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Efficient Synthesis of Dibenzazepine Lactams via a Sequential Pd-Catalyzed Amination and Aldol Condensation Reaction

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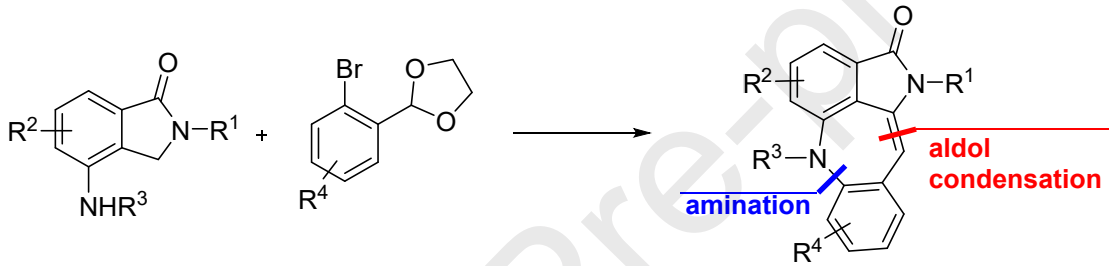
Abstract



A simple and efficient reaction was developed for the synthesis of dibenzazepine lactam derivatives. The core 7-membered azepine ring was formed by a stepwise sequence involving a palladium-catalyzed amination and an aldol condensation.

Keywords

Dibenzazepine; Pd-catalyzed amination; Aldol condensation; Polycyclic compound

Bioactive molecules possessing a dibenz[*b*,*f*]azepine scaffold play an important role in drug discovery.[1, 2] The unique tricyclic dibenzazepine ring system lies at the heart of a wide array of constitutionally diverse compounds exhibiting profound therapeutic properties.[3] This class of dibenzazepines, which includes carbamazepine (**1**),[4] oxcarbazepine (**2**),[5] eslicarbazepine acetates (**3**),[6] trimipramine (**4**),[7] and clozapine (**5**),[8] show antimicrobial, antifungal, antioxidant, antiepileptic, and anticonvulsant, as well as anticancer activities (Figure 1).

