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Selective Functionalization of Aminoheterocycles by a Pyrylium Salt

Daniel Moser[†], Yaya Duan[†], Feng Wang, Yuanhong Ma, Matthew J. O'Neill and Josep Cornella*

Abstract: The functionalization of aminoheterocycles via a pyrylium tetrafluoroborate reagent (Pyry-BF_4) is presented. This reagent efficiently condenses with a great variety of heterocyclic amines and primes the C–N bond for nucleophilic aromatic substitution. More than 60 examples of C–O, C–N, C–S or C–SO_2R are disclosed herein. In contrast to C–N activation via diazotization and polyalkylation, this method is characterized by its mild conditions and impressive functional group tolerance. In addition to small molecule derivatization, Pyry-BF_4 allows for the introduction of functional groups in a late-stage fashion to furnish highly functionalized structures.

The construction of molecular complexity through small fragment connection constitutes a fundamental pillar in drug discovery. To this end, robust methodologies have been developed for the formation of C–N,[1] C–O,[2] C–S[3] and C–C[4] bonds to elaborate heterocyclic frameworks. Indeed, reactions based on transition metal catalysts such as the Buchwald-Hartwig amination,[1] Ullmann[2] or Chan-Lam[5] couplings immediately come to mind as methods to construct these linkages. Despite the tremendous power of these protocols, comprehensive surveys of the literature reveal that nucleophilic aromatic substitution (S_NAr) still dominates in industrial contexts.[6] In this sense, a large proportion of candidates to undergo S_NAr are highly functionalized heterocycles, since they represent the core of most contemporary small-molecule therapeutics.[7] Accordingly, the S_NAr persists as a cornerstone reaction highly coveted by pharmaceutical and agrochemical industries, as it provides a reliable and scalable approach to expediently assemble complexity.[8] Notably, the S_NAr reaction is still largely restricted to the use of a heteroaryl halide as the electrophilic partner, which is in turn prepared via the Vilsmeier-Haack reaction from an amide (Figure 1A);[9] this reaction usually requires strong acids, thus leading to functional group incompatibilities. More importantly, due to their high electrophilicity, some of these heteroaromatic halides are unstable and prone to decomposition in the absence of special precautions.[10] Although several reports have sought to develop more stable electrophilic partners,[11] they uniformly require prefunctionalization through the respective amide. Therefore, methods to obviate this restrictive electrophile scope would greatly expand the synthetic potential of this method.

Accordingly, aminoheterocycles occupy a sizeable fraction of natural chemical space, as well as synthetic pharmaceuticals and agrochemicals.[7][12] Moreover, the presence of amino groups in a variety of existing medicinally relevant compounds makes them a perfect handle for further late-stage modifications. These factors collectively render aminoheterocycles as perfect candidates to serve as electrophiles in *ipso* substitutions. However, the conversion of C(sp^2)-NH_2 into leaving groups has traditionally been restricted to the generation of the diazonium salt[13] or the polyalkylation of the amine[14] (*path a* and *b*, Figure 1B). In the former, strong oxidants and acids are required to generate the diazonium salt which in turn is unstable at high temperatures, shock sensitive, and explosive. The use of alkylating agents for the latter example has been restricted to the activation of simple anilines, since the presence of Lewis-basic atoms makes this approach unfeasible. Inspired by the work of Baeyer and Piccard[15] and later by Balaban[16] and Katritzky,[17] we envisaged that activation of C(sp^2)–NH_2 bonds could be achieved by a simple condensation with a pyrylium reagent (*path c*, Figure 1B); however, such condensation present several challenges due to the low nucleophilicity of the NH_2 group in aminoheterocycles as shown by the inefficient reactivity with a Zincke reagent.[18] Indeed, pyrylium salts have successfully been utilized in the past for the activation of C(sp^3)–NH_2 groups in a variety of synthetically useful contexts.[19][20] However, exploitation of this concept for the derivatization of C(sp^2)–NH_2 in aminoheterocyclic frameworks still remains an enormous challenge in synthesis.[21] In this report, we describe a practical synthesis of a pyrylium reagent (Pyry-BF_4, **1**) which is capable of selectively activating amino groups in heterocycles (Scheme 1A), thus priming them for S_NAr to obtain high value compounds through C–O, C–N, C–S and C–SO_2R bond formation.[22]

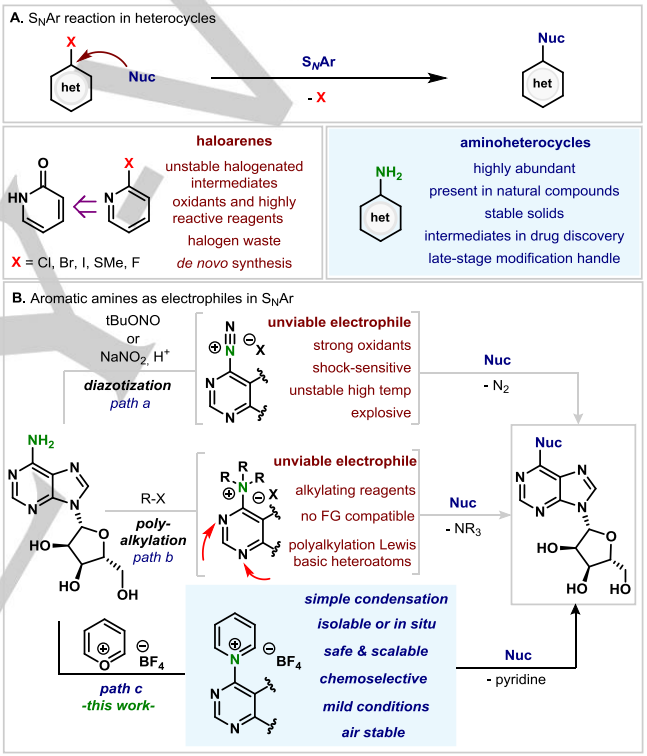

Figure 1. (**A**) Importance of S_NAr reaction for functionalization of heterocycles; (**B**) Aminoheterocycles as electrophiles.

The synthesis of the pyrylium tetrafluoroborate **1** (Pyry-BF_4) was achieved by a two-step sequence comprising base-mediated ring opening/acid-mediated ring closing reactions starting from readily available and cheap pyridine sulfur trioxide (PST, $14/mol).[23] After crystallization of the crude mixture, **1** is obtained as an off-white-beige solid. Pyry-BF_4 features a series of attractive characteristics: (1) *non-explosive*; (2) *readily preparable* from PST; (3) *scalable* without risk of explosion.[24] At this point, the reactivity of **1** was benchmarked with the most common and simple pyrylium reagents, traditionally utilized to activate C–N bonds.[19][20] As shown in Scheme 1B, 4-aminopyridinium salt derivative of 2,4,6-triphenylpyrylium (**3**) remained unaltered in S_NAr upon heating with toluidine. Notably, sterically less encumbered 2,4,6-trimethylpyrylium was not suitable for condensation with **2**. However, when salt **4** was used instead, smooth C–N bond was obtained in mild conditions (80 °C); the robustness and simplicity of this protocol is highlighted by the tolerance of a variety of solvents. The difference in reactivity between pyridinium salts is attributed to the interruption of the co-planarity: when 2,4,6-trisubstituted pyridiniums are used, steric protection of the *ipso* carbon prevents an optimal angle for the incoming nucleophile.[25]

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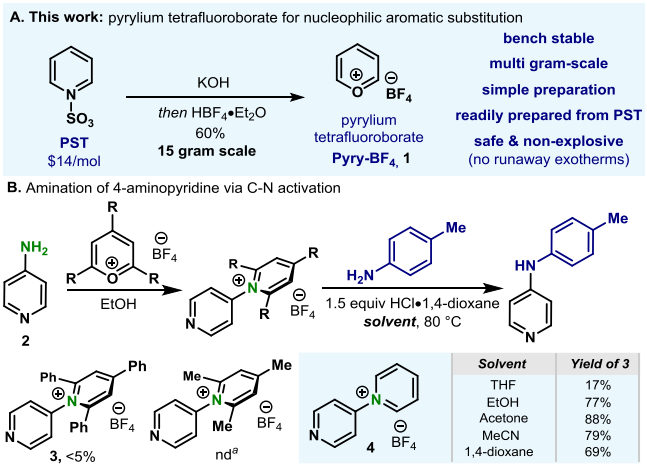

Scheme 1. (**A**) Synthesis of pyrylium tetrafluoroborate (Pyry-BF_4); (**B**) Comparison between Pyry-BF_4 and commonly employed pyryliums. [a]Condensation could not be achieved with 2,4,6-trimethylpyrylium BF_4.

As shown in Table 1, Pyry-BF_4 reacted smoothly with pyridines bearing electron-donating (**5**, **7**, **9**, **12**) and electron-withdrawing groups (**10**, **16**, **17, 19**). Pyridines substituted at the 2-position with Me (**6**) and Ph (**8**) could also be accommodated. Substitution next to the amino center posed no problem for the synthesis of the pyridinium salt as exemplified by the fluorine-containing pyridinium salt **13**. The method could also be applied to other aminoheterocyclic frameworks such as 4-aminopyrimidines (**11**), 2-aminopyrimidines (**14**), 2-aminobenzothiazole (**15**) or the 5-membered 2-aminothiadiazole **18**. In all cases, the pyridinium salt can be carried on further without the need of isolation if desired (*in situ*).

A variety of anilines smoothly reacted with the pyridinium salt in the presence of 1 equiv of HCl at 80–110 °C, thus affording the desired C–N coupling product. The transamination is characterized by its functional group tolerance, proceeding in the presence of nitriles (**20**), ketones (**21**), esters (**35**), fluorides (**33**), trifluoromethyl group (**29**), tertiary amines and amides (**31**), and ethers (**32**). Anilines bearing functional groups susceptible to reactivity under Ullmann or Buchwald-Hartwig such as iodides (**34**) and chlorides (**24**) smoothly delivered the corresponding C–N linkage in good yields. Unfortunately, more nucleophilic amines such as butylamine or morpholine afforded ring-opened products in a Zincke-type reactivity. The reaction is not limited to primary anilines; methylaniline (**24**) or 4-chloro-methylaniline (**37**) could be accommodated. Substituted pyridines with a 2-chloro group (**27**) represent a clear example of the orthogonality of this transformation in the presence of other leaving groups. Amination was further accomplished with thiadiazole (**28**) and benzothiazole pyridinium salts (**30**); the lower yields in the former are the consequence of competing ring opening events of the 5-membered ring. This protocol was also effective in the area of C–O bond formation.[26] The diversity of counterparts span from aromatic phenol derivatives (**38-44**) to linear alkyl alcohols (**45**). The presence of electron-donating (**41**), electron-withdrawing (**45**) or neutral aminoheterocycles (**38-40**, **42-44**) bode well in the coupling.

The protocol was successfully expanded to sulfur containing nucleophiles such as thiols and sulfinates.[27][28] The reaction of sulfinates forged the desired sulfones for an abundance of different heterocyles; pyridines bearing morpholine (**48**), nitro (**49**), ethers (**52**, **58**), chloro (**55**) and trifluoromethyl (**53**) substituents smoothly coupled with good to excellent yields (Table 2C). Substituted aryl sulfinates bearing diverse substituents in the aromatic ring (**54**, **56**, **59**), as well as alkyl sulfinates (**47**) bode well with this protocol. The formation of C–S bonds was successfully realized with a wide variety of thiols bearing bromo (**60**, **71**), chloro (**64**), fluoro (**65**), ethers (**63**) and nitro (**66**) groups as well as extended aromatic thiols (**69**, **70**, **72**). *Ortho*-substituted thiols smoothly reacted with excellent yields thus overriding steric effects (**60**, **61**, **71**). Pyridines containing tertiary amines (**72**, **73**), nitro (**74**) and fluoro (**75**) as well as pyrimidines (**68**) could also be accommodated in the formation of C–S bond. As exemplified in Table 2, the reaction could successfully be performed from the pyridinium salt or from the *in situ* generated pyridinium salt, without isolation. Coupling of pyridinium salts **7**, **13** and **19** was carried out by a simple solvent exchange subsequent to condensation with Pyry-BF_4, thus enabling a simple, practical and economical one-pot procedure.

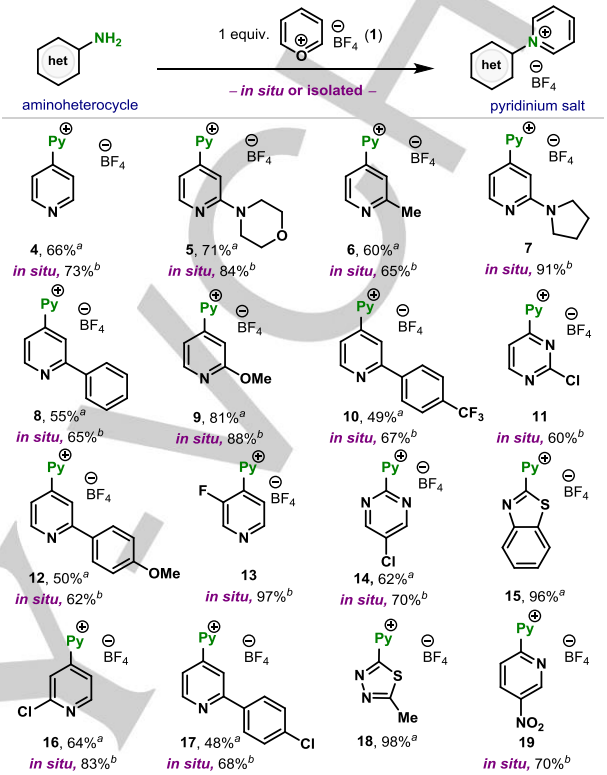

Table 1. Synthesis of pyridinium salts. *Reaction conditions*: aminoheterocycle (1 equiv.), Pyry-BF_4 (1 equiv.) in EtOH at 75 °C. [a]Isolated yields. [b]Yields determined by NMR using mesitylene as internal standard.

With the importance of late-stage modification in drug discovery, the mild conditions of our protocol enable the use of C(sp^2)–NH_2 groups as points for diversification (Figure 2A). For example, the oncology therapeutic ibrutinib, could be successfully modified at its amino group with the *in situ* protocol to forge a new C–S bond (**77**, 42%). The highly nitrogenated anti-anxiety pharmaceutical prazosin smoothly reacted with Pyry-BF_4, permitting the substitution with simple sodium ethoxide (**80**, 35%). Naturally occurring substances such as estradiol also reacted chemoselectively with the phenolic C–OH bond (**78**, 58%). (+)-δ-Tocopherol (Vitamin E) smoothly delivered the coupling product in good yields (**76**, 55%). Fungicide fenhexamid was also functionalized with excellent yield and chemoselectivity (**79**, 54%). To explore the limits of functional group compatibility, we turned our attention to adenosine. Current strategies for the modification of this natural riboside rely on pre-functionalization to the halide or phosphonium reagent, with inosine as the starting material (Figure 2B). This sequence involves the protection of the sugar moiety, since $POCl_3$ or the respective alternatives are generally not compatible with free alcohols.[29] Addition of the nucleophile followed by overall deprotection delivers the substituted adenosine. In contrast to this lengthy route, **1** smoothly reacted with simple adenosine to deliver the pyridinium salt, which was functionalized *in situ* with a thiol and an alcohol to obtain compounds **81** and **82** in 71% and 63% isolated yields, respectively. These examples further highlight the versatility of the Pyry-BF_4 as a reagent and it is envisioned that the protocol could access chemical space in challenging contexts such as nucleobase modifications in chemical biology and epigenetics.[30]

