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Efficient Synthesis of the 3-Benzazepine Framework via Intramolecular Heck Reductive Cyclization

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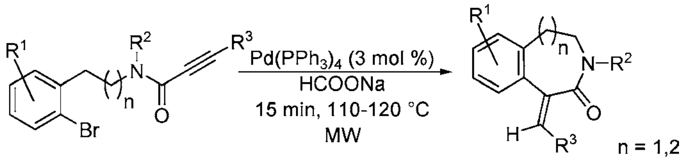
ABSTRACT



A microwave-assisted protocol based on reductive Heck reaction was developed for regio- and stereoselective construction of the 3-benzazepine core.

The 3-benzazepine framework is widespread among natural compounds and important pharmaceuticals. Considerable efforts have been made toward the synthesis of alkaloids as aphanorphine,[1] lennoxamine,[2] and cephalotaxine[3] (Figure 1) because of their challenging chemical structures and interesting biological activity. The renal vasodilator fenoldopam relates to the class of 1-substituted tetrahydro-3-benzazepines and is a peripheral dopamine D1 receptor agonist.[4] The tetracyclic MK-801 (dizocilpine) represents a noncompetitive NMDA receptor antagonist and has been extensively studied for treatment of neurodegenerative diseases such as Huntington's, Alzheimer's, and amyotrophic lateral sclerosis.[5]

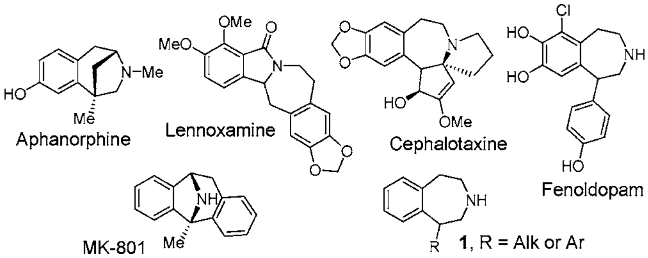


Figure 1. Alkaloids containing the 3-benzazepine framework and NMDA receptor antagonists.

Variously substituted at position 1, 3-benzazepine structure **1** has also been studied for the synthesis of potent NMDA receptor antagonists.[6]

Most often the construction of the medium-sized ring of the 3-benzazepine scaffold is achieved via intramolecular

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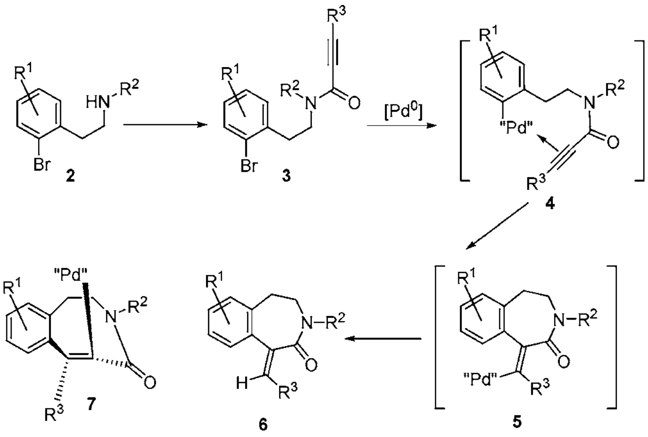
Friedel−Crafts alkylation.[1b−d,5b,7] However, this method demands an excess of Lewis acid and lacks flexibility for variation of substituents. Alternatively, ring closure is accomplished upon formation of the C−N bond via intramolecular reductive amination.[6a] Intramolecular radical cyclization was successfully applied for the synthesis of the 7-membered ring in aphanorphine.[1a,e] Particularly useful for the syntheses of natural compounds and analogues is the corresponding 3-benzazepinone structure, as alkylation allows further introduction of substituents, for example, giving rise to bridged structures.[1c,d,8]

Transition-metal-catalyzed reactions were also used for generating the 3-benzazepine scaffold. Thus, the Heck reaction of olefins proved to be high yielding and reliable.[3a,b,6b,9] Though this approach regioselectively leads to 7-membered rings, a problem with the geometry and location of the resulting double bond still remains, due to the unselective elimination of palladium−hydrogen species at the final step of the Heck reaction.[1e,3a,9a] A regioselective synthesis of 4-substituted 3-benzazepinones via intramolecular hydroamidation of the triple bond incorporated in the noncyclic precursor has also recently been reported.[10a,b]

We have elaborated a new pathway toward the synthesis of 1-substituted 3-benzazepinones **6**, based on a Heck intramolecular reductive cyclization reaction (Scheme 1).

