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Acidic Deep Eutectic Solvents as Active Media for Sustainable Synthesis of Biindoles Starting from 2,2'-Diaminotolanes and Aldehydes

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We describe an alternative and more sustainable method for the synthesis of 2,2'-disubstituted 3,3'-biindoles starting from 2,2'-diaminotolanes and (hetero)arylaldehydes. The key feature of the approach is the use of an acidic Deep Eutectic Solvent (DES) able to exploit a double activity, i.e., solvent and Brønsted Acid (BA) catalyst, avoiding the use of Volatile Organic Compounds (VOCs) as solvents and additional acid catalysts. By this way, we synthesized twenty-five biindoles, including eight-een new compounds. The reactions run quickly under mild conditions by microwave heating at 70 °C, with yields ranging from good to very good. The reaction scope is rather broad. The medium demonstrated to be reusable at least five times with only a slight reduction in yields. Based on experimental evidence and previous literature findings, a plausible mechanism is proposed.

Introduction

The importance of the 3,3'-biindole structural motif is related to its presence as common backbone of some interesting natural alkaloids,[1] biologically active compounds,[2] and functional materials.[3] Different synthetic methodologies to obtain 3,3'-biindoles have been proposed in the literature. A common strategy involves the coupling reaction between two indole units.[4] These reactions can occur on 3-activated indoles by palladium-catalyzed cross-coupling reaction,[4a,b] or by oxidative couplings of 3-unfunctionalised indole units, catalyzed by different reagents such as palladium salts,[4c] iron trichloride,[4d] oAC (oxidised active carbon),[4e] and iodine.[4f] Moreover, an

unusual p-TSA-promoted heteroarylation of 2-indolylmethanols has been recently reported.[5] Other noteworthy methods involving the coupling of heteroaryl moieties are the copper-catalyzed Friedel-Crafts propargylation/hydroamination/ aromatization cascade of indoles and benzooxazin-2-ones[6] and an original silver-catalyzed nucleophilic addition/cycloisomerization of indoles and 2-(indol-1-yl)benzaldehyde derivatives.[7] Other different methods include the reductive cyclization of nitrobenzene and nitroarylbutadienes derivatives.[8] A conceptually different strategy involves the cyclization of differently functionalized o-alkynylaniline derivatives (Scheme 1).[9] Lopez-Sanchez and Helaja reported a method catalyzed by C-supported gold nanoparticles that involve a subsequent homocoupling step (Scheme 1, a).[9a] Conversely, starting from 2,2'-diaminotolanes and arylaldehydes in the presence of a Brønsted acid, 3,3'-biindoles have been obtained in good yields (Scheme 1, b).[9b] As applicative example of this strategy, some 2,2'-disubstituted-3,3'-biindoles have been developed also as a novel class of double D-π-A branched organic dyes for dye-sensitized solar cells.[10]

For many years we have been interested in the development of alternative strategies for the synthesis of heterocycles and organic scaffolds, with the aim to increase the degree of sustainability of the processes. We have tried to pursue this goal by exploiting domino[11] and multicomponent[12] approaches, coinage metal catalysis,[13] alternative energy sources,[14] and more eco-friendly solvent and reagents.[15] In particular, in two recent works, we developed alternative approaches for the synthesis of 3,4-fused 2-pyranones[15a] and propargylamines[15b] based on the use of a more effective energy, source as microwaves, and the substitution of traditional solvents and catalysts with deep eutectic solvents (DESs) as "active" media able to promote the reaction under investigation.[16] These choices resulted in a general increase in the efficiency and sustainability of the processes. The key

