Regioselective Dearomative Benzylation of an Unsubstituted Pyrylium Salt

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Heterocycles are critical motifs in natural products and pharmaceuticals. Nitrogen and oxygen heterocycles are of particular interest given their relative abundance in these compounds (Fig. 1).

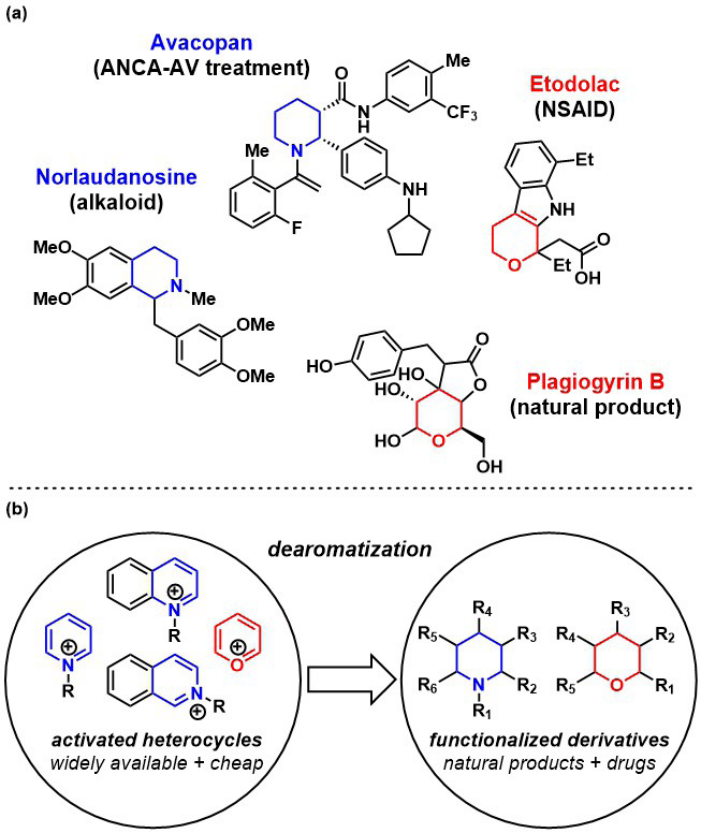

Fig. 1 (a) Selected examples of heterocyclic compounds in natural products and pharmaceuticals. (b) Dearomatization of activated heterocycles as a strategy for accessing functionalized products.

Compared to traditional strategies of accessing heterocyclic derivatives such as cyclization reactions, cross-electrophile couplings are an attractive alternative method. Cross-electrophile couplings avoid the preparation of sensitive organometallic nucleophiles and are less affected by the stereoelectronic constraints of cycloaddition methods. A variety of efficient cross-electrophile couplings involving nitrogen heterocycles exist, including our group's prior work with dearomative alkylation of heteroarenium salts (Fig. 2b). In contrast to nitrogen heterocycles, dearomative cross-coupling strategies utilizing oxygen heterocycles are relatively unexplored. Taylor et al. synthesized 4-substituted pyrylium salts via a range of organometallic nucleophiles (Fig. 2a). While regioselective alkylated products were obtained in moderate yields, Taylor's methodology requires low temperatures, long reaction times, and organometallic coupling partners. Building on our prior work using zinc as a terminal reductant, we investigated pyrylium salts as substrates for alkylation (Fig. 2c).

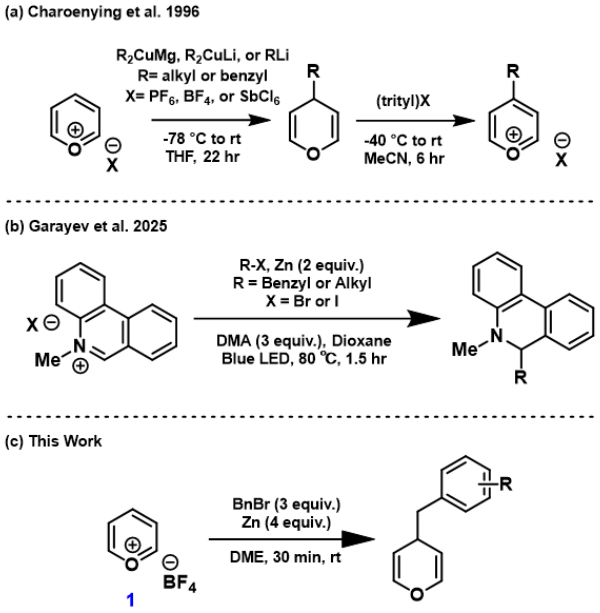

Fig. 2 (a) Prior work from Taylor on regioselective alkylation of pyrylium salts using various organometallic reagents. (b) Our lab's previous work with the dearomative cross coupling of heteroarenium salts using Zn as a terminal reductant. (c) This work.

