



Cite this: *RSC Adv.*, 2025, **15**, 6737

Received 7th February 2025
 Accepted 21st February 2025

DOI: 10.1039/d5ra00909j
rsc.li/rsc-advances

Three-step process for the synthesis of 10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-10-ol derivatives†

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We reported the synthesis of 10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-10-ol derivatives, a class of compounds that has been limitedly investigated in the literature. Our approach streamlines the synthetic process, allowing straightforward access to various substituted 10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-10-ol derivatives. This advancement not only enhances the accessibility of these derivatives for further research but also contributes to the development of potential therapeutic agents targeting various medical conditions.

Introduction

Dibenzazepine derivatives are a significant class of compounds in medicinal chemistry, recognized for their wide range of biological activities and therapeutic potential. The tricyclic dibenzazepine system, characterized by a fused bicyclic skeleton containing a sandwiched azepine ring between two benzene rings, displays a distinctive three-dimensional configuration that enables interactions with a wide range of biological targets.¹ Dibenzazepine derivatives synthesis has attracted much attention. Several approaches, including cyclization reactions, ring expansion, and multicomponent reactions, are used to produce structurally different analogs efficiently.²

In the same context, the dibenzo[*b,f*]azepine scaffold-containing compounds are known to possess an abundance of pharmacological features, making their biological activity extremely impressive, including anticancer, anti-inflammatory, antiepileptic, and antidepressant activities (Fig. 1).³ Their capacity to impact neurotransmitter systems, especially those in the central nervous system, has made them useful in creating medications such as novel antiepileptic drugs and mood disorders. Furthermore, certain dibenzo[*b,f*]azepine derivatives have shown encouraging results in blocking GPR4, suggesting their potential as a therapeutic lead for the treatment of myocardial infarction.⁴

In particular, a 10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-10-ol derivative, eslicarbazepine acetate, was quite recently

commercialized as a novel antiepileptic drug indicated for the treatment of partial-onset seizures.⁵ Eslicarbazepine acetate improves upon its predecessors, carbamazepine, and oxcarbazepine, by being available in a once-daily treatment, interacting with a reduced range of drugs, and causing lower side effects.^{3e} 10,11-Dihydro-5*H*-dibenzo[*b,f*]azepin-10-ol derivatives are usually synthesized through the ketone reduction of oxcarbazepine derivatives.⁶ Despite the critical importance of this class of heterocycles in medicinal chemistry, there is a lack of efficient and straightforward methods for their preparation. Even though the influence of the substituent on the nitrogen was already well-documented, studies on the effect of substituents on both phenyl rings are minimal. In this context, there is a need for a new process for preparing 10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-10-ol derivatives with broad substitution patterns to modulate their biological activity. Indeed, the importance of 10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-10-ol derivatives lies not only in their therapeutic potential but also in their role as scaffolds for exploring novel pharmacophores in the quest for new and effective treatments.

Therefore, we aim to develop a rapid and highly productive synthesis method of phenyl-substituted 10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-10-ol derivatives.

Results and discussion

In our endeavor, and in continuation of our previous studies to discover novel biologically active organic compounds,⁷ we established only a three-step process for the synthesis of novel 10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-10-ol compounds from commercially available starting materials.

Tetrakis(dimethylamino)ethylene (TDAE) is an organic reducing agent, that reacts with halogenated derivatives to generate a carbanion under mild conditions.⁸ In particular, from *o*-nitrobenzyl chloride, TDAE was able to generate the corresponding *o*-nitrobenzyl carbanion, which can react with 2-

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† Electronic supplementary information (ESI) available: General procedures, characterization data, and NMR spectra. CCDC 2391789. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d5ra00909j>