Scheme 1

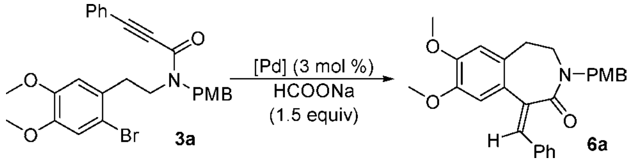


The sequence starts with the readily available 2-bromophenylethylamines **2**[12a] which, after coupling with variously 3-substituted 2-propynoic acids, deliver the substrates **3** for intramolecular cyclization. Due to the syn-addition to the triple bond during Heck reaction, our strategy provides exclusively compounds possessing the *Z*-conformation of the exocyclic double bond.

Moreover, the regioselectivity of the Heck reaction and, as a result, the ring size of the generated medium-sized ring, is also determined by the mechanism of the reaction. As the initially generated arylpalladium π-complex **4** is transformed into a σ-vinyl palladium complex **5** via simultaneous syn-addition to the triple bond, endocyclization via a hypothetical intermediate **7** is fairly unlikely due to the high strain exerted by the trans geometry around the double bond in the 8-membered ring. The Pd(0) catalyst is regenerated with a reducing agent present in the reaction mixture.

Our first attempts to find optimal conditions for the reductive Heck reaction (Table 1) were carried out with the amide **3a**, generated from the corresponding amine and phenylpropiolic acid chloride. The reaction was run under conventional heating in the presence of 3 mol % of Pd(PPh$_3$)$_4$ as the catalyst and sodium formate as the reducing agent. The optimal solvent system for the cyclization was found to be a DMF/water mixture. In the absence of water the reaction failed, probably because of the ineffectiveness of the reducing agent under anhydrous conditions.

Table 1. Optimization of the Reaction Conditions[a]



entry	time (h)	solvent (v/v)	catalyst	dilution (mM)	yield (%)
1	12	DME/H$_2$O (4:1)	Pd(PPh$_3$)$_4$	170	60
2	12	DMF/H$_2$O (3:1)	Pd(PPh$_3$)$_4$	170	67
3	3	DMF/H$_2$O (3:1)	Pd(PPh$_3$)$_4$	70	80
4 (MW)	0.25	DMF/H$_2$O (3:1)	Pd(PPh$_3$)$_4$	70	81
5 (MW)	0.25	DMF/H$_2$O (3:1)	Pd(OAc)$_2$ + 2Ph$_3$P	70	79
6 (MW)	0.25	DMF/H$_2$O (3:1)	Hermann's palladacycle	70	81

[a] Reactions were run on a 0.4 mmol scale of **3a**; for entries 1−3, the mixture was heated at 100 °C (oil bath temperature) in a sealed vial; for entries 4−6, MW irradiation at 110 °C and 300 W maximum power was employed.

Best yields for cyclization were found using high dilution conditions. The structure of the obtained compound **6a** was fully confirmed with 2D-NMR spectroscopy. The *Z*-configuration of the resulting exocyclic double bond was assigned on the basis of a NOE effect between the vinylic proton of the double bond and the neighboring proton of the aryl ring.

Thus, having found appropriate conditions under conventional heating for generating the medium-sized ring of model compound **6a**, we investigated the protocol applying micro-

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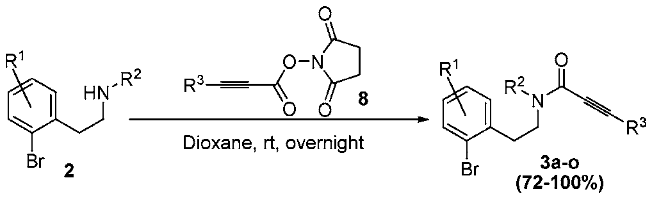
wave irradiation. Experiments were carried out in a multimode Milestone MicroSYNTH microwave reactor in a sealed vial applying a maximum power level of 300 W. Under these conditions, the reaction rate was dramatically increased, while the yield remained satisfactorily high (81%; Table 1, entry 4) using otherwise the same conditions. While the reaction required 3 h to reach completion upon conventional oil bath heating, the microwave-assisted cyclization was finished after a mere 15 min. Switching to other Pd catalysts (Table 1, entries 5 and 6) as, for example, Pd(OAc)$_2$−Ph$_3$P combination or Hermann's palladacycle,[11] does not have any important effect on the yield or the rate of the reaction. With this optimized microwave-assisted protocol at hand, we started to explore the scope and limitations of the procedure by generating a small library of analogues.

