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COMMUNICATION

Synthesis of 2-Substituted Indoles through Cyclization and Demethylation of 2-Alkynyldimethylanilines by Ethanol

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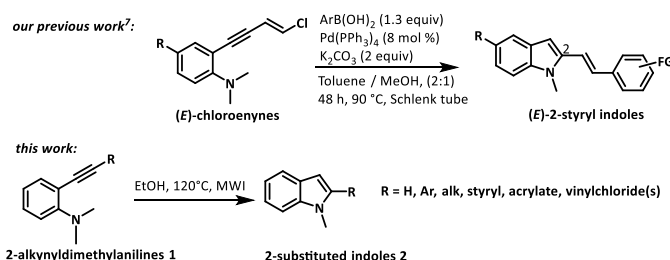
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Herein, we demonstrated that 2-alkynyldimethylamines easily cyclize in EtOH according to a 5-*endo-dig* annulation into 2-substituted indoles without the aid of any additive or any metal catalyst to activate the triple bond. Thus, a variety of functionalized 2-styrylindoles, 2-arylindoles, 2-alkynylindoles, and 2-alkylindoles were prepared in high to excellent yields according to an environmentally friendly protocol. The mechanism has been explored to better understand this eco-friendly access to 2-substituted indoles and DFT computations rationalized the role of the solvent in this *N*-annulation/dealkylation process.

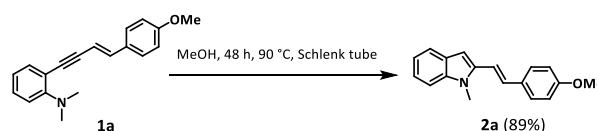
1 Introduction

Indoles are important heterocycles in biologically active natural products¹ and are also frequently found in various pharmaceutical products.^{2,3} Consequently, this important structural motif has led to the development of a very large number of synthetic methodologies. Among them, the 5-*endo-dig* hetero-annulation of alkynyldimethylanilines in the presence of electrophiles (ICl, I₂, ArSCL...) developed by Larock⁴ and others,⁵ as well as transition-metal catalyzed transformations,⁶ played a major role in this field. In this challenging context, we recently reported the one-pot synthesis of 2-styrylindoles from *ortho*-substituted chloroenynes.⁷ In a hot toluene/MeOH mixture, using a Pd(0) catalyst, boronic acids and K₂CO₃, 2-alkynyldimethylanilines **1** were transformed into 2-styrylindoles after successive Suzuki arylation,⁸ *N*-cyclization and *N*-demethylation reactions (Scheme 1).



Scheme 1. Our approaches for the synthesis of 2-substituted indoles

The success of this *N,N*-dimethyl-cyclization/*N*-demethylation process prompted us to examine the role of each reagent in this transformation. To this end, we have removed one by one all of the reagents used in our previous protocol to transform **1a**⁸ into **2a** (Scheme 2).



Scheme 2. Synthesis of (*E*)-2-(2-chlorovinyl)-1-methyl-1H-indole **2a** from cyclization of **1a** followed by a *N*-demethylation reaction

In the presence of only hot MeOH, we were delighted to observe the transformation of diarylenyne **1a** into indole **2a** with an excellent yield (89%). Even if the *N*-cyclization of *ortho*-alkynylanilines into indole derivatives is well-known, to our knowledge, this result shows that the formation of a 2-substituted-*N*-methylindole can be carried out in the absence of any activating agent since a simple heating in MeOH is sufficient to promote the *N*-cyclization and the *N*-demethylation reactions. For comparison, Ribecai reported in 2009 the cyclization of 2-alkynylanilines into 2-substituted-1H-indoles in water at 200 °C under microwave heating in the absence⁹ or in the presence of additives¹⁰ (e.g. KCl, NaHCO₃, pyrrolidine,...), necessary to increase yields and the scope of the cyclization reactions.

In this paper, we wish to present our results concerning the development of this "green" annulation/demethylation process, its application to a wide range of functionalized substrates and also a possible reaction mechanism which is supported by DFT calculations.