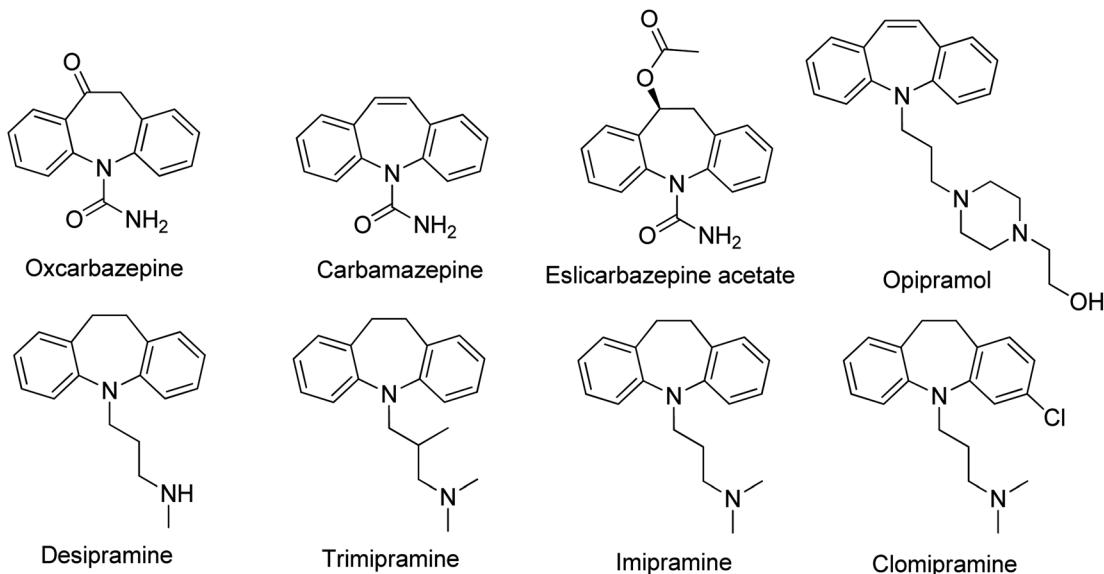
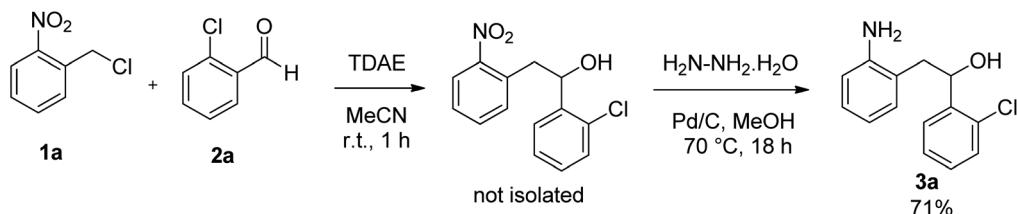
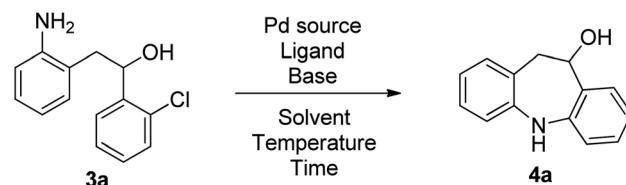


Fig. 1 Biologically active compounds possessing dibenzazepine core.



Scheme 1 Synthesis of 2-(2-aminophenyl)-1-(2-chlorophenyl)ethanol 3a.