A number of propynoic acid amides **3a**−**o** (Scheme 2) was synthesized using a two-step, one-pot coupling procedure of 2-bromophenylethylamines **2**[12a] with in situ generated NHS derivatives of the corresponding 3-substituted propynoic acids **8**.

Scheme 2

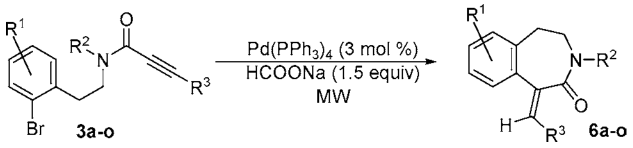


Amides **3a**−**o** were obtained in excellent yields mostly as 1/1 mixtures of *Z*/*E* rotamers. Microwave-assisted cyclization of the substrates **3a**−**o** into the 3-benzazepinones **6a**−**o** proceeded very smoothly with a complete conversion of the starting material in a mere 15 min (Table 2). The 7-membered ring is formed in good yields with the exception of compounds **6c**,**h**−**j** (Table 2, entries 3, 8−10) where a significant fall of the yield was observed. In the case of the cyclization of the secondary amides **3i**,**j** (entries 9 and 10), this could presumably be ascribed to a competitive interaction of the unprotected nitrogen with Pd in the catalytic intermediate.

However, these 3-benzazepinones **6i**,**j** may be alternatively prepared in good overall yield using acid-catalyzed PMB deprotection of the corresponding benzazepines **6a**,**b** (entries 1 and 2).[12b]

On the other hand, the TMS-propynoic acid amides **3c**,**h** underwent hydrolysis of the TMS group in 15 min applying the optimized conditions. The deprotected acetylenes could be recovered in 75% yield. Unfortunately, during prolonged reaction time these terminal acetylenes themselves were found to be unstable under the described conditions and underwent degradation. However, when the reaction was run upon microwave irradiation in DME/water (4:1) at a ceiling temperature of 120 °C, with 3 equiv of sodium formate, the desired compounds **6c**,**h** could be obtained in 36 and 32%, respectively (Table 3, entries 3 and 8) next to decomposed material due to the competitive cleavage of the labile TMS-protecting group. Attempts to run the reaction with the terminal acetylenes under anhydrous conditions in DMF using ammonium formate as the reducing agent,[2b] resulted in recovery of the starting material.

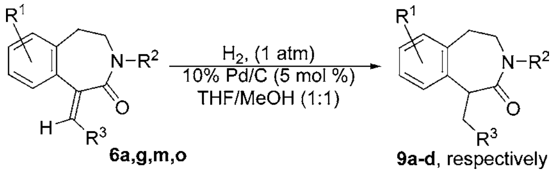
Table 2. Heck Reductive Cyclization of the Amides **3a**−**o**[a]



entry	R¹	R²	R³	yield (%)
1 (**6a**)	3-MeO, 4-MeO	PMB	Ph	81
2 (**6b**)	3-MeO, 4-MeO	PMB	Me	65
3 (**6c**)	3-MeO, 4-MeO	PMB	TMS	36
4 (**6d**)	3-MeO, 4-MeO	PMB	*p*-methoxyphenyl	77
5 (**6e**)	3-MeO, 4-MeO	Me	*p*-methoxyphenyl	71
6 (**6f**)	3-MeO, 4-MeO	Me	Ph	68
7 (**6g**)	3-MeO, 4-MeO	Me	Me	61
8 (**6h**)	3-MeO, 4-MeO	Me	TMS	32
9 (**6i**)	3-MeO, 4-MeO	H	Ph	39
10 (**6j**)	3-MeO, 4-MeO	H	Me	53
11 (**6k**)	H	Me	*n*-Pentyl	81
12 (**6l**)	H	Me	*p*-methoxyphenyl	80
13 (**6m**)	H	Me	Me	61
14 (**6n**)	H	*i*-Pr	*p*-methoxyphenyl	87
15 (**6o**)	H	*i*-Pr	3,4,5-trimethoxyphenyl	90

