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NH_4PF_6-Promoted Cyclodehydration of α-Amino Carbonyl Compounds: Efficient Synthesis of Pyrrolo[3,2,1-*ij*]quinoline and Indole Derivatives †

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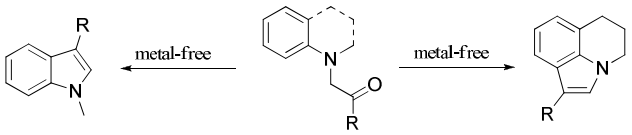
NH_4PF_6 is an inexpensive, safe, and low-toxicity inorganic salt; it was found to promote the cyclodehydration of α-amino carbonyl compounds in the absence of metal reagents. This simple cyclodehydration strategy enables highly atom-economic formation of pyrrolo[3,2,1-*ij*]quinoline and indole derivatives, which are significant pharmacophores.

Pyrrolo[3,2,1-*ij*]quinolines[1] and indoles[2] are important structural units, and are found in numerous pharmaceuticals and natural products. Extensive studies have demonstrated that pyrrolo[3,2,1-*ij*]quinolines are lead candidates for fungicides active against rice blast disease,[1d] and in potential treatments for asthma,[1e] epilepsy, and obesity.[1f] In addition, it has been reported in numerous patents that pyrrolo[3,2,1-*ij*]quinoline is a promising skeleton in drug development.[3] Considerable efforts have been devoted to the synthesis of pyrroloquinolines.[4–12] Early reported methods generally suffer from drawbacks such as harsh reaction conditions, limited substrate scope or low yields.[4] In the past decade, synthetic methodologies including Michael-type annulations,[5] free radical cyclizations,[6] sigmatropic rearrangements[7] and multicomponent reactions[8] have been used for pyrroloquinolines synthesis, albeit with narrow substrate scope. Broader substrate scope can be achieved by transition metal-catalyzed reaction. For instance, palladium- or copper-catalyzed intramolecular cyclization of 8-alkynylated tetrahydroquinolines,[9,10] indium-catalyzed intramolecular Friedel-Crafts annulations of modificated indoles,[11] and zirconium-catalyzed cycloaddition of tetrahydroquinoline hydrazines with interal alkynes.[12] However, these substrates require complicated pre-functionalization. The development of efficient synthetic methods for pyrrolo[3,2,1-*ij*]quinolines preparation is therefore urgent.

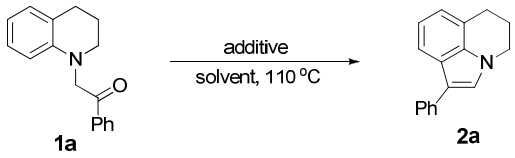
Indoles, because of their wide-ranging biological activity, continue to promote numerous researchers to focus on efficient synthetic methodologies.[2a, 13] Among indole synthesis, an intriguing approach would start from an *ortho*-unsubstituted anilines or mono-substituted arene, followed by direct cyclization with C–C or C–N bond formation to a C–H bond.[13b] This type of approach includes Fischer indole synthesis,[14] Bischler indole synthesis,[15] Hemetsberger indole synthesis,[16] Nenitzescu indole synthesis,[17] Bartoli indole synthesis[18] and et al. We hypothesized that the Bischler reaction[15] would provide a suitable pathway for the preparation of pyrrolo[3,2,1-*ij*]quinolines and indoles, because the sole by-product is water, and α-amino carbonyl compounds are readily prepared.[19] An improved Bischler reaction involves a microwave-assisted approach, which allows one-pot synthesis of 2-arylindoles under solvent-free and metal-free conditions, albeit with moderate yields.[20] Metal catalysts such as rhodium carbenoids,[21] cationic iridium complexes,[22] $Ru_3(CO)_{12}$[23] and $Zn(TfO)_2$[24] give efficient indole synthesis *via* the Bischler reaction. However, most of these metal reagents are expensive, which has limited synthetic applications. Recently, a modified Bischler reaction was developed for the preparation of *N*-aryl-2,3-disubstituted indoles, although expensive and unstable arynes are used as reaction partners.[25] Based on previous reports of Bischler indole synthesis,[15, 20–25] we strive to use eco-friendly reagents to synthesize pyrrolo[3,2,1-*ij*]quinolines and indoles *via* the Bischler reaction; this will contribute to sustainable development in chemistry (Scheme 1). Here, we report a NH_4PF_6-promoted efficient method for the synthesis of pyrrolo[3,2,1-*ij*]quinolines and indoles by cyclodehydration of α-amino carbonyl compounds in the absence of metals.



Scheme 1. Green synthesis of pyrrolo[3,2,1-*ij*]quinolines

Major limitations in scaling up reactions arise from the use of corrosive acids and metal pollution, therefore we focused on using inorganic salts that are eco-friendly, readily post-treated, and compatible with functional groups to achieve the cyclodehydration of α-amino carbonyl compounds. We reasoned that ammonium salts would promote cyclodehydration because the NH_4^+ cation can activate the carbonyl group.[26, 27] Based on this supposition, we used the cyclodehydration of **1a** as the model reaction. NH_4Cl, NH_4OAc, and NH_4PF_6 were used to explore the reaction in CH_3CN at 110 °C (Table 1, entries 1–3). As expected, the reaction occurred in the presence of NH_4Cl or NH_4OAc, giving the desired products in 8% and 10% yields, respectively (Table 1, entries 1 and 2). Under the NH_4PF_6-promoted reaction conditions, the yield increased to 56% (Table 1, entry 3). We then attempted to improve the reactivity by using the more soluble $(n\text{-Bu})_4NPF_6$. However, only a 12% yield was obtained (Table 1, entry 4). We speculated that the PF_6^- anion may be crucial for the reaction, therefore we investigated KPF_6 and $AgPF_6$ in the reaction, respectively. No target product was obtained in the reaction with KPF_6 or $AgPF_6$ (Table 1, entries 5 and 6). In terms of the solvent effect, 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) significantly enhanced the reactivity of NH_4PF_6, affording the target product in 95% yield (Table 1, entry 11). HFIP, as a strong polar solvent, may help to dissolve NH_4PF_6, leading to amplifying the reactivity. In contrast, other solvents, *e.g.*, toluene, DCE, and DMF, did not affect the reaction (Table 1, entries 7–9); while EtOH gave a rather low yield (Table 1, entry 10). To further test the effect of HFIP, the reaction with NH_4Cl or NH_4OAc in HFIP was conducted, respectively; to our delight, both yields were enhanced to 75% (Table 1, entries 12 and 13). It was showed that addition of 2 equiv of H_2O would slightly decrease the yield to 87% (Table 1, entry 14). We next reduced the NH_4PF_6 loading and lowered the reaction temperature, repectively. Decreasing the NH_4PF_6 loading gave a lower yield (Table 1, entry 15), and the yield at 90 °C decreased to 69% (Table 1, entry 16). Several Lewis acids ($FeCl_3$, $ZnCl_2$, $AlCl_3$, and AgOTf) and Brønsted acids (HCl, H_2SO_4, AcOH, F_3CCOOH, TsOH, and HPF_6) were evaluated (see the Supplementary Information). In comparison with NH_4PF_6, these reagents showed poor reactivity and gave low yields. Control reactions, in the absence of NH_4PF_6, were conducted in CH_3CN and HFIP, respectively. No reaction occurred in CH_3CN, which suggested that ammonium salts were crucial for the reaction (Table 1, entries 1–3 and 17); interestingly, a 48% yield was obtained in HFIP without NH_4PF_6 (Table 1, entry 18), which demonstrated that the unique solvent effect of HFIP may decrease the reaction energy barrier, thus facilitating the cyclodehydration under 110 °C. Moreover, HFIP can act as an acid to promote the reaction. Finally, we found that a combination of NH_4PF_6 as the promoter and HFIP as the solvent, at 110 °C, gave the best yield.

Table 1. Screening of Optimal Conditions[a]



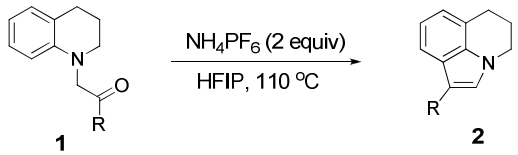
entry	Additive	Solvent	Yield (%)[b]
1	NH_4Cl	CH_3CN	8
2	NH_4OAc	CH_3CN	10
3	NH_4PF_6	CH_3CN	56
4	$(n\text{-Bu})_4NPF_6$	CH_3CN	12
5	KPF_6	CH_3CN	0
6	$AgPF_6$	CH_3CN	0
7	NH_4PF_6	Toluene	trace
8	NH_4PF_6	DCE	trace
9	NH_4PF_6	DMF	0
10	NH_4PF_6	EtOH	24
11	NH_4PF_6	HFIP	95
12	NH_4Cl	HFIP	75
13	NH_4OAc	HFIP	75
14[c]	NH_4PF_6	HFIP	87
15[d]	NH_4PF_6	HFIP	72
16[e]	NH_4PF_6	HFIP	69
17	—	CH_3CN	0
18	—	HFIP	48

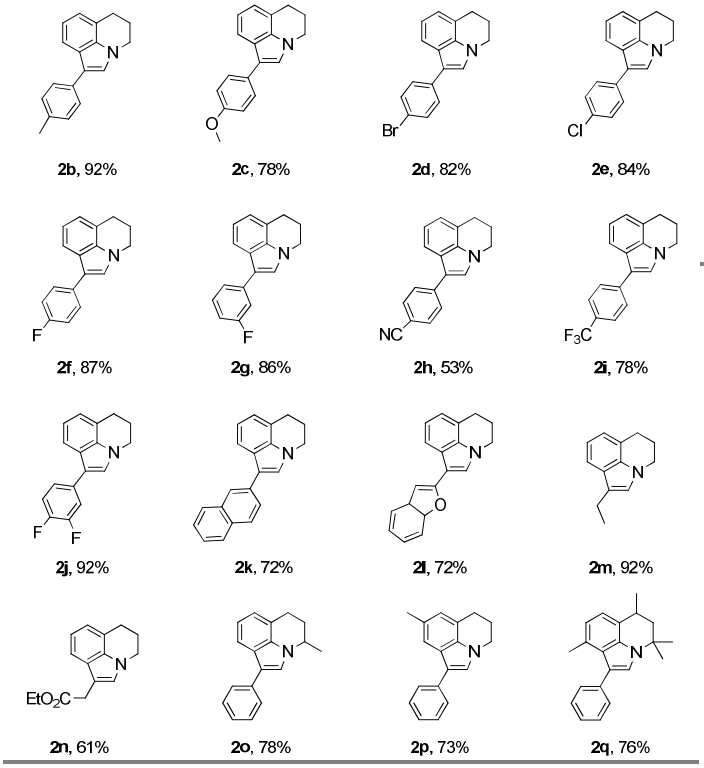
[a] Reaction conditions: **1a** (0.2 mmol), additive (0.4 mmol, 2 equiv) in solvent (2 mL) at 110 °C for 24 h. [b] Isolated yields. [c] H_2O (2 equiv) was added. [d] NH_4PF_6 (0.2 mmol, 1 equiv). [e] At 90 °C.

With this new Bischler reaction procedure in hand, the scope of α-amino carbonyl compounds tolerated was investigated (Table 2). Substituents such as Me, MeO, Br, Cl, F, CN, and CF_3 groups on the aromatic ring of the 1-arylethanone moiety are tolerated well under the standard conditions (products **2b**–**2i**); for example, substrate **1b**, which has a methyl group, gave a high yield of **2b** (92%). The presence of a MeO group on substrate **1c** was tolerated, providing the corresponding product **2c** in 78% yield. Halo-substituted substrates also gave good yields, these are synthetically useful for further modifications, because of the diverse reactivities of halo groups (products **2d**–**2g**). These results showed that different halo-substituted substrates had similar reactivity (products **2d**–**2g**). For example, the *para*- and *meta*- fluoro-substituted substrates almost had the same yields (products **2f** and **2g**). Reactions of substrates with electron-withdrawing groups such as cyano and trifluoromethyl were also carried out, affording the corresponding products **2h** and **2i** in 53% and 78% yields, respectively. A difluoro-substituted substrate had better reactivity, giving the desired product **2j** in 92% yield. Despite the steric hindrance effect of the naphthalene, substrate **1k** underwent cyclodehydration smoothly to afford the target product **2k** in 72% yield. The benzofuran moiety, which is a useful pharmacophore, was tolerated, providing the corresponding product **2l** in 72% yield. An alkyl ketone showed excellent reactivity in the reaction, affording the desired product **2m** in 92%. An α-amino ester

performed smoothly under the optimal conditions (product **2n**), enabling further modifications that are important for the preparation of diverse pyrrolo[3,2,1-*ij*]quinolines. Substituted tetrahydroquinolines were also investigated to test the scope (products **2o**–**2q**). 2-methyl and 6-methyl substituted tetrahydroquinolines proceeded smoothly to give the target product in good yields (products **2o** and **2p**). To our delight, substrate **1q** with two methyl group at the 2-position of tetrahydroquinoline also performed well, giving the target product in 76% yield (product **2q**)

Table 2. NH_4PF_6-Promoted Synthesis of Pyrrolo[3,2,1-*ij*]quinolines.[a]

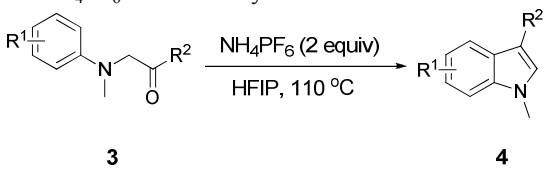


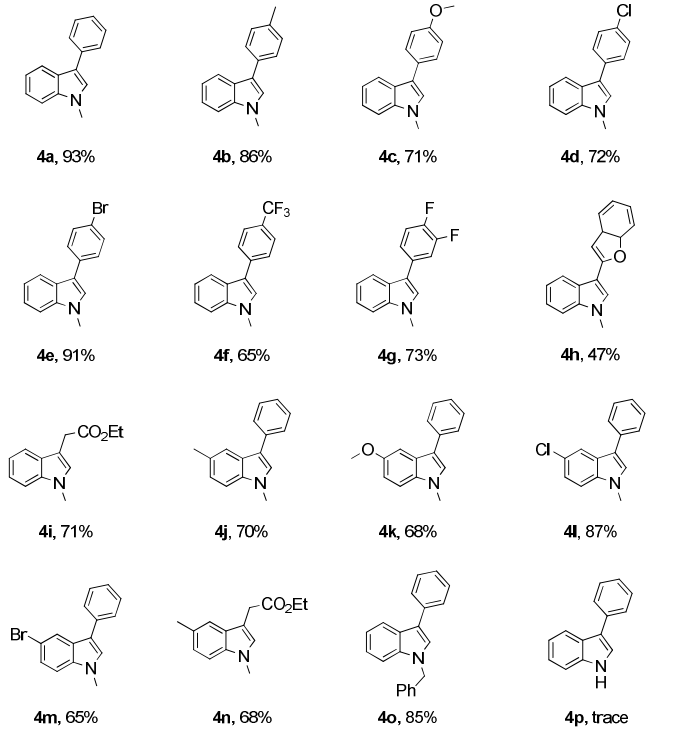


[a] Reaction conditions: **1** (0.2 mmol), NH_4PF_6 (0.4 mmol, 2 equiv) in HFIP (2 mL) at 110 °C for 24 h.

Having demonstrated the efficiency of NH_4PF_6 in the synthesis of pyrrolo[3,2,1-*ij*]quinolines, we investigated whether this approach was generally applicable to the synthesis of indoles. A wide range of α-amino carbonyl compounds **3** (Table 3, products **4a**–**4p**) were subjected to the optimal conditions. The cyclodehydration of **3a** in HFIP gave product **4a** in 93% yield. Substituents such as Me, MeO, Cl, Br, and CF_3 were compatible with the optimal conditions, providing the corresponding products **4b**–**4f** in moderate to high yields. Importantly, chlorinated and bromated arenes on α-amino carbonyl compounds **3** were well tolerated, facilitating possible further modifications at the halogenated positions (**4d** and **4e**). Cyclodehydration of the difluoro-substituted substrate **3g** proceeded smoothly to afford the expected product **4g** in 73% yield. Substrate **3h**, which has a benzofuran motif, also underwent cyclodehydration to yield the corresponding product **4h** in 47% yield. The poor yield resulted from partial decomposition and low conversion rate of substrate **3h**. It is worth noting that a yield of 71% was obtained in the reaction of substrate **3i**, which has an ester group. To further test the scope of this protocol, compounds with Me, MeO, Cl, and Br substituents on the aromatic ring of aniline were evaluated for the reaction; and the corresponding products were obtained in yields of 65–87% (**4j**–**4n**). Finally, the effect of protecting group on nitrogen atom was examined. Benzyl protected aniline gave a good yield of 85% (product **4o**). Unfortunately, unprotected aniline **3p** was decomposed under standard conditions, only a large amounts of N-methylaniline was observed on GC-MS (product **4p**).

