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Benzoazabicyclo[4.3.1] derivatives by intramolecular Michael addition of piperidinone enolates to enoates

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Abstract

Piperidinones with a 2-bromobenzyl substituent in the 5-position were subjected to a Heck coupling reaction with ethyl acrylate resulting in the highly functionalized cinnamates **9a–d**. A subsequent deprotonation of the piperidinones using $NaN(SiM_3)_2$ in THF induced an intramolecular Michael addition of the enolate to the cinnamate part. In this way, a range of novel 2,6-methano-4*H*-4-benzazonines **10–13** were obtained. In each case, a separable mixture of *endo*/*exo*-diastereomers was obtained.

Keywords: Heck coupling; Alkaloid; Michael addition; Benzazonine

The benzomorphan substructure **1** as present in the alkaloid morphine (**2**) has inspired the design and synthesis of many related analogs (Fig. 1).[1] Thus, various substitutents have been introduced. Moreover, derivatives with a repositioned nitrogen atom were reported in the literature.[1] Finally, azabenzobicycloalkanes with smaller or homologated rings were targeted.[2,3] An example for an analog with repositioned nitrogen atom and smaller ring is varenicline (**3**), which is used as a drug for smoking cessation.[4]

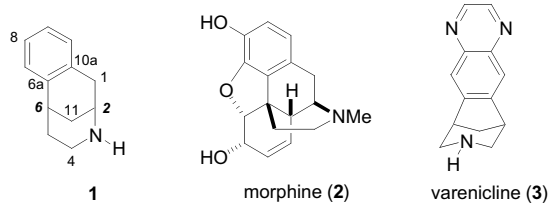
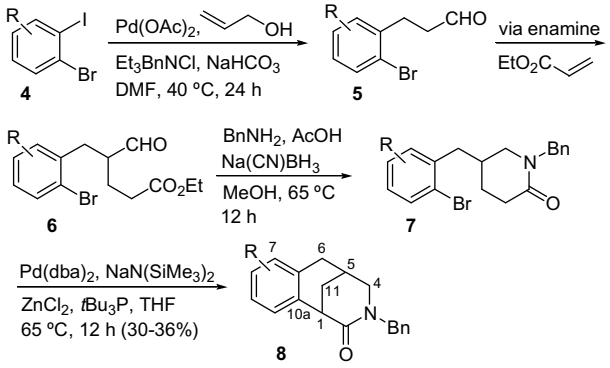


Fig. 1. Structures of the benzomorphan skeleton (**1**), morphine (**2**), and varenicline (**3**).

In the course of a program directed at the synthesis of azabenzobicycloalkanes using organometallic transformations as a key step, we could recently demonstrate the synthesis of 1,5-methano-3-benzazocines by intramolecular Buchwald–Hartwig arylation of 2-piperidinones (Scheme 1).[5] The corresponding substrates were fashioned from bromoiodobenzenes via a short sequence consisting of a Jeffery–Heck reaction[6] with allylalcohol, enamine formation of the resulting aldehydes, Michael addition of the



Scheme 1. Intramolecular Buchwald–Hartwig route toward the synthesis of 1,5-methano-3-benzazocines.

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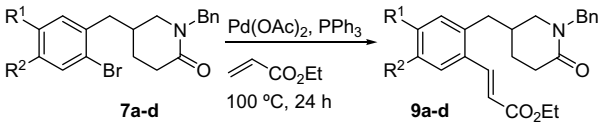
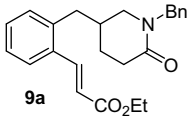
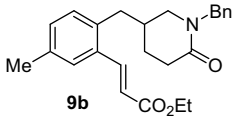
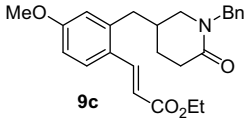
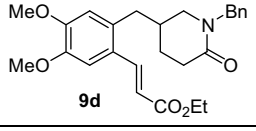
enamine to ethylacrylate producing 4-formylesters,[7] and finally a reductive amination with benzylamine and sodium cyanoborohydride. The overall yield for the three-step sequence from **4** to **7** amounts to 20–33% (compounds **7a–c**). Compound **7d** was prepared by a slightly different sequence. Thus, the bromine was introduced at the stage of the corresponding amide.[5] The intramolecular Buchwald–Hartwig arylation of the piperidinones via the corresponding zinc enolate[8] opened a novel route to 1,5-methano-3-benzazocines.

