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Microwave assisted synthesis of 3-benzazepin-2-ones as building blocks for 2,3-disubstituted tetrahydro-3-benzazepines

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ABSTRACT

Microwave assisted condensation of primary amines with keto acids **1a**–**c** provided directly 3,4-disubstituted 1,3-dihydro-3-benzazepin-2-ones **2**. Whereas small amine size, such as NH_3 afforded high yields of secondary lactams **2a**, **2d**, and **2g**, primary amines with larger substituents in α-position led to lower yields of **2** or even to regioisomeric indanone derivatives **4**. However, subsequent alkylation of **2a**, **2d**, and **2g** with various alkyl halides provided the corresponding *N*-substituted 3-benzazepin-2-ones **2** in good yields. Hydrogenation of **2** followed by BH_3 reduction led to 3-benzazepines **9**. 3-Benzyl-2-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**9c**) reveals high σ_1 affinity and selectivity over σ_2 and NMDA receptors.

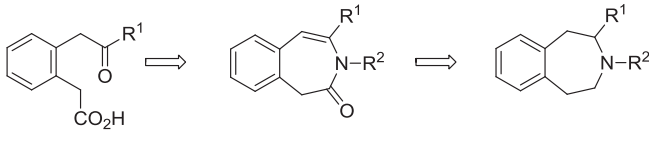
1. Introduction

Seven-membered *N*-heterocycles, in particular tetrahydro-3-benzazepines, have been extensively studied as dopamine receptor agonists and antagonists.[1–3] Furthermore, several 3-benzazepines have also been examined for pharmacological effects, which are not mediated by dopamine receptors.[4–7] Some 3-benzazepines have been shown to be active in animal models of various neurological disorders including Parkinson's disease[8] and Alzheimer's disease.[9]

Recently, it was reported that differently substituted tetrahydro-3-benzazepines interact with high affinity and selectivity with σ_1 receptors.[10–14] The σ_1 receptor represents the best characterized subtype of the σ receptor family. It is well established as non-opioid, non-phencyclidine but haloperidol sensitive receptor with a characteristic ligand binding profile and a characteristic distribution in the central nervous system (CNS) as well as in some peripheral tissues like kidney, liver, lung, and heart.[15,16] Ligands for σ_1 receptors have a potential for the treatment of epileptic disorders,[17] depression,[18] and drug abuse.[19] They also show neuroprotective,[20] antiamnesic,[21] and analgesic activity[21] and may also be used for tumor imaging purposes.[22]

The seven-membered lactam **2** represents a versatile building block for the synthesis of various 3-benzazepines **9**, since it allows the introduction of various substituents in almost all positions of the *N*-containing heterocyclic part (position 1–5) of the ring system (Fig. 1). Modifications of positions 2–4 are described in this manuscript, position 1 can be substituted by enolate chemistry as shown for similar systems[11–14] and position 5 can be modified by enamide chemistry.

In the literature only few methods for the synthesis of 3-benzazepin-2-ones of type **2** with an aldehydic/ketonic carbon at position 4 (*N*/*O*-acetal, enamine) are described. Intra- or intermolecular condensation of various 2-(2-oxoalkyl)phenylacetic acid derivatives with phenylglycinol led to 3-benzazepin-2-ones



1 2 9

Fig. 1. 3-Benzazepin-2-ones **2** as key building blocks for the synthesis of diversely substituted tetrahydro-3-benzazepines.

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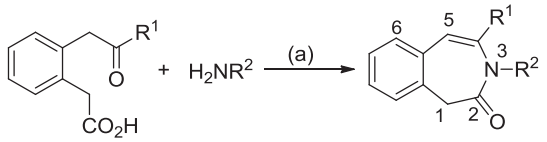
with an *N*/*O*-acetalic group in position 4.[11–14] 3-Benzazepinones of type **2** were regioselectively synthesized by intramolecular hydroamidation of *ortho*-alkynylphenylacetamides.[23] The synthesis of *N*-unsubstituted 3-benzazepinones of type **2** was reported by condensation of ε-oxo acids with ammonium acetate in glacial acetic acid.[24] Furthermore, a 3-benzazepinone of type **2** was formed as side product during the synthesis of fully conjugated seven and eight membered heterocyclic systems.[25]

Herein we wish to report the synthesis of both *N*-unsubstituted and *N*-substituted 3-benzazepin-2-ones **2** under microwave irradiation by direct combination of keto acids **1** and primary amines. According to our strategy keto acids **1** provide all carbon atoms of the final heterocyclic system and the remaining *N*-atom is coming from ammonia or a primary amine (Fig. 1). The resulting 3-benzazepin-2-ones **2** are further developed into potent σ_1 ligands **9**.

2. Synthesis

The synthesis of the 3-benzazepinones **2** started with keto acids **1**, which are available by reaction of *o*-phenylenediacetic acid with an excess of organolithium reagents[26] Reaction of methyl keto acid **1a** with benzylamine in refluxing toluene for 1 day led to the 3-benzazepinone **2c** in 20% yield together with some non-identified products (Scheme 1). Increasing the amount of benzylamine up to 10 equiv and the reaction time up to 3 days did not improve the yield of **2c**.



1a-c **2a-g**

1	R^1
a	Me
b	Bu
c	Ph

2	R^1	R^2	yield (%)
a	Me	H	50
b	Me	Me	30
c	Me	Bn	34
d	Bu	H	56
e	Bu	Me	32
f	Bu	Bn	26
g	Ph	H	60

Scheme 1. Reagents and reaction conditions: (a) microwave irradiation, toluene, 120 °C, 2–3 h, 150 W, 5 bar.