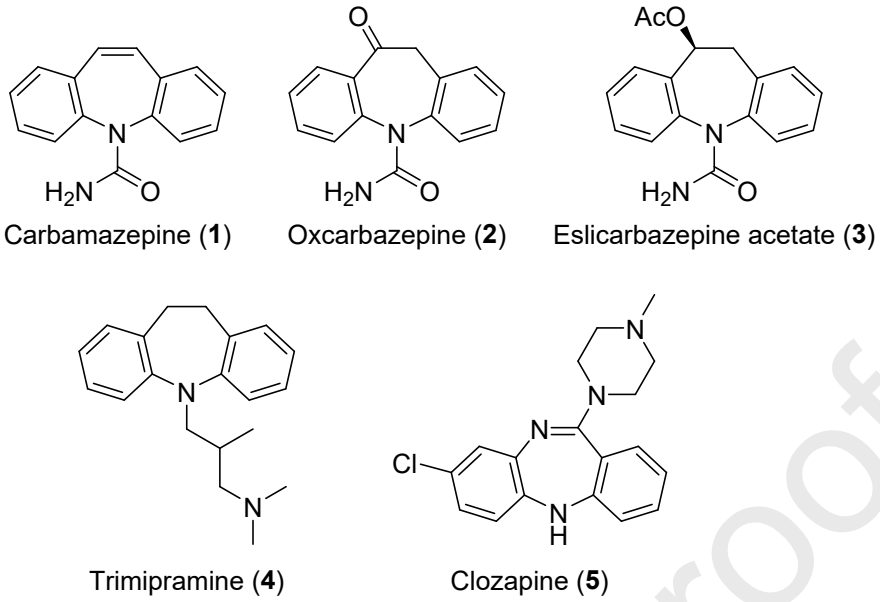
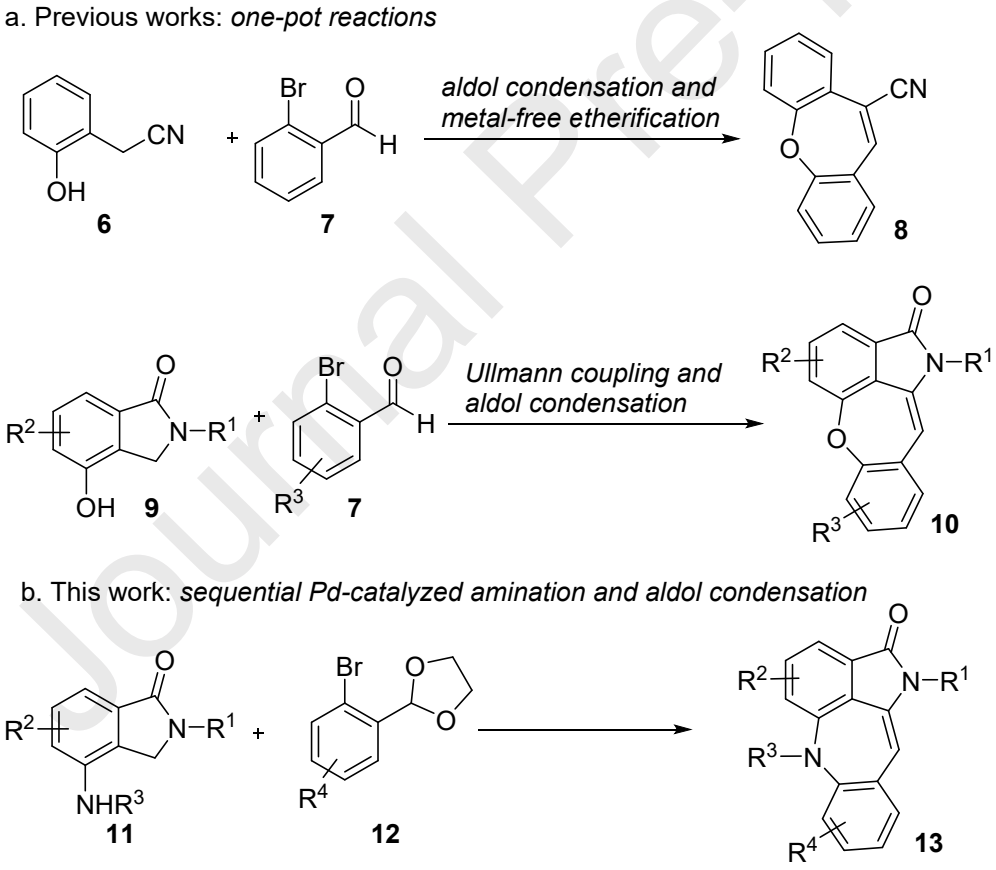


Figure 1. Pharmaceutical and bioactive compounds possessing a dibenzazepine scaffold.

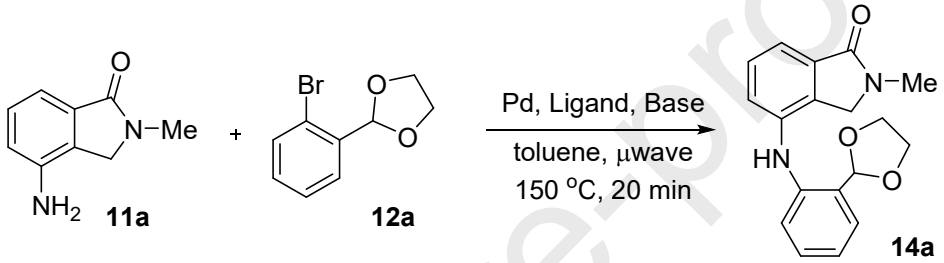


Scheme 1. Synthetic strategies for accessing dibenzazepine lactam analogues.

