ORGANIC
LETTERS

2011
Vol. 13, No. 23
6224–6227

Synthesis of a New Class of β-Iodo *N*-Alkenyl 2-Pyridones

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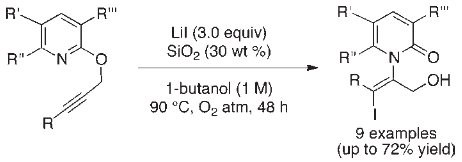
Received October 5, 2011

ABSTRACT



A new method for the synthesis of β-iodo *N*-alkenyl 2-pyridones from substituted 2-propargyloxypyridines has been discovered . These compounds present a unique complement of orthogonal functionality and structural characteristics that are unavailable via other routes. The ready access to these compounds renders them an important entry point for the preparation of more complex *N*-alkyl pyridone-containing targets.

N-Alkenyl pyridones, exemplified by compounds **1**−**4**, have been the object of much synthetic interest over the past few decades (Figure 1). Frequently utilized as either monomers for polymerization[1] or substrates for Diels−Alder reactions,[2] simple *N*-vinyl and *N*-alkenyl pyridones have been prepared from 2-pyridone in a variety of ways, including additions to electron-deficient alkynes,[3,4] additions to vinyl bromides,[5] and aldol condensations after C−N bond formation.[6] While synthetically straightforward, each of these transformations is limited to a particular archetype. Alternatively, α-bromo *N*-alkenyl pyridone **3** was prepared while trying to access α-haloenamides,[7] and Cu-catalyzed Suzuki-type couplings of alkenyl boronic acids or boronate salts have been utilized to improve access to *N*-alkenyl pyridones.[8] However, neither method appears to be general.

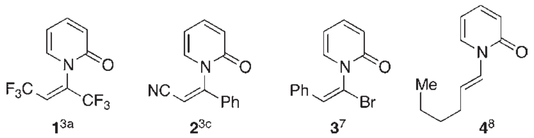


Figure 1. Previously synthesized *N*-alkenyl pyridones.

More complex *N*-alkenyl pyridone motifs are poised to serve as important building blocks for the incorporation of *N*-alkyl pyridones into complex scaffolds, including natural products[9] and pharmacologically relevant targets.[10] During our studies toward the synthesis of *N*-propargyl

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[1] (a) Ueda, N.; Kondo, K.; Kono, M.; Takemoto, K.; Imoto, M. *Makromol. Chem.* **1968**, *120*, 13–20. (b) Pitha, J.; Ts'o, P. O. P. *J. Org. Chem.* **1968**, *33*, 1341–1344. (c) Kaye, H. *J. Polymer Sci., Part B: Polymer Lett.* **1969**, *7*, 1–5.

[2] Review: Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111–9171.

[3] (a) Paquette, L. A. *J. Org. Chem.* **1965**, *30*, 2107–2108. (b) Acheson, R. M.; Tasker, P. A. *J. Chem. Soc. (C)* **1967**, 1542–1543. (c) Yadla, R.; Rehman, H.; Rao, J. M. *Tetrahedron* **1989**, 7093–7098.

[4] (a) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595–7596. (b) Meunier, S.; Siaugue, J.-M.; Sawicki, M.; Calbour, F.; Dezard, S.; Taran, F.; Mioskowski, C. *J. Comb. Chem.* **2003**, *5*, 201–204. (c) Yavari, I.; Alborzi, A. R.; Mohtat, B. *J. Chem. Res.* **2007**, 397–399. (d) Mohtat, B.; Jabbar, S.; Ghasemi, A.; Yavari, I. *J. Chem. Res.* **2008**, 601–603.

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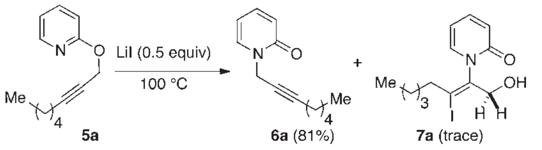
10.1021/ol202679t © 2011 American Chemical Society
Published on Web 11/09/2011

Scheme 1. Observation of *β*-Iodo *N*-Alkenyl Pyridone **7a**

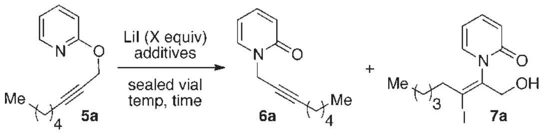


pyridones **6a**,[11,12] *β*-iodo *N*-alkenyl pyridone **7a** was observed as a minor byproduct (Scheme 1). The unique complement of orthogonal functionality found in compound **7a** makes it an optimal intermediate for the synthesis of other, more complex pyridone scaffolds.

