Amino Nitrile 7a

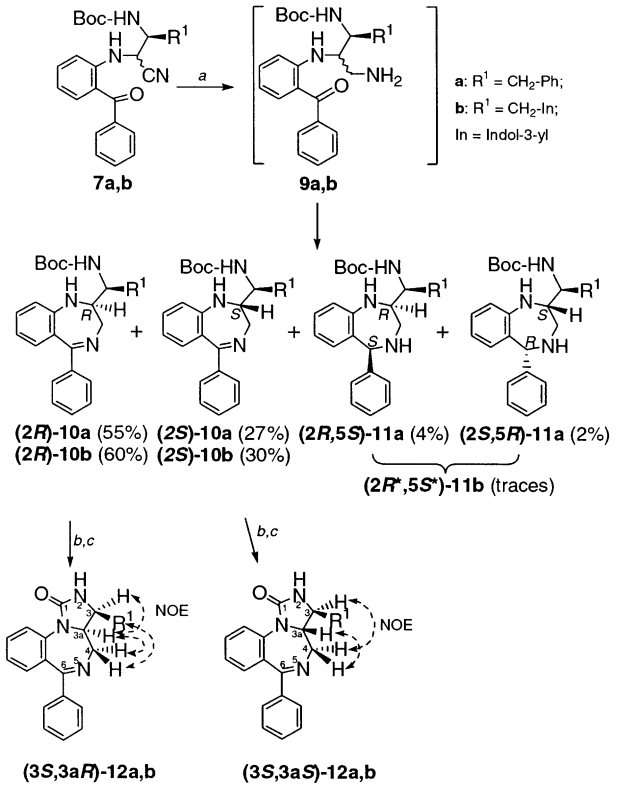
solvent	*T* (°C)	*t* (h)	% **7a**
MeOH[a]	−20	1	30
MeOH[a]	0	1	37
MeOH[b]	20	12	59
MeOH[b]	65	12	83
benzene[b]	80	12	20

[a] Conditions for the formation of imine **6a**, followed by reaction with TMSCN at 0 °C for 24 h. [b] Conditions for the formation of imine **6a**, followed by reaction with TMSCN at room temperature for 24 h.

were obtained as minor compounds (30%) along with cyanohydrins **8a**,**b** (50%). This result indicated that, due to the lower nucleophilic character of the aniline amino group of **5**, in comparison with the amino group of amino acids, a low formation of the imines **6a**,**b** had occurred when the TMSCN was added, and, therefore, the reaction equilibrium was shifted toward the faster formation of cyanohydrins **8**. The formation of imines **6** was detected by TLC and RP-HPLC, but they could be neither isolated nor quantified, as they reverted to 2-amino-benzophenone and the corresponding amino aldehyde **4a** or **4b**. To improve the yield of amino nitriles **7**, it was necessary to increase the temperature and reaction time for the imine formation up to 65 °C and 24 h (Table 1), as well as the temperature of the subsequent in situ reaction with TMSCN up to room temperature. Under these conditions, amino nitriles **7a** and **7b** were obtained in 83 and 86% yields, respectively, as (1:2) (*R*,*S*)-epimeric mixtures at the new stereogenic center, which could not be resolved. It is interesting to note that attempts to obtain the imine **6a** by azeotropic distillation in benzene of a mixture of **4a** and **5**, followed by in situ reaction with TMSCN at room temperature in the presence of $ZnCl_2$, gave the amino nitrile **7a** only in 20% yield within a complex mixture of degradation compounds. In all cases the reaction was selective at the aldehyde carbonyl group, and no reaction was detected at the benzophenone ketone group.

The reduction of both epimeric pairs of amino nitriles **7a** and **7b** was satisfactorily carried out by Raney nickel-catalyzed hydrogen transfer from hydrazine monohydrate

SCHEME 3. Synthesis and Configuration Assignment of 5-Phenyl-2,3-dihydro-1*H*-1,4-benzodiazepines[a]



[a] Reagents: (a) Raney Ni, $NH_2-NH_2 \cdot H_2O$, MeOH; (b) 2.5 N HCl in EtOAc; (c) $(Cl_3CO)_2CO$, TEA, CH_2Cl_2.

in refluxing MeOH,[11] which directly led to the 5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepines (2*R*)- and (2*S*)-**10a**,**b**, without detection of the formation of the corresponding triamine intermediates **9a** and **9b**. As shown in Scheme 3, the 2,3,4,5-tetrahydro derivatives **11a**,**b** were also obtained as minor products of reduction. The phenylalanine derivatives (2*R*)- and (2*S*)-**10a** and (2*R*,5*S*)- and (2*S*,5*R*)-**11a** were chromatographically resolved in a 28:14:2:1 ratio. In the case of the reduction of the tryptophan-derived amino nitriles **7b**, the pair of 2,3-dihydro-1*H*-1,4-benzodiazepines (2*R*)- and (2*S*)-**10b** was isolated and resolved in a 2:1 ratio, while the traces of 2,3,4,5-tetrahydro derivatives (2*R**,5*S**)-**11b** could not be isolated. To assign the C_2 absolute configuration, the 2,3-dihydro derivatives (2*R*)- and (2*S*)-**10a**,**b** were transformed into their 1-oxo-2,3,3a,4-tetrahydroimidazo[3,4-*a*][1,4]-benzodiazepine derivatives (3*S*,3a*R*)- and (3*S*,3a*S*)-**12a**,**b**, by *N*-Boc protection removal, followed by reaction with bis(trichloromethyl)carbonate. The NOE effects observed in the DPGSE-NOE spectra of compounds **12a**,**b**, shown in Scheme 3, allowed the configuration assignment at C_{3a} and, therefore, at C_2 in **10a**,**b**.

Although no racemization had been observed in our previous syntheses of amino acid-derived amino nitriles,[7−10] taking into account the known configurational unstability of α-amino aldehydes and the stronger reaction conditions required for the synthesis of amino

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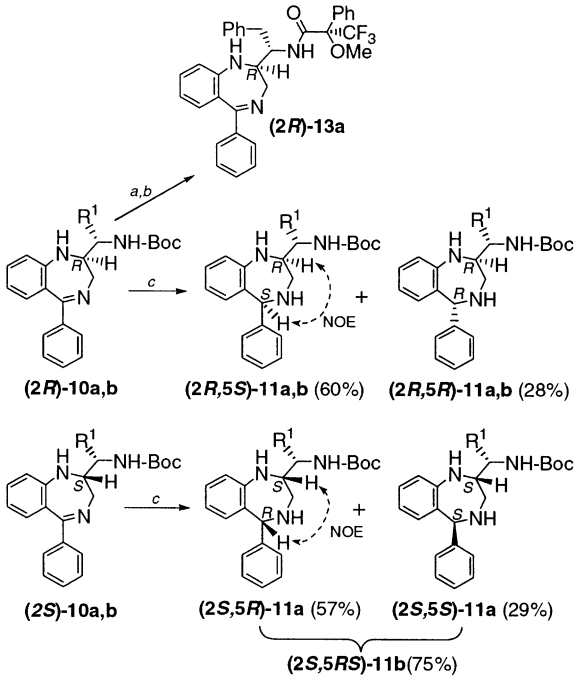
SCHEME 4. Mosher Acid Amide and Reduction of 2,3-Dihydro-1*H*-1,4-benzodiazepines[a]



[a] Reagents: (a) 2.5 N HCl, EtOAc; (b) (*R*)-MTPA−Cl, TEA, CH_2Cl_2; (c) $NaBH_3CN$, AcOH, CH_3CN.

nitriles **7a**,**b**, the possibility of racemization could not be now discharged. To clarify this point, the major epimer of the phenylalanine-derived 1,4-benzodiazepine (2*R*)-**10a** was *N*-Boc deprotected and treated with an excess of the Mosher acid chloride [(*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid chloride [(*R*)-MTPA-Cl]]. As shown in Scheme 4, this treatment yielded the corresponding amide derivative (2*R*)-**13a**, whose RP-HPLC and ^{1}H NMR analyses did not show the presence of signal duplicity. This result indicated the absence of racemization.