As part of our work for the construction of polycyclic compounds for inclusion in libraries,[9] a

series of dibenzoxepines **8** were prepared via a one-pot aldol condensation and metal-free etherification (Scheme 1a).[9e] In addition, we developed a highly efficient synthesis of dibenzoxepine lactam **10** based on a one-pot Ullmann coupling reaction and an aldol condensation.[9f] Inspired by these developments, we envision that the formation of more challenging dibenzazepine lactam **13** could be achievable. However, the first attempt with 4-aminoindolinone **11** and 2-bromobenzaldehyde **7** failed to provide any desired product, presumably due to the rapid formation of the imine between the amine and aldehyde groups. Instead, acetal-protected arylbromide **12** was selected as a coupling partner for the Pd-catalyzed amination (Scheme 1b). Here, we present the first synthesis of dibenzazepine lactams from 4-aminoisoindolin-1-ones.

Table 1. Optimization of Pd-catalyzed amination reaction conditions[a]

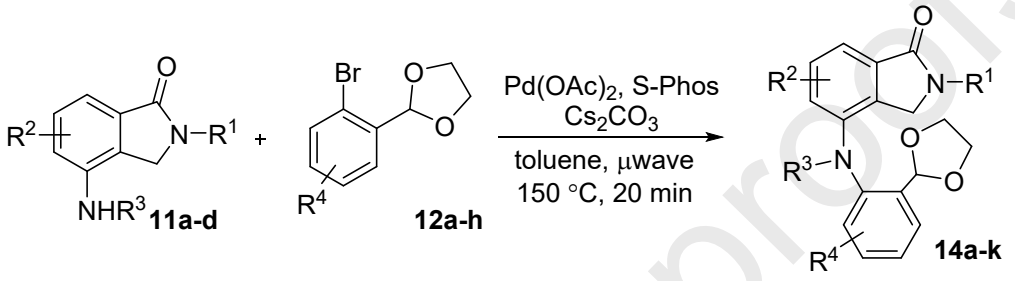


Entry	Pd	Ligand	Base	Yield (%)
1	$Pd(OAc)_2$	BINAP	NaO^tBu	27
2	$Pd(OAc)_2$	BINAP	K_3PO_4	29
3	$Pd(OAc)_2$	BINAP	K_2CO_3	6
4	$Pd(OAc)_2$	BINAP	Cs_2CO_3	80
5	$Pd_2(dba)_3$	BINAP	Cs_2CO_3	86
6	$PdCl_2(CH_3CN)_2$	BINAP	Cs_2CO_3	57
7	$Pd(PPh_3)_4$	BINAP	Cs_2CO_3	39
8	$Pd(OAc)_2$	DPEphos	Cs_2CO_3	77
9	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	50
10	$Pd(OAc)_2$	Davephos	Cs_2CO_3	58
11	$Pd(OAc)_2$	Cy-Johnphos	Cs_2CO_3	28
12	$Pd(OAc)_2$	X-Phos	Cs_2CO_3	88
13	$Pd(OAc)_2$	S-Phos	Cs_2CO_3	92
14	$Pd(OAc)_2$	DIOP	Cs_2CO_3	49
15	$Pd(OAc)_2$	dppf	Cs_2CO_3	33
16	$Pd_2(dba)_3$	S-Phos	Cs_2CO_3	59

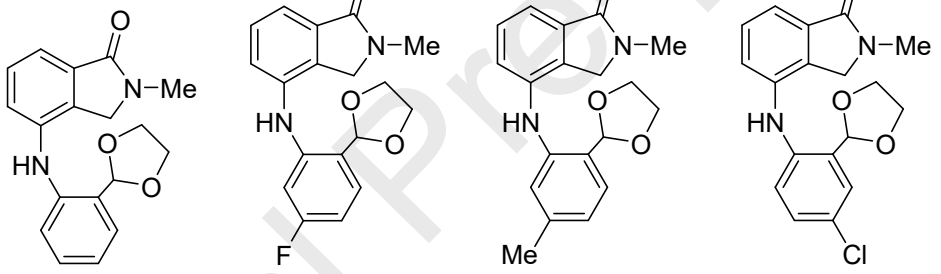
[a] Reaction conditions: Amino-isoindol-1-one (0.6 mmol), ArBr (0.5 mmol), Pd (3.0 mol %), ligand (4.5 mol %), base (1.4 equiv), toluene (3.0 mL), microwave 150 °C, 20 min.