[a] All reactions were run on a 0.4 mmol scale; for all entries except 3 and 8, Pd(PPh$_3$)$_4$ (3 mol %), HCOONa (1.5 equiv), in 6 mL of solvent DMF/H$_2$O (3:1), at 110 °C, maximum power 300 W for 15 min. For entries 3 and 8,same conditions as for all other entries with the exception of HCOONa (3 equiv), solvent DME/H$_2$O (4:1), 120 °C.

Table 3. Double-Bond Hydrogenation[a]



entry	R¹	R²	R³	yield (%)
1 (**9a**)	3-MeO, 4-MeO	PMB	Ph	90
2 (**9b**)	3-MeO, 4-MeO	Me	Me	96
3 (**9c**)	H	Me	Me	96
15 (**9d**)	H	*i*-Pr	3,4,5-trimethoxyphenyl	95

[a] Reactions were run on a 0.3−0.4 mmol scale under H$_2$ atmosphere (1 atm), in 6−10 mL of THF/MeOH (1:1) with 10% Pd/C (5 mol %) at rt for 24 h.

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(12) See the Supporting Information: (a) synthesized following known procedures; (b) MW-assisted deprotection in acidic media proceeds with 80−84% yield; (c) synthesized in 75% yield from 2-bromo-4,5-dimethoxycinnamic acid.

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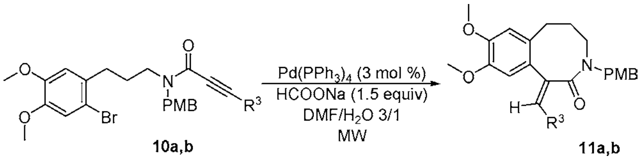
In view of generating 1-alkyl-substituted 3-benzazepinones, which further may be reduced[5b,8] to the corresponding 3-benzazepines, we explored the reduction of the double bond of the enones **6a**,**g**,**m**,**o**. Hydrogenation over Pd/C in THF/MeOH (1:1) proceeded smoothly rendering the 1-alkyl-3-benzazepinones **9a−d** in excellent yields after 24 h under atmospheric pressure of hydrogen (Table 3).

To explore the general applicability of our strategy for the synthesis of medium-sized rings, we evaluated the protocol for the generation of 8-membered N-containing rings. Similar tetrahydrobenzo[*d*]azocine structures have been previously synthesized via palladium-catalyzed heteroannulation of allenes.[13] Howeve, this procedure renders the compounds as an *E*/*Z* mixture of isomers of the exocyclic double bond. On the contrary, our method should produce only *Z*-isomers following the mechanism of ring closure. The substrates **10a**,**b** bearing an extended alkyl chain were synthesized starting from [3-(2-bromo-4,5-dimethoxyphenyl)-propyl]-(4-methoxybenzyl)amine.[12c] Applying our microwave-assisted protocol cyclization of **10a**,**b** occurred in 35 and 55% respectively next to the partial decomposition of the starting material. As expected, the compounds were isolated as single Z-isomers **11a**,**b** (Table 4). The lower yields could probably be ascribed to the higher conformational freedom of the starting amides **10a**,**b**.

Table 4. Heck Reductive Cyclization of the Amides **10a**,**b**[a]



entry	R^3	yield (%)
1 **(11a)**	Me	55
2 **(11b)**	Ph	35

[a] Reactions were run on a 0.4 mmol scale in 6 mL of DMF/H_2O (3:1) under MW irradiation at 110 °C and 300 W maximum power for 15 min.

In summary, we have developed an efficient new procedure for the synthesis of 1-substituted 3-benzazepinones. The medium-sized ring is constructed applying a microwave-assisted reductive intramolecular Heck reaction, which occurs with full regio- and stereoselectivity. The applicability of this strategy for the synthesis of some benzazepine alkaloids and analogues is under current investigation.

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Supporting Information Available: Spectroscopic data for all new compounds prepared, as well as detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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