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Microwave-assisted synthesis of indole- and azaindole-derivatives in water via cycloisomerization of 2-alkynylanilines and alkynylpyridinamines promoted by amines or catalytic amounts of neutral or basic salts

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ABSTRACT

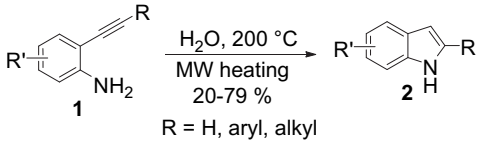
An efficient methodology is described and exploited for the preparation of differently substituted indoles and azaindoles via microwave-assisted cycloisomerization in water of 2-alkynylanilines and alkynylpyridinamines, which is promoted by catalytic amounts of neutral or basic salts or by stoichiometric weak organic bases. Good to high yields in the cyclization can be achieved for a variety of 2-amino (hetero)aryl alkynes. Reactions are run without any added metal catalyst. A comparison with the cycloisomerization conducted under conventional heating is also described.

1. Introduction

The indole and azaindole ring systems are common moieties in a vast number of biologically active natural and unnatural compounds and in pharmaceutically important molecules.[1] Among the many approaches described for their synthesis and functionalization, the cyclization reactions of 2-alkynylanilines and alkynylpyridinamines represent a major procedure to obtain 2-substituted and 2,3-disubstituted indoles[2] and their aza-analogues.[3] In fact, the starting 2-alkynylanilines and aminopyridines can be prepared easily by a Sonogashira-type alkynylation from a large variety of commercially available substrates.[4,16c] Typically, the cyclization of the alkynes is achieved using strong bases[3e,5] (like metal alkoxides, metal hydrides and metal amides) or transition metal catalysts.[2,6–16] Moreover, most of the cited methods require the use of moisture-sensitive bases, harsh or strong basic conditions, which are incompatible with a wide range of functional groups. Nonetheless, only a small number of these methods deal with *N*-unprotected 2-alkynylanilines or aminopyridines, which cyclize in the presence of expensive metal sources and/or high catalyst loadings,[6g,h,13a] with the additional drawback of potential metal-contamination of the products.

With the aim of developing cleaner and more benign processes, the use of microwaves for reaction mixture heating has found significant application in heterocyclic synthesis.[17–19] Among the applications of microwaves, particularly worthy of note are synthetic organic reactions run in water and under superheated conditions.[20]

In a previous work,[21] we presented the first example of microwave-assisted cyclization of 2-alkynylanilines achieved without any added metal catalyst (Scheme 1). We demonstrated that 1*H*-indole and 2-substituted indoles can be obtained by a straightforward methodology, which involves a microwave-promoted cycloisomerization in water, taking place via intramolecular hydroamination from the corresponding 2-alkynylanilines. The cyclization proceeds without any additive, either acid or basic and without any metal catalyst.



Scheme 1.

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For the preparation of the required 2-alkynylanilines without significant metal-contamination, we applied a copper-free procedure we had previously developed employing Pd EnCat™ catalysts; the products were obtained with Pd contents lower than 0.1 ppm by AAS.[22] In addition, we showed that the residual Pd salts (ppb) that could be present in the precursors do not affect the yields significantly, and that the reactions do not proceed under thermal heating conditions.

However, even if moderate to good yields were achieved for a variety of substrates, the methodology presented clear limitations especially in terms of applicability. In fact, if high yields were obtained for compounds bearing electron-donating substituents, the introduction of electron-withdrawing groups caused a significant decrease in yields. Moreover, when we tried to increase the concentration of the substrates above 0.1 mmol/mL, the yield dropped in most cases, and, after significant efforts, it appeared clear that a further improvement of these conditions was not straightforward. In this paper we describe the work performed to develop a more efficient method, which still makes use of water and applies simple conditions, but appears suitable for a wider range of both substrates and concentrations.

2. Results and discussion

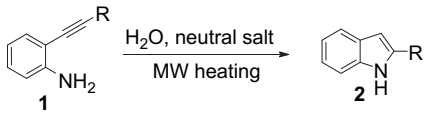
In the search for more efficient cyclization conditions and with the aim of expanding our own efforts towards the development of a more general method suitable for diversified substituents and substrates, we tried to find species that, if added to water, could help the cyclization, enhance the interaction of the substrates with microwaves and/or possibly increase the solubility in water of the less reactive substrates. Our first intent was to explore the effect of the addition of small amounts of inorganic salts (neutral, acid or basic). In fact, it is well known[20a,b] that the dielectric loss of water (and as a consequence the loss tangent) can be significantly increased by the addition of small amounts of inorganic salts, thus improving microwave absorbance by ionic conduction. Moreover, we speculated that relatively low salt concentrations (0.03–0.001 M) could influence the reactivity of the near-critical water medium.

Several salt screens were performed to identify a possible effect on the cycloisomerization. We worked on two model substrates, the terminal alkyne 2-ethynylaniline, **1a**, to obtain 1*H*-indole, **2a**, and the diarylalkyne 2-(phenylethynyl)aniline, **1b**, to obtain 2-phenylindole, **2b**. Both substrates **1a** and **1b** were prepared according to our aforementioned procedure.[22] The results obtained from the neutral salt screening are summarized in Table 1. Although substrate **1a** showed a considerable instability under our set of conditions, an encouraging yield of 35% in indole, **2a**, could be obtained after 15 min at 200 °C by adding 0.1 equiv of KCl (Table 1, entry 2). However, all the other salts tested under the same conditions gave rise to degradation and/or to hydrolysis to 2-aminoacetophenone (Table 1, entries 3–7). On the other hand, the second model compound, **1b**, proved stable under the applied conditions without significant hydrolysis but appeared rather less reactive than **1a**. For this reason the salt screening was run at 200 °C with 30 min of microwave irradiation, where significant amounts of indole **2b** were formed. The screening indicated that, also for **2b**, most of the salts are able to improve the yields respect to water alone. In particular, the best result was obtained in the presence of KCl, where after 30 min a 60% yield in **2b** was observed (Table 1, entry 11).

In a second instance we examined basic and acid inorganic additives with both model substrates (Table 2).

Not surprisingly, all the basic salts tested allowed a significant improvement in the cyclization yields with respect to water alone after 30 min at 200 °C. Nonetheless, the best results were obtained with $NaHCO_3$ for both **1a** and **1b** with 60% and 70% yield, respectively (see Table 2, entries 3 and 8). On the other hand, when an acid salt like ammonium chloride was used, hydrolysis of the triple bond was the main reaction observed (Table 2, entries 4 and 15).