As traces of the 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine derivatives **11** had been obtained in the reduction of amino nitriles **7** by Raney nickel-catalyzed hydrogen transfer from hydrazine monohydrate, these conditions were initially attempted to prepare the phenylalanine-derived compounds **11a** from their 2,3-dihydro analogues (2*R*)- and (2*S*)-**10a**. However, after the reaction mixture in MeOH was refluxed for 24 h, (2*R*)- and (2*S*)-**10a** were recovered unchanged. Similar results were obtained by 10% Pd(C)-catalyzed hydrogenation (at 3 atm of H_2 pressure and 50 °C) or by reaction with $NaBH_4$ or $LiAlH_4$, conditions usually described for the reduction of 2,3-dihydro-1,4-benzodiazepines.[12] Finally, this reduction was satisfactorily carried out by treatment with $NaBH_4CN$ in CH_3CN in the presence of acetic acid. Interestingly, the use of the this reduction agent in MeOH and in the presence of $ZnCl_2$ gave negative results. As it is shown in Scheme 4, the reduction of both epimers (2*R*)- and (2*S*)-led to a 2:1 mixture of two diastereoisomeric 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepines **11**, epimers at position 5. Independently on the configuration at position 2 in the starting 2,3-dihydro-1,4-benzodiazepines **10**, the

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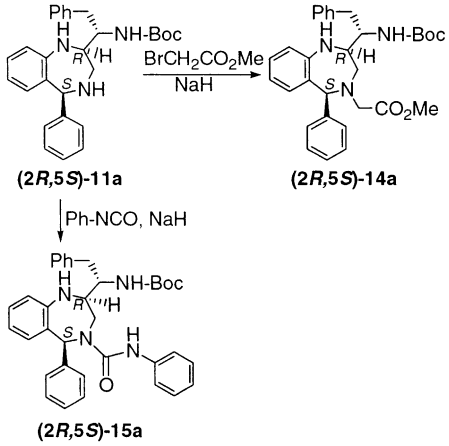
SCHEME 5. Alkylation and Acylation of 2,3,4,5-Tetrahydro-1*H*-1,4-benzodiazepines



hydride attacked preferably from the face opposite to that in which the 2-substituent is situated, giving in each case the corresponding 2,5-cis isomer as the major reduction product. All the epimeric pairs **11** were chromatographically resolved, except for (2*S*,5*RS*)-**11b** resulting from the tryptophan derivative (2*S*)-**10b**. The assignment of absolute configuration at position 5 in the phenylalanine derivatives **11a** was based on the NOE effects between 2-H and 5-H observed in the DPGSE-NOE spectra of (2*R*,5*S*)- and (2*S*,5*R*)-**11a**, shown in Scheme 4, indicative of a relative 2,5-cis-diaxial relative disposition for those protons. However, in tryptophan derivatives **11b**, the analysis of their NOE effects was hampered because the signal corresponding to 2-H appeared overlapped with the signals corresponding to the 3-H and the indolylmethylenic protons. Therefore, the configuration of these compounds was tentatively assigned by comparison of their ^{1}H and ^{13}C NMR chemical shifts with those of their phenylalanine analogues **11a**, in particular observing that in the 2,5-cis isomers, the 2-H proton appeared at a lower field than in the 2,5-trans isomer, while the 5-H appeared at a higher field.

In the major diastereoisomer of the phenylalanine-derived 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepines, we explored the functionalization at position 4 by N-alkylation and N-acylation reactions. Thus, as shown in Scheme 5, the treatment of (2*R*,5*S*)-**11a** with NaH, followed by reaction with methyl bromoacetate, led to the selective alkylation at position 4, with no detection of any alkylation at position 1. It is worth mentioning that the resulting 1,4-benzodiazepine derivative (2*R*,5*S*)-**14a** represents a N- and C-orthogonally protected and conformationally restricted tripeptide analogue, which could be used for introducing conformational restrictions into larger peptides. On the other hand, due to the importance of arylureido groups as privileged structures in cholecystokinin (CCK) receptor ligands,[6a] we also explored the introduction of these groups by acylation at position 4. The treatment of (2*R*,5*S*)-**11a** with phenyl isocyanate in the presence of NaH led, also selectively, to the product of acylation at position 4 (2*R*,5*S*)-**15a**.

All the 1,4-benzodiazepine derivatives described herein (**10**−**15**) were evaluated as CCK_1 and CCK_2 receptor ligands by measuring the inhibition of the specific [^{3}H]-propionyl-CCK-8 binding to rat pancreas and cerebral

cortex homogenates.[13] Unfortunately, none of these compounds showed significant binding affinity for any of these receptor subtypes at concentrations below 10^{-5} M.

In conclusion, herein we report an efficient and versatile methodology for the synthesis of new highly functionalized chiral 1,4-benzodiazepine derivatives from amino acid-derived amino nitriles, which opens access to a variety of scaffolds of potential use in the search for peptidomimetics.

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Supporting Information Available: Experimental procedures and characterization data for compounds **7**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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