Synthesis of Indole-Fused 1,4-Diazepinones via Photoredox-Catalyzed Cascade Cyclization Reaction

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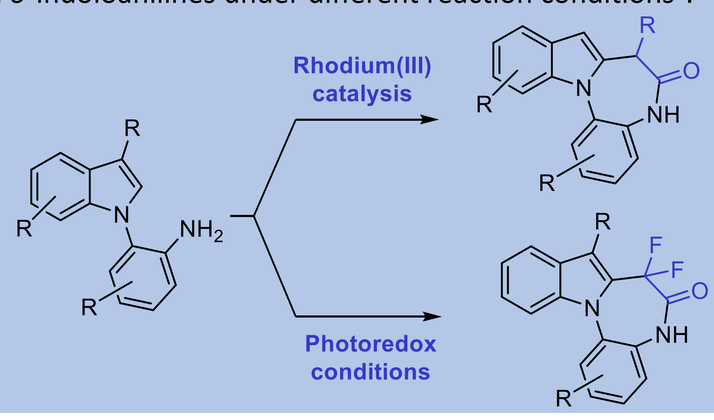
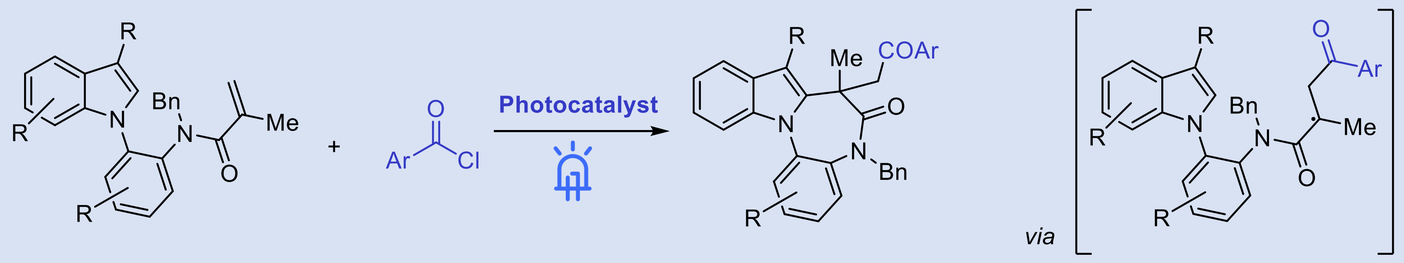
Introduction

Indole-fused 1,4-diazepinones are an important class of biologically active molecules[1]. Their synthesis has recently been reported starting from *o*-indoloanilines under different reaction conditions[2]:

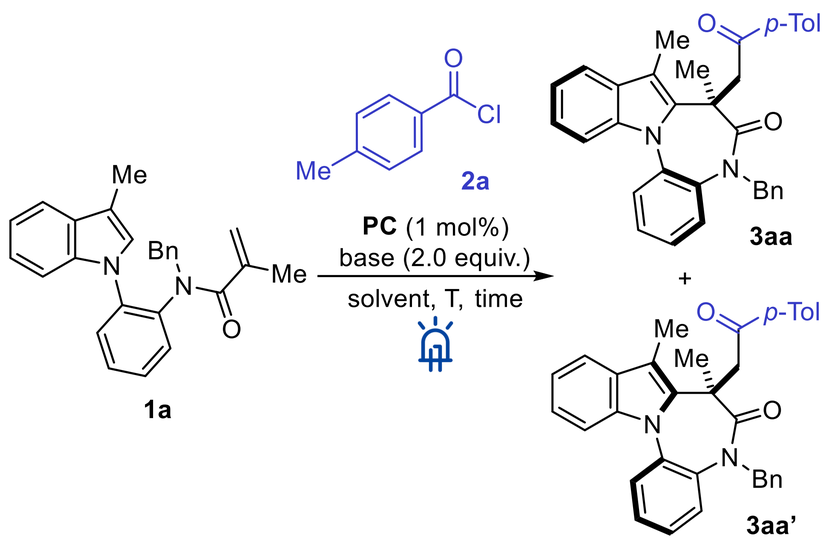


Our goal

Photoredox catalyzed synthesis of complex [1,4]diazepino[1,7-*a*]indol-6(7*H*)-ones by a cascade radical addition on C–C double bond followed by intramolecular cyclization.