Table 3. NH_4PF_6-Promoted Synthesis of Indoles.[a]

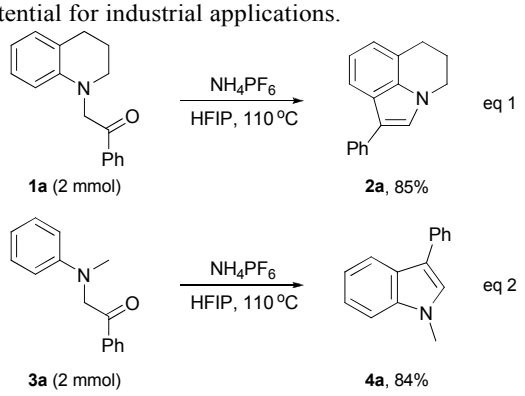




[a] Reaction conditions: **1** (0.2 mmol), NH_4PF_6 (0.4 mmol, 2 equiv) in HFIP (2 mL) at 110 °C for 24 h.

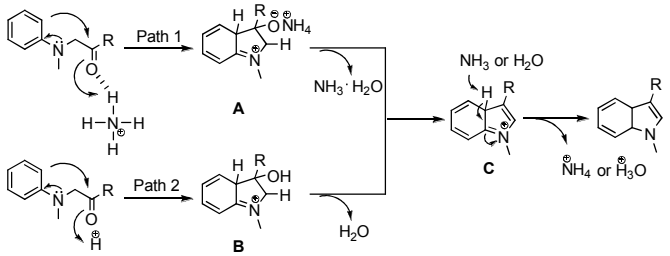
To test their potential in large scale synthesis, the reactions of **1a** and **3a** were conducted at 0.502 g (2 mmol) and 0.45 g (2 mmol) scales, respectively, giving **2a** and **4a** in 85% and 84%

yields, respectively (Scheme 2). Additionally, HFIP is readily recovered by distillation, because its boiling point is 59 °C. These results suggest that the newly established reaction system has potential for industrial applications.



Scheme 2. Reaction scale up

According to the classical Bischler reaction mechanism[15] and the present results, possible reaction pathways were illustrated as showed in Scheme 3. The role of NH_4^+ may activate the carbonyl that facilitates the Friedel-Crafts cyclization to produce an intermediate **A** and $NH_3{\cdot}H_2O$.[26,27] The intermediate **A** undergoes a dehydration process to give an intermediate **C**, followed by a deprotonation route to afford the target product (Path 1). Alternatively, the present reaction may involve an acid-promoted process, because NH_4PF_6 may be subjected to a hydrolytic reaction under the standard conditions, resulting in *in-situ* formation of HPF_6, which is likely to promote the cyclization to afford intermediate **B** (Path 2). The role of HFIP can be concluded on two aspects: firstly, HFIP can improve the reactivity of ammonium salts; secondly, HFIP is serving as an polar, acidic solvent that promotes the reaction itself.



Scheme 3. Possible reaction pathways.

In summary, we discovered that an inorganic salt, NH_4PF_6, efficiently promotes the Bischler reaction in HFIP. The new strategy provides a convenient and efficient route for the preparation of pyrrolo[3,2,1-*ij*]quinolines and indoles, without using metal reagents, which were required in previous methods.[21–24] Moreover, the reaction can be scaled up under conventional means, and have better yields than those in microwave-assisted method.[20] The simple post-treatment and easy recovery of HFIP help to protect the environment.

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Notes and references

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† Electronic Supplementary Information (ESI) available: detailed condition screening table, experimental details, and ^1H and ^{13}C NMR spectra of the products. See DOI: 10.1039/c000000x/

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