Homologation of the Fischer Indolization: A Quinoline Synthesis via Homo-Diaza-Cope Rearrangement

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Abstract: We disclose a new Brønsted acid promoted quinoline synthesis, proceeding via homo-diaza-Cope rearrangement of N-aryl-N'-cyclopropyl hydrazines. Our strategy can be considered a homologation of Fischer’s classical indole synthesis and delivers 6-membered N-heterocycles, including previously inaccessible pyridine derivatives. This approach can also be used as a pyridannulation methodology toward constructing polycyclic polyheteroaromatics. A computational analysis has been employed to probe plausible activation modes and to interrogate the role of the catalyst.

Among N-heterocycles, quinoline derivatives occupy a place of particular relevance in chemical synthesis,[1] medicinal chemistry,[2] material science,[3] and industry.[4] Quinolines can generally be obtained by using several very reliable and powerful reactions of aniline derivatives, including those named after Skraup, Doebner-von Miller, Friedländer, Pfützinger, Conrad-Limpach, and Combes.[5,6] In recent years, our group has utilized the Fischer indole synthesis as a design platform for several new enantioselective processes, including a catalytic asymmetric Fischer indolization itself.[7] Inspired by these investigations, we wondered if a homologous variant of this powerful transformation could be designed. The key steps of the Fischer indole synthesis involves a diaza-Cope rearrangement of an ene-hydrazone to an iminoethyl aniline, followed by cyclization and aromatization with loss of ammonia (Figure 1A). We envisioned that homologation to a cyclopropyl hydrazone, should lead, upon rearrangement, to an iminopropyl aniline, which could cyclize and oxidatively aromatize to the corresponding quinoline derivative in an overall pyridannulation (Figure 1B). Here we report on the successful realization of this conceptual design.

Considering the significant π-character and pseudo-sp² hybridization, bonding and chemical properties of cyclopropane derivatives are often compared to those of the corresponding alkenes.[9] This analogy has also been applied to pericyclic reactions, where double bonds have been replaced with cyclopropanes, leading to homologous versions of the parent pericyclic reaction.[8b,c] However, while nitrogen-substituted cyclopropane derivatives display interesting reactivity, which manifests in ring strain driven ring-opening reactions[8d,e] and rearrangements,[8e–g] to the best of our knowledge, the homo-sigmatropic rearrangement principle has not yet been applied to the 3,4-diaza-Cope rearrangement.

We initiated our studies by evaluating the reactivity of a toluene solution of bis-Boc-protected N-aryl-N'-cyclopropylhydrazine 1a in the presence of a variety of acids (Table 1). Hydrochloric acid (in ether) at room temperature proved to be of insufficient reactivity to promote the desired reaction (entry 1). When we used aluminum chloride instead, full conversion of hydrazine 1a was observed but only decomposition of the starting material to several unidentified products was observed (entry 2). Interestingly, with triflic acid full consumption of the starting material was observed and 1,2,3,4-tetrahydrobenzo[f]quinoline (3a) was obtained in 10% yield next to other unidentified compounds (entry 3). Remarkably, when the reaction was performed with p-toluenesulfonic acid at elevated temperature, a promising mixture of products 2a and 3a was obtained (entry 4). Trifluoroacetic acid (entry 5) and phosphoric acid (85%; entry 6) were also found to be suitable, albeit mixtures of product 2a and 3a were again obtained in moderate yields. H₃PO₄ (85%) was found to be a superior acid in terms of the overall yield (entry 7).

**Table 1:** Reaction optimization[a]

| Entry | Acid          | Solvent | T (°C) | Yield 2a,3a (%) |
|-------|---------------|---------|--------|-----------------|
| 1     | HCl (ether)   | PhMe    | rt     | –               |
| 2     | AlCl₃        | PhMe    | rt     | –               |
| 3[a]  | TFOH         | PhMe    | 0:10   | 33;15           |
| 4[a]  | p-TSA        | PhMe    | 110    | 33;17           |
| 5[a]  | TFA          | PhMe    | 110    | 42;18           |
| 6     | H₃PO₄ (85%)  | PhMe    | 110    | 43;26           |
| 7[a]  | H₃PO₄ (85%)  | 1,2-DCB | 170    | 63;10           |
| 8[a]  | H₃PO₄ (85%)  | 1,2-DCB | 170    | 76;0            |

[a] Reactions were performed on 0.15 mmol scale under argon at 0.025 M concentration using 10 equiv of acid. [b] Yields were determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] Reactions were run for 2 h. [d] Reactions were performed under air. [e] Reaction was performed at 0.015 M concentration.

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combined chemical yields of 2a and 3a (68%) and was selected for further optimizations.

We reasoned that toward increasing the yield of the desired product 2a, an effective dehydrogenative aromatization of an anticipated dihydropyridine intermediate would be required. Indeed, when we heated the reaction mixture to 170°C under air for 24 h in 1,2-dichlobenzene, we could observe an increase in selectivity toward product 2a (entry 7). Gratifyingly, under these conditions, benzo[f]quinoline 2a was formed exclusively in good yield (76%) when the reaction was diluted from 0.025 M to 0.015 M (entry 8).

With the optimized conditions in hand, we next explored the scope and generality of our new pyridannulation methodology (Scheme 1). Substrates 1 were readily obtained from the corresponding aryl bromides or aryl triflates. Our method was found to be well-suited for aryl hydrazines with both electron-donating and electron-withdrawing groups. Irrespective of the nature and position of the substituent, both substrates 1b and 1c gave the desired products 2b and 2c in good yields. Similarly, the isomer of product 2a, benzo[h]quinoline 2e could also be obtained in acceptable yields. When polycyclic hydrazines were exposed to the optimized reaction conditions, the formation of higher quinolines with four rings (2d–2f)–h and five rings (2i) was observed in good yields. Even quinolines themselves can be obtained as illustrated with product 2j. Furthermore, symmetric, doubly-annulated products 2k and 2l could be obtained as well, even though in these cases the yields were significantly reduced. Our approach enables access to heteropolycycles 2b, 2c and 2i, which were previously unknown.

The proposed mechanism of our new quinoline synthesis is illustrated in Figure 2. First, N-Boc deprotection of 1a with acid occurs to generate doubly (or mono) protonated hydrazine salt A. This species then engages in the corresponding pseudo-sigmatropic rearrangement to form iminium ion B. A tautomerizing rearomatization then furnishes intermediate C. Subsequently, cyclization to piperidine D proceeds, followed by loss of ammonia to furnish intermediate E. Depending on the reaction conditions, this intermediate can either undergo disproportionation (i) to form products 2a and 3a, or is oxidized (ii) by air to furnish product 2a. Furthermore, intermediate E can react in a Mannich
type dimerization via tautomerization to the corresponding imine, followed by C–C bond formation and air oxidation to form product 4. Indeed, when the reaction was performed in the presence of p-TSA (Table 1, entry 4), a significant amount of dimer 4 was obtained (20%), indirectly supporting the existence of intermediate E.

Towards a mechanistic understanding of our reaction, we employed DFT calculations using the ORCA suite (see SI).\textsuperscript{[11]} The activation barrier associated with the critical uncatalyzed pseudo-sigmatropic C–C bond forming step is 84.56 kcal mol\(^{-1}\) at the B3LYP-D3/def2-TZVP//PBE-D3/def2-SVP level of theory.\textsuperscript{[12]} Notably, the high activation barrier is consistent with the breaking of a sigma bond and the dearomatization in the transition state (TS). Furthermore, the overall transformation is highly exothermic (\(\Delta H = -56.85\) kcal mol\(^{-1}\)) in nature, highlighting the importance of the rearomatization in driving the process. While computing the key transition states in the presence of the catalyst (H\(_3\)PO\(_4\)), we considered several modes of activation. Mono-protonation of the hydrazine with a single molecule of H\(_3\)PO\(_4\) within the TS leads to two distinct arrangements based on the site of the protonation (see SI). Alternatively, a highly organized di-protonated transition state via the involvement of two catalyst molecules (TS\(_1\) in Figure 2) can be envisioned.\textsuperscript{[7d,13]} Indeed, di-protonated TS\(_1\) is significantly more stable (\(\Delta H = -5\) kcal mol\(^{-1}\)) than the two mono-protonated counterparts. Such an observation is intriguing given the entropic penalty associated with this TS. A closer inspection of the competing transition states revealed several additional non-covalent interactions in TS\(_1\),\textsuperscript{[14]} which are absent in the alternative transition states (see SI), underscoring the importance of enthalpy in overcoming the entropic bias. Furthermore, our effort to quantify CH-O interaction using AIM\textsuperscript{[15]} indicates the difference is largely electrostatic in nature.\textsuperscript{[16]} Notably all these additional non-covalent stabilizations also contribute significantly to the 20 kcal mol\(^{-1}\) reduction of the activation barrier as compared to the uncatalyzed reaction.