Table 1 Optimization of Buchwald-Hartwig coupling reaction conditions^a

Entry	Pd source (10 mol%)	Ligand (10 mol%)	Base (2 equiv.)	Solvent ($\text{C} = 0.5 \text{ mol L}^{-1}$)	Temperature ($^\circ\text{C}$)	Time (h)	Yield ^b (%)
1	$\text{Pd}(\text{OAc})_2$	Xantphos	K_2CO_3	THF	60	2	9
2	$\text{Pd}(\text{OAc})_2$	Xantphos	K_2CO_3	THF ^c	60	2	10
3	$\text{Pd}(\text{OAc})_2$	Xantphos	K_2CO_3	THF	60	16	13
4	$\text{Pd}(\text{OAc})_2$	Xantphos	K_2CO_3	THF	100	48	27
5	$\text{Pd}_2(\text{dba})_3$	XPhos	NaOt-Bu	Toluene	110	16	<5
6	$\text{Pd}_2(\text{dba})_3$	XPhos	NaOt-Bu	1,4-Dioxane	110	16	<5
7	$\text{Pd}(\text{OAc})_2$	XPhos	NaOt-Bu	1,4-Dioxane	110	16	<5
8	$\text{Pd}(\text{OAc})_2$	BINAP	Cs_2CO_3	Toluene	110	16	7
9	$\text{Pd}(\text{OAc})_2$	BINAP	K_2CO_3	Toluene	110	16	8
10	$\text{Pd}(\text{OAc})_2$	Xantphos	K_2CO_3	Toluene	110	16	14
11	$\text{Pd}(\text{OAc})_2$	Xantphos	K_2CO_3	Toluene	110 ^d	8	16
12	$\text{Pd}(\text{OAc})_2$	Xantphos	K_2CO_3	Toluene	150 ^d	8	31
13	$\text{Pd}(\text{OAc})_2$	Xantphos	K_2CO_3	Toluene	170 ^d	8	52

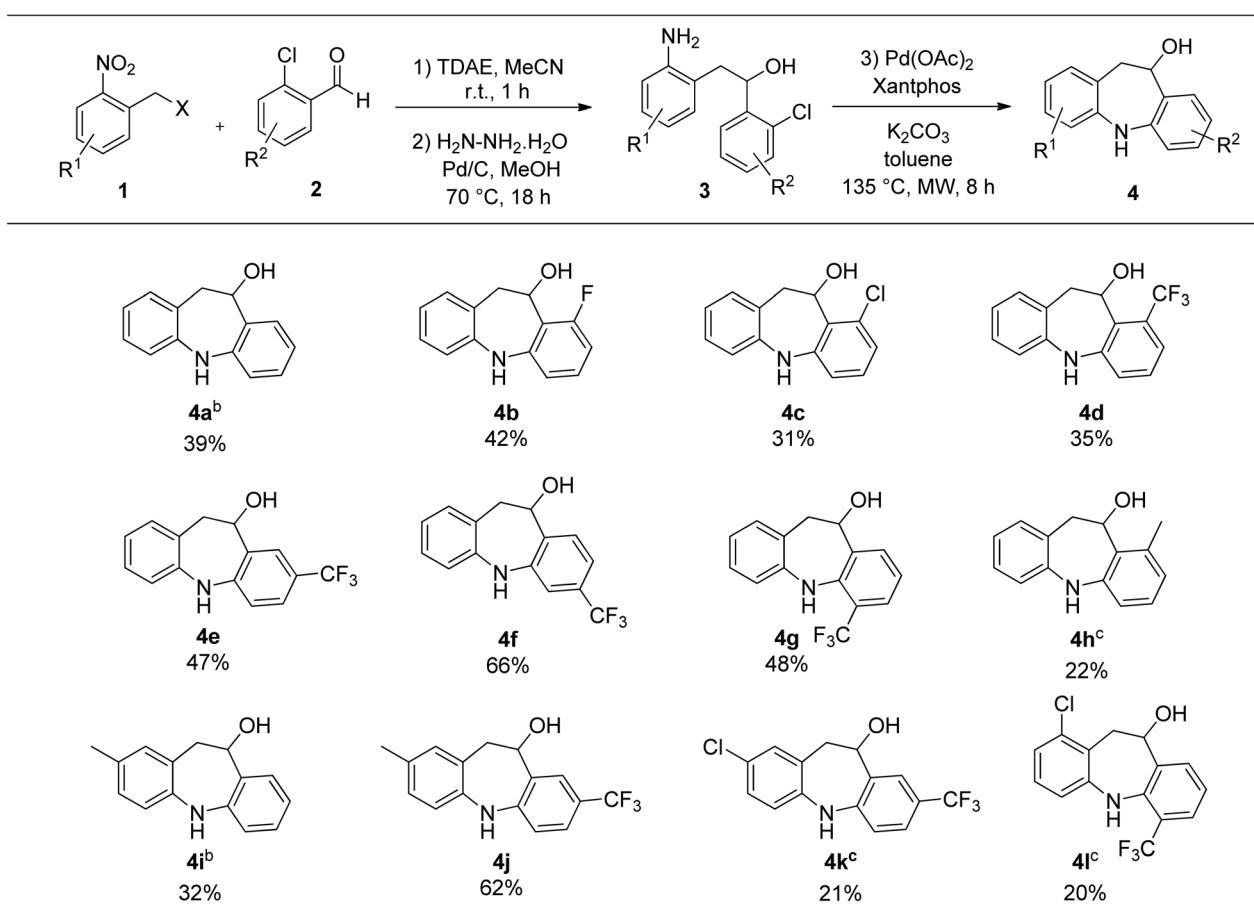
^a Reactions are performed on a 0.2 mmol scale. ^b Isolated yields. ^c THF was degassed with N_2 . ^d Performed under microwave irradiation.

