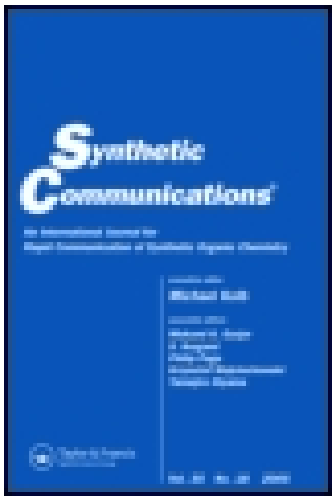

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A Facile and Simple Synthesis of N-Alkyl and N-Aryl 2-Benzazepines by Nucleophilic Heteroannulation

A. K. Srinivasan [a], K. Rajashekar [a], Shyamapada Banerjee [a] & U. K. Syam Kumar [a]

[a] Custom Pharmaceutical Services, Dr Reddy's Laboratories Limited, Bollaram Road, Miyapur, Hyderabad, India

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A Facile and simple synthesis of *N*-Alkyl and *N*-Aryl 2-Benzazepines by nucleophilic heteroannulation

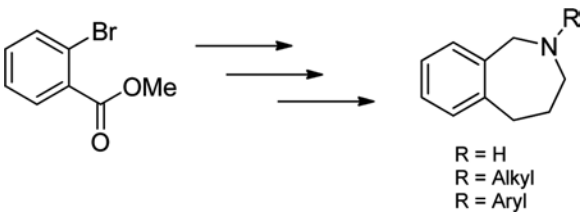
A. K. Srinivasan[1], K. Rajashekar[1], Shyamapada Banerjee[1], U. K. Syam Kumar[1]

[1]Custom Pharmaceutical Services, Dr Reddy's Laboratories Limited, Bollaram Road, Miyapur, Hyderabad, India

Corresponding Email: srinivasanak@drreddys.com

Abstract

An efficient and practical synthesis of N-alkyl and N-aryl 2-benzazepine has been developed. The key steps involved in the synthesis were palladium mediated Heck reaction followed by aza heterocyclic ring construction by nucleophilic heteroannulation. This four step sequence synthetic protocol gave moderate to good yield for a wide range of substrates. Subsequently, functionalization of the synthesized compound was carried out under Heck and Suzuki reaction conditions.



KEYWORDS: 2-benzazepine, Heck reaction, nucleophilic heteroannulation, Suzuki reaction.

INTRODUCTION

The 2-benzazepine is not only a unique aromatic fused aza-heterocyclic structure but also is a core component of a number of pharmacologically important compounds [1]. Benzazepine derivatives exhibit a variety of biological activities such as analgesic, antiarrhythmic, anticonvulsant, hypertensive activities [2] and peptide mimic of RGD motif [3]. Further; it would be useful antagonists of muscarinic (M3) receptors. In addition, these compounds are helpful for treatment of mental disorders and hypoxia [4]. Recently benzazepine derivatives are reported as a potential drug candidate to prevent cell-cell adhesion [5]. Benzazepine skeleton is a main part for many naturally available alkaloids of the *amaryllidaceae* group such as *cripowellin A lycoramine*, *narwedine etc.,* and equally benzazepine core structure found in various active pharmaceuticals ingredients such as *mirtazapine, galanthamine*[6] *etc.* Due to the diverse pharmacological properties, benzazepine heterocycles have drawn our attention to explore the synthesis of novel 2-benzazepines *via* an efficient methodology.

