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Anticancer-Active *N*-Heteroaryl Amines Syntheses: Nucleophilic Amination of *N*-Heteroaryl Alkyl Ethers with Amines

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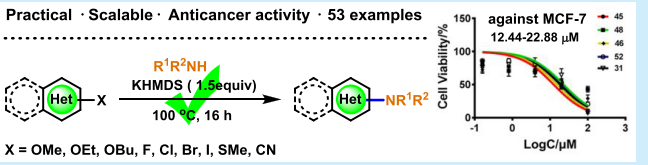
Supporting Information

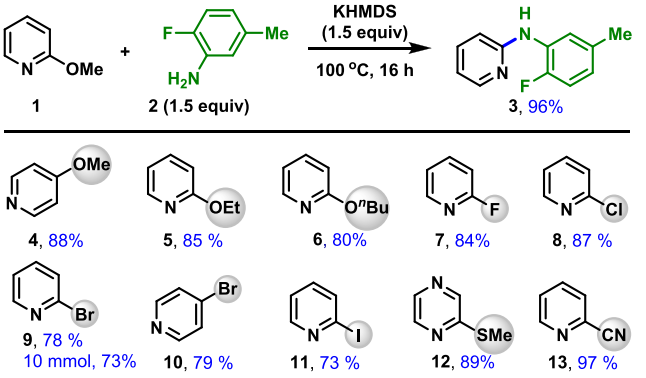
ABSTRACT: A mild amination protocol of *N*-heteroaryl alkyl ethers with various amines is described. This transformation is achieved by utilizing simple and readily available base as promoter via C−O bond cleavage, offering a new amination strategy to access several anticancer-active compounds. This work is highlighted by the excellent functional group compatibility, scalability, wide substrate scope, and easy derivatization of a variety of drugs.



N-Heteroaryl aryl amines frequently constitute cores of a wide range of anticancer pharmaceuticals.[1] For example, erlotinib as an epidermal growth factor receptor (EGFR) inhibitor possesses a *N*-phenylquinazolin-4-amine skeleton,[2] and neratinib, a human epidermal growth factor receptor-2 (HER2) inhibitor holding a *N*-phenylquinolin-4-amine structure.[3] Motivated by recognizing the importance of *N*-heteroaryl aryl amines in drugs, the cost-effective and facile synthesis of them thus have attracted intensive attention from organic synthetic chemists in the last few decades.[4] Among these, the amination of *N*-heteroaryl halides with readily available amines have been the subjects of a great deal of investigation and achieved marvelous progresses.[5] For example, Buchwald−Hartwig,[6] Ullmann type,[7] and Chan-Lam type couplings[8] have become three of the most widely employed techniques for C−N bond formation.[9] Nevertheless, the amination of heteroaryl methyl ether with aniline derivative via transition-metal-catalyzed C−OMe bond cleavage have not yet been achieved to the best of our knowledge. This might be explained by the high activation energy of C(sp^2)−OMe bond[10] and the inherent coordination property of heteroarenes.[11] As part of our interest in developing practical and cost-effective C−N bond formation reactions,[12] we wondered if the amination of *N*-heteroaryl methyl ethers could be achieved by metal-free process due to the electron-deficient nature of them.[13] We herein describe a base enabled practical amination protocol that can incorporate various aryl amines into *N*-heteroarenes, thus allowing us to obtain pharmaceutically significant *N*-heteroaryl aryl amines and find several anticancer active molecules.

We started our study by investigating the amination of 2-methoxypyridine **1** with aniline **2**, and obtained optimal reaction conditions after a detailed screening. The desired product **3** was generated in 96% isolated yield under the optimized reaction conditions: potassium bis(trimethylsilyl) amide (KHMDS, 1.5 equiv) in THF at 100 °C for 16 h (Scheme 1). Efforts were next

Scheme 1. Amination of Pyridyl Ethers and Other Nucleofuges[a]



[a]Reaction conditions: *N*-heteroaryl alkyl ether (0.5 mmol), aniline (0.75 mmol), KHMDS (0.75 mmol, 1.0 M in THF), 100 °C, 16 h.

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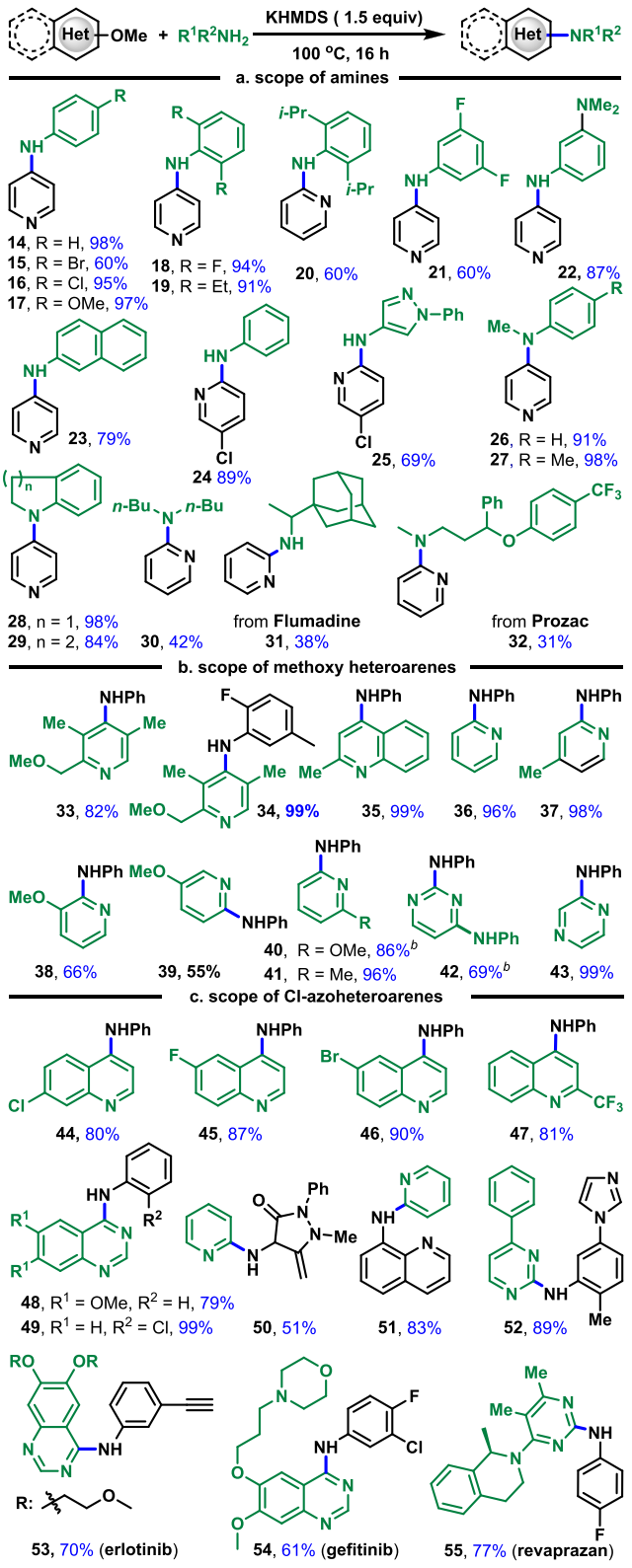
dedicated to the amination of other *N*-heteroarenes with **2**. Gladly, other alkoxy pyridines such as **4**, **5**, and **6** could take part in the transformation in high efficiency. The use of 2-fluoro- and 2-chloropyridines (**7**, **8**) led to the generation of **3** in 84% and 87% yield, respectively. Although the reaction conditions were not fully optimized, our protocol was also allowed to achieve the amination of 2-bromo (**9**), 4-bromo (**10**), and 2-iodo (**11**) substituted pyridines, excellent reactivities were observed for these transformations. It is worth noting that the amination reaction of **9** could be scaled up to 10 mmol, generating the aimed amine in 73% yield (1.485 g). These results nicely demonstrated the remarkable advantages of our C−N bond formation strategy since the amination of **9**, **10**, or **11** was usually problematic even with transition-metal-catalyst and choreographed ligand.[6c,d] In addition, 2-methylthiopyrazine and 2-cyanopyridine underwent amination smoothly via C−S[14] and C−C bond cleavage,[15] the corresponding products were obtained in excellent yields (**12**, **13**).

Encouraged by these results, we next studied the scope of aromatic amines as pictured in Scheme 2, the anilines possessing bromo-, chloro-, or fluoro- could participate this transformation without any problem (**15**, **16**, **18**),[12] thus leaving the handle for further complex setting such as transition-metal-catalyzed crossing couplings.[16] Not surprisingly, electron-rich anilines were compatible with this protocol, generating **17** and **22** in 97% and 87% yield, respectively. Electron-deficient aromatic amines are also suitable starting materials for this reaction as proved by **18** and **21**. Additionally, sterically bulky 2,6-diethylaniline and 2,6-diisopropylaniline are well tolerated, producing **19** and **20** smoothly. Although **25** was produced in slightly decreased yield, it demonstrated that five-membered *N*-heteroaromatic amine was compatible with the reaction conditions. Secondary acyclic and cyclic amine derivatives could also undergo amination, providing the corresponding products in excellent yields (**26**−**29**). Apart from aromatic amines, we also found that the use of aliphatic amines such as dibutylamine (**30**), flimadine (**31**, an anti-influenza virus drug),[17] and prozac (**32**, an antidepressant drug)[18] could gave the desired products albeit in moderate efficiency.

