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Pyridine-Directed Organolithium Addition to an Enol Ether

Jingyue Yang^a and Gregory B. Dudley^{a,*}

^a Department of Chemistry and Biochemistry, Florida State University, Tallahassee, FL 32306-4390, U.S.A. Fax: (+1)-850-644-8281; phone: (+1)-850-644-2333; e-mail: gdudley@chem.fsu.edu

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Abstract: A previously reported anionic rearrangement of benzyl 2-pyridyl ethers can now be accessed by a distinct and unusual mechanism: addition of alkyllithium reagents to α -(2-pyridyloxy)-styrene triggers an anionic rearrangement to afford tertiary pyridyl carbinols. The process is explained by invoking a contra-electronic, pyridine-directed carbolithiation of the enol ether π -system.

Keywords: anionic rearrangement; contra-electronic carbolithiation; electron transfer; enol ethers; pyridine; reactive intermediates

In this update, we present indirect evidence of a unique and unexpected carbolithiation of an enol ether [pyridyl ether **1**, Eq (1)],^[1] in which organolithium nucleophiles^[2] add *inter*-molecularly across the electron-rich alkene in a manner opposite to the normal polarization preferences of an enol ether (contra-electronically).^[3] This observation provides insight into the unusual behavior of highly reactive species^[4,5] and reveals an alternative entry into our reported anionic rearrangement of benzyloxypyridines [Eq (2)].^[6]

The observation is as follows: addition of 1.3 equivalents of *n*-butyllithium to a solution of α -pyridyloxystyrene **1** in THF provides an 84% yield of tertiary pyridyl carbinol **2a** [Eq. (1)]. To explain this, one must account for (i) C–C bond formation at the β carbon of the enol ether, and (ii) migration of the pyridyl group from oxygen to the α -carbon.

Given that directed metallation of benzyl pyridyl ethers triggers an anionic rearrangement to give tertiary pyridyl carbinols [e.g., Eq (2)],^[6] the simplest explanation^[7] involves carbolithiation of enol ether **1** $\{\mathbf{1}\rightarrow [\mathbf{Ia}], \text{Eq. }(1)\}$.

The presumed carbolithiation $(1 \rightarrow [Ia])$ is the first example to the best of our knowledge of the enol ether π -system reacting with an electron-rich (nucleophilic) reagent.^[1] Moreoever, the nucleophilic attack occurs at the more electron-rich terminus of the enol ether.^[8,9]

The contra-electronic organolithium addition to **1** proceeded to the exclusion of alternative potential reaction pathways [Eq (3) and Eq. (4)]. Namely, pyridine-directed carbolithiation could be envisioned to occur in alignment with the polarization of enol **1**, but the expected products of such a process [**4** and **5**, Eq. (3), arising from β -elimination of the lithium alkoxide] could not be detected. Another "reasonable" reaction process would be for the alkyllithium reagent



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No dipole-aligned carbolithiation





to attack the electron-deficient pyridine ring [addition at C-2, followed by elimination of the enolate, Eq. (4)]. Although nucleophilic aromatic substitutions at the 2-position of pyridine are well known, no such products are observed in this process.

The central importance of the 2-pyridyloxy group in directing the alkyllithium addition to 1 is supported by the control experiments shown in Eq. (5), Eq. (6) and Eq. (7). Although carbolithiation of styrene derivatives is known,^[10] this is *not* an example of a phenyl substitutent overriding the normal reactivity profile of an enol ether. The 2-pyridyloxy group, not the phenyl, controls the regioselectivity of the process: n-butyllithium reacts with stilbene derivative 8 to produce tertiary alcohol 9 [i.e., by the addition/rearrangement process, cf. Eq. (1)] to the exclusion of 10, the expected product of regioisomeric addition and elimination [cf. Eq. (3)]. 4-Pyridyloxy analogue 11, in which pyridine complexation does not produce a proximity effect, does not undergo the same addition/rearrangement process [Eq. (6)]. Instead, starting material is recovered along with small amounts of products derived from addition of n-butyllithium to

The 2-pyridyloxy group, not phenyl, directs the regioselective carbolithiation



The 4-pyridyloxy group does not direct carbolithiation



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 α -Methoxystyrene is unreactive under these conditions

the 2-position of pyridine. Likewise and as expected, α -methoxystyrene^[11] (13) is completely unreactive under these conditions [Eq. (7)].