Based on our previous work on microwave-promoted palladium-catalyzed aminations of arylhalides,[10] we investigated the reaction of 4-amino-2-methylisoindolin-1-one (**11a**) with arylbromide **12a** in the presence of a Pd catalyst (Table 1).[11] The reaction using $Pd(OAc)_2$ in combination with BINAP and NaO^tBu in toluene gave **14a** in a low yield (entry 1). Changing the base dramatically impacted the yields. The catalytic system with K_3PO_4 and K_2CO_3

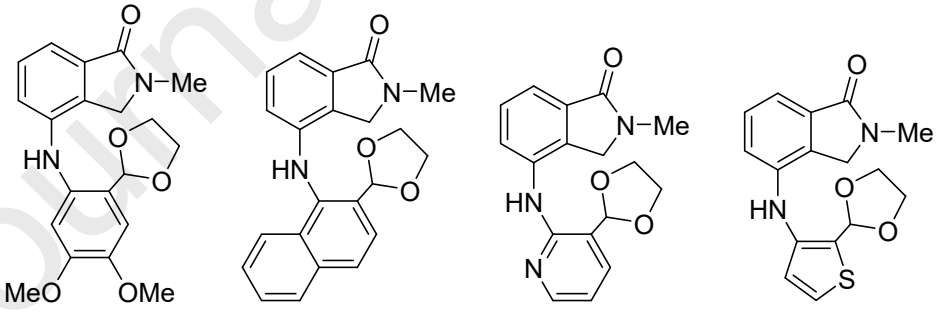
provided **14a** in a low yield (entries 2 and 3), but a great improvement was observed with Cs_2CO_3 in 80% yield (entry 4). Next, screening palladium sources revealed $Pd_2(dba)_3$ as the most active catalyst, as it provided an 86% yield (entries 4 – 7). Although $Pd_2(dba)_3$ showed slightly better result, we decided to use $Pd(OAc)_2$ as the easy-to-handle catalyst. Furthermore, we screened a wide range of phosphine ligands with $Pd(OAc)_2$ as the catalyst (entries 8-15). Among the tested ligands, biaryl-based X-Phos and S-Phos proved to be very effective, providing 88% and 92% yields, respectively (entries 12 and 13). Additionally, the combination of $Pd_2(dba)_3$ and S-Phos gave **14a** in 59% yield.