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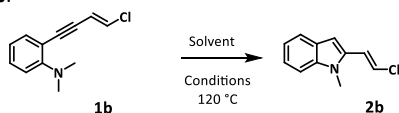
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2 Results and discussion

Before studying the scope of this process using EtOH as only reagent, we first examined the influence of other solvents on the cyclization and demethylation steps of (*E*)-chloroenyne **1b**, a poorly cooperative substrate in which the chlorine atom, useful for further transformations,¹¹ disfavoured the 5-*endo-dig* annulation reaction.¹² The results of this solvent and experimental screening are reported in Table 1.

Table 1. Effects of solvents and experimental conditions on the transformation of (*E*)-chloroenyne **1b** into 2-(2-chlorovinyl)-1-methyl-1*H*-indole **2b**.^a

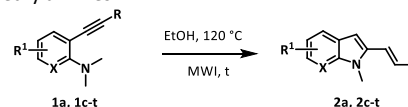


Entry	Solvent(s)	Conditions	Time (h)	Yield ^b (%)
1	MeOH	Schlenk tube	48	40 ^c
2	MeOH	MWI ^d	2	70
3	EtOH	MWI	2	75
4	<i>i</i> -PrOH	MWI	2	30
5	HFIP	MWI	2	^e
6	Toluene	MWI	2	0
7	H ₂ O	MWI	2	trace
8	H ₂ O/EtOH (1/1)	MWI	2	35
9	H ₂ O/acetone (1/1)	MWI	2	40

^aTypical reaction conditions: a mixture of **1b** (0.5 mmol) was stirred in EtOH (3 mL) at 120 °C under MWI. After completion (estimated by TLC), the mixture was allowed to cool to room temperature and EtOH or MeOH was removed under reduced pressure. The crude material was purified by silica gel column chromatography to give **2b**. ^bIsolated yield. ^cReaction achieved at 90 °C. ^d30W Microwave irradiation. ^eComplex mixture.

Under the conditions used in Scheme 2, **1b** was transformed into indole **2b** after 48 h of reaction in a poor yield of 40% (entry 1). Compound **1b** was then heated in MeOH for 2 h at a higher temperature of 120 °C under microwave irradiation (MWI). Gratifyingly, after 2 h, **2b** was isolated in 70% yield (entry 2). We next replaced MeOH by EtOH, *i*-PrOH, hexafluoroisopropanol (HFIP), toluene and H₂O to evaluate the influence of other solvents (entries 3-7) and found that EtOH and MeOH gave nearly similar yields (70-75%, entries 2,3). A more congested alcohol as *i*-PrOH allowed the expected transformation but with a poor performance (30%, entry 4), while the reaction run in HFIP or toluene was inefficient (entries 5,6). Moreover, as it could be observed in entries 7-9, water and its association with EtOH or acetone did not provide indole **2b** with satisfactory yields. The scope of this metal- and additive-free process was then evaluated with a variety of *N,N*-dimethylanilines **1** bearing various alkyne substrates at the *ortho*-position using EtOH as only reagent at 120 °C under MWI. The results of this study are reported in Table 2. As it can be seen, under our optimal conditions, alkynes **1a**, **1c-t** were transformed into indoles **2a**, **2c-t** with excellent yields. In details, diarylenynes **1a** and **1c**, (di)chloroenynes **1d-f** and conjugated ethyl acrylate **1g** reacted well in hot EtOH or MeOH (to avoid esterification, entry 7) under MWI to provide the expected indoles **2a**, **2c-h** in good yields (entries 1-7).

Table 2. Synthesis of 2-substituted indoles **2** from 2-alkynyldimethylanilines **1**.^a



o-Alkynyldimethylanilines 1c-t		Indoles 2c-s		t (h)	Yield ^b (%)
1		1a		2	90
2		1c		2	90
3		1d		4	56
4		1e		6	42 ^c
5		1f		2	85
6		1g		2	90
7		1g		2	88 ^d
8		1h		10	93
9		1i		10	91
10		1j		10	94
11		1k		10	95
12		1l		10	95
13		1m		2	74
14		1n		2	95
15		1o		2	80
16		1p		2	79
17		1q		10	90 ^e
18		1r		4	89
19		1s		4	87
20		1t		4	88

^aReaction conditions are identical to those described in footnote^a of Table 1. ^bIsolated yield. ^cReaction achieved at 140 °C. ^dReaction achieved in MeOH. ^eReaction achieved at 160 °C.

