FACILE AND SIMPLE SYNTHESIS OF N-ALKYL AND N-ARYL 2-BENZAZEPINES BY NUCLEOPHILIC HETEROANNULATION

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GRAPHICAL ABSTRACT

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 yields 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

2-Benzazepine is not only a unique aromatic fused aza-heterocyclic structure but also a core component of a number of pharmacologically important compounds.[1] Benzazepine derivatives exhibit a variety of biological activities such as analgesic, antiarrhythmic, anticonvulsant, and hypertensive activities[2] and are peptide mimics of the RGD motif.[3] Further, they 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 potential drug candidates to prevent cell–cell adhesion.[5] The benzazepine skeleton is a main part for many naturally available alkaloids of the amaryllidaceae group.

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such as cripowellin A, lycoramine, narwedine, etc., and equally the benzazepine core structure is found in various active pharmaceuticals ingredients such as mirtazapine and galanthamine.[6] Because of their diverse pharmacological properties, benzazepine heterocycles have drawn our attention to 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] ring-closing metathesis methodology,[10] functionalized benzyl amine or benzyl chlorides cyclization,[11] and one-pot transformation of the Bayliss–Hillman adducts via the simultaneous Ritter and Houben–Hoesch reactions.[12] Other striking syntheses are TMSOTf-promoted Friedel–Crafts reaction of vinyloxirane,[13] rhodium-catalyzed hydroaminomethylation,[14] construction of 2-benzazepine by TiCl4-mediated tandem Mannich reaction,[15] and 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 interesting because of their versatility and high functional group tolerance. Among all palladium-mediated coupling reactions, the Heck reaction is more attractive because of their clean reaction profile and formation of fewer side products in 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 framework. It could be easily converted into 2-benzazepine derivatives by nucleophilic heteroannulation reaction. In our present work, we now report preparation of N-alkyl and N-aryl 2-benzazepines and also further functionalization of 2-benzazepine for generating novel and structurally diversified benzazepines derivatives.

RESULTS AND DISCUSSION

Our approach started with 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 catalysts in various solvents and bases. The details are listed in Table 1. The best result was obtained when the reaction was carried out with 5 mol% Pd(PPh3)2Cl2 in the presence of triethylamine in toluene at 100 °C. The prepared diester intermediate 2 was subjected to LAH reduction, but failed to get a cleaner reaction profile even at higher temperature. This was due to the presence of a 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 and 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 we 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 heteroannulation with a nitrogen nucleophile. Initially we have checked the heteroannulation with methanolic ammonia, but the reaction did not proceed well because of the 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 heteroannulation (Table 2), a series of N-substituted 2-benzazepines 6(b–l) were prepared in moderate to good yields with various nucleophiles (aliphatic and aromatic amines). The reactivity of heteroannulation reaction was varied with respect to the nucleophile. If the nucleophile is an aliphatic amine

![Scheme 1. Preparation of 2-benzazepine via nucleophilic heteroannulation. Reagents and conditions: (a) Pd(PPh3)2Cl2, Et3N, toluene, methyl acrylate, 100 °C, 6 h, 94%; (b) 5% Pd/C, methanol, rt, 1 h, 96%; (c) LAH, THF, rt, 3 h, 95%; (d) MsCl, Et3N, CH2Cl2, 0 °C, 3 h; (e) (i) methanolic ammonia, 15–20 psi of ammonia, rt 7 h; (ii) aliphatic amine, CH2Cl2, 0 °C, 3 h to 8 h; (iii) aryl amine, CH2Cl2, rt, 18 h to 26 h.](image)

Table 1. Optimization of reaction conditions for the Heck reaction

| Entry | Catalyst | Solvent | Base    | Temp. (°C) | Time (h) | Yield\(^a\) (%) |
|-------|----------|---------|---------|------------|----------|-----------------|
| 1     | Pd(PPh3)4 | DMF     | Na₂CO₃  | 130        | 14       | 84              |
| 2     | Pd(PPh3)4 | DMF     | TEA     | 130        | 24       | 60              |
| 3     | Pd(PPh3)4 | Toluene | TEA     | 110        | 24       | 45              |
| 4     | Pd(dppf)Cl2·CH2Cl2 | DMF | TEA | 130       | 24       | 66              |
| 5     | Pd(dppf)Cl2·CH2Cl2 | Toluene | TEA | 100       | 18       | 71              |
| 6     | Pd(PPh3)2Cl2 | Toluene | TEA | 100       | 6        | 94              |
| 7     | Pd(PPh3)2Cl2 | DMF | TEA | 130       | 18       | 81              |
| 8     | PdCl2    | DMF     | TEA     | 130        | 24       | 24              |
| 9     | PdCl2    | Toluene | TEA | 100       | 36       | 48              |

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

\(^a\)Isolated yield by column purification. Remaining unreacted starting material was recovered.
Table 2. Scope and generality of nucleophilic heteroannulation reactions

| Entry | Amine                  | Product (6) | Yield (%) | Time (h) |
|-------|------------------------|-------------|-----------|----------|
| a     | Methanolic·NH₃         | ![Image](image1) | 73        | 7        |
| b     | ![Image](image2)      | ![Image](image3) | 79        | 3        |
| c     | ![Image](image4)      | ![Image](image5) | 74        | 4        |
| d     | ![Image](image6)      | ![Image](image7) | 73        | 5        |
| e     | ![Image](image8)      | ![Image](image9) | 69        | 4        |
| f     | ![Image](image10)     | ![Image](image11) | 71        | 8        |
| g     | ![Image](image12)     | ![Image](image13) | 71        | 18       |
| h     | ![Image](image14)     | ![Image](image15) | 78        | 18       |

(Continued)
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 structures of the compounds were characterized by spectral data.

As we prepared 2-(2-bromophenyl)-2,3,4,5-tetrahydro-1H-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). The Suzuki reaction was carried out by using 6i (1.0 equiv), a boronic acid (1.15 equiv.), Pd(PPh3)4 (5 mol%), and K3PO4 (2 equiv) in dimethoxy ethane at 90°C (Table 3, entries a–c). The Heck reaction was carried out by using 6i (1.0 equiv), methyl

| Entry | Amine | Product (6) | Yield (%) | Time (h) |
|-------|-------|-------------|-----------|----------|
| i     | ![Image] | ![Image] | 75        | 20       |
| j     | ![Image] | ![Image] | 70        | 21       |
| k     | ![Image] | ![Image] | 69        | 18       |
| l     | ![Image] | ![Image] | 61        | 26       |
acrylate (2.0 equiv), Pd(PPh₃)₂Cl₂ (5 mol%), and K₂CO₃ (2.5 equiv) in toluene at 100°C (Table 3, entry d). After usual workup, the corresponding coupled products were isolated with good yields.

Table 3. Heck and Suzuki coupling reactions of 6i

| Entry | Reactants | Product (7) | Yield (%) | Time (h) |
|-------|-----------|-------------|-----------|----------|
| a     | (HO)₂B    | ![Screen Shot 2023-01-14 at 12.26.13 PM.png](Screen Shot 2023-01-14 at 12.26.13 PM.png) | 87 | 12 |
| b     | (HO)₂B    | ![Screen Shot 2023-01-14 at 12.26.22 PM.png](Screen Shot 2023-01-14 at 12.26.22 PM.png) | 86 | 13 |
| c     | (HO)₂B    | ![Screen Shot 2023-01-14 at 12.26.31 PM.png](Screen Shot 2023-01-14 at 12.26.31 PM.png) | 84 | 12 |
| d     | ![Screen Shot 2023-01-14 at 12.26.40 PM.png](Screen Shot 2023-01-14 at 12.26.40 PM.png) | ![Screen Shot 2023-01-14 at 12.26.49 PM.png](Screen Shot 2023-01-14 at 12.26.49 PM.png) | 93 | 10 |
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 yields. 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

All reactions were carried out in oven-dried glassware under an atmosphere of N₂. ¹H and ¹³C NMR spectra were recorded in CDCl₃ and dimethylsulfoxide (DMSO-d₆) on a Varian Gemini 400-MHz FT spectrometers. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ 0.00) as internal standard and expressed in parts per million (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 (TLC) 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)**

Triethylamine (3.4 g, 30.1 mmol) was added to a solution of 3-(2-(hydroxymethyl)phenyl)propan-1-ol (4) (1 g, 6.02 mmol) and dichloromethane (20 mL). 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, and dried over MgSO₄. 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)**

Boronic acid (117 mg, 0.76 mmol) and K₃PO₄ tribasic (280 mg, 1.32 mmol) were added to a solution of 2-(2-bromophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6i) (200 mg, 0.66 mmol) in 10 mL of dimethoxyethane. The mixture was degassed and then Pd(PPh₃)₄ (38 mg, 0.03 mmol) was added. The reaction mixture was stirred at 90°C for 12 h. The reaction mixture was cooled to room temperature, filtered on a celite bed, and washed with EtOAc (20 mL). The organic layer was washed with water and brine, dried (MgSO₄), 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).
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SUPPORTING INFORMATION

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

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