There are several known synthetic reports available in the literature for the synthesis of 2-benzazepine, such as Pictet-Spengler cyclization [7], Bischler-Napieralski protocol [8], Beckmann or Schmidt rearrangements of 3, 4-dihydro-1(*2H*)-naphthalenone[9], using ring-closing metathesis methodology [10], functionalized benzyl amine or benzyl chlorides cyclization [11] and using one-pot transformation of the Baylis–Hillman adducts *via* the simultaneous Ritter and Houben–Hoesch reactions [12]. Other striking synthesis are TMSOTf promoted Friedel–Crafts reaction of vinyloxirane [13], Rhodium-Catalyzed hydroaminomethylation [14], construction of 2-benzazepine by $TiCl_4$-Mediated Tandem Mannich Reaction [15] and synthesized from substituted cinnamylamide *via* an

intramolecular Friedel−Crafts reaction [16]. Though synthesis of 2-benzazepine was widely reported, significant efforts have been made to develop a simple and efficient synthesis of 2-benzazepine.

Palladium-mediated coupling reactions are very much interested due to their versatility and high functional group tolerance. Among all palladium-mediated coupling reactions, Heck reaction is more attractive due to their clean reaction profile and less formation of side product towards the formation of C–C bond of aryl halides or vinyl halide with activated olefins [17]. The Heck cross coupling was employed for the synthesis of the key intermediate 3-(2-(hydroxymethyl)phenyl)propan-1-ol (**4**) which is the structural requirement for the synthesis of benzazepine frame work. It could be easily converted in to 2-benzazepine derivatives by nucleophilic heteroanulation reaction. In our present work, we wish to now report preparation of *N*-alkyl and *N*-aryl 2-benzazepines and also like to report further functionalization of 2-benzazepine for generating novel and structurally diversified benzazepines derivatives.

RESULTS & DISCUSSION

Our approach started for the synthesis of 2-benzazepine from commercially accessible methyl 2-bromobenzolate (**1**) (Scheme 1). It was treated with methyl acrylate using Heck reaction protocol which afforded *E*-arylalkene diester **2**[18]. To find the best experimental conditions for the Heck coupling reaction we have carried out the reaction with different palladium catalyst in various solvents / bases. The details are listed in Table 1. It was found that the best result was obtained when the reaction was carried out with 5 mol%

$Pd(PPh_3)_2Cl_2$ in the presence of triethylamine in toluene at 100 °C, Thus prepared diester intermediate **2** was subjected for LAH reduction, but failed to get cleaner reaction profile even at higher temperature. This was due to the presence of different functional group in ester **2.** Hence, intermediate **2** was hydrogenated with 5 % Pd/C which yielded saturated diester **3.** The ester **3** was subjected to LAH reduction to our delight, the reaction proceeded smoothly and afforded the diol **4** in a cleaner profile with more than 95 % yield [19]. The obtained diol **4** was converted into bismesylated product (**5**) by using 2.5 equiv. of methanesulfonyl chloride and triethylamine condition, which could act as a better leaving group [20] during nucleophilic heteroannulation reaction. It has been observed that mesylated product (**5**) was quite unstable during distillation, so it was planned to move forward with next step without isolation.

With bismesylated (**5**) product in hand, our approach was to evaluate the synthesis of benzazepine (**6**) ring *via* heteroanuulation with a nitrogen nucleophile. Initially we have checked the heteroanuulation with methanolic ammonia, but the reaction did not proceed well, due to weak nucleophilicity of ammonia. Then the reaction was carried out with methanolic ammonia in the presence of 15-20 psi of ammonia pressure at room temperature. The reaction went well and 2-benzazepine **6a** was isolated [21]. To assess the scope and limitations of synthesis of 2-benzazepine **6** *via* versatile nucleophilic heteroanuulation (Table 2), a series of *N*-substituted 2-benzazepine **6** (**b-l**) were prepared with moderate to good yield with various nucleophile (aliphatic and aromatic amines). The reactivity of heteroanuulation reaction was varied with respect to the nucleophile. If the nucleophile is an aliphatic amine the reaction was fast at 0 °C, whereas with aromatic

amine the reaction was slow even at room temperature. Nevertheless, the reaction proceeded well and the pure products were isolated by column chromatography. The structure of the compounds was characterized by spectral data.

