Regiochemistry of the microwave-assisted reaction between aromatic amines and α-bromoketones to yield substituted 1*H*-indoles†

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The scope and regioselectivity of the Bischler (or Bischler–Möhlau) reaction between aromatic amines and α-bromoketones has been studied by computational and experimental techniques. It has been found that in many cases the reaction yields are improved under microwave irradiation and working in the absence of solvent. When di- and trisubstituted amines are used as substrates the regioselectivity of the reaction is different to that obtained with the corresponding primary anilines. The reaction between benzene-1,2-diamine and α-bromoacetophenones under the same conditions yields 2-substituted quinoxalines instead of indoles. Finally, when pyridin-2-amines and pyrimidine-2-amines are allowed to react with the corresponding α-bromoacetophenones, the corresponding imidazo[1,2-*a*]pyridines and imidazo[1,2-*a*]pyrimidines are obtained, respectively.

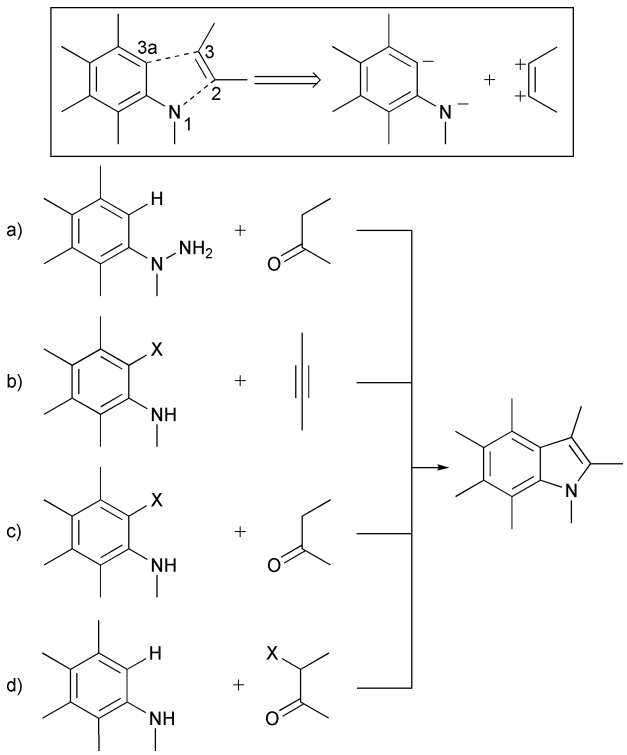
Introduction

1*H*-Indoles are among the most important families of heterocycles.[1] These bicyclic compounds have been included in the category of "privileged structures"[2] since, according to the definition proposed by Evans,[3] indoles constitute a "molecular framework able to provide ligands for diverse receptors". Therefore, there is a consensus in that indoles probably represent the most important of all structural classes in drug discovery.[2a,4]

Among the different methods for the synthesis of 1*H*-indoles,[5] those that rely on the simultaneous disconnection of the N1–C2 and C3–C3a bonds are of special relevance in terms of convergence and accessibility of the reactants (Scheme 1). The first implementation of this approach is the well-known Fischer indole synthesis,[6] which has been extensively used since its discovery in 1883.[7] Within this approach, other methods based on related [3,3] sigmatropic rearrangements have been proposed.[8]

Another group of indole synthesis is based on the reaction between *ortho*-iodo anilines and alkynes catalyzed by transition metals (Scheme 1, entry b). The most prominent example of this approach is the Larock synthesis[9] and related methods.[10,11] Alternatively, ketones can be used as electrophiles in this kind of reaction (Scheme 1, entry c),[12] thus complementing the Fischer method.

Finally, another method based on the above-mentioned disconnection consists of the Bischler[13] (or Bischler-Möhlau[14]) indole synthesis. This reaction takes place between an *ortho*-unsubstituted aniline and an α-halogenated ketone (Scheme 2). Other suitable electrophiles can be α-diazo-β-ketoesters,[15] α-hydroxyketones[16] and α-aminoketones.[17]



Scheme 1 Main indole syntheses based on the disconnection of the N1–C2 and C3–C3a bonds. Substituents at the various positions are unspecified, unless indicated.

Although the reactants for the Bischler reaction are readily available, two issues have hampered further developments: first, the yields of the isolated indoles are usually low, and second, the regiochemistry of the reaction is not predictable (Scheme 2). Very recently, and during the studies described in this paper, it has

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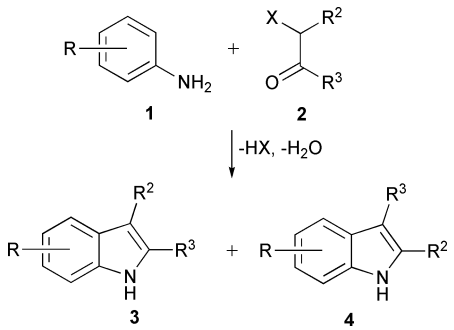


Scheme 2 General reaction between anilines and α-haloketones.

been shown that the outcome of the reaction between anilines and α-bromoketones can be improved by means of microwave irradiation.[18]

Within this context and in view of the above-mentioned previous work, the aim of the present work has been to improve our knowledge of the Bischler reaction in order to understand the reason for its regioselectivity and to explore the scope of this interesting reaction, which has otherwise been largely ignored in the recent indole literature.[2a,5a,19]

Results and discussion

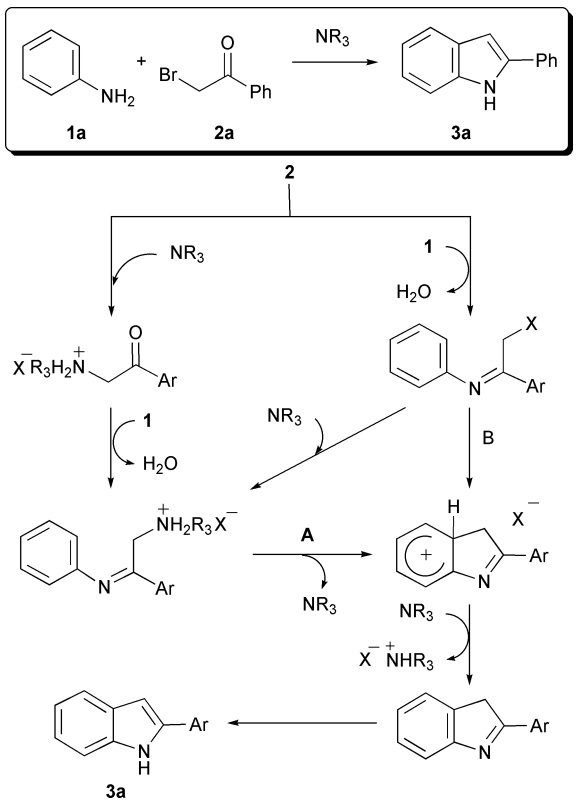
Mechanistic considerations

Despite its formal simplicity, the mechanism of the Bischler reaction is not clear because many pathways can be operating at the same time. Thus, the carbonyl group of the α-haloketone **2a** can react with one equivalent of base or with the aniline **1a** to yield imino intermediates, whose 5-*exo*-tet S_N2-type cyclization (Scheme 3, steps A,B) should lead to 2-substituted-1*H*-indole **3a**.

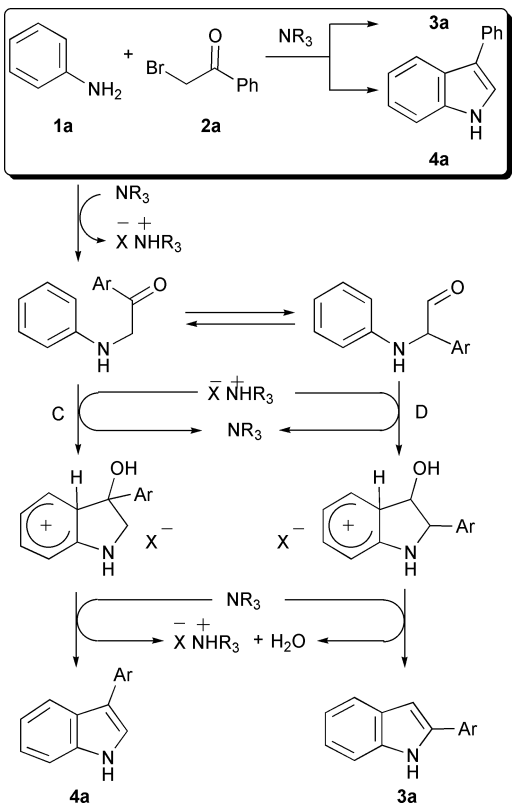
An alternative general mechanistic pathway consists of the inital S_N2 reaction between aniline **1a** and α-haloketone **2a** to yield 2-aminoketones, which can then cyclize by 5-*exo*-trig processes to yield 3-substituted-1*H*-indole **4a** (Scheme 4, path C). In addition, the above-mentioned 2-aminoketones can rearrange to the corresponding aldehydes both under acid catalysis[20] or neutral conditions.[21] Reaction of these rearranged carbonyl compounds by 5-*exo*-trig cyclization should yield the 2-substituted-1*H*-indoles **3** (Scheme 4, path D).

In order to test the feasibility of the 5-*exo*-tet and 5-*exo*-trig cyclizations, we selected the model reactions shown in Scheme 5. These reactions incorporate the main features of the cyclizations A–D shown in Schemes 3 and 4. The main geometric data of the corresponding transition structures **TS1–4** are shown in Fig. 1. According to our results, 5-*exo*-tet cyclizations are clearly disfavoured, the activation energies associated with both **5a**→**6a** and **5b**→**6a** being considerably higher than those found for the alternative 5-*exo*-trig cyclizations of type **5c**→**6b** and **5d**→**6c** (Scheme 5, Fig. 1).

In particular, the lowest calculated activation energy is for the **5d**→**6c** transformation *via* **TS4**. This saddle point is earlier than **TS3**, and the calculated activation energy is *ca.* 4 kcal mol^{-1} lower than that computed for the **5c**→**6b** transformation. This result is in line with the higher electrophilicity of aldehydes with respect to related ketones. Therefore, if only the cyclization step of the



Scheme 3 Mechanistic proposals based on 5-*exo*-tet cyclizations.



Scheme 4 Mechanistic proposals based on 5-*exo*-trig cyclizations. For further details on the rearrangement prior to the cyclization steps C and D, see Scheme 6.

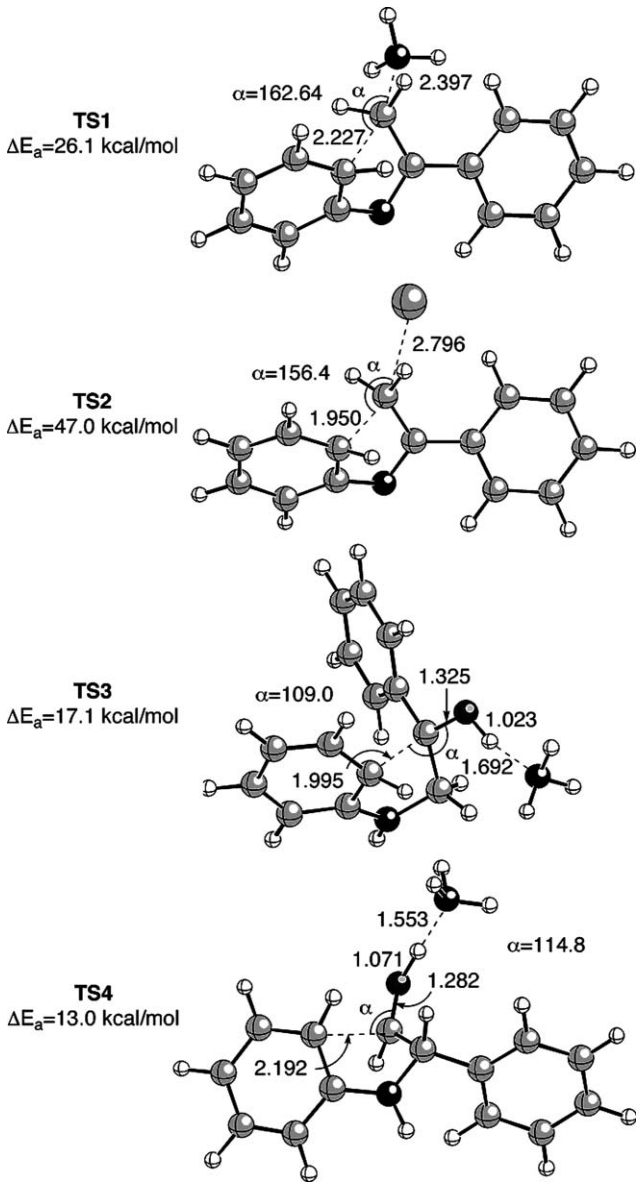
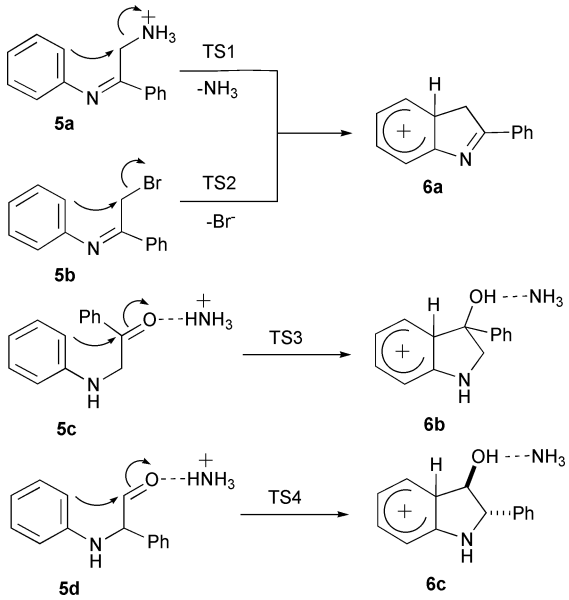


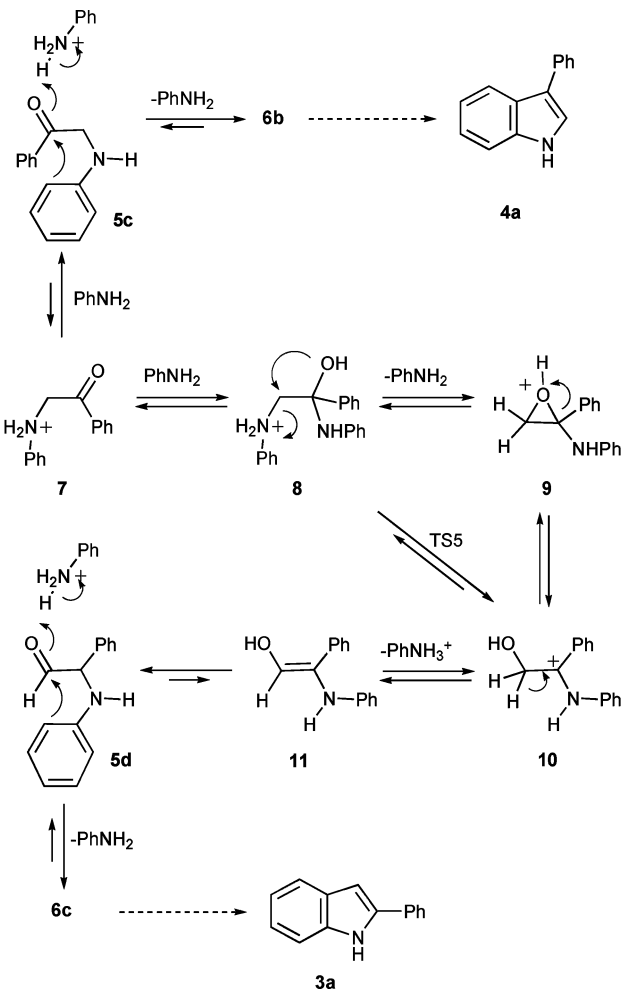
Fig. 1 Fully optimized structures (at the B3LYP/6-31G* level of theory) associated with transition structures **TS1–4** (Scheme 5). Bond distances and angles are given in Å and deg, respectively. The activation energies have been computed at the B3LYP/6-31G*+ΔZPVE level.

reaction is considered, preferential or exclusive formation of 2-substituted-1*H*-indoles is predicted, *via* structures similar to **TS4**.

However, these latter cyclizations require the rearrangement indicated in Scheme 4. Intensive experimental work[21] led to the mechanistic proposal shown in Scheme 6. According to this proposal, the rearrangement requires the nucleophilic addition of second equivalent of aniline to the cationic intermediate **7**. An intramolecular S_N2 reaction on intermediate **8** leads to a protonated oxirane intermediate, the cleavage of the C–O bond in which yields the stabilized cation **10**. Subsequent E1 reaction and keto–enol isomerization leads to aldehyde **5d**. This electrophilic aldehyde is transformed into cyclic intermediate **6c** *via* **TS4**. Alternatively, an additional equivalent of aniline can directly yield ketone **5c**, 5-*exo*-trig cyclization of which should yield cation **6b** *via* **TS3** and, finally, the unrearranged 3-phenyl-1*H*-indole **4a**.



Scheme 5 Model cyclization steps computed at the B3LYP/6-31G* level.



Scheme 6 Mechanistic proposals for the formation of rearranged and unrearranged 1*H*-indoles.

We have explored intensively the potential energy hypersurface associated with this particular rearrangement and we have been unable to locate and characterize the protonated epoxide **9**, either in the gas phase or in solution. Instead, all our attempts led to the direct conversion of **8** to **10** *via* saddle point **TS5** (Fig. 2). In this transition structure the departure of the aniline group is more advanced than the formation of the O1–C2 bond. The process is exothermic and there is a strong resonance stabilization of the C3 center. Thus, the C3–N5 bond distance in **10** is significantly shorter than that computed for **8** (Fig. 2).

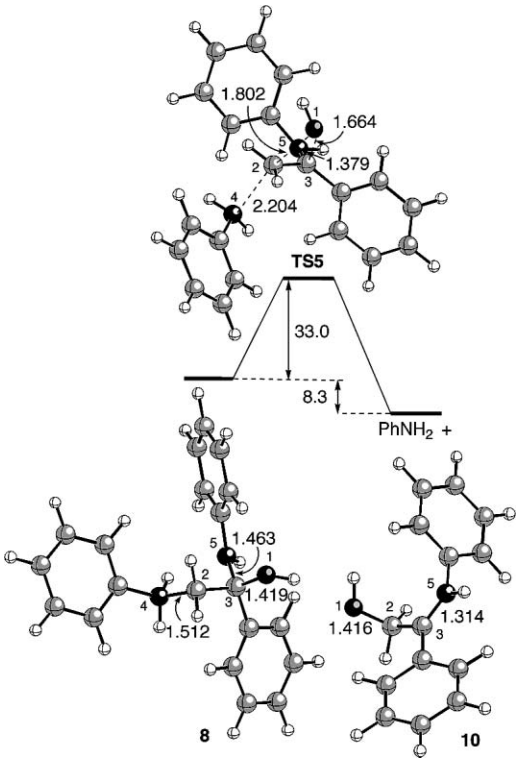
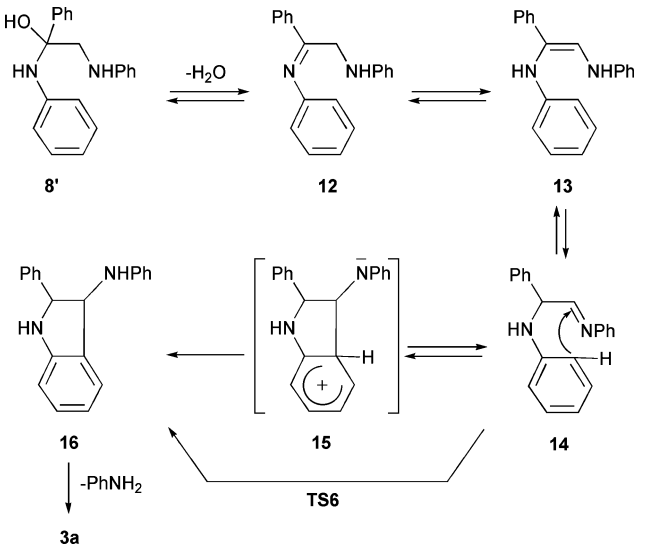


Fig. 2 Fully optimized structures (at the B3LYP/6-31G* level of theory) associated with the **8**→**10** transformation (Scheme 6). Bond distances are given in Å. The relative Gibbs energies have been computed at the B3LYP/6-31G*+ΔZPVE level and are given in kcal mol^{-1}.

Another pathway for the formation of 2-substituted 1*H*-indoles consists of the dehydration of intermediate **8** to yield **12**.[22] Tautomerization of this imine to isomeric intermediate **14** and subsequent 5-*exo*-trig cyclization leads to intermediate **16**, whose elimination of one equivalent of aniline yields the 2-phenyl-1*H*-indole **3a** (Scheme 7). Exploration of this mechanistic pathway from intermediate **14** to zwitterion **15** did not result in an energetically accessible transition structure, probably because of the penalty associated with charge separation and the lower electrophilicity of the neutral imine moiety. However, activation of the imine with one equivalent of HBr resulted in saddle point **TS6**·HBr (Fig. 3), in which the C1–H bond is slightly relaxed with respect to precursor **14**·HBr. Our calculations also show a direct obtention of intermediate **16**·HBr, in which the aromaticity lost in **15** is recovered. The activation barrier computed for this step is comparable to those obtained for the **5c,d**→**6b,c** conversions *via* **TS3** and **TS4** (Fig. 1), and significantly lower than the activation energy associated with the **8**→**10** conversion *via* **TS5** (Fig. 2).



Scheme 7 Formation of 2-substituted indoles from intermediate imines.

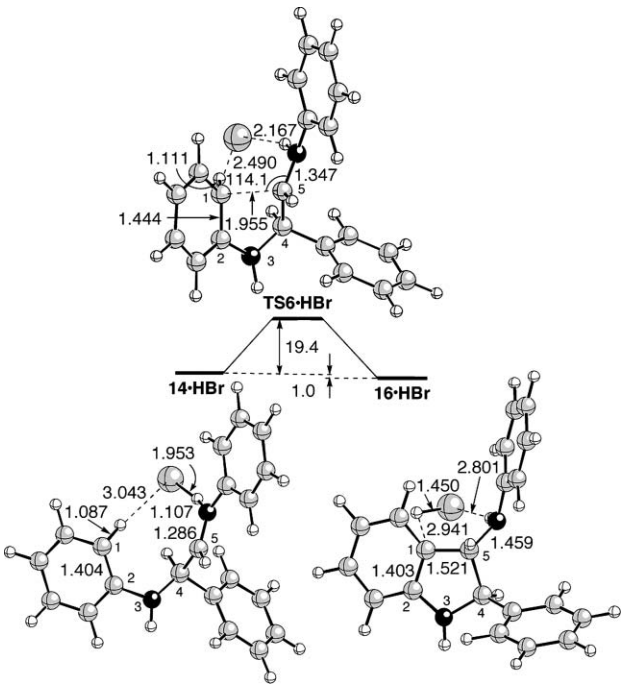


Fig. 3 Fully optimized structures (B3LYP/6-31G* level theory) associated with the **14**→**16** transformation (Scheme 7). Bond distances and angles are given in Å and deg. The relative Gibbs energies have been computed at the B3LYP/6-31G*+ΔZPVE level and are given in kcal mol^{-1}.

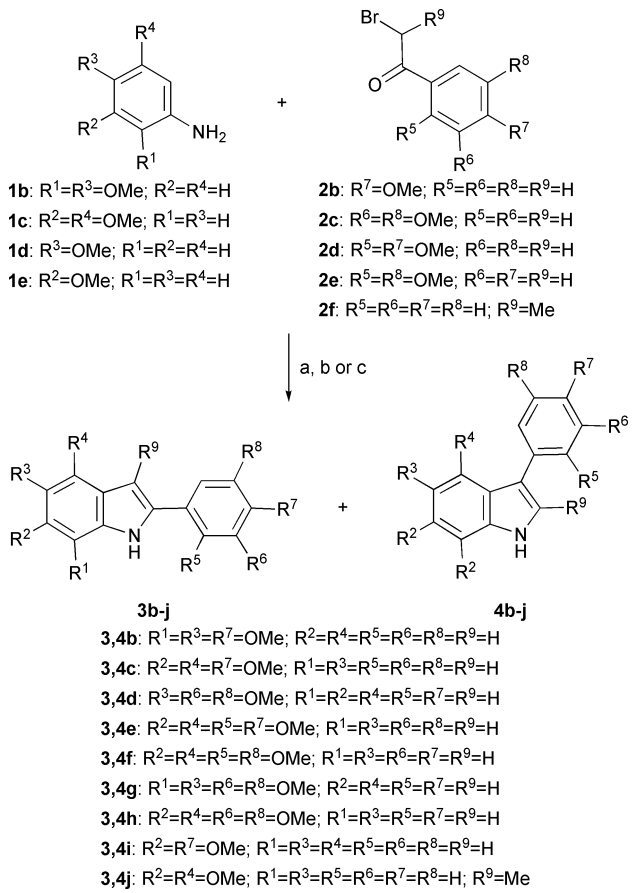
Therefore, we conclude that the mechanism shown in Scheme 7 is the preferred one for the formation of 2-substituted 1*H*-indoles, at least in the presence of an excess of aniline.

In summary, the kinetic **3**:**4** ratio obtained in the Bischler–Möhlau reaction results from a complex process that depends on the relative activation energies associated with the possible 5-*exo*-trig processes (the latter in its activated version shown in Fig. 3). It is also noteworthy that the different steps described in Schemes 4–7 involve very polar reaction intermediates and transition structures. Therefore, the whole reaction is a suitable

candidate for microwave-assisted acceleration, even in the absence of solvents having large loss tangent values.[23,24]

Microwave-assisted Bischler reaction between anilines and α-bromoketones

We carried out the Bischler reactions shown in Scheme 8 in order to test the mechanistic scheme that emerged from our computational study on the key steps of this transformation. First, we included anilines possessing an activating group such as methoxy at different positions of the phenyl group. We also tested different experimental conditions in order to compare the outcomes obtained under dielectric and thermal heating. Thus, method A (Scheme 8, Table 1) consisted of heating a mixture of aniline **1**, the α-bromoketone **2**, and *N*,*N*-dimethylaniline in the absence of solvent at 150 °C for 10 min and under microwave irradiation, with a power of 100 W and under 20 psi. The conditions of method B were chosen to reproduce the usual experimental conditions under thermal heating at 170 °C using xylene as solvent. Under these conditions, the reaction time required for good conversions was 3 hours. Finally, the reaction conditions of method C were chosen to be as close as possible to those using heating by microwave irradiation. Therefore, the reaction time was 10 min, no solvent was used, the temperature was monitored with a fibre-optic probe, and the reaction carried out at 150 °C in a closed vessel identical to that used in the microwave experiments. It was observed that under these conditions the selected temperature was reached in *ca.* 3 min, whilst under microwave irradiation this temperature was obtained after 23 s (See Fig. S1, ESI†). The results obtained for the Bischler–Möhlau reaction between anilines **1b–e** and α-bromoketones **2b–f** are gathered in Table 1.



Scheme 8 *Reagents and conditions*: (a) Microwaves (μW), 100 W, 20 psi, 10 min, 150 °C (Method A). (b) Xylene, reflux, 170 °C, 180 min (Method B). (c) 150 °C, 10 min (Method C).

Table 1 Formation of indoles **3**,**4b–j** from anilines **1b–d** and α-bromoketones **2b–e** (Scheme 7) under dielectric heating (Method A) and thermal heating (Methods B and C)[a]

		Yield of **3** (%)[b]			Ratio **3**:**4**[c]	
Entry	Reaction	A	B	C	A	B
1	**1b** + **2b** → **3b**	30	10	17	>98 : 2	>98 : 2
2	**1c** + **2b** → **3c** + **4c**	52	53	31	68 : 32	77 : 23
3	**1d** + **2c** → **3d**	48	19	0	>98 : 2	>98 : 2
4	**1c** + **2d** → **3e** + **4e**	43	45	45	65 : 35	82 : 18
5	**1c** + **2e** → **3f** + **4f**	61	51	51	82 : 18	>98 : 2
6	**1b** + **2c** → **3g**	16	0	0	>98 : 2	—
7	**1c** + **2c**→ **3h** + **4h**	80	55	37	86 : 14	90 : 10
8	**1e** + **2b** → **3i** + **4i**	75	4	4	79 : 21	50 : 50
9	**1c** + **2f** → **3j** + **4j**	28	43	37	40 : 60	65 : 35

[a] Method A: Microwaves, 100 W, 20 psi, 10 min, 150 °C. Method B: Xylene, reflux, 180 min, 170 °C. Method C: 150 °C, 10 min. [b] Yields of isolated pure product **3**. [c] Ratio determined by ^{1}H-NMR on the crude reaction mixtures.

From these results, we conclude that when the starting amine has favourable substituent effects, similar results are obtained under microwave irradiation and thermal heating. For example, reaction between aniline **1c**, which incorporates two favourably oriented methoxy groups, and α-bromoketone **2e** results in the formation of 1*H*-indoles **3f** and **4f** with similar yields, the thermal reaction being more regioselective (Table 1, entry 5). In contrast, when the aniline incorporates the methoxy groups in an unfavourable orientation, microwave irradiation is superior. For instance, the reaction between α-bromoketone **2c** and aniline **1b**, which incorporates two methoxy groups *meta*-oriented with respect to the C–C bond to be formed, results in the formation of 1*H*-indole **3g** with low yield only when method A was used (Table 1, entry 6). These results agree with the computational model in which the 5-*exo*-trig cyclization step results in the formation of cyclic cations of type **6** (Scheme 5). These cations can be stabilized by properly located methoxy groups.

Our experimental results also indicate that the Bischler reaction involving α-methyl-α-bromoacetophenone **2f** is not regioselective. Thus, reaction between aniline **1c** an **2f** (Table 1, entry 9) results in similar quantities of **3j** and **4j**.

This result is also in line with those obtained in the computational study of the cyclization step, since in this case the 5-*exo*-trig process involves nucleophilic additions on ketones or imines having similar electrophilicities.

The characterization of 1*H*-indoles **3** and **4** was carried out by means of NMR and X-ray diffraction analysis of compound **3e** (see ESI†). Using this compound as a reference, the structure of the remaining compounds was determined by correlation analysis of the ^{1}H-NMR and ^{13}C-NMR spectra (See Fig. S2–S5, ESI†). Thus, the C–H groups at the C-3 position of molecules **3b–j** generated diagnostic signals at *ca.* 6.8 ppm and *ca.* 95.0 ppm in the ^{1}H-NMR and ^{13}C-NMR spectra, respectively. In contrast, the C–H groups

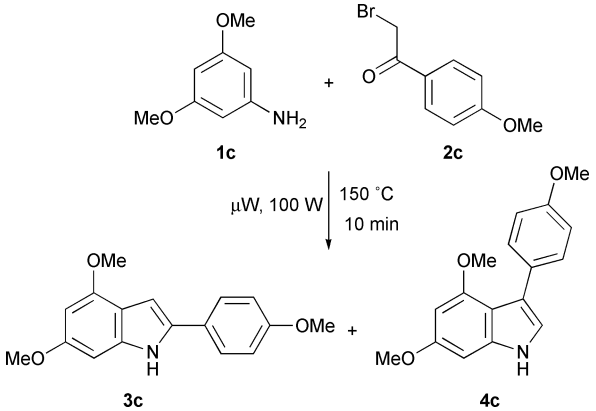
Table 2 Microwave-assisted synthesis of indoles **3** and **4c** in the presence of different bases

Entry	Base	Ratio **1**:**2**:base	Ratio **3c**:**4c**[a]	Yield (%)[b]
1	Et_3N	2 : 1 : 3	35 : 65	40
2	DIPEA	2 : 1 : 3	35 : 65	45
3	DIPEA	1 : 1 : 3	0 : 100	36
4	Py	2 : 1 : 3	85 : 15	63
5	Py	1 : 1 : 3	50 : 50	20
6	Methyl nicotinate	2 : 1 : 3	78 : 22	22

[a] Ratio determined by ^{1}H-NMR on the crude reaction mixtures. [b] Yield of isolated pure major product.

at the C-2 position in regioisomers **4c–j** appeared at *ca.* 7.00 ppm and *ca.* 120.0 ppm in the respective ^{1}H-NMR and ^{13}C-NMR spectra.

We also studied the effect of the base on the reaction. As model system we selected the reaction between **1c** and **2b** to yield **3c** and **4c** (Table 1, entry 2; Scheme 9); the results are gathered in Table 2. We observed that it is possible to modulate the regioselectivity of the reaction. Thus, stronger bases such as triethylamine or DIPEA (diisopropylethylamine) favour the formation of the unrearranged product **4c** (Table 2, entries 1–3), whereas in the presence of weaker bases such as pyridine or methyl nicotinate the rearranged indole **3c** is the major regioisomer (Table 2, entries 4–6). The obtention of product **4c** as the major regioisomer in the presence of stronger bases is consistent with a lower participation of the mechanism outlined in Scheme 7 and Fig. 3, since in this case the acidic activation of the intermediate imine during the 5-*exo*-trig step is less efficient.



Scheme 9 Reaction between **1c** and **2c** in the presence of different bases (See Table 2).

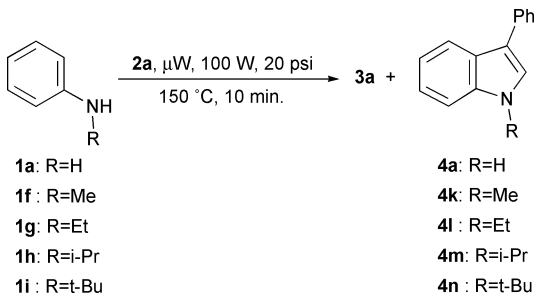
The next step in our study was to analyze the regioselectivity of the reaction between *N*-alkyl anilines **1a–i**, and α-bromobenzophenone **2a** under microwave irradiation (Scheme 10, Table 3). According to our results, when aniline **1a** reacts with **2a**, only the rearranged 1*H*-indole **3a** is obtained with good yields under microwave irradiation. In contrast, the presence of *N*-alkyl groups (Table 3, entries 2–4) results in the formation of variable amounts of unrearranged 1-alkyl-3-phenyl-1*H*-indoles **4k–n**. The exception is the reaction with amine **1i**, in which the presence of the *tert*-butyl group results in the exclusive formation of the rearranged 1*H*-indole **3a** in quantitative yield.

Table 3 Microwave-assisted synthesis of indoles **4a,k–n** from α-bromoacetophenone **2a** and *N*-alkyl anilines **1a,f–i** (Scheme 10)

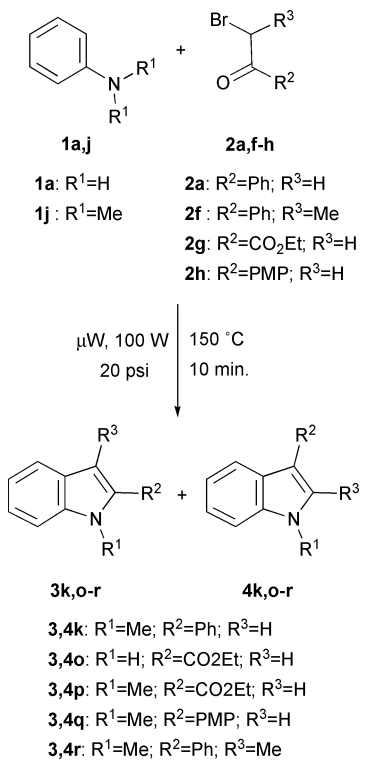
Entry	Reaction	R	**3a** (%)[a]	**4** (%)[a]
1	**1a** + **2a** → **3a** + **4a**	H	80	0
2	**1f** + **2a** → **3a** + **4k**	Me	35	47
3	**1g** + **2a** → **3a**+ **4l**	Et	25	57
4	**1h** + **2a** → **3a**+**4m**	*i*-Pr	30	34
5	**1i** + **2a** → **3a** + **4n**	*t*-Bu	100	0

[a] Yields of isolated pure products.

We also studied the behavior of *N*,*N*-dimethylaniline **1j** in the presence of α-bromoaketones **2a,f–h** (Scheme 11) and under microwave irradiation. The results obtained are shown in Table 4. We have found that in the presence of **1j** only the unrearranged *N*-methyl-1*H*-indoles **4k,o–r** are obtained. Therefore, opposite



Scheme 10 Microwave-assisted synthesis of *N*-alkyl-1*H*-indoles from *N*-alkyl anilines.



Scheme 11 Microwave-assisted synthesis of *N*-alkyl-1*H*-indoles from *N*,*N*-dialkyl anilines.

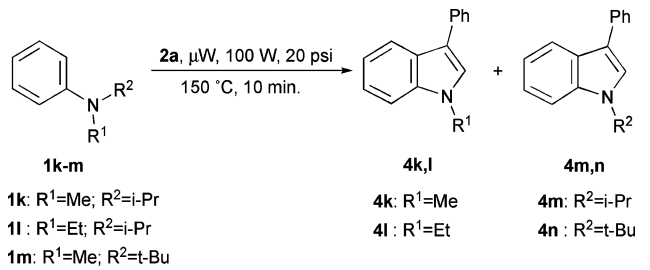
Table 4 Microwave-assisted synthesis of indoles **3k,o–r** and **4k,o–r** from α-bromoketones **2a,f–h** and amines **1a,j** (Scheme 9)

Entry	Reaction	R^1	R^2	R^3	**3** (%)[a]	**4** (%)[a]
1	**1j** + **2a** → **3k** + **4k**	Me	Ph	H	0	53
2	**1a** + **2g** → **3o** + **4o**	H	CO_2Et	H	31	0
3	**1j** + **2g** → **3p** + **4p**	Me	CO_2Et	H	0	34
4	**1j** + **2b** → **3q** + **4q**	Me	PMP[b]	H	0	60
5	**1i** + **2 f** → **3a** + **4r**	Me	Ph	Me	0	51

[a] Yields of isolated pure products. [b] PMP: *p*-methoxyphenyl.

regiochemistries can be obtained depending on the substitution pattern of the starting amine. For example, the reaction between aniline **1a** and α-bromoacetophenone **2a** yields only 2-phenyl-1*H*-indole **3a** (Table 2, entry 1). In contrast, irradiation of *N*,*N*-dimethylaniline **1j** and **2a** results in the exclusive formation of 1-methyl-3-phenyl-1*H*-indole **4k** (Table 3, entry 1). The same outcome was observed in the reaction of ethyl 3-bromo-2-oxopropanate **2g** and amines **1a,j** (Table 3, entries 2 and 3). Finally, it is interesting to note that the same result was obtained with racemic 2-bromopropiophenone **2f** and amine **1j**, and only the unrearranged 1,2-dimethyl-3-phenyl-1*H*-indole **4r** was obtained (Table 3, entry 5), in contrast with the lack of regiocontrol observed in the reaction between **2f** and α-bromoaketone **1c** (Table 1, entry 9, *vide supra*).

In a different series of experiments, we analyzed the outcome of the reaction between *N*,*N*-dialkylamines **1k–m** and **2a** under microwave irradiation (Scheme 12, Table 5). We observed that in the case of amines **1k,l**, comparable distributions of the possible 1-alkyl-1*H*-indoles **4k–m** were obtained. In contrast, when amine **1m** was irradiated in the presence of **2a**, only 1-methyl-3-phenyl-1*H*-indole **4k** was obtained.

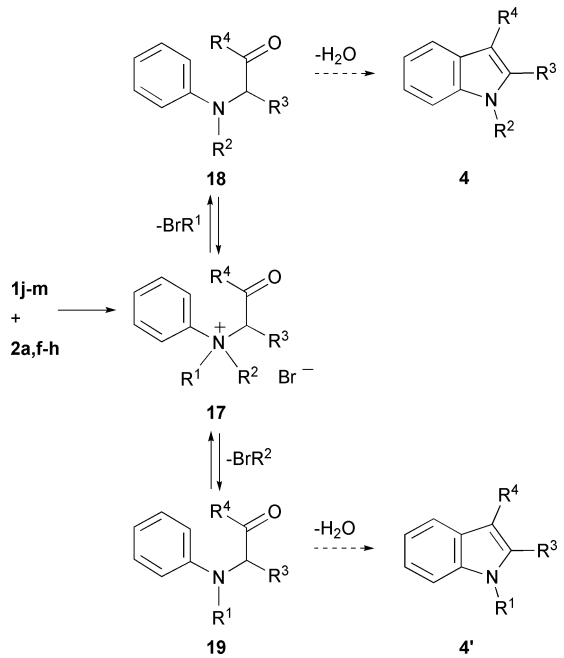


Scheme 12 Microwave-assisted synthesis of *N*-alkyl-1*H*-indoles from *N*,*N*-dialkyl anilines.

These results indicate that trisubstituted anilines are much more regioselective since only 3-substituted (*i.e.* unrearranged) 1*H*-indoles are obtained. This suggests that when only *N*,*N*-dialkylanilines are present, the pathway shown in Scheme 7 and Fig. 3 is not possible.[25] Instead, the quaternary intermediates **17** are formed (Scheme 13). These intermediates evolve toward

Table 5 Microwave-assisted synthesis of indoles **4k–n** from amines **1k–m** and α-bromoacetophenone **2a**

Entry	Reaction	R^1	R^2	Isolated yield (%)
1	**1k** + **2a** → **4k** + **4m**	Me	*i*-Pr	16 (**4k**) +30 (**4m**)
2	**1l** + **2a** → **4l** + **4m**	Et	*i*-Pr	23 (**4l**) +12 (**4m**)
3	**1m** + **2a** → **4k**	Me	*t*-Bu	44 (**4k**)

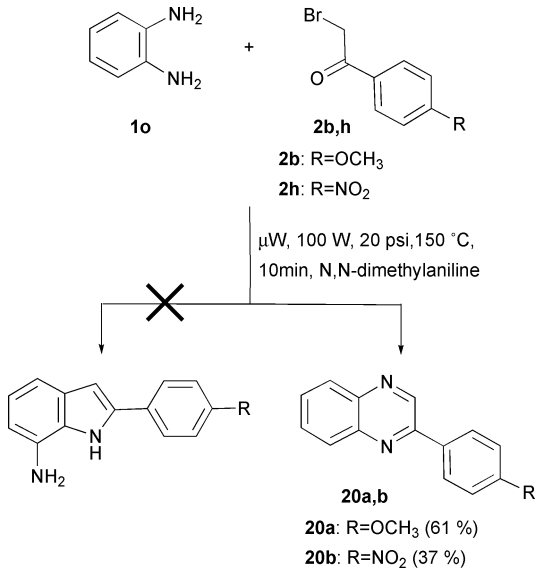


Scheme 13 Possible pathways for the formation of *N*-alkyl-1*H*-indoles.

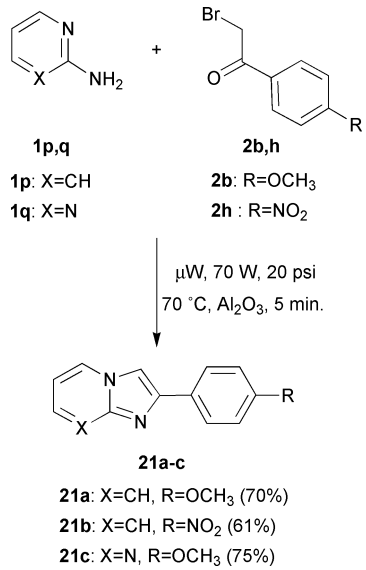
intermediates **18** and **19** to yield finally the corresponding 1*H*-indoles **4**. Our results also indicate that, in general, the distribution of the intermediates **18** and **19** is shifted toward the formation of the most substituted alkyl bromide.

We also explored the reaction between α-bromoketones **2** and amines incorporating active substituents. We have found that when 1,2-phenylenediamine **10** was subjected to microwave irradiation in the presence of α-bromoketones **2b,h** the corresponding 2-arylquinoxalines[26] **20a,b** were obtained instead of 7-amino-2-aryl-1*H*-indoles (Scheme 14). It is interesting to note that a similar reaction in the absence of microwaves required overnight stirring to proceed.[27]

We have also studied the reaction between amines **1p,q** and phenacyl bromides **2b,h** in order to assess the role of additional nitrogen atoms present in the aromatic ring. This reaction has been studied by several authors under thermal conditions,[28] and very recently under microwave irradiation.[29] In this latter case, Dimauro *et al.*[29a] irradiated the reaction mixtures of phenacyl bromide **2a** and boronic esters derived from 2-aminopyridine at 130 °C for 30 min using ethanol as solvent, whereas Cai *et al.*[9b,29] carried out the reaction using titanium(IV) chloride as a strong dehydrating agent. Since Ponnala *et al.*[30] performed the synthesis of these heterocycles using Al_2O_3 as a solid medium, we decided to test the same reaction under microwave irradiation. We observed that under solvent-free conditions and in the presence of Al_2O_3, only 5 min was required to carry out the reaction between compounds **1p,q** and **2b,h** (Scheme 15), working at 70 W, 70 °C and 20 psi. Therefore, these conditions appear to be very convenient for the synthesis of 2-arylimidazo[1,2-*a*]pyridines (or -pyrimidines) such as **21a,c** (Scheme 15). We think that in these cases the reaction proceeds by nucleophilic attack of the nitrogen atom in the aromatic heterocycles, followed by ring closure of *N*-alkylpyridinium (or -pyrimidinium) intermediates, according to the mechanism proposed by Hand *et al.*[31]



Scheme 14 Synthesis of quinoxalines from 1,2-phenylendiamine and α-bromoketones.



Scheme 15 Synthesis of 2-arylimidazo[1,2-*a*]pyridines (X = CH) and 2-arylimidazo[1,2-*a*]pyrimidines (X = N)

Conclusions

Microwave irradiation is a convenient method for the Bischler reaction between aromatic amines and α-bromoketones. Only *ca.* 10 min is required to carry out the reaction at 150 °C and 20 psi. The reaction takes place by 5-*exo*-trig cyclizations involving intermediate aldehydes, ketones or imines. A 1,2-migration of an hydroxyl group or, more likely, the formation of an intermediate imine are critical to obtain rearranged 2-substituted 1*H*-indoles. Further *N*-substitution allows the modulation of the regioselectivity of the reaction, the unrearranged 3-substituted-1*H*-indoles being the major or exclusive products. The presence of active functional groups results in the formation of other heterocycles like quinoxalines or imidazo[1,2-*a*]pyridines (or -pyrimidines).

Experimental

Computational studies

All the calculations reported in this paper were performed within Density Functional Theory,[32] using the hybrid three-parameter functional commonly denoted as B3LYP.[33] The standard 6-31G* basis set,[34] as implemented in the GAUSSIAN 03[35] suite of programs, was used in all cases. All the stationary points were characterized by harmonic analysis.[36] Activation energies (ΔE_a) and reaction energies (ΔE_{rxn}) were computed at the B3LYP/6-31G* level including zero-point vibrational energy (ZPVE) corrections.

General

Microwave irradiations were conducted in a focused microwave reactor CEM Discover, at the power and for the time indicated. All melting points are uncorrected. NMR data were obtained using TMS as an internal standard. Column chromatographies were carried out with 230–400 mesh silica gel. Reagents were purchased from commercial suppliers or prepared according to literature procedures. *N*-*tert*-Butylaniline **1i** was obtained following the procedure described by Canle *et al.*[37] *N*-Isopropyl-*N*-methylaniline **1l** and *N*-methyl-*N*-*tert*-butylaniline **1m** were prepared according to the methods reported by Totah *et al.*[38] and Hunter *et al.*,[39] respectively. 2-Bromo-1-(3,5-dimethoxyphenyl)ethanone **8b** was prepared according to the method reported by Chen *et al.*[40]

General methods for the synthesis of 1*H*-indoles

Method A. A mixture of the aniline **1** (2.0 mmol), the α-bromoketone **2** (1.0 mmol), and *N*,*N*-dimethylaniline (0.42 ml, 3.3 mmol) was irradiated with microwaves (150 W) at 150 °C and 20 psi for 10 min. The resulting mixture was dissolved in EtOAc and washed with 2 N HCl. After drying (Na_2SO_4), the solution was evaporated and purified by flash chromatography (ethyl acetate–hexanes) to yield the corresponding 1*H*-indoles, which were crystallized from Et_2O–hexanes.

Method B. A mixture of the aniline **1** (2.0 mmol), the α-bromoketone **2** (1.0 mmol), and *N*,*N*-dimethylaniline (0.42 ml, 3.3 mmol) was refluxed in xylene at 170 °C for 180 min. The treatment described above led to the corresponding pure products **3** and **4**.

Method C. A mixture of the aniline **1** (2.0 mmol), the α-bromoketone **2** (1.0 mmol), and *N*,*N*-dimethylaniline (0.42 ml, 3.3 mmol) was heated in an oil bath at 150 °C (internal temperature monitored by a fibre-optic probe) for 10 min. The treatment described above led to the corresponding pure products **3** and **4**.

4,6-Dimethoxy-2-(2,4-dimethoxyphenyl)-1*H*-indole (3e). White solid, 43% yield; mp 171–172 °C; ν_{max}/cm^{-1} (KBr) 3427, 1587, 1472, 1301, 1216, 1126; ^{1}H NMR (δ/ppm, 500 MHz, $CDCl_3$) 9.38 (s, 1H), 7.68 (d, 1H, J = 8.4 Hz), 6.77 (s, 1H), 6.57 (d, 1H, J = 8.7 Hz), 6.55 (s, 1H), 6.51 (s, 1H), 6.20 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (δ/ppm, 500 MHz, $CDCl_3$) 159.9, 157.4, 156.7, 153.4, 137.2, 133.5, 128.6, 114.5, 113.8, 106.0, 99.5, 95.5, 91.7, 87.0, 56.0, 55.8, 55.6, 55.5. Anal. Calcd. For $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.80; H, 6.11, N, 4.62.

4,6-Dimethoxy-3-(2,4-dimethoxyphenyl)-1*H*-indole (4e). Oil, 23% yield; ν_{max}/cm^{-1} (KBr) 3407, 1552, 1211, 1161 cm^{-1}; ^1H NMR (δ/ppm, 500 MHz, $CDCl_3$) 8.02 (s, 1H), 7.32 (d, 1H, $J = 8.2$ Hz), 7.01 (d, 1H, $J = 2.0$ Hz), 6.57–6.51 (m, 2H), 6.49 (d, 1H, $J = 1.3$ Hz), 6.21 (d, 1H, $J = 1.3$ Hz), 3.87 (s, 3H), 3.85 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (δ/ppm, 500 MHz, $CDCl_3$) 159.6, 158.7, 157.5, 155.2, 137.8, 132.5, 120.9, 118.1, 113.4, 112.0, 103.5, 98.6, 92.2, 86.9, 55.7, 55.6, 55.5, 55.4.

Synthesis of quinoxalines 20

A mixture of *ortho*-phenylendiamine (0.227 g, 2.1 mmol), the α-bromoketone (1.0 mmol), and *N*,*N*-dimethylaniline (0.42 ml, 3.3 mmol) was microwave-irradiated (150 W) at 150 °C and 20 psi for 10 min. The resulting mixture was dissolved in EtOAc and washed with 2 N HCl. After drying (Na_2SO_4), the solution was evaporated and purified by flash chromatography (ethyl acetate–hexanes) to yield the corresponding product, which was purified by crystallization from Et_2O–hexanes.

Synthesis of 2-arylimidazo[1,2-*a*]pyridines and arylimidazo[1,2-*a*]pyrimidines 21

A mixture of pyridine-2-amine **1p** or pyrimidine-2-amine **1q** (1 mmol), α-bromoketone **2** (1.0 mmol), and neutral Al_2O_3 (1 g) was microwave-irradiated (150 W) at 150 °C and 20 psi for 5 min. After completion of the reaction, the contents were diluted with chloroform (5 ml) and filtered through a Celite pad, washed with 2 ml of chloroform, and evaporated. The residue was purified by chromatography on silica gel using hexane–ethyl acetate as eluent to give the required product, which was purified by crystallization.

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