A Convenient Protocol for a Zinc-catalysed Synthesis of Electron-Poor Indoles.

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Abstract

A convenient catalytic protocol for the synthesis of electron-poor indoles was envisioned. A cyclisation reaction of electron-deficient 2-(alkynyl)-anilines, catalysed by Zn(II) salts, was successfully developed and applied to the synthesis of an API precursor. A two-step one-pot procedure starting from aniline derivatives was successfully developed. The use of a readily available, non-noble metal further enhanced the value of the protocol.

Keywords: Indole, Cyclisation, Zinc, API precursor, Alkynyl group

Indole represents one of the privileged scaffolds present in nature.[1] In the last century, chemists have unveiled the extraordinary role of this moiety in different fields; however, applications in medicinal chemistry deserve a special mention, considering the wide range of indole-containing biologically active molecules endowed of pharmaceutical properties (**Figure 1**).[2-5].

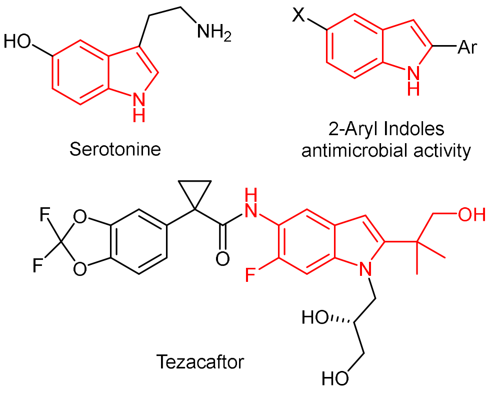


Figure 1 Examples of relevant Indole scaffolds

Therefore, chemists have devoted a lot of effort into discovering different synthetic routes to obtain libraries of indole derivatives, from the well-known Fischer synthesis[6] to more modern strategies,[7] including electrochemical synthesis.[8]

Our work focused on the metal catalysed synthesis of indoles through a cyclisation reaction of alkynyl anilines mediated by earth-abundant metals. Typically, the metal of choice for this transformation is palladium, a noble metal that acts as a jolly in different reactions due to its versatility.[9] Examples are the Larock,[10] Cacchi,[11] Buchwald-Hartwig[12]reactions. Other than palladium, Au,[13] Ru[14], and the less expensive Fe[15] and Ni[16] have found application in this field.

Our investigation wished to specifically address the intramolecular cyclisation of electron-deficient 2-(alkynyl)-anilines to afford electron-poor indoles, by using convenient, relatively inexpensive and easily available metal salts. And, in particular, we decided to investigate the use of zinc salts. A special attention was pointed to the preparation of the heterocyclic scaffold present in Tezacaftor, a drug for treating cystic fibrosis (**Figure 2**).[17]

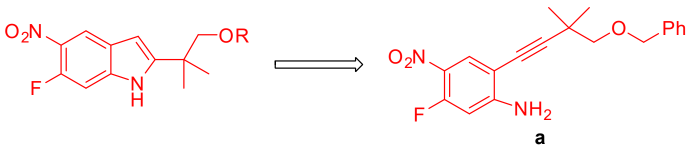


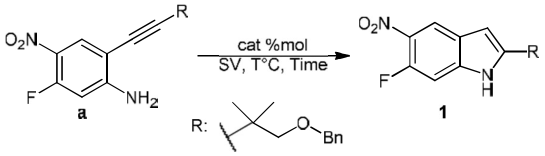
Figure 2 Retrosynthetic analysis for Tezacaftor advanced intermediate

In literature, Zn is already known to catalyse indole formation starting from hydrazine derivatives,[18] while the use of an organozinc catalyst was necessary to promote the reaction of alkynyl sulfonamides.[19] As far as we know, following the pioneer work by Okuma in 2009,[20] almost no examples of reaction with anilines bearing electron withdrawing groups (EWG) are known in zinc catalysed reactions.[21] Therefore, we decided to study specifically the reactivity of polysubstituted electron-poor 2-alkynyl anilines in the cyclization reaction using halo-zinc salts, to afford differently substituted indole rings.[22]

As model substrate, aniline **a**, featuring a nitro group on the aromatic ring, a well-established starting material of the Tezacaftor intermediate, indole **1**, was selected, and its cyclisation was studied under different experimental conditions.