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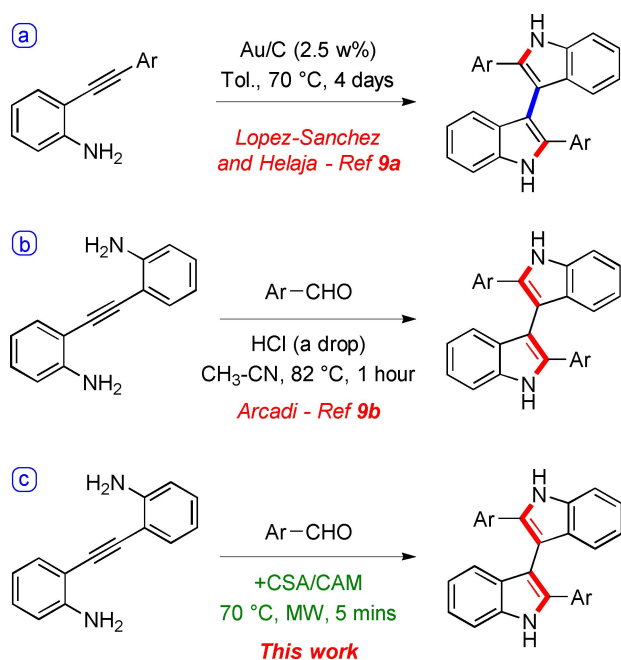Via Golgi 19, 20133 Milano (Italy)
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Scheme 1. Literature synthesis of 3,3′-biindole derivatives starting from o-alkynylaniline derivatives and this work.

strategy in these works was the replacement of Lewis/Brønsted acid catalysts necessary to promote the oxo-cyclization or the multicomponent coupling, respectively, with a carefully selected DES characterized by a fine-tuned pKa of the acidic component.

Inspired by these successful results and the above-mentioned work,[9b] we envisaged trying the solvent/catalyst substitution approach for the synthesis of biindoles starting from 2,2′-diaminotolanes Scheme 1, c). We reasoned that the possibility of replacing an undesired VOC such as acetonitrile, already defined as a "problematic" solvent,[17] and a strong acid such as HCl with a single benign entity able to act as solvent and catalyst could be an outstanding improvement in term of sustainability. Additional advantages in the use of our "active" DESa are the absence of toxicity, volatility, and flammability, not secondary aspects to simplify and increase the degree of sustainability. Moreover, due to their dipolar nature, DESs are suitable media for dielectric heating that is a well-recognized effective and economic energy source, able to improve selectivity and reduce reaction times.[18] For these reasons, we chose to study and develop our approach under microwave heating. From a holistic viewpoint of the green metrics,[19] our "solvent-shift" strategy position itself at a Zero/First Pass Level paying particular attention to health and safety, and energy optimization. In this paper, we report our results.

Results and Discussion

We start our investigation by choosing the reaction between 2,2′-diaminotolane **1a** and 4-methylbenzaldehyde **2a** as a model system. We tested different DESs (Figure 1), reaction temperatures, and times.

The results of this screening are reported in Table 1.

In the previously reported optimized reaction condition[9b] (acetonitrile at 82 °C) this transformation was successfully catalyzed by a single drop of hydrochloric acid (pKa ≈ −5.9). So, firstly we tested a DES with a strong acidic component, i.e., TSA/CAM under microwave heating at 80 °C for 60 min (Table 1, entry 1). The formation of the desired product was observed in
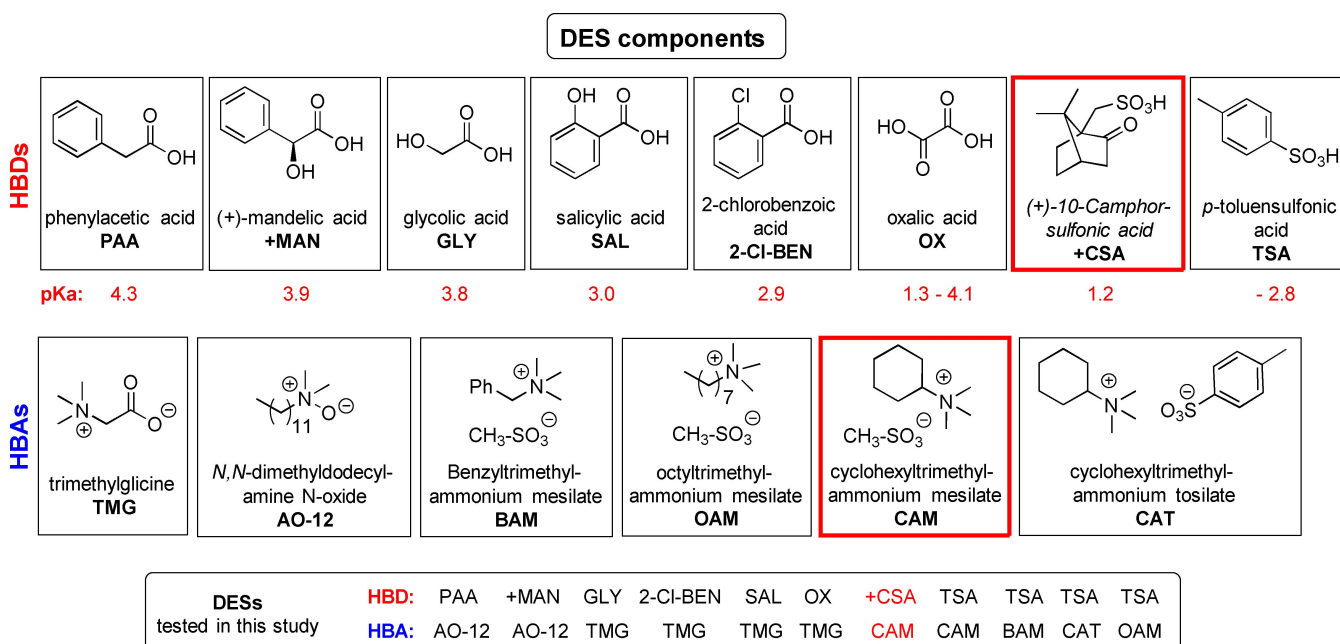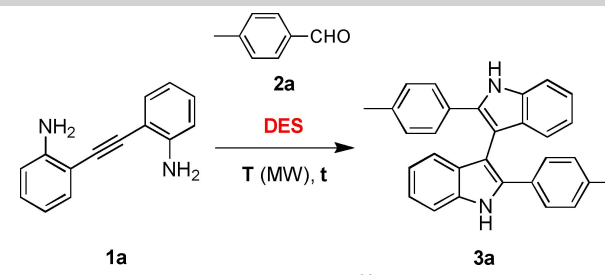