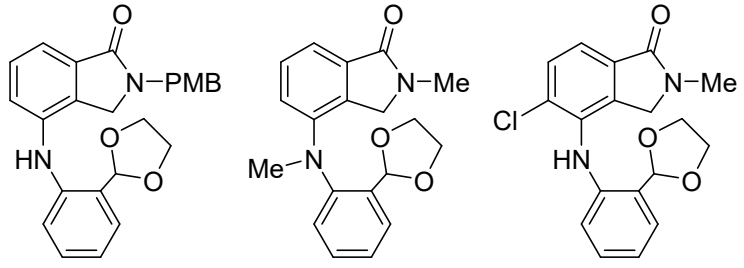
11a-d **12a-h** **14a-k**



14a, 92% **14b**, 93% **14c**, 98% **14d**, 98%



14e, 64% **14f**, 75% **14g**, 60% **14h**, 89%

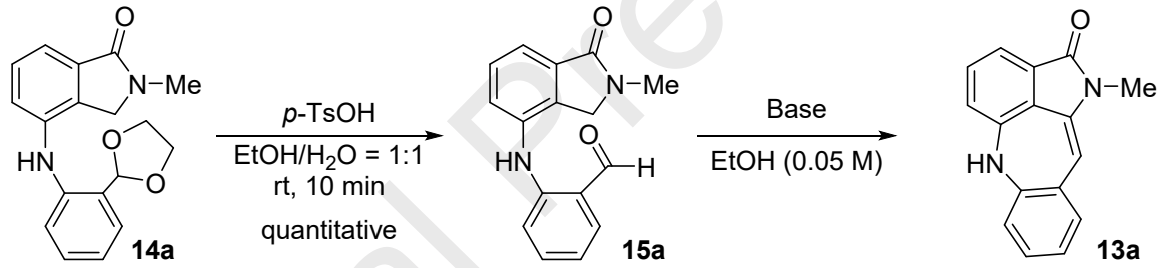


14i, 98% **14j**, 45% **14k**, 50%

Scheme 2. Substrate scope for the Pd-catalyzed amination. [a] Reaction conditions: Amino-isoindol-1-one (0.6 mmol), ArBr (0.5 mmol), $Pd(OAc)_2$ (3.0 mol %), S-Phos (4.5 mol %), Cs_2CO_3 (1.4 equiv), toluene (3.0 mL), microwave 150 °C, 20 min.

With an effective catalytic system in hand ($Pd(OAc)_2$, S-Phos, and Cs_2CO_3), we then explored the scope of the amination reaction (Scheme 2). The coupling reactions of **11a** with halo- or methyl-substituted arylbromides **12b-d** proceeded smoothly to provide corresponding products **14b-d** in 93-98% yields. When highly electron-rich dimethoxyphenylbromide **12e** was used, the reaction was less effective, and **14e** was obtained in 64% yield. This coupling reaction was also expanded to naphthyl- and heteroaryl-bromides, including pyridine and thiophene derivatives, which provided good to excellent yields. Interestingly, the 1-PMB-substituted derivative of 4-aminoindolin-1-one provided desired product **14i** in 98% yield. Substrate 4-(*N*-methylamino)indolin-1-one **11c** was compatible with this transformation, albeit giving **14j** in a 45% yield. Additionally, the use of 5-chloro-substituted **11d** was well tolerated and provided **14k** in good yield.

Table 2. Optimization of the reaction conditions for the base-mediated aldol condensation[a]

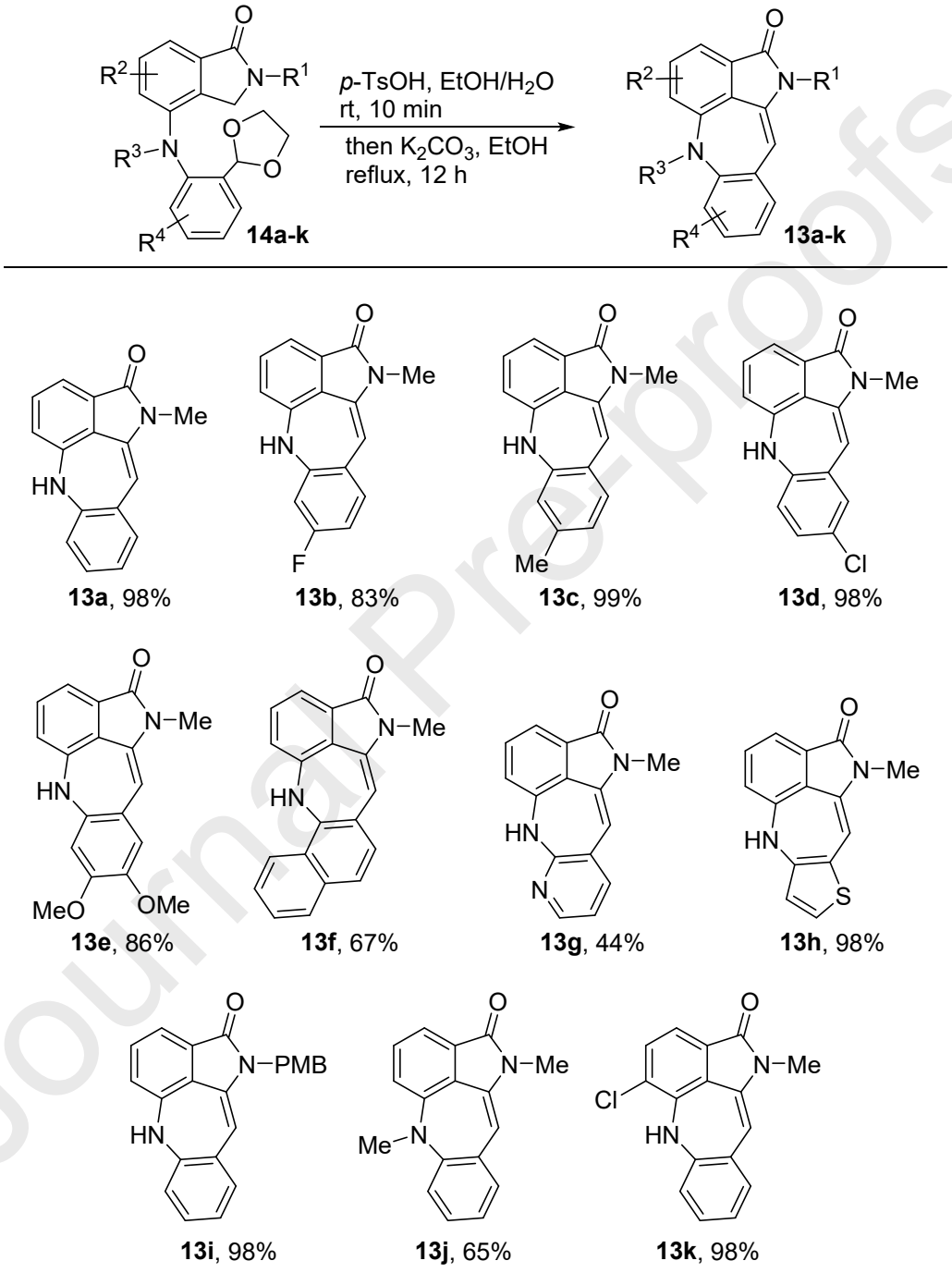


Entry	Base (equiv)	Temp (°C)	Time (h)	Yield (%)
1	10% NaOH (3.0)	70	2	10
2	NaO^{t}Bu (3.0)	70	2	56
3	K_2CO_3 (3.0)	reflux	4	34
4	K_2CO_3 (3.0)	reflux	12	98
5	Cs_2CO_3 (3.0)	reflux	12	98
6[b]	K_2CO_3 (3.0)	reflux	12	98

[a] Reaction conditions: aldehyde **15a** (0.3 mmol), base (3 equiv), EtOH (6 mL). [b] The one-pot reaction was proceeded directly from **14a** without isolation of **15a** (reaction conditions: **14a** (0.3 mmol), *p*-TsOH (1 equiv), EtOH/H_2O (2.0 mL/2.0 mL), rt, 10 min, then K_2CO_3 (3 equiv), EtOH (6.0 mL), reflux, 12 h)

Next, the removal of the acetal protecting groups was easily accomplished in quantitative yields by using standard acidic conditions. The subsequent aldol cyclization was examined under basic conditions (Table 2). Among the various inorganic bases screened, both K_2CO_3 and Cs_2CO_3 afforded cyclic product **13a** in an excellent yield. Then, we further investigated a one-pot tandem process for the acetal deprotection and aldol condensation. Applying the conditions reported for the acid/base-promoted aldol condensation reaction,[9d] **14a** afforded expected

product **13a** in yield compatible to that obtained when the two reactions are conducted separately (Table 2, entry 6).



Scheme 3. Substrate scope for the one-pot aldol condensation. [a] Reaction conditions: acetal (0.3 mmol), *p*-TsOH (1 equiv), EtOH/H_2O (2.0 mL/2.0 mL), rt, 10 min, then K_2CO_3 (3 equiv), EtOH (6.0 mL), reflux, 12 h.