We have designed and developed a new approach to quinolines. Starting from the corresponding N-aryl-N’-cyclopropylhydrazines and using phosphoric acid as mediator under aerobic conditions, various valuable heterocyclic products are obtained. We propose that our reaction takes place via a homo-Fischer-indolization-type mechanism, featuring a pseudo-pericyclic homo-diaza-Cope rearrangement as the key step. Contrary to the conventional mono-protonated mechanism,\textsuperscript{[7e,17]} our computational analysis has identified a favorable di-protonated pathway and offers a basis for the non-linear effect observed in an analogous asymmetric benzidine rearrangement. Beyond the conceptual advancement, our pyridannulation methodology could complement existing approaches toward the synthesis of polycyclic quinoline derivatives for biological and material science applications, with the potential benefit of avoiding difficult to obtain and highly toxic aniline derivatives as intermediates.

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Conflict of interest

The authors declare no conflict of interest.

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[1] a) C. Hou, P. Chen, G. Liu, Angew. Chem. Int. Ed. 2020, 59, 2755–2759; Angew. Chem. 2020, 132, 2757–2761; b) Z. Jin, X. Wang, H. Huang, X. Liang, J. Ye, Org. Lett. 2011, 13, 564–567; c) R. M. Shanahan, A. Hickey, L. M. Bateman, M. E. Light, G. P. McGlacken, J. Org. Chem. 2020, 85, 2855–2856; d) J. He, R. Takise, H. Fu, J. Qi, J. Am. Chem. Soc. 2015, 137, 4618–4621.

[2] For selected reviews, see: a) X. F. Shang, S. L. Morris-Natschke, G. Z. Yang, Y. Q. Liu, X. Guo, X. S. Xu, M. Goto, J. C. Li, J. Y. Yiang, K. H. Lee, Med. Res. Rev. 2018, 38, 1614–1660; b) X. F. Shang, S. L. Morris-Natschke, G. Z. Yang, Y. Q. Liu, X. Guo, X. S. Xu, M. Goto, J. C. Li, J. Y. Yiang, K. H. Lee, Med. Res. Rev. 2018, 38, 775–828.

[3] a) V. Thangarajie, P. Rajamalli, J. Jayakumar, M. J. Huang, Y. W. Chen, C. H. Cheng, ACS Appl. Mater. Interfaces 2019, 11, 17128–17133; b) S. K. Kang, J. Woo, S. E. Lee, Y. K. Kim, S. S. Yoon, Mol. Liq. Cryst. 2019, 265, 114–123; c) A. V. Sánchez-Mendoza, V. G. Ibarra-García, J. R. Velázquez-Hernández, O. J. Hernández-Ortiz, J. Carrillo, L. Palacios-Huerta, I. Cosme, A. Alvarez-Hernandez, K. Alemán-Ayala, R. A. Vázquez-García, J. Mater. Sci. Mater. Electron. 2019, 30, 19718–19730; d) B. Liu, M. A. Jabeed, J. Guo, W. Xu, S. L. Brown, A. Ugrinov, E. K. Hobbie, S. Kilina, A. Qin, W. Sun, Inorg. Chem. 2019, 58, 14377–14388; e) K. Sun, Y. L. Zhang, X. L. Chen, H. F. Su, Q. C. Peng, B. Yu, L. B. Qu, K. Li, ACS Appl. Bio Mater. 2020, 3, 505–511; f) K. P. Kawahara, W. Matsuoka, H. Ito, K. Itami, Angew. Chem. Int. Ed. 2020, 59, 6383–6388; g) Z. Zeng, H. Jin, K. Sekine, M. Rudolph, F. Rominger, A. S. K. Hashmi, Angew. Chem. Int. Ed. 2018, 57, 6935–6939; Angew. Chem. 2018, 130, 7051–7056.

