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An efficient one-pot microwave assisted synthesis of dibenzoazepinones

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ABSTRACT

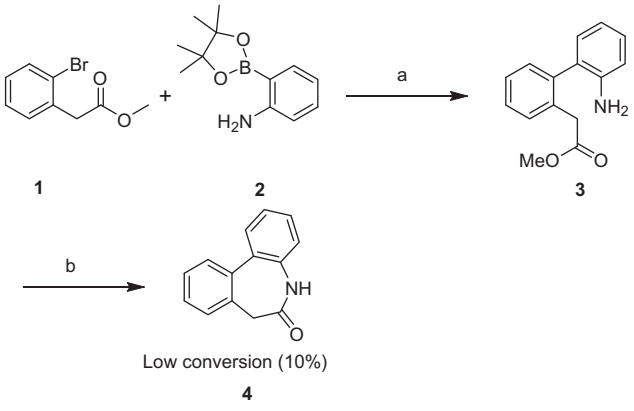
Microwave assisted one-pot synthesis of substituted 5*H*-dibenzo[*b*,*d*]azepin-6(7*H*)-ones from 2-(2-bromophenyl)acetic acid esters and 2-aminophenyl boronates has been described. This approach gives direct access to seven membered lactams with a shorter cycle time of synthesis and high yields.

Biaryl lactams have attracted the attention of researchers as these are the privileged core, identified in many alkaloids and pharmaceutically relevant organic molecules.[1] This moiety is also very important due to it being a core intermediate for LY411575,[2,3] an γ-secretase inhibitor, a clinical candidate for Alzheimer's disease. The synthesis of dibenzoazepinone has been previously reported by Stolle cyclization[4] of N-([1,1′-biphenyl]-2-yl)-2-chloroacetamide and $AlCl_3$ at elevated temperature in poor yields (18–20%). Several other methods have also been reported such as palladium-catalyzed borylation–Suzuki reaction,[5] cyclization of hydroxylamides in neat trifluoromethanesulfonic acid,[6a] intramolecular Staudinger–Aza-Wittig reaction of an azido pentafluorophenylester,[6b] and the hydrogenation of methyl 2-nitro-2′-biphenylacetate.[6c] These reported protocols result in low yields of the desired product and involve multistep synthesis with tedious purification from byproducts. Recently, there is a report on the synthesis of biologically active phenanthridinones and related lactams from C–H arylation of the aniline ring using potassium *tert*-butoxide,[7] whereas, another report describes the one pot synthesis of lactams utilizing *N*-methoxybenzamides and aryl iodide/arene as coupling partners.[8a,8b] However, these methods were focused primarily on the synthesis of six-membered lactams.

Our current interest is to develop a robust, effective, and high yielding methodology for the synthesis of dibenzoazepinones. Herein, we report a synthetic approach which involves a palladium catalyzed arylation, followed by intramolecular amide formation for the synthesis of substituted 5*H*-dibenzo[*b*,*d*]azepin-6(7*H*)-ones.

A model reaction was carried out between 2-(2-bromophenyl)acetic acid esters **1** and 2-aminophenyl boronate **2** in the presence of $Pd(PPh_3)_4$ and Cs_2CO_3 in dimethoxyethane at 125–30 °C for 4 h (Scheme 1).

As expected, C–C coupling reaction was successful with greater than 90% conversion by LCMS. However, intermediate **3** did not cyclize to the desired product, dibenzoazepinone **4** in this condition. We even carried out this reaction in a microwave (Biotage® Initiator) at 125 °C for 30 min and obtained similar results. The smooth conversion to intermediate **3** under thermal and microwave conditions encouraged us to investigate the optimum reaction conditions for the cyclization to the product **4**, with increased nucleophilicity of amine. In order to facilitate the reaction, we added 3.0 equiv of trimethylaluminium[9] (1.0 M solution in toluene) and heated the reaction mixture at 100 °C for 4 h. We observed the occurrence of cyclization by LCMS with poor conversion (~10%).



Scheme 1. Reagents and conditions: (a) $Pd(PPh_3)_4$, Cs_2CO_3, 125 °C, DME, MW, 30 min or thermal, 4 h, 85%; (b) $AlMe_3$, 100 °C, 4 h, 10%.

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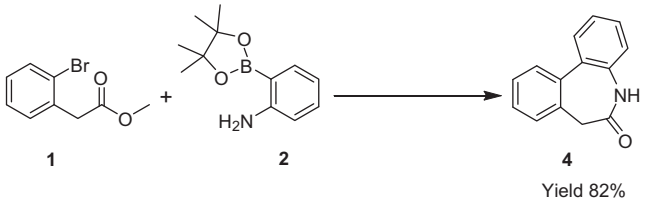


Scheme 2. Reagents and conditions: $Pd(PPh_3)_4$, Cs_2CO_3, 125 °C, DME, MW, 30 min; add KO*t*Bu, 0 °C, 10 min.

Table 1
Optimization of reaction conditions in MW

Entry	Catalyst	Base	Solvent	Time (min)	Yield[a] (%)
1	$Pd(PPh_3)_4$	Cs_2CO_3	DME	30	–
2	$Pd(PPh_3)_4$	Cs_2CO_3/KO*t*Bu	DME	30	82
3	$Pd(PPh_3)_4$	Cs_2CO_3	DME:H_2O	30	53
4	$Pd(PPh_3)_4$	Na_2CO_3	DME:H_2O	30	42
5	$PdCl_2(PPh_3)_2$	Cs_2CO_3	DME	30	45
6	$PdCl_2(PPh_3)_2$	Cs_2CO_3	DME:H_2O	30	42
7	$PdCl_2(PPh_3)_2$	Na_2CO_3	DME:H_2O	30	80
8	$PdCl_2$(dppf)	Cs_2CO_3	DME	30	60
9	$PdCl_2$(dppf)	Na_2CO_3	DME:H_2O	30	26

[a] Isolated yields obtained using 1–1.2 mmol of substrates,[10] 2–3.2 mmol of base, and 21 mol % of catalyst, MW, 125 °C.

This result gave us further direction to use strong basic environment step-wise in the same reaction mixture to test the feasibility of cyclization. In one of the reaction conditions, after completion of C–C bond formation under microwave condition (30 min), we added 1.5 equiv of potassium *tert*-butoxide to reaction mass at 0 °C and stirred the reaction mixture for 10 min. We observed complete conversion of the reaction mixture to the desired product **4** (Scheme 2, Table 1, entry 2).

The cyclization of intermediate **3** with the addition of extra base encouraged us to reiterate the thermal or microwave reaction for a longer time to influence one-pot synthesis of dibenzoazepinone. To our surprise, we observed poor conversion of the product after 36 h of conventional heating at 125 °C. Similar results were obtained under microwave heating at 125 °C for 4 h, along with several impurities in the reaction mixture.

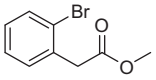
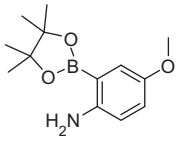
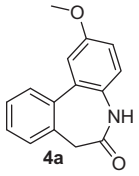
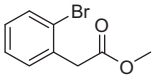
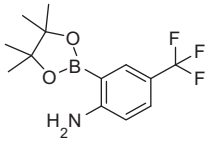
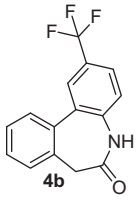
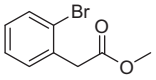
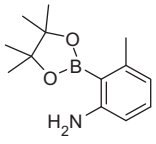
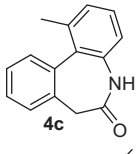
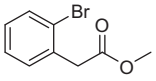
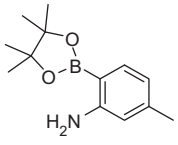
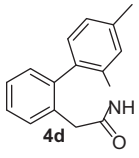
To optimize the reaction condition for one-pot formation of 5*H*-dibenzo[*b*,*d*]azepin-6(7*H*)-ones, we investigated various catalysts, bases, and solvents under MW condition as summarized in Table 1. We observed good one-pot conversion to product **4** with $Pd(PPh_3)_2/Cs_2CO_3$ and DME:H_2O as solvent system (entry 3). The reaction was successful even with a milder base like Na_2CO_3, but with comparatively lower yield (entry 4). The best one-pot conversion was optimized with $PdCl_2(PPh_3)_2/Na_2CO_3$ and DME:H_2O as solvent system in good yield (entry 7).

This extensive screening cascade gave us two best reaction conditions 1 (entry 2) and 2 (entry 7).[10] Their applicability was investigated further on various substrates as described in Table 2. In general, we obtained better yield in condition 1, it might be due to anhydrous environment of the reaction medium.

The influence of various groups on substrates (1 and 2, Table 2) was studied for general applicability of these reaction conditions leading to substituted 5*H*-dibenzo[*b*,*d*]azepin-6(7*H*)-ones. Yet these results were not decisive to reflect the influence of substitutions or reaction conditions on product yields.

To extend the applicability of this methodology, we investigated the synthesis of *N*-alkylated dibenzoazepinone. The reactions were carried out with *N*-alkylated anilines (Substrate 2, Table 3) under optimized reaction conditions. The prime objective of this exploration was to make exclusively *N*-alkylated substrate, yet, we observed a similar pattern of product yields. The results of these experiments have been summarized in Table 3.

Table 2
Microwave mediated synthesis of substituted dibenzoazepinones[10] (**4a**–**4n**)

Entry	Substrate 1	Substrate 2	Product	Isolated yield (%)-condition1/2
1			 **4a**	60/50
2			 **4b**	75/68
3			 **4c**	58/30
4			 **4d**	82/71

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