At first, the reaction was carried out in toluene with a stoichiometric amount of zinc catalyst (Table 1). While Zn (II) triflate did not promote the reaction, Zn (II) halides proved to be effective catalysts for the reaction; in particular, with zinc bromide indole **1** was produced in 91% yield after 16 hours reaction. Therefore, $ZnBr_2$ was selected as catalyst of choice for further optimization studies; other zinc salts gave somehow lower yields, as well as indium (III) chloride and bromide were not effective in promoting the reaction.

Table 1 Explorative studies on catalytic cyclisation of model 2-(alkynyl)-aniline **a** to afford indole **1**



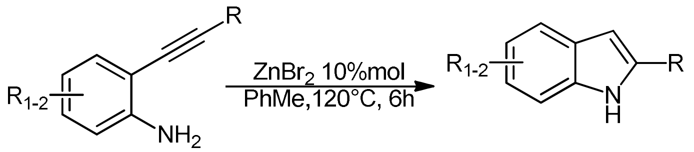
Entry	**Solvent**	**Catalyst**	**%mol**	**T°C**	**Time h**	**Yield%[a]**
1	PhMe	$Zn(OTf)_2$	100	110	16	-
2	PhMe	$ZnBr_2$	100	110	16	90
3	PhMe	$ZnBr_2$	20	110	16	90
4	PhMe	$ZnBr_2$	10	110	16	**91**
5	PhMe	$ZnBr_2$	5	110	16	75
6	PhMe	$ZnBr_2$	10	60	16	-
7	ACN	$ZnBr_2$	10	60	16	-
8	**PhMe**	**$ZnBr_2$**	**10**	**110**	**6**	**82**
9	ACN	$ZnCl_2$	100	110	16	65
10	PhMe	$ZnCl_2$	100	110	16	41
11	PhMe	ZnI_2	100	110	6	77
12	ACN	ZnI_2	100	60	16	39
13	PhMe	$InCl_3$	100	110	6	12
14	PhMe	$InBr_3$	100	110	6	-
15	PhMe	-	-	110	6	-

[a] ^{1}HNMR yield, 1,3,5-trimethoxybenzene as internal standard

Then, different loadings of zinc bromide were tested at different temperatures and reaction times (entries 3-8 of Table 1). From the data collected, a catalytic loading of about 10% mol of $ZnBr_2$ at 110°C resulted in the best condition, while at lower temperature no conversion was observed. After 16 hours the product was isolated in 91% overall yield. In toluene, the solvent of choice, after 6h, only a marginal yield decrease was observed (entries 8 vs 4, 82% vs 91% yield).

After identifying the best reaction conditions (entry 8, Table 1), other 2-(alkynyl)-aniline derivatives were synthesized and the reaction scope was then investigated (Table 2).

Table 2 Reaction Scope



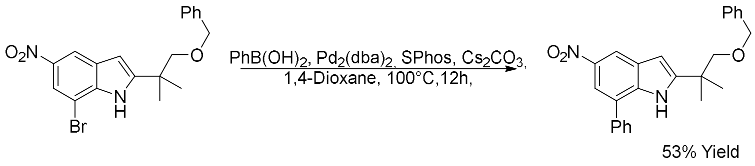
Entry	Substrate	Isolated Yield
1		
2		
3		
4		
5		
6		

-

The reaction conditions resulted quite robust and applicable to different, electron deficient, functionalised substrates, allowing to obtain a small library of indole derivatives. First, the behaviour of electron poor anilines, featuring in 2 position the 4-benzyloxi-3,3-dimethyl-1-butynyl moiety, was studied. Different functional groups on the aromatic ring were well tolerated, and the products were isolated in higher than 90% yields (Table 2, entries 1-3).

The methodology could be applied to linear alkyl alkynes (entry 4, 97% yield for compound **5**), and also to a phenyl acetylene derivative (entry 5, 94% yield of product **6**). Furthermore, the reaction works also with nitro-anilines featuring a Br atom on the aromatic ring; indole **7** was successfully synthesized in 55% isolated yield (entry 6). However, any attempt to perform the reaction of bromo-nitroanilines featuring aromatic acetylenes failed or gave only traces of product.

The presence of a Br atom on the indole ring was exploited in a post-functionalisation strategy, that allowed to introduce an aromatic ring on the indole scaffold by Pd-catalysed coupling reaction with phenyl boronic acid (see Scheme 1).



Scheme 1 Indole post-functionalisation

To further enhance the attractiveness of the methodology, we turned our interest back to the synthesis of the indole core of Tezacaftor. In particular, we focused our attention on performing a one-pot, two-step synthesis of the API precursor starting from the 2-bromoaniline derivative **S1** and alkyne **S2.** The addition of $ZnBr_2$ together with the regents of the Sonogashira reaction did not lead to the desired product. When Zn salt was added separately, after 6 hours of Pd/CuI catalyzed cross-coupling reaction, indole **1** was obtained in only 12% yield.

Finally, a two-step one-pot procedure was successfully developed: after the Pd-catalysed coupling reaction was completed, acetonitrile was evaporated, and toluene was added to the crude reaction mixture within zinc salt. The reaction was reacted for 6 hours at 120°C, affording the final product, indole **1**, in 77% overall yield.

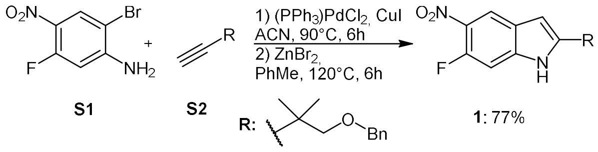


Figure 3 Two-step One-Pot synthetic protocol

To summarise, a very simple protocol was envisioned for the synthesis of electron-poor indole. $ZnBr_2$, a non-noble metal salt, gave the best results, and promoted the formation of indole derivatives in high yields, constantly higher than 90%, including the precursor of the API Tezacaftor **1**.[23] As further improvement, it was possible to synthesize the pharmaceutical precursor in a very convenient two-step, one-pot procedure in overall 77% yield.

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Supporting Information

YES (this text will be updated with links prior to publication)

Conflict of Interest

The authors declare no conflict of interest.

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(23) **General procedure:** In an oven dried Schlenck under nitrogen, the ethynylaniline (1 eq.) was dissolved in dry toluene (0.25M) and the solution was degassed for ten minutes with nitrogen. After $ZnBr_2$ (10% mol) was added, the mixture was heated under inert atmosphere for 6h at 120°C. After cooling, the reaction was diluted with dichloromethane and then the solvent was evaporated. The crude product was purified by flash chromatography (Hex:EtOAc). **2-(1-(benzyloxy)-2-methylpropan-2-yl)-6-fluoro-5-nitro-1H-indole, 1** Using general procedure starting from 2-(4-(benzyloxy)-3,3-dimethylbut-1-yn-1-yl)-5-fluoro-4-nitroaniline, obtained yellow solid, 96% yield. **^{1}H-NMR** ($CDCl_3$): δ 9.36 (bs, 1H), 8.31 (d, J = 7.24 Hz, 1H), 7.40-7.33 (m, 5H), 7.04 (d, J = 11.72 Hz, 1H), 6.34 (s, 1H), 4.61 (s, 2H), 3.54 (s, 2H) (s, 2H), 4.30 (bs, 2H), 3.54 (s, 2H), 1.39 (s, 6H). **^{13}CNMR** ($CDCl_3$): δ 152.5 (d, J = 254.1 Hz, *C*F), 150.9, 138.3 (d, J = 11.40 Hz, CCF), 131.7 (d, J = 8.9 Hz, *C*CF),128.8, 128.3, 127.9, 123.5, 118.5, 99.1, 98.7, 79.6, 74.0, 36.3, 25.5. **^{19}FNMR** ($CDCl_3$): δ -126.42. **HRMS** (ESI-): calc. $C_{19}H_{18}N_2O_3F$: 341.1301 found: 341.1309.