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[1,2]-Anionic Rearrangement of 2-Benzyloxypyridine and Related Pyridyl Ethers

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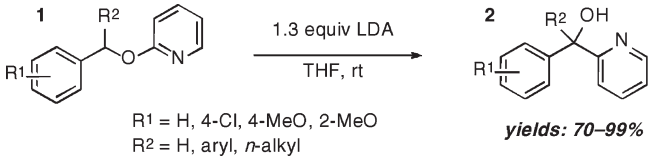

An anionic rearrangement of 2-benzyloxypyridine is described. Pyridine-directed metalation of the benzylic carbon leads to 1,2-migration of pyridine via a postulated associative mechanism (addition/elimination). Several aryl pyridyl carbinols were obtained in high yields. A formal synthesis of carbinoxamine, an antihistamine drug used for the treatment of seasonal allergies and hay fever, emerges from this methodology.

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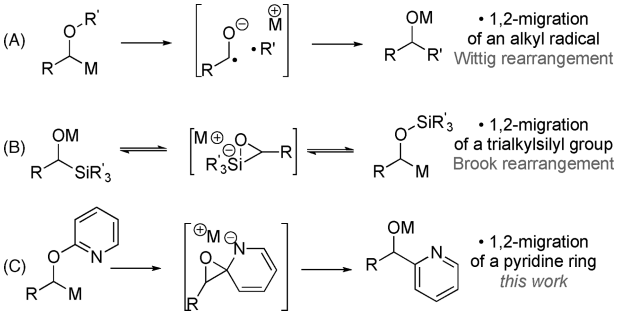
[1,2]-Anionic rearrangements such as those pioneered by Wittig[1] and Brook[2] are important tools for altering the complexity of molecules at hand. Rearrangement reactions interconvert pairs of structural isomers; this interconversion is especially valuable if one of the two isomers is more accessible than the other. Parallels can be drawn between the Wittig and Brook reactions and the anionic rearrangement of pyridyl ethers described herein (Scheme 1).

The [1,2]-Wittig rearrangement[3] involves conversion of an α-alkoxy-carbanion into a more stable oxyanion with concomitant migration of the alkyl group (Scheme 1A). Experimental evidence generally points to a stepwise, dissociative mechanism involving carbon−oxygen-bond homolysis and recombination of the resulting pair of intermediate radicals.[4] The [1,2]-Wittig process provides insight into the reactivity profile of reactive carbanion intermediates, but its value in synthesis[5] is limited due to difficulties associated with guiding complex molecular systems along the high-energy radical reaction pathway.

SCHEME 1. Representative [1,2]-Anionic Rearrangements



In the [1,2]-Brook rearrangement,[6] it is a silyl group that migrates between the carbinol center to the adjacent oxygen atom. Silyl migration is reversible (see the retro-Brook[7] reaction) and likely proceeds via a pentavalent silicate intermediate (Scheme 1B). This reaction is enjoying renewed interest, in part due to acylsilane methodologies that produce α-silyl alcohol substrates for the [1,2]-Brook reaction.[8]

The [1,2]-anionic rearrangement of 2-alkoxypyridines (Scheme 1C) was identified while studying the synthetic chemistry of 2-benzyloxypyridine (**1a**, Scheme 2)[9] as part of our interest in developing electrophilic reagents for the synthesis of arylmethyl ethers and esters.[10] We had envisioned making derivatives of **1a** via directed metalation using the complex-induced proximity effect (CIPE),[11] followed by trapping with electrophiles (**1a** → **4** → **5**, Scheme 2, not observed). Instead, prior to addition of the electrophile, we observed an unexpected product: phenyl(2-pyridyl)methanol (**2a**, Scheme 2).