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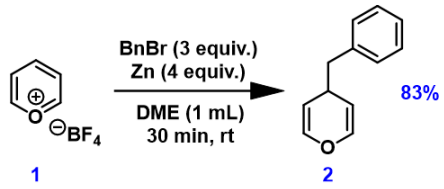
Table 1 Optimization of the benzylation reaction, with qNMR yields obtained using dimethyl terephthalate as an internal standard. All optimization reactions were conducted at the 0.05 mmol scale with degassed solvents under N_2 atmosphere.



Entry	Variation from Optimized	Yield (%)
1	15 min	61
2	45 min	60
3	2.0 equiv. Zn	66
4	4.0 equiv. Zn	70
5	1.5 equiv. BnBr	67
6	4.0 equiv. BnBr	81
7	4 °C	62
8	80 °C	76
9	2 mL DME	78
10	Dioxane	63
11	THF	75

We began reaction optimization by conducting time and temperature studies with pyrylium tetrafluoroborate 1 and benzyl bromide as the alkyl halide coupling partner. Activated zinc powder serves as the terminal reductant, with the obtained product being 4-benzylpyran 2. The optimal reaction time was found to be 30 minutes, with shorter and longer times giving lower yields (Table 1, Entries 1-2). The reaction requires no external heating, with additional heat and lower temperatures reducing yield (Table 1, Entries 7-8). Stoichiometric excesses of zinc and benzyl bromide are required for optimal yield, although further increasing their equivalents did not significantly impact the reaction (Table 1, Entries 3-6). Optimal yield is obtained in 1,2-dimethoxyethane (DME). Dilution of the reaction did not improve yields (Table 1, Entry 9). Additionally, the reaction is tolerant of other ethereal solvents such as 1,4-dioxane and tetrahydrofuran (THF) (Table 1, Entries 10-11). Unlike our prior work, we did not detect the formation of dimeric products under optimized conditions. 2-benzylpyran or ring opened products were not detected, indicating that the alkylation is regioselective. Attempts to use alkyl halides other than benzyl bromides with optimized conditions proved to be unsuccessful, limiting our scope to benzylated products.

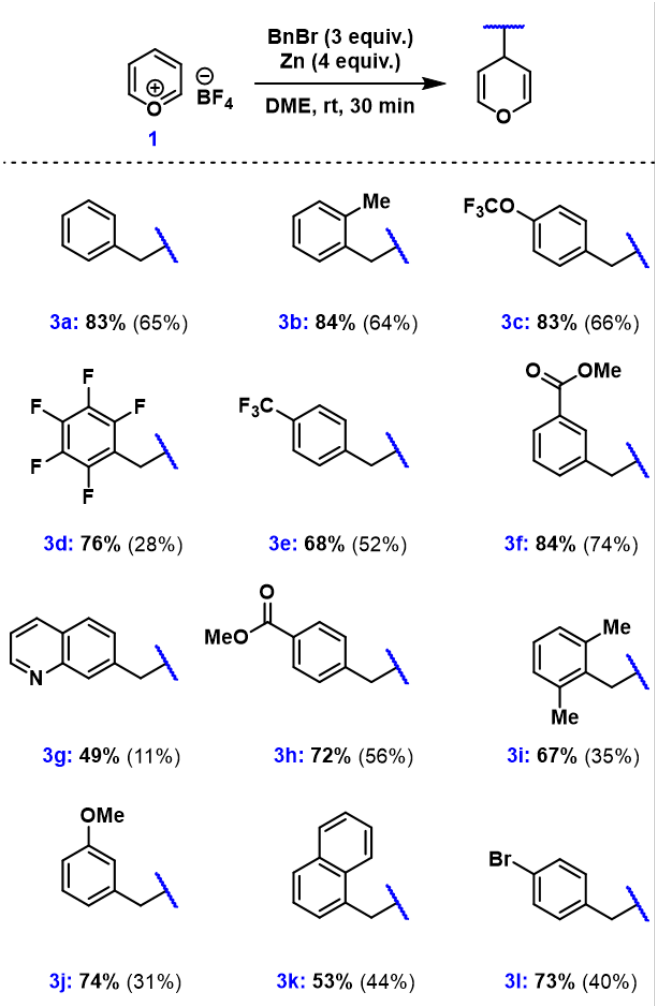


Fig. 3 Representative scope of the reaction, with qNMR 4-benzylpyran yields in bold and isolated 4-benzyltetrahydropyran yields in parentheses. Yields were determined by ^{1}H NMR analysis of crude reaction mixtures using dimethyl terephthalate as an internal standard. Products were isolated after hydrogenation and flash chromatography as 4-benzyltetrahydropyrans. All products were fully characterized via ^{1}H, ^{13}C, and ^{19}F (when relevant) NMR, as well as HRMS.

With optimized reaction conditions known, we investigated the scope of the benzyl bromides with pyrylium tetrafluoroborate 1 (Fig. 3). The reaction proved to be fairly robust, with a variety of functional groups and stereoelectronic environments tolerated on the benzyl ring. Simple alkyl-substituted benzyl bromides gave products in good yields (3a, 3b, and 3i), with a polyaromatic product obtained in moderate yield (3k). Methoxy- (3j) and ester-substituted (3f and 3h) benzyl bromides gave close to optimal yields, although alcohols did not result in desired product formation.

Halide substituents were also successful, with a 4-bromo substituent (3l) and multiple fluorine-containing groups (3c, 3d, and 3e) yielding product. A quinoline derivative afforded product in moderate yield (3g).

While the scope of our reaction is limited to benzylation at the time of publication, our group is actively investigating regioselective alkylation using modified conditions. Additionally, we are looking into the functionalization of pyran products, including their use as precursors for valuable N-aryl pyridinium salts.

Statement of Research Advisor

Emma's contributions to this project have been instrumental in developing this methodology for the synthesis of oxygen heterocycles. This pyrylium dearomatization project has been initiated and developed into a practical method by Emma with only advisory input from a graduate student Agshin Garayev and myself. All experiments described herein have been conducted by her.

- Rashad R. Karimov, Department of Chemistry and Biochemistry, College of Sciences and Mathematics

References

Charoenying, P., Hemming, K., McKerrecher, D., Taylor, R. J. K., "The Preparation of 4-Substituted Pyrylium Salts and Their Use in Dienal Synthesis," J. Heterocycl. Chem., 33 (4), pp. 1083–1089, (1996).

Delost, M. D., Smith, D.T., Anderson, B.T., Njardarson, J. T., "From Oxiranes to Oligomers: Architectures of U.S. FDA Approved Pharmaceuticals Containing Oxygen Heterocycles," J. Med. Chem., 61, 24, pp. 10996–11020, (2018).

Garayev, A., Drake, E.E., Miliordos, E., Karimov, R.R., "Dearomative Alkylation of Heteroarenium Salts via Blue Light Enabled Homolytic C–C Bond Cleavage," Org. Lett., 27, 7, pp. 1644–1649, (2025).

Marshall, C. M., Federice, J. G., Bell, C. N., Cox, P. B., Njardarson, J. T., "An Update on the Nitrogen Heterocycle Compositions and Properties of U.S. FDA-Approved Pharmaceuticals (2013–2023)," J. Med. Chem., 67, 14, pp. 11622–11655, (2024).

Authors Biography

Emma E. Drake is a senior-year undergraduate student pursuing an B.S. degree in Chemistry with an Honors distinction at Auburn University. She joined the Karimov Lab in January of 2023, working on dearomative cross-electrophile coupling strategies for both nitrogen and oxygen heterocycles. She will be attending Rice University to pursue a PhD in Chemistry after graduation.

Agshin Garayev is a PhD candidate in the Department of Chemistry and Biochemistry at Auburn University. He received a B.S. degree in Chemistry from Bilkent University in 2020. Since 2021, he has been working in the Karimov Lab focusing on cross-electrophile couplings of heteroarenium salts.

Dr. Rashad Karimov completed his Bachelor's degree at the Lomonosov Moscow State University. While there he worked on rearrangement reactions of gem-dibromospiropentanes under the supervision of Elena Averina. Subsequently he moved to United States to pursue his Master's degree under the supervision of Viktor Zhdankin at University of Minnesota Duluth working on the synthesis of hypervalent iodine reagents. In 2014, he obtained his PhD degree from Cornell University-Rockefeller University-Memorial Sloan-Kettering Cancer Center Tri-Institution-

al Program in Chemical Biology. His dissertation has focused on total synthesis of a saponin natural product under the supervision of Derek Tan and David Gin. After his PhD he was a postdoctoral fellow with John Hartwig at UC Berkeley working on transition metal catalysis. In 2017 he started his independent career at Auburn University as an Assistant Professor and was promoted to Associate Professor in 2023. Currently he is the S.D. and Karen H. Worley Associate Professor in the Department of Chemistry and Biochemistry at Auburn University.