SHORT COMMUNICATION

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Calcium-Catalyzed Synthesis of 1,2-Disubstituted 3-Benzazepines

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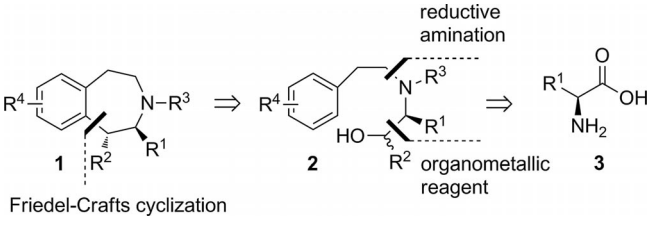
A short and highly stereoselective chiral pool synthesis of tetrahydro-3-benzazepines as potential drug molecules is described, using simple enantiopure amino acids as the chiral building blocks. Intramolecular Friedel–Crafts alkylation towards seven-membered rings was achieved with high diastereoselectivity for the first time and accomplished by a biocompatible calcium catalyst. The simple and cost efficient approach allows for the variation of all substituents in the 3-benzazepine by a change of the substitution pattern in one or more of the reagents, while leaving the general synthetic route unchanged. Furthermore, assignment of the absolute configuration of the 3-benzazepine derivative is straightforward, based on the amino acid building block employed.

Introduction

N-Heterocycles containing a phenylethylamine substructure are found in many natural products and biologically active molecules.[1] A class of compounds that contain such a structural subunit are the tetrahydro-3-benzazepines, which play a vital role in treatments of neurodegenerative diseases such as Alzheimer's or Parkinson's disease, due to their structural analogy to the corresponding neurotransmitters.[2] As a consequence of these interesting biological properties, derivatives of the 3-benzazepines have been synthesized and evaluated pharmacologically in the past. For example, strategies for the preparation of 3-benzazepine compounds have been developed based on transition-metal-mediated cyclizations,[3] such as the Heck reaction,[4] using expensive and highly toxic transition-metal catalysts unsuitable for large-scale applications. A transition-metal-free alternative is an acid-mediated Friedel–Crafts cyclization[5] using a large excess of acid, traditionally as the solvent. Unfortunately, these S_N1 processes suffer from poor diastereoselectivity, generally in the range of 1:1[6] to 3:1,[7] thereby precluding the formation of enantiopure 3-benzazepines through operationally simple chiral pool synthesis. First diastereoselective transformations proceeding by an S_N1 mechanism, were published only recently.[8]

Therefore, stereoselective approaches have focused so far on ring enlargements, such as the Stevens rearrangement, as good diastereoselectivities were achieved by these methods.[6b,9]

Our group has recently developed an efficient Friedel–Crafts alkylation reaction based on a $Ca(NTf_2)_2/Bu_4NPF_6$ catalyst system, which allows the selective alkylation of arenes using benzylic, allylic, and propargylic alcohols.[10] Moreover, model studies towards the diastereoselective alkylation of chiral α-benzylic carbocations (unpublished) encouraged us to elaborate a new stereoselective strategy for the synthesis of differently substituted tetrahydro-3-benzazepines by using a calcium-catalyzed intramolecular Friedel–Crafts reaction as the key step. The straightforward and highly modular strategy towards the cyclization precursors **2**, shown in Scheme 1, is based upon the linkage of three readily available building blocks through classical synthetic operations. Simple enantiopure amino acids **3**, provide the stereochemical information. They are coupled to the arene building block by reductive amination, followed by treatment with an organometallic reagent for the incorporation of the R^2-moiety. Thereby, every single substituent in the lead molecule can be varied by a simple change of the substitution pattern in one or more reagents, leaving the general synthetic route unchanged. This is a very cost effective strategy, which, in addition, allows for a straightforward assignment of the absolute stereochemistry in the final drug molecule, based on the configuration of the amino acid.



Scheme 1. Diastereoselective chiral pool synthesis of 3-benzazepines **1**.

Results and Discussion

With these considerations in mind we set out to synthesize a small series of tetrahydro-3-benzazepines as a proof

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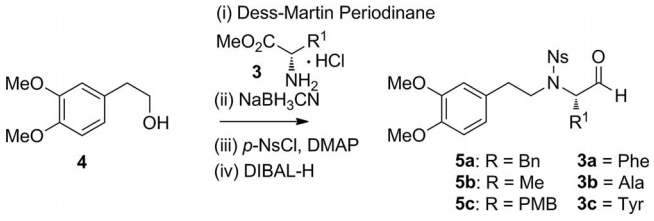
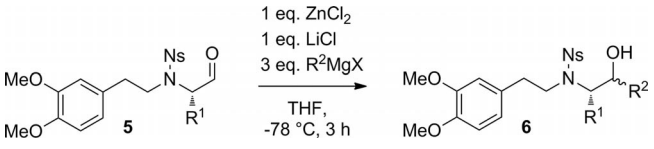
of concept. The synthesis of the cyclization precursor **2** starts from commercially available alcohol **4**, which was oxidized and subjected to reductive amination with the respective amino acid methyl ester hydrochloride **3a**–**3c** under standard reaction conditions (Scheme 2). The resulting amines were protected to prevent difficulties in the subsequent organometallic reaction as well as the calcium-catalyzed Friedel–Crafts cyclization. As initial attempts to use an *N*-tosyl group failed a later deprotection, a *p*-nitrobenzenesulfonyl (*p*-nosyl) group was selected, which can be easily removed (vide infra).



Scheme 2. Synthesis of α-chiral aldehydes **5a**–**5c**: (i) CH_2Cl_2, 15 min, room temp.; (ii) MeOH, 12 h, room temp.; (iii) py, 3 h, room temp.; (iv) CH_2Cl_2, 2 h, –78 °C.

Reduction with DIBAL in dichloromethane at –78 °C, followed by reoxidation in the case of **5c**, provided aldehydes **5a** and **5b**. Initial attempts to add a simple Grignard reagent to these aldehydes resulted in complex reaction mixtures. To discourage side reactions and to lower the risk for racemization of the stereocenter in the α-chiral aldehydes **5**, the in situ formation of milder organometallic reagents by transmetalation was envisaged. The addition of stoichiometric amounts of either LiCl or $ZnCl_2$ to PhMgCl in THF gave again mixtures of undesired side products and only a small amount of the desired product could be isolated. Also, a change of solvent, to Et_2O did not improve the results. To our delight, the combination of one equivalent of each, LiCl and $ZnCl_2$ with 3 equiv. of PhMgCl dramatically increased the yield of **6**. Under these optimized reaction conditions aldehydes **5a**–**5c** were converted into the corresponding cyclization precursors **6a**–**6c** (Table 1). In addition, the reaction was performed exemplarily with two further Grignard reagents yielding the alcohols **6d** and **6e**.

Table 1. Addition of organometallic reagents to aldehyde **5**.



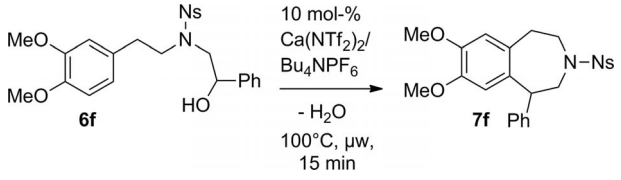
Entry[a]	Amino acid	R^1	R^2MgX	Product	Yield [%][b]
1	Phe	Bn	PhMgCl	**6a**	68
2	Ala	Me	PhMgCl	**6b**	63
3	Tyr	PMB	PhMgCl	**6c**	61
4	Phe	Bn	4-$MeOC_6H_4MgCl$	**6d**	50
5	Phe	Bn	4-ClC_6H_4MgCl	**6e**	68

[a] LiCl, $ZnCl_2$ and Grignard reagent were stirred in THF at 0 °C for 45 min. The solution was cooled to –78 °C and aldehyde **5** was added. The mixture was stirred at –78 °C for 3 h. [b] Isolated yield.

All products **6a**–**6e** were obtained as mixtures of diastereomers. As the newly formed stereocenter will be erased and reset in the subsequent cyclization step, no further attention was required and diastereomeric ratios remained unanalyzed.