As we discovered, the arylbromide in piperidinones **7** with the 2-bromobenzyl substitutent could be engaged in a classical Heck reaction[9,10] with ethyl acrylate leading to acrylates **9a–d** in good chemical yields (Table 1). These Heck coupling reactions were performed in DMF at 100 °C in the presence of ethyl acrylate (3 equiv), $Pd(OAc)_2$ (10 mol %), Ph_3P (20 mol %), Et_3N (5 equiv), and Cs_2CO_3 (2 equiv) in 24 h. Due to the difficulties in removing the byproduct triphenylphosphine oxide from the Heck product **9c**, the reaction of **7c** with ethyl acrylate was carried out with the Buchwald ligand *N*-[2′-(dicyclohexylphosphino)-1,1′-biphenyl-2-yl]-*N*,*N*-dimethylamine.[11] The acrylate function in cinnamates **9a–d** presents itself for Diels–Alder or Michael-additions. In fact, intramolecular Michael addition-based methods represent a classical and important strategy for intramolecular C–C bond formations.[12] For example, this strategy has found a broad use for the synthesis of bicyclic systems.[13] Furthermore, the double Michael domino reaction is an important method for the construction of complex molecular architectures.[14,15]

Table 1
Heck coupling of ethyl acrylate with the 5-(2-bromobenzyl)-piperidinones **7a–d**[a,b]



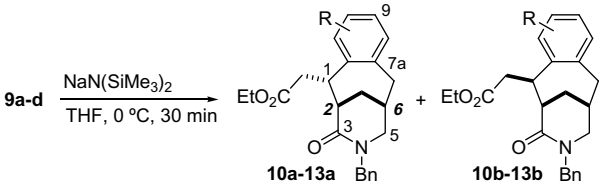
Entry	Bromide **7a–d**	Heck product **9a–d**	Yield of **9** (%)
1	**7a**	 **9a**	70
2	**7b**	 **9b**	76
3[c]	**7c**	 **9c**	73
4	**7d**	 **9d**	77

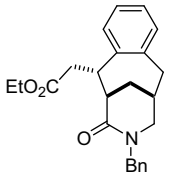
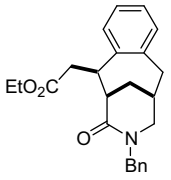
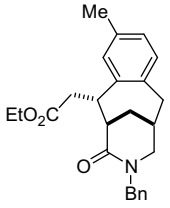
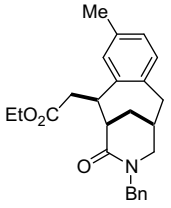
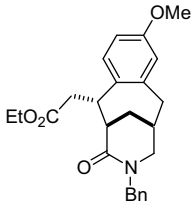
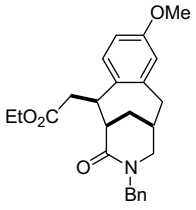
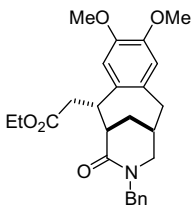
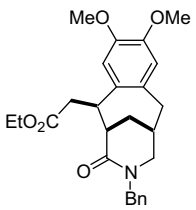
[a] Reaction conditions: 0.3 M in DMF, acrylate (3 equiv), Ph_3P (0.2 equiv), Cs_2CO_3 (2 equiv), $Pd(OAc)_2$ (0.1 equiv), Et_3N (5 equiv), 100 °C, 24 h.

[b] **7a**: $R^1 = R^2 = H$; **7b**: $R^1 = H$, $R^2 = Me$; **7c**: $R^1 = OMe$, $R^2 = H$; **7d**: $R^1 = R^2 = OMe$.

[c] *N*-[2′-(Dicyclohexylphosphino)-1,1′-biphenyl-2-yl]-*N*,*N*-dimethylamine (0.2 equiv) was used as ligand.

Table 2
Intramolecular Michael addition of the piperidinone enolates generated from **9a–d** to the enoate function yielding the 2,6-methano-4*H*-4-benzazonines **10a,b–13a,b**[a]



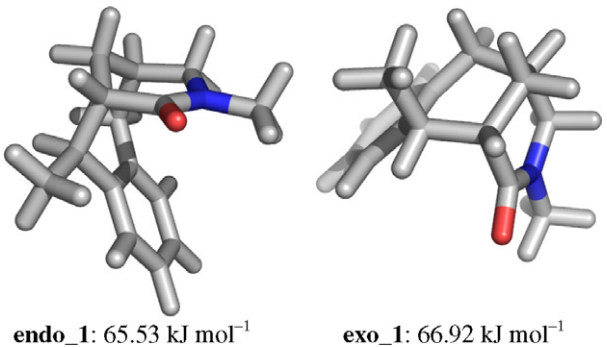
Entry	*endo*-Isomer (yield %)	*exo*-Isomer (yield %)
1	 **10a** (39%)	 **10b** (24%)
2	 **11a** (37%)	 **11b** (25%)
3	 **12a** (29%)	 **12b** (31%)
4	 **13a** (30%)	 **13b** (33%)

[a] Reaction conditions: 0.05 M in THF, $NaN(SiMe_3)_2$ (2 equiv), 0 °C, then room temperature, 30 min.