As we have prepared 2-(2-bromophenyl)-2, 3, 4, 5-tetrahydro-1*H*-benzo[c]azepine (**6i**), It was picked further for structural elaboration through various palladium mediated coupling reactions for molecular assortment (Scheme 2). Accordingly, bromo derivative **6i** was subjected to Heck, and Suzuki coupling reactions (Table 3). Suzuki reaction was carried out by using **6i** (1.0 equiv), a boronic acid (1.15 equiv.), $Pd(PPh_3)_4$ (5 mol%), and K_3PO_4 (2 equiv) in dimethoxy ethane at 90 °C (Table 3, entries a-c). Heck reaction was carried out by using **6i** (1.0 equiv), and methyl acrylate (2.0 equiv), $Pd(PPh_3)_2Cl_2$ (5 mol%), K_2CO_3 (2.5 equiv) in Toluene at 100 °C (Table 3, entry d). After usual workup, corresponding coupled products were isolated with good yields.

CONCLUSION

In summary, we have developed a novel methodology for the preparation of 2-benzazepine derivatives from commercially available methyl 2-bromobenzolate in four steps. The methodology involves heteroanuulation of *in situ* prepared bismesylated diol with various nitrogen nucleophiles to afford the 2-benzazepine derivatives in moderate to good yield. The molecular diversity of 2-benzazepine derivatives was demonstrated by Heck and Suzuki cross coupling reactions. Studies are in progress to expand the scope of this methodology for the synthesis of more complex natural products.

EXPERIMENTAL

General methods: All reactions were carried out in oven dried glassware under an atmosphere of N_2. ^1H & ^{13}C NMR spectra were recorded in $CDCl_3$ & DMSO-d_6 on *Varian Gemini 400 MHz FT* spectrometers. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet). Coupling constants (*J*) are given in Hertz. Mass spectra were obtained on a HP-5989A Mass Spectrometer. Thin layer chromatography was performed on silica gel plates (SRL 230-400 mesh). All solvents used are commercially available and were distilled before use.

General Procedure For Synthesis Of *N*-Alkyl And *N*-Aryl 2-Benzazepine (6b-L)

To a solution of 3-(2-(hydroxymethyl)phenyl)propan-1-ol (**4**) (1 g, 6.02 mmol), dichloromethane (20 mL) was added triethylamine (3.4 g, 30.1 mmol). The reaction mixture was cooled to 0 °C; methanesulfonyl chloride (1.72 g, 15.1 mmol) was added at 0 °C and stirred for 3 h. The reaction mixture was washed with water and brine, dried over $MgSO_4$. To the mesylate solution respective amine (6.3 mmol) was added. Upon reaction completion the reaction mass was washed with water and concentrated under reduced pressure. The products were purified by column chromatography over silica gel using hexane-ethyl acetate to afford the pure product (61-79 % yield).

General Procedure For Suzuki Coupling Reaction (7a-C)

To a solution of 2-(2-bromophenyl)-2, 3, 4, 5-tetrahydro-1*H*-benzo[c]azepine (**6i**) (200 mg, 0.66 mmol) in 10 mL of dimethoxyethane was added respective boronic acid (117

mg, 0.76 mmol) and K_3PO_4 tribasic (280 mg, 1.32 mmol). The mixture was degassed and then $Pd(PPh_3)_4$ (38 mg, 0.03mmol) was added. The reaction mixture was stirred at 90 °C for 12 h. The reaction mixture was cooled to room temperature and filtered on celite bed and washed with EtOAc (20 mL). The organic layer washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The products were purified by column chromatography over silica gel using hexane-ethyl acetate to afford the pure product (84-87 % yield).

SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

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ACCEPTED MANUSCRIPT

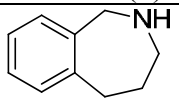
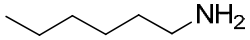
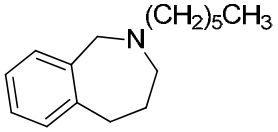
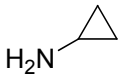
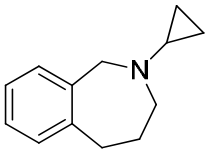
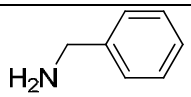
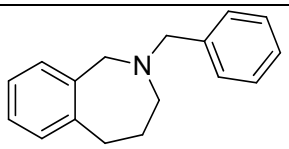
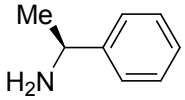
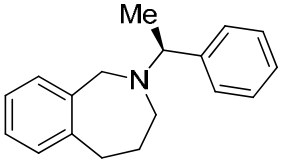
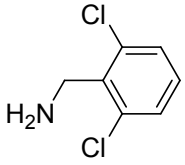
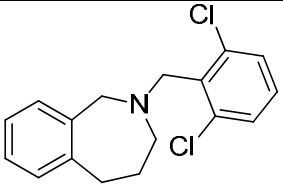
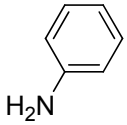
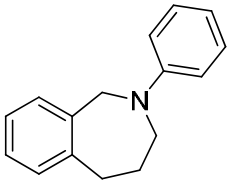
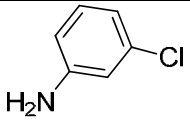
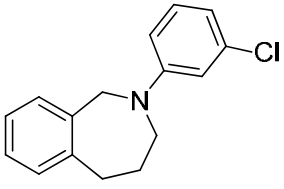
Table 1. Optimization of reaction conditions for the Heck reaction

Entry	Catalyst	Solvent	Base	Temp °C	Time h	Yield * %
1	$Pd(PPh_3)_4$	DMF	Na_2CO_3	130	14	84
2	$Pd(PPh_3)_4$	DMF	TEA	130	24	60
3	$Pd(PPh_3)_4$	Toluene	TEA	110	24	45
4	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	DMF	TEA	130	24	66
5	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	Toluene	TEA	100	18	71
6	$Pd(PPh_3)_2Cl_2$	Toluene	TEA	100	6	94
7	$Pd(PPh_3)_2Cl_2$	DMF	TEA	130	18	81
8	$PdCl_2$	DMF	TEA	130	24	24
9	$PdCl_2$	Toluene	TEA	100	36	48

*Condition: All reactions were carried out by using compound **1** (1.0 equiv), Methylacrylate (1.5 equiv), catalyst (5 mol %) and base (3 equiv.).*

* *Isolated yield by column purification, Remaining un reacted starting material was recovered.*

Table 2. Scope and generality of nucleophilic heteroannulation reactions

Entry	Amine	Product (**6**)	Yield (%)	Time (h)
a	Methanolic.NH_3		73	7
b			79	3
c			74	4
d			73	5
e			69	4
f			71	8
g			71	18
h			78	18