Rearrangement of benzyllithium **4** accounts for the formation of α-pyridyl alcohol **2a**. The mechanism likely involves an associative process, akin to the Brook pathway, in which the

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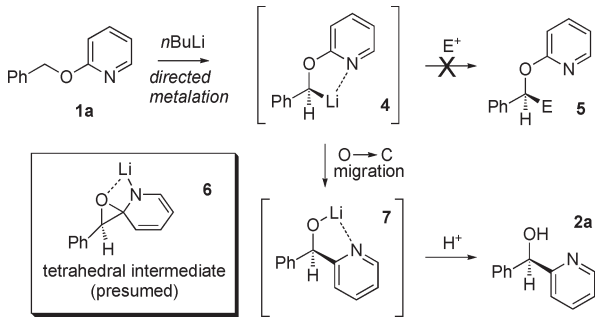
SCHEME 2. Discovery of the Anionic Rearrangement of 1a

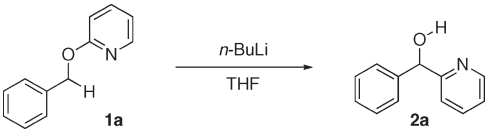


migrating carbon atom transiently expands to a tetrahedral (sp^3) intermediate (cf. **6**, Scheme 2) that is hypervalent relative to the trigonal planar (sp^2) ground state structure. Complexation between the pyridine nitrogen and the lithium ion is maintained throughout the nucleophilic aromatic substution (addition/elimination) of the electron-deficient pyridine ring. Related [1,2]-anionic rearrangements of α-carbamoyloxy-carbanions (from directed metalation of carbamates) are known,[12] as is the [1,4]-migration of pyridine rings onto urea-derived α-amino-carbanions.[13]

α-Pyridyl alcohols (**2**) are of general interest in synthesis and medicinal chemistry,[14] and we wanted to gain access to them via the [1,2]-anionic rearrangement pathway. To the best of our knowledge, the [1,2]-anionic rearrangement of 2-alkoxypyridines has not been observed previously.[15]

Key experiments related to identifying optimal conditions for the *n*-butyllithium-promoted rearrangement of 2-benzyloxypyridine are recounted in Table 1. The efficiency of the reaction is highly sensitive to minor changes in the reaction protocol. Full conversion requires a slight molar excess of *n*-BuLi (1.2 equiv), but too much base is detrimental (cf. entries 1−3 and 7).[16] When using specifically 1.2 equiv of *n*-BuLi, a reaction temperature of −60 °C provides results superior to when temperatures slightly higher or lower are employed (cf. entries 4−6). Optimally, treatment of 2-benzyloxyridine (**1a**)

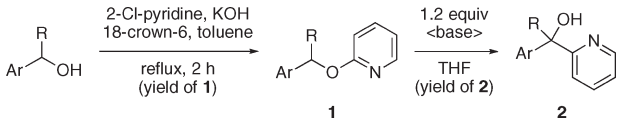
TABLE 1. Optimization of the *n*-Butyllithium-Promoted [1,2]-Anionic Rearrangement of 2-Benzyloxypyridine (1)



entry	*n*-BuLi	temp	recovery of **1a**[a]	yield of **2a**
1	1.1 equiv	−78 °C to rt	5−10%	nd
2	1.2 equiv	−78 °C to rt	—[b]	77%
3	2.0 equiv	−78 °C to rt	—[b]	nd[c]
4	1.2 equiv	−78 °C	42%	nd
5	1.2 equiv	−60 °C	—[b]	85%
6	1.2 equiv	−40 °C	17%	nd
7	1.3 equiv	−60 °C	—[b]	77%

[a]Estimated by ^{1}H NMR spectroscopy. [b]Complete consumption of **1a**. [c]Significant decomposition was apparent in the TLC analysis of the reaction mixture.