These data, coupled with our earlier report [*cf.* Eq. (2)],^[6] support the reaction pathway outlined in Eq. (1): pyridine-directed addition of *n*-butyllithium to enol ether **1** triggers anionic rearrangement of the resulting α -(2-pyridyloxy)benzyllithium, [**Ia**]. The question is: Why does the apparently contra-electronic addition pathway predominate? Given that addition to enol ether **1** occurs, why does the *n*-butyl group attack the β -carbon and not the α -carbon, which would generate a primary organolithium intermediate {[**II**], Eq. (3)} and trigger facile β -elimination of lithio-acetophenone?

In considering reasonable mechanisms for this unusual addition/rearrangement sequence $(1\rightarrow 2)$, we favour a process in which carbolithiation $(1 \rightarrow [I])$, Scheme 1) leads directly into the previously reported anionic rearrangement^[6] ([**I**] \rightarrow **2**). To explain the apparently contra-electronic carbanion addition, it is helpful to invoke the electron-transfer properties of highly reactive organolithium nucleophiles.^[12] Precomplexation between the lithium reagent and the pyridine nitrogen ([IV], Scheme 1) produces the proximity effect^[13] necessary for directed carbolithiation, which is thermodynamically favourable.^[14] We postulate that carbolithiation of enol ether 1 may involve rate-determining electron-transfer to produce a transient enol ether radical anion [V], followed almost instantaneously by radical recombination to [I]. The observed regioselectivity would then be consistent with radical recombination $([V] \rightarrow [I])^{[15]}$ guided by sterics and/or proximity effects. Pyridyloxylithium [I] undergoes anionic rearrangement, as described previously.^[6]

 α -Pyridyloxystyrene **1** was prepared as shown in Scheme 2. Oxidation of monoglyme and addition of phenylmagnesium bromide to the resulting aldehyde provided benzyl alcohol derivative **15**, which was converted into pyridyl ether **16** using nucleophilic aromatic substitution of 2-chloropyridine.^[16] LDA-promoted elimination of 2-methoxyethanol from **16**^[17] provides α -pyridyloxystyrene **1**.

A brief screening of organolithium nucleophiles revealed a correlation between organolithium reactivity and reaction efficiency (Table 1). Methyllithium reacted with $\mathbf{1}$ along the presumed carbolithiation and anionic rearrangement pathway to give $\mathbf{2b}$ in 84% yield (entry 1), which is comparable to the 84% yield observed in the reaction of $\mathbf{1}$ with *n*-butyllithium



Scheme 1. Postulated mechanism: alkyllithium addition $(1 \rightarrow [I])$ triggers an anionic rearrangement^[6] $([I] \rightarrow 2)$.



Scheme 2. Preparation of α -(2-pyridyloxy)styrene (1).

Table 1. Scope of the nucleophilic addition to α -pyridyloxy-styrene 1.^[a]

	1.3 e	quiv. < R–Li > ► THF, r.t.	HO N R 2
Entry	< R–Li >	Product	Yield
1	Me–Li	2b (R = Me)	84%
2	(MeMgBr)	2b (R = Me)	0% ^[b]
3	<i>n</i> -Bu–Li	2a (R = <i>n</i> -Bu)	84%
4	<i>s</i> -Bu–Li	2c (R = <i>s</i> -Bu)	86%
5	<i>t</i> -Bu–Li	2d (R = <i>t</i> -Bu)	97%
6	Ph–Li	2e (R = Ph)	75%
7	L-Selectride	2f (R = H)	—% ^[c]

^[a] Styrene **1** in THF treated with organometallic reagent at room temperature under nitrogen.

^[b] No reaction.

^[c] ¹H NMR spectroscopic analysis of the crude reaction mixture revealed a complex mixture of products, including starting material and acetophenone [*cf.* Eq (4)].

(entry 3). Methylmagnesium bromide, on the other hand, was unreactive under similar conditions (entry 2). The more reactive secondary and tertiary butyllithium isomers produced higher yields of tertiary alcohol product:[^{18]} *s*-BuLi, 86%, entry 4; *t*-BuLi, 97%, entry 5. Reaction of **1** with phenyllithium, which is less nucleophilic than most alkyllithium reagents, gave rise to alcohol **2e** in a relatively modest 75% yield (entry 6), and the hydride reagent produced a mixture of products including acetophenone (**6**), which presumably arises from hydride addition to pyridine at C-2 [*cf.* Eq. (4)].

In summary, organolithium addition to an enol ether has been observed within the context of a previously reported anionic rearrangement of lithiated benzyl pyridyl ethers.^[6] Specifically, pyridine-directed, contra-electronic addition of reactive alkyllithium reagents to α -(2-pyridyloxy)-styrene (1) triggers the anionic rearrangement to provide tertiary pyridyl carbinols. We postulate a mechanism in which the organolithium reagent attacks 1 in a dipole-opposed (contraelectronic) fashion, perhaps *via* a single electron transfer mechanism, with the carbanionic moiety reacting at the more electron-rich terminus of the enol ether. Further exploration of this novel reaction pathway will be reported in due course.

Experimental Section

 α -Pyridyloxystyrene **1** (20 mg, 1 equiv.) was dissolved in 1 mL of dry THF under nitrogen at room temperature and *n*-butyllithium (1.3 equiv.) was added dropwise. The reaction mixture was stirred overnight (or until TLC analysis of the reaction mixture showed complete consumption of the enol ether), then diluted with H₂O (5 mL) and extracted with EtOAc (4×5 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, concentrated under vacuum, and purified on silica gel to obtain 1-phenyl-1-pyridylhexanol (**2a**); yield: 84%.

Calculations were performed at the B3LYP 6-31+G(d,p) level, for results, see Figure 1 and Figure 2.



Figure 1. Calculated π -bond polarization (*in italics*) and selected net atomic charges (in **bold**) for 2-pyridyloxystyrenes **1**, complex **[IV]**, and α -methoxystyrene **(13)**.



Figure 2. Relative energies calculated for [IV], [I], and [VII].

Acknowledgements

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References

 To the best of our knowledge, carbolithiation of an enol ether has not been observed previously. For selected examples of directed carbolithiation of other types of electron-rich alkenes, see: a) A.-M. L. Hogan, D. F. O'Shea, J. Org. Chem. 2007, 72, 9557 (ortho-aminostyrenes); b) J. G. Peters, M. Seppi, R. Frohlich, B. Wibbeling, D. Hoppe, Synthesis 2002, 381 (enol carbamates); c) B. Cottineau, I. Gillaizeau, J. Farard, M.-L. Auclair, G. Coudert, Synlett 2007, 1925 (enol carbamates); d) C. Unkelbach, C. Strohmann, J. Am. Chem. Soc. 2009, 131, 17044 (vinylsilanes); e) R. L. Funk, G. L. Bolton, K. M. Brummond, K. E. Ellestad, J. B. Stallman, J. Am. Chem. Soc. 1993, 115, 7023 (alkoxyacetylenes); f) J. Clayden, M. Donnard. J. Lefranc, A. Minassi and D. J. Tetlow, J. Am. Chem. Soc. **2010**, 132, 6624 (vinyl ureas).

- [2] a) Organolithium compounds/solvated electrons, (Ed.: N. M. Alpatova), Springer-Verlag, New York, Berlin, 1987; b) The Chemistry of Organolithium Compounds, (Ed.: B. J. Wakefield), Pergamon Press, Oxford, New York, 1974.
- [3] *The Chemistry of Alkenes*, (Ed.: S. Patai), Interscience Publishers, London, New York, **1964**, Vol. 1.
- [4] Carbolithiation of ethylene, see: a) P. D. Bartlett, S. Friedman, M. Stiles, J. Am. Chem. Soc. 1953, 75, 1771;
 b) P. D. Bartlett, S. J. Tauber, W. P. Weber, J. Am. Chem. Soc. 1969, 91, 6362.
- [5] Intramolecular carbolithiation (cyclization) reactions of electron-rich alkenes are less unusual, although no less noteworthy. For reviews, see: a) W. F. Bailey, T. V. Ovaska, in: Advances in Detailed Reaction Mechanisms, Vol. 3, (Ed.: J. M. Coxon), JAI Press, Greenwich, CT, 1994, pp 251–273; b) M. J. Mealy, W. F. Bailey, J. Organomet. Chem. 2002, 646, 59; c) J. Clayden, Organolithiums: Selectivity for Synthesis Pergamon Press, New York, 2002, pp 293–335; recent papers: d) W. F. Bailey, X. L. Jiang, Tetrahedron 2005, 61, 3183; e) I. Coldham, K. N. Price, R. E. Rathmell, Org. Biomol. Chem. 2003, 1, 2111.
- [6] J. Yang, G. B. Dudley, J. Org. Chem. 2009, 74, 7998.
- [7] Ockham's (Occam's) razor favours the simplest explanation, but it is not an irrefutable principle of logic.
- [8] Calculations at the B3LYP 6-31+G(d,p) level suggest that the pyridyloxy group, like the methoxy group, is electron-releasing. Although the pyridyloxy group is a weaker donor than methoxy, the majority (51.46%) of the alkene π -electron density is localized near the β -carbon of **1** (Figure 1). A similar pattern is calculated for **[IV]**, after complexation of the alkyllithium.
- [9] This unusual reaction would not be classified as an "umpolung" process. The term "umpolung" (meaning, "reversed polarity") refers to an altered form of a common functional group that displays reactivity opposite to that of the normal pattern (e.g., lithiated 1,3-di-thiane vs. aldehyde). In contrast, Eq. (1) represents a rare example in which the unaltered functional group in this case, an enol ether displays reactivity opposite to the expected pattern. For a discussion on umpolung reactivity strategies, see: D. J. Ager, in: Umpoled Synthons: A Survey of Sources and Uses in Synthesis, (Ed.: T. A. Hase), John Wiley & Sons, New York, 1987, pp 19–72.
- [10] a) Anionic Polymerization: Principles and Practice, (Ed.: M. Merton), Academic Press, New York, 1983;
 b) R. Waack, M. A. Doran, J. Org. Chem. 1967, 32, 3395;
 c) X. Wei, P. Johnson, R. J. K. Taylor, J. Chem. Soc. Perkin Trans. 1 2000, 1109.
- [11] N. D. Willmore, D. A. Hoic, T. J. Katz, J. Org. Chem. 1994, 59, 1889.
- [12] For reviews, see: a) H. Yamataka, K. Yamada, K. Tomioka, in: *Chemistry of Organolithium Compounds*, (Eds.: Z. Rappoport, I. Marek), Wiley, New York, 2004, Vol. 2, pp 901–939; b) H. Yamataka, N. Fujimura, Y. Kawafuji, T. Hanafusa, *J. Am. Chem. Soc.* 1987, 109, 4305; c) H. Yamataka, Y. Kawafuji, K. Na-

gareda, N. Miyano, T. Hanafusa, J. Org. Chem. 1989, 54, 4706.

- [13] M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, Angew. Chem. 2004, 116, 2256; Angew. Chem. Int. Ed. 2004, 43, 2206.
- [14] The relative energies of alkyllithium [**IV**], benzyllithium [**I**], and lithium alkoxide [**VII**] were calculated at the B3LYP 6-31+G(d,p) level (R=*n*-Bu, Figure 2). Both the addition and the rearrangement appear to be highly exothermic. We thank a referee for suggesting that we examine the energetics of the conversion of $[IV] \rightarrow [I] \rightarrow [VII]$.
- [15] A more concerted process, in which radical anion [V] undergoes the anionic rearrangement directly without generating α -pyridyloxy-benzyllithium [I], cannot be ruled out at this time.

- [16] a) A. J. Serio Duggan, E. J. J. Grabowski, W. K. Russ, Synthesis 1980, 573; b) K. W. C. Poon, P. A. Albiniak, G. B. Dudley, Org. Synth. 2007, 84, 295; c) S. S. Lopez, G. B. Dudley, Beilstein J. Org. Chem. 2008, 4, 44.
- [17] Incidentally, this reaction was originally designed and performed as a competition experiment between E2 elimination and the anionic rearrangement described previously (ref.^[6]). It shows, not surprisingly, that elimination of the lithium alkoxide is faster than the anionic rearrangement [*cf.* Eq. (2)]. In one compromised run of this competition experiment, we used LDA that was contaminated with a small amount *n*-butyllithium, which resulted in isolation of **2a** and identification of the contra-electronic alkyllithium addition reaction.
- [18] Similar reactivity trends have been documented for other directed carbolithiation reactions; see refs.^[1a,1d,4]