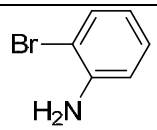
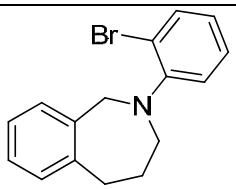
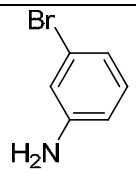
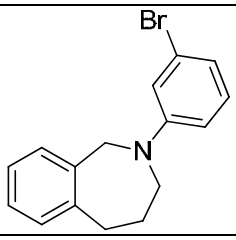
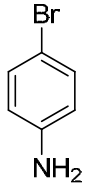
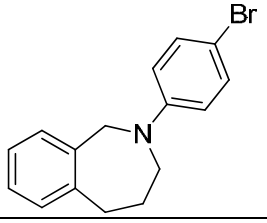
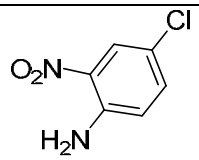
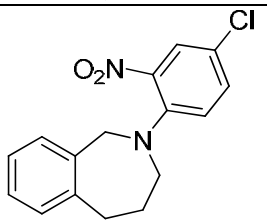
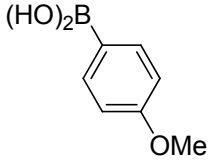
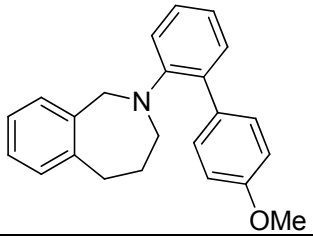
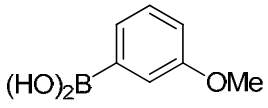
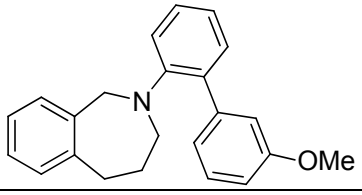
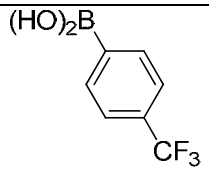
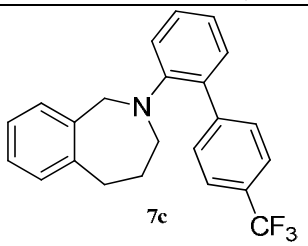
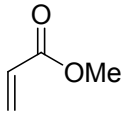
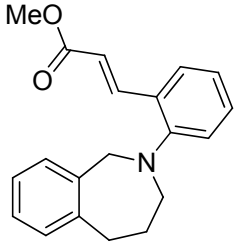
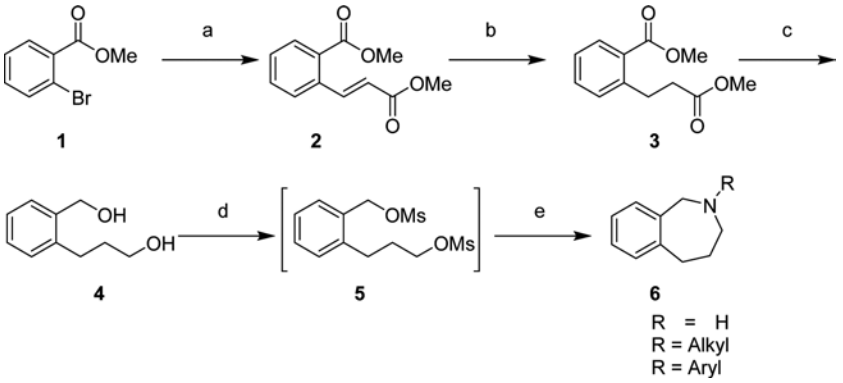
i			75	20
j			70	21
k			69	18
l			61	26

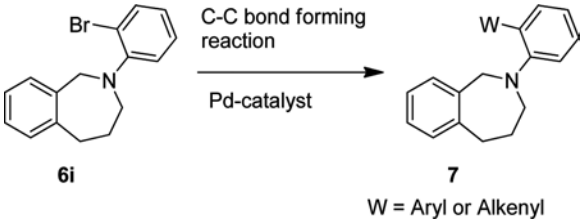
Table 3. Heck and Suzuki coupling reactions of 6i

Entry	Reactants	Product (**7**)	Yield (%)	Time (h)
a			87	12
b			86	13
c		 **7c**	84	12
d		 **7d**	93	10

Scheme 1. Preparation of 2-benzazepine via nucleophilic heteroannualation; Reagents & conditions; a)$Pd(PPh_3)_2Cl_2$,Et_3N, Toluene, Methyl acrylate, 100°C, 6h, 94%;b)5% Pd/C, Methanol, rt, 1h, 96%;c)LAH, THF, rt,3h, 95%; d)MsCl, Et_3N, CH_2Cl_2, 0°C, 3h; e)(i) methanolic ammonia, 15–20 psi of ammonia, rt, 7h; (ii) Aliphatic amine, CH_2Cl_2, 0°C, 3h t0 8h; (iii) Aryl amine, CH_2Cl_2, rt, 18h to 26h.



Scheme 2. Heck and Suzuki coupling reactions of 6i



6i **7**

W = Aryl or Alkenyl