Under the optimized conditions for the one-pot deprotections/aldol condensation, the intramolecular cyclization occurred smoothly to furnish the desired dibenzazepine lactams (Scheme 3). When electron-rich methyl (**13c**) and dimethoxy (**13e**) groups were used, the corresponding products were obtained in excellent yields. Electron-withdrawing substituents including halogens (**13b**, **13d,** and **13k**) were well tolerated. In addition, heteroaryl substituents (**14f–h**) also proved suitable, leading to heterodibenzazepine lactams **13f–h** in reasonable to good yields. Notably, *N*-PMB protected lactam **14i** smoothly afforded corresponding dibenzazepine lactam **13i** in 98% yield. The cyclization of **14j** with tertiary-methylamine effectively gave **13j** in 65% yield.

In summary, we have developed an efficient synthesis of dibenzazepine lactams via a Pd-catalyzed amination of 4-amino-1-isoindolones with acetal-protected aryl bromides, followed by a one-pot deprotection/aldol condensation. Biological evaluations of these derivatives for pharmaceutical use are currently underway.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://

References and notes

1. (a) Kricka, L. J.; Ledwith, A. *Chem. Rev*. **1974**, *74*, 101; (b) Boichenko, M. A.; Chagarovskiy, A. O. *Chem. Heterocycl. Comp*. **2017**, *53*, 1280.

2. (a) Tsvelikhovsky, D.; Buchwald, S.L. *J. Am. Chem. Soc.* **2010**, *132*, 14048; (b) Elliott, E.-C.; Bowkett, E. R.; Maggs, J. L.; Bacsa, J.; Park, B. K.; Regan, S. L.; O'Neill, P. M.; Stachulski, A. V. *Org. Lett*. **2011**, *13*, 5592; (c) Elliott, E.-C.; Maggs, J. L.; Park, B. K.; O'Neill, P. M.; Stachulski, A. V. *Org. Biomol. Chem*. **2013**, *11*, 8426; (d) MacNeil, S. L.; Gray, M.; Gusev, D. G.; Briggs, L. E.; Snieckus, V. *J. Org. Chem*. **2008**, *73*, 9710; (e) Wang, R.; Jin, R.-X.; Qin, Z.-Y.; Bian, K.-J.; Wang, X.-S. *Chem. Commun*. **2017**, *53*, 12229.

3. (a) Rao, G. K.; Kaur, R.; Pai, P. N. S. *J. Chem. Pharm. Res*. **2010**, *2*, 489; (b) Kumar, H. V.; Naik, N. *Eur. J. Med. Chem*. **2010**, *45*, 2; (c) Sadashiva, M. P.; Basappa; Nanjundaswamy, S.; Li, F.; Manu, K. A.; Sengottuvelan, M.; Prasanna, D. S.; Anilkumar, N. C.; Sethi, G.; Sugahara, K.; Rangappa, K. S. *BMC Chem. Biol.* **2012**, *12*, 5; (d) Learmonth, D. A.; Benes, J.; Parada, A.; Hainzl, D.; Beliaev, A.; Bonifácio, M. J.; Matias, P. M.; Carrondo, M. A.; Garrett. J.; Soares-da-Silva, P. *Eur. J. Med. Chem*. **2001**, *36*, 227; (e) Sun, W.; Tanaka, T. Q.; Magle, C. T.; Huang, W.; Southall, N.; Huang, R.; Dehdashti, S. J.; McKew, J. C.; Williamson, K. C.; Zheng, W. *Sci. Rep*. **2014**, *4*, 3743; (f) Singh, R. P.; Axconapé, J. J. *J. Cent. Nerv. Syst. Dis.* **2011**, *3*, 179.

4. (a) Albani, F.; Riva, R.; Baruzzi, A. *Pharmacopsychiatry* **1995**, *28*, 235; (b) Ambrósio, A.

F.; Soares-da-silva, P.; Carvalho, C. M.; Carvalho, A. P. *Neurochem. Res*. **2002**, *27*, 121; (c) Ravinder, B.; Reddy, S. R.; Sridhar, M.; Mohan, M. M.; Srinivas, K.; Reddy, A. P.; Bandichhor, R. *Tetrahedron Lett*. **2013**, *54*, 2841.