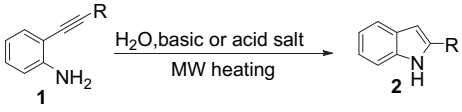
Table 1
Microwave-assisted cycloisomerization: screening of neutral salts[a]



Entry	R	1	Salt	Equiv of salt	Temperature, °C (time, min)	2	Yield of 2[b] (%)
1	H	**1a**	–	—	200 (15)	**2a**	15[c]
2	H	**1a**	KCl	0.1	200 (15)	**2a**	35[c]
3	H	**1a**	KBr	0.1	200 (15)	**2a**	25[c]
4	H	**1a**	KI	0.1	200 (15)	**2a**	23[c]
5	H	**1a**	$(n\text{-Bu})_4NBr$	0.1	200 (15)	**2a**	27[c]
6	H	**1a**	KCl	0.1	200 (5)	**2a**	15[c]
7	H	**1a**	KCl	0.1	200 (30)	**2a**	25[c]
8	Ph	**1b**	–	–	200 (30)	**2b**	14
9	Ph	**1b**	LiCl	0.1	200 (30)	**2b**	30
10	Ph	**1b**	NaCl	0.1	200 (30)	**2b**	41
11	Ph	**1b**	KCl	0.1	200 (30)	**2b**	60
12	Ph	**1b**	LiBr	0.1	200 (30)	**2b**	40
13	Ph	**1b**	NaBr	0.1	200 (30)	**2b**	38
14	Ph	**1b**	KBr	0.1	200 (30)	**2b**	37
15	Ph	**1b**	LiI	0.1	200 (30)	**2b**	38
16	Ph	**1b**	NaI	0.1	200 (30)	**2b**	30
17	Ph	**1b**	KI	0.1	200 (30)	**2b**	33
18	Ph	**1b**	$(n\text{-Bu})_4NCl$	0.1	200 (30)	**2b**	15
19	Ph	**1b**	$(n\text{-Bu})_4NBr$	0.1	200 (30)	**2b**	16
20	Ph	**1b**	$(n\text{-Bu})_4NI$	0.1	200 (30)	**2b**	21

[a] Reaction conditions: 2-aminophenylalkyne **1** (0.1 mmol) was suspended in water (2 mL) and heated to 200 °C in the presence of the corresponding salt by microwave irradiation for the time reported in the table.
[b] Yields in solution determined by HPLC, using a calibration curve.
[c] 2-Aminoacetophenone was the main product, along with considerable degradation.

Table 2
Microwave-assisted cycloisomerization: screening of basic and acid salts[a]

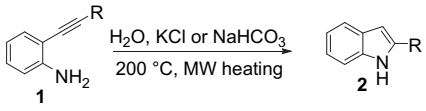


Entry	R	1	Salt	Equiv of salt	Temperature, °C (time, min)	2	Yield of 2[b] (%)
1	H	**1a**	NaOH	0.1	200 (30)	**2a**	66
2	H	**1a**	$NaHCO_3$	0.1	200 (15)	**2a**	45
3	H	**1a**	$NaHCO_3$	0.1	200 (30)	**2a**	60
4	H	**1a**	NH_4Cl	0.1	200 (15)	**2a**	<1[c]
5	Ph	**1b**	LiOH	0.1	200 (30)	**2b**	65
6	Ph	**1b**	NaOH	0.1	200 (30)	**2b**	53
7	Ph	**1b**	KOH	0.1	200 (30)	**2b**	40
8	Ph	**1b**	$NaHCO_3$	0.1	200 (30)	**2b**	70
9	Ph	**1b**	Na_2CO_3	0.1	200 (30)	**2b**	48
10	Ph	**1b**	$KHCO_3$	0.1	200 (30)	**2b**	58
11	Ph	**1b**	K_2CO_3	0.1	200 (30)	**2b**	66
12	Ph	**1b**	Na_2HPO_4	0.1	200 (30)	**2b**	46
13	Ph	**1b**	KF	0.1	200 (30)	**2b**	55
14	Ph	**1b**	AcONa	0.1	200 (30)	**2b**	30
15	Ph	**1b**	NH_4Cl	0.1	200 (30)	**2b**	10[d]

[a] Reaction conditions: 2-aminophenylalkyne **1** (0.1 mmol) was suspended in water (2 mL) and heated to 200 °C in the presence of the corresponding salt by microwave irradiation for the time reported in the table.
[b] Yields in solution determined by HPLC, using a calibration curve.
[c] 2-Aminoacetophenone was the main product isolated in 75% yield.
[d] 1-(2-Aminophenyl)-2-phenylethanone was the main product isolated in 85% yield.

Having demonstrated that the addition of a salt (neutral or basic) facilitates the cycloisomerization, we worked with the objective to render our reaction even more attractive not only for the novelty of the methodology but also for its applicability. In our previous work we showed that an increase in the concentration of the substrates caused a drastic decrease in the yield of the cycloisomerization in water alone. The use of aqueous salt solutions as the cyclization media proved extremely effective to overcome this limitation. However, the presence of the salt, even if beneficial for the yield, was accompanied by a significant increase of the pressure, which was developed during the heating to 200 °C inside the reaction vials. In our equipment, this caused leakages from the reaction caps with loss of water and compounds, especially at the higher substrate concentrations. As we previously described,[21] the application of short cycles of microwave-heating circumvented the problem and provided the same irradiation times in conditions less stressful for the equipment (reaction vials are cooled and de-pressurized between one cycle of heating and the other). The effect of salt and substrate concentrations and of MW irradiation times were investigated for a group of model substrates, as shown in Table 3.

Table 3
Condition optimization for the cycloisomerization of 2-aminophenylalkynes in water with KCl or $NaHCO_3$[a]



Entry	R	1	MW cycles		mmol of 1	Total time (h)	Salt	Equiv of salt	2	Yield[b] (%)
			Cycle number	Cycle time (min)						
1	H	**1a**	1	20	0.2	0.33	KCl	0.1	**2a**	30
2	H	**1a**	1	20	0.5	0.33	KCl	0.1	**2a**	28
3	H	**1a**	4	5	0.5	0.33	KCl	0.1	**2a**	50
4	H	**1a**	4	5	0.5	0.33	KCl	0.2	**2a**	60
5	H	**1a**	6	5	2	0.5	KCl	0.2	**2a**	51
6	H	**1a**	1	30	2	0.5	$NaHCO_3$	0.2	**2a**	60
7	H	**1a**	6	5	2	0.5	$NaHCO_3$	0.2	**2a**	61
8	Ph	**1b**	1	30	0.1	0.5	KCl	0.1	**2b**	56
9	Ph	**1b**	1	30	0.1	0.5	KCl	0.2	**2b**	77
10	Ph	**1b**	1	30	0.1	0.5	KCl	0.05	**2b**	14
11	Ph	**1b**	1	30	0.1	0.5	KCl	0.3	**2b**	66
12	Ph	**1b**	1	30	0.1	0.5	KCl	0.4	**2b**	55
13	Ph	**1b**	1	30	0.1	0.5	KCl	0.5	**2b**	54
14	Ph	**1b**	6	10	0.2	1	KCl	0.1	**2b**	69
15	Ph	**1b**	12	5	0.2	1	KCl	0.1	**2b**	73
16	Ph	**1b**	18	5	0.5	1.5	KCl	0.1	**2b**	75
17	Ph	**1b**	18	5	0.5	1.5	KCl	0.2	**2b**	59
18	Ph	**1b**	18	5	1.0	1.5	KCl	0.1	**2b**	45
19	Ph	**1b**	1	30	0.1	0.5	$NaHCO_3$	0.1	**2b**	68
20	Ph	**1b**	1	30	0.1	0.5	$NaHCO_3$	0.2	**2b**	60
21	Ph	**1b**	18	5	0.5	1.5	$NaHCO_3$	0.1	**2b**	70
22	Ph	**1b**	18	5	1.0	1.5	$NaHCO_3$	0.1	**2b**	46

[a] Reaction conditions: the specified amount of 2-aminophenylalkyne **1** was suspended in water (2 mL) and the corresponding amount of salt was added. The mixture was heated to 200 °C under MW irradiation for the time reported in the table.
[b] Yields in solution determined by HPLC, using a calibration curve.