chlorobenzaldehyde to allow the formation of 1-(2-chlorophenyl)-2-(2-nitrophenyl)ethanol. Then, the nitro group was reduced in the presence of Pd/C and hydrazine hydrate to afford 2-(2-aminophenyl)-1-(2-chlorophenyl)ethanol **3a** in 71% overall yield (Scheme 1).

The final and more challenging step was an intramolecular Buchwald–Hartwig coupling to obtain the dibenzazepine scaffold. The reaction conditions optimization for this step was performed on 2-(2-aminophenyl)-1-(2-chlorophenyl)ethanol **3a** (Table 1). In the literature, a recent patent⁹ described exactly this reaction using palladium acetate as palladium source, Xantphos as ligand, K_2CO_3 as base, and tetrahydrofuran as solvent at 50–60 °C for 2 h. So, we tried these conditions for the intramolecular Buchwald–Hartwig coupling of 2-(2-aminophenyl)-1-(2-chlorophenyl)ethanol **3a**. Unfortunately, we obtained the dibenzazepine **4a** in only 9% yield (entry 1, Table 1). No significant improvement was observed with degassed THF (entry 2). Increasing the reaction time (entry 3) and the temperature (entry

4) afforded dibenzazepine **4a** in low yields. We do not have any satisfying explanation about the impossibility for us to reproduce the high yield (85–95%) described in the patent. The large scale (49.5 g, 0.2 mol of **3a**) described in the patent may be more suitable for this reaction. We tried the reaction with a maximum of 5 mmol of 2-(2-aminophenyl)-1-(2-chlorophenyl)ethanol **3a** but no improvement was observed. Our purpose to discover novel biologically active organic compounds was not suitable for large scale experiment. So, we performed the optimization reactions in a 0.2 mmol scale. Our studies began with screening palladium sources, ligands, bases, and solvents. Our first results (entries 5–7, Table 1) indicated that the Xphos/NaOt-Bu combination is unsuitable for the reaction. Using Cs_2CO_3 or K_2CO_3 , poor and similar yields were obtained with a catalytic amount of $Pd(OAc)_2$ and BINAP in toluene at 110 °C (entries 8 and 9). A slightly better yield was achieved using Xantphos as a ligand (entry 10). Performing the reaction under microwave irradiation and increasing the temperature allowed better yields (entries 11–13). So, the best

Table 2 Scope of the reaction^{a,d}



^a Reaction conditions: (1) **1** (1 mmol), **2** (1.2 mmol), and TDAE (1.2 mmol) in MeCN (4 mL) were stirred at r.t. for 1 h under an inert atmosphere. (2) After evaporation of MeCN, MeOH (5 mL), Pd/C (5%, 46 mg), and hydrazine hydrate (50–60%, 312 μ L) were added and the reaction was stirred at 70 °C for 18 h under an inert atmosphere. (3) Intermediate **3**, $Pd(OAc)_2$ (22.5 mg, 0.1 mmol, 0.1 equiv.), Xantphos (58 mg, 0.1 mmol, 0.1 equiv.), K_2CO_3 (276 mg, 2 mmol, 2 equiv.) and anhydrous toluene (2 mL) were stirred under microwave irradiation at 135 °C for 8 h. ^b Microwave temperature for step (3) was 170 °C. ^c Microwave temperature for step (3) was 150 °C. ^d Isolated overall yields of the three steps are given.