With cyclization precursors **6a**–**6e** in hand, the intramolecular Friedel–Crafts reaction in the presence of our calcium-based catalyst system consisting of $Ca(NTf_2)_2$ and Bu_4NPF_6 was investigated (Table 2). The process was examined with **6f** as a model substrate. Even though conventional heating gave approximately the same results, we opted for carrying out the reaction under microwave conditions as this considerably shortened the reaction times. Hence, after 15 min of microwave irradiation at 100 °C in 1,2-dichloroethane, the desired 3-benzazepine **7f** was isolated in an excellent yield of 95% (Table 2, entry 1). When the reaction was performed at 70 °C, full conversion was not achieved. Decreasing the amount of the calcium catalyst to 5 mol-% considerably slowed down the conversion of the starting material. Other solvents, such as toluene or dichloromethane, considerably decreased the reaction rate (Table 2, entry 2), whereas in $MeNO_2$ the yield was only slightly lower in comparison to 1,2-dichloroethane. The attempt to perform the cyclization at room temperature gave only 23% yield of 3-benzazepine **7a** after 3 days (Table 2, entry 3). Among other Lewis acids, the calcium catalyst clearly showed superior reactivity, as only in the presence of $Zn(OTf)_2$ or $BF_3{\cdot}OEt_2$ a moderate yield of **7f** was obtained (Table 2, entries 4–12). Complete conversion was also not achieved under Brønsted "super" acid catalysis ($HNTF_2$, Table 2, entry 13).

Table 2. Optimization of the Ca^{2+}-catalyzed Friedel–Crafts cyclization.



Entry[a]	Catalyst	Bu_4NPF_6 [mol-%]	Solvent	T [°C]	Yield[c] [%]
1	$Ca(NTf_2)_2$	10	DCE	100	95
2	$Ca(NTf_2)_2$	10	toluene	100	35
3[b]	$Ca(NTf_2)_2$	10	DCE	25	23
4	$Sc(OTf)_3$	10	DCE	100	–
5	AgOTf	10	DCE	100	–
6	$Al(OTf)_3$	10	DCE	100	–
7	$Al(OTf)_3$	10	DCE	100	–
8	$InCl_3$	10	DCE	100	–
9	$Ga(OTf)_3$	10	DCE	100	–
10	$Ga(OTf)_3$	10	DCE	100	–
11	$Zn(OTf)_2$	10	DCE	100	74
12	$BF_3{\cdot}OEt_2$	10	DCE	100	67
13	$HNTf_2$	10	DCE	100	75

[a] Catalyst and Bu_4NPF_6 and $Ca(NTf_2)_2$ were added to amino alcohol **6f** (0.25 mmol) in 1 mL of solvent and stirred for 15 min under microwave irradiation at 100 °C. [b] Reaction was stirred at 25 °C for 72 h. [c] Isolated yield.

Using the optimized conditions the amino alcohols **6a**–**6e** were converted into the desired products**7a**–**7e**, giving excellent yields of 91–96% (Figure 1). To showcase the versatility of the calcium-catalyzed Friedel–Crafts cyclization also for substrates with non-activated benzene rings model compound **7g** was included. Moreover, the reaction occurs highly diastereoselectively despite the high reaction temperature of 100 °C, yielding exclusively the *trans*-diastereomer in all cases. The minor *cis*-diastereomer was not detected by NMR spectroscopy or HPLC analysis. The *trans*-configuration was unambiguously determined by NOE experiments.

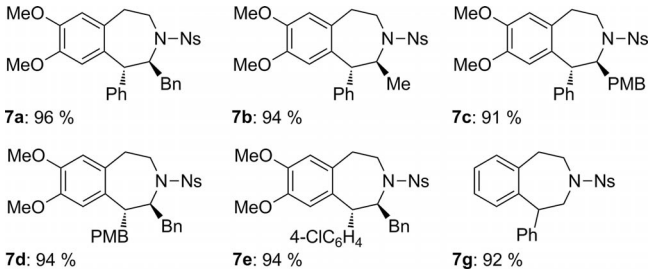


Figure 1. Results of the Ca^{2+}-catalyzed diastereoselective cyclization.