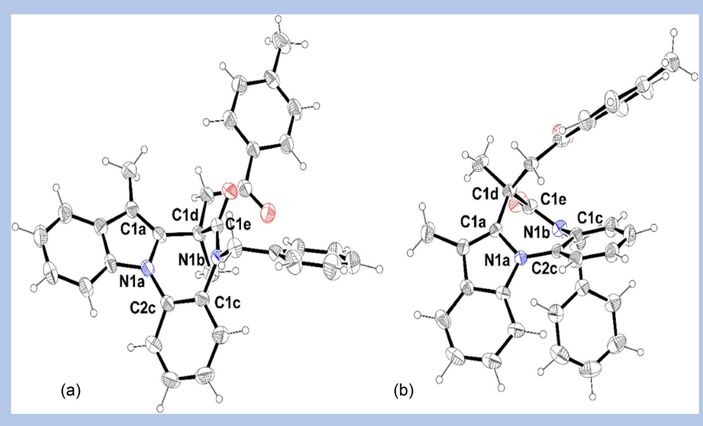


Screening of the reaction conditions



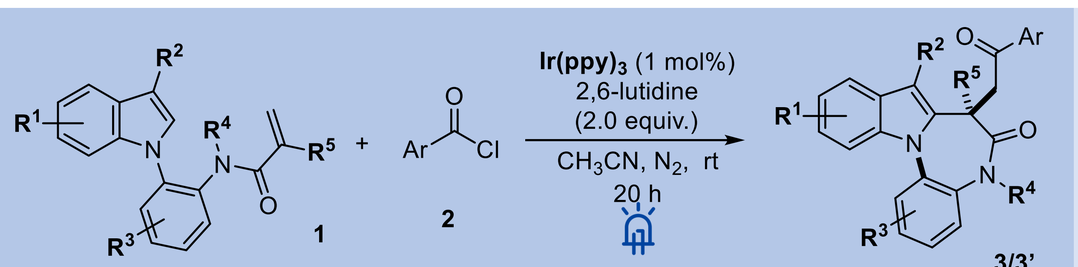
Entry	PC (mol%)	Base	Solvent	Yield [%]	**3aa/ 3aa'**
1	$Ru(bpy)_3(PF_6)_2$ (1)	2,6-lutidine	CH_3CN	-	n.d.
2	Eosin Y (1)	2,6-lutidine	CH_3CN	25	n.d.
3	$Ir(ppy)_3$ (5)	2,6-lutidine	CH_3CN	91	1.3:1
4	$Ir(ppy)_3$ (5)	Et_3N	CH_3CN	78	1.3:1
5	$Ir(ppy)_3$ (5)	DIPEA	CH_3CN	-	n.d.
6	$Ir(ppy)_3$ (5)	K_2CO_3	CH_3CN	44	1:1.3
7	$Ir(ppy)_3$ (5)	Na_2HPO_4	CH_3CN	29	1:1.2
8	$Ir(ppy)_3$ (5)	2,6-lutidine	1,2-DCE	61	4:1
9	$Ir(ppy)_3$ (5)	2,6-lutidine	DMF	33	3.2:1
10	$Ir(ppy)_3$ (1)	2,6-lutidine	CH_3CN	88	1.3:1
11[a)]	Ir(ppy)3 (1)	2,6-lutidine	CH_3CN	-	n.d.

*Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), photocatalyst (1-5 mol%), base (2.0 equiv.) in CH_3CN (2 ml, 0.1 M) at rt for 20 h under 40 W blue led irradiation (λmax = 440 nm).*
a) Reaction conducted in the dark

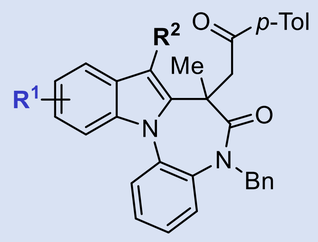


*The structure of **3aa** (a) and **3aa'** (b) characterized by the presence of a center of axial chirality on the indole N–C(aryl) axis was confirmed by X-Ray analysis.*

Scope of the reaction



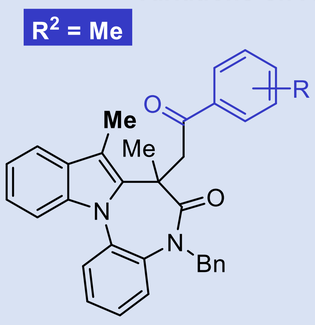
Variations on Indole scaffold



R^1	R^2		Yield (%)	3/3'
5-OMe	Me	**3ar/ar'**	88	1:1.3
5-OMe	H	**3as/as'**	99	1:2.5
5-F	H	**3at/at'**	62	1:3.3
6-OMe	H	**3au/au'**	51	1:3.3
6-CF_3	H	**3av/av'**	90	1:2.5

