JOC The Journal of Organic Chemistry

Article

Access to Fluorazones by Intramolecular Dehydrative Cyclization of Aromatic Tertiary Amides: A Synthetic and Mechanistic Study

Béla Mátravölgyi, Tamás Hergert, Erika Bálint, Péter Bagi, and Ferenc Faigl

J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 22 Jan 2018

Just Accepted

ACS Publications

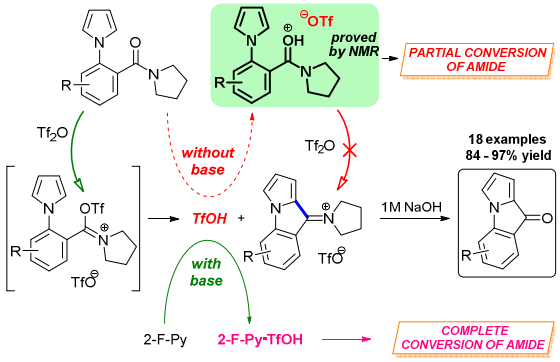
The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Access to Fluorazones by Intramolecular Dehydrative Cyclization of Aromatic Tertiary Amides: A Synthetic and Mechanistic Study

Béla Mátravölgyi,* Tamás Hergert, Erika Bálint, Péter Bagi and Ferenc Faigl

Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, H-1111 Budapest, Budafoki út 8., Hungary

*E-mail: bmatravolgyi@mail.bme.hu



ABSTRACT: An efficient synthesis has been developed for the preparation of 9*H*-pyrrolo[1,2-*a*]indol-9-ones (fluorazones) from readily available anthranilic acid derivatives via a one-pot amide- and pyrrole-formation step, followed by an intramolecular cyclodehydration. The cyclodehydration process is mediated by the activation of aromatic tertiary amides by triflic anhydride (Tf_2O). Comparison of various benzo-substituents is shown in order to demonstrate the high functional group tolerance of this transformation. In addition, study of the reaction mechanism is also presented to unfold the exact role of the applied base additive. Herein, as a first example, we report our findings that Tf_2O-mediated amide activation is obstructed by the easy protonation of amides by the formed triflic acid during the activation step. Additionally, it has been also proven that the base additive is not involved in the transformation of *O*-triflyliminium triflates into reactive species (e.g. nitrilium triflates), it is only responsible to neutralize the superacid to avoid the protonation of both the secondary or tertiary amides.

INTRODUCTION

In recent years, many research papers have been published describing the versatile methodology for the synthesis of 9*H*-pyrrolo[1,2-*a*]indol-9-ones (fluorazones). Fluorazones and their analogues are still important targets for researchers due to their promising biological and pharmaceutical activities[1] as well as optical and electronic properties.[2] The fused tricyclic unit can be found in a wide range of biologically important compounds representing psychostimulant activity[1d] and cytotoxic properties.[3] Moreover, fluorazone serves as a precursor for 9*H*-pyrrolo[1,2-*a*]indole, the basic skeleton of cytostatic mytomycin derivatives.[4] In addition, our recent progress on developing novel chromophores demonstrated the promising application of dyes having fluorazone linker as photosensitizers for solar cells.[5]

Among the many methods developed for the synthesis of fluorazones, intramolecular ring closure reaction serves as classical technique.[6] Due to the growing interest, several new synthetic ways have been published in the last few years.[7] Direct cyclization strategies represent new approaches,[8] however, the scope of these methods is somewhat limited. Both the direct double metalation of substituted 1-phenylpyrroles followed by reaction with *N*,*N*-dimethylcarbamate carbonylating agent,[8a] and the Pd-catalyzed cyclocarbonilation[8c] restricted to the synthesis of specific regioisomers of substituted fluorazones, due to the directing effects of functional groups.[9] In addition, the preparation of the corresponding bromo or iodo derivatives applicable in cross-coupling reactions[5] is infeasible via these organometallic ways, as halogen-metal exchange can occur during these transformations.[8b,10]

On the other hand, classical type ring closure requires the derivatives of 2-(pyrrol-1-yl)benzoic acid (acid,[6a] acid chloride,[6b] aldehyde,[7a] benzyl alcohol,[7c] tertiary amide[11]) which could only be obtained in multi-step processes from anthranilic acids. Moreover, due to the sensitivity of the pyrrole moiety, the generally applied acidic or harsh reaction conditions for cyclizations (e.g. polyphosphoric acid[6a], chlorinating agent as PCl_5,[6b,11] strong Lewis acid[6b] or high temperature[7a]) usually lead to uncontrolled polymerization and decomposition, resulting low overall yields. Besides these methods, the one-pot sequential pyrrolation-cyclization of

anthranilic acids catalyzed by 4-chloropyridine hydrochloride and the intramolecular acylation of 2-(pyrrol-1-yl)benzoic acids in the presence of bis(trichloromethyl) carbonate offer simple procedures for the synthesis of fluorazones, however, we found these methods to have poor reproducibility.[12] Despite these facts, anthranilic acids have exceptional synthetic potential as a wide range of substituted derivatives are easily accessible. Therefore, the development of valuable alternative methods under mild reaction conditions would extend the scope of the known synthetic routes and provide an efficient access to a diverse array of fluorazones.

Amides are generally considered to be one of the least reactive carboxylic acid derivatives, thus their utilization for the synthesis of aromatic ketones by acylation[13] is less widespread compared to other Friedel-Crafts-type reagents.[14] Although, the chemoselective activation of amides in the presence of triflic anhydride (Tf_2O) has proven to be a powerful strategy in the past few years and this approach found a broad range of applications in synthetic organic chemistry.[15] Very recently, Huang and co-workers published the chemoselective synthesis of aromatic ketimines by the intermolecular coupling of arenes with secondary amides, where a subsequent acidic hydrolysis afforded the desired ketones (Scheme 1/a).[16] They found that Tf_2O-promoted nitrilium ion generation from secondary amides is a valuable method for the dehydrative coupling of electron-rich arenes such as anisole, *N*,*N*-dimethylaniline, furan, pyrrole or indole derivatives. It is worth mentioning that during the investigation of *N*-methylpyrrole a phthalic acid derived diamide was also involved to test chemoselectivtiy. Interestingly, the reaction showed preference for the secondary amido over the tertiary amido group affording the corresponding ketimine in excellent yield. This phenomenon is attributed to the fact that only a nitrilium intermediate formed from a secondary amide could serve as active electrophile during Tf_2O-activation.[17]

Our previous work with fluorazone-based conjugated systems and the recent developments on the field of amide activation inspired us to pursue a complementary strategy towards these heterocycles.[5] We aimed to develop operationally simple conditions that can be

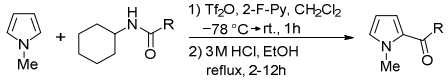
used to introduce a wide variety of benzo-substituted patterns within the 9*H*-pyrrolo[1,2-*a*]indoles scaffold. In this paper, the convenient synthesis of fluorazones via a Tf_2O-mediated intramolecular dehydrative cyclization is described. In addition, a simple one-pot synthesis of the key tertiary amide intermediates (**3**) from readily available anthranilic acids, and a study on the determination of the exact role of the base additive as a "missing piece" of the mechanism of Tf_2O-mediated amide activation are also presented.

RESULTS AND DISCUSSION

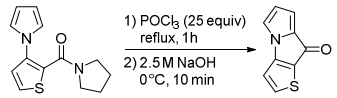
In order, to implement a novel intramolecular cyclization for fluorazone from amide derivatives, initially we investigated the synthesis of **3** precursors. We envisioned a simple one-pot strategy, where the amide group and the pyrrole moiety are formed in consecutive reactions from the functional groups of anthranilic acid. C-C bond formation by direct C-H functionalization, based on amide activation with Tf_2O has never been published for aromatic tertiary amides. However, considering the cyclization strategy of Rault and co-workers, *N*,*N*-disubstituted carboxamides are also potential functional groups for an intramolecular ring closure reaction (Scheme 1/b).[3] Additionally, the final hydrolytic step has decisive synthetic aspects, which depends on the amide precursor. Subsequent acidic hydrolysis of fused ketimine heterocycles requires elevated temperature, which can lead to product degradation.[7a] On the other hand, the hydrolysis of iminium salts formed by the reaction of tertiary amides can be achieved under mild basic conditions to afford ketones.[3] Therefore, we opted for merging the advantageous properties of the Tf_2O-activation technique and the application of tertiary amides as electrophilic reaction partners (Scheme 1/c).

Scheme 1. Methods for the Synthesis of α-Keto-pyrroles via Dehydrative C-C Coupling of Amides

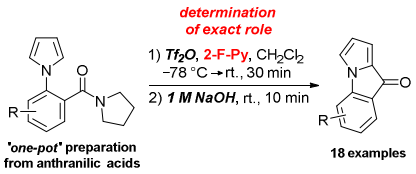
(a) Tf_2O-mediated activation of secondry amide



(b) $POCl_3$-mediated activation of tertiary amide



(c) This work: Tf_2O-mediated activation of tertiary amide

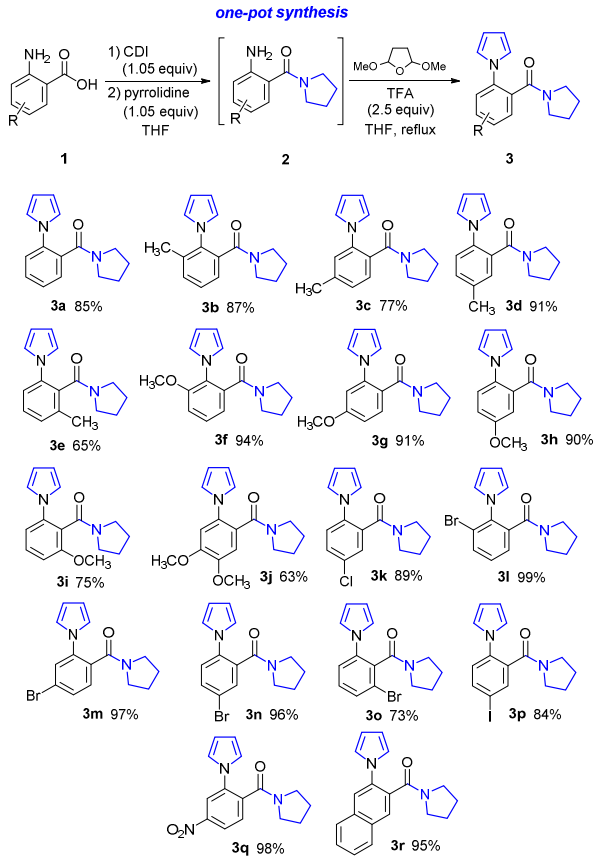


On the basis of our previous experience with 1-phenylpyrroles,[10,18] we optimized the overall transformation of the anthranilic acid derivatives (**1**) towards 1-arylpyrrole carboxamides (**3**, Scheme 2). Amide formation was promoted by 1,1'-carbonyldiimidazole (CDI) followed by the addition of pyrrolidine. The subsequent treatment of the reaction mixture with trifluoroacetic acid (TFA) using Clauson-Kaas synthesis with 2,5-dimethoxytetrahydrofurane afforded the desired 1-arylpyrrole derivative **3a** in excellent 85% yield. Tetrahydrofuran (THF) was found to be suitable solvent for both transformations to realize one-pot synthesis.