Having in mind a deeper exploration of the structure-activity relationships of *iso*Combretastatin A4¹³ derivatives by replacing its B-ring with substituted-indoles,^{7,14} 2-chlorovinyl-indoles **2d** and **2e** in which the chlorine atom will be useful for further transformations, were obtained in acceptable yields regardless of the configuration of the chloroenyne double bond (entries 3, 4). Interestingly, diarylalkynes **1h-j**, arylheteroarylalkynes **1k,l** bearing a thiophene or a pyridine moiety, and diaryldiyne **1m** were transformed into the expected 2-substituted indoles **2i-n** with excellent yields (entries 8-13). Alkyl groups on the alkyne triple bond were also well tolerated in this process as indole derivatives **2o-q** and azaindole **2r** were obtained in good yields (entries 14-17). A terminal alkyne such as **1r** was well tolerated to give 1-methyl-1*H*-indole **2s** in a good 89 % yield (entry 18) In entries 19 and 20, we noted that silylated alkynes **1s,t** were also transformed into indole derivatives **2s,t** with good yields, but the TMS-group did not survive under these conditions. To summarize this study, this protocol is found to be practical for a variety of alkyne substrates in which a great number of functionalized group are well tolerated. Intrigued by the large scope of this transformation, we then checked that there were no traces of metals (Pd and Cu) in our samples since alkynes **1** were prepared according to Sonogashira and Suzuki reactions.

We thus purified diarylenyne **1i** one (sample 1, S1), two (S2) and three times (S3) on silica gel. These three samples were then reacted in hot EtOH¹⁵ under MWI, using new magnetic stir bars¹⁶ and new microwave tubes in view of their transformation into the expected 2-arylindole **2i** (Fig. 1).

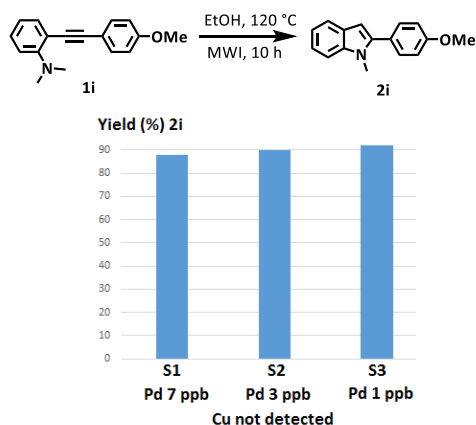
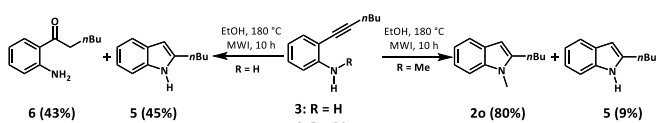


Fig 1. Synthesis of **2i** from metal-free samples of **1i**

The results indicated that these samples (S1, S2 and S3) gave similar yields in **2i** (88, 90 and 92% respectively). The quantity of residual traces of Pd and Cu in these samples was quantified by atomic absorption after mineralization of the samples. The results, obtained with internal standards, indicated that no traces of Cu in the three samples (below 5 ppb if any) and that Pd quantities were also negligible (7 (S1), 3 (S2) and 1 ppb (S3), respectively).

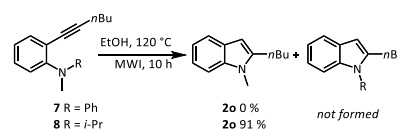
Encouraged by these results, we turned our attention to examining primary and secondary anilines **3** and **4** (Scheme 3).



Scheme 3. Reactions of anilines **3** and **4** in hot EtOH under MWI.