Furthermore, we examined the generality of *N*-heteroarenes of our newly developed amination protocol. The employment of sterically hindered pyridine substrates did not suppress the reactivity, and **33** and **34** were isolated in excellent yields. Aniline could also be incorporated into 4-position of quinoline (**35**) and 2-position of pyridines in quantitative yields (**35**, **36**). Interestingly, excellent regioselectivity was observed for the 2,3- or 2,5-dimethoxy substituted pyridine, the amination proceeded exclusively at the *ortho*-positions of pyridines, whereas the methoxy groups at *meta*-positions of pyridines were remained unreacted (**38**, **39**). We also witnessed the difference in terms of reactivity between dimethoxy substituted pyridine and pyrimidine. As shown, while the use of pyridine offered a monoamination product **40**, double amination took place for pyrimidine substrate (**42**). This might be explained by the fact that pyrimidine is more reactive than pyridine due to more electron-deficient nature of pyrimidine. The utilization of 2-methoxypyrazine also afforded the targeted amine in quantitative yield (**43**).

We then focused on chloroquinoline substrates since quinoline structure widely exists in many pharmaceutics such as anticancer drug neratinib.[3] As presented, halogens such as fluoro-, bromo-, and chloro- are well-tolerated, and the corresponding diarylated amines **44**-**46** were provided in 80%, 87%, and 90% yield, respectively. The presence of trifluoromethyl group did not significantly affect the reactivity of quinoline (**47**). The protocol could be further applied to

Scheme 2. Scope of Amination Reaction[a]



[a]Reaction conditions: *N*-heteroarene (0.5 mmol), amine (0.75 mmol), KHMDS (0.75 mmol, 1.0 M in THF), 100 °C, 16 h. [b]Three equivalents of amine and KHMDS were used.

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synthesize more complicated amines in good to excellent yields (**48**, **49**). Heterocyclic amines were also compatible with the standard reaction conditions, giving the final products in moderate to excellent yields (**50**−**52**). To further demonstrate the utility of newly developed method, we then turned our attention to the preparation of several drugs. We chose anticancer drugs erlotinib[2] (**53**) and gefitinib[19] (**54**), and antigastritis drug revaprazan[20] (**55**) as our aimed molecules to synthesize. Although not fully optimized, erlotinib, gefitinib, and revaprazan could be produced in 70%, 77%, and 61% yield under the given reaction conditions.

After having the substrate scope in hand, we next moved to examine the anticancer activity of the synthesized diaryl amines. We tested the activity of all the products on various human tumor cell lines such as HCT-116, MDA-MB-231, H1299, MCF-7, HeLa, HepG2, and A549. We found out that several *N*-heteroaryl amines such as **45**, **46**, **48**, and **52** have comprehensive toxicity toward the cell lines that we tested (see Figures 1A, S1, and S2). Interestingly, small molecules **45**

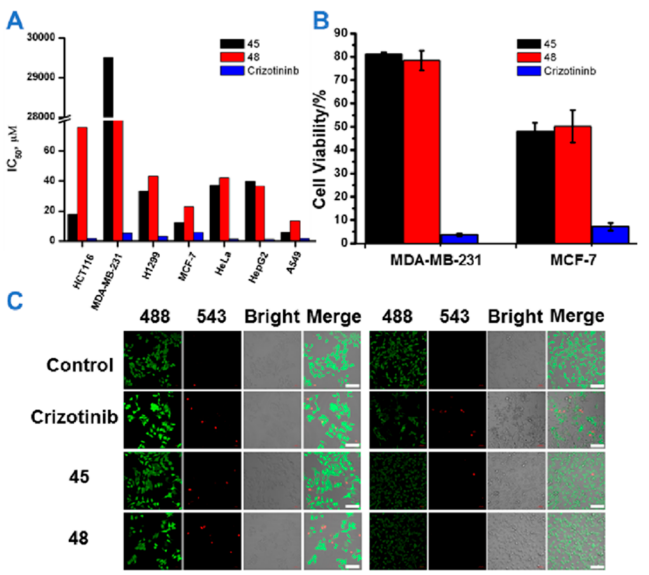

Figure 1. Cell cytotoxicities of **45** and **48** to cancer cell lines. (A) IC_{50} of **45**, **48**, and crizotinib for 72 h to different cancer cell lines, HCT116, MDA-MB-231, H1299, MCF-7, HeLa, HepG2, and A549 cells. (B) Cell viabilities of MCF-7 and MDA-MB-231 cells treated with 20 μM **45**, **48**, and crizotinib for 72 h, respectively. (C) Confocal laser scanning microscopy images of MCF-7 (left) and MDA-MB-231 (right) treated with 20 μM **45** or **48** or 5 μM crizotinib for 48 h respectively, as stained with calcein-AM and PI. Scale bar = 100 μm.

(IC_{50} = 12.44 μM) and **48** (IC_{50} = 22.88 μM) could selectively induce the death of breast cancer cell (MCF-7 cell) at 20 μM, while they had negligible anticancer effect against triple-negative breast cancer cell (MDA-MB-231 cell, Figures 1B and S2). Confocal images were then taken to visualize the anticancer effect of **45** and **48**. We utilized calcein-AM and propidium iodiate (PI) to stain the live and dead cells, respectively. While calcien-AM was activated by cytosolic esterase in live cells and showed green fluorescence by using the confocal imaging at the wavelength of 488 nm, red fluorescent PI permeated into the dead cells and stained the nucleic acid (536 nm excitation). Through the bright field, the total number of cells were easy to observe. Ratios of red fluorescence in MCF-7 cells treated by **45**, **48**, and crizotinib (an anaplastic lymphoma kinase and c-ros oncogene 1 inhibitor) were higher than the nontreated cells.

As for MDA-MB-231 cell, these two molecules showed no activity when compared with crizotinib. These results are in line with the quantitative toxicity assay (Figure 1C). To further confirm the anticancer activity of compounds **45** and **48** for MCF-7 cell, we then carried out Annexin V/PI apoptosis assay by flow cytometry. As shown in Figure 2A, the apoptosis

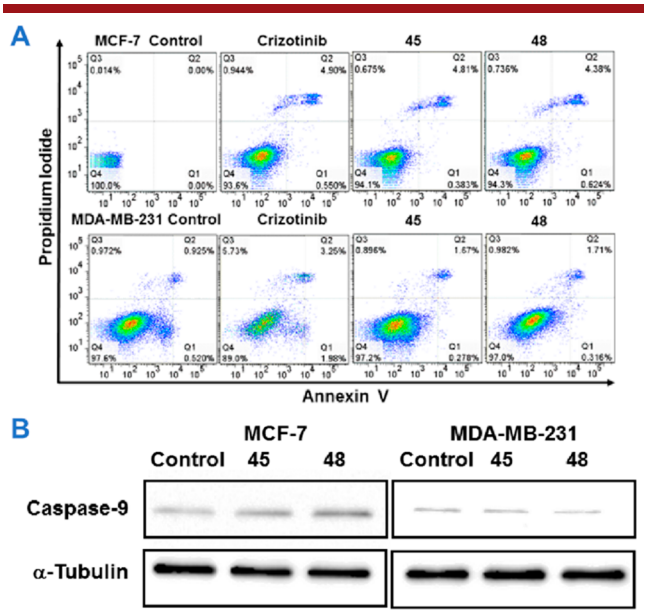

Figure 2. Cell apoptosis of MCF-7 and MDA-MB-231 cell induced by **45** and **48**. (A) Annexin V/PI apoptosis assay. The concentration of **45** and **48** was 20 μM and crizotininb was 5 μM. The cells were incubated with these small molecules for 12 h. (B) Expression of caspase-9 of these two cell lines after treated with 20 μM **45** or **48** or 5 μM crizotinib for 24 h. α-Tubulin was the reference protein.

percentages of MCF-7 cell that were induced by **45** and **48** at the concentration of 20 μM were close to crizotinib at the concentration of 5 μM for 12 h. In contrast, **45** and **48** were not as efficient as crizotinib when they were incubated with MDA-MB-231 cells. To rationalize these results, we examined the expression of caspase-9, an enzyme that is critical to the apoptotic pathway found in many tissues. As expected, while the increased expression of caspase-9 was detected when MCF-7 cell was treated with **45** or **48** (Figure 2B), MDA-MB-231 cell did not display obvious difference between control and these two molecules, which is in line with the quantitative toxicity assay. All the cell cytotoxicity evaluation results indicated that compounds **45** and **48** might have a different anticancer mechanism as crizotinib.

In summary, we have reported a practical and environmentally benign amination protocol that is capable of efficiently incorporating both aromatic and aliphatic amines into *N*-heteroarenes, generating the drug relevant amines in good to excellent yields. This strategy is distinguished by its excellent substrate scope: a wide range of amines include primary and bulky secondary amines were suitable to undergo amination. The usefulness of our method has been verified by the production of drugs such as revaprazan, erlotinib, and gefitinib, gram-scale-reactions, and the derivatization of a variety of drugs and biologically active molecules. Furthermore, we tested the anticancer activity of all the generated products and found out

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45 and **48** could efficiently inhibit the growth of a range of cancer cell lines. The preliminary mechanistic studies implied that **45** and **48** are different from crizotinib as anticancer compounds. Further detailed mechanistic studies are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01711.

Details on the reaction conditions optimization, general procedure of amination, NMR data, characterization, cell experiments, and Western blot assay (PDF)

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Notes

The authors declare no competing financial interest.

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