Figure 1. DESs used in this study[20]

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Table 1. Screening of optimal reaction conditions.

Entry	DES	T MW [°C][a]	t [min]	Yield[b] [%]
1	TSA/CAM	80	60	11[c]
2	TSA/CAM	80	15	32[c]
3	TSA/CAM	80	5	47
4	TSA/CAM	70	5	61
5	TSA/CAM	60	5	58
6	TSA/CAT	70	5	44
7	TSA/BAM	70	5	53
8	TSA/OAM	70	5	24[c]
9	PAA/AO-12	70	30	–[d]
10	+MAN/AO-12	70	30	–[d]
11	GLY/TMG	70	30	–[d]
12	SAL/TMG	70	30	24[e]
13	2-Cl-BENZ/TMG	70	30	36
14	OX/TMG	70	30	16[f]
15	+CSA/CAM	70	30	76
16	**+CSA/CAM**	**70**	**5**	**76**
17[g]	+CSA/CAM	70	5	70
18	+CSA/CAM	70[h]	120	65
19	–	70[h]	240	–[i]

[a] Conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), DES (0.5 mL); [b] yields referred to pure isolated products (flash column chromatography); [c] mainly unidentified by-products; [d] mainly starting materials recovered unreacted; [e] mixture of starting material and unidentified by-products; [f] degradation of the DES; [g] **2a** (0.5 mmol); [h] conventional oil-bath heating; [i] the complex mixture of unreacted aldehyde decomposition products (¹H NMR of the crude).
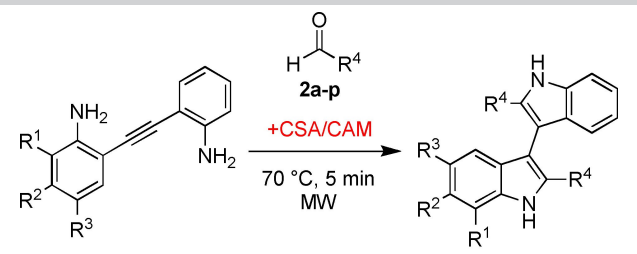
low yield, besides many unidentified by-products. We were pleased to observe that a reduction of reaction times (Table 1, entries 2 and 3) and a fine-tuning of reaction temperature (Table 1, entries 4 and 5) resulted in a consistent increase in yields. Then, we explored the effect of the HBA (Hydrogen Bond Acceptor) component, (Table 1, entries 6–8). The nature of the HBA seemed to play a not negligible role in this reaction because CAM remains the higher-yield choice. Next, we studied and fine-tuned the effect of the pKa of the acidic HBD (Hydrogen Bond Donor) component of the DES on the reaction outcome. We tested seven DESs characterized by decreasing pKa values of the acidic component, ranging from 4.3 to 1.2 (Table 1, entries 9–15). To offset the reduction of the acidity of the media we initially increase the reaction time to 30 min. The reaction with too weak acidic DESs failed and the starting materials were recovered unreacted (Table 1, entries 9–11). Benzoic acid-based DESs gave the desired product in modest yields (Table 1, entries 12 and 13), whereas oxalic acid demonstrated to be unsuitable because an over stoichiometric amount of tar was obtained, maybe arising from partial degradation of the DES (Table 1, entry 14). The best result (76% yield) was obtained using the DES which has the chiral camphorsulfonic acid as acidic partner (Table 1, entry 15). The new DES was so effective that the reaction time can be reduced from 30 to 5 min without loss in yield (Table 1, entry 16). Conversely, a reduction of the aldehyde/alkyne ratio resulted in a 5% lower

yield (Table 1, entry 17). Finally, two control experiments confirmed the advantages of dielectric heating in terms of reaction yield and time (Table 1, entry 18) and the requirement of +CSA/CAM as active solvent/catalyst for the success of the transformation (Table 1, entry 19).

With the best reaction conditions in hands, we explored the scope and limitations of the approach. The 2,2′-diaminotolanes **1a**–**f**,**h**–**k** were prepared by a Sonogashira cross-coupling[21] between 2-iodoaniline and properly substituted 2-ethynylanilines. Compound **1g** was prepared in two steps by reaction of 2-bromo-6-methoxyaniline TMS-acetylene followed by deprotection of alkyne terminus from the TMS group and a second coupling with 2-iodoaniline. The results of bis-cyclization reactions are summarized in Table 2.

The approach well tolerates benzaldehyde derivatives with substituents characterized by different electronic and steric properties (Table 2, entries 1–12). Yields are in general good with benzaldehydes bearing electron withdrawing (EW) or electron donating (ED) groups. With strong ED groups in *ortho* and *para* position, the yields are a bit lower, probably due to the mesomeric ED character of the methoxy group which hampers the formation of iminium intermediate by reducing the electrophilicity of the carbonyl carbon (Table 2, entries 5 and 7). This effect is reduced when the methoxy substituent is in the *meta*-position where only inductive effects are relayed to carbonyl carbon (Table 2, entry 6). When neutral or EW-

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Table 2. Scope and limitation of the approach.

Entry	1	R^1	R^2	R^3	2	R^4	3	Yield[b] [%]
1	a	H	H	H	a	p-Tol	a	76
2	a	H	H	H	b	m-Tol	b	75
3	a	H	H	H	c	o-Tol	c	64[c]
4	a	H	H	H	d	Ph	d	65
5	a	H	H	H	e	p-MeO-C$_6$H$_4$	e	58
6	a	H	H	H	f	m-MeO-C$_6$H$_4$	f	78
7	a	H	H	H	g	o-MeO-C$_6$H$_4$	g	59[d]
8	a	H	H	H	h	p-Cl-C$_6$H$_4$	h	63
9	a	H	H	H	i	m-Cl-C$_6$H$_4$	i	50
10	a	H	H	H	j	o-Cl-C$_6$H$_4$	j	70[c]
11	a	H	H	H	k	p-CN-C$_6$H$_4$	k	75
12	a	H	H	H	l	p-NO$_2$-C$_6$H$_4$	l	73
13	a	H	H	H	m	β-Naphtyl	m	75[c]
14	a	H	H	H	n	α-Thiophenyl	n	57[c]
15	a	H	H	H	o	γ-Pyridinyl	o	30[c]
16	a	H	H	H	p	n-Pr	p	–
17	b	H	H	Me	a	p-Tol	q	74
18	c	H	H	Br	a	p-Tol	r	51
19	d	H	H	Cl	a	p-Tol	s	77
20	e	H	H	OMe	a	p-Tol	t	64
21	f	H	H	CN	a	p-Tol	u	78
22	g	OMe	H	H	a	p-Tol	v	57
23	h	F	H	F	a	p-Tol	w	60
24	i	H	Me	H	a	p-Tol	x	64
25	j	H	Cl	H	a	p-Tol	y	75
26	k	Cl	H	H	a	p-Tol	z	80

[a] Conditions: **1** (0.2 mmol), **2** (0.6 mmol), +CSA/CAM (0.5 mL); [b] yields referred to pure isolated products (flash column chromatography); [b] Reaction time: 10 min; [d] After 10 min heating the yield was the same.

substituents are in the *ortho* position an extension of the reaction time to 10 min can increase a bit the yields (Table 2, entries 3 and 10). Surprisingly, also challenging substrates such as *p*-formylbenzonitrile (**2k**) and *p*-nitrobenzaldehyde (**2l**) gave the desired products **3k** and **3l** in good yield (Table 2, entries 11 and 12). 2-Naphthaldehyde (**2m**) and thiophene-3-carbaldehyde (**2n**) gave the corresponding 2,2'-biindoles **3m** and **3n** in good yields in a slightly prolonged reaction time (Table 2, entries 13 and 14), whereas the reaction with isonicotinaldehyde (**2o**) was low yielding (Table 2, entry 15). Aliphatic aldehydes, do not seem to be tolerated as the reaction with propanal **2p** failed (Table 2, entry 16). Different patterns of substitution are well tolerated also on the 2,2'-diaminotolan reaction partner (Table 2, entries 17 and 26). This behaviour is of particular interest because it opens the door to the prompt construction of challenging unsymmetric 2,2'-biindoles **3q**–**z**.

Finally, to evaluate the reusability features of the DES, a recycling trial was carried out on the model reaction between **1a** and **2a**. The reaction was performed on a slightly higher scale under our optimized conditions (0.48 mmol of **1a** in 4 mL of DES) and the concentration of the substrate was maintained

almost constant in each cycle. The reaction crudes were poured into water and extracted twice with ethyl acetate, a recommended solvent for its safety and low impact on the environment[22] compared to the other commonly used organic solvents. The reaction yields were evaluated via ^{1}H NMR using dibromomethane as internal standard. The aqueous layer was evaporated under reduced pressure to recover the DES, then it was reused for a new cycle. This sequence was successfully repeated five times providing the desired product **3a** in quite constant good yields, ranging from 60 to 72% (Figure 2).

Finally, based on previous findings[23] and experimental evidence, a plausible reaction mechanism for this cascade process is proposed in Scheme 2. The acidic DES promotes the formation of the iminium ion **I** by reaction of **1** with two equiv. of the aldehyde **2**. Both exocyclic and endocyclic nucleophile-promoted iminium ion-alkyne cyclization reactions have been reported.[24] In our case, the iminium ion **I** undergo an aza-Prins[25] type 5-*endo-trig* cyclization (**II**) quenched by the nucleophilic addition of the adventitious water (amount of water in +CSA/CAM quantified by Karl-Fischer titration=5.2% w/w) to give intermediate **III**.[26] Deprotonation of the oxygen
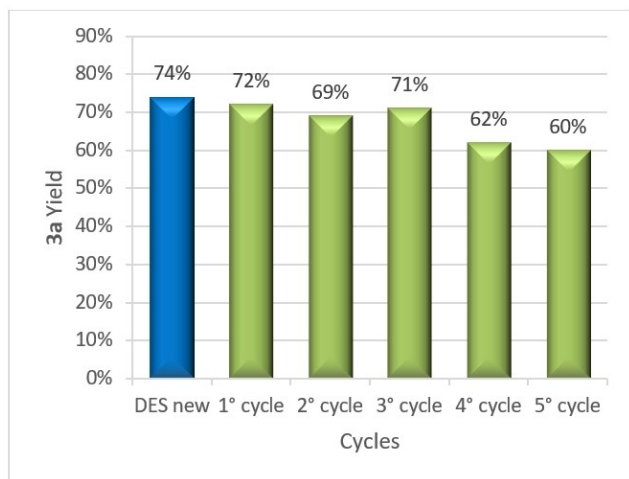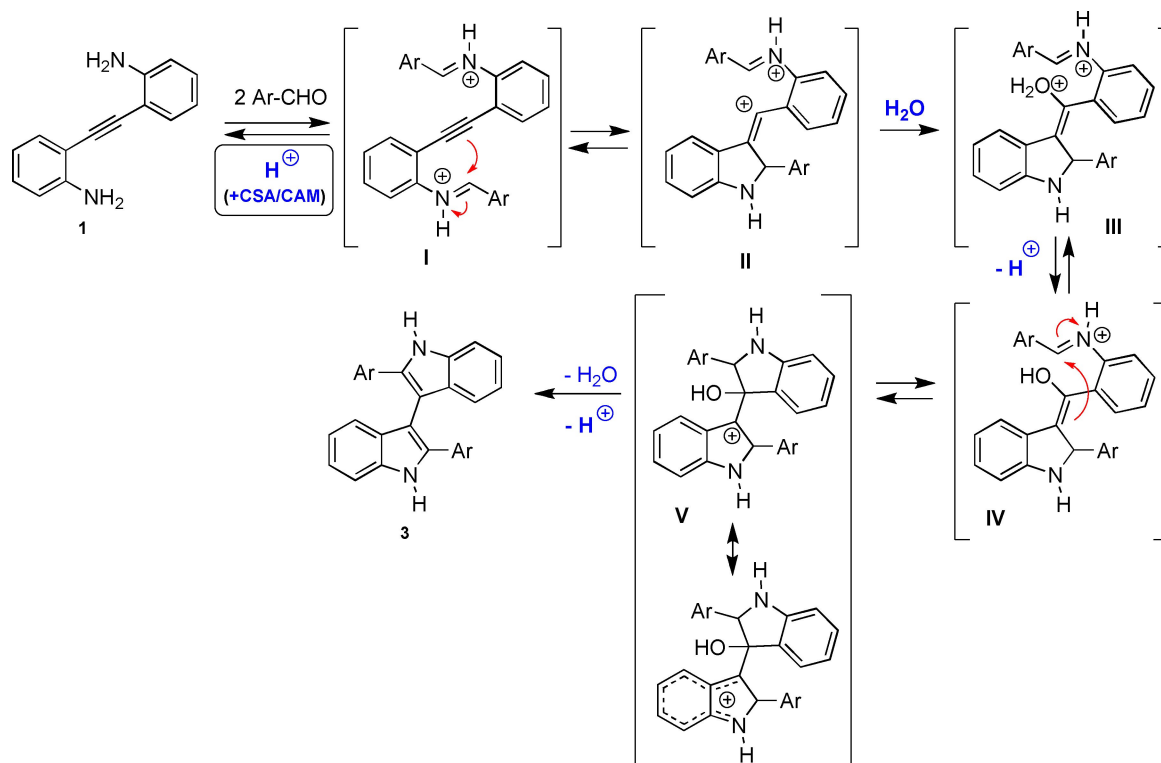
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Figure 2. Reuse trials (yields determined by ^{1}H NMR spectroscopy using CH_2Br_2 as internal standard).

gives the iminium intermediate **IV** which undergoes a nucleophilic attach from the exocyclic double bond to give the benzylic carbocation intermediate **V** stabilized by the possible resonance on the electron-rich phenyl ring. Finally, the loss of a molecule of water and the catalytic proton provide the desired biindoles **3**.

Conclusion

We developed a new method for the synthesis of symmetric and non-symmetric 2,2'-substituted-3,3'-biindoles. The method allows the synthesis of the bi-heterocycles in yield ranging from 30 to 79%. Compared to the original approach,[9b] reaction yields are average a bit lower. On the other hand, so many critical points increased the sustainability of this approach, i.e., i) the substitution of a solvent defined as "problematic" such as acetonitrile, and a strong acid as acid chloride with an accurately selected acidic DES as a benign "active solvent" able to exert the double action of solvent and catalyst, ii) the use of microwaves as a highly-effective energy source, able to reduce dramatically the reaction times (5/10 min vs 1/3 hs) at a lower reaction temperature (70 vs 82 °C) iii) the reusability of the medium, which complies the second of the 4Rs rules of waste hierarchies. Moreover, the reaction scope is quite broad allowing the preparation of a huge variety of biindoles with different patterns of substitution.

Experimental Section

General procedure for the synthesis of bis-indole 3 a–z: In a microwave test tube, the 2,2'-(ethyne-1,2-diyl)dianiline **1 a–k** (0.2 mmol) and the aldehyde (3 equiv.) **2 a–p** were added to the selected DES (0.5 mL). The mixture was heated at 70 °C under microwave heating for 5 min. Then, water was added to the mixture and extracted with EtOAc. The organic layers were dried with Na_2SO_4, filtered and evaporated under reduced pressure. The crude material was purified by flash column chromatography over silica

Scheme 2. Proposed mechanism.

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gel to yield the corresponding 2,2′-disubstituted 3,3′-biindoles **3a–z**.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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