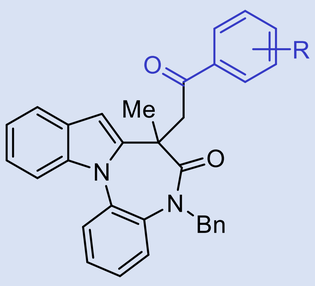
Variations on Aroyl chloride

R^2 = Me

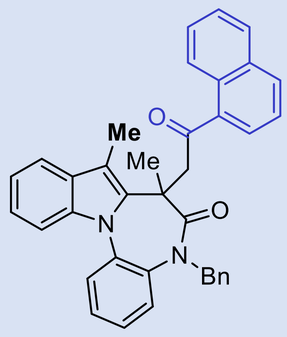


R		Yield (%)	3/3'
H	**3ab/ab'**	99	1:1
4-OMe	**3ac/ac'**	90	1:1
4-F	**3ad/ad'**	99	1:1.7
4-Br	**3ae/ae'**	63	1.7:1
2-Me	**3af/af'**	75	1:1
2-Cl	**3ag/ag'**	62	1:1.4
3-Me	**3ah/ah'**	65	1:1.4
3-Cl	**3ai/ai'**	64	1.5:1

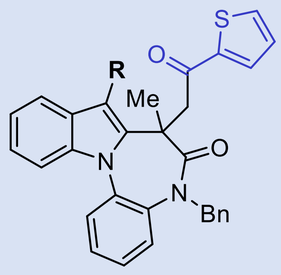
R^2 = H



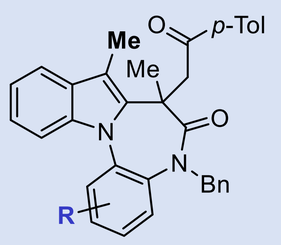
R		Yield (%)	3/3'
4-Me	**3aj/aj'**	92	1:2.5
4-OMe	**3ak/ak'**	99	1:2.5
4-F	**3al/al'**	99	1:1.4
2-Me	**3am/am'**	78	1:1.7
3-Me	**3an/an'**	57	1:2.5

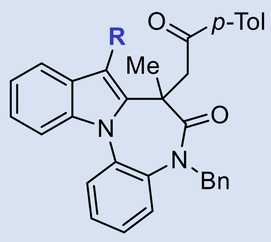


3ao/ao', 61%, (1.3:1)



R = Me, 3ap/ap', 61%, (1:1.7)
R = H, 3aq/aq', 80%, (1:1.25)

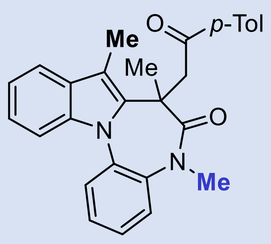




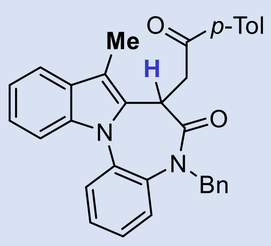
R		Yield (%)	3/3'
p-Me	**3aw/aw'**	85	1:1
m-Me	**3ax/ax'**	78	1:1
m-Cl	**3ay/ay'**	77	1:1.5
o-Me	**3az/az'**	84	2.8:1

R		Yield (%)	3/3'
Et	**3ba/ba'**	89	1:1
COMe	**3bb/bb'**	71	1:1
Ph	**3bc/bc'**	84	2.7:1
p-Tol	**3bd/bd'**	99	3.3:1
2,6-diMe-Ph	**3be**	65	>20:1

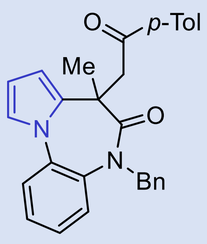
Other variations



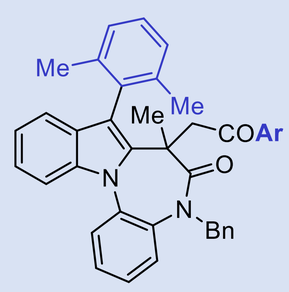
3bf/bf', 82%, (1:1)