In fact, when a THF solution of cinnamate **9a** was treated with a solution of $NaN(SiMe_3)_2$ (2 equiv) at 0 °C followed by stirring of the mixture for 30 min at this temperature, the novel 2,6-methano-4*H*-4-benzazonines **10a** and **10b** were produced (Table 2). The two diastereomers could be separated by chromatography. In a related manner, the other acrylates **9b–d** were cyclized to the corresponding benzoazabicyclo[4.3.1] derivatives **11–13**. Other bases, like LDA or $LiN(SiMe_3)_2$ turned out to be less efficient in promoting this anionic cyclization. Performing the cyclization with 3 equiv of $NaN(SiMe_3)_2$ at 0 °C followed by allowing the mixture to warm to room temperature within 5 h gave essentially the same ratios. However, the yields of the products were lower, at the expense of very polar side products. In the case of **9a** and **9b**, the ratio of the *endo*/*exo*-diastereomers was around 3:2. With the substrates containing methoxy groups in the aryl ring (**9c** and **9d**), the ratio was roughly 1:1.

In order to find out whether the product ratios are the result of kinetic or thermodynamic control, pure diastereomer **11a** was treated with $NaN(SiMe_3)_2$ (2 equiv) under various conditions. Stirring the resulting mixture at room temperature for 30 min or at 0 °C for 1 h left **11a** unchanged. The other diastereomer **11b** could not be detected. If a substoichiometric amount of $NaN(SiMe_3)_2$ (0.95 equiv) was employed at room temperature, followed by quenching of the reaction after 10 min, a ratio of 1:2:1 (**9b**, **11a**,**b**) was observed. From these experiments, it can be concluded that the diastereomeric ratios are the result of kinetic control.

The assignment of the relative stereochemistry of the two diastereomers required the knowledge of their preferred conformation and the detection of significant differences in the NMR spectra. According to calculations performed by Chem3D 9.0 (MM2) on the simple model compound **14**, the tricyclic compounds ***endo*-14** and ***exo*-14** each can exist in two conformations. In both cases, one conformer is significantly favored over the other one. The most stable conformer for each diastereomer is shown in Figure 2. Therefore, it is reasonable to just consider the low-energy conformation for each diastereomer. In the NOESY NMR spectrum of **10a** (*endo*-isomer), 1-H showed



endo_1: 65.53 kJ mol^{-1} **exo_1**: 66.92 kJ mol^{-1}

Fig. 2. Calculated conformations for the *endo*- and *exo*-isomers of the model compound **14**.

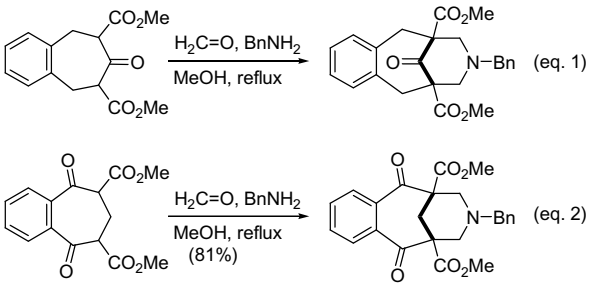
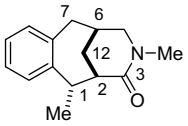
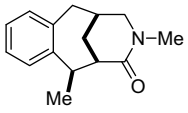


Fig. 3. Representative 2,6-methano-4*H*-4-benzazonines prepared by Mannich reactions.

a characteristic cross-peak with one of the protons of the one carbon bridge (12-H). Furthermore, a cross-peak is visible between 1-H and one 7-H. However, due to signal overlapping, this is less clear-cut. In contrast, in the *exo*-isomer **10b**, these NOESY interactions do not occur.



***endo*-14**



***exo*-14**

The *endo*- and *exo*-isomers of these 2,6-methano-4*H*-4-benzazonines show a distinct difference in their ^{1}H NMR spectra. For example, in the *endo*-isomer **10a**, 2-H ($\delta = 2.76$ ppm) appears as a doublet ($J = 4.3$ Hz). In contrast, 2-H ($\delta = 2.90$ ppm) of the *exo*-isomer **10b** couples to two neighboring protons, showing a doublet of doublet ($J = 5.3$, 5.3 Hz). This can be explained by an almost 90° dihedral angle between 1-H/2H in the *endo*-isomers. The calculated angle for ***endo*-14** is 82°.

The literature contains a few examples for 2,6-methano-4*H*-4-benzazonines. Typically, they are prepared by Mannich reaction. Two representative examples are shown in Figure 3 (Eq. 1)[16] and (Eq. 2).[17,18]

In conclusion, we could develop a novel strategy to 2,6-methano-4*H*-4-benzazonines. Key steps include a Heck reaction on aryl bromides with a piperidinone appendage. Treatment of the resulting cinnamate containing piperidinones with base induced an anionic cyclization (Michael addition) to provide the azabicyclo[4.3.1]systems. The average overall yields for this operational simple sequence leading to the functionalized benzazonine derivatives **10–13** are about 10%.

Acknowledgments

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a postdoctoral fellowship. Useful comments by the referees are acknowledged as well.

Supplementary data

Experimental procedures, NMR spectra and analytical data for all new compounds are provided. In addition, the less stable calculated conformers of model compounds are depicted. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.067.

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