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Microwave-assisted synthesis of indole-derivatives via cycloisomerization of 2-alkynylanilines in water without added catalysts, acids, or bases

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ABSTRACT

An unprecedented green methodology is described for the preparation of differently substituted indoles via microwave-assisted cycloisomerization of 2-alkynylaniline derivatives in water. Moderate to good yields in the cyclization can be achieved for a variety of 2-aminoaryl alkynes. Reactions are run without any added metal catalyst, acid, or base, and do not take place by applying conventional heating.

The indole ring system is a structural component of a vast number of biologically active natural and unnatural compounds, and it can be found in many pharmaceutical agents.[1] The synthesis and functionalization of indoles has been a major area of focus for synthetic organic chemists and numerous methods have been developed.[2] Among the many described approaches, the cyclization reaction of both N-substituted and N-unsubstituted-2-alkynylaniline derivatives is a major procedure for the construction of 2,3-disubstituted and 2-substituted indoles.[2] In fact, there is the significant advantage of ready availability of the starting 2-alkynylanilines which can be prepared easily by Sonogashira-type alkynylations from a large variety of commercially available substrates.[3] Typically, the cyclization is achieved using strong bases (like metal alkoxides, metal hydrides, and metal amides)[4] or transition metals.[2,5–14] Furthermore, a recent example describes electrochemical-mediated cyclization of 2-alkynylanilines without metal catalysts.[15] However, most of the cited methods require the use of moisture-sensitive bases, harsh or strongly basic conditions which are incompatible with a wide range of functional groups. As regards the use of transition metals, the cyclization of 2-alkynylanilines and 2-alkynylanilides typically takes place in the presence of catalytic amounts of Pd(II) salts or Pd(0) complexes,[2g,5] stoichiometric or catalytic Cu(I) and Cu(II) salts or complexes,[6] and catalytic Au(III) salts.[7] In addition, also the use of platinum,[8] molybdenum,[9] iridium,[10] rhodium,[2f,11] zinc,[12] mercury,[13] iron,[14] and indium[16] has recently been described for preparing substituted indoles. Nonetheless, only a small number of these methods deal with N-unprotected 2-alkynylanilines, which cyclize in the presence of expensive metal sources and/or high catalyst loadings, with the additional drawback of potential metal contamination of the products.

Curiously, a very few examples describe the application of microwave irradiation in this type of cyclization.[17] On the other hand, the need to develop cleaner and more benign processes is becoming ever more urgent.[18] In this novel perception, reactions conducted in aqueous media as well as the application of microwaves for heating the reaction mixture have been receiving increasing attention. Recently, microwave irradiation was applied with significant advantages in heterocyclic synthesis allowing to reach higher temperatures quickly and to obtain faster reactions than by conventional heating.[19] Many examples of microwave-assisted reactions are reported in water[20] or without solvent.[21] Particularly worthy of note are synthetic organic reactions run in water and under superheated conditions.[20b,c] An interesting example is represented by the hydration of terminal alkynes in superheated water at 200 °C under microwave irradiation described by Vasudevan et al.[22] In 2006 Alami and co-workers[23a] expanded the scope of hydration of alkynes and demonstrated the positive effect of microwave heating toward the hydration of arylalkynes, diarylalkynes as well as arylpropargylic alcohols performed in ethanol with *p*-toluenesulfonic acid.[23] Recently, the same authors

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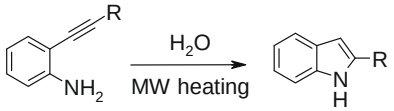
showed that this methodology can successfully afford 2-arylsubstituted benzofurans and benzothiophenes from diarylalkynes.[23c]

Bearing in mind all these considerations, we put forward the idea that a microwave-assisted cycloisomerization of 2-alkynylanilines taking place via an intramolecular hydroamination might be a feasible way to prepare substituted indoles. In particular, we wanted to explore the use of water as the solvent and apply microwave irradiation to reach the water 'near critical'[20b,c] region. To the best of our knowledge, this methodology is unprecedented and represents the first example of microwave-assisted cyclization of 2-alkynylanilines achieved without any added metal catalyst. As model substrates we chose one terminal alkyne, the commercially available 2-ethynylaniline, **1a**, to give the un-substituted indole, **2a**, and one diarylalkyne, 2-(phenylethynyl)aniline, **1b**, to obtain 2-phenylindole, **2b**. The main results of our first attempts are summarized in Table 1.

For the preparation of the required **1b** without significant metal-contamination, we applied a copper-free procedure we had previously developed with Pd EnCat™ catalysts.[24] The product was obtained with a Pd content lower than 0.1 ppm by AAS.[25] To test the cyclization in water, we prepared a suspension of the substrate (0.1 mmol) in 2 ml of water and we applied microwave irradiation to heat it to 200 °C.[26] In order to avoid potential metal contaminants, we used ACS UltraTrace water, where most common transition and nontransition metals are present at a 10^{-5} ppm level. In addition, we always employed new glassware. In a first instance, we worked to identify the temperature required for the cyclization, starting with 2-ethynylaniline, **1a**. Although this substrate showed some instability with temperature, a certain amount of indole, **2a**, could be obtained at 200 °C (Table 1, entry 1), while at lower temperatures no significant conversions were observed. However, prolonged heating at 200 °C proved detrimental since degradation of both product and starting material occurred and, what is more, 2-aminoacetophenone, resulting from the hydrolysis of the starting alkyne, was formed along with the desired indole, **2a** (Table 1, entries 2 and 3). The second model compound, **1b**, showed a good stability in the applied conditions without significant hydrolysis but proved rather less reactive than **1a** in shorter reaction times. However, a not negligible amount of indole **2b** was formed when the reaction mixture was heated to 200 °C for longer times (Table 1, entries 5 and 6).

To make a comparison between thermal heating and microwave irradiation, we did some cycloisomerization trials on 2-(phenylethynyl)aniline, **1b**, using pressure-resistant sealed tubes. In the trials, 0.3 mmol of substrate was suspended in 2 ml of UltraTrace water and the reaction was heated to 200 °C in an oil bath and monitored for 7 h, sampling at different reaction times. No trace of 2-phenylindole, **2b**, could be found and the not reacted starting material was the only recovered product (Table 1, entry 7). Since the experiments with thermal heating were conducted in transparent pressure-resistant glass vials we could also verify that the compound was soluble in water under the applied conditions.

Table 1
First attempts in microwave-assisted cycloisomerization[a]



1 **2**

Entry	R	1	Temperature (°C)	Time (min)	2	Yield of 2[b] (%)
1	H	**1a**	200	10	**2a**	23
2	H	**1a**	200	30	**2a**	17[c]
3	H	**1a**	200	60	**2a**	6[c]
4	Ph	**1b**	200	30	**2b**	14
5	Ph	**1b**	200	60	**2b**	17
6	Ph	**1b**	200	120	**2b**	33
7	Ph	**1b**	200	7 h	**2b**	0[d]

[a] Reaction conditions: 2-alkynylaniline (0.1 mmol), water (2 ml).
[b] Yields in solution determined by HPLC, using a calibration curve.
[c] 2-Aminoacetophenone was the main product, isolated in a 65% yield and 60% yield, respectively.
[d] Thermal heating was applied to a mixture of 2-(phenylethynyl)aniline, **1b**, (0.3 mmol) and water (2 ml).

Table 2
Solvent screening for the microwave-assisted cycloisomerization of 2-phenylethynylaniline, **1b**[a]

Entry	Solvent	Water (v/v %)	Temperature, °C (time, min)	Yield[b] (%)
1	EtOH	—	200 (30)	2
2	*n*-BuOH	—	200 (30)	3
3	DMF	—	200 (30)	1
4	CH_3CN	—	200 (30)	1
5	THF	—	200 (30)	1
6	NMP	—	200 (30)	2
7	1,2-Dichlorobenzene	—	200 (30)	2
8	Toluene	—	200 (30)	—
9	DMSO	—	200 (30)	—[c]
10	$[BMIm]BF_4$	—	200 (30)	—
11	EtOH	25	200 (30)	6
12	NMP	25	200 (30)	3
13	DMF	25	200 (30)	10[c]
14	$[BMIm]BF_4$	25	200 (30)	—[c]

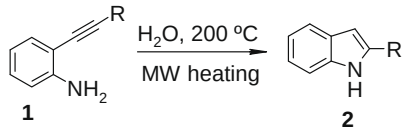
[a] Reaction conditions: 0.1 mmol of **1b**, solvent (2 ml).
[b] Yields in solution determined by HPLC, using a calibration curve.
[c] Significant degradation of starting material observed.

In order to understand if the cycloisomerization of **1b** could occur more efficiently under different conditions, we tested many of the common solvents and we found, to our surprise, that the reaction was not giving significant amounts of 2-phenylindole in media different from water (Table 2, entries 1–10). The addition of small amounts of water to the screened solvents did not give significant advantages (Table 2, entries 11–14).

Since the presence of water appears so important for the cycloisomerization, we worked on the optimization of these conditions by trying in a first instance to extend microwave irradiation times in order to further improve the yields. However, prolonged heating at 200 °C (for 2 h or more) was often accompanied in our equipment by leakage from the reaction caps with loss of water and compounds and some degradation of the substrates. For this reason we thought that the application of short cycles of microwave heating could provide an overall long irradiation but under conditions less stressing for the equipment, since reaction vials are cooled and de-pressurized between one cycle of heating and the other. The effect of microwave short cycles was investigated for four different substrates, as shown in Table 3. Also substrates **1c** and **1d** were prepared according to our procedure[24] with Pd contents lower than 0.1 ppm by AAS.[25]

What we immediately observed was that not only leakages and degradations were minimized but also yields were significantly improved when shorter cycles were applied (see Table 3, compare entries 2–4, entries 7–9, and entries 12–14), except for 2-ethynylaniline, **1a**, where the yield remained low (compare Table 1, entries 1 and 2 and Table 3, entry 1). Having in hands these interesting results, we focused our attention on 2-arylethynylanilines and we tried to increase the concentration of substrates up to a 0.3 mmol scale. However, when concentrations were doubled lower yields were observed for **2b** and **2d** (Table 3, entries 5 and 15), except for **2c** (Table 3, entry 10), mainly as a result of the presence of not reacted starting materials. A further increase in the

Table 3
Optimization of conditions for the cycloisomerization of 2-aminophenylalkynes[a]



1 2

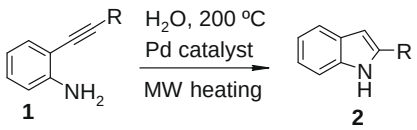
Entry	R	1	MW cycles		mmol of 1	Total time (h)	2	Yield[b] (%)
			Cycles number	Cycle time (min)				
1	H	**1a**	3	5	0.1	0.25	**2a**	16[c]
2	Ph	**1b**	3	30	0.1	1.5	**2b**	63
3	Ph	**1b**	9	10	0.1	1.5	**2b**	65
4	Ph	**1b**	18	5	0.1	1.5	**2b**	69
5	Ph	**1b**	18	5	0.2	1.5	**2b**	59
6	Ph	**1b**	18	5	0.3	1.5	**2b**	44
7	4-MeO-Ph	**1c**	3	30	0.1	1.5	**2c**	56
8	4-MeO-Ph	**1c**	9	10	0.1	1.5	**2c**	58
9	4-MeO-Ph	**1c**	18	5	0.1	1.5	**2c**	77
10	4-MeO-Ph	**1c**	18	5	0.2	1.5	**2c**	78
11	4-MeO-Ph	**1c**	18	5	0.3	1.5	**2c**	31
12	4-Cl-Ph	**1d**	3	30	0.1	1.5	**2d**	36
13	4-Cl-Ph	**1d**	9	10	0.1	1.5	**2d**	49
14	4-Cl-Ph	**1d**	18	5	0.1	1.5	**2d**	65
15	4-Cl-Ph	**1d**	18	5	0.2	1.5	**2d**	40
16	4-Cl-Ph	**1d**	18	5	0.3	1.5	**2d**	26

[a] Reaction conditions: the specified amounts of 2-aminoaryl alkyne were suspended in water (2 ml) and heated to 200 °C by microwave irradiation for the time reported in the table.
[b] Yields in solution determined by HPLC, using a calibration curve.
[c] Degradation observed; 2-aminoacetophenone was the main product.

concentrations caused a more drastic decrease in the yield for all the substrates (Table 3, entries 6, 11, and 16).

With the objective to verify that our cycloisomerization reactions were not taking place because of the presence of Pd salts, we studied the potential effect of Pd possibly contaminating our starting arylalkynes. In other words, we wanted to show that the effect of Pd was negligible at concentrations surely lower than 0.1 ppm (corresponding to a loading lower than 2×10^{-5} mol %). These results are reported in Table 4. A first screening of catalyst loadings showed that the presence of Pd salts has indeed an important effect at certain concentrations. When the reaction was run with a 0.1 mol % of palladium, cyclization of **1b** to **2b** was visibly accelerated even if considerable degradation of starting materials occurred (Table 4, entries 1–3). If a lower amount of palladium was applied, down to 0.01 mol %, cyclization yields were not significantly higher than in the absence of added catalyst (compare Table 1, entry 4 and Table 4, entries 4 and 5). Also, a low yield was observed when a Pd-contaminated starting alkyne was used without added Pd species (Table 4, entry 6).

Table 4
Cyclization of **1b** with Pd sources[a]



1 2

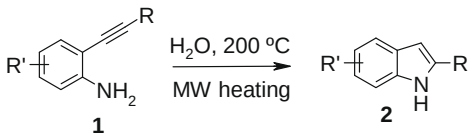
Entry	R	Palladium		Time (min)	Ratio **2**/**1**	Yield[b] (%)
		Catalyst	Loading (mol %)			
1	Ph	$PdCl_2$	0.1	30	99/1	56
2	Ph	$Pd(OAc)_2$	0.1	30	17/83	15
3	Ph	$Pd(OAc)_2$	0.1	90	70/30	51
4	Ph	$PdCl_2$	0.01	30	18/82	16
5	Ph	$Pd(OAc)_2$	0.01	30	20/80	19
6	Ph	n.d.	0.013[c]	30	15/85	12

[a] Reaction conditions: **1b** (0.3 mmol), water (2 ml), and the specified amount of Pd catalyst. Reactions were heated to 200 °C under microwave irradiation for the time reported in the table.
[b] Yields in solution determined by HPLC, using a calibration curve.
[c] Palladium present as a contaminant in the starting material.[25]

With the aim of extending the scope of our cyclization conditions, we explored the reactivity of different substrates. We prepared a series of differently substituted 2-aminophenylacetylenes and applied the most efficient conditions found to achieve cyclization. After the screening of concentration we chose the 0.1 mmol/ml concentration to run our reactions, which is, as already shown, a good compromise between efficiency and applicability. In Table 5, we summarized our results. Moderate to good isolated yields could be obtained for 2-(arylethynyl)anilines (Table 5, entries 2–9), except for **1j** (20%, Table 5, entry 10), with the best cyclization yields obtained with substrates bearing electron-donating substituents. Low yields in **2a** were obtained starting from both **1a** and the corresponding trimethylsilyl derivative **1l** (Table 5, entries 1 and 12), whereas the (alkylethynyl)aniline **1k** gave **2k** in a very low yield (Table 5, entry 11).

In summary, we demonstrated that indole and 2-substituted indoles can be obtained by a simple and straightforward methodology which involves the microwave-promoted cycloisomerization from the corresponding 2-alkynylanilines in water. Neither acid or basic additives, nor metal catalysts were added to promote the reactions. The residual Pd salts (ppb) that could be present in the precursors do not seem to affect the yields significantly, whereas microwave heating proved necessary. Moderate to good yields can be achieved for a variety of substrates; higher yields are obtained for compounds bearing electron-donating substituents. More experiments are ongoing to elucidate the mechanism of this microwave-assisted cycloisomerization as well as to improve its scope.

Table 5
Preparation of indole-substrates via cycloisomerization reactions of different 2-aminoaryl alkynes[a]



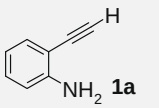
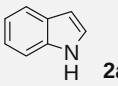
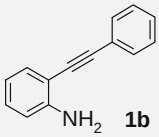
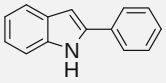
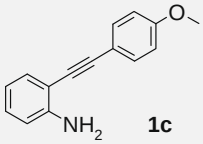
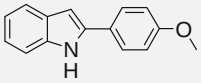
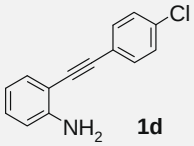
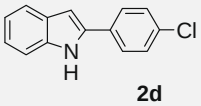
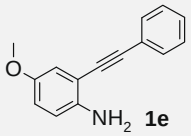
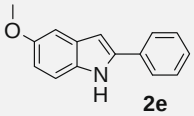
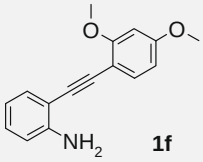
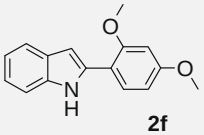
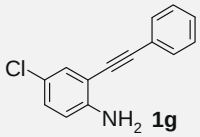
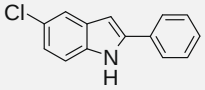
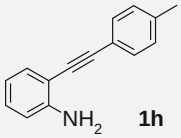
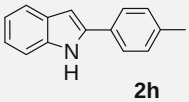
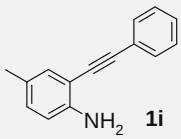
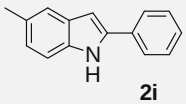
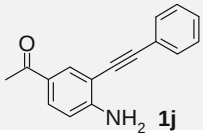
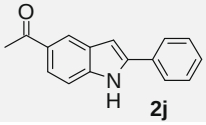
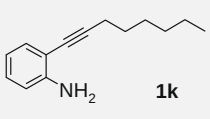
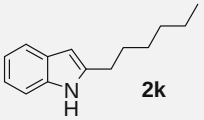
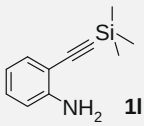
Entry	Arylalkynes **1**	Aryl indole **2**	Yields[b] (%)
1	 **1a**	 **2a**	23
2	 **1b**	 **2b**	46
3	 **1c**	 **2c**	79
4	 **1d**	 **2d**	34
5	 **1e**	 **2e**	59[c]
6	 **1f**	 **2f**	50
7	 **1g**	 **2g**	49
8	 **1h**	 **2h**	33
9	 **1i**	 **2i**	46
10	 **1j**	 **2j**	20

Table 5 (*continued*)

Entry	Arylalkynes **1**	Aryl indole **2**	Yields[b] (%)
11	 **1k**	 **2k**	9[d]
12	 **1l**	 **2a**	20

[a] Reactions were run in sealed tubes with 0.4 mmol of 2-aminoaryl alkyne suspended in 4 ml of water and the suspension was heated to 200 °C under microwave irradiation applied in 18 cycles of 5 min for a total time of 90 min.
[b] Isolated yields.
[c] Microwave irradiation was applied in 10 cycles of 5 min for a total time of 50 min until complete consumption of starting material was achieved.
[d] The main product was 1-(2-aminophenyl)-1-octanone which was isolated in 67% yield.

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Supplementary data

Supplementary data (experimental procedures and characterization data for all substrates **1a–k** and the cyclization products **2a–k**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.135.

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25. The AAS results are described more in detail in the Supplementary data.
26. Microwave experiments were performed in 10 ml sealed pressure tubes, using a CEM Explorer reactor; see Supplementary data.