To our delight, applying this one-pot methodology a series of anthranilic acid derivatives bearing either electron-donating groups (Me, OMe, Scheme 2, **3b-j**) or electron-withdrawing groups (Cl, Br, I and NO_2, Scheme 2, **3k-q**) reacted smoothly to give the corresponding 1-arylpyrrole carboxamides **3b-q** in good to excellent yields (63−99%).

3-Amino-2-naphthoic acid (**1r**) reacted similarly affording the corresponding **3r** in 95% yield. Interestingly, in the cases of 6-substituted 2-aminobenzoic acids (**1e**, **1i**, **1o**) the amide formations via CDI activation showed the presence of a significant steric hindrance. Due to this phenomenon the activation-amide formation process gave satisfactory results only at high temperature. Consequently, the overall yields were slightly lower in these cases and compounds **3e**, **3i** and **3o** were obtained in yields of 65%, 75% and 73%, respectively (Scheme 2).

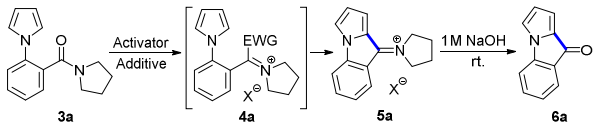
Scheme 2. One-pot Synthesis of 1-Arylpyrrole Derived Tertiary Amides



Recently, we have successfully applied Rault's method for the cyclization of **3n** and **3p** to prepare halo-substituted fluorazones. However, the corresponding 7-bromo- (**6n**) and 7-iodo (**6p**) products were obtained in good 81% and 78% yields,[5] respectively, showing that the $POCl_3$-promoted amide-activation suffers from disadvantages. On the one hand, the activator is used practically as the solvent of the reaction (25 equiv of $POCl_3$), which eventuate a

difficult work-up. On the other hand, the slow cyclization takes place only by means of heating (80 °C, 8h). Moreover, due to these reaction conditions and the large excess of the strong dehydrative agent, merely electron-withdrawing group stabilized arylpyrroles give good results (e.g. **6n** and **6p**), and in other cases significant acidic degradation can occur. An example of such event is the unsubstituted **3a** carboxamide, which was found to give fluorazone (**6a**) only in yield of 58%. In addition, the procedure was assayed for reducing the amount of $POCl_3$ used. Surprisingly, a more intense degradation took place in solvents such as CH_2Cl_2 or toluene (Table 1, entries 2 and 3), therefore fluorazone (**6a**) was isolated in only yields of 15% and 34%, respectively.

Table 1. Optimization of the Conditions of the Tf_2O-mediated Ring Closure Reaction[a]



Entry	Activator (equiv)	Additive (equiv)	Solvent	Yield of **6a** (%)[g]
1[b]	$POCl_3$ (25)	–	–	58
2[c]	$POCl_3$ (2.0)	–	CH_2Cl_2	15
3[b]	$POCl_3$ (2.0)	–	toluene	34
4[d]	Tf_2O (1.1)	–	CH_2Cl_2	64 (29)[h]
5[d]	Tf_2O (1.5)	–	CH_2Cl_2	62 (26)[h]
6[d]	Tf_2O (2.0)	–	CH_2Cl_2	68 (12)[h]
7[e]	Tf_2O (1.1)	–	CH_2Cl_2	79 (14)[h]
8[d,f]	Tf_2O (1.1)	2-F-Py (0.6)	CH_2Cl_2	82 (7)[h]
9[d,f]	Tf_2O (1.1)	2-F-Py (1.2)	CH_2Cl_2	91
10[d,f]	Tf_2O (1.1)	Py (1.2)	CH_2Cl_2	42 (38)[h]
11[d,i]	Tf_2O (1.1)	Py (1.2)[j]	CH_2Cl_2	88
12[d,i]	**Tf_2O (1.1)**	**2-F-Py (1.2)**	**CH_2Cl_2**	**93**
13[d,f]	Tf_2O (1.1)	TfOH (4.0)	CH_2Cl_2	8 (83)[h]

[a]Reaction conditions: 0.5 mmol **3a**, 1.2 mL solvent, **5a** was not isolated; in case of $POCl_3$: EWG = Cl, X = PO_2Cl_2; in case of Tf_2O: EWG, X = OTf. [b]8h (80 °C). [c]8h (40 °C). [d]30 min (5 min, –78 °C;

25 min –78 °C to rt). [e]45 h (5 min, –78 °C than rt). [f]Protocol A: additive was added before Tf_2O at –78 °C. [g]Isolated yields. [h]Recovered starting material. [i]Protocol B: additive was added after Tf_2O in 5 min at –78 °C. [j]Pyridine (Py) was added in consecutive 0.3 equiv portions.

After these discouraging results, we turned our attention to examine the feasibility of an efficient Tf_2O-mediated cyclization. In the first attempt, **3a** amide was treated with 1.1 equiv of Tf_2O in CH_2Cl_2 at −78 °C and after 5 min the mixture was allowed to warm to room temperature. We were pleased to determine that the reaction proceeded smoothly after 30 min, and with successive workup with aqueous NaOH and purification, fluorazone (**6a**) was isolated in yield of 64% (Table 1, entry 4). It is important to mention, that 29% of the starting material **3a** was also recovered. Increasing the amount of the activator to 1.5 or 2.0 equiv was nearly ineffective to accomplish complete conversion of **3a**, and fluorazone (**6a**) was obtained in the same yields, along with the amide precursor (entries 5 and 6). The effect of prolonged reaction time was also studied, however, the result was not remarkably better even after 45 h (entry 7). The transformation afforded the desired product (**6a**) in an increased yield of 79%, but residue of the starting material was still detectable (14% of **3a**).

As it was exemplified in different Tf_2O-mediated electrophilic activations of amides, the addition of non-nucleophilic basic additives was found to be crucial to achieve a considerable level of efficiency.[17,19] Substituted pyridines, especially 2-fluoropyridine (2-F-Py) was found to be generally eligible for this purpose.[19-20] On the basis of these findings, pretreatment of the solution of carboxamide **3a** with 2-F-Py followed by the addition of Tf_2O proved to be highly effective. Moreover, the complete activation of the amide **3a** was achieved using a slight excess of the base (1.2 equiv). Thus, this protocol resulted **6a** in excellent 91% yield (Table 1, entry 9).

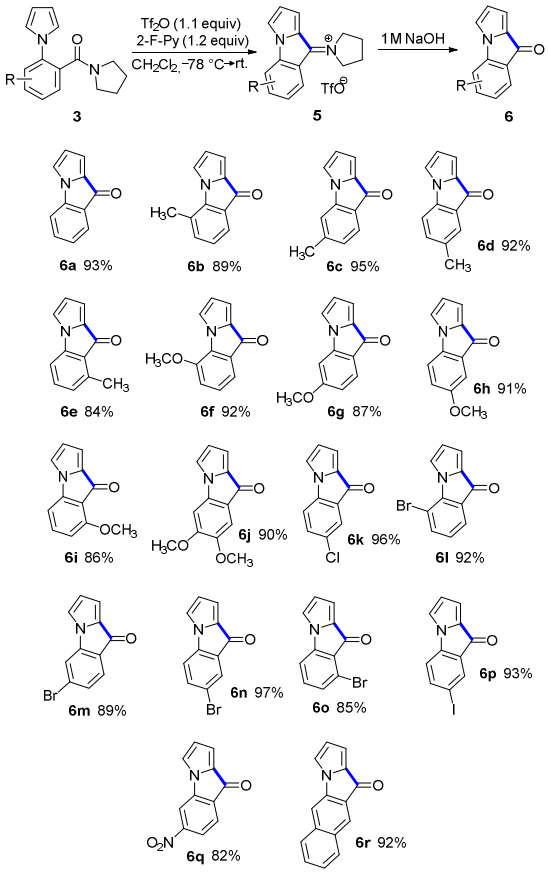
Although, unsubstituted pyridine (Py) would be the choice regarding to cost efficiency, 2-fluoropyridine is a more preferred base in many publications,[17,19,21] as it has a decreased nucleophilic character.[22] The low efficiency of pyridine could be partially attributed to the

formation of *N*-(trifluoromethylsulfonyl)-pyridinium triflate, which is a side product from the reaction of pyridine and Tf_2O.[19,23] Searching for a better understanding of this phenomenon, we decided to test pyridine as a base in our cyclization aiming to compare two approaches: namely the cases when the base is added before or after the activator. Pretreatment of the solution of **3a** with 1.2 equiv of pyridine followed by subsequent addition of 1.1 equiv of Tf_2O resulted in partial conversion only, therefore fluorazone **6a** was isolated in low 42% yield (Table 1, entry 10, Protocol A). Interestingly, in the case of the reverse order of reagent addition, unexpected result was observed. To minimize the undesired formation of *N*-(trifluoromethylsulfonyl)-pyridinium triflate, pyridine was added in consecutive 0.3 equiv portions at −78 °C after the activation of the amide with Tf_2O (Table 1, entry 11). To our surprise, this strategy proved to be highly effective leading to the complete conversion of **3a**, thus fluorazone was obtained in respectable 88% yield. Inspired by this result, we surveyed the ring closure of **3a** using the reversal addition protocol with 2-F-Py. In this case, the difference was not as significant as when pyridine was used, but by means of this approach, fluorazone was isolated in a slightly more increased yield (93%, Table 1, entry 12). Based on these results it can be concluded, that the order of the reagent addition could have a crucial role on the outcome of the activation process. Moreover, we were able to demonstrate, that pyridine could also serve as efficient base additive for Tf_2O-mediated electrophilic activation of amides employing 'post-treatment' strategy.

As a proof of concept, after the efficient reaction conditions for both the amido-pyrrole derivatization and intramolecular cyclization reactions were established, the substrate scope was studied (Scheme 3). This process was found to be effective in the presence of various carboxamides **3**, tolerating different functional groups on the benzene moiety. Thus the corresponding products (**6**) were obtained uniformly in high yields (82–97%). Using this procedure, derivatives bearing electron-donating groups (**6b-i**) were also efficiently cyclized into ketiminium salts. Moreover, the highly electron rich dimethoxy-substituted 1-arylpyrrole carboxamide (**3j**) also reacted smoothly, providing **6j** in 90% yield after hydrolysis

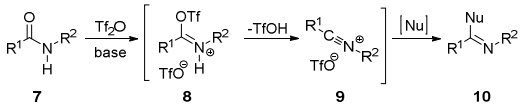
(Scheme 3). It is noteworthy, that these species (**6f-j**) may not be prepared using $POCl_3$-mediated amide activation, which was found to be detrimental for **6a** (Table 1, entries 1-3).

Scheme 3. Synthesis of Fluorazones by Tf_2O-Mediated Activation of Tertiary Amides



The mechanism of Tf_2O-promoted amide activation has been studied by several research groups to explore the nature of the transformation.[17,19,24] It has been revealed that nitrilium ion **9**, formed via an *O*-triflyliminium triflate intermediate **8**, serves as the active electrophile for the reaction of secondary amides (**7**) with various substrates (Scheme 4). It is important to note, that the studies published generally describe the fact that iminium triflates **8** can be obtained in complete conversion by a simple Tf_2O-activation. Additionally, it is also described in various publications, that the addition of an equivalent base is necessary to achieve a considerable level of efficiency. In spite of these findings, the exact role of the base additive still remained unclear.

Scheme 4. The Generally Proposed Mechanism of Tf_2O-Mediated Activation of Secondary Amides



Earlier attempts to describe the mechanism mainly focused on studying the activation step in the presence of pyridine. Charette and Gregon proposed that *N*-(trifluoromethylsulfonyl)-pyridinium triflate – formed by the reaction of triflic anhydride and pyridine – serves as the activating reagent in the initial stage of the reaction.[24] In contrast, later findings by others suggested, that this process could inhibit the amide activation significantly. In order to eliminate this disadvantageous effect of pyridine non-nucleophilic base additives were introduced to this field by Medley and Movassaghi.[21,25] Since their pioneering work 2-F-Py become a generally used reagent for the accomplishment of highly efficient electrophilic activations of amides. They observed, that optimal conditions require a balance between the need for a base additive to promote electrophilic activation of the amide substrate and avoidance of nucleophilic inhibition of the transformation. However, the specific role of the base during the amide activation step was not revealed. Very recently, Huang and co-wokers published an innovative study on the investigation of the exsistance of the presumed highly electrophilic nitrilium ion intermediate (**9**).[17] Its formation was proven by detailed NMR experiments due to the characteristic triplet resonance and the coupling constant of nitrilium moiety in ^{13}C NMR spectrum. Additionally, they examined the base-free amide activation, which showed, that the absence of base leads to partial conversion of the first formed *O*-triflyliminium triflate (**8**) into nitrilium ion (**9**) in a ratio of 37:63. They found, that the less reactive iminium triflate (**8**) was an unreactive species in the addition reaction to styrene, and it hydrolysed upon work-up to regenerate the initial amide in a considerable yield (31%). In addition, using an equivalent amount of 2-F-Py a complete conversion of *O*-triflyliminium triflate (**8**) into nitrilium ion (**9**) was determined by NMR.

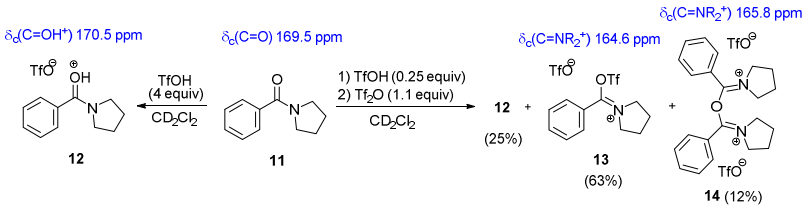
Reviewing the optimization of our Tf_2O-mediated ring closure reaction a very similar tendency can be observed (Table 1). In the case of substrate **3a**, complete transformation could be achieved only by the addition of 2-F-Py (entry 9), and absence of base resulted in the recovery of a significant amount of starting material (entry 4). However, the formation of nitrilium ion (**9**) from tertiary amide **3a** could not take place, the results obtained suggest, that the transformation of amide **3a** into ketiminium salt **5a** undergoes the same mechanistical steps. These experimental findings and the NMR study published by Huang and co-workers[17] inspired us to take a closer inspection of the reaction mechanism, focusing on founding evidence for the privileged role of the base additive.

Although, the effects of various bases on this transformation are well-studied, the effects of acids have never been investigated. Considering the fact, that base-free ring closures of **3a** resulted on average of 65% conversion (Table 1, entries 4–6), we envisioned that the concentration of the TfOH formed has the determinative role in the prevention of the ongoing reaction. To prove our assumption, the ring closure was implemented in the presence of a large excess of TfOH (4 equiv). To our delight, TfOH significantly inhibited the transformation, thus the initial amide was recovered in 83% yield (Table 1, entry 13). This novel approach clearly suggested, that the Tf_2O-activation of amide is inhibited by the increasing concentration of acid during the progress of the reaction. To provide experimental proofs for this suspicion a series of NMR experiments were carried out.

First, pyrrolidine derived benzamide (**11**), as a comparative model to **3a** was assayed for preliminary NMR studies.[26] Both, the effects of TfOH and Tf_2O were investigated (Scheme 5). The initial experiment was carried out by addition of an excess of acid (4 equiv TfOH) to **11** in CD_2Cl_2. However, decisive spectral changes were not observed, the slight upfield shift of proton signals indicated that TfOH interacts with amide **11**. In addition, the shift of the carbonyl carbon signal to higher ppm (from 169.5 to 170.5 ppm) also suggests that the lower electron density on the carbonyl carbon can be attributed to the protonation of amide **11** by TfOH (**12**). However, superacids are known to be able to protonate amides,[13] this

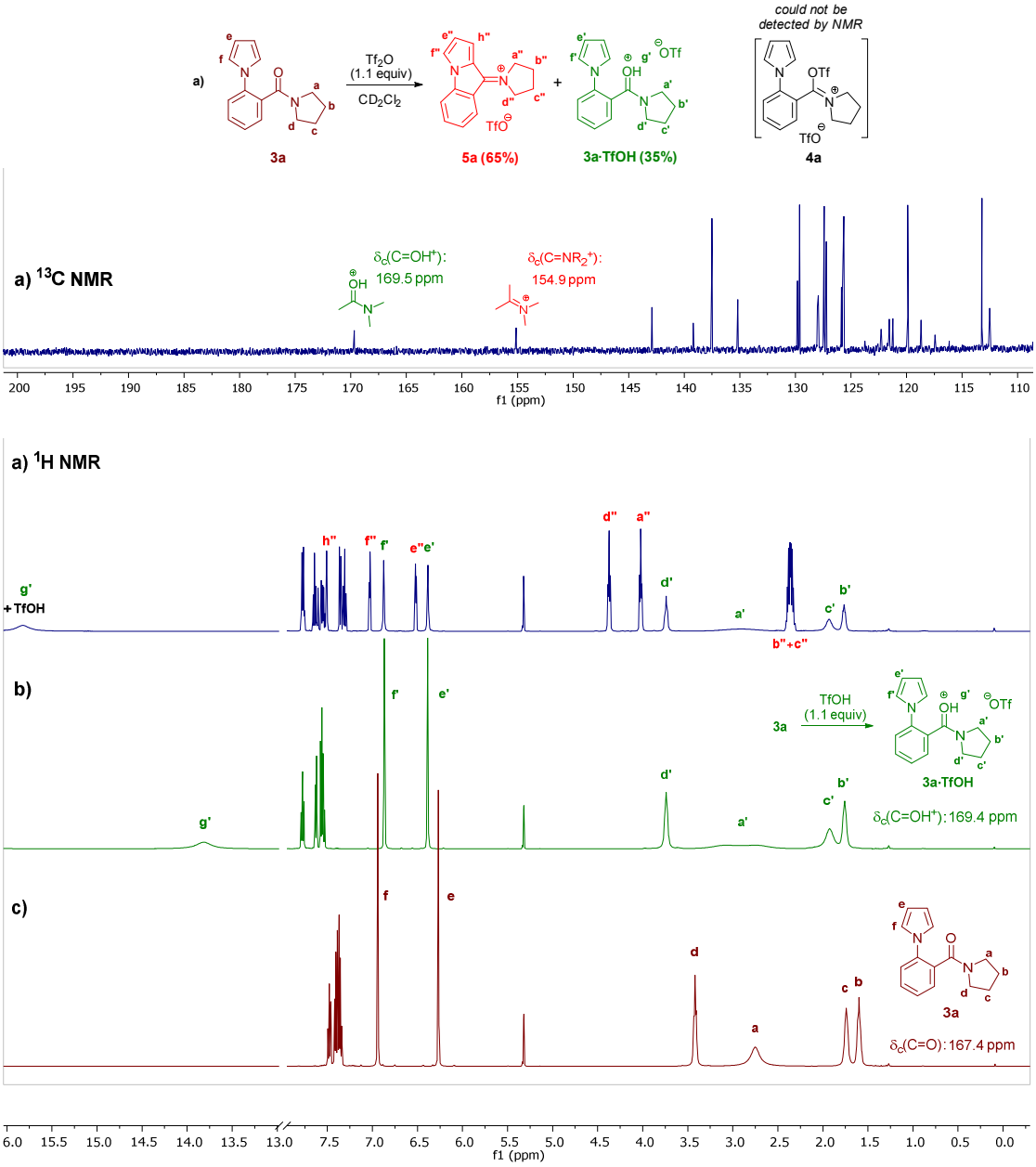
phenomenon has never been investigated in the field of Tf_2O-mediated amide activation. Generally, amide bonds tend to prefer *O*-protonation.[27] In order to found further evidence for the existence of **12**, the reaction of **11** and Tf_2O (1.1 equiv) in the presence of preliminary added TfOH (0.25 equiv) was also studied. To our delight, the protonated amount of **11** (25%) was unreactive towards Tf_2O. Additionally, along with *O*-triflyliminium derivative **13** (63%), the formation of a dicationic ether salt **14** from 12% of the starting amide was also observed, which presumably arise from the attack of amide **11** on the *O*-triflyliminium triflate **13** (Scheme 5).[24,26,28]

Scheme 5. Study of the Effect of Tf_2O/TfOH on the Activation of Pyrrolidine Derived Benzamide (11) by NMR



Next, tertiary amide **3a** was chosen for the mechanistic studies and base-free amide activation with Tf_2O was first investigated (Figure 1/a). After the addition of Tf_2O into the solution of amide **3a**, the formation of iminium salt **5a** with 65% conversion along with 35% of unreacted arylpyrrole derivative were observed (Figure 1/a, ^{1}H NMR). This result is in good accordance with that obtained in bench reaction, which afforded fluorazone **6a** in 64% yield (Table 1, entry 4). The existence of **5a** iminium salt was manifested by the characteristic chemical shift of the iminium carbon which appeared at δ_C = 154.9 ppm (Figure 1/a, ^{13}C NMR). Moreover, the ^{13}C NMR spectrum of the reaction mixture also showed the first decisive evidence for the nature of the unreacted compound. Although, remains of the easily formed *O*-triflyliminium triflate **4a** would have been expected based on literature,[17,24] the chemical shift of the corresponding carbon atom of the unknown species indicated a type of carbonyl compound (Figure 1/a, δ_C = 169.5 ppm). According to the preliminary NMR study of benzamide **11**, it was assumed that this unknown species is the protonated **3a**.

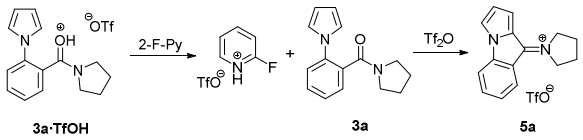
Figure 1. NMR Investigation of the Mechanism of the Tf_2O-mediated cyclodehydration of Tertiary Amide 3a



In order to prove the formation of **3a·TfOH**, the amide **3a** was treated with 1.1 equiv triflic acid in a separate experiment. Similarly, to the case of benzamide **11** (Scheme 5), the spectra obtained resulted only in a slight shifts of signals in both ^{1}H and ^{13}C NMR (^{1}H NMR, Figure 1/b) compared to the spectra of starting material **3a**. However, those spectral changes were not pivotal at first sight, the individual signals of spectrum Figure 1/b were exactly the same as the signals of the unknown species (Figure 1/a, ^{1}H NMR signals with green letters).[26]

As a consequence of these findings, we concluded that during the Tf_2O-mediated amide activation the triflic acid formed can easily protonate the starting amide. Thus it loses its nucleophilic character towards the anhydride and remains unreacted in the mixture. Therefore, the role of the base additive (e.g. 2-F-Py) could be attributed to its protective effect against protonation of the amide, via the neutralization of TfOH, which is produced in an equivalent amount during the transformation (Scheme 6). It is noteworthy, that the formation of *O*-triflyliminium triflate **4a** could not be detected by NMR experiment (Figure 1/a). Presumably, due to its high reactivity, it transformed instantaneously into iminium salt **5a**.

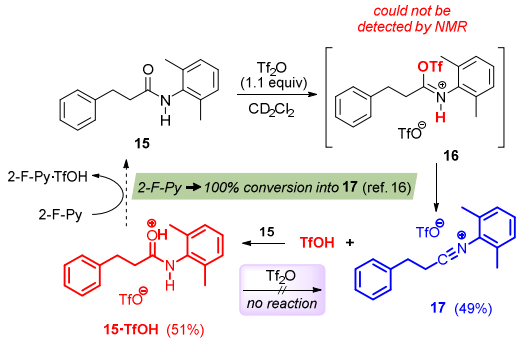
Scheme 6. Role of the Base Additive in the Activation Process of Amide 3a



In order to provide additional evidence for the above described mechanism, finally a secondary amide was involved in the same detailed NMR experiments as in the case of **3a** (Scheme 7). 2,6-Xylidene derived phenylpropanoic amide **15**, a model recently investigated by Huang and co-workers[17] was chosen to identify the protonation process and add a complementary study towards this transformation. Recently, they have shown by NMR investigations that the complete activation of **15** by Tf_2O can be achieved via the addition of equivalent amount of 2-F-Py.[17] Our results obtained from the investigation of the effects of Tf_2O/TfOH on **15** by NMR confirmed that secondary amides can also undergo protonation by the formed superacid.[26] Moreover, we have found, that – contrary to previous suspicion[17] –the formation *O*-triflyliminium derivative **16** could not be observed in this case neither, similarly to the case of tertiary amide **3a** (Figure 1).[26] Due to its high instability, species **16** immediately converts into nitrilium ion **17** and triflic acid. The results obtained also confirmed that the partial conversion of amide **15** (49%) into nitrilium triflate **17** in a base-free method is attributed to the protonation of the secondary amide moiety (**15·TfOH**, 51%,

Scheme 7).[26] Thus, according to these findings it can be conclude, that the base is not involved in the transformation of *O*-triflyliminium derivative **16** into nitrilium triflate **17**, only responsible to neutralize the acid.

Scheme 7. Plausible Mechanism of the Tf_2O-Mediated Activation of Secondary Amides



CONCLUSION

In summary, we have successfully developed a mild intramolecular cyclodehydration process through Tf_2O-mediated activation of aromatic tertiary amides. The methodology was applied for the synthesis of a wide range of fluorazones. Comparison of a series of benzo-substituted patterns demonstrated the high functional group tolerance of the transformation. In addition, we have shown evidence for the exact role of the base additive as a 'missing piece' of the reaction mechanism of Tf_2O-mediated activation of amides. Detailed NMR studies have revealed, that the base additive is not involved to promote the transformation of *O*-triflyliminium triflates into reactive species (e.g. nitrilium triflate **13**), but through neutralization its role is to avoid the easy protonation of amides by the superacid (TfOH) formed. We expect this mechanistic finding to be useful for the application of Tf_2O-activation strategies.

EXPERIMENTAL SECTION

General Information. All starting materials were purchased from commercial source and were used without further purification. Anhydrous solvents were typically dried and stored over 4 Å molecular sieves. All glassware was oven-dried prior to use. The reactions were

carried out in Schlenk-flasks under a dry nitrogen atmosphere. Reactions were monitored by thin-layer chromatography or LC-MS. TLC was carried out on Kieselgel 60 F254 aluminium sheets, visualization of the product was made by exposing the plate to UV radiation or by staining it with the aqueous solution of $(NH_4)_6Mo_7O_{24}$, $Ce(SO_4)_2$ and sulphuric acid. Flash column chromatography was performed using gradient elution in normal (silica column; hexane – ethyl acetate) or reversed phase modes (C18-silica column; water (0.1% NH_4OAc) – acetonitrile (0.1% NH_4OAc + 8% water)) Sample loadings were performed in case of silica flash column by drying the sample onto silica cartridge, in case of C18-silica flash column by direct liquid injections of the concentrate solutions of the samples in DMF. Routine ^1H and ^{13}C spectra were obtained on 300 or 500 MHz spectrometers. The chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) in Hz. Deuterated chloroform ($CDCl_3$) with tetramethylsilane (TMS), methylene chloride-d_2 (CD_2Cl_2) and dimethyl sulfoxide-d_6 (DMSO-d_6) were used as solvents, and signal positions were measured relative to the signals of TMS or the residual peak of solvents (δ_{TMS} = 0 ppm, $\delta_{CH_2Cl_2}$ = 5.32 ppm, δ_{DMSO} = 2.50 ppm for ^1H NMR and δ_{TMS} = 0 ppm, $\delta_{CH_2Cl_2}$ = 53.8 ppm, δ_{DMSO} = 39.5 ppm for ^{13}C NMR). Infrared spectra are reported in reciprocal centimetres (cm^{-1}). Melting points were obtained on a melting point apparatus and are uncorrected. LC-MS was performed on an HPLC system using Gemini RP C18 column (150 × 4.6 mm, 3μm, 256 nm, 40°C, 0.6 mL/min, gradient elution: water (0.1% NH_4HCO_3) – acetonitrile (0.1% NH_4HCO_3 + 8% water) in ESI mode. High resolution mass spectra were performed by positive electrospray ionization on a TOF analyzer. The ^{79}Br (*M* = 78.9183371) and the ^{35}Cl (*M* = 34.9688527) isotopes were used for the calculation and data interpretation of these halogen containing compounds.

Experimental procedures and characterisation data.

General procedure for the one-pot synthesis of tertiary amides 3a-r.

To an extensively stirred solution of 2-aminobenzoic acid derivative (**1**, 10.0 mmol) in dry THF (6 mL) carbonyldiimidazole (CDI, 10.5 mmol, 1.70 g) was added in small portions at room temperature. The obtained slurry mixture was stirred for a further 15 min, than pyrrolidine (10.5 mmol, 0.86 mL) was added, resulted in a clear solution. After stirring for 15 min, trifluoroacetic acid (30.0 mmol, 2.30 mL) and 2,5-dimethoxytetrahydrofuran (12.0 mmol, 1.55 mL) were added and the mixture was kept at 80 °C for 30 min. After cooling, RO-water (30 mL, water purified by reverse osmosis technique) was added and extracted with ethyl acetate (3 × 30 ml). The combined organic phases were treated with a solution of $NaHCO_3$ (2 M in water, 10 mL) for neutralization, and after phase separation the organic layer was dried over sodium sulphate and concentrated on a rotary evaporator. The concentrate solution of the crude product was filtered through a pad of silica, eluted completely with a mixture of 30% hexane in ethyl acetate and concentrated *in vacuo* to yield pure products (purities >96% (HPLC)). The steps of the one-pot reactions were monitored by TLC. Analytical pure compounds **3** were prepared by flash column chromatography on silica using gradient elution of hexane and ethyl acetate.

Characterisation data of tertiary amides 3a-r.

(2-(1*H*-Pyrrol-1-yl)phenyl)(pyrrolidin-1-yl)methanone (3a).

Following the general procedure, the known amide **3a**[11] was obtained as an off white solid (2.04 g, 85%). R_f = 0.38 (eluent: Hexane/EtOAc = 1/2); m.p. 53−54 °C; ν_{max} (KBr) 2975, 2964, 1698, 1624, 1507, 1474, 1419, 1338 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 − 7.41 (m, 2H), 7.40 − 7.30 (m, 2H), 6.97 (dd, J = 2.2, 2,1 Hz, 2H), 6.28 (dd, J = 2.2, 2.1 Hz, 2H), 3.48 (t, J = 6.9 Hz, 2H), 2.72 (br.s, 2H), 1.75 (dt, J = 13.2, 6.4 Hz, 2H), 1.59 (dt, J = 13.2, 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 137.2, 132.3, 130.3, 128.5, 126.75, 124.1, 121.1 (2C), 110.2 (2C), 47.1, 45.4, 25.6, 24.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{16}N_2O$ 241.1341; Found 241.1347.

(3-Methyl-2-(1*H*-pyrrol-1-yl)phenyl)(pyrrolidin-1-yl)methanone (3b).

Following the general procedure **3b** was obtained as a slightly yellow solid (2.21 g, 87%). R_f = 0.60 (eluent: Hexane/EtOAc = 1/2); m.p. 61−63 °C; ν_{max} (KBr) 3097, 2980, 2876, 1734, 1616, 1518, 1435, 1375, 1229 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 − 7.27 (m, 2H), 7.25 − 7.15 (m, 1H), 6.75 (br.s, 2H), 6.25 (t, J = 1.8 Hz, 2H), 3.36 (t, J = 6.6 Hz, 2H), 3.01 (t, J = 6.4 Hz, 1H), 2.17 (s, 3H), 1.75 (dt, J = 12.9, 6.3 Hz, 2H), 1.67 (dt, J = 12.9, 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 136.4, 136.4, 135.5, 131.5, 128.0, 124.6, 122.1 (2C), 108.8 (2C), 48.1, 45.1, 25.6, 24.4, 17.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{19}N_2O$ 255.1497; Found 255.1491.

(4-Methyl-2-(1*H*-pyrrol-1-yl)phenyl)(pyrrolidin-1-yl)methanone (3c).

Following the general procedure **3c** was obtained as a slightly yellow solid (1.96 g, 77%). R_f = 0.58 (eluent: Hexane/EtOAc = 1/2); m.p. 110−111 °C; ν_{max} (KBr) 3101, 3058, 2982, 2877, 1739, 1609, 1507, 1435, 1333, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 7.7 Hz, 1H), 7.17 (s, 1H), 7.15 (d, J = 7.7 Hz, 1H), 6.95 (t, J = 2.1 Hz, 2H), 6.27 (t, J = 2.1 Hz, 2H), 3.47 (t, J = 7.0 Hz, 2H), 2.71 (br.s, 2H), 2.41 (s, 3H), 1.74 (dt, J = 13.9, 6.6 Hz, 2H), 1.58 (dt, J = 13.9, 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 140.5, 137.2, 129.4, 128.4, 127.5, 124.6, 121.0 (2C), 110.1 (2C), 47.1, 45.4, 25.6, 24.3, 21.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{19}N_2O$ 255.1497; Found 255.1499.

(5-Methyl-2-(1*H*-pyrrol-1-yl)phenyl)(pyrrolidin-1-yl)methanone (3d).

Following the general procedure **3d** was obtained as a yellow solid (2.31 g, 91%). R_f = 0.59 (eluent: Hexane/EtOAc = 1/2); m.p. 81−82 °C; ν_{max} (KBr) 2973, 2874, 1635, 1558, 1509, 1430, 1319, 1247 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 − 7.22 (m, 3H), 6.93 (t, J = 2.1 Hz, 2H), 6.26 (t, J = 2.1 Hz, 2H), 3.47 (br.s, 2H), 2.72 (br.s, 2H), 2.39 (s, 3H), 1.82 − 1.66 (m, 2H), 1.65 − 1.51 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 136.7, 134.9, 132.1, 130.9, 128.8, 124.0, 121.1 (2C), 109.9 (2C), 47.1, 45.4, 25.5, 24.3, 20.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{19}N_2O$ 255.1497; Found 255.1495.

(6-Methyl-2-(1*H*-pyrrol-1-yl)phenyl)(pyrrolidin-1-yl)methanone (3e).

The activation step by CDI was implemented at reflux temperature. With this exception, following the general procedure **3e** was obtained as a slightly yellow solid (1.65 g, 65%). R_f = 0.62 (eluent: Hexane/EtOAc = 1/2); m.p. 76–77 °C; ν_{max} (KBr) 3124, 2975, 2875, 1733, 1624, 1490, 1420, 1333, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (t, J = 7.7 Hz, 1H), 7.18 (d, J = 7.7 Hz, 2H), 6.98 (t, J = 2.2 Hz, 2H), 6.25 (t, J = 2.2 Hz, 2H), 3.53 (dt, J = 12.3, 6.8 Hz, 1H), 3.39 (dt, J = 12.3, 6.8 Hz, 1H), 2.88 (dt, J = 10.7, 6.7 Hz, 1H), 2.69 (dt, J = 10.7, 6.7 Hz, 1H), 2.36 (s, 3H), 1.97 − 1.36 (sym. m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 137.3, 136.1, 132.6, 129.4, 128.6, 122.1, 121.5 (2C), 109.7 (2C), 47.2, 45.0, 25.5, 24.4, 19.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{19}N_2O$ 255.1497; Found 255.1506.

(3-Methoxy-2-(1*H*-pyrrol-1-yl)phenyl)(pyrrolidin-1-yl)methanone (3f).

Following the general procedure **3f** was obtained as a slightly yellow solid (2.54 g, 94%). R_f = 0.47 (eluent: Hexane/EtOAc = 1/2); m.p. 67–68 °C; ν_{max} (KBr) 3104, 2971, 2882, 1738, 1617, 1499, 1428, 1337, 1230 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (t, J = 7.9 Hz, 1H), 7.04 (d, J = 7.9 Hz, 1H), 7.01 (d, J = 7.9 Hz, 1H), 6.89 (s, 2H), 6.24 (s, 2H), 3.81 (s, 3H), 3.38 (t, J = 6.2 Hz, 2H), 2.88 (t, J = 6.2 Hz, 2H), 1.74 (p, J = 6.2 Hz, 2H), 1.61 (p, J = 6.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 153.8, 136.0, 128.5, 126.5, 122.5 (2C), 119.4, 112.8, 108.7 (2C), 56.2, 47.6, 45.2, 25.6, 24.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{19}N_2O_2$ 271.1447; Found 271.1439.

(4-Methoxy-2-(1*H*-pyrrol-1-yl)phenyl)(pyrrolidin-1-yl)methanone (3g).

Following the general procedure **3g** was obtained as a slightly yellow solid (2.46 g, 91%). R_f = 0.44 (eluent: Hexane/EtOAc = 1/2); m.p. 105–106 °C; ν_{max} (KBr) 3116, 3095, 2971, 2878, 1733, 1608, 1489, 1412, 1350, 1234 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 − 7.33 (m, 1H), 6.95 (t, J = 2.0 Hz, 2H), 6.88 (dd, J = 6.0, 2.4 Hz, 1H), 6.87 (s, 1H), 6.28 (t, J = 2.0 Hz, 2H), 3.85 (s, 3H), 3.46 (t, J = 7.0 Hz, 2H), 2.69 (br.s, 2H), 1.74 (p, J = 6.8 Hz, 2H), 1.58 (p, J = 6.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 160.9, 138.6, 129.9, 124.7,

121.0 (2C), 112.3, 110.3 (2C), 109.5, 55.6, 47.1, 45.5, 25.6, 24.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{19}N_2O_2$ 271.1447; Found 271.1449.

(5-Methoxy-2-(1*H*-pyrrol-1-yl)phenyl)(pyrrolidin-1-yl)methanone (3h).

Following the general procedure **3h** was obtained as a slightly yellow solid (2.43 g, 90%). R_f = 0.47 (eluent: Hexane/EtOAc = 1/2); m.p. 96–97 °C; ν_{max} (KBr) 2971, 2881, 2840, 1733, 1634, 1488, 1434, 1294, 1231 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 8.1 Hz, 1H), 7.05 − 6.93 (m, 2H), 6.90 (t, J = 2.0 Hz, 2H), 6.25 (t, J = 2.0 Hz, 2H), 3.84 (s, 3H), 3.46 (t, J = 6.9 Hz, 2H), 2.77 (br.s, 2H), 1.74 (p, J = 6.2 Hz, 1H), 1.59 (p, J = 6.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 158.2, 133.4, 130.6, 125.7, 121.2 (2C), 116.4, 112.5, 109.7 (2C), 55.7, 47.2, 45.4, 25.5, 24.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{19}N_2O_2$ 271.1447; Found 271.1443.

(6-Methoxy-2-(1*H*-pyrrol-1-yl)phenyl)(pyrrolidin-1-yl)methanone (3i).

The activation step by CDI was implemented at reflux temperature. With this exception, following the general procedure **3i** was obtained as a slightly yellow solid (2.03 g, 75%). R_f = 0.56 (eluent: Hexane/EtOAc = 1/2); m.p. 131–132 °C; ν_{max} (KBr) 3128, 2884, 2842, 1733, 1636, 1492, 1420, 1290, 1251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (t, J = 8.2 Hz, 1H), 6.99 (t, J = 2.1 Hz, 2H), 6.97 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.25 (t, J = 2.1 Hz, 2H), 3.88 (s, 3H), 3.59 (dt, J = 12.5, 6.7 Hz, 1H), 3.38 (dt, J = 12.5, 6.7 Hz, 1H), 3.02 (dt, J = 10.5, 6.5 Hz, 1H), 2.76 (dt, J = 10.5, 6.5 Hz, 1H), 1.96 − 1.41 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 156.7, 138.5, 130.3, 122.2, 121.4 (2C), 116.9, 109.8 (2C), 109.2, 56.2, 47.2, 45.1, 25.5, 24.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{19}N_2O_2$ 271.1447; Found 271.1445.

(4,5-Dimethoxy-2-(1*H*-pyrrol-1-yl)phenyl)(pyrrolidin-1-yl)methanone (3j).

Following the general procedure **3j** was obtained as a slightly yellow solid (1.70 g, 63%). R_f = 0.53 (eluent: Hexane/EtOAc = 1/2); m.p. 134–135 °C; ν_{max} (KBr) 3096, 2971, 2882, 1737, 1615, 1530, 1435, 1291, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.92 (t,

J = 1.9 Hz, 2H), 6.85 (s, 1H), 6.27 (t, *J* = 1.9 Hz, 2H), 3.92 (s, 6H), 3.46 (t, *J* = 7.0 Hz, 2H), 2.72 (s, 2H), 1.74 (p, *J* = 6.4 Hz, 2H), 1.59 (p, *J* = 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 150.1, 147.8, 130.9, 124.1, 121.1 (2C), 110.7, 109.9 (2C), 107.7, 56.2, 56.2, 47.2, 45.5, 25.6, 24.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{21}N_2O_3$ 301.1552; Found 301.1547.

(5-Chloro-2-(1*H*-pyrrol-1-yl)phenyl)(pyrrolidin-1-yl)methanone (3k).

Following the general procedure **3k** was obtained as a slightly yellow solid (2.44 g, 89%). R_f = 0.30 (eluent: Hexane/EtOAc = 4/1); m.p. 83−84 °C; ν_{max} (KBr) 2974, 2926, 2876, 1627, 1476, 1431, 1389, 1277, 1202 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 − 7.38 (m, 2H), 7.31 (d, *J* = 8.5 Hz, 1H), 6.93 (t, *J* = 2.1 Hz, 2H), 6.29 (t, *J* = 2.1 Hz, 2H), 3.47 (t, *J* = 6.9 Hz, 2H), 2.73 (br.s, 2H), 1.75 (p, *J* = 6.3 Hz, 2H), 1.61 (p, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 135.8, 133.5, 132.4, 130.3, 128.6, 125.4, 121.0 (2C), 110.6 (2C), 47.1, 45.5, 25.5, 24.2; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{16}ClN_2O$ 275.0951; Found 275.0944.

(3-Bromo-2-(1*H*-pyrrol-1-yl)phenyl)(pyrrolidin-1-yl)methanone (3l).

Following the general procedure **3l** was obtained as a slightly yellow solid (3.15 g, 99%). R_f = 0.38 (eluent: Hexane/EtOAc = 1/2); m.p. 120−121 °C; ν_{max} (KBr) 3097, 2968, 2857, 1629, 1541, 1426, 1338, 1309, 1190 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.36 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.28 (t, *J* = 7.7 Hz, 1H), 6.83 (t, *J* = 1.7 Hz, 2H), 6.28 (t, *J* = 1.7 Hz, 2H), 3.36 (t, *J* = 6.2 Hz, 2H), 2.99 (t, *J* = 6.4 Hz, 2H), 1.76 (dt, *J* = 12.7, 5.6 Hz, 2H), 1.68 (dt, *J* = 12.7, 5.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 138.3, 131.0, 130.0, 129.8, 127.0, 123.6, 120.9 (2C), 110.8 (2C), 47.1, 45.5, 25.5, 24.2; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{16}BrN_2O$ 319.0446; Found 319.0452.

(4-Bromo-2-(1*H*-pyrrol-1-yl)phenyl)(pyrrolidin-1-yl)methanone (3m).

Following the general procedure **3m** was obtained as a slightly yellow solid (3.08 g, 97%). R_f = 0.23 (eluent: Hexane/EtOAc = 4/1); m.p. 82−83 °C; ν_{max} (KBr) 3094, 2977, 2883, 1617, 1590, 1496, 1437, 1319, 1199 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 1.9 Hz, 1H),

7.48 (dd, J = 8.1, 1.9 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 6.94 (t, J = 2.2 Hz, 2H), 6.29 (t, J = 2.2 Hz, 2H), 3.47 (t, J = 6.9 Hz, 2H), 2.70 (br.s, 2H), 1.75 (p, J = 6.6 Hz, 2H), 1.60 (p, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 138.3, 131.0, 130.0, 129.8, 127.0, 123.6, 120.9 (2C), 110.8 (2C), 47.1, 45.5, 25.5, 24.2; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{16}BrN_2O$ 319.0446; Found 319.0437.

(5-Bromo-2-(1*H*-pyrrol-1-yl)phenyl)(pyrrolidin-1-yl)methanone (3n).

Following the general procedure the known **3n**[5] was obtained as a slightly yellow solid (3.05 g, 96%). R_f = 0.31 (eluent: Hexane/EtOAc = 4/1); m.p. 92−93 °C; ν_{max} (KBr) 3098, 3061, 2973, 2878, 1627, 1489, 1431, 1386, 1322, 1104 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 − 7.50 (m, 2H), 7.24 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 2.1 Hz, 2H), 6.29 (d, J = 2.1 Hz, 2H), 3.46 (t, J = 6.8 Hz, 2H), 2.72 (br.s, 2H), 1.75 (p, J = 6.6 Hz, 2H), 1.61 (p, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 136.3, 133.8, 133.3, 131.5, 125.7, 121.0 (2C), 120.1, 110.7 (2C), 47.1, 45.5, 25.6, 24.2; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{16}BrN_2O$ 319.0446; Found 319.0453.

(6-Bromo-2-(1*H*-pyrrol-1-yl)phenyl)(pyrrolidin-1-yl)methanone (3o).

The activation step by CDI was implemented at reflux temperature. With this exception, following the general procedure **3o** was obtained as a slightly yellow solid (2.33 g, 73%). R_f = 0.33 (eluent: Hexane/EtOAc = 1/2); m.p. 128−129 °C; ν_{max} (KBr) 3098, 2968, 2857, 1629, 1558, 1493, 1338, 1309, 1135 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, J = 6.5, 2.5 Hz, 1H), 7.31 (s, 1H) 7.30 (dd, J = 12.5, 7.9 Hz, 1H), 6.98 (t, J = 2.1 Hz, 2H), 6.27 (t, J = 2.1 Hz, 2H), 3.58 (dt, J = 12.5, 6.3 Hz, 1H), 3.40 (dt, J = 12.5, 6.3 Hz, 1H), 3.05 (dt, J = 10.7, 6.3 Hz, 1H), 2.74 (dt, J = 10.7, 6.3 Hz, 1H), 1.94 − 1.51 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 138.9, 134.5, 131.0, 130.5, 124.0, 121.6 (2C), 120.5, 110.3 (2C), 47.3, 45.2, 25.6, 24.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{16}BrN_2O$ 319.0446; Found 319.0458.

(5-Iodo-2-(1*H*-pyrrol-1-yl)phenyl)(pyrrolidin-1-yl)methanone (3p).

Following the general procedure the known **3p**[5] was obtained as a yellow solid (3.07 g, 84%). R_f = 0.52 (eluent: Hexane/EtOAc = 1/2); m.p. 132−133 °C; ν_{max} (KBr) 3109, 3069, 2968, 2883, 1612, 1470, 1381, 1340, 1227, 1105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 − 7.62 (m, 2H), 7.11 (d, J = 8.7 Hz, 1H), 6.93 (t, J = 2.1 Hz, 2H), 6.29 (t, J = 2.1 Hz, 2H), 3.46 (t, J = 6.7 Hz, 2H), 2.71 (br.s, 2H), 1.84 − 1.67 (m, 2H), 1.67 − 1.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 139.2, 137.3, 136.9, 133.9, 125.8, 120.9 (2C), 110.7 (2C), 90.9, 47.1, 45.5, 25.5, 24.2; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{16}IN_2O$ 367.0307; Found 367.0305.

(4-Nitro-2-(1*H*-pyrrol-1-yl)phenyl)(pyrrolidin-1-yl)methanone (3q).

The activation step by CDI was implemented at reflux temperature. With this exception, following the general procedure **3q** was obtained as a yellow solid (2.78 g, 98%). R_f = 0.15 (eluent: Hexane/EtOAc = 4/1); m.p. 125−126 °C; ν_{max} (KBr) 3105, 3035, 2974, 2879, 1617, 1525, 1492, 1447, 1387, 1199 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.19 (d, J = 8.2 Hz, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.02 (s, 2H), 6.35 (s, 2H), 3.51 (t, J = 6.7 Hz, 2H), 2.72 (br.s, 2H), 1.94 − 1.71 (m, 2H), 1.71 − 1.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 148.7, 138.2, 137.6, 130.0, 121.3, 121.0 (2C), 119.2, 111.6 (2C), 47.0, 45.7, 25.6, 24.2; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{16}N_3O_3$ 286.1113; Found 286.1107.

(3-(1*H*-Pyrrol-1-yl)naphthalen-2-yl)(pyrrolidin-1-yl)methanone (3r).

Following the general procedure **3r** was obtained as a yellow oil (2.76 g, 95%). R_f = 0.38 (eluent: Hexane/EtOAc = 1/2); ν_{max} (KBr) 2971, 2876, 1624, 1488, 1424, 1361, 1316, 1225, 1192 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.86 (t, J = 8.5 Hz, 2H), 7.81 (s, 1H), 7.54 (qt, J = 6.9, 3.5 Hz, 2H), 7.07 (t, J = 2.0 Hz, 2H), 6.32 (t, J = 2.0 Hz, 2H), 3.52 (t, J = 6.8 Hz, 2H), 2.78 (br.s, 2H), 1.76 (p, J = 6.4 Hz, 2H), 1.59 (p, J = 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 135.2, 133.7, 131.8, 131.5, 128.3, 128.1, 127.7, 127.5, 126.6, 122.1, 121.5 (2C), 110.3 (2C), 47.4, 45.5, 25.6, 24.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{19}N_2O$ 291.1497; Found 291.1499.

General procedure for the synthesis of fluorazones 6a-r.

To an oven-dried and nitrogen-flushed 10 mL Schlenk tube with a magnetic stirrer was added the amide (**3**, 0.5 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (1.2 mL). The reaction mixture was cooled to −78 °C. Triflic anhydride (93 μL, 0.55 mmol, 1.1 equiv) was added dropwise via syringe, the reaction mixture was stirred for 5 min at −78 °C, than 2-fluoropyridine (2-F-Py) (52 μL, 0.6 mmol, 1.2 equiv) was added via syringe. The mixture was stirred for additional 5 min at −78 °C, than was allowed to warm to rt. After 20 min the reaction was quenched by the addition of MeOH (1 mL) at 0 °C. The mixture was evaporated under reduced pressure until the removal of CH_2Cl_2, then solution of NaOH (3 mL, 1 M) was added dropwise and stirred at rt for 10 min. The product was extracted with EtOAc (3 x 5 ml). The collected organic layers were dried over sodium sulphate and concentrated. The residue thus obtained was purified by flash chromatography over high performance reversed phased silica gel (24 g column) Fractions containing 9*H*-pyrrolo[1,2-*a*]indol-9-ones (**6**) were concentrated, the residue was dissolved in CH_2Cl_2, dried over the mixture of sodium sulphate and sodium bicarbonate and were concentrated to dryness.

Characterisation data of fluorazones 6a-r.

9*H*-Pyrrolo[1,2-*a*]indol-9-one (6a).

Following the general procedure the known **6a**[8c] was obtained as a yellow solid (314 mg, 93%). $R_f = 0.72$ (eluent: Hexane/EtOAc = 3/2); m.p. 115−116 °C; ν_{max} (KBr) 3118, 1698, 1617, 1542, 1522, 1457, 1339 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.19 − 7.03 (m, 3H), 6.78 (d, J = 3.3 Hz, 1H), 6.31 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7, 143.8, 134.1, 132.0, 130.3, 125.5, 124.5, 119.5, 115.9, 114.0, 110.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_7NO$ 170.0600; Found 170.0593.

5-Methyl-9*H*-pyrrolo[1,2-*a*]indol-9-one (6b).

Following the general procedure the known **6b**[7d] was obtained as a yellow solid (326 mg, 89%). $R_f = 0.70$ (eluent: Hexane/EtOAc = 3/2); m.p. 119−120 °C; ν_{max} (KBr) 3109, 1698, 1623, 1522, 1489, 1436, 1339 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (t, J = 7.8 Hz, 1H),

7.02 (d, J = 1.9 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 6.87 (d, J = 7.8 Hz, 1H), 6.73 (d, J = 3.5 Hz, 1H), 6.28 (dd, J = 3.5, 2.7 Hz, 1H), 2.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.1, 144.1, 139.9, 133.4, 132.1, 128.1, 127.0, 118.6, 115.5, 113.0, 107.8, 17.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_9NO$ 184.0757; Found 184.0761.

6-Methyl-9*H*-pyrrolo[1,2-*a*]indol-9-one (6c).

Following the general procedure the known **6c**[8c] was obtained as a yellow solid (345 mg, 95%). R_f = 0.74 (eluent: Hexane/EtOAc = 3/2); m.p. 140−141 °C; ν_{max} (KBr) 3115, 1684, 1624, 1522, 1457, 1309, 1247 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 7.9 Hz, 1H), 7.03 (dd, J = 2.4, 0.4 Hz, 1H), 6.95 – 6.87 (m, 2H), 6.74 (d, J = 3.6 Hz, 1H), 6.28 (dd, J = 3.6, 2.8 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7, 145.6, 144.2, 132.4, 127.8, 125.9, 124.4, 119.1, 115.6, 113.6, 111.2, 22.2; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_9NO$ 184.0757; Found 184.0755.

7-Methyl-9*H*-pyrrolo[1,2-*a*]indol-9-one (6d).

Following the general procedure the known **6d**[8c] was obtained as a yellow solid (337 mg, 92%). R_f = 0.61 (eluent: Hexane/EtOAc = 4/1); m.p. 99−101 °C; ν_{max} (KBr) 3117, 2879, 1683, 1558, 1473, 1360, 1216, 1080 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 1H), 7.16 (d, J = 7.8 Hz, 1H), 7.00 (s, 1H), 6.94 (d, J = 7.8 Hz, 1H), 6.72 (d, J = 3.4 Hz, 1H), 6.25 (br.s, 1H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.9, 141.6, 135.3, 134.3, 132.1, 130.3, 125.0, 119.4, 115.5, 113.6, 110.0, 21.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_9NO$ 184.0757; Found 184.0761.

8-Methyl-9*H*-pyrrolo[1,2-*a*]indol-9-one (6e).

Following the general procedure **6e** was obtained as a yellow solid (307 mg, 84%). R_f = 0.76 (eluent: Hexane/EtOAc = 3/2); m.p. 129−130 °C; ν_{max} (KBr) 3142, 3094, 2976, 1674, 1559, 1470, 1361, 1290, 1074 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 7.4 Hz, 1H), 7.20 (d, J = 7.7 Hz, 1H), 7.18 (dd, J = 2.4, 0.6 Hz, 1H), 7.02 (t, J = 7.5 Hz, 1H), 6.80 (dd, J = 3.7, 0.6 Hz, 1H), 6.31 (dd, J = 3.7, 2.6 Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.0,

142.3, 136.8, 132.5, 130.4, 125.4, 122.3, 122.3, 121.9, 115.8, 113.5, 17.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_9NO$ 184.0757; Found 184.0753.

5-Methoxy-9*H*-pyrrolo[1,2-*a*]indol-9-one (6f).

Following the general procedure **6f** was obtained as a yellow solid (366 mg, 92%). $R_f = 0.67$ (eluent: Hexane/EtOAc = 3/2); m.p. 153−154 °C; ν_{max} (KBr) 3114, 1699, 1558, 1474, 1340, 1272, 1051 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (dd, J = 2.5, 0.8 Hz, 1H), 7.19 (dd, J = 7.1, 1.1 Hz, 1H), 7.06 (dd, J = 8.3, 7.1 Hz, 1H), 7.02 (dd, J = 8.3, 0.9 Hz, 1H), 6.77 (dd, J = 3.7, 0.8 Hz, 1H), 6.23 (dd, J = 3.7, 2.5 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.8, 146.2, 132.0, 131.7, 131.4, 126.3, 123.9, 117.6, 116.6, 115.1, 114.0, 56.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_9NO_2$ 200.0706; Found 200.0721.

6-Methoxy-9*H*-pyrrolo[1,2-*a*]indol-9-one (6g).

Following the general procedure the known **6g**[8c] was obtained as a yellow solid (346 mg, 87%). $R_f = 0.56$ (eluent: Hexane/EtOAc = 3/2); m.p. 128−129 °C; ν_{max} (KBr) 3122, 1684, 1625, 1525, 1308, 1182, 1077 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 8.3 Hz, 1H), 7.03 (dd, J = 2.6, 0.6 Hz, 1H), 6.73 (dd, J = 3.6, 0.6 Hz, 1H), 6.64 (d, J = 2.1 Hz, 1H), 6.57 (dd, J = 8.3, 2.1 Hz, 1H), 6.29 (dd, J = 3.6, 2.6 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.2, 165.3, 145.9, 133.0, 126.1, 123.1, 118.8, 115.7, 113.1, 109.0, 98.2, 56.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_9NO_2$ 200.0706; Found 200.0720.

7-Methoxy-9*H*-pyrrolo[1,2-*a*]indol-9-one (6h).

Following the general procedure the known **6h**[7d] was obtained as a yellow solid (362 mg, 91%). $R_f = 0.65$ (eluent: Hexane/EtOAc = 3/2); m.p. 119−120 °C; ν_{max} (KBr) 3109, 1696, 1608, 1492, 1352, 1289, 1224 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J = 2.6 Hz, 1H), 7.06 – 6.97 (m, 2H), 6.91 (dd, J = 8.4, 2.5 Hz, 1H), 6.76 (dd, J = 3.7, 0.6 Hz, 1H), 6.25 (dd, J = 3.7, 2.6 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 157.9, 137.5, 132.3, 131.6, 119.6, 119.3, 115.4, 114.2, 111.0, 109.78, 55.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_9NO_2$ 200.0706; Found 200.0716.

8-Methoxy-9*H*-pyrrolo[1,2-*a*]indol-9-one (6i).

Following the general procedure **6h** was obtained as a yellow solid (342 mg, 86%). R_f = 0.43 (eluent: Hexane/EtOAc = 3/2); m.p. 191−192 °C; ν_{max} (KBr) 3110, 1685, 1593, 1508, 1465, 1270, 1168 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, J = 8.5, 7.9 Hz, 1H), 7.02 (dd, J = 2.6, 0.6 Hz, 1H), 6.76 − 6.68 (m, 2H), 6.66 (d, J = 8.5 Hz, 1H), 6.27 (dd, J = 3.5, 2.6 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.5, 158.2, 145.4, 136.1, 131.9, 118.9, 116.4, 115.6, 113.0, 109.4, 103.16, 56.1; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_9NO_2$ 200.0706; Found 200.0706.

6,7-Dimethoxy-9*H*-pyrrolo[1,2-*a*]indol-9-one (6j).

Following the general procedure the known **6j**[8c] was obtained as a yellow solid (412 mg, 90%). R_f = 0.46 (eluent: Hexane/EtOAc = 3/2); m.p. 147−148 °C; ν_{max} (KBr) 3094, 2932, 1684, 1617, 1506, 1258, 1218, 1094 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.11 (s, 1H), 6.97 (dd, J = 2.6, 0.7 Hz, 1H), 6.70 (d, J = 3.7, 0.7 Hz, 1H), 6.69 (s, 1H), 6.22 (dd, J = 3.7, 2.6 Hz, 1H), 3.98 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.7, 154.4, 146.9, 139.8, 132.5, 130.9, 121.6, 119.0, 115.0, 113.7, 107.4, 95.3, 56.6, 56.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{11}NO_3$ 230.0812; Found 230.0818.

7-Chloro-9*H*-pyrrolo[1,2-*a*]indol-9-one (6k).

Following the general procedure the known **6k**[8c] was obtained as a yellow solid (390 mg, 96%). R_f = 0.73 (eluent: Hexane/EtOAc = 3/2); m.p. 140−142 °C; ν_{max} (KBr) 3104, 1690, 1617, 1542, 1508, 1391, 1267 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J = 2.0 Hz, 1H), 7.39 (dd, J = 8.2, 2.0 Hz, 1H), 7.09 − 7.01 (m, 2H), 6.80 (dd, J = 3.7, 0.4 Hz, 1H), 6.33 (dd, J = 3.7, 2.6 Hz, 1H); ^{13}C NMR (75 MHz, CDCl3) δ 178.0, 142.0, 133.5, 132.1, 131.8, 131.2, 124.9, 119.9, 116.4, 114.8, 111.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_7NOCl$ 204.0211; Found 204.0217.

5-Bromo-9*H*-pyrrolo[1,2-*a*]indol-9-one (6l).

Following the general procedure **6l** was obtained as a yellow solid (456 mg, 92%). $R_f = 0.79$ (eluent: Hexane/EtOAc = 3/2); m.p. 120–121 °C; ν_{max} (KBr) 3122, 1698, 1609, 1558, 1489, 1339, 1274 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 2.5 Hz, 1H), 7.63 – 7.43 (m, 2H), 7.00 (t, J = 7.7 Hz, 1H), 6.86 (d, J = 3.7 Hz, 1H), 6.35 (d, J = 3.7, 2.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 142.0, 138.1, 132.7, 132.4, 126.5, 123.5, 123.0, 115.9, 114.8, 104.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_6NOBr$ 247.9706; Found 247.9711.

6-Bromo-9*H*-pyrrolo[1,2-*a*]indol-9-one (6m).

Following the general procedure **6m** was obtained as a yellow solid (441 mg, 89%). $R_f = 0.79$ (eluent: Hexane/EtOAc = 3/2); m.p. 192–193 °C; ν_{max} (KBr) 3115, 1698, 1609, 1558, 1508, 1419, 1290 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J = 8.3 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.06 (dd, J = 2.5, 0.6 Hz, 1H), 6.81 (dd, J = 3.2, 0.6 Hz, 1H), 6.34 (dd, J = 3.2, 2.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 144.5, 132.2, 129.2, 128.5, 128.5, 125.6, 119.6, 116.6, 114.6, 114.1; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_6NOBr$ 247.9706; Found 247.9701.

7-Bromo-9*H*-pyrrolo[1,2-*a*]indol-9-one (6n).

Following the general procedure the known **6n**[5] was obtained as a yellow solid (481 mg, 97%). $R_f = 0.56$ (eluent: Hexane/EtOAc = 4/1); m.p. 145–146 °C; ν_{max} (KBr) 3121, 1698, 1616, 1558, 1508, 1457, 1339 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 1.7 Hz, 1H), 7.53 (dd, J = 8.2, 1.9 Hz, 1H), 7.06 (dd, J = 2.6, 0.6 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.80 (dd, J = 3.7, 0.6 Hz, 1H), 6.33 (dd, J = 3.7, 2.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 142.4, 136.4, 132.0, 131.9, 127.7, 119.9, 118.5, 116.5, 114.7, 111.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_7NOBr$ 247.9706, Found 247.9704.

8-Bromo-9*H*-pyrrolo[1,2-*a*]indol-9-one (6o).

Following the general procedure **6o** was obtained as a yellow solid (422 mg, 85%). R_f = 0.71 (eluent: Hexane/EtOAc = 3/2); m.p. 175–176 °C; ν_{max} (KBr) 3108, 1698, 1615, 1542, 1508, 1434, 1245; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 − 7.21 (m, 2H), 7.12 − 7.03 (m, 2H), 6.80 (dd, J = 3.7, 0.6 Hz, 1H), 6.34 (dd, J = 3.7, 2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 144.5, 132.2, 129.2, 128.5, 128.5, 125.6, 120.0, 116.6, 114.6, 114.1; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_7NOBr$ 247.9706; Found 247.9713.

7-Iodo-9*H*-pyrrolo[1,2-*a*]indol-9-one (6p).

Following the general procedure the known **6p**[5] was obtained as a yellow solid (551 mg, 93%). R_f = 0.76 (eluent: Hexane/EtOAc = 3/2); m.p. 182–183 °C; ν_{max} (KBr) 3121, 2883, 1685, 1610, 1541, 1520, 1385, 1242 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90 (dd, J = 8.1, 1.8 Hz, 1H), 7.73 (d, J = 1.8 Hz, 1H), 7.66 (dd, J = 2.7, 0.6 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 6.85 (dd, J = 3.7, 0.6 Hz, 1H), 6.38 (dd, J = 3.7, 2.7 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 177.0, 142.74, 142.71, 131.9, 131.3, 130.4, 122.4, 116.5, 114.5, 113.9, 110.3, 89.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_7NOI$ 295.9527; Found 295.9545.

6-Nitro-9*H*-pyrrolo[1,2-*a*]indol-9-one (6q).

Following the general procedure **6q** was obtained as a yellow solid (349 mg, 82%). R_f = 0.70 (eluent: Hexane/EtOAc = 3/2); m.p. 197−198 °C; ν_{max} (KBr) 3120, 1687, 1616, 1525, 1479, 1341, 1284 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.49 (d, J = 1.9 Hz, 1H), 8.03 (dd, J = 8.1, 1.9 Hz, 1H), 7.91 (dd, J = 2.6, 0.6 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 6.97 (dd, J = 3.7, 0.6 Hz, 1H), 6.47 (dd, J = 3.7, 2.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 176.4, 151.5, 143.7, 134.4, 131.8, 124.6, 123.5, 121.4, 117.3, 115.8, 107.2; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_6N_2O_3$ 214.0378; Found 214.0375.

11*H*-Benzo[*f*]pyrrolo[1,2-*a*]indol-11-one (6r).

Following the general procedure **6r** was obtained as a yellow solid (403 mg, 92%). R_f = 0.70 (eluent: Hexane/EtOAc = 3/2); m.p. 170−171 °C; ν_{max} (KBr) 3116, 1685, 1645, 1476, 1340, 1270, 1155 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.74

(d, J = 8.1 Hz, 1H), 7.52 (t, J = 7.3 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.36 (s, 1H), 7.21 (d, J = 2.1 Hz, 1H), 6.82 (d, J = 3.7 Hz, 1H), 6.41 (dd, J = 3.7, 2.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ178.8, 138.6, 136.3, 133.8, 131.3, 130.7, 130.4, 129.2, 128.0, 126.1, 125.8, 119.1, 117.0, 113.0, 106.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_9NO$ 220.0757; Found 220.0762.

General procedure for synthesis of amides 11 and 15.

To a mixture of amine (3.0 mmol, 1 equiv) and triethylamine (0.63 mL, 4.5 mmol, 1.5 equiv) in dry CH_2Cl_2 (5 mL) a solution of acid chloride (3.0 mmol, 1 equiv) in dry CH_2Cl_2 (5 mL) was added dropwise at 0 °C. After 15 min aqueous solution of HCl (1 M, 5 mL) was added to the mixture then the phases were separated. The organic layer was washed with an aqueous solution of $NaHCO_3$ (1 M, 5 mL), dried over sodium sulphate and concentrated to dryness after filtration. The obtained crude material was purified by flash column chromatography on silica using gradient elution of hexane and ethyl acetate.

Characterisation data of amides 11 and 15.

Phenyl(pyrrolidin-1-yl)methanone (11).

Following the general procedure, the known amide **11**[29] was obtained as a colourless oil (467 mg, 89%) from the reaction of pyrrolidine and benzoyl chloride. R_f = 0.53 (eluent: Hexane/EtOAc = 1/1); ν_{max} (KBr) 3062, 2975, 2880, 1721, 1627, 1425 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.55 – 7.45 (m, 2H), 7.45 – 7.35 (m, 3H), 3.58 (t, J = 6.9 Hz, 2H), 3.39 (t, J = 6.5 Hz, 2H), 1.94 (p, J = 6.6 Hz, 2H), 1.85 (p, J = 6.4 Hz, 2H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 169.7, 138.2, 130.1, 128.7, 127.5, 54.2, 50.0, 46.6, 26.9, 25.0; MS (ESI) *m/z*: $[M+H]^+$ 176.