Analysis of *β*-Iodo *N*-Alkenyl Pyridone 7a. The structure of byproduct **7a** was initially determined by X-ray crystallography.[13] Further evaluation using ^{1}H NMR spectroscopy ($CDCl_3$) showed that **7a** possesses an unusually strong coupling between the hydroxyl proton and adjacent diastereotopic methylene protons (J = 4.8, 7.4 Hz).[14] This interaction suggests that proton exchange with adventitious water is not occurring on the NMR time scale and supports the presence of an intramolecular H-bond between the hydroxyl proton and the carbonyl of the pyridone. Support for this constrained conformation was obtained by applying standard computational methods to a truncated version of **7a**.[15] In this way, the H-bound conformation was found to be stabilized by 2.2 kcal/mol relative to the non-bound structure at the B3LYP/6-31+G(d,p)/LANL2DZ level of theory. Additional evidence for an intramolecular H-bond was provided by calculating the ^{1}H NMR chemical shifts for these same conformations using the gauge independent atomic orbital method (GIAO) at the B3LYP/cc-pVTZ and B3LYP/6-311++G(d,p) levels of theory.[15] Using this method, a strong correlation was observed between the calculated and experimental values for the hydroxyl proton in the H-bound conformation ($<$ 0.5 ppm difference), while a difference of more than 3 ppm exists in the conformer without the H-bond.

Unlike the solution phase structure of *N*-alkenyl pyridone **7a**, the solid state structure does *not* contain an intramolecular hydrogen bond.[13] Rather, when the molecules interact in the solid state, a network of intermolecular H-bonds is observed. This change in preference seems to be directed by the formation of a short iodine–oxygen halogen bond (2.99 Å).[16] Such halogen bonds have been observed in many halogenated materials and, of late, have been utilized as a means for supramolecular organization and crystal engineering.[17]

Table 1. Optimization of Reaction Conditions for the Formation of *N*-Alkenyl Pyridone **7a**



entry	LiI (equiv)	additives	temp (°C)	time (h)	**6a**:**7a**	yield **7a** (%)[a]
1	0.5	none	100	26	–	trace[b]
2	0.5	0.1 equiv butanol	100	72	1.0:1.1	20%
3	0.5	0.1 equiv butanol	80	72	0:1.0	17%
4	0.5	0.1 equiv butanol 10 wt % SiO_2	80	72	1.0:1.8	21%
5	0.5	butanol (5 M) 10 wt % SiO_2	80	72	1.0:4.2	21%
6	1.0	butanol (3 M) 10 wt % SiO_2 10 wt % H_2O	80	72	1.4:1.0	13%

[a] Isolated yield. [b] 81% yield of alkyne **6a** isolated.

Optimization of Reaction Conditions. Compound **7a** was initially observed upon treatment of pyridine **5a** with 0.5 equiv of LiI at 100 °C in the absence of solvent, conditions designed to generate the formal [1,3]-migration product **6a** (Table 1, entry 1).[11] As the rate of formal [1,3]-migration is sensitive to substrate concentration and temperature, 1-butanol was added to the reaction and the temperature was decreased (entries 2 and 3). 1-Butanol was utilized as early studies had shown that it provided improved product ratios and yields relative to other solvents (e.g., $CHCl_3$ or CH_3CN). Introduction of silica gel to the reaction was found to increase the overall conversion to both alkyne **6a** and alkene **7a**, but even after 72 h the yield of compound **7a** remained undesirably low (entries 4 and 5).[18]

We postulate that alkene **7a** is formed when iodine, generated upon oxidation of LiI under the reaction conditions, activates alkyne **5a**, giving unsymmetrical iodenium ion **8** (Scheme 2). Ring opening by the proximal pyridine nitrogen in a 5-*exo* manner would then yield pyridinium ion **9** with the proper geometry around the newly formed alkene. Similar pyridinium rings have been observed in related systems.[3b,19] Opening of the five-membered ring by a nucleophile, originally assumed to be adventitious

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(9) Representative examples: (a) Camptothecin alkaloids: Wall, M. E.; Wani, M. C. *J. Ethnopharmacol.* **1996**, *51*, 239–253. (b) Lupin alkaloids: Gray, D.; Gallagher, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 2419–2423. (c) Mappicine: Govindachari, T. R.; Ravindranath, K. R.; Viswanathan, N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1215–1217.

(10) Representative examples: (a) Huffman, J. W.; Lu, J.; Hynd, G.; Wiley, J. L.; Martin, B. R. *Bioorg. Med. Chem.* **2001**, *9*, 2863–2870. (b) Parlow, J. J.; South, M. S. *Tetrahedron* **2003**, *59*, 7695–7701.

(11) Lanni, E. L.; Bosscher, M. A.; Ooms, B. D.; Shandro, C. A.; Ellsworth, B. A.; Anderson, C. E. *J. Org. Chem.* **2008**, *73*, 6425–6428.

(12) Ryu, K.-A.; Anderson, C. E. *Unpublished work*.

(13) Structure was solved at 0.74 Å resolution. For full details of the structure and solid-state packing, see Supporting Information.

(14) The hydroxyl resonance undergoes exchange when the ^{1}H NMR spectrum is recorded in methanol-d_4. See Supporting Information.

(15) Frisch, M. J. et al. *Gaussian 03*, revision E.02; Gaussian, Inc.: Wallingford CT, 2004. See Supporting Information for full computational details.

(16) (a) Clark, T.; Hennemann, M.; Murray, J. S.; Politzer, P. *J. Mol. Model.* **2007**, *13*, 291–296. (b) Politzer, P.; Lane, P.; Concha, M. C.; Ma, Y.; Murray, J. S. *J. Mol. Model* **2007**, *13*, 305–311.

(17) (a) Metrangolo, P.; Neukirch, H.; Pilati, T.; Resnati, G. *Acc. Chem. Res.* **2005**, *38*, 386–395. (b) Metrangolo, P.; Meyer, F.; Pilati, T.; Resnati, G.; Terraneo, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6114–6127.

(18) For further evaluation of solid supports, see Supporting Information.

(19) Dugstad, H.; Undheim, K. *Synth. Commun.* **2008**, *38*, 1846–1854.

Scheme 2. Proposed Mechanism

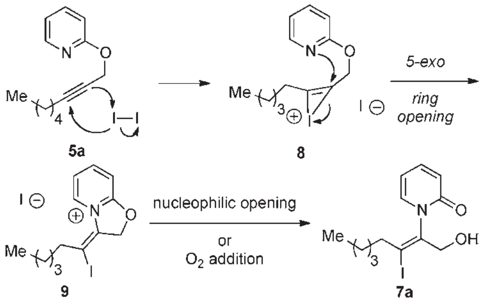
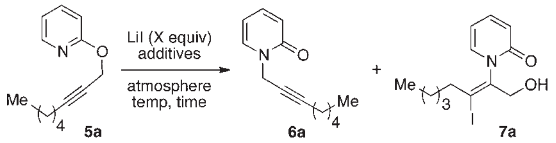


Table 2. Optimization of Atmospheric Conditions



entry	LiI (equiv)	additives	temp (°C)	atm	time (h)	**6a**:**7a**	yield **7a** (%)[a]
1	1.0	butanol (3 M) 10 wt % SiO$_2$	80	air	72	1.0:1.4	29%
2	1.5	butanol (3 M) 20 wt % SiO$_2$	80	air	72	1.0:3.1	43%
3	3.0	butanol (1 M) 30 wt % SiO$_2$	80	air	72	1.0:8.0	56%
4	3.0	butanol (1 M) 30 wt % SiO$_2$	90	O$_2$	48	0:1.0	68%[b]
5	3.0	butanol (1 M) 30 wt % SiO$_2$	90	O$_2$	72	0:1.0	41%[c]
6	1.5	butanol (3 M) 30 wt % SiO$_2$	80	N$_2$	72	1.0:0	0%[d]
7	3.0	butanol (1 M) 50 wt % SiO$_2$	100	air	48	1.0:1.5	38%

[a] Isolated yield. [b] Mean value of duplicate experiments (±3%). [c] Without agitation. [d] 67% isolated yield of compound **6a**.

water, followed by proton transfer would then provide the observed product **7a**. To test this mechanistic hypothesis, water was added to the reaction mixture; however, a decrease in both the product ratio and isolated yield was observed (Table 1, entry 6).

Given this result, a modified mechanism was proposed in which molecular oxygen could be directly incorporated to provide the newly formed allylic alcohol. To evaluate this hypothesis, the reaction was conducted under different atmospheric conditions (Table 2). In the presence of air, alkene **7a** was isolated in 29% yield (entry 1). Further optimization of the amount of lithium iodide, silica gel, and solvent facilitated the formation of the desired product **7a** in 56% isolated yield and an 8:1 ratio relative to alkyne **6a** (entries 2 and 3). The reaction was then performed under pure oxygen, with and without mixing (entries 4 and 5). In this environment, only **7a** was isolated, and the yield improved. However, while **7a** was isolated in 68% yield with agitation, only a 41% yield was observed in the absence of mixing. When oxygen was excluded entirely, the reaction yielded only the undesired alkyne **6a** in 67% yield (entry 6), lending further support to the updated mechanism. At this time, it was also discovered that increasing the temperature to 90 °C allowed comparable yields in only 48 h, without loss of product selectivity (entry 4). Increasing the temperature to 100 °C, however, was found to severely erode the yield and selectivity of the rearrangement (entry 7).