It has been shown that microwave irradiation often leads to reduced reaction times (increased reaction rate) and improved yields.[27] Thus, the mixture of keto acid **1a** and benzylamine in toluene was irradiated by microwaves, which increased the yield of the 3-benzazepinone **2c** to 34%. Replacement of the solvent toluene with DMF, THF or methanol did not lead to a further improvement of the yield. Therefore, the optimized reaction conditions (microwave irradiation, toluene) were applied on the transformation of the three keto acids **1a**–**c** with NH_4OAc, methylamine, and benzylamine, respectively, which led to the expected 3-benzazepinones **2a**–**g** in yields of 26–60 %.

The NMR data of **2a** (singlet at 6.15 ppm for 5-H; signals at 113.9 and 134.7 ppm for C-5 and C-4) show the presence of the C4–C5 double bond, which is further confirmed by recording an X-ray crystal structure. Recrystallization of **2a** with CH_2Cl_2/*n*-hexane mixture led to crystals suitable for X-ray crystal structure analysis. Moreover, the three-dimensional structure of the 3-benzazepinone system is shown by the crystal structure (Fig. 2). With exception of the sp^3-hybridized carbon atom in 1-position, all atoms of the ring

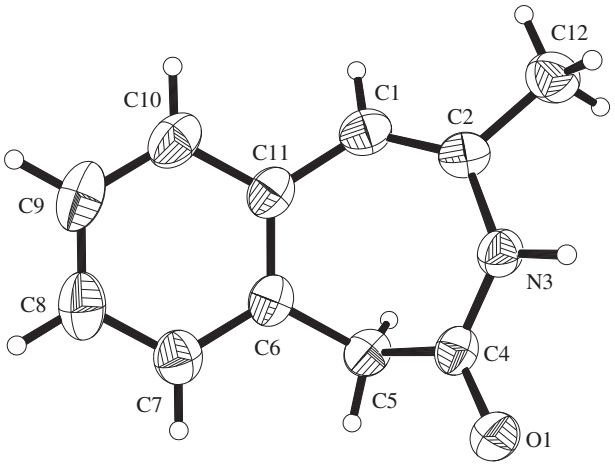


Fig. 2. X-ray crystal structure analysis of **2a**.

system are sp^2-hybridized indicating a rather planar system. Due to the tetrahedral structure of C-1, a deviation from coplanarity is only observed around this carbon atom. The carbonyl moiety and the adjacent *N*-atom are lying above the ring plane. This structure is very similar to the structure of a comparable 3-benzazepine reported recently by Liu and co-workers.[23b]

The table in Scheme 1 clearly indicates that the yields of the 3-benzazepinones **2** decreased with increasing size of the amine residue. The best yields (50–60 %) were obtained by reaction of keto acids **1** with the very small amine NH_3 (from NH_4OAc), the analogous condensations of **1** with methylamine and benzylamine afforded considerably lower yields of the corresponding *N*-methyl and *N*-benzyl derivatives. We assume that shielding of the *N*-atom in the intermediates analogously to **3** inhibits the formation of seven-membered lactams.

When using (*S*)-1-phenylethylamine bearing two substituents in α-position of the amino moiety for the condensation with keto acids **1a** and **1b**, the indanones (*S*)-**4a** and (*S*)-**4b** were isolated instead of the expected 3-benzazepin-2-ones **2** (Scheme 2). Careful analysis of the reaction mixtures did not provide any hints for the presence of 3-benzazepinones. We assume that the electron rich double bond of the enamine intermediate **3** reacted faster with the carboxy group than the shielded amino moiety. An analogous indanone derivative was also formed as side product during the reaction of the sterically most demanding phenyl derivative **1c** with phenylglycinol.[13]

A similar observation was made during the reaction of *o*-phenylenediacetic acid (**5**) with (*R*)-phenylglycinol, which provided exclusively the 1-substituted indanone derivative (*R*)-**7**. Again a fast reaction of the electron rich double bond of the intermediate ketene-*N*/*O*-acetal **6** with the carboxy group is the reason for the formation of the indanone (*R*)-**7**. Recrystallization of (*R*)-**7** from CH_2Cl_2/*n*-hexane led to crystals, which were suitable for an X-ray crystal structure analysis (Fig. 3). This X-ray crystal structure analysis proves the indanone structure of the product (*R*)-**7** and, moreover, the (*E*)-configuration of the exocyclic double bond leading to an *H*-bond between the carbonyl moiety and the NH-group. Due to similar chemical shifts in the ^1H and ^{13}C NMR spectra of (*S*)-**4a**,**b** and (*R*)-**7**, we assume similar structures for (*S*)-**4a** and (*S*)-**4b**, i.e. (*Z*)-configuration of the exocyclic double bond. The enantiomers (*R*)-**4a**,**b** and (*S*)-**7** were synthesized in the same way using (*R*)-1-phenylethylamine and (*S*)-phenylglycinol, respectively.

In order to improve the yields of *N*-substituted lactams, the secondary lactams **2a**, **2d**, and **2g** were alkylated with methyl iodide or benzyl bromide in the presence of concd KOH and tetrabutylammonium iodide (Bu_4NI) (Scheme 3).[28] The differently substituted dihydro-3-benzazepinones **2** were hydrogenated with