As it can be seen, heating *N*-methylaniline **4** at a higher temperature of 180 °C furnished mostly indole **2o** (80%) accompanied with a small quantity of *NH*-indole **5** (9%) which is consistent with our proposition of mechanism involving an ammonium intermediate and where an ethanolate anion, in this case, acted as a base rather than a nucleophile. This process is less suitable for primary anilines as **3** since indole **5** and ketone **6**, resulting from the hydration of the triple bond, were obtained in equivalent quantities.

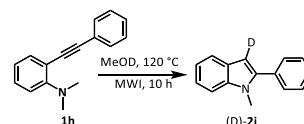
Next, we were interested to examine the behaviour of tertiary anilines **7** and **8** (Scheme 4) having respectively on their nitrogen atom, two different groups (Me and Ph for **7**, Me and *i*-Pr for **8**).



Scheme 4. Cyclization attempts of anilines **7** and **8** under MWI in EtOH

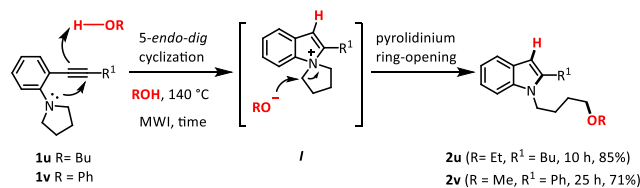
After heating **7** in EtOH for 10 h at 120 °C under MWI irradiation, we did not observe any transformation of the poorly nucleophilic and encumbered diphenylmethylaniline **7**, which was totally recovered unchanged. On the contrary, under similar conditions, a careful examination of the crude mixture by ¹H NMR revealed that aniline **8** was successfully transformed into *N*-methylindole **2o** (91 %) with no trace of 2-butyl-1-isopropylindole. In this case, it is reasonable to think that the ethanolate anion formed during this process acted as base to eliminate 1-propene rather than a nucleophile (see Scheme 6).

To gain mechanistic insight into cyclization/demethylation process observed with dimethylanilines, a series of experiments was then conducted. First, *o*-hexynyl dimethylaniline **1n** was heated in EtOH for 2 hours at 120 °C under MWI in the presence of 1 equiv of 2,2,6,6-tetramethylpiperidinyl-*N*-oxyl (TEMPO), a well-established radical scavenger.¹⁷ The presence of TEMPO did actually significantly alter the yield in indole **2o** (84% vs 95% without TEMPO), which does not support a radical pathway.



Scheme 5. Synthesis of (D)-**2i**

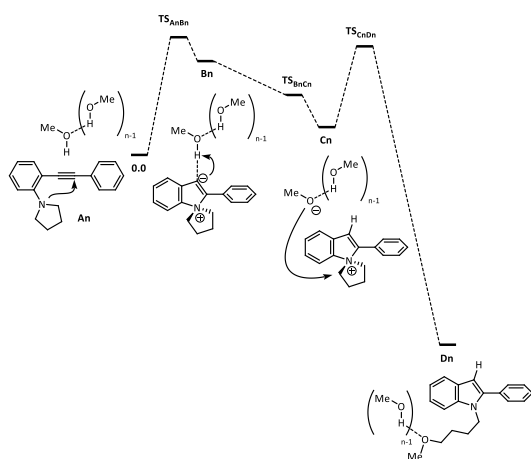
Our second interrogation concerned the activation of the alkyne triple bond as EtOH or MeOH were the only reagents used in this protocol. Therefore, we have heated diarylalkyne **1h** in MeOD at 120 °C under MWI (Scheme 5). In the crude mixture, after 10 h of reaction, we observed the unique formation of (D)-**2i** indicating that MeOD may activate the alkyne triple bond of **1h**. Next, to demonstrate the fundamental role of EtOH or MeOH as being also the nucleophilic reagents responsible for the *N*-demethylation step, we performed other experiments on *ortho*-substituted anilines **1u** and **1v** in which the nitrogen atom is included into a ring (Scheme 6).



Scheme 6. Synthesis of indoles **2u,v** and possible mechanism.