Finally, alternate sources of cationic iodide (NIS and I$_2$) were evaluated (Scheme 3). When NIS was used in place of LiI, pyridine **5a** could be recovered in significant quantities, but no product or related species could be detected. Conversely, upon treatment with 1 equiv of iodine in the presence of silica gel and oxygen at 90 °C, butyl ether **10** was isolated in 37% yield. In this case, it is assumed that intermediate **9** is intercepted by 1-butanol rather than reacting with oxygen. This implies that the lithium cation must be playing an important role in the ring opening by oxygen, as no butyl ether has been observed in the presence of LiI.

Evaluation of Reaction Scope. Table 3 summarizes the reaction of eight representative 2-propargyloxypyridines **5** under the optimized conditions (3.0 equiv of LiI, 30 wt % SiO$_2$, 90 °C, O$_2$ atmosphere, 48 h). In all cases the reaction is robust, producing only the desired vinyl iodide product in moderate to good yields. Alternate alkyl chains, including those with increased steric crowding on the alkyne terminus, are well tolerated (entries 1 and 2). The reaction permits extended conjugation near the alkyne, such as in phenyl substrate **5d**, which was found to undergo rearrangement in 67% yield (entry 3). The inclusion of heteroatoms in the propargyl unit also proceeded without difficulty, giving silyl ether **7e** in 67% yield (entry 4). In addition, methyl substitution on the pyridine ring at either C3 or C5 has no significant impact on the overall reactivity or efficiency of the reaction (entries 5 and 6). In contrast, substitution adjacent to the nitrogen at C6 does reduce the reaction efficiency with substituted pyridone **7h** being produced in only 41% yield (entry 7). Alternatively, methyl substitution at the propargylic position is well tolerated, allowing pyridone **7i**, containing a new chiral center at the allylic position, to be isolated in 71% yield as a 2:1 mixture of diastereomeric conformations as determined by ^{1}H NMR analysis (entry 8). This stereochemical outcome is imparted by

Scheme 3. Evaluation of Alternate I$^+$ Sources

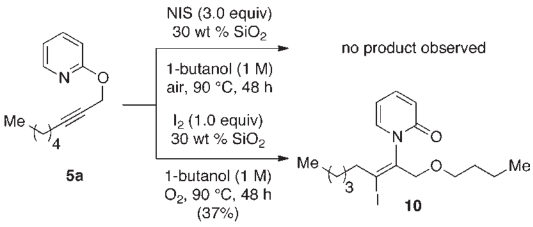
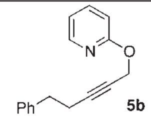
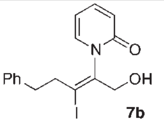
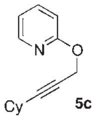
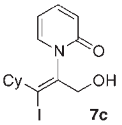
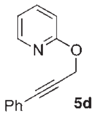
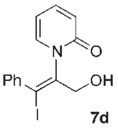
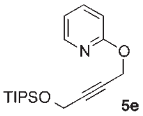
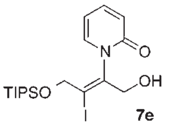
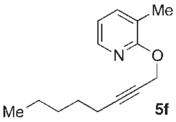
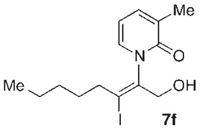
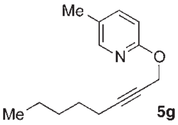
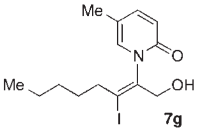
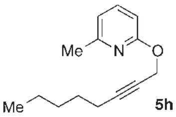
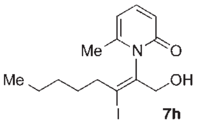
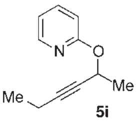
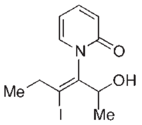


Table 3. Evaluation of Substrate Scope[a]

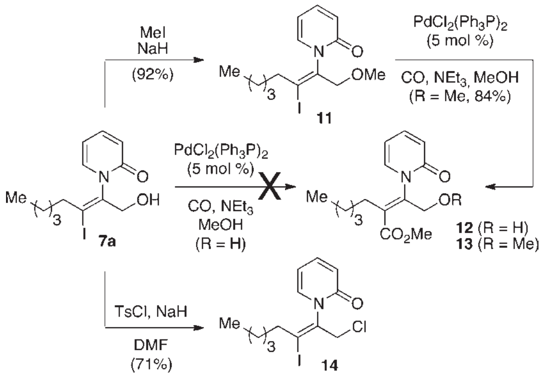
entry	substrate	product	yield[b]
1	 5b	 7b	72%
2	 5c	 7c	70%
3	 5d	 7d	67%
4	 5e	 7e	67%[c]
5	 5f	 7f	68%
6	 5g	 7g	67%
7	 5h	 7h	41%
8	 5i	 7i	71%[d,e]

[a] Conditions: LiI (3.0 equiv), SiO