TABLE 2. Substituent Effects and an Alternative Set of Conditions for Promoting the [1,2]-Anionic Rearrangement



entry	Ar	R	yield of **1**	base	temp	yield of **2**
1	2-MeO-C_6H_4	H	90% (**1b**)	*n*-BuLi	−60 °C	48%[a] (**2b**)
2	4-MeO-C_6H_4	H	92% (**1c**)	*n*-BuLi	−60 °C	33%[a] (**2c**)
3	C_6H_5	Me	96% (**1d**)	*n*-BuLi	−60 °C to rt	24%[b] (**2d**)
4	C_6H_5	Me	96% (**1d**)	LDA[c]	rt	95% (**2d**)

[a]Mass balance was recovered starting material (52% of **1b** and 67% of **1a**). [b]Starting material and undesired byproduct recovered. [c]1.3 equiv of LDA employed.

in THF[17] with 1.2 equiv of *n*-BuLi at −60 °C furnishes phenyl(2-pyridyl)methanol (**1a** → **2a**) in 85% yield (entry 5). The delicate balance of reaction conditions required for optimal results is indicative of a complicated reaction pathway. It appears that *n*-BuLi competitively metallates both the substrate and the product.[16]

Changing the substrate from 2-benzyloxypyridine to related derivatives changes the kinetic profile of the reaction; the conditions described in entry 5 of Table 1 are not generalizable (Table 2). For example, the reaction conversion drops significantly for methoxy-substituted ethers **1b** and **1c**, likely due to competing metalation pathways, although the yields of **2** based on recovered starting material remain high (estimated >95%, entries 1 and 2). α-Branching in **1d** was detrimental in other ways (entry 3): conversion to tertiary alcohol **2d** was incomplete, and a new byproduct emerged, resulting from addition of *n*-butyllithium to the pyridine ring.[18]

Rather than attempt to reoptimize the reaction protocol for each substrate (**1** → **2**) individually, a unified set of

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(16) Deuterium is incorporated to a minor extent into the product alcohol (at the carbinol carbon) when the reaction is quenched with MeOD. Thus, in situ metalation of the product must be occurring, which consumes *n*-butyllithium and explains the need for a precise excess of *n*-butyllithium for optimal results. Further mechanistic experiments are in progress.

(17) A brief screening of other solvents and/or cosolvents—Et_2O, toluene, hexane, HMPA, DMPU—failed to identify a superior option.

(18) The byproduct was determined to be 2-butyl-6-(1-phenylethoxy)-pyridine (shown below), from addition of *n*-butyllithium to the pyridine ring followed by autoxidation.

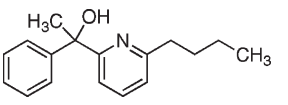

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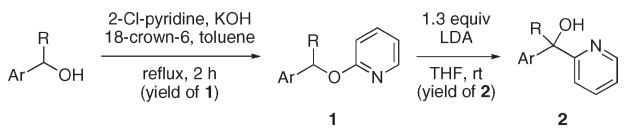
TABLE 3. Scope and Limitations of the LDA-Promoted [1,2]-Anionic Rearrangement of Arylalkoxypyridines



entry	Ar	R	yield of **1**	yield of **2**
1	C_6H_5	H	95% (**1a**)	98% (**2a**)
2	2-MeO-C_6H_4	H	90% (**1b**)	99% (**2b**)
3	4-MeO-C_6H_4	H	92% (**1c**)	99% (**2c**)
4	4-CF_3-C_6H_4	H	75% (**1e**)	0%
5	4−Cl-C_6H_4	H	93% (**1f**)	70% (**2f**)
6	C_6H_5	Me	96% (**1d**)	95% (**2d**)
7	C_6H_5	Et	96% (**1g**)	86%[a] (**2g**)
8	C_6H_5	Cy[b]	63% (**1h**)	20%[a] (**2h**)
9	C_6H_5	*t*-Bu	57% (**1i**)	0%[a]
10	C_6H_5	Ph	99% (**1j**)	97% (**2j**)

[a]Mass balance was recovered starting material (**1**). [b]Cy = cyclohexyl

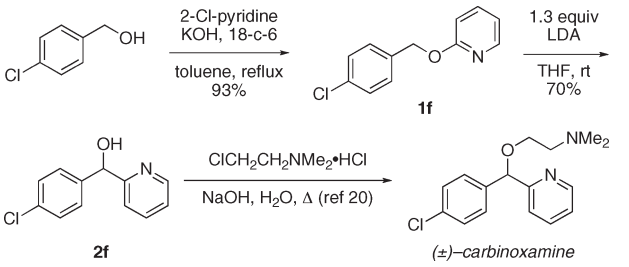
conditions with applicability across a broader range of substrates was sought. Lithium diisopropylamide (LDA) was the preferred chioce from among several[19] potential bases (Table 2, entry 4).