When **1u,v** were heated in EtOH or MeOH under MWI, we were very pleased to observe the formation of **2u** and **2v** demonstrating the fundamental role of MeOH or EtOH in the last alkylation/dealkylation steps (demethylation in the case of dimethylanilines). A possible reaction mechanism is proposed in Scheme 6. First, the nitrogen atom of the pyrrolidine reacts with the triple bond (possibly activated by EtOH) according to a 5-*endo-dig* cyclization to give intermediate **I**. Then, EtOH as solvent or possibly an ethanolate species generated during the cyclization process reacts on one of the methylene groups close to the ammonium center by S_N2 to open the pyrrolidinium intermediate to promote **2u,v**.

Density functional theory (DFT) calculations were carried out to understand the origin of the activation of the substrates under the reaction conditions. The above experiments having put aside the intervention of radical species, the main issue to address was the feasibility of an ionic mechanism triggered by just the solvent. The Gaussian 09 software package was used for the calculations.¹⁸ Gas phase geometry optimization was carried out at the M06-2X¹⁹/6-31G(d,p)²⁰ level of theory with the grid=ultrafine keyword.



Scheme 7. Computed Steps.

Correction to the Gibbs free energy was computed at 393.15 K. The values presented include solvent correction obtained with the PCM²¹ solvation model for methanol. This solvent was chosen rather than EtOH to save computer time, as it provides similar experimental results. The model substrate is presented in Scheme 7. Its cyclization was studied in the presence of H-bonded methanol clusters $(\text{MeOH})_n$ of various sizes ($n = 1-6$).²² Linear clusters were privileged to be able to bridge the reactive sites. We found three steps starting from the molecular system **An** comprising the substrate and $(\text{MeOH})_n$ optimized together: *i*) a 5-*endo-dig* cyclization yielding the vinyl anion ammonium species **Bn**, *ii*) a proton transfer from the $(\text{MeOH})_n$ cluster to the vinyl anion center to give the H-bonded methylate/ammonium species **Cn**, and *iii*) S_N2 reaction to give the final dealkylated product **Dn**.

The relative free energies of the computed intermediates and transition states are collected in Table 3 as a function of n , taking **An** as a reference. With only one MeOH molecule ($n = 1$), the cyclization of **A1** into **B1** requires a high free energy of activation of 29.9 kcal/mol and is markedly endergonic by 27.2 kcal/mol. No other steps could be computed. With $n = 2$, the first barrier is 26.4 kcal/mol, which is significantly lower than with $n = 1$. The cyclization is endergonic by 23.4 kcal/mol. The deprotonation step could not be computed. The S_N2 step was achieved through a transition state lying at 26.9 kcal/mol above **A2**. Product **D2** is obtained in a strongly

exergonic fashion, as it lies 38.7 kcal/mol below **A2**. With $n = 3-6$, the full pathway could be calculated. It can be seen that the rate-determining step is the first one in all cases. The lowest barrier for this first step is 24.4 kcal/mol. It corresponds to a cluster of 4 MeOH. Clearly, the formation of a network of H-bonded molecules has a positive impact on the cyclization, but the effect is not linear as the barrier increases with $n > 4$. Focusing on $n = 4$, the cyclization step is endergonic by 18.5 kcal/mol (Scheme 8). The next step, the proton transfer connecting **B4** to **C4**, is achieved through a transition state that has a lower energy than **B4**. This unusual situation is typical of what is referred to as a collapse mechanism and means that **B4** is a very unstable intermediate, which, if it exists, is immediately transformed into **C4**. This species is less stable than **A4** by 3.6 kcal/mol. What funnels the reaction towards the final product is the dealkylation step. The corresponding transition state TS_{C4D4} , lies 20.2 kcal/mol above **A4**. This step is strongly exergonic, **D4** being located at -35.2 kcal/mol on the free energy surface. Overall, the calculated free energies of activation are realistic with regard to the experimental conditions and the reaction is a highly favorable process. The free energy profile and the geometry of the intermediates and transition states with $n = 4$ are displayed in Scheme 8. The MeOH molecule that donates its proton to the vinyl anion does not become the methanolate of the cluster. It is simultaneously reprotonated by the nearby MeOH molecule, which is in turn reprotonated by the third one. The proton transfer stops here, leaving the third molecule of the cluster as a doubly H-bonded methanolate. The S_N2 step could not be achieved from this methanolate but from the less hindered tail MeOH, which is simultaneously deprotonated by the methanolate. Looking at higher clusters in Table 3 ($n = 5, 6$), similar characteristics can be drawn, notably regarding the instability of **Bn** and its straightforward collapse to **Cn**. However, the $n = 4$ case appears to be the best compromise in terms of free energy for the entire process. This does not mean that only linear $(\text{MeOH})_4$ clusters are active species in solution for this reaction, but the feasibility of an ionic mechanism based on the simple activation of the substrate by methanol aggregates is validated by these computations.