3bg, 72%

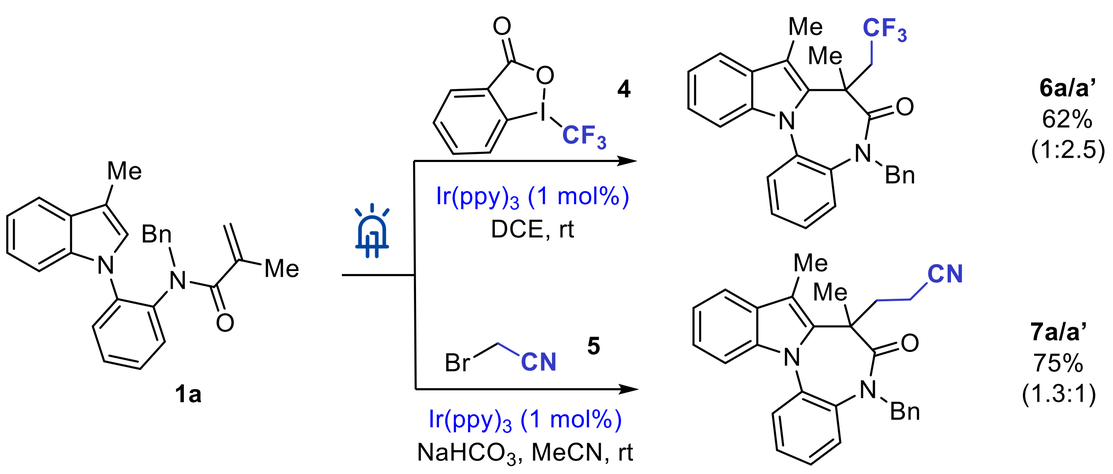


5a/a', 57%, (4:1)

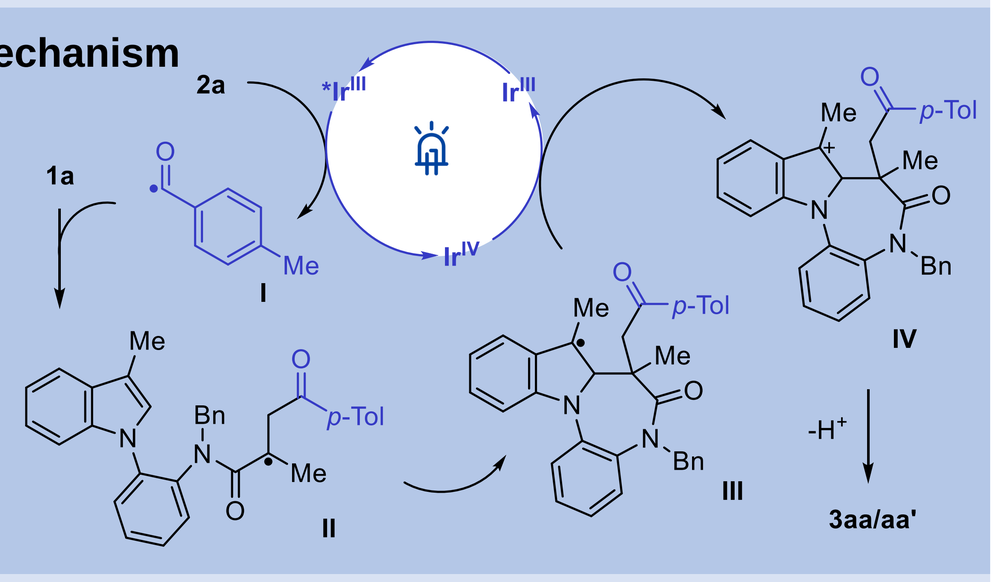


3bh, **Ar = 4-OMe-C_6H_4**, 53%, (>20:1)
3bi, **Ar = 4-F-C_6H_4**, 54%, (>20:1)

Expantion of the applicability to other radicals



Proposed mechanism



Conclusions

- Design of a **new** complex **cascade** reaction promoted by **photoredox catalysis** for the synthesis of [1,4]diazepino[1,7-*a*]indol-6(7*H*)-one derivatives starting from *N*-indolyl phenylacrylamides and aroyl chlorides.[3]
- Development of an **efficient** and **high yielding** methodology for the synthesis of indole-fused 1,4-dizepinoses with **mild reaction condition** and **wide scope.**
- Extension of the protocol to **pyrrole derivatives** as well to **other radical precursors** such as Togni II reagent and bromoacetonitrile.

Acknowledgements

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References

1) a. Zheng et al. *Bioorg. Med. Chem. Lett.* 2011, **21**, 2925–2929; *b*. Putey et al. *Eur. J. Med. Chem.* 2014, **83**, 617–629; *c.* Lee et al. *J. Med. Chem.* 2019, **62**, 3971–3988.
2) a. Sun et al. *Adv. Synth. Catal.* 2019, **361**, 2916–2925; *b.* Sun et al. *J. Org. Chem.* 2019, **84**, 9322–9329.
3) doi: 10.1002/adsc.202300708