[4] a) F. Aribe, A. Panossian, J. P. Vors, S. Pazenok, F. R. Leroux, Eur. J. Org. Chem. 2018, 3792–3802; b) S. Lawrance, S. Varghese, E. M. Varghese, A. K. Asok, M. S. Jisha, Biocatal. Agric. Biotechnol. 2019, 18, 101096; c) R. Belcher, Anal. Chem. Acta 1951, 5, 27–29; d) R. Belcher, Anal. Chem. Acta 1951, 5, 30–32; e) M. Phillips, M. J. Goss, J. Am. Chem. Soc. 1926, 48, 825–826.

[5] a) R. C. Eldridge, Heterocyclic compounds, Wiley, New York, 1960; b) S. M. Prajapati, K. D. Patel, R. H. Vekariya, S. N. Panchal, H. D. Patel, Rsc Adv. 2014, 4, 24463–24476; c) V. F. Batista, D. C. Pinto, A. M. Silva, ACS Sustainable Chem. Eng. 2016, 4, 4064–4078.

[6] a) M. Mortén, M. Hemnum, T. Bose-Hansen, Beilstein J. Org. Chem. 2015, 11, 1944–1949; b) C. W. Rees, C. E. Smithen, J. Chem. Soc. 1964, 928–937.

[7] a) S. Müller, M. J. Webber, B. List, J. Am. Chem. Soc. 2011, 133, 18534–18537; b) A. Martínez, M. J. Webber, S. Müller, B. List, Angew. Chem. Int. Ed. 2013, 52, 9486–9490; Angew. Chem. 2013, 125, 9664–9668; c) L. Kötzer, M. J. Webber, A. Martínez, C. De Fusco, B. List, Angew. Chem. Int. Ed. 2014, 53, 5202–5205; Angew. Chem. 2014, 126, 5303–5306; d) C. K. De, F. Pesciolioli, B. List, Angew. Chem. Int. Ed. 2013, 52, 9293–9295; Angew. Chem. 2013, 125, 9463–9465; e) G.-Q. Li, H. Gao, C. Keene, M. Devonas, D. H. Ess, L. Kurti, J. Am. Chem. Soc. 2013, 135, 7414–7417; f) A. W. Schamman, B. W. Boal, L. Zu, T. Mesghanaw, N. K. Garg, Tetrahedron 2010, 66, 4687–4695; g) L. Kötzer, M. Leutzsch, S. Sievers, S. Patil, H. Waldmann, Y. Zheng, W. Thié, B. List, Angew. Chem. Int. Ed. 2016, 55, 7693–7697; Angew. Chem. 2016, 128, 7824–7828; h) S. Huang, L. Kötzer, C. K. De, B. List, J. Am. Chem. Soc. 2015, 137, 3446–3449.

[8] a) A. de Meijere, Angew. Chem. Int. Ed. Engl. 1979, 18, 809–826; Angew. Chem. 1979, 91, 867–884; b) S. Krüger, T. Gaich, Beilstein J. Org. Chem. 2014, 10, 163–193; c) E. B. Hay, H. Zhang, D. P. Curran, J. Am. Chem. Soc. 2015, 137, 322–327; d) D. Cremer, J. Gauss, J. Am. Chem. Soc. 1986, 108, 7467–7477; e) V. A. Rassadin, Y. Six, Tetrahedron 2016, 72, 4701–4715; f) T. Clark, G. W. Spitznagel, R. Klose, P. von Rague Schleyer, J. Am. Chem. Soc. 1984, 106, 4412–4419; g) K. Lovato, U. Bhakta, Y. P. Ng, L. Kurti, Org. Biomol. Chem. 2020, 18, 3281–3287.

[9] Substrates 1 were prepared via Buchwald-Hartwig coupling from a commercially available and easily synthesizable hydrazide: