Deaminative chlorination of aminoheterocycles

Clément Ghiazza, Teresa Faber, Alejandro Gómez-Palomino and Josep Cornella

Selective modification of heteroatom-containing aromatic structures is in high demand as it permits rapid evaluation of molecular complexity in advanced intermediates. Inspired by the selectivity of deaminases in nature, herein we present a simple methodology that enables the NH₂ groups in aminoheterocycles to be conceived as masked modification handles. With the aid of a simple pyrylium reagent and a cheap chloride source, C(sp²)–NH₂ can be converted into C(sp²)–Cl bonds. The method is characterized by its wide functional group tolerance and substrate scope, allowing the modification of >20 different classes of heteroaromatic motifs (five- and six-membered heterocycles), bearing numerous sensitive motifs. The facile conversion of NH₂ into Cl in a late-stage fashion enables practitioners to apply Sandmeyer- and Vilsmeier-type transforms without the burden of explosive and unsafe diazonium salts, stoichiometric transition metals or highly oxidizing and unselective chlorinating agents.

It is demonstrated to be applicable to five different classes of heteroaromatic compounds, natural products, vitamins, DNA, RNA and so on (Fig. 1b–e). Hence, the conversion of the NH₂ group into a modular electrophilic C(sp²)–Cl bond is desired. The method smoothly converts NH₂ groups from heteroaromatic compounds into heteroaryl chlorides by means of a simple and commercially available pyrylium reagent (Pyry-BF₄, 1)² and various chloride sources (Fig. 1d). The method is demonstrated to be applicable to >20 distinct types of heterocyclic motifs, including both five- and six-membered rings containing N, O and S atoms. Importantly, the protocol is characterized by the broad functional group tolerance, thus permitting the formation of electrophilic C(sp²)–Cl bonds onto complex pharmaceuticals, agrochemicals and natural products in a late-stage fashion. To contextualize the functional group tolerance of the reported methodology, we benchmarked our system with the state-of-the-art Sandmeyer conditions, demonstrating that our protocol is truly enabling in providing the heteroaryl chloride. Finally, we show that this reactivity is not limited to chloride anions, and we demonstrate that bromide as well as fluoride can also deliver the halogenated product.

Results and discussion

Our investigations started with an interesting behaviour observed for the Zincke salt in solution. When 1-chloro-2,4-dinitrobenzene (2) is refluxed in the presence of pyridine (3), the Zincke salt precipitates in quantitative yields (4) and is easily separated and purified by filtration (Fig. 2a). Yet, when 4 is dissolved in MeCN, partial formation of 2 and 3 was observed in a 1:1 ratio, suggesting a reversible process. Increasing the temperature and diluting the solution led to the almost quantitative recovery of the 1-chloro-2,4-dinitrobenzene (2) as well as pyridine (3). Despite the wealth of literature for the reaction of nucleophiles with the Zincke salt, the use of the chloride counterion as a nucleophile to recover the parent aryl chloride 2 remained largely underexplored. Although a plethora of examples of nucleophilic aromatic substitution exist with Cl regarded as

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the leaving group, reports on its role as nucleophile are comparatively much less exploited\(^{20-21}\). Inspired by these observations, we speculated that a similar behaviour could be translated to other arylpyridinium chloride systems, namely the product of oxidative deaminative chlorination strategy. To test this hypothesis, we subjected oxazole (Fig. 2b) to promote the formation of pyridinium chloride with Pyry-BF\(_4\). This result immediately suggested that this phenomenon is not restricted to activated aryl moieties but also extends to heteroaromatic substrates. Our group has recently reported on the synthesis and properties of a simple pyrylium reagent (Pyry-BF\(_4\), 1) and its capacity to engage certain azines in Zincke-type reactivity\(^{25-27}\); although narrow in scope, the Pyry-BF\(_4\) displayed high chemoselectivity for amino groups. Then, we envisaged that a merger of the reactivity observed in Fig. 2b in combination with the selectivity offered by Pyry-BF\(_4\) would provide an opportunity for a broad and chemoselective deaminative chlorination strategy. To test this hypothesis, we subjected oxazole 9 to pyridinium formation with Pyry-BF\(_4\) (1), which smoothly afforded pyridinium tetrafluoroborate 10 (Fig. 2c). At this point, various chloride sources were examined to effect an anion exchange and trigger the conversion of the C(sp\(^2\))–Cl bond to a C(sp\(^2\))–N bond (Fig. 2c, inset table). When using an etherated HCl solution, complete chlorination was obtained at room temperature (Fig. 2c, entry 1, inset table). The use of a non-Brønsted acid counterion such as MgCl\(_2\) boded well and smoothly delivered 11 at 80 °C (Fig. 2c, entry 2, inset table). Noteworthily, 2.0 equivalents of trimethylsilyl chloride (TMSCl) quantitatively furnished the desired oxazolyl chloride 11 under milder conditions (Fig. 2c, entry 3, inset table). Anticipating potential issues when translating this methodology to complex molecules bearing acid-sensitive functionalities, we tested a chloride source bearing a non-coordinating cation. The use of 4.0 equivalents of \(^{11}\)Bu\(_2\)NCl displaced the pyridine and forged 11 in excellent yields (Fig. 2c, entry 4, inset table). To provide facile and practical set-ups, a single-flask operation was established, which enables the formation of the pyridinium salt and subsequent chlorination in high yields with no special precautions required (Fig. 2d). In order to increase the translational potential of the methodology, we demonstrated that alternative solvents with higher boiling points than MeCN such as benzonitrile, \(\sigma\)-xlenes or propylene carbonate were also amenable for this one-pot sequence.

Having established a protocol using various chloride sources, we turned our attention to explore the scope of the aminoheterocycle (Table 1). First, we engaged a panel of 4- and 2-aminopyridines (7, 12–20). Tuning the temperature turned out to be crucial to achieve satisfactory yields and accommodate functionalities such as halides (12, 14), aromatic rings (16, 17), an ester (15), a morpholine (18), a nitro (19) or a cyano (20). Diazines, including pyrimidine (21, 22)
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which include drugs such as riluzole, boded well with the protodeamination process for successfully chlorinated at the two position of the pyridine motif (Fig. 2). Gratifyingly, when the deaminative protocol was applied to hepatitis B pro-drug adefovir diethyl, analogue 11 was tolerating the presence of the rather weak N-O bond of oxadiazole, among others. Insecticide fipronil bearing a cyano and a trifluoromethylsulfoxide embedded in a pyrazolyl ring posed no difficulties for chlorination (50). Despite the presence of a Michael acceptor and a piperidinyl moiety, chlorination of the pyrazolopyrimidine core of anti-cancer brivanib smoothly occurred in 87% yield (51). Benzothiazole derivative from sulfadoxine was smoothly converted, yielding 45% of 11. Benzo fused five-membered rings bearing other heteroatoms, such as benzoazole and isobenzothiazoles, which include drugs such as sulfoxide, were smoothly converted to their chlorinated analogues in very good yields (26 and 27). Contrary to most strategies based on the Vilsmeier approach, our protocol boded well with five-membered heteroaromatic amines. For example, fused triazolopyridine, a motif present in certain sodium current inhibitors, smoothly afforded compound 28 in excellent yields (34). Benzo fused five-membered rings bearing other heteroatoms, such as benzoazole and isobenzothiazoles, which include drugs such as sulfoxide, were smoothly converted to their chlorinated analogues. Simple five-membered rings bearing sensitive functionalities such as ester or oxime were also well tolerated, as exemplified by 11 and 32. To further study the functional group tolerance, a variety of oxazole-based compounds bearing pendant functionalities were scrutinized. The presence of halogens (Cl, I, Br, F), pyridine, cinnamonyl, cyano, methylsulfonyl or even aldehyde posed no difficulties for chlorination (33–40). Heterocycles bearing three heteroatoms prone to ring-opening such as thiazoiazole and oxadiazole (41, 42) were smoothly chlorinated in high yields. The presence of a free secondary alcohol in 43 required the use of Bu4NCl to avoid side reactions through Mg-induced dehydration. Based on the functional group tolerance observed, we envisaged our protocol to be applicable to more complex and densely functionalized bioactive molecules. Gratifyingly, when the deaminative protocol was applied to hepatitis B pro-drug adefovir diethyl, analogue 44 was obtained in 57% yield. The anti-inflammatory ameloxan was successfully chlorinated at the two position of the pyridine motif (45).

Thiazole derivatives from amoxapine, paroxetine or SF3-containing building blocks behaved well and were smoothly converted to the corresponding chloride in high yields (46–48). Remarkably, chlorination of the pyrimidine moiety in lipoygenase-activating protein antagonist (BI-665915) was obtained in 38% yield (49), tolerating the presence of the rather weak N-O bond of oxadiazole, among others. Insecticide fipronil bearing a cyano and a trifluoromethylsulfoxide embedded in a pyrazolyl ring posed no difficulties for chlorination (50). Despite the presence of a Michael acceptor and a piperidinyl moiety, chlorination of the pyrazolopyrimidine core of anti-cancer brivanib smoothly occurred in 87% yield (51). Benzothiazole derivative from sulfadoxine was smoothly converted, yielding 54% of 52 using HCl at room temperature. Interestingly, when MgCl2 at high temperature was used instead, chlorination was accompanied by a demethylation of one –OMe group from the pyrimidine (Supplementary Information, page 36 for details). Finally, another anti-cancer medication such as dabrafenib was also similarly subjected to chlorination, obtaining 40% of 53. To fully benchmark the usefulness of the protocol developed herein, some of the most critical examples were also tested under state-of-the-art Sandmeyer conditions. Whereas 24, 30 and 32 could be obtained under Sandmeyer conditions, the yields were comparably lower than when our protocol was applied. Although the Sandmeyer conditions were not optimized for each substrate and a general protocol was applied, no product was detected in any of the other ten challenging substrates tested. Decomposition of the compounds leading to intractable mixtures was the general trend.

Unlocking a late-stage deaminative chlorination strategy permits the incorporation of all the well-known reactions for aryl halides to be applied in a late-stage functionalization context (Fig. 3a). For example, C(sp2)=C(sp2), C(sp3)=C(sp2) and C(sp3)=C(sp3) cross-couplings can now be carried out in substrates where such reactivity was limited (Negishi 54, Suzuki 55 and Sonogashira 56).
Nucleophilic aromatic substitution, one of the most robust and utilized reactions with aryl halides, is also within reach; aliphatic amines, both primary and secondary, including duloxetine, can be incorporated in high yields through simple protocols (37, 58). Secondary alcohols such as cholesterol can be easily decorated with a benzothiazole group in good yield (57, 59). Other nucleophiles, namely...
fluoride and azide, were also engaged and displaced the Cl atom, leading to valuable products (60, 61). With the aim of highlighting the practicality of the method, a telescoped three-step sequence to the pyrrolidine-functionalized analogue of 62 was attempted; 63 could be obtained in 47% yield without the need for purification of the pyridinium or chlorinated intermediate (Fig. 3b).

The scalability of the protocol was demonstrated by the gram-scale reaction performed on 64 without erosion of the yield (32; Fig. 4a). The deaminative halogenation was also extended to other halogens. For example, both five- and six-membered rings could be smoothly brominated using simple LiBr or MgBr₂ (other halogens. For example, both five- and six-membered rings; Fig. 4a). The deaminative halogenation was also extended to 32 (64 gram-scale reaction performed on 62 without erosion of the yield the pyridinium or chlorinated intermediate (Fig. 3b). could be obtained in 47% yield without the need for purification of 63 was attempted; 60 to the pyrrolidine-functionalized analogue of 62 was attempted; 63 could be obtained in 47% yield without the need for purification of the pyridinium or chlorinated intermediate (Fig. 3b).

Conclusions

Inspired by natural deaminases, we herein report a synthetic tool that enables the conversion of C(sp²)-NH₂ groups into C(sp²)-Cl in high chemoselectivity under mild conditions. The use of the simple Pyry-BF₄ selectively targets the NH₂ attached to a heterocyclic motif and primes it for reactivity by converting it into a pyridinium intermediate, which further reacts with a chloride source. This protocol merges the potential of the venerable Vilsmeier reaction to decorate aromatic heterocycles, with the ubiquity of aminoheterocycles, resulting in a deaminative chlorination protocol that avoids the use of explosive intermediates or strongly oxidizing reagents. As a result, the high chemoselectivity permits the chlorination of >40 compounds containing a myriad of functional groups, embedded in >20 different aminoheterocycles including five- and six-membered rings. The method is easily scalable, without the need for air-extrusion and without problematic runaway exotherms. Deaminative bromination of the amino group has also

Fig. 3 | Deaminative chlorination bridges the wide availability of aminoheterocycles with the powerful chemistry of aryl chlorides. a. Examples of derivatization of aryl chlorides from the parent aminoheterocycle. Details for the procedures for each particular example can be found in the Supplementary Information, section VI, ‘Post-functionalization’. b. Telescoped deaminochlorination followed by nucleophilic aromatic amination. DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; 1°, primary; 2°, secondary; SnAr, nucleophilic aromatic substitution.

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been demonstrated with a similar efficiency. More importantly, this deaminative chlorination protocol was applicable to the late-stage chlorination of various drugs and agrochemicals, thus permitting post-modification of complex structures beyond the realms of the Sandmeyer reaction. The method has been shown to extend to other halogenation processes, namely bromination and fluorination. We believe this methodology provides practitioners with an alternative tool that will permit the scrutiny of unexplored chemical space and ultimately accelerate the drug discovery process.

Online content
Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41557-021-00812-0.

Received: 30 March 2021; Accepted: 13 September 2021; Published online: 16 December 2021

References
1. Blakemore, D. C. et al. Organic synthesis provides opportunities to transform drug discovery. Nat. Chem. 10, 383–394 (2018).
2. Bode, J. W. Chemical protein synthesis with the α-ketoacid–hydroxylamine ligation. Acc. Chem. Res. 50, 2104–2115 (2017).
3. Ko, T.-P. et al. Crystal structure of yeast cytosine deaminase. J. Biol. Chem. 278, 19111–19117 (2003).
4. Sklenak, S., Yao, L., Cuikier, R. I. & Yan, H. Catalytic mechanism of yeast cytosine deaminase: an ONIOM computational study. J. Am. Chem. Soc. 14879–14889 (2004).
5. Luo, Y. R. Comprehensive Handbook of Chemical Bond Energies (CRC Press, 2007).
6. Baumann, M. & Baxendale, I. R. An overview of the synthetic routes to the best selling drugs containing 6-membered heterocycles. Beilstein J. Org. Chem. 9, 2265–2319 (2013).
7. Saini, M. S., Kumar, A., Dwivedi, J. & Singh, R. A review: biological significances of cyclohexyclic compounds. Int. J. Pharm. Sci. Res. 4, 66–77 (2013).
8. Vitakü, E., Smith, D. T. & Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. J. Med. Chem. 57, 10257–10274 (2014).
9. Levy, J. N. et al. Selective halogenation of pyridines using designed phosphine reagents. J. Am. Chem. Soc. 142, 11295–11305 (2020).
10. He, L., Qiu, G., Gao, Y. & Wu, J. Removal of amino groups from anilines through diazonium salt-based reactions. Org. Biomol. Chem. 12, 6965–6971 (2014).
11. Mo, F., Dong, G., Zhang, Y. & Wang, J. Recent applications of arene diazonium salts in organic synthesis. Org. Biomol. Chem. 11, 1582–1593 (2013).
12. Firth, J. D. & Fairlamb, I. J. S. A need for caution in the preparation and application of synthetically versatile ary1 diazonium tetrafluoroborate salts. Org. Lett. 22, 7057–7059 (2020).
13. Sheng, M., Frurip, D. & Gorman, D. Reactive chemical hazards of diazonium salts. J. Loss Prev. Process Ind. 38, 114–118 (2015).
14. Ashworth, I. W., Dirat, O., Teasdale, A. & Whiting, M. Potential for the formation of N-nitrosoamines during the manufacture of active pharmaceutical ingredients: an assessment of the risk posed by trace nitrite in water. Org. Process Res. Dev. 24, 1629–1646 (2020).
15. Su, W. et al. Recent progress in the use of Vilsmeier-type reagents. Org. Prep. Proced. Int. 52, 503–555 (2010).
16. Joule, J. A. & Mills, K. Heterocyclic Chemistry (John Wiley & Sons, 2008).
17. Pang, Y., Moser, D. & Cornella, J. Pyrrole salts: selective reagents for the activation of primary amino groups in organic synthesis. Synthesis 52, 489–503 (2020).
18. Michels, T. D., Rhee, I. U. & Vanderwal, C. D. Synthesis of 8-trifluoromethyl-α βγ,β-unsaturated aldehydes from pyridines. Org. Lett. 10, 4787–4790 (2008).
19. Fier, P. S. A bifunctional reagent designed for the mild, nucleophilic functionalization of pyridines. J. Am. Chem. Soc. 139, 9499–9502 (2017).
20. Ullmann, F. & Nádai, G. Über die herstellung von α-nitrierten aminen aus den entsprechenden phenoldervaten. Ber. Dtsch. Chem. Ges. 41, 1870–1878 (1908).
21. Bunnett, J. F. & Zahler, R. E. Aromatic nucleophilic substitution reactions. Chem. Rev. 49, 273–412 (1951).
22. Attia, M. et al. Linear free energy relationships in the thiophene series. Part 3. A kinetic study of chlorine-isotopic exchange between lithium chloride and some 2-chloro-3-nitro-5-X-thiophenes. J. Chem. Soc.Perkin Trans. 2, 1637–1641 (1984).
23. Sekiguchi, S., Ishikura, H., Hirosawa, Y. & Ono, N. Aromatic nucleophilic substitution reactions of 1-dialkylamino-substituted activated benzenes with various amines in dimethyl sulfoxide. Tetrahedron 46, 5567–5578 (1990).
24. Gurinov, A. A., Lesnichin, S. B., Limbach, H.-H. & Shenderovich, I. G. How short is the strongest hydrogen bond in the proton-bound homodimers of pyridine derivatives? J. Phys. Chem. A 118, 10804–10812 (2014).
25. Gómez-Palomo, A. & Cornella, J. Selective late-stage sulfonyl chloride formation from sulfonamides enabled by Pyry-BF3. Angew. Chem. Int. Ed. 58, 18235–18239 (2019).
26. Moser, D. et al. Selective functionalization of aminoheterocycles by a pyrylium salt. Angew. Chem. Int. Ed. 57, 11035–11039 (2018).
27. Pérez-Palau, M. & Cornella, J. Synthesis of sulfonyl fluorides from sulfonamides. Eur. J. Org. Chem. 2020, 2497–2500 (2020).
28. Koltun, D. O. et al. Discovery of triazolopyridine GS-458967, a late sodium current inhibitor (Late $I_{Na}$) of the cardiac NaV 1.5 channel with improved efficacy and potency relative to ranolazine. *Bioorg. Med. Chem. Lett.* 26, 3202–3206 (2016).

29. Becher, J. Synthesis and reactions of glutacinaldehyde and 5-amino-2,4-pentadienals. *Synthesis* 1980, 589–612 (1980).

30. Kearney, A. M. & Vanderwal, C. D. Synthesis of nitrogen heterocycles by the ring opening of pyridinium salts. *Angew. Chem. Int. Ed.* 45, 7803–7806 (2006).

31. Sowmiah, S., Esperança, J. M. S. S., Rebelo, L. P. N. & Afonso, C. A. M. Pyridinium salts: from synthesis to reactivity and applications. *Org. Chem. Front.* 5, 453–493 (2018).

32. Liu, W. et al. Biochemical and structural analysis of the *Klebsiella pneumoniae* cytidine deaminase CDA. *Biochem. Biophys. Res. Commun.* 519, 280–286 (2019).
Methods

General procedure for the chlorination of amino heteroaromatic compounds.

Unless otherwise specified, an 18 ml screw-capped tube under normal atmosphere is charged with pyrylium tetrafluoroborate 1 (1.5 equiv) and MgCl2 (2.0 equiv). The starting material (1.0 equiv) is then added and directly followed by CH3CN (0.1 M). The resulting mixture is then stirred 5 minutes at 25 °C and then 16 hours at 120 °C. The reaction is allowed to cool to 25 °C. The crude mixture is partitioned between water and EtOAc. The aqueous layer is extracted with EtOAc (3 × 10 ml). The combined organic layers are dried over Na2SO4, concentrated to dryness and purified on silica gel to afford the desired product.

Data availability

The Supplementary Information contains all experimental procedures and analytical data (1H, 19F, 31P, 13C, high-resolution mass spectrometry and crystallographic data) for all compounds, all reversibility experiments and the complete optimization study as well as a limitations section. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2070324 (43) and 2086010 (52). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.

Acknowledgements

Financial support for this work was provided by Max Planck Gesellschaft, Max Planck Institut für Kohlenforschung and Fonds der Chemischen Industrie (FCl-VCI). C.G. thanks the Alexander von Humboldt Stiftung for a postdoctoral fellowship. We thank J. Kan for the picture render of the deaminase in Fig. 1a. We are also grateful to the Open Innovation Portal of Boehringer Ingelheim (OpnMe) for providing samples of BI-665915. We thank M. Leutzsch for help with the NMR and R. Goddard and N. Nothling for X-ray support. We specially thank A. Fürstner for insightful discussions and generous support.

Author contributions

C.G. optimized the process, designed the approach, performed the experiments, analysed the experimental data, prepared the Supplementary Information and helped in the manuscript preparation. T.F. contributed to expanding the applicability of the protocol to certain five-membered rings. A.G.-P. contributed at the initial stages of the project and found conditions in the chlorination and bromination. J.C. conceived the idea, directed the investigations and prepared the manuscript.

Funding

Open access funding provided by Max Planck Society.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41557-021-00812-0.

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Peer review information Nature Chemistry thanks Patrick Fier and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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