***N*-(2,6-Dimethylphenyl)-3-phenylpropanamide (15).**

Following the general procedure, the known amide **15**[17] was obtained as a white solid (467 mg, 73%) from the reaction of 2,6-xylidine and 3-phenylpropanoyl chloride. R_f = 0.28 (eluent: Hexane/EtOAc = 1/1); m.p. 136−137 °C; ν_{max} (KBr) 3436, 3227, 3023, 2923, 1649,

1601 cm^{-1}; Main isomer (data obtained from the spectrum of the mixture of isomers): ^1H NMR (500 MHz, CD_2Cl_2) δ 7.30 (t, J = 7.4 Hz, 2H), 7.26 (d, J = 7.2 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 7.09 (t, J = 7.2 Hz, 1H), 7.03 (d, J = 7.2 Hz, 2H), 3.03 (t, J = 7.6 Hz, 2H), 2.68 (t, J = 7.6 Hz, 2H), 2.06 (s, 6H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 170.4, 141.0, 135.7 (2C), 134.3, 128.5 (2C), 128.5 (2C), 127.9 (2C), 127.1, 126.2, 38.0, 31.6, 18.0; MS (ESI) *m/z*: $[M+H]^+$ 254.

General procedure for the mechanistic NMR investigations.

To an oven-dried screw-cap NMR tube was sealed and it was flushed with dry nitrogen via a pair of needles through septa. Then a solution of amide (**3a**, **11** or **15**, 0.1 mmol) in CD_2Cl_2 (0.75 mL) was transferred to the tube via syringe. At this point ^1H and ^{13}C NMR were taken giving spectra of amides (e.g. Figure 1/c). Then the tube was kept in an acetone/dry ice bath, and after cooling TfOH (8.9 μL, 1.1 equiv or 32.2 μL, 4 equiv) was added via syringe. The NMR tube was allowed to warm and slightly shaken at rt for 10 min. Then ^1H and ^{13}C NMR were taken giving spectra of protonated amides (e.g. Figure 1/b). To another solution of amide (0.1 mmol) in CD_2Cl_2 (0.75 mL) cooled by acetone/dry ice bath Tf_2O (16.8 μL, 1.1 equiv) was added, then the NMR tube was allowed to warm and slightly shaken at rt for 10 min. At this point the third row of ^1H and ^{13}C NMR spectra were taken obtaining a mixture of products (e.g. Figure 1/a). In a final experiment additional TfOH (32.2 μL 4 equiv) was added to the previous mixture at rt.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.xxxxxx.

^1H and ^{13}C NMR spectra of all products and detailed spectra of mechanistic characterization data. (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: bmatravolgyi@mail.bme.hu.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported through funding from the National Research, Development and Innovation Office of Hungary (NKFIH) PD121217, K104528 and FIEK_16-1-2016-0007 (Higher Education and Industrial Cooperation Center). T.H. is grateful for the scholarships of New National Excellence Program of the Ministry of Human Capacities of Hungary (ÚNKP-17-3-I-BME-50).

REFERENCES

(1) (a) Weidner, M. F.; Sigurdsson, S. T.; Hopkins, P. B. *Biochemistry* **1990**, *29*, 9225-9233. (b) Li, V.-S.; Choi, D.; Wang, Z.; Jimenez, L. S.; Tang, M.-s.; Kohn, H. *J. Am. Chem. Soc.* **1996**, *118*, 2326-2331. (c) Diana, P.; Stagno, A.; Barraja, P.; Montalbano, A.; Carbone, A.; Parrino, B.; Cirrincione, G. *Tetrahedron* **2011**, *67*, 3374-3379. (d) Rault, S.; Lancelot, J. C.; Bouyazza, L.; Robba, M.; Quermonne, M. A.; Nammathao, B.; Louchahi-Raoul, J.; Marcy, R. *Eur. J. Med. Chem.* **1991**, *26*, 939-946. (e) Lisowski, V.; Enguehard, C.; Lancelot, J.-C.; Caignard, D.-H.; Lambel, S.; Leonce, S.; Pierre, A.; Atassi, G.; Renard, P.; Rault, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2205-2208.

(2) (a) Bauer, R.; Heisler, G.; Königstein, C. *Spectrochimica Acta Part A: Molecular Spectroscopy* **1994**, *50*, 57-67. (b) Yoshihara, T.; Druzhinin, S. I.; Zachariasse, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8535-8539.

(3) Lisowski, V.; Léonce, S.; Kraus-Berthier, L.; Sopková-de Oliveira Santos, J.; Pierré, A.; Atassi, G.; Caignard, D.-H.; Renard, P.; Rault, S. *J. Med. Chem.* **2004**, *47*, 1448-1464.

(4) Fogassy, K.; Kovacs, K.; Keser, G. M.; Toke, L.; Faigl, F. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1039-1043.

(5) Mátravölgyi, B.; Hergert, T.; Thurner, A.; Varga, B.; Sangiorgi, N.; Bendoni, R.; Zani, L.; Reginato, G.; Calamante, M.; Sinicropi, A.; Sanson, A.; Faigl, F.; Mordini, A. *Eur. J. Org. Chem.* **2017**, 1843-1854.

(6) (a) Josey, A. D.; Jenner, E. L. *J. Org. Chem.* **1962**, *27*, 2466-2470. (b) Bailey, A. S.; Scott, P. W.; Vandrevala, M. H. *J. Chem. Soc., Perkin Trans. 1* **1980**, 97-101.

(7) (a) Kobayashi, K.; Himei, Y.; Fukamachi, S.; Tanmatsu, M.; Morikawa, O.; Konishi, H. *Tetrahedron* **2007**, *63*, 4356-4359. (b) Giacometti, R. D.; Ramtohul, Y. K. *Synlett* **2009**, 2010-2016. (c) Aiello, F.; Garofalo, A.; Grande, F. *Tetrahedron* **2010**, *66*, 274-277. (d) Wang, S.; Yang, Q.; Dong, J.; Li, C.; Sun, L.; Song, C.; Chang, J. *Eur. J. Org. Chem.* **2013**, 7631-7634.

(8) (a) Kashulin, I. A.; Nifant'ev, I. E. *J. Org. Chem.* **2004**, *69*, 5476-5479. (b) Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 5616-5620. (c) Liao, F.; Shi, R.; Sha, Y.; Xia, J.; Liao, W.; Lei, A. *Chem. Commun.* **2017**, *53*, 4354-4357.

(9) (a) Faigl, F.; Thurner, A.; Vass, B. *Journal of Chemical Research (Synopses)* **2003**, *3*, 132-133. (b) Faigl, F.; Fogassy, K.; Szűcs, E.; Kovács, K.; Keserű, G. M.; Harmat, V.; Böcskei, Z.; Tőke, L. *Tetrahedron* **1999**, *55*, 7881-7892. (c) Faigl, F.; Fogassy, K.; Thurner, A.; Tőke, L. *Tetrahedron* **1997**, *53*, 4883-4888.

(10) Faigl, F.; Mátravölgyi, B.; Deák, S.; Holczbauer, T.; Czugler, M.; Balázs, L.; Hermecz, I. *Tetrahedron* **2012**, *68*, 4259-4266.

(11) Rault, S.; de Sévricourt, M. C.; Godard, A. M.; Robba, M. *Tetrahedron Lett.* **1985**, *26*, 2305-2308.

(12) We attempted to use the procedures cited herein on substrates 5-bromo-anthranilic acid and 2-(pyrrol-1-yl)benzoic acid, respectively, but were not able to isolate any product,

see: (a) Aiello, F.; Garofalo, A.; Grande, F. *Tetrahedron Lett.* **2011**, *52*, 5824-5826. (b) Aiello, F.; Garofalo, A.; Grande, F. *Tetrahedron Lett.* **2010**, *51*, 6635-6636.

(13) Raja, E. K.; DeSchepper, D. J.; Nilsson Lill, S. O.; Klumpp, D. A. *J. Org. Chem.* **2012**, *77*, 5788-5793.

(14) Kaiser, D.; Maulide, N. *J. Org. Chem.* **2016**, *81*, 4421-4428.

(15) (a) Kaiser, D.; Teskey, C. J.; Adler, P.; Maulide, N. *J. Am. Chem. Soc.* **2017**, *139*, 16040-16043. (b) Di Mauro, G.; Maryasin, B.; Kaiser, D.; Shaaban, S.; González, L.; Maulide, N. *Org. Lett.* **2017**, *19*, 3815-3818. (c) Huang, P.-Q.; Lang, Q.-W.; Wang, Y.-R. *J. Org. Chem.* **2016**, *81*, 4235-4243. (d) Régnier, S.; Bechara, W. S.; Charette, A. B. *J. Org. Chem.* **2016**, *81*, 10348-10356, and references cited therein.

(16) Huang, P.-Q.; Huang, Y.-H.; Xiao, K.-J. *J. Org. Chem.* **2016**, *81*, 9020-9027.

(17) Huang, P.-Q.; Huang, Y.-H.; Geng, H.; Ye, J.-L. *Sci. Rep.* **2016**, *6*, 28801-28811.

(18) (a) Faigl, F.; Deák, S.; Mucsi, Z.; Hergert, T.; Balázs, L.; Sándor, B.; Balázs, B.; Holczbauer, T.; Nyerges, M.; Mátravölgyi, B. *Tetrahedron* **2016**, *72*, 5444-5455. (b) Deák, S.; Mátravölgyi, B.; Feczku, G.; Erdélyi, Z.; Nyerges, M.; Faigl, F. *Tetrahedron: Asymmetry* **2015**, *26*, 593-599. (c) Faigl, F.; Erdélyi, Z.; Deák, S.; Nyerges, M.; Mátravölgyi, B. *Tetrahedron Lett.* **2014**, *55*, 6891-6894.

(19) Medley, J. W.; Movassaghi, M. *J. Org. Chem.* **2009**, *74*, 1341-1344.

(20) (a) Bechara, W. S.; Pelletier, G.; Charette, A. B. *Nat. Chem.* **2012**, *4*, 228-234. (b) Huang, P.-Q.; Huang, Y.-H.; Xiao, K.-J.; Wang, Y.; Xia, X.-E. *J. Org. Chem.* **2015**, *80*, 2861-2868. (c) Huang, P.-Q.; Lang, Q.-W.; Hu, X.-N. *J. Org. Chem.* **2016**, *81*, 10227-10235. (d) Tona, V.; Maryasin, B.; de la Torre, A.; Sprachmann, J.; González, L.; Maulide, N. *Org. Lett.* **2017**, *19*, 2662-2665.

(21) Movassaghi, M.; Hill, M. D. *Org. Lett.* **2008**, *10*, 3485-3488.

(22) In aqueous solution the pK_a: 5.17 of pyridine, pK_a: –0.44 of 2-fluoropyridine; see: Brown, H. C.; McDaniel, D. H. *J. Am. Chem. Soc.* **1955**, *77*, 3752-3755.

(23) Charette, A. B.; Chua, P. *J. Org. Chem.* **1998**, *63*, 908-909.

(24) Charette, A. B.; Grenon, M. *Can. J. Chem.* **2001**, *79*, 1694-1703.

(25) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096-10097.

(26) For detailed ^{1}H and ^{13}C specta obtained by NMR experiments see supporting information.

(27) Cox, C.; Lectka, T. *Acc. Chem. Res.* **2000**, *33*, 849-858.

(28) Gramstad, T.; Husebye, S.; Sæbø, J. *Tetrahedron Lett.* **1983**, *24*, 3919-3920.

(29) Mane, R. S.; Bhanage, B. M. *J. Org. Chem.* **2016**, *81*, 1223-1228.