The reaction conditions involving LDA as the base instead of *n*-BuLi were then used to explore the scope of the rearrangement reaction (Table 3). The title substrate (2-benzyloxypyridine, **1a**) rearranged to **2a** in 98% yield (entry 1). Electron-donating groups on the benzene ring are well tolerated: rearrangement of substrates with either an *o*-methoxy (**1b**) or *p*-methoxy (**1c**) substituent proceeded each in 99% yield (entries 2 and 3). The yield of **2** decreased to 70% when the electron-withdrawing *p*-chloro substituent was in place (**1f** → **2f**, entry 5), and *p*-trifluoromethylated substrate **1e** decomposed under the reaction conditions (entry 4).

For making tertiary α-pyridyl alcohols (entries 6−10), the anionic rearrangement seems to depend on whether or not metalation occurs. Sterics and kinetic acidity play an important role (entries 6−9); the reaction conversion of alkyl-substituted pyridyl ethers and the isolated yield of the α-pyridyl alcohol relate inversely to the size of the branching substituent at the benzylic ether position. The relevance of thermodynamic acidity can be inferred from entry 10; 2-(diphenylmethoxy)pyridine (**1j**), presumably the most acidic of the substrates included in Table 3, furnishes tertiary alcohol **2j** in 97% yield.

α-Pyridyl alcohol (±)-**2f** (see Table 3, entry 5) has been converted in one step into (±)-carbinoxamine[20] (Scheme 3),

SCHEME 3. Synthesis of Carbinoxamine



the resolution of which is accomplished with use of *d*-tartaric acid.[21,22] Carbinoxamine is an antihistamine drug (histamine H_1 antagonist) used for the treatment of seasonal allergies and hay fever.[23]

In conclusion, a [1,2]-anionic rearrangement of 2-benzyloxypyridine and its derivatives is reported. According to our postulated mechanism, pyridine-directed metalation at the benzylic position triggers an intramolecular nucleophilic aromatic substitution reaction (addition/elimination) via an intermediate spiroepoxide (**6**, Scheme 2). This new discovery provides a link between two disparate reaction pathways: the [1,2]-Wittig rearrangement (in which arene migration is rare) and the tandem directed metalation/nucleophilic acyl substitution methodologies developed by Snieckus, Gawley, Clayden, and others.[12,13] Pyridyl ethers **1** are readily available from the corresponding alcohols and 2-chloropyridine. A variety of secondary and tertiary α-pyridyl alcohols were prepared in good to excellent yield.

Experimental Section

General Procedure: [1,2] Anionic Rearrangement. To a solution of LDA (1.3 equiv) in THF at room temperature was added benzyloxypyridines **1** (100 mg, 1.0 equiv) in THF (1 mL) dropwise, and the solution was stirred overnight or until all the starting material was consumed. The resulting mixture was diluted with H_2O (5 mL) and extracted with EtOAc (4 × 5 mL). The combined organic extract was then washed with brine, dried (Na_2SO_4), filtered, concentrated under vacuum, and purified on silica gel to yield pyridine alcohols **2**.

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Supporting Information Available: Detailed experimental procedures, characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) The bases included *s*-BuLi, *t*-BuLi, PhLi, BnLi, Ph_3CLi, LDA, LiHMDS, LiDMSO, LiN(OMe)Me, LiTMP, LiH, and alkyl Grignard reagents. LDA was sufficiently reactive to promote the rearrangement, and no competing addition to the pyridine ring was observed. After brief optimization (not shown) and screening against multiple substrates, 1.3 equiv of LDA at rt emerged as the optimal set of conditions.

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