5. (a) Liu, K.-C.; Sakya, S. M..; O'Donnell C. J; Flick,. A.C.; Li, J. *Bioorg. Med. Chem*. **2011**, *19*, 1136; (b) Learmonth, D. A.; Grasa, G. A. PCT Int. Appl. 2007012793; (c) Susan, M.; Faulds, D. *Drugs* **1992**, *43*, 873.

6. (a) Dulsat, C. M. N.; Castaner, R.; Bolos, J. *Drugs Fut.* **2009**, *34*, 189; (b) Galiana, G. L.; Gauthier, A. C.; Mattson, R. H. *Drug in R&D* **2017**, *17*, 329.

7. Berger, M.; Gastpar, M. *Eur. Arch. Psychiatry Clin. Neurosci.* **1996**, *246*, 235.

8. Wenthur, C. J.; Lindsley, C. W. *ACS Chem. Neurosci*. **2013**, *4*, 1018.

9. (a) Goh, Y. H.; Kim, G.; Kim, B. T.; Heo, J.-N. *Heterocycles* **2010**, *80*, 669; (b) Park, K.-Y.; Kim, B. T.; Heo, J.-N. *Eur. J. Org. Chem*. **2014**, 164; (c) Kim, J. K.; Kim, Y. H.; Nam, H. T.; Kim, B. T.; Heo, J.-N. *Org. Lett*. **2008**, *10*, 3543; (d) Choi, Y. L.; Yu, C.-M.; Kim, B. T.; Heo, J.-N. *J. Org. Chem.* **2009**, *74*, 3948; (e) Choi, Y. L.; Lim, H. S.; Lim, H. J.; Heo, J.-N. *Org. Lett.* **2012**, *14*, 5102; (f) Lim, H. S.; Choi, Y. L.; Heo, J.-N. *Org. Lett.* **2013**, *15*, 4718.

10. (a) Heo, J.-N.; Song, Y. S.; Kim, B. T. *Tetrahedron Lett*. **2005**, *46*, 4621; (b) Kim, Y. H.; Kim, Y.-J.; Chang, S.-Y.; Kim, B. T.; Heo, J.-N. *Bull. Korean Chem. Soc*. **2007**, *28*, 777.

11. For recent reviews for Pd-catalyzed amination, see: (a) Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564; (b) Surry, D. S.; Buchwald, S. L. *Chem. Sci*. **2011**, *2*, 27; (c) Schlummer, B.; Scholz, U. *Adv. Synth. Catal*. **2004**, *346*, 1599.

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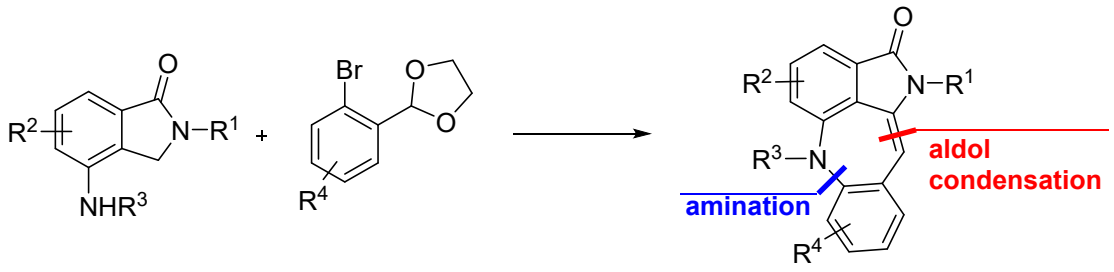
Graphical Abstract



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Tetrahedron Letters

Highlights,

- Synthesis of novel dibenzazepine lactams via Pd-catalyzed amination and aldol condensation
- Rapid approaches of Pd-catalyzed amination using microwave irradiation
- One-pot process for cyclization with sequential acetal deprotection/aldol condensation

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: