Direct Assembly of Prenylated Heteroarenes through a Cascade Minisci Reaction/Dehydration Sequence

Dong-Hang Tan, Yao-Fu Zeng, Yao Liu, Wen-Xin Lv, Qingjiang Li, and Honggen Wang*[^a]

The prenyl group is an important component in bioactive compounds. Herein, we report the assembly of prenylated heteroarenes through a cascade Minisci reaction and acid-promoted dehydration sequence. The use of potassium (3-hydroxy-3-methylbut-1-yl)trifluoroborate as a new coupling reagent allows the direct introduction of prenyl and 3-hydroxy-3-methylbutyl groups to a wide variety of electron-deficient heteroarenes. Synthetic application is also demonstrated.

The prenyl group is prevalent as a key pharmacophore element in numerous naturally occurring bioactive compounds.[1] For example, many prenylated flavonoids[^1b] and indole alkaloids[^2] have been identified to exhibit diverse bioactivities (Figure 1). It was evidenced that the prenyl group has good binding affinity with proteins, and its incorporation could usually enhance membrane permeability, thereby improving the bioactivity and bioavailability of the corresponding prenylated compounds.[1b] On the other hand, aromatic N-heterocycles are widely occurring in drugs.[3] It is, therefore, of paramount interest to develop synthetic methods for the assembly of prenylated aromatic N-heterocycles, which may find potential applications in drugs, but are nevertheless synthetically challenging to chemists.

In nature, prenyl groups are introduced through enzymatic reactions with prenyl pyrophosphate.[4] The necessity to use specific substrates may limit their synthetic utilities. Alternatively, different synthetic approaches are available to access prenylated arenes in the literature, among which the most common strategy relies on metal-catalyzed cross-coupling reactions (Scheme 1a).[5] The limitation of this strategy is that pre-functionalized arenes and noble-metal catalysts are often needed. Friedel–Crafts-type prenylation of electron-rich arenes offers another straightforward route, with poor regioselectivity and overreaction typically observed (Scheme 1b).[2a, 6] In addition, Claisen rearrangement of allyl ethers is amenable to synthesize prenylated phenols (Scheme 1c).[7] Recently, metal-catalyzed direct prenylations of aryl C–H bonds have been developed,[8] yet the em-
The past years have witnessed the great power of the Minisci reaction for the direct functionalization of heteroarenes, wherein an in situ-generated, nucleophilic, carbon-centered radical reacts with an electron-deficient N-aromatic compound, providing a simple and effective method for late-stage modification of complex heteroarene structures. For instance, in 2010, Baran and co-workers disclosed that aryl radicals generated from aryloboronic acids could add to heterocycles at ambient temperature.

Shortly after that, Molander et al. showed that trifluoroborates served as good radical precursors to realize the direct alkylation of various heterocycles. To develop a general and practical protocol for the synthesis of prenylated heteroarenes, we were drawn to the possibility of using a radical-based transformation. However, the direct use of prenylboron as the prenyl source might be problematic, owing to the propensity of radicals to react with the double bond. To obviate this possibility, we envisioned that potassium (3-hydroxy-3-methylbut-1-yl)trifluoroborate 1, bearing a hydroxyl group might be well suited for this purpose (Scheme 1e).

Our investigation began with the preparation of boronate 2a could be synthesized from arylboronic acids could add to heterocycles at ambient temperature. The 3-hydroxy-3-methylbutyl side chain was introduced, an acid-promoted dehydration of the corresponding tertiary alcohol would give the final prenylated product. Challenges might exist, because the presence of a proximal hydroxyl will attenuate the nucleophilicity of A.

It should be noted that the 3-hydroxy-3-methylbutyl group itself is also a frequently encountered substituent in natural products (Figure 1, in blue).

Effective for the reaction (entries 3 and 4). Different solvents were then screened (entries 5–13). A mixture of TFE/AcOH (4:1, v/v) gave a significantly better result, providing 3a in an 1H NMR yield of 32 %. The elevation of temperature to 60 °C shortened the reaction time and increased the yield to 45 % (entries 14 and 15). The use of TFA as an additive was beneficial for the reactivity, as its omission gave a decreased yield (entry 16). To fulfill a better conversion, increased loadings of 1 (5.0 equiv) and oxidant (6.5 equiv) were employed, and a higher yield of 68 % was obtained (entries 17–19). The use of TFA/AcOH (1:1) as the solvent ensures better reproducibility, owing to an improved solubility of the oxidant (entry 20).

The scope of the reaction was then evaluated on a broad range of nitrogen-containing heteroarenes. As shown in Table 2, 4-bromoquinoline could also be converted to the desired product in 50 % yield (3b). Isoquinoline 2c gave the mono- and bis-alkylated products in a combined yield of 49 %. In addition, benzimidazoles (2d, 2e) and benzothiazoles (2f–h) were also suitable for this transformation. Interestingly, when 5-chloro-benzothiazole 2g was applied, the bis-alkylated...
product at both the C2 and C4 positions was also observed, probably owing to the electron-withdrawing nature of the chloro substituent. Furthermore, phthalazine underwent the reactions smoothly to afford the bis-alkylated product in moderate yield. In accordance with the previous observations, the reaction of pyridines gave a regioisomeric mixture (3j) with alkylation taking place predominantly at the electron-deficient C2 and C4 positions. The use of 2,6-disubstituted pyridine rendered the reaction selective at the C4 position (3k, 3l). Pyridazine (2m), pyrazine (2n), and pyrimidine (2o) bearing two heteroatoms in the aromatic ring all delivered the corresponding products successfully. Five-membered heteroarenes such as thiazole (2p–r) and imidazole (2s) were amenable to alkylation as well. It should be noted that halogen functional groups were tolerated in several cases (3b, 3c, 3g, 3m, 3n, and 3q), thus providing good handles for further derivation of the products.

Having successfully established the method for the introduction of 3-hydroxy-3-methylbutyl group, we turned our attention to the follow-up dehydration reaction. Upon treatment with p-toluenesulfonic acid (1.5 equiv) in toluene at 100 °C, 3a could be smoothly dehydrated to give the desired prenylated product 4a in 87% yield, along with a minor (11%) terminal olefin 5a [Eq. (2)]. This result encouraged us to test the viability of a telescoping synthesis of 4a. Thus, starting from quinoline 2a without the isolation of the intermediate 3a, a decent yield (59%) of 4a was obtained for two steps [Eq. (3)].

The protocol for the telescoping synthesis of prenylated heteroarenes could also be extended to other heterocyclic substrates (Table 3). It was found that isoquinoline (4b), pyridines (4c, 4d), benzothiazoles (4e), benzimidazoles (4f, 4g), pyridazine (4h), and thiazole (4i) all successfully delivered the corresponding prenylated products. Although low yields were obtained in certain cases, the ability for straightforward and late-stage modification of heteroarenes still make this protocol valuable in medicinal chemistry.
In conclusion, to realize the prenylation of N-heteroarenes by using the Minisci reaction, we have designed and synthesized a new coupling reagent, potassium (3-hydroxy-3-methylbut-1-yl)trifluoroborate 1. The reaction of 1 enables the direct introduction of 3-hydroxy-3-methylbutyl and the prenyl group, both of which are frequently encountered in bioactive compounds. Owing to the importance of N-heteroarenes in medicinal chemistry, we anticipate this protocol will find application in the drug-discovery process.

Acknowledgements
We are grateful for the support of this work by The National Key Research and Development Program of China (2016YFA0602900), “1000-Youth Talents Plan”, a Start-up Grant from Sun Yat-sen University and National Natural Science Foundation of China (Nos. 81402794, 21472250 and 21502242).

Keywords: dehydration · heteroarenes · Minisci reaction · prenylation · radical addition

In 2013, Weizhou Zhang, E. Skucas, M. J. Krische, H. Kakeya, G. Okada, R. Onose, H. Osada, J. Antibiot. 1996, 49, 527.

[1] a) V. P. Papageorgiou, A. N. Assimopoulou, E. A. Couladouros, D. Hepworth, K. C. Nicolau, Angew. Chem. Int. Ed. 1999, 38, 270; Angew. Chem. 1999, 111, 280; b) B. Botta, A. Vitali, P. Menendez, D. Misiti, G. Del-ле Monache, Curr. Med. Chem. 2005, 12, 713; c) K. Yasaki, K. Sasaki, Y. Tsurumaru, Phytochemistry 2009, 70, 1739; d) A. M. Alhasan, M. I. Abdullahi, A. Uba, A. Umar, Trop. J. Pharm. Res. 2014, 13, 307; e) A. Visconti, M. Solfrizzo, Food Addit. Contam. 1995, 12, 515; f) S. Wang, Q. Li, M. Jing, E. Alba, X. Yang, R. Sabaté, Y. Han, R. Pli, W. Lan, X. Yang, J. Chern, Neurochem. Res. 2016, 41, 1806; g) C. B. Cui, H. Kakeya, G. Okada, R. Onose, H. Osada, J. Antibiot. 1996, 49, 527.

[2] a) S.-M. Li, Nat. Prod. Rep. 2010, 27, 57; b) L. Lindel, N. Marsch, S. K. Adla, Top. Curr. Chem. 2012, 309, 67.

[3] For selected reviews on aromatic N-heterocycles in drugs, see: a) W. R. Pitt, D. M. Perry, G. C. Room, J. Med. Chern. 2009, 52, 2952; b) N. A. McGrath, M. Brichacek, J. T. Njardarson, J. Chern. Educ. 2010, 87, 1348; c) M. Baumann, I. R. Baxendale, S. V. Ley, N. Nikbin, Beilstein J. Org. Chern. 2011, 7, 442; d) M. Baumann, I. R. Baxendale, Beilstein J. Org. Chern. 2013, 9, 2265; e) R. D. Taylor, M. MacCoss, A. D. G. Lawson, J. Chern. Med. Chern. 2014, 57, 5845.

[4] T. Kuzuyama, J. P. Noel, S. B. Richard, Nature 2005, 435, 983.

[5] For selected metal-catalyzed cross-coupling reactions, see: a) B. H. Lipshutz, S. K. Kim, P. Mollard, P. A. Blomgren, K. L. Stevens, Tetrahedron 1998, 54, 6999; b) F. Kaiser, H.-G. Schmalz, Tetrahedron 2003, 59, 7345–7355; c) D. C. Gerbino, S. D. Mandolesi, H.-G. Schmalz, J. C. Podestá, Eur. J. Org. Chern. 2009, 3964–3972; d) M. Iwasaki, H. Yomitsui, K. Oshima, Bull. Chern. Soc. Jpn. 2009, 82, 249–253; e) K. Anderson, F. Calo, T. Pfaf- feneder, A. J. P. White, A. G. M. Barrett, Org. Lett. 2011, 13, 5748–5750; f) J. L. Farmer, H. N. Hunter, M. G. Organ, J. Am. Chern. Soc. 2012, 134, 17470; g) Y. Yang, T. J. L. Mustard, P. H. Y. Cheong, S. L. Buchwald, Angew. Chern. Int. Ed. 2013, 52, 14098; Angew. Chern. 2013, 125, 14348; h) Y. Yang, S. L. Buchwald, J. Am. Chern. Soc. 2013, 135, 10642; i) T.-Y. Chen, M. J. Krische, Org. Lett. 2013, 15, 2994–2997; j) C. Thomas, Q. Kateeva, A. W. Schmidt, H.-J. Knöller, Org. Biomol. Chern. 2014, 12, 872–875; k) L. Xu, Z. Liu, W. Dong, J. Song, M. Miao, J. X. Hu, R. Ren, Org. Biomol. Chern. 2015, 13, 6333; l) Z. Zhang, L. Xu, Z. Chen, Z. Liu, M. Miao, J. Song, H. Ren, Synlett 2015, 26, 2784; m) M. Ellwart, P. Knochel, Angew. Chem. Int. Ed. 2015, 54, 10662; Angew. Chern. 2015, 127, 10808.

[6] For selected Lewis acid catalyzed prenylation reaction, see: a) S. Araki, S. Manabe, Y. Butsugan, Bull. Chern. Soc. Jpn. 1984, 57, 1433; b) M. S. Ramachandran, G. V. Subbarao, Synth. Commun. 2006, 36, 3723; c) K. E. Judd, L. Caggiano, Org. Biomol. Chern. 2011, 9, 5201; d) S. N. Jager, E. O. J. Porta, G. R. Labadie, Mol. Diversity 2016, 20, 407; e) A. J. Villani-Gale, C. C. Eichman, Eur. J. Org. Chern. 2016, 3925.

[7] For selected Caisen rearrangement induced prenylation, see: a) R. D. H. Murray, M. M. Ballantyne, K. P. Mathai, Tetrahedron Lett. 1970, 11, 243; b) N. Takamatsu, S. Inoue, Y. Kishi, Tetrahedron Lett. 1971, 12, 4661; c) R. D. H. Murray, M. Sutcliffe, M. Hasegawa, Tetrahedron 1975, 31, 2966; d) K. Kyogoku, K. Katayama, S. Yokomori, T. Seki, I. Tanaka, Agric. Biol. Chern. 1975, 39, 667; e) J. B. Daskiewicz, C. Bayet, D. Barron, Tetra- hedron Lett. 2001, 42, 7241; f) S. Gester, P. Metz, O. Zierau, G. Vollmer, Tetrahedron 2001, 57, 1015; g) R. S. Mali, P. P. Joshi, P. K. Sandhu, A. I. Manekar-Tilve, Chem. Soc. Perkin Trans 1 2002, 371; h) T. Kawamura, M. Hayashi, R. Mukai, J. Terao, H. Nemoto, Synthesis 2012, 44, 1308–1314.

[8] For selected metal-catalyzed C-H prenylation reactions, see: a) V. J. Zhang, E. Skucas, M. J. Krische, Org. Lett. 2009, 11, 4248; b) R. Zeng, C. J. Fu, S. Ma, J. Am. Chern. Soc. 2012, 134, 9597; c) H. Wang, N. Schröder, F.

General Procedure for the Synthesis of 4
Under an atmosphere of argon, manganese(III) acetate (3.2 mmol, 6.5 equiv), potassium (3-hydroxy-3-methylbut-1-yl)trifluoroborate 1 (2.5 mmol, 5.0 equiv), heteroarene 2 (0.5 mmol, 1.0 equiv), trifluoroacetic acid (0.5 mmol, 1.0 equiv), and a 1:1 mixture of trifluoroethanol/acetonic acid (5 mL) were added in turn to a 15 mL Schlenk tube charged with a magnetic stirring bar. The Schlenk tube was stirred at 60°C for 4 h. The mixture was then allowed to cool to room temperature. The solvent was removed under vacuum and the residue was slowly added to a saturated aqueous solution of sodium bicarbonate (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and washed with brine and dried over sodium sulfate. After being concentrated under reduced pressure, the residues were purified by flash column chromatography on silica with an appropriate eluent to afford the pure product 4.