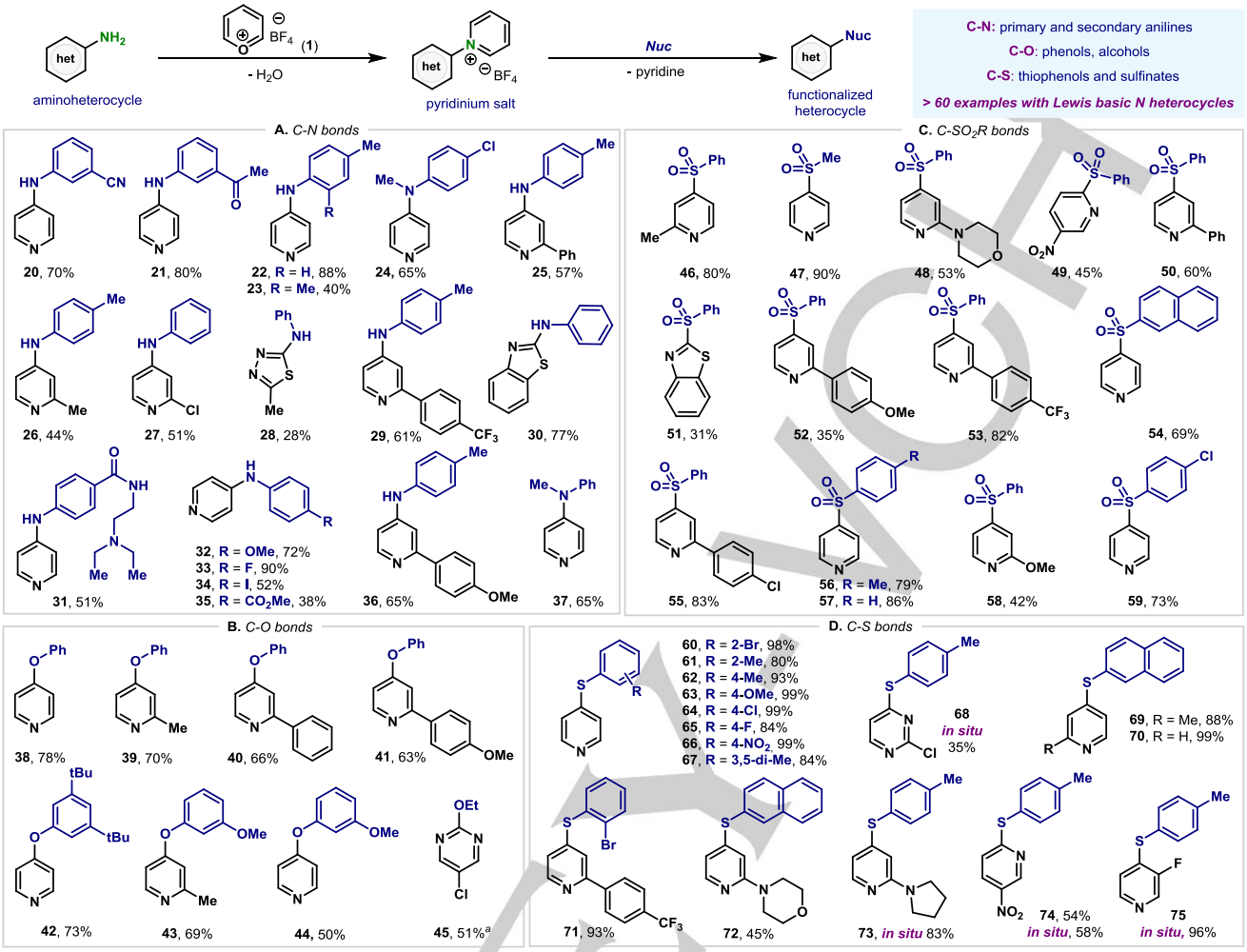

Table 2. Scope of the S_NAr mediated by Pyry-BF_4 salt. *Reaction conditions*: (**A**) pyridinium salt (1 equiv.), amine (1 – 1.5 equiv.), HCl in 1,4-dioxane (1.5 equiv.), DMSO or EtOH at 80–110 °C; (**B**) pyridinium salt (1 equiv.), phenol (1.5 equiv.) at 110–150 °C; (**C**) pyridinium salt (1 equiv.), sodium sulfinate (1.5 equiv.), HCl in 1,4-dioxane (1.0 equiv.) in DMSO or EtOH at 25 - 60 °C; (**D**) pyridinium salt (1 equiv.), thiophenol (1.5 equiv.) in DMSO or EtOH at 25–60 °C. [a] NMR yield using mesitylene as internal standard.

In conclusion, a method for the nucleophilic aromatic substitution of amino groups has been developed, which avoids the need for alkylating agents or the formation of diazonium salts. Pyrylium tetrafluoroborate serves as activating agent of aminoheterocycles and primes them for S_NAr reactions after simple condensation with the amino group. The method has proven robust in the synthesis of C–O, C–N, C–S and C–SO_2R bonds in a variety of aminoheterocycles. The excellent chemoselectivity of Pyry-BF_4 to condense with amino groups has served for the facile modification of both natural products and synthetic drugs. Importantly **1**, could also be applied in the context of nucleoside synthesis as exemplified by the simple and practical modification of adenosine.

Keywords: pyrylium • amination • C–N activation • late-stage functionalization • heterocycles

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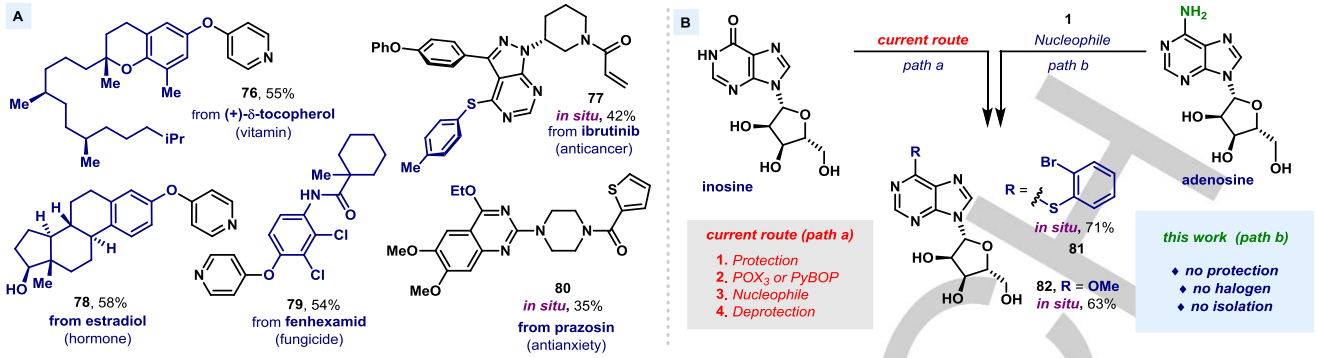

Figure 2. (**A**) Pharmaceuticals, agrochemicals and natural products; (**B**) Modification of nucleoside adenosine.

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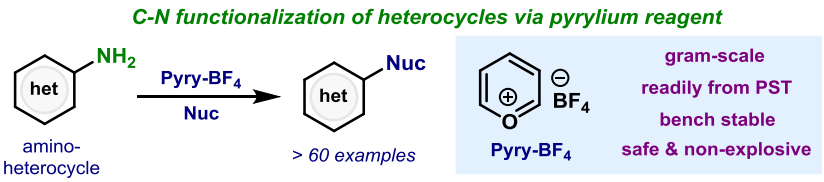

Pyry-BF_4 has been identified as a broadly useful reagent for the activation of heteroaromatic amines and subsequent functionalization to forge C–N, C–O and C–S bonds. The transformation displays remarkable chemoselectivity enabling its use in late-stage contexts.