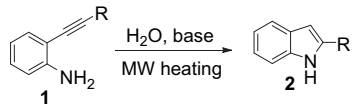
The study demonstrates that the addition of catalytic amounts of a salt like KCl or $NaHCO_3$ is able to accelerate the cyclization considerably and, in addition, to work with substrate concentrations up to 1 mmol/mL. After a careful optimization which involved salt concentration, reaction times, number and time of MW-cycles, we were able to obtain good yields for the indoles **2a** and **2b**. The cyclization of 2-ethynylaniline, **1a**, proceeded with a yield of 30% in the presence of 0.1 equiv of KCl but it could be raised up to 60% when 0.2 equiv of KCl and MW-irradiation in cycles of 5 min were applied (Table 3, entries 1–4). Also, satisfying results could be achieved using $NaHCO_3$, which allowed a rise in the cyclization yield up to 61% minimizing the decomposition of **1a** (Table 3, entries 6 and 7). Moreover, we verified that an increase in loading of **1a** up to 1 mmol/mL did not affect the yields significantly. As for the cyclization of 2-(phenylethynyl)aniline, **1b**, very good yields of 75% and 70% were obtained with 0.1 equiv of both KCl and $NaHCO_3$, respectively, after 1.5 h of MW-irradiation cycles (Table 3, entries 16 and 21). However, for substrate **1b**, a raise in the concentration above 0.25 mmol/mL caused a certain decrease in yields (Table 3, compare entries 16 and 21 with entries 18 and 22, respectively).

The data in Table 3 show a definite effect of neutral and basic inorganic salts. However, the results obtained were only moderately satisfactory in the instance of **1a**. The literature describes that strong bases, such as NaOH, *t*-BuOK or KH,[5] promote the cyclization of 2-alkynylanilines. Remarkably, a few examples report the use of Et_3N in the cyclization of 2-alkynyl(trifluoroanilides) to indoles.[3d,6d] We decided to investigate the effect of milder organic bases under our conditions to improve the yields. Catalytic to stoichiometric amounts of organic bases were tested, presuming they could offer a good compatibility with various functionalities in the starting 2-alkynylanilines. The screening was run working on a selection of model substrates as shown in Table 4.

Notably, most of the organic bases tested did show an effect on all the model compounds, with really good results obtained especially when pyrrolidine was added (Table 4, entries 6, 8, 15 and 22). The beneficial effect was particularly evident for substrate **1a**, where a yield of 90% was obtained after 15 min at 200 °C in the presence of 2 equiv of pyrrolidine (Table 4, entry 8). Also good results were obtained when piperidine was used (Table 4, entries 4 and 5). In addition, pyrrolidine gave remarkable results in the case of 2-(arylethynyl)anilines with a 54% yield for **1b** and a 74% for **1c** after 30 min at 200 °C (Table 4, entries 15 and 22). Good yields were obtained also for **1d**, which cyclized with a 65% yield after 30 min (Table 4, entry 24).

The screening and optimization studies done for the model substrates **1a**–**d** showed that the yields previously described for the cyclization in water alone can be considerably improved if a salt like KCl or $NaHCO_3$ or an organic base, pyrrolidine in particular,

Table 4
Microwave-assisted cycloisomerization: screening of organic bases[a]



Entry	R	1	Base	Base equiv	Temperature, °C (time, min)	2	Yield (%)[b]
1	H	**1a**	Et_3N	1	200 (15)	**2a**	28
2	H	**1a**	DBU	1	200 (15)	**2a**	41
3	H	**1a**	DABCO	1	200 (15)	**2a**	65
4	H	**1a**	Piperidine	1	200 (15)	**2a**	84
5	H	**1a**	Piperidine	2	200 (15)	**2a**	85
6	H	**1a**	Pyrrolidine	1	200 (15)	**2a**	79
7	H	**1a**	Pyrrolidine	0.5	200 (15)	**2a**	49
8	H	**1a**	Pyrrolidine	2	200 (15)	**2a**	90
9	Ph	**1b**	Et_3N	1	200 (30)	**2b**	8
10	Ph	**1b**	$(i\text{-}Pr)_2EtN$	1	200 (30)	**2b**	9
11	Ph	**1b**	$t\text{-}BuNH_2$	1	200 (30)	**2b**	12
12	Ph	**1b**	DABCO	1	200 (30)	**2b**	38
13	Ph	**1b**	DBU	1	200 (30)	**2b**	46
14	Ph	**1b**	Pyridine	1	200 (30)	**2b**	10
15	Ph	**1b**	Pyrrolidine	1	200 (30)	**2b**	54[c]
16	Ph	**1b**	Pyrrolidine	1	200 (60)	**2b**	53
17	Ph	**1b**	Pyrrolidine	2	200 (30)	**2b**	36
18	Ph	**1b**	Piperidine	1	200 (30)	**2b**	26
19	Ph	**1b**	Piperidine	2	200 (30)	**2b**	50
20	Ph	**1b**	Morpholine	2	200 (30)	**2b**	12
21	4-MeO–Ph	**1c**	Pyrrolidine	1	200 (30)	**2c**	70
22	4-MeO–Ph	**1c**	Pyrrolidine	2	200 (30)	**2c**	74
23	4-Cl–Ph	**1d**	Pyrrolidine	1	200 (30)	**2d**	56
24	4-Cl–Ph	**1d**	Pyrrolidine	2	200 (30)	**2d**	65

[a] Reaction conditions: 2-aminoarylalkyne **1** (0.1 mmol) and the specified base were added to water (2 mL) and the mixture 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] A similar yield of 52% was obtained when 6 cycles of 5 min of MW-irradiation was applied.

were added. With the aim of extending the scope of these cyclization conditions, we explored the reactivity of different substrates. We used our procedure, which ensures low Pd-contents[21,22] to prepare a series of differently substituted 2-aminoarylacetylenes and 2-aminopyridinylacetylenes and we applied the most efficient conditions found (methods A–C in Table 5). After a screening, we chose a substrate concentration of 0.25 mmol/mL, which represents, as already shown, a good compromise between efficiency and applicability.

In Table 5, we summarized the results obtained for a series of (hetero)arylalkynylanilines and arylalkynylpyridines. Good to very good isolated yields ranging from 60 to 99% could be observed for the majority of both electron-rich and electron-poor substrates. Worthy of note is the behaviour of the heteroarylalkynes examined since in most instances they seemed to cyclize more easily than the considered arylalkynes, giving elevated yields by using both KCl and $NaHCO_3$. Only low or moderate yields were obtained for octynylpyridinamine **1o**, which gave 5% yield with 0.2 equiv KCl and 52% with 0.2 equiv of $NaHCO_3$ (Table 5, entry 14). The use of pyrrolidine was tested only for some representative substrates (**1b–d**, entries 1–3, Table 5), or when neither KCl nor $NaHCO_3$ gave acceptable results as for the propynol **1m**, which cyclized rather effectively in the presence of 2 equiv of base (entry 12, Table 5).

Differently from **1a**, substituted 2-ethynylanilines **1p** and **1q** and 2-ethynylaminopyridines **1r** and **1s** were less unstable under the applied conditions and gave the corresponding indoles **2p** and **2q** and azaindoles **2r** and **2s** in very high yields and without significant degradation or hydrolysis. In particular, each of the three methods applied (the addition of catalytic amounts of KCl and $NaHCO_3$ or of 2 equiv of pyrrolidine) proved efficient in promoting the cyclization. In Table 6 we reported these results.

To have a comparison between thermal heating and microwave irradiation we did some cycloisomerization trials on 2-ethynylaniline, **1a**, and 2-(phenylethynyl)aniline, **1b**, using pressure resistant sealed tubes. In the trials, 0.1 mmol of substrate were suspended in 2 mL of Ultra Trace water and the required amount of additive was introduced. The reactions were heated to 200 °C in an oil bath and monitored for 7 h, sampling at different reaction times. The results are summarized in Table 7.

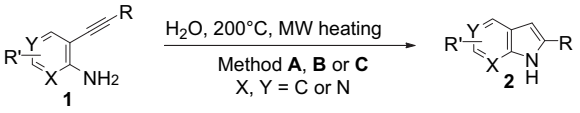
In the instance of 2-ethynylaniline, **1a**, the cycloisomerization proceeds efficiently under thermal heating conditions just in the presence of pyrrolidine, and, even if considerably slower than under microwave irradiation, it gives a 95% yield in **2a** after 4 h at 200 °C (Table 7, entry 3). On the other hand, in pure water or when KCl or $NaHCO_3$ were added, negligible amounts of indole were obtained (Table 7, entries 1, 4 and 5).

In the instance of 2-phenylindole, **2b**, only traces of product could be observed in most cases from **1b** under thermal heating conditions. Not reacted starting material was the only recovered product, even after 7 h at 200 °C and just when 0.1 equiv of KCl were added, a 21% yield was observed after 7 h at 200 °C (Table 7, entry 8). Neither $NaHCO_3$ nor pyrrolidine proved more efficient than pure water (Table 7, entries 6, 10 and 11).

3. Conclusions

In summary, we demonstrated that differently substituted indoles and azaindoles can be obtained by a simple and straightforward methodology, which involves the microwave-promoted cycloisomerization of 2-alkynylanilines and alkynylpyridinamines in water. The cyclization is efficiently expedited by the use of catalytic amounts of inorganic salts such as KCl and $NaHCO_3$ or by the addition of pyrrolidine. We obtained good to very good yields for a variety of both electron-rich and electron-poor substrates, even bearing labile functional groups. By comparing the results obtained under thermal heating conditions, we showed that microwave

Table 5
Preparation of 2-substituted indoles and azaindoles via cycloisomerization reactions of 2-amino(hetero)arylalkynes[a]



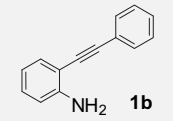
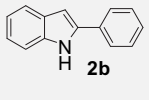
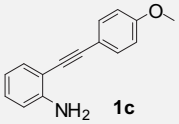
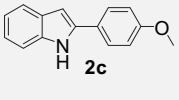
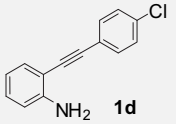
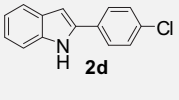
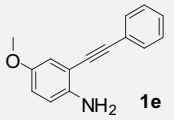
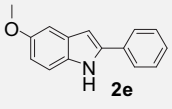
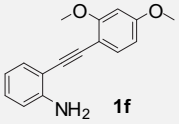
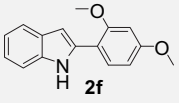
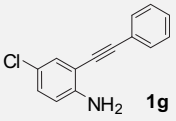
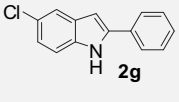
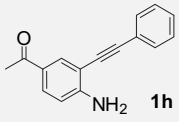
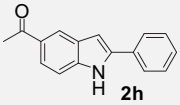
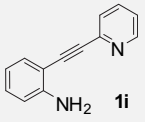
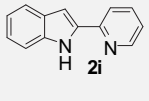
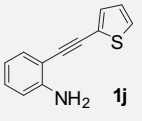
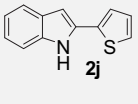
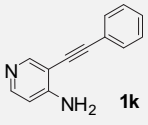
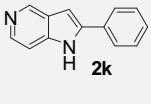
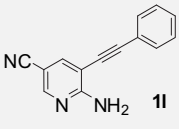
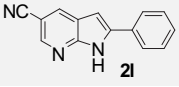
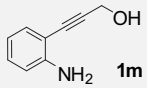
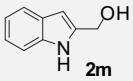
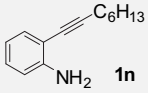
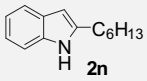
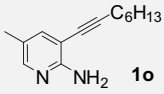
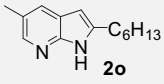
Entry	Alkyne **1**	Product **2**	Method[b]	Yields[c] (%)
1	 **1b**	 **2b**	A B C	75 70 85
2	 **1c**	 **2c**	A B C	72 61 79
3	 **1d**	 **2d**	A B C	55 62 77
4	 **1e**	 **2e**	A B	83 87
5	 **1f**	 **2f**	A B	60 48
6	 **1g**	 **2g**	A B	68 67
7	 **1h**	 **2h**	A B	77 88
8	 **1i**	 **2i**	A B	85[d] 96
9	 **1j**	 **2j**	A B	87[e] 95[e]
10	 **1k**	 **2k**	A B	98[e] 99
11	 **1l**	 **2l**	A B	45[f] –[g]

Table 5 (*continued*)

Entry	Alkyne **1**	Product **2**	Method[b]	Yields[c] (%)
12	 **1m**	 **2m**	A B C	10 23 53[h]
13	 **1n**	 **2n**	A B C	31[i] 60[j] 25
14	 **1o**	 **2o**	A B	5[i] 52[j]

[a] Reactions were run in sealed tubes where 0.5 mmol of 2-amino(hetero)arylalkyne **1** were suspended in 2 mL of water and the suspension heated to 200 °C by microwave irradiation applied in 18 cycles of 5 min for a total time of 90 min in the presence of the corresponding salt or base.
[b] Method A: 0.1 equiv of KCl were added. Method B: 0.1 equiv of $NaHCO_3$ were added. Method C: 2 equiv of pyrrolidine were added.
[c] Isolated yields.
[d] Microwave irradiation was applied in 9 cycles of 5 min for a total time of 45 min.
[e] Microwave irradiation was applied in 12 cycles of 5 min for a total time of 60 min.
[f] 2-Phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylic acid was obtained as a by-product in 35% yield after chromatography.
[g] Complete hydrolysis to 6-amino-5-(phenylethynyl)-3-pyridinecarboxylic acid was observed, without cyclization product.
[h] 1 equiv of pyrrolidine was added. The use of 2 equiv of pyrrolidine gave a 25% yield.
[i] 0.2 equiv of KCl were added.
[j] 0.2 equiv of $NaHCO_3$ were added.

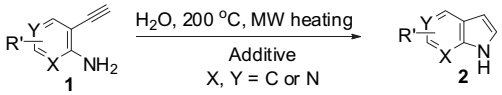
heating is necessary to obtain significant yields in short reaction times.

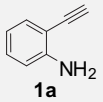
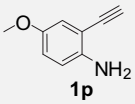
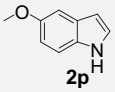
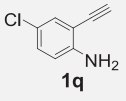
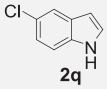
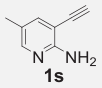
4. Experimental section

4.1. General experimental

All materials were obtained from commercial suppliers and used without further purification. 2-Alkynylanilines and pyridines **1b**–**s** were prepared from commercially available starting materials, according to the procedure for the copper-free Sonogashira coupling described below. 2-Ethynylaniline, **1a**, and Pd EnCat™ 40 used in the copper-free Sonogashira couplings were purchased from Aldrich; all the calculations for the required amount of catalyst were based on a Pd loading of 0.4 mmol/g (as given in the Aldrich catalogue). KCl and $NaHCO_3$ were purchased from Aldrich with a purity of 99.99% trace metal basis. All reactions were carried out in air without particular care for anhydrous or inert environment. For the microwave-assisted reactions a CEM Explorer with infrared temperature control system was applied as a focused microwave unit; the reactions were conducted in 10 mL reaction tubes sealed with septa caps. The pressure was measured by the system by an Intellivent® pressure control module. Purifications of the crude products were conducted with a Biotage Flash+® Purification System with pre-packed silica cartridges. The yields in solutions indicated in Tables 1–4 and 7 were determined using an Agilent 1100 HPLC system. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Inova 400 spectrometer. For mass spectra an Agilent 1100 Series LC/MSD with APCI source was used. Atomic absorption spectrophotometry (AAS) analyses for compounds **1b**–**d** were carried out with a Perkin–Elmer 4100 ZL spectrophotometer,

Table 6
Preparation of indoles and azaindoles via cycloisomerization reactions of different 2-amino(hetero)arylalkynes[a]



Entry	Alkyne **1**	Product **2**	Additive	Equiv of additive	Temperature, °C (time, min)	Yields[b] (%)
1	 **1a**	 **2a**	KCl $NaHCO_3$ Pyrrolidine	0.2 0.2 2	200 (20)[c] 200 (20)[c] 200 (15)	60 61 90
2	 **1p**	 **2p**	KCl $NaHCO_3$ Pyrrolidine	0.1 0.1 2	200 (20)[c] 200 (20)[c] 200 (15)	87 89 90
3	 **1q**	 **2q**	KCl $NaHCO_3$ Pyrrolidine	0.1 0.1 2	200 (20)[c] 200 (20)[c] 200 (15)	72 78 86
4	 **1r**	 **2r**	KCl $NaHCO_3$ Pyrrolidine	0.1 0.1 2	200 (20)[c] 200 (20)[c] 200 (15)	79 80 82
5	 **1s**	 **2s**	KCl $NaHCO_3$ Pyrrolidine	0.1 0.1 2	200 (30)[c] 200 (20)[c] 200 (15)	98 60 72

[a] Reactions were run in sealed tubes with 0.5 mmol of 2-amino(hetero)arylalkyne **1** suspended in 2 mL of water according to conditions reported in the table.
[b] Isolated yields.
[c] Microwave irradiation was applied in cycles of 5 min, until complete consumption of starting material was achieved.

Table 7
Thermal heating experiments[a]

Entry	Aryl alkyne	Additive	Time	Yield of **2**[b] (%)
1	**1a**	None	7 h	2
2	**1a**	Pyrrolidine (2 equiv)	30 min	11
3	**1a**	Pyrrolidine (2 equiv)	4 h	95
4	**1a**	KCl (0.1 equiv)	7 h	2
5	**1a**	$NaHCO_3$ (0.1 equiv)	7 h	1
6	**1b**	None	7 h	n.d.
7	**1b**	KCl (0.1 equiv)	30 min	1
8	**1b**	KCl (0.1 equiv)	7 h	21
9	**1b**	$NaHCO_3$ (0.1 equiv)	30 min	n.d.
10	**1b**	$NaHCO_3$ (0.1 equiv)	7 h	1
11	**1b**	Pyrrolidine (2 equiv)	7 h	n.d.

[a] Reaction conditions: 2-aminophenylalkyne **1** (0.1 mmol) was suspended in water (2 mL) with the corresponding amount of additive, and heated to 200 °C in an oil bath for the time reported in the table.
[b] Yields in solution determined by HPLC, using a calibration curve.

equipped with an electrothermally heated graphite furnace and a longitudinal Zeeman effect background corrector. The limit of detection (lod) calculated for palladium and copper was 2 ppb.

4.2. Typical procedure for the copper-free Sonogashira cross-coupling of (hetero)aryl halides with acetylenes to prepare (hetero)arylethynylanilines and aminopyridines 1b–l

The (hetero)aryl halide (4 mmol), the alkyne (1.5 equiv, 6 mmol), pyrrolidine (2 equiv, 8 mmol) and 1 mg of Pd EnCat 40 catalyst (0.01 mol% of Pd) were mixed and the resulting mixture was stirred at 85 °C for the required time until consumption of starting (hetero)aryl halide. Ethyl acetate (2×20 mL) and a saturated NH_4Cl aqueous solution (20 mL) were added and the collected organic layers washed with water (20 mL), separated and dried over Na_2SO_4. After filtration and evaporation of the solvent the resulting crude products were purified by chromatography on silica gel using cyclohexane/ethyl acetate as eluent.

*4.2.1. 2-(Phenylethynyl)aniline (**1b**).* White solid (650 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58–7.51 (m, 2H), 7.43–7.31 (m, 4H), 7.16 (ddd, J=8.29, 7.32, 1.56 Hz, 1H), 6.77–6.70 (m, 2H), 4.29 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 132.2, 131.5, 129.7, 128.4, 128.2, 123.3, 118.0, 114.4, 108.0, 94.7, 85.8. Spectral properties were in accordance with the literature.[23]

*4.2.2. 2-{[4-(Methyloxy)phenyl]ethynyl}aniline (**1c**).* White solid (804 mg, 90%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J=9.0 Hz, 2H), 7.36 (dd, J=8.2, 1.6 Hz, 1H), 7.17–7.11 (m, 1H), 6.89 (d, J=9.0 Hz, 2H), 6.75–6.70 (m, 2H), 4.27 (br s, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 147.6, 132.9, 132.0, 129.4, 118.0, 115.4, 114.3, 114.0, 108.3, 94.6, 84.4, 55.3. Spectral properties were in accordance with the literature.[24]

*4.2.3. 2-[(4-Chlorophenyl)ethynyl]aniline (**1d**).* White solid (802 mg, 88%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J=8.6 Hz, 2H), 7.38–7.31 (m, 3H), 7.19–7.13 (m, 1H), 6.76–6.71 (m, 2H), 4.27 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 134.2, 132.6, 132.2, 129.9, 128.7, 121.8, 118.0, 114.4, 107.5, 93.5, 86.9. Spectral properties were in accordance with the literature.[8a]

*4.2.4. 4-(Methyloxy)-2-(phenylethynyl)aniline (**1e**).* Pale yellow solid (581 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57–7.51 (m, 2H), 7.40–7.32 (m, 3H), 6.94 (d, J=2.8 Hz, 1H), 6.80 (dd, J=8.8, 2.8 Hz, 1H), 6.70 (d, J=8.8 Hz, 1H), 4.02 (br s, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 142.0, 131.5, 128.4, 128.3, 123.2,

117.4, 115.9, 115.8, 108.6, 94.6, 85.9, 55.8. Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87. Found: C, 80.86; H, 5.93. $[M+H]^+$=224. Spectral properties were in accordance with the literature.[25]

*4.2.5. 2-{[2,4-bis(Methyloxy)phenyl]ethynyl}aniline (**1f**).* Pale yellow solid (517 mg, 51%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J=8.2 Hz, 1H), 7.35 (dd, J=7.6, 1.4 Hz, 1H), 7.15–7.08 (m, 1H), 6.76–6.67 (m, 2H), 6.53–6.47 (m, 2H), 4.47 (br s, 2H), 3.90 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 160.9, 147.8, 133.2, 131.1, 129.1, 117.6, 114.0, 108.6, 105.3, 104.8, 98.4, 91.3, 89.1, 55.8, 55.5. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97. Found: C, 75.97; H, 6.12. $[M+H]^+$=254.

*4.2.6. 4-Chloro-2-(phenylethynyl)aniline (**1g**).* Yellow solid (811 mg, 89%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.56–7.50 (m, 2H), 7.40–7.34 (m, 4H), 7.09 (dd, J=8.7, 2.5 Hz, 1H), 6.67 (d, J=8.7 Hz, 1H), 4.28 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.3, 131.5, 131.3, 129.6, 128.5, 128.4, 122.8, 122.3, 115.4, 109.3, 95.6, 84.6. Anal. Calcd for $C_{14}H_{10}ClN$: C, 73.85; H, 4.43. Found: C, 73.47; H, 4.62. $[M+H]^+$=228.

*4.2.7. 1-[4-Amino-3-(phenylethynyl)phenyl]ethanone (**1h**).* Pale yellow solid (470 mg, 50%); ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J=1.9 Hz, 1H), 7.81 (dd, J=8.6, 1.9 Hz, 1H), 7.58–7.51 (m, 2H), 7.41–7.35 (m, 3H), 6.73 (d, J=8.6 Hz, 1H), 4.76 (br s, 2H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 151.6, 133.8, 131.5, 130.4, 128.6, 128.5, 127.5, 122.7, 113.3, 106.7, 95.2, 84.6, 26.09. Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57. Found: C, 81.85; H, 5.71. $[M+H]^+$=236.

*4.2.8. 2-(2-Pyridinylethynyl)aniline (**1i**).* Yellow solid (661 mg, 85%); ^1H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, J=5.3 Hz, 1H), 7.68 (dd, J=7.9, 1.8 Hz, 1H), 7.52 (d, J=7.9 Hz, 1H), 7.42 (d, J=8.3 Hz, 1H), 7.23 (dd, J=7.5, 4.8 Hz, 1H), 7.19–7.14 (m, 1H), 6.72 (d, J=7.9 Hz, 2H), 4.41 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0, 148.5, 143.5, 136.1, 132.6, 130.4, 126.9, 122.5, 117.8, 114.3, 106.6, 94.0, 86.1. Spectral properties were in accordance with the literature.[16b]

*4.2.9. 2-(2-Thienylethynyl)aniline (**1j**).* Yellow oil (574 mg, 72%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.35 (m, 1H), 7.30–7.28 (m, 2H), 7.19–7.13 (m, 1H), 7.04–7.01 (m,1H), 6.76–6.69 (m,2H), 4.26 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 132.0, 131.7, 129.9, 127.2, 127.1, 123.2, 117.9, 114.3, 107.5, 89.5, 87.6. Spectral properties were in accordance with the literature.[26]

*4.2.10. 3-(Phenylethynyl)-4-pyridinamine (**1k**).* Yellow solid (715 mg, 92%); ^1H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1H), 8.16 (d, J=5.7 Hz, 1H), 7.57–7.50 (m, 2H), 7.42–7.32 (m, 3H), 6.58 (d, J=5.7 Hz, 1H), 4.80 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 152.6, 149.1, 131.5, 128.6, 128.4, 122.6, 108.2, 104.9, 97.1, 82.5. Spectral properties were in accordance with the literature.[27]

*4.2.11. 6-Amino-5-(phenylethynyl)-3-pyridinecarbonitrile (**1l**).* Off-white solid (579 mg, 66%); ^1H NMR (400 MHz, DMSO-d_6): δ 8.37 (d, J=2.2 Hz, 1H), 8.01(d, J=2.2 Hz, 1H), 7.69–7.65 (m, 3H), 7.45–7.41 (m, 2H), 7.40–7.20 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.8, 155.7, 152.6, 142.2, 131.7, 129.0, 128.5, 121.9, 118.0, 101.4, 95.3, 83.2. Anal. Calcd for $C_{14}H_9N_3$: C, 76.70; H, 4.14. Found: C, 76.81; H, 4.53. $[M+H]^+$=220.

4.3. Typical procedure for the copper-free Sonogashira cross-coupling of aryl halides with alkylacetylenes to prepare 2-(ethynyl)anilines and pyridines 1m–o

The (hetero)aryl halide (4 mmol), alkynylethyne (1.5 equiv, 6 mmol), pyrrolidine (2 equiv, 8 mmol) and 20 mg of Pd EnCat 40 catalyst (0.2 mol % of Pd) were mixed and the reaction mixture was heated to 85 °C until consumption of starting aryl halide. Ethyl acetate (2×20 mL) and a saturated NH_4Cl aqueous solution (20 mL) were added and the collected organic layers washed with water (20 mL), separated and dried over Na_2SO_4. The resulting crudes were purified by chromatography on silica gel using cyclohexane/ethyl acetate as eluent.

*4.3.1. 3-(2-Aminophenyl)-2-propyn-1-ol (**1m**).* Pale yellow solid (230 mg, 39%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.26 (m, 1H), 7.16–7.12 (m, 1H), 6.71–6.67 (m, 2H), 4.55 (s, 2H), 4.34–4.14 (br s, 2H), 1.99–1.58 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0, 132.3, 129.9, 117.9, 114.4, 107.2, 92.6, 82.4, 51.7. Spectral properties were in accordance with the literature.[5d]

*4.3.2. 2-(1-Octyn-1-yl)aniline (**1n**).* Yellow oil (322 mg, 40%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (dd, J=7.7, 1.5 Hz, 1H), 7.11–7.05 (m, 1H), 6.71–6.64 (m, 2H), 4.17 (br s, 2H), 2.47 (t, J=7.0 Hz, 2H), 1.68–1.59 (m, 2H), 1.53–1.43 (m, 2H), 1.37–1.31 (m, 4H), 0.92 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 132.0, 128.7, 117.8, 114.1, 109.0, 95.8, 76.9, 31.3, 28.9, 28.6, 22.6, 19.6, 14.0. Spectral properties were in accordance with the literature.[16b]

*4.3.3. 5-Methyl-3-(1-octyn-1-yl)-2-pyridinamine (**1o**).* Pale yellow solid (510 mg, 59%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J=2.2 Hz, 1H), 7.31 (d, J=2.2 Hz, 1H), 4.78 (br s, 2H), 2.45 (t, J=7.2 Hz, 2H), 2.15 (s, 3H), 1.65–1.58 (m, 2H), 1.49–1.42 (m, 2H), 1.36–1.29 (m, 4H), 0.93–0.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0, 146.9, 140.4, 122.4, 103.8, 96.6, 75.9, 31.3, 28.7, 28.6, 22.5, 19.6, 17.2, 14.0. Anal. Calcd for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32. Found: C, 77.91; H, 9.74. $[M+H]^+$=217.

4.4. Typical procedure for the copper-free Sonogashira cross-coupling of (hetero)aryl halides with acetylenes to prepare 2-(ethynyl)anilines and pyridines 1p–s

The (hetero)aryl halide (4 mmol), ethynyl(trimethyl)silane (1.5 equiv, 6 mmol), pyrrolidine (2 equiv, 8 mmol) and 10 mg of Pd EnCat 40 catalyst (0.1 mol % of Pd) were mixed in a 10 mL glass microwave vial equipped with a magnetic stirrer. The vessel was placed in the microwave apparatus and irradiated at an initial power of 200 W to ramp the temperature from room temperature to 100 °C where it was held with stirring by modulating the microwave power for 30 min or until consumption of starting (hetero) aryl halide. Ethyl acetate (2×20 mL) and a saturated NH_4Cl aqueous solution (20 mL) were added and the collected organic layers washed with water (20 mL), separated and dried over Na_2SO_4. After filtration and evaporation of the solvent the resulting crude products were dissolved in 20 mL of MeOH and 20 mL of 2 N NaOH were added. The mixture was stirred overnight at room temperature then evaporated to dryness. The resulting crude was purified by chromatography on silica gel using cyclohexane/ethyl acetate as eluent.