Therefore, the preferred conformation of 3-benzazepine **7a** was assigned by DFT-based computational methods. Figure 2 shows the observed NOE interactions for 3-benzazepine **7a**, found between H-1 and H-2, as well as between H-4 and one of the benzylic hydrogen atoms. Furthermore, the value of the coupling constant ($J_{1,2}$ = 5.4 Hz) was in accordance with previously reported *trans*-1,2-disubstituted 3-benzazepines.[8,11]

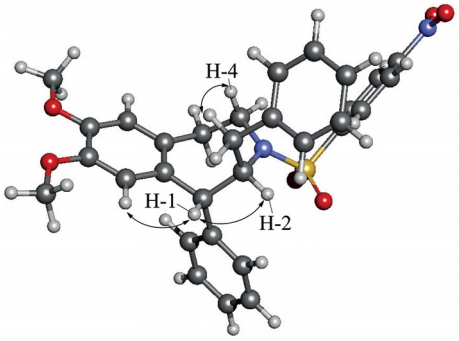


Figure 2. Preferred conformation of **7a** and observed NOE signals.

The remarkable diastereoselectivity of the reaction can be explained by the particular potency of the Lewis acidic calcium catalyst, due to which the formation of the carbocation **8** (Figure 3) is highly efficient and occurs quantitatively.

In previous studies, mostly in the presence of several equivalents of strong Brønsted acids as ionization promoters,[12] a low to moderate diastereoselectivity was observed. This was explained by a cyclization that proceeds only in part through an S_N1 mechanism. The inefficient ionization imparted by the acid requires the assistance of a pronounced neighboring group participation of the nucleophilic arene substituent. This leads to a larger proportion of an S_N2-like mechanism, resulting in net inversion of the stereocenter at the hydroxyl moiety and thus poor diastereoselectivity because the reaction is no longer governed solely by steric factors. As mentioned above, the high efficiency of the calcium catalyst ensures quantitative ionization and thus, the S_N2-like pathway does not interfere with the ionic pathway. Hence, the stereochemical outcome of the cyclization is exclusively determined by virtue of the steric repulsion induced by the R^1 substituent (the former amino acid) which renders the two faces of the planar carbocation **8** diastereotopic.

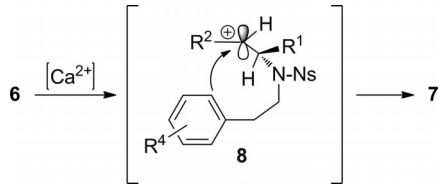
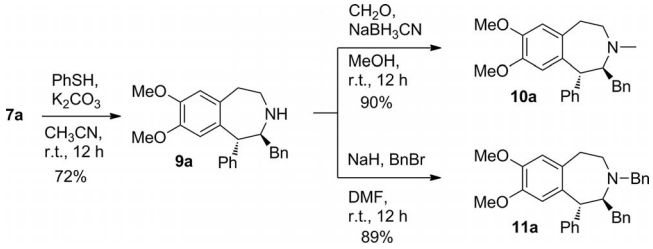


Figure 3. Proposed transition state for the diastereoselective S_N1 reaction.

After the successful synthesis of the 3-benzazepines, we focused on further elaboration at the nitrogen atom. For these derivatizations we chose once more 3-benzazepine **7a** as a model compound. The *p*-nosyl group was easily removed in the presence of PhSH and K_2CO_3. Reductive amination of the resulting amine **9a** with formaldehyde provided **10a** in 90% yield. Alkylation with benzyl bromide in the presence of NaH yielded 3-benzazepine **11a** (Scheme 3).



Scheme 3. Derivatization of 3-benzazepine **7a**.

Conclusions

We have developed a simple and efficient chiral pool synthesis for the stereoselective formation of 1,2-disubstituted tetrahydro-3-benzazepines. These compounds were obtained through a Friedel–Crafts cyclization that was achieved with high diastereoselectivity for the first time, owing to the particular potency of the calcium catalyst used for the ionization of the cyclization precursor. Evaluation of the bioactivity of the newly synthesized compounds is currently underway.

Experimental Section

General Procedure for the Diastereoselective Calcium-Catalyzed Friedel–Crafts Cyclization: Bu_4NPF_6 (10 mol-%) and $Ca(NTf_2)_2$

(10 mol-%) were added to a solution of the cyclization precursor (0.05 mmol) in DCE (1 mL) and the mixture was stirred in a microwave vial at 100 °C at 300 W maximum power level for 15 min. Saturated aqueous $NaHCO_3$ solution was added to the reaction mixture and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography (hexane/EtOAc, 2:1).

Acknowledgments

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