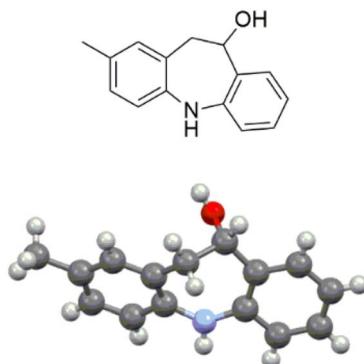


Fig. 2 X-ray structure of dibenzazepine 4i.

reaction conditions for the intramolecular Buchwald–Hartwig coupling of compound **3a** was the use of palladium acetate as palladium source, Xantphos as ligand, K_2CO_3 as base, and toluene as solvent at 170 °C under microwave irradiation for 8 h (entry 13, Table 1). As the crude NMR of compound **3a** was quite clean and to save time and money, we decided not to purify intermediate **3a** with column chromatography. Thus, after the two first steps, crude intermediate **3a** was directly cyclized by an intramolecular Buchwald–Hartwig coupling using the previously optimized reaction conditions to give dibenzazepine **4a** with a 39% overall yield (Table 2, **4a**). In comparison, when intermediate **3a** was purified, dibenzazepine **4a** was isolated with a 37% overall yield (71% for **3a** and 52% for **4a**). Given this result and to save time and money, we selected the process without intermediate purification to do the scope of the reaction.

Starting from di-halogenated aldehydes, dibenzazepines **4b** and **4c** were obtained in 42 and 31% overall yields (Table 2). Interestingly, the presence of an electron-withdrawing substituent allowed the temperature of the Buchwald–Hartwig coupling to decrease to 135 °C. As the trifluoromethyl group could enhance the biological activity, metabolic stability, lipophilicity, and pharmacokinetic properties of heterocyclic drug molecules,¹⁰ diversely trifluoromethyl-substituted dibenzazepines were synthesized in modest to excellent overall yields for the three-step process (Table 2, **4d–4g**). An electron-donating methyl group was well-tolerated on both aromatic parts of the dibenzazepine (Table 2, **4h–4j**). The structure of product **4i** was unequivocally established by X-ray analysis (Fig. 2). Even though the reactivity was lower by introducing a chlorine atom on the left aromatic part of the dibenzazepine, compounds **4k** and **4l** were afforded in 21 and 20% overall yields (Table 2). Remarkably, the chlorine atom could be replaced by selected substituents, such as aromatic patterns with palladium-catalyzed cross-coupling reactions. This is a great advantage to further explore structure–activity relationship of the 10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-10-ol scaffold.

Conclusions

In conclusion, we have successfully reported a new, practical, and straightforward approach for synthesizing 10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-10-ol derivatives in only three steps.

Firstly, using TDAE as a mild reductant allowed the nucleophilic addition reaction of diversely substituted *o*-nitrobenzyl chlorides to different 2-chlorobenzaldehydes. Then, reduction of the nitro group afforded 2-(2-aminophenyl)-1-(2-chlorophenyl) ethanol intermediates **3**. Finally, an intramolecular Buchwald–Hartwig coupling was carried out to obtain the dibenzazepine scaffold with substitution on one or both phenyl rings, contrary to the patent⁹ which only described the synthesis of dibenzazepine **4a**.

Data availability

The data supporting this article have been included as part of the ESI.† CCDC-2391789 (<https://www.ccdc.cam.ac.uk/mystructures/viewinaccessstructures/39ce8207-9c8c-ef11-96ca-00505695281c>) contains the supplementary crystallographic data of compound **4i** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Farid Sroor greatly appreciates the postdoctoral scholarship from the French embassy in Cairo and Institut Français d'Egypte (IFE) at Aix-Marseille University. This work was supported by the CNRS and Aix-Marseille University. The authors also thank the Spectropole team for their elemental analysis.

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