*4.4.1. 2-Ethynyl-4-(methyloxy)aniline (**1p**).* Yellow oil (289 mg, 49%); ^1H NMR (400 MHz, $CDCl_3$): δ 6.88 (d, J=2.6 Hz, 1H), 6.79 (dd, J=8.8, 3.0 Hz, 1H), 6.66 (d, J=8.8 Hz, 1H), 3.98 (br s, 2H), 3.79 (s, 3H), 3.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 142.7, 117.8, 116.3, 115.9, 107.2, 82.4, 80.6, 55.8. Anal. Calcd for C_9H_9NO: C, 73.45; H, 6.16. Found: C, 73.73; H, 5.97. $[M+H]^+$=148.

*4.4.2. 4-Chloro-2-ethynylaniline (**1q**).* Pale yellow solid (479 mg, 79%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, J=2.2 Hz, 1H), 7.10 (dd, J=8.5, 2.4 Hz, 1H), 6.63 (d, J=8.3 Hz, 1H), 4.25 (br s, 2H), 3.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1, 131.8, 130.2, 122.0, 115.4, 107.9,

83.4, 79.3. Spectral properties were in accordance with the literature.[28]

*4.4.3. 3-Ethynyl-4-pyridinamine (**1r**).* Yellow oil (388 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 8.15 (d, J=5.7 Hz, 1H), 6.55 (d, J=5.7 Hz, 1H), 4.76 (br s, 2H), 3.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 153.1, 149.5, 149.4, 109.3, 108.2, 85.1. Anal. Calcd for $C_7H_6N_2$: C, 71.17; H, 5.12. Found: C, 70.93; H, 5.37. $[M+H]^+$=119.

*4.4.4. 3-Ethynyl-5-methyl-2-pyridinamine (**1s**).* Yellow solid (355 mg, 67%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J=1.6 Hz, 1H), 7.40 (d, J=2.0 Hz, 1H), 4.90 (br s, 2H), 3.39 (s, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5, 148.4, 141.2, 122.3, 101.4, 83.2, 79.5, 17.2. Spectral properties were in accordance with the literature.[16b]

4.5. Typical procedure for the microwave-assisted cycloisomerization to prepare 1*H*-(aza)indoles 2a–s

The required 2-alkynylaniline or alkynylpyridine (0.5 mmol) and 2 mL of water were charged in a 10 mL glass microwave vial equipped with a magnetic stirrer. The corresponding amount of salt or base was added as indicated in Tables 5 and 6 where the yields obtained were also reported. The vessel was placed in the microwave apparatus and irradiated at an initial power of 200 W to ramp the temperature from room temperature to 200 °C where it was held with stirring by modulating the microwave power for the specified reaction times. The mixture was then cooled down to room temperature and extracted twice with ethyl acetate (2×20 mL). The organic layer was dried over Na_2SO_4. After filtration and evaporation of the solvent the resulting crude product was purified by chromatography on silica gel using dichloromethane or methanol/ethyl acetate as eluent.

*4.5.1. 1H-Indole (**2a**).* White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (br s, 1H), 7.73 (dd, J=7.8, 1.0 Hz, 1H), 7.45 (dd, J=8.1, 1.0 Hz, 1H), 7.31–7.24 (m, 2H), 7.23–7.17 (m, 1H), 6.65–6.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7, 127.8, 124.1, 121.9, 120.7, 119.8, 111.0, 102.6. Spectral properties were in accordance with the literature.[29]

*4.5.2. 2-Phenyl-1H-indole (**2b**).* White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (br s, 1H), 7.71–7.64 (m, 3H), 7.50–7.40 (m, 3H), 7.38–7.32 (m, 1H), 7.25–7.20 (m, 1H), 7.18–7.13 (m, 1H), 6.87–6.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 136.8, 132.4, 129.2, 129.0, 127.7, 125.1, 122.3, 120.6, 120.3, 110.9, 100.0. Spectral properties were in accordance with the literature.[30]

*4.5.3. 2-[4-(Methyloxy)phenyl]-1H-indole (**2c**).* White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.40 (s, 1H), 7.79 (d, J=9.0 Hz, 2H), 7.49 (d, J=7.8 Hz, 1H), 7.37 (dd, J=8.0, 1.0 Hz, 1H), 7.09–6.94 (m, 4H), 6.76 (dd, J=2.1, 0.8 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.7, 137.7, 136.9, 128.8, 126.3, 124.9, 121.0, 119.6, 119.2, 114.3, 111.0, 97.3, 55.2. Spectral properties were in accordance with the literature.[30]

*4.5.4. 2-(4-Chlorophenyl)-1H-indole (**2d**).* White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (br s, 1H), 7.65 (d, J=7.8 Hz, 1H), 7.59 (d, J=8.6 Hz, 2H), 7.45–7.39 (m, 3H), 7.26–7.20 (m, 1H), 7.18–7.12 (m, 1H), 6.83 (dd, J=2.0, 0.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.9, 136.6, 133.4, 130.8, 129.2, 129.1, 126.3, 122.7, 120.7, 120.4, 110.9, 100.5. Spectral properties were in accordance with the literature.[30]

*4.5.5. 5-(Methyloxy)-2-phenyl-1H-indole (**2e**).* White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (br s, 1H), 7.68–7.63 (m, 2H), 7.48–7.42 (m, 2H), 7.36–7.28 (m, 2H), 7.11 (d, J=2.3 Hz, 1H), 6.88 (dd, J=8.8, 2.3 Hz, 1H), 6.79–6.76 (m, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 138.6, 132.4, 132.0, 129.7, 129.0, 127.6, 125.0, 112.6, 111.6, 102.2, 99.8, 55.8. Spectral properties were in accordance with the literature.[30]

*4.5.6. 2-[2,4-Bis(methyloxy)phenyl]-1H-indole (**2f**).* Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53 (br s, 1H), 7.76 (d, J=8.4 Hz, 1H), 7.62 (d, J=7.5 Hz, 1H), 7.41 (d, J=8.1 Hz, 1H), 7.19–7.07 (m, 2H), 6.79 (dd, J=2.1, 0.8 Hz, 1H), 6.65–6.58 (m, 2H), 4.01 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 156.9, 136.1, 135.9, 129.2, 128.2, 121.3, 119.9, 119.7, 113.8, 110.7, 105.8, 99.3, 98.5, 55.8, 55.5. Spectral properties were in accordance with the literature.[31]

*4.5.7. 5-Chloro-2-phenyl-1H-indole (**2g**).* Off-white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (br s, 1H), 7.70–7.63 (m, 2H), 7.62–7.58 (m, 1H), 7.51–7.43 (m, 2H), 7.40–7.29 (m, 2H), 7.15 (dd, J=8.6, 1.9 Hz, 1H), 6.80–6.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.3, 135.1, 131.8, 130.3, 129.1, 128.1, 125.8, 125.2, 122.6, 120.0, 111.8, 99.5. Spectral properties were in accordance with the literature.[32]

*4.5.8. 1-(2-Phenyl-1H-indol-5-yl)ethanone (**2h**).* Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (br s, 1H), 8.33–8.30 (m, 1H), 7.89 (dd, J=8.6, 1.6 Hz, 1H), 7.73–7.67 (m, 2H), 7.51–7.34 (m, 4H), 6.93 (dd, J=2.1, 0.8 Hz, 1H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.4, 139.5, 139.5, 131.7, 130.3, 129.1, 128.8, 128.2, 125.2, 122.8, 122.6, 110.8, 101.1, 26.6. Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57. Found: C, 81.93; H, 5.67. $[M+H]^+$=236.

*4.5.9. 2-(2-Pyridinyl)-1H-indole (**2i**).* Off-white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (br s, 1H), 8.60 (d, J=4.8 Hz, 1H), 7.83 (d, J=7.9 Hz, 1H), 7.73 (dd, J=7.9, 1.8 Hz, 1H), 7.68 (d, J=7.9 Hz, 1H), 7.40 (d, J=7.5 Hz, 1H), 7.24 (t, 7.5 Hz, 1H), 7.21–7.16 (m, 1H), 7.15–7.11 (m, 1H), 7.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4, 149.1, 136.7, 136.6, 129.1, 123.1, 122.0, 121.1, 120.1, 119.9, 111.4, 111.3, 100.6. Spectral properties were in accordance with the literature.[16b]

*4.5.10. 2-(2-Thienyl)-1H-indole (**2j**).* Off-white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (br s, 1H), 7.62 (d, J=8.3 Hz, 1H), 7.38 (d, J=8.3 Hz, 1H), 7.30 (d, J=6.1 Hz, 1H), 7.27–7.25 (m, 1H), 7.21(m, 1H), 7.15 (d, J=7.9 Hz, 1H), 7.11–7.08 (m, 1H), 6.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.5, 135.6, 132.3, 129.1, 127.9, 124.6, 122.9, 122.5, 120.5, 120.4, 110.7, 100.4. Spectral properties were in accordance with the literature.[33]

*4.5.11. 2-Phenyl-1H-pyrrolo[3,2-c]pyridine (**2k**).* Yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.01 (br s, 1H), 8.81 (s, 1H), 8.17 (d, J=5.7 Hz, 1H), 7.90 (d, J=7.5 Hz, 2H), 7.49 (t, J=7.7 Hz, 2H), 7.40–7.33 (m, 2H), 7.04 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 142.9, 140.4, 140.3, 138.9, 131.4, 129.0, 128.1, 125.7, 125.4, 106.6, 97.5. Spectral properties were in accordance with the literature.[34]

*4.5.12. 2-Phenyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**2l**).* White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.8 (br s, 1H), 8.60 (d, J=2.2 Hz, 1H), 8.48 (d, J=2.2 Hz, 1H), 8.01–7.93 (m, 2H), 7.52–7.47 (m, 2H), 7.43–7.39 (m, 1H), 7.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 145.4, 139.6, 132.1, 131.2, 130.6, 129.0, 128.9, 125.7, 120.3, 97.9. Anal. Calcd for $C_{14}H_9N_3$: C, 76.70; H, 4.14. Found: C, 76.67; H, 4.18. $[M+H]^+$=220. 2-*Phenyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid*. White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.4 (br s, 1H), 8.75 (d, J=2.2 Hz, 1H), 8.44 (d, J=1.8 Hz, 1H), 8.01–7.94 (m, 2H), 7.52–7.47 (m, 2H), 7.43–7.39 (m, 1H), 7.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 150.8, 143.1, 128.9, 128.3, 127.4, 125.4, 122.5, 119.9, 97.9. $[M+H]^+$=239.

*4.5.13. 1-H-Indol-2-ylmethanol (**2m**).* White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (br s, 1H), 7.60 (d, J=7.7 Hz, 1H), 7.29 (d, J=8.12 Hz, 1H), 7.22–7.18 (m, 1H), 7.14–7.11 (m, 1H), 6.49 (d,

J=1.1 Hz, 1H), 4.79 (s, 2H), 2.16–2.02 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 136.3, 128.0, 122.1, 120.6, 119.9, 110.9, 100.5, 58.6. Spectral properties were in accordance with the literature.[35]

*4.5.14. 2-Hexyl-1H-indole (**2n**).* Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (br s, 1H), 7.55–7.51 (m, 1H), 7.33–7.28 (m, 1H), 7.14–7.04 (m, 2H), 6.26–6.23 (m, 1H), 2.76 (t, J=7.6 Hz, 2H), 1.78–1.68 (m, 2H), 1.46–1.29 (m, 6H), 0.95–0.87 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.9, 136.0, 128.9, 120.9, 119.7, 119.5, 110.2, 99.4, 31.6, 29.2, 29.0, 28.3, 22.6, 14.1. Spectral properties were in accordance with the literature.[35]

*4.5.15. 2-Hexyl-5-methyl-1H-pyrrolo[2,3-b]pyridine (**2o**).* Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (d, J=2.0 Hz, 1H), 8.00 (d, J=8.3 Hz, 1H), 7.89 (s, 1H), 7.34 (d, J=8.3 Hz, 1H), 3.08–2.93 (m, 2H), 2.53 (s, 3H), 1.88 (quin, J=7.0 Hz, 2H), 1.51–1.14 (m, 6H), 0.90 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 155.1, 136.2, 135.2, 130.8, 122.4, 120.5, 39.2, 31.7, 29.2, 22.5, 18.5, 14.0. Spectral properties were in accordance with the literature.[36]

*4.5.16. 5-Methyloxy-1H-indole (**2p**).* White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (br s, 1H), 7.29 (d, J=8.8 Hz, 1H), 7.19 (t, J=2.6 Hz, 1H), 7.14 (d, J=2.2 Hz, 1H), 6.89 (dd, J=8.8, 2.2 Hz, 1H), 6.53–6.48 (m, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 130.9, 128.2, 124.8, 112.3, 111.7, 102.4, 102.3, 55.8. Spectral properties were in accordance with the literature.[36]

*4.5.17. 5-Chloro-1H-indole (**2q**).* White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (br s, 1H), 7.65–7.60 (m, 1H), 7.32 (d, J=8.4 Hz, 1H), 7.26–7.22 (m, 1H), 7.17 (dd, J=8.6, 2.0 Hz, 1H), 6.54–6.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.1, 129.2, 128.9, 125.5, 122.3, 120.1, 111.9, 102.4. Spectral properties were in accordance with the literature.[37]

*4.5.18. 1H-Pyrrolo[3,2-c]pyridine (**2r**).* White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (s, 1H), 8.28 (d, J=5.7 Hz, 1H), 7.36 (d, J=5.7 Hz, 1H), 7.32 (d, J=3.1 Hz, 1H), 6.67 (d, J=4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 139.9, 139.5, 126.0, 125.0, 106.9, 101.8. Spectral properties were in accordance with the literature.[38]

*4.5.19. 5-Methyl-1H-pyrrolo[2,3-b]pyridine (**2s**).* White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.86–10.64 (m, 1H), 8.20 (d, J=1.8 Hz, 1H), 7.77 (s, 1H), 7.34 (d, J=3.5 Hz, 1H), 6.44 (d, J=3.3 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4, 143.5, 128.9, 125.2, 124.7, 120.2, 100.0, 18.5. Anal. Calcd for $C_8H_8N_2$: C, 72.70; H, 6.10. Found: C, 72.27; H, 5.98. $[M+H]^+$=133.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.06.083.

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