From Anilines to Aryl Ethers: A Facile, Efficient, and Versatile Synthetic Method Employing Mild Conditions

Dong-Yu Wang, Ze-Kun Yang, Chao Wang,* Ao Zhang,* and Masanobu Uchiyama*

In memory of Keiji Morokuma

Abstract: We have developed a simple and direct method for the synthesis of aryl ethers by reacting alcohols/phenols (ROH) with aryl ammonium salts (ArNMe$_3^+$), which are readily prepared from anilines (ArNR$_2$, R$^\prime$ = H or Me). This reaction proceeds smoothly and rapidly (within a few hours) at room temperature in the presence of a commercially available base, such as KOtBu or KHMDS, and has a broad substrate scope with respect to both ROH and ArNR$_2$. It is scalable and compatible with a wide range of functional groups.

Amino groups are present in an enormous variety of natural products, as well as in pharmaceuticals, dyes, and many functional molecules. In addition, various amines are produced on an industrial scale and are available at reasonable cost. Therefore, efficient and selective C–N bond transformation methods are of great interest.[1] However, the C–N bonds of amines are generally very stable, and direct transformation of the amino group is difficult even in the presence of transition-metal (TM) catalysts under severe conditions.[2] One approach to overcome this issue is pre-activation of the C–N bond. For example, quaternary organo-ammonium salts can be prepared easily from various amines in high/quantitative yield, and are extremely stable. In 1988, Wenkert et al. pioneered a method for TM-catalysed cross-coupling of ammonium salts through C–N bond cleavage,[3] and it is now well established that ammonium salts show diverse reactivity and synthetic utility as efficient substitutes for halides.[4] Besides TM-catalysed C–C bond-forming reactions, fluorination of aryl C–N bonds in ammonium salts through an S$_2$Ar mechanism has also been reported,[5] and is now used for labeling bioactive molecules with $^{18}$F.

However, although oxygen is an electronegative element like fluorine, there are few reports on the reaction of ammonium salts with alcohols or phenols to afford ethers, despite the great utility that a suitable method would have. Interestingly, ether formation by reacting alcohol (used as EtONa) with ArNMe$_3^+$ salts through cleavage of the aryl C–N bond, leading to ArOEt, was first observed as a side reaction of demethylation of ArNMe$_3^+$ as early as 1942.[6] However, this etherification reaction has since been largely neglected, probably because many other methods for the formation of (aryl) ethers have been developed.[7] Nevertheless, many of these existing methods require harsh conditions, such as a large excess of ROH, high reaction temperature, or undesirable solvent, and hence there is still a requirement for novel, efficient methods. Herein, we report an efficient, selective and easy-handling method for the conversion of anilines (via their ammonium salts) into aryl ethers through reaction with alcohols/phenols in the presence of a base at room temperature, without the need for any TM catalyst.

Aryltrimethyrammonium salts 1 were readily synthesised from various anilines bearing a NH$_2$, NHMe, or NMe$_2$ group[4,8] (for details, see the Supporting Information). We initially examined the reaction of 1a as a model compound with various alcohols and/or phenols 2 (Scheme 1). Optimization of reaction conditions showed that the counterion of the base (e.g., Na$^+$, K$^+$, Cs$^+$) and 1a (e.g., TIO-, I$^-$, BF$_4^-$), and the solvent critically influenced this transformation (Table S1 in the Supporting Information). Under the optimized conditions (KOtBu or KHMDS as a base, DMF solvent, room temperature,[9] within 3 hours), we found that most of the reactions proceeded smoothly to give the desired ether products 3 in good to excellent yields without detectable formation of a demethylation byproduct (Scheme 1). Reactions with simple alcohols such as methanol (2a), ethanol (2b), and iso-propanol (2c) quantitatively afforded ethers 3aa–3ac. Importantly, even bulky tertiary alcohols, including tert-butanol (2d), tert-amy alcohol (2e), and 1-adamantanol (2f) reacted with 1a to form the corresponding products 3ad–3af in high yields. Alcohols bearing a terminal alkylketone moiety (2g) or (free) amino groups (2h–l), as well as allyl or benzyl alcohols 2j–l and diol 2m, also reacted without difficulty, generating the desired etheric products 3ag–3am in 70–96% yield.

[1] Dr. D.-Y. Wang, Prof. Dr. A. Zhang
CAS Key Laboratory of Receptor Research and the State Key Laboratory of Drug Research
Shanghai Institute of Materia Medica (SIMM)
Chinese Academy of Sciences, Shanghai 201203 (China)
and
University of Chinese Academy of Sciences
Beijing 100049 (China)
E-mail: azhang@simm.ac.cn
Z.-K. Yang, Prof. Dr. C. Wang, Prof. Dr. M. Uchiyama
Graduate School of Pharmaceutical Sciences, University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
and
Elements Chemistry Laboratory, RIKEN
2-1 Hirosawa, Wako-shi, Saitama 351-0198 (Japan)
E-mail: chaowang@mol.f.u-tokyo.ac.jp
uchiyama@mol.f.u-tokyo.ac.jp
Prof. Dr. A. Zhang
School of Life Science and Technology, ShanghaiTech University,
Shanghai 201201 (China)

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
https://doi.org/10.1002/anie.201712618.
isolated yields. It is noteworthy that fluorinated alcohols 2n–r were highly reactive towards 1a under the same conditions, affording fluoroalkyl ethers 3an–3ar in good to quantitative yields. Such results indicate broad applicability of the current method for introducing fluorine-containing functional groups during the development of pharmaceuticals and functional materials. Finally, phenols 2s–w and polyphenol 2x also afforded the diaryl ethers 3as–3ax in 64–81% yield of isolated product. It is noteworthy that Br, I, and even boronate were compatible with the reaction conditions, which would facilitate diverse functionalization of the products.

To further investigate the synthetic applicability of this method, we examined the reactions of 1a with various pharmaceuticals, bioactive molecules, natural products, or their derivatives containing an OH moiety (Scheme 2). Despite their complex structures and variety of functional groups, most reactions involving these functional molecules proceeded smoothly and chemoselectively under the same reaction conditions. Not only primary (2A–D) and secondary (2E–L) alcohols, but also sterically congested tertiary ones (2M–N) reacted with 1a to give the corresponding etheric derivatives 3aA–3aN in good to excellent yields. Furthermore, several functionalized phenols (2O–T) underwent this reaction, affording 3aO–3aT with high efficiency, although the yield was significantly reduced when sterically bulky propofol 2S was used.

Next, we investigated the substrate scope with respect to anilines in this reaction (Scheme 3) using commercially available KOR as representative alcohol partners of 2a, 2b, and 2d. Ammonium salts 1 from a variety of anilines reacted smoothly to give the desired ether products 3. First, electron-deficient anilines showed excellent reactivity and chemoselectivity, establishing compatibility of the reaction conditions with a wide range of functional moieties, including nitrile (1a,b), ester (1e), ketone (1d–f), nitro (1g), and sulfone (1h) groups, affording the corresponding aromatic ethers in good to quantitative yields. Second, ammonium salts bearing a halogen (Cl, Br, I) on the phenyl ring (1i–n) could also be used for the reaction, albeit with lower yield in some cases. Third, anilines with an extended π-system, such as 1o–q, reacted without difficulty, affording etheric products in 75–90% yield. More importantly, ammonium salts prepared from dye, bioactive, and pharmaceutical compounds (1A–D) also afforded the etheric derivatives without difficulty, thus suggesting the potential of this reaction for efficient late-stage derivatization of functional molecules.

Limitations and features of this reaction include: 1) ammonium salts derived from electron-rich anilines (e.g., p-R-C_6H_4-NMe_2^+, R = Me, MeO) showed little or no reactivity toward alcohols/phenols; 2) electron-withdrawing groups at the ortho-position of anilines (1b) had little effect on the reactivity or selectivity, whereas the reactions of meta-substituted anilines (e.g., m-R-C_6H_4-NMe_2^+, R = CN, COOEt) were very sluggish; and 3) while bulky alcohols/phenols could participate in the reactions (e.g., 3aM, 3aN, 3Ad, 3Bd, 3Cd), they were much less reactive than sterically unhindered ROH compounds.[10]

As regards the mechanism, ICP-MS analysis of the reaction mixture of 3ad showed that Fe, Co, Ni, Cu, Ru, Rh, Pd, Ag, Os, Ir, Pt, and Au were below the detection limit (1 ppb), so it is very unlikely that TM catalysis plays a significant role. In addition, when the reaction of 1a and 2d was performed in the dark or in the presence of TEMPO...
as a radical scavenger (see Table S1 in the Supporting Information), the yield of 3ad hardly changed, thus excluding radical involvement.\cite{11} Overall, our findings suggest that the current reaction occurs through an $S_{N}Ar$ mechanism,\cite{12} rather than through TM catalysis or a radical process. Detailed mechanistic studies of this reaction are in progress, using both experimental and theoretical methods.\cite{13}

Additional reactions were performed to further examine the scope of this etherification method. Compounds with multiple OH groups (2y and 2z) reacted smoothly with 1a at the less hindered position to give 3ay and 3az, respectively, in high yield as the sole etherified products (Scheme 4A). Furthermore, substrate 1f, which has two ammonium moieties, could react with two different alcohols, 2p and 2a, to afford hybrid etherified product 3f–pa as the main products (Scheme 4B). Finally, we examined the applicability of this reaction for synthesis of pharmaceutical or bioactive molecules. We obtained nitrofen (3ga'; a herbicide) directly from ammonium compound 1g and phenol 2a' in high yield on a gram scale (Scheme 4C). Clorgyline (a monoamine oxidase inhibitor; Scheme 4D) and triparanol (a cholesterol-lowering drug; Scheme 4E) were also synthesized in satisfactory yields by simple transformations of the ether products 3jb' and 3rc', which were readily prepared from 1j/2b' and 1r/2c', respectively.

In summary, we have developed a direct C–O bond formation method involving the reaction of alcohols/phenols with aryl ammonium salts, which are easily prepared from anilines. This reaction proceeds efficiently and selectively at room temperature within a few hours in the absence of any TM catalyst. A great variety of functional molecules containing NR$_2$ or OH moieties, including natural products, pharmaceuticals, and dyes, afforded the corresponding ethers in high yields, and the reaction was also applied to synthesize several molecules of pharmaceutical interest. We believe that this method will be useful for the preparation and/or late-stage derivatization of a wide variety of functional molecules. Mechanistic studies are in progress, as well as further synthetic applications.
Scheme 3. Scope of the reactions of various arylammoniums 1 with 2a, 2b, and 2d as representative alcohol partners (directly used as corresponding potassium alkoxides). Yields were calculated based on NMR (bold) and isolation (in parentheses).

Scheme 4. Scope of the reactions of compounds with two hydroxy or ammonium groups, and applications to the synthesis of pharmaceuticals or bioactive molecules. Yields were calculated based on NMR (bold) and isolation (in parentheses).
Acknowledgements

This work was supported by grants (to A.Z. and D.-Y.W.) from the Chinese NSF (81773565, 81430080, 21702216), the National Program on Key Basic Research Project of China (2015CB910603), the International Cooperative Program (GJHZ1622) and the Key Program of Frontier Science (160621) of the Chinese Academy of Sciences, the Shanghai Commission of Science and Technology (16XD1404600, 14431905300, 14431900400). D.-Y.W. gratefully acknowledges the support of SA-SIBS Scholarship Program and China Postdoctoral Science Foundation. This work was also supported by a JSPS Grant-in-Aid for Scientific Research on Innovative Areas (No. 17H05430), and JSPS KAKENHI (S) (No. 17H06173) (to M.U.), and by grants from Kobayashi International Scholarship Foundation (to M.U. and C.W.), and YakuGaku ShinKeKi Foundation (to C.W.). Z.-K.Y. is grateful for a Junior Research Associate fellowship provided by RIKEN.

Conflict of interest

The authors declare no conflict of interest.

Keywords: amines · C−N cleavage · C−O formation · ethers · late-stage functionalization

How to cite: Angew. Chem. Int. Ed. 2018, 57, 3641–3645
Angew. Chem. 2018, 130, 3703–3707

[9] Room temperature (RT) ranged from 22 to 27°C.
For example, when βBuOK was used as the base, no β-butoxidized products were observed. Furthermore, βBuOK is also less reactive than MeOK toward ortho-substituted anilines such as 1g, 11, and 1m.
[12] Our preliminary DFT calculations suggest that the cation–π interaction might enhance the interaction between the nucleophile and electrophile, stabilizing the transition state (TS) and the Meisenheimer intermediate. However, we are currently examining other possible pathways/important chemistry, such as a counterion-recruited TS, as well as the critical roles of T0 and K−.

Manuscript received: December 8, 2017
Revised manuscript received: February 5, 2018
Accepted manuscript online: February 12, 2018
Version of record online: March 6, 2018