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Keteniminium Salts as Key Intermediates for the Efficient Synthesis of 3-Amino-Indoles and -Benzofurans

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Herein, we describe a high yielding approach towards the synthesis of 3-amino-indoles and –benzofurans *via* 6π-electrocylization. This was made possible by taking advantage of the high reactivity of keteniminium salts, formed *in-situ* by treating with triflic anhydride and 2-fluoropyridine amides bearing at the *alpha* position either an aniline or a phenoxy moiety. These mild conditions, on top of furnishing rapidly the 3-aminobenzoheteroles, allow the tolerance of various functional groups. Control experiments were carried out to highlight that the keteniminium is, indeed, in most cases the reactive intermediate and conformational preferences of such species were investigated *via* a DFT study.

Keywords: Aminoindole • Aminobenzofuran • Keteniminium • Electrocyclization

Introduction

3-aminoindoles is a rare motif present in nature[1-4] and none of its benzofuran analogues were isolated to the best of our knowledge (**Figure 1**). However, both scaffolds are found in synthetic compounds showing attractive properties in various areas. For example, 3-aminoindole is the core of antiviral compounds against hepatitis B virus[5] and of anti-proliferative agents[6,7] and such anti-mitotic properties were also observed with 3-aminobenzofuran based molecules.[8] Those benzofurans are reported to be involved in potent ischemic cell death inhibitors[9] and anti-microbiotics[10,11] as well as in selective fluorescent chemosensors of Zn^{2+} and CN^- ions.[12,13]

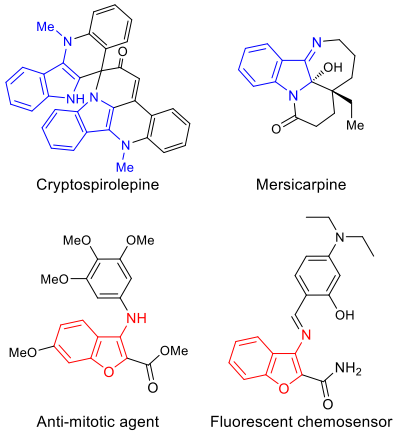
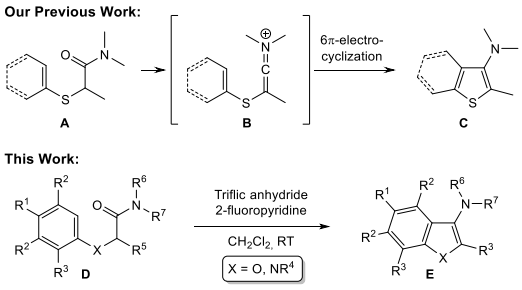


Figure 1. Examples of natural and synthetic 3-aminobenzoheteroles

In the literature, the synthesis of 3-amino-indoles and -benzofurans is achieved following three main strategies. The first one is the functionalization of the naked benzoheterole *via* either direct amination[14-16] or a nitr(os)ation / reduction sequence.[5, 17] The second is the generation of the heterocyclic core followed by *in-situ* amination of the latter[18,19] and the third is the one-step formation of the 3-aminobenzoheterole moiety. In this last approach, the main reaction reported is a *Thorpe-Ziegler* cyclization[6-11, 20-23] or variants[24-28] and actually only a few other methods exist.[29-35]



Scheme 1. General approach towards the synthesis of 3-amino(benzo)heteroles using the keteniminium chemistry

Based on our previous work on the direct formation of 3-amino(benzo)thiophenes **C** from easily accessible thioacetamides **A**,[41-43] through a 6π-electrocyclization involving a keteniminium[36-40] salt intermediate **B**, we are pleased to report herein the expansion of this method towards the facile synthesis of 3-aminoindoles and 3-aminobenzofurans **E** (**Scheme 1**).[44-45]

Results and Discussion

3-aminoindoles

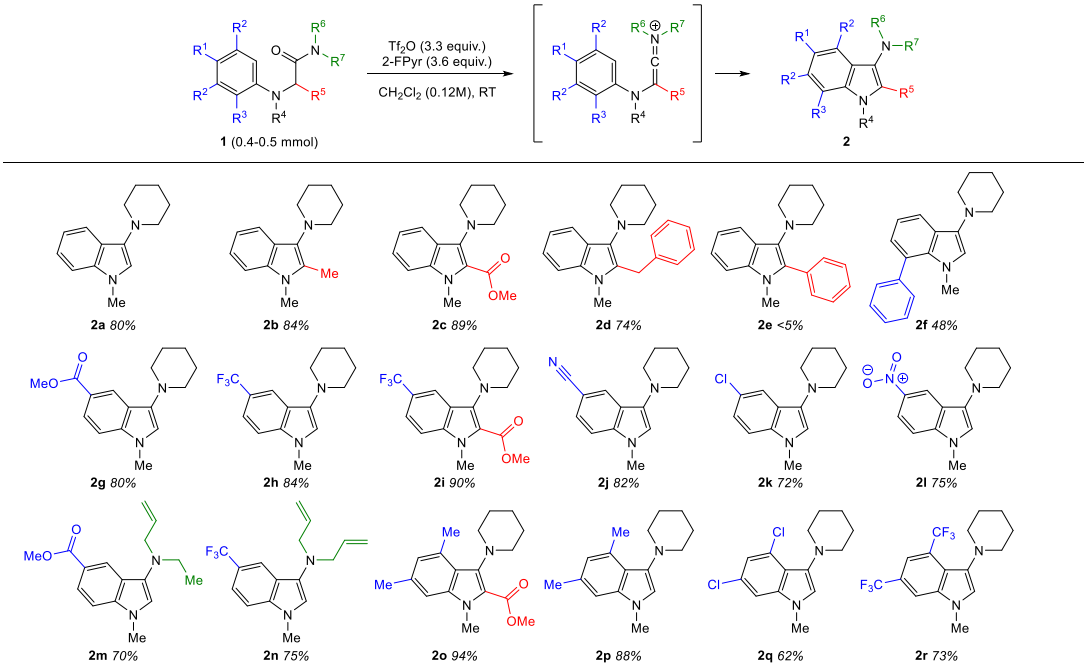
We started our investigation with a simple *N*-piperidylamide **1a** bearing at the *alpha* position a *N*-methylaniline moiety. Using the optimized conditions used previously for the sulfur series (1.1 equiv. of triflic anhydride and 1.2 equiv. of 2-fluoropyridine at room temperature), the expected 3-aminoindole was formed but incomplete conversion of the starting materials was observed. This problem was simply overcome by using an excess of reagents (3.3 equiv. of Tf_2O and 3.6 equiv. of 2-FPyr) and desired **2a** was isolated in 80% yield.

Next, the goal was to extend the scope of this reaction and it proved to be very general. As depicted in **Scheme 2**, high yields are obtained with alkyl, benzyl, ester or even simple hydrogen substituents at the *alpha* position of the amide, corresponding to the position 2 of the formed indole (**2a** to **2d**). The ester group, which activates the keteniminium intermediate and stabilizes the final product by blocking the reactive position 2 and by decreasing the electron density on the nitrogen (position 3), allows us to perform the reaction with electron rich or poor substituents on the aromatic ring of the aniline (**2i** and **2o**). In order to really determine the limitation of this methodology, we decided not to carry out the remaining scope with the help of this ester group but actually with the less favorable substrates, being the unsubstituted *alpha* position of the amide. By comparing the two indoles **2a** and **2c**, we can see a slight decrease of the yield and it was previously observed that formation of 3-aminobenzothiophene, unsubstituted at the position 2, was obtained also in lower yield compared to the substituted ones.[41]

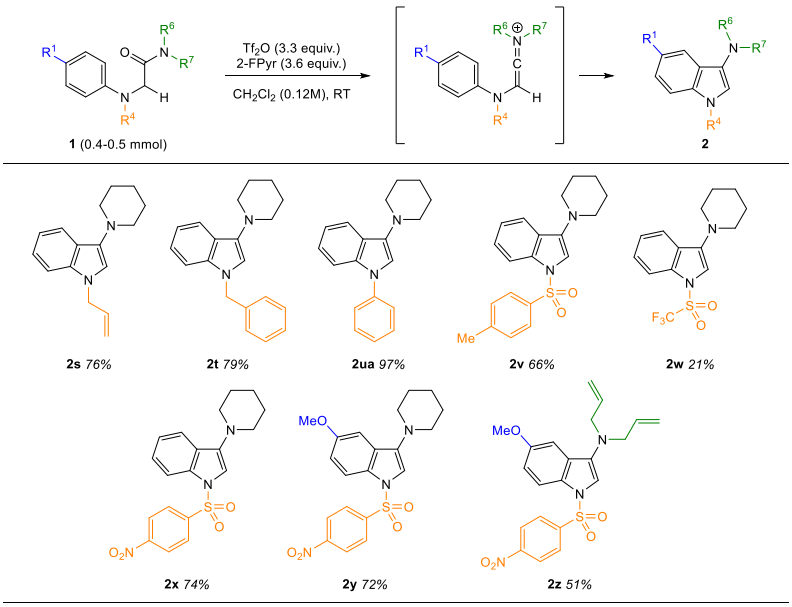
Even using the most challenging substrates, the reaction can still tolerate electron-donating or withdrawing groups on the aromatic ring (**2p** to **2r**). Various functionalities can also be inserted in this ring in an efficient manner, such as halogens, ester, cyano or nitro, which would allow further functionalization of the 3-aminoindoles (**2g** to **2l**). Having those substituents in para- or meta-positions of the aniline proved to be a non-limiting factor and even large ortho-substituent (**2f**) could be inserted, albeit in moderate yield.

Of course, this methodology is not limited to the use of *N*-piperidylamide derivatives. Indeed, acyclic *N*-substituted amides can be used and, more importantly, mono- or di-allyl substituents on the nitrogen are tolerated (**2m** and **2n**) which would allow further deprotection of this nitrogen.[41,46,47]

Then, the substituent on the nitrogen of the aniline motif was investigated and proved to be broader than expected, as shown in **Scheme 3**. Indeed, this methodology is not limited to alkyl group such as methyl, allyl or benzyl. A phenyl or even strong electron-withdrawing groups like tosyl or nosyl could be tolerated, albeit the cyclization is slightly slower in the two latter cases. We were also surprised to observe formation, even in low yield, of the desired indole core **2w** having a triflyl substituent, one of the strongest electron-withdrawing group which decreases dramatically the electron density on the nitrogen of the aniline. Starting with a nosylated aniline, we could insert on the aromatic ring strong electron-donating functionality such as methoxy (**2y**) that otherwise would not be possible. Indeed, it was observed that, starting from an *N*-methyl-paramethoxy aniline derivative, sulfonylation of the aromatic core with triflic anhydride occurred. The decreased nucleophilicity of the aniline caused by the nosyl prevents this side reaction and the nosyl, being a very useful protective group, could be replaced later with the desired substituent. Again, the *N*-piperidyl amide could be replaced by diallyl-substituents and, combined with the nosylated aniline, could afford the 3-aminoindole **2z** bearing two nitrogens with orthogonal protective groups.

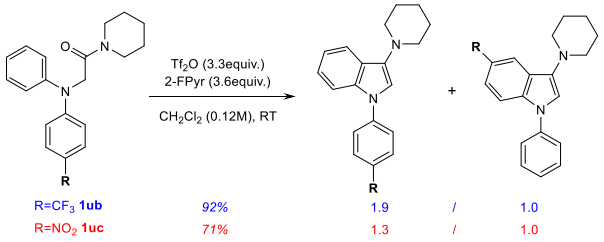


Scheme 2. Access to 3-aminoindoles with variation of the substituents in α-position to the amide and on the aromatic ring



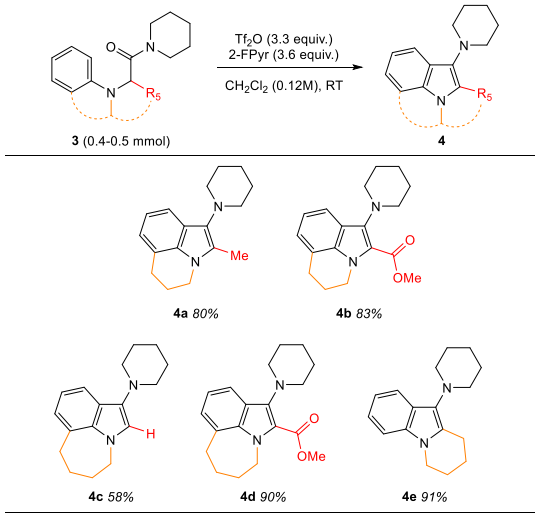
Scheme 3. Access to 3-aminoindoles with variation of the substituent on the aniline nitrogen

In the case of diarylamines, we wanted to study the influence of the substituents in order to discriminate one of the two aromatic rings in the cyclization reaction (**Scheme 4**). When the electronic effect is purely inductive, such as a CF_3 group, the more electron-rich ring intervenes preferentially into the cyclization step (ratio: 1.9/1.0), as expected. However, when the CF_3 was replaced by a nitro, which is supposedly more electron-withdrawing, a closer ratio of 1.3/1.0 was obtained. This could be explained by the ability of the nitro group to force the delocalization of the lone pair of the aniline nitrogen into the nitroaromatic and putting it preferentially in a coplanar conformation, better suited for the electrocylization.



Scheme 4. Competition reactions involving unsymmetrical diarylamines

Finally, we were interested to know if we could form polycyclic structures starting from an amide containing at the *alpha* position either a tetrahydroquinoline or tetrahydrobenzoazepine core and this proved to be the case (**Scheme 5**). With our methodology we could easily synthesize tetrahydropyrido[1,7]indole as well as tetrahydroazepino[1,7]indole in very good yields. It is noteworthy to mention that we could also access efficiently tetrahydropyrido[1,2]indole **4e** starting from a N(1)-phenylpiperidine-2-carboxamide derivative.

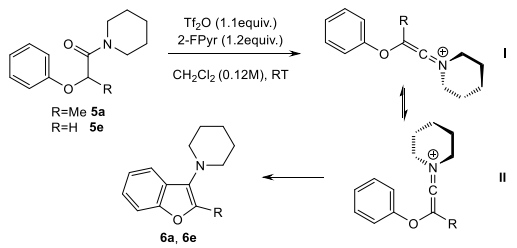


Scheme 5. Access to polycyclic 3-aminoindoles

3-aminobenzofurans

By replacing the aniline at the *alpha* position of the amide by a phenoxy, like in substrate **5a**, the expected 3-aminobenzofuran was formed in high yield (69%). However, contrary to the 3-aminoindoles, the unsubstituted (position 2) benzofuran **6e** could not be formed in an efficient manner at room temperature. Indeed, consumption of the starting material **5e** was very slow, even with an excess of reagents, and the formation of the desired heterocycle occurred with various side products. As depicted in **Scheme 6**, we assume that when R=H, the favored conformation is **I** to avoid clash between the keteniminium and the aromatic ring, therefore preventing the cyclization. On the contrary, when R=Me, the conformer **II** would be preferred to avoid this time interaction of the bulkier methyl group with the phenyl ring. In the case of aminoindoles, the additional substituent on the nitrogen of the aniline

probably disturbs the conformer **I** and favors **II**, even when R=H. In the computational rationalization section, we investigated the R substituent effect on the favored conformations of the keteniminiums in **Scheme 6**.



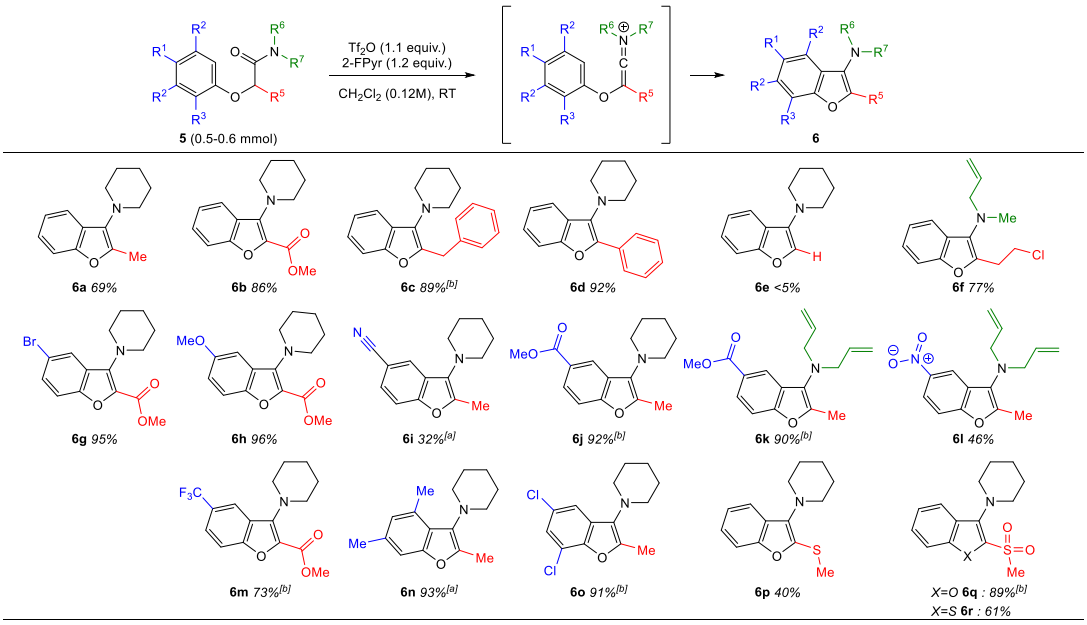
Scheme 6. Conformational considerations for the cyclization step

Despite this, the scope proved to be fairly broad and is detailed in **Scheme 7**. On the position 2 of the 3-aminobenzofuran are tolerated functionalizable alkyl chain, benzyl and even a phenyl group (**6a** to **6f**), which gave in the case of the nitrogen series complete decomposition of the substrate. Heteroatoms such as alkylsulfide and sulfone can be inserted in moderate to good yields and this is also the case with the benzothiophene family (**6p** to **6r**). The substrates bearing an ester group either at the *alpha* position of the amide or directly on the phenoxy ring give the corresponding 3-aminobenzofurans in excellent yields. Other functions on the aromatic ring, such as halogens, nitrile, methylether and nitro are again tolerated (**6g** to **6l**). The latter function combined with the *N*-diallylamide afford a 3-aminobenzofuran possessing two orthogonally protected nitrogens. It is worth mentioning that the electronic effect of the substituents and their position on the aromatic ring, even in ortho, have hardly an influence on the isolation yields (**6m** to **6o**).

With substrates **5m** and **5q** an interesting side reaction was observed. Indeed, after short reaction time (2-3 hours) we could observe and isolate a side product **7** possessing a pyridine moiety (**Scheme 8**). We assume that the enamine intermediate **ENA**, which should afford spontaneously the keteniminium **KET**, is too stabilized in those cases and therefore favors a higher concentration of this species in the medium. The enamine then interacts with the 2-fluoropyridinium salt in a S_NAr reaction. More interestingly, with longer reaction time (1-4 days), we could observe complete conversion of this kinetic product **7** towards the desired heterocycles **6** which means that the S_NAr is actually reversible. This reversibility is reasonable considering the high electrophilicity of the bis positively charged intermediate **INT** presumably present in the reaction mixture. Besides, in the case of **5m**, when we replaced the 2-fluoropyridine by the chloro analogue, we observed the same S_NAr product **7m** but further demethylation and decarboxylation of the ester moiety were also detected. This supports the fact that nucleophilic halides are present in the medium.

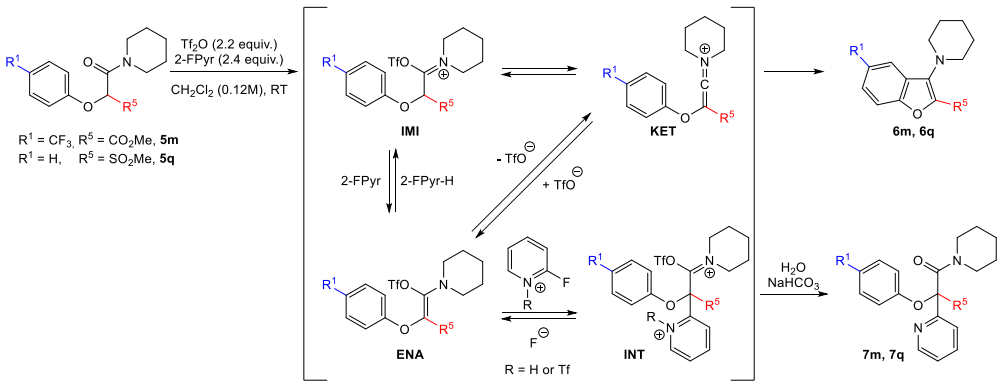
Control Experiments

We wanted to highlight that the cyclization step occurred indeed on the keteniminium salt, and not on the iminium intermediate resulting from the triflation of the amide. Previously, we demonstrated this by carrying out the reaction in the absence of base.[41,43] Activation of the amide by triflic anhydride would give rapidly the iminium **IMI2** but without the 2-fluoropyridine in the medium, the formation of the keteniminium **KET2** would occur very slowly (**Table 1**). By comparing the formation rates of the product with or without base, we could determine which intermediate is most likely the reactive one.



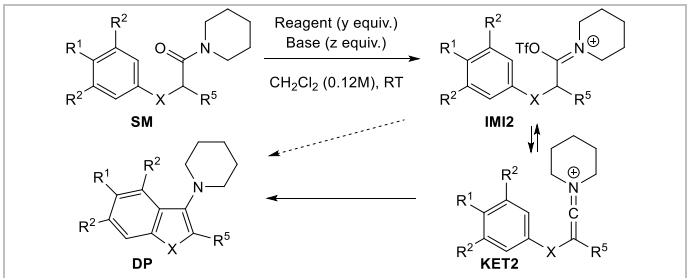
[a] 1.6 equiv. of Tf_2O and 1.8 equiv. of 2-FPyr were used
[b] 2.2 equiv. of Tf_2O and 2.4 equiv. of 2-FPyr were used

Scheme 7. General access to 3-aminobenzofurans



Scheme 8. Proposed mechanism for the formation of side products **7**

Table 1. Control experiments to highlight the formation of a keteniminium salt intermediate



Entry	X[a]	R¹	R²	Reagent	Base	Time	DP[b]	SM[b]
1a[c]	O	CO_2Me	H	Tf_2O	FPyr	2.5h	93	0
1b[c]	O	CO_2Me	H	Tf_2O	/	15h	4	94
2a[d]	O	H	Me	Tf_2O	FPyr	2h	92	0
2b[d]	O	H	Me	Tf_2O	/	15h	42	54
2c[d]	O	H	Me	Tf_2O	/	72h	67	31
3a[e]	NMe	H	CF_3	Tf_2O	FPyr	3h	73	0
3b[e]	NMe	H	CF_3	Tf_2O	/	4h	51	35
3c[e]	NMe	H	CF_3	Tf_2O	/	15h	52	23
3d[e],[f]	NMe	H	CF_3	$POCl_3$	FPyr	20h	0	nd[g]
3e[e],[f]	NMe	H	CF_3	$POCl_3$	/	20h	0	nd[g]
4a[e]	NMe	H	Me	Tf_2O	FPyr	2h	88	0
4b[e]	NMe	H	Me	Tf_2O	/	4h	69	27
4c[e]	NMe	H	Me	Tf_2O	/	15h	76	16
4d[e],[f]	NMe	H	Me	$POCl_3$	FPyr	15h	13	82
4e[e],[f]	NMe	H	Me	$POCl_3$	/	15h	14	79

[a] When X=O, R⁵=Me and when X=NMe, R⁵=H
[b] Yields in %
[c] y=2.2 equiv.; z=2.4 equiv.
[d] y=1.6 equiv.; z=1.8 equiv.
[e] y=3.3 equiv.; z=3.6 equiv.
[f] Reaction performed at 60°C
[g] Non-determined

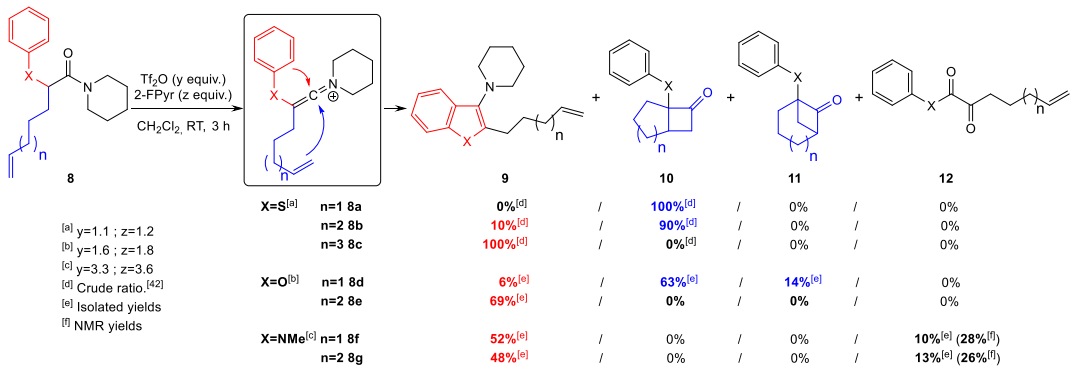
In the case of benzofuran, and by starting with an electron-deficient phenol (**Table 1**, entry 1), we could observe a dramatic decrease of the product yield in the absence of base, despite a much longer reaction time. This confirms that the keteniminium is required for the reaction to occur efficiently. However, when an electron-rich phenol (entry 2) was employed, we can see slow but decent conversion to the desired product. In this case, the cyclization *via* a 6π-electrocylization with the keteniminium **KET2** is probably the fastest pathway, but the competitive *Friedel-Crafts* addition onto the iminium intermediate **IMI2** cannot be excluded.

Unfortunately, we cannot completely use this approach for the indole series. Indeed, the starting materials bearing intrinsically a base, the aniline, can take the role of the 2-fluoropyridine and help the formation of the keteniminium salt. This was supported experimentally by treating **1r** exclusively with Tf_2O and which gave rapidly 50% of the 3-aminoindole together with protonated starting aniline (entry 3). With longer reaction time, we only observed slow decomposition of the remaining starting materials. To overcome this issue, we replaced the triflating reagent by the well-known amide activator $POCl_3$ which cannot formed efficiently a keteniminium due to the nucleophilic counter anion chloride.[36,39,40] As expected, no aniline cyclization onto the iminium intermediate was observed with or without base, even with higher temperature and longer reaction time. Similarly to the benzofuran, when electron-rich aniline was used (entry 4), partial cyclization was observed with $POCl_3$, thus the *Friedel-Crafts* pathway involving **IMI2** cannot again be excluded in this case.[48] This was also supported by formation over 50% of indole **2p** by treating **1p** exclusively with triflic anhydride.

Competition Experiments

Next, we designed substrates in order to compare kinetically the formation of the different aminobenzoheteroles, *via* 6π-electrocyclization, with the formation of cyclobutanones, obtained by intramolecular [2+2] cycloaddition between an alkene and the keteniminium salt. Previously, in the case of phenylsulfide, the [2+2] cycloaddition reaction was predominant with short alkene chain (n=1 or 2) in order to form the corresponding bicyclo[3.2.0]heptane or [4.2.0]octane systems. With longer chain, the electrocyclization was the fastest pathway (**Scheme 9**).[42]

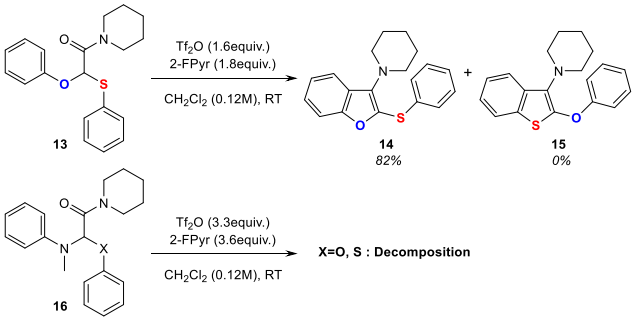
In the case of the phenyl ether, the [2+2] was still favored when n=1, giving a mixture of two regioisomers,[43,49] but when n=2, no cycloadduct was observed and the 3-aminobenzofuran was the only isolable product. With the aniline derivative, in each case, no product arising from a [2+2] cycloaddition was observed and only formation of the desired indoles, together with an unexpected side ketoamide product, were isolated.



Scheme 9. Intramolecular competition reactions between formation of 3-aminobenzoheteroles and [2+2] cycloadducts

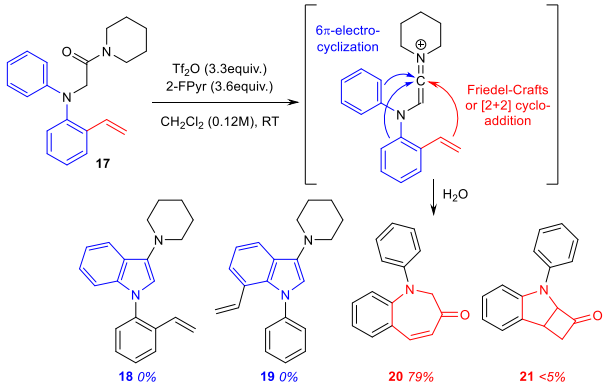
Those observations are not surprising considering that the 6π-electrocyclization is dependent on the electron density of the aromatic ring, with the aniline being electronically the richest and the thiophenol the most deficient.

With these experiments, we can already deduce that formation of the 3-aminoindoles are faster than the corresponding benzofurans and the latter are faster than the benzothiophenes. However, we were interested to confirm this by directly putting in competition the aniline, phenol and thiophenol (**Scheme 10**). Unfortunately, substrates bearing at the *alpha* position of the amide an aniline and either a phenol or thiophenol proved to be unstable and decomposed under the reaction conditions. Nonetheless, we were able to submit under the typical conditions the substrate bearing both phenol and thiophenol and, as expected, the 3-aminobenzofuran was the only product formed.



Scheme 10. Attempts to compare directly the formation rates of the different 3-aminoheteroles

Finally, we wanted to submit a substrate bearing a styrenic diarylamine **17** as depicted in **Scheme 11**. Such scaffold, upon treatment with triflic anhydride and 2-fluoropyridine, could produce in theory several products. Indeed, formation of two different 3-aminoindoles (**18, 19**) could occur, by reaction of each aromatic ring in a 6π-electrocyclization, but not only. Formation of a cyclobutanone **21** or a 7-membered cyclic enone **20**, arising respectively from a [2+2] cycloaddition or *Friedel-Crafts* reaction of the styrenic double bond with the keteniminium salt, has to be considered. It was demonstrated previously that the selectivity between these two latter outcomes was dependent on the electron density of the starting aniline.[50] In our present case, the *Friedel-Crafts* was the fastest pathway compared to the other processes, with isolation of the cyclic enone in 79% yield, albeit a tiny amount of cycloadduct was observed in the reaction mixture.[51]



Scheme 11. Intramolecular competition between 6π-electrocylization and Friedel-Crafts reactions

Computational Rationalization

The conformational preferences of the R substituted keteniminium intermediates (R=H, CH_3) depicted in **Scheme 6** were computationally investigated in order to elucidate the R substituent's effect on the electrocyclization reaction. All optimizations were performed at the M06-2X[52-53] / 6-31+G(d,p) [41-42,46-47,54] with IEF-PCM[55-56] in dichloromethane (CH_2Cl_2) as implemented in Gaussian 16 (G16, Revision A.03)[57]. Energy refinements were carried out using double hybrid B2PLYP[58] functional in order to accurately evaluate the relative Gibbs free energies. In case of R=H, the computed data revealed that the relative Gibbs free energies of the open **I** and closed **II** conformations are isoenergetic (**Figure 2**). Structurally, C-C-O bond angle of the closed conformation **II** (124.8°, **Figure 2**) is larger than a regular trigonal planar bond angle and the C-H-π stacking distances (4.41 Å and 4.46 Å) are also quite large in the closed conformer **II**, somewhat destabilizing this conformation. Moreover, a C-H-π interaction (CH···π distance = 3.58 Å) contributes to the stabilization of the open conformer **I**. Hence, the conformational equilibrium shifts slightly towards the open conformation **I**. Conversely, for the methyl substituent, the closed conformation **II** is energetically strongly preferred

over the open conformation **I** (ΔG_{rel}= 3.1 kcal/mol) favoring the formation of the benzofuran derivative. The methyl group also sterically prevents the rotation of the lowest energy conformer **II** to the open conformer **I**. Moreover, in **Figure 3** non-covalent interactions (NCI) including C-H-π and cation-π were also investigated using the NCIplot program.[59] Cation-π interaction distances of the methyl substituted closed conformer **II** is 3.94Å whereas this distance for –H substituted conformer **II** is 4.02Å. This is due to the more positive cation of the methyl substituted keteniminium, the cation interacts with the quadrupole of phenyl more strongly and stabilizes the closed conformation **II** leading to the formation of 3-aminobenzofuran (**6a**) in the methyl substituted case. A full computational study thoroughly investigating the factors (heteroatom, substituent effect, etc.) influencing keteniminium electrocyclizations is currently underway.

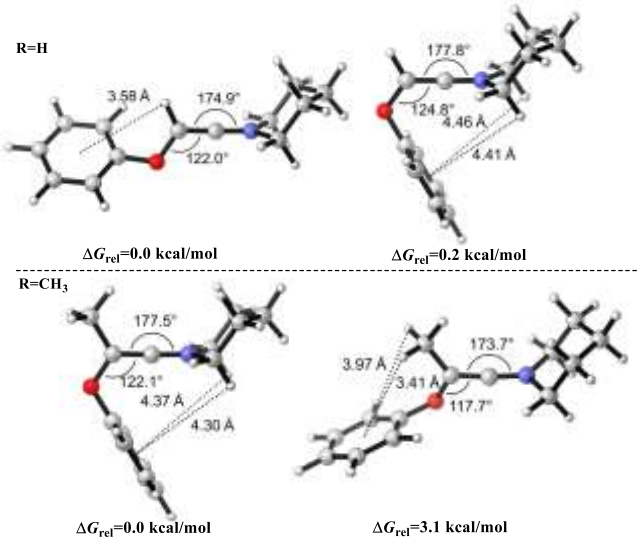


Figure 2. Optimized structures and relative free energies of the Ket intermediates. B2PLYP/6-31+G(d,p)//M06-2X/6-31+G(d,p) in CH_2Cl_2.

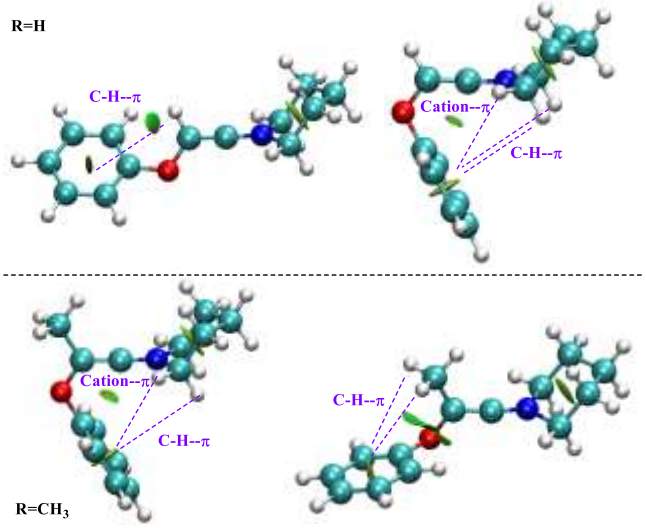


Figure 3. The non-covalent interaction (NCI) plots of the optimized structures. The NCI isosurface value= 0.5 au using SCF densities.

Conclusions

Herein we have reported an efficient and general route for the synthesis of 3-amino-indoles and -benzofurans from easily accessible acetamides, bearing respectively an aniline and a phenoxy group. The mild reaction conditions allow the tolerance of a wide range of functional groups and this method is not limited by the electronic or steric effect of the aromatic substituents. We demonstrated that the reaction requires in most cases a keteniminium salt intermediate to occur. However, it was shown that the cyclization directly onto the iminium intermediate cannot be neglected when electron-rich anilines or phenols were employed. Competition experiments were also conducted in order to confirm the ease of formation of the different 3-aminobenzoheteroles with indole being the fastest and benzothiophene the slowest, with benzofuran in between. Additionally, effect of R substituent on the conformational preference of the keteniminiums and their propensity toward electrocyclization were discussed *via* a DFT study.

Experimental Section

*General Procedure for the Synthesis of 3-Aminoindoles **2** and **4***

In a dried flask under argon charged with a solution of amide **1** or **3** (0.40-0.50 mmol, 1.0 equiv.) in CH_2Cl_2 (c = 0.12 M) was added dropwise at room temperature 2-fluoropyridine (3.6 equiv.) and then, over a period of 20-30 min, triflic anhydride (3.3 equiv.). The resulting mixture was stirred at room temperature until complete consumption of the starting materials (from 2 h to 7 h). The reaction was then diluted with CH_2Cl_2, quenched with a saturated aqueous solution of $NaHCO_3$ until pH 8-9 and stirred vigorously for 30 min at room temperature. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (x2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude by flash column chromatography on silica gel (Cyclohexane/EtOAc: from 95/5 to 70/30) afforded desired 3-aminoindole **2** or **4**.

*General Procedure for the Synthesis of 3-Aminobenzofurans **6***

In a dried flask under argon charged with a solution of amide **5** (0.50-0.60 mmol, 1.0 equiv.) in CH_2Cl_2 (c = 0.12 M) was added dropwise at room temperature 2-fluoropyridine (1.2-2.4 equiv.) and then, over a period of 15-25 min, triflic anhydride (1.1-2.2 equiv.). The resulting mixture was stirred at room temperature until complete consumption of the starting materials (from 2 h to 6 h). The reaction was then diluted with CH_2Cl_2, quenched with a saturated aqueous solution of $NaHCO_3$ until pH 8-9 and stirred vigorously for 30 min at room temperature. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (x2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude by flash

column chromatography on silica gel (Cyclohexane/EtOAc: from 95/5 to 85/15) afforded the desired 3-aminobenzofuran **6**.

Supplementary Material ((optional))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/MS-number. ((Please delete this text if not appropriate))

Acknowledgements ((optional))

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Author Contribution Statement

The project and experiments were designed by D. D., A. K., P. Q., A. L., S. S.-M. and A. De M. The experimental work was performed by D. D. and A. K. and the computational work was conducted by G. T. and S. C. All authors contributed to the manuscript writing and review process.

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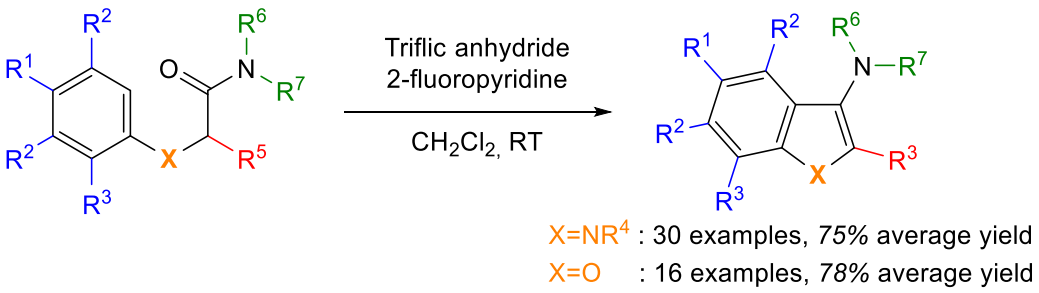

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