Conclusions

In summary, a variety of 2-substituted indoles **2** were prepared in high yields from the annulation/demethylation process of 2-alkynyldimethylanilines. A simple heating of these compounds readily accessible in EtOH allowed rapid and efficient access to various *N*-methylindoles with high yields. This approach, which does not require metal catalysts or additives, and which is applicable to different types of alkynes bearing various functional groups, is in perfect harmony with the requirements of modern environmentally friendly chemistry.

Conflicts of interest

There are no conflicts to declare.

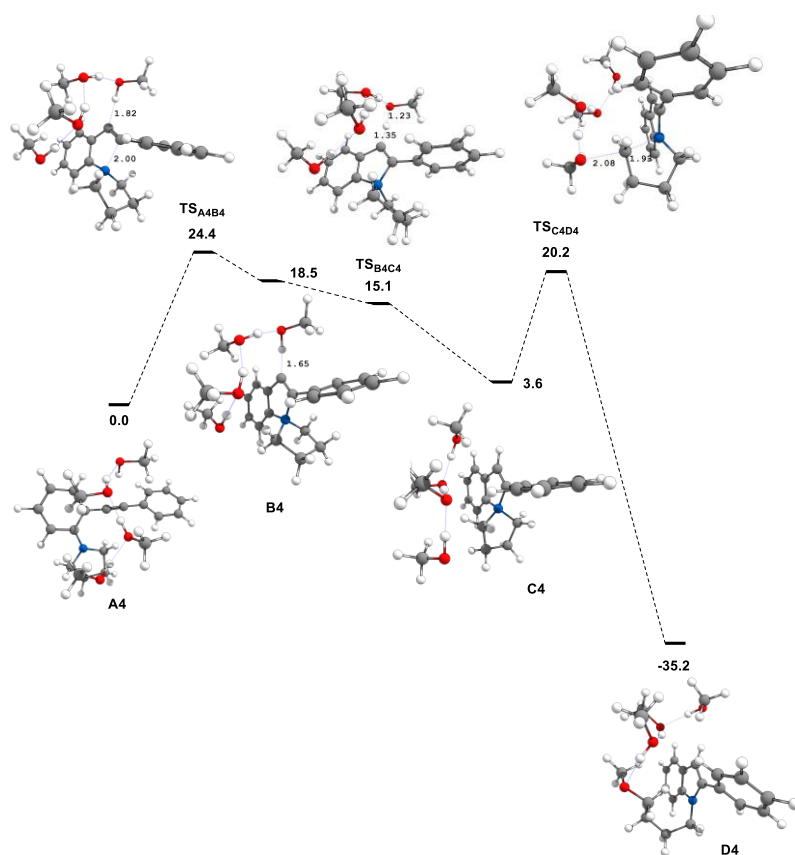
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Table 3. Free energies (ΔG_{393} , kcal/mol) of the computed species shown in Scheme 7.

n	TS _{AnBn}	Bn	TS _{BnCn}	Cn	TS _{CnDn}	Dn
1	29.9	27.2	-	-	-	-
2	26.4	23.4	-	16.7	26.9	-38.7
3	26.0	20.0	14.8	8.1	24.1	-39.2
4	24.4	18.5	15.1	3.6	20.2	-35.2
5	28.3	20.8	18.2	3.0	19.9	-31.5
6	27.5	19.5	16.3	1.7	22.9	-28.6

**Scheme 8.** Free energy profile (ΔG_{393} , kcal/mol) for n = 4; Geometry of the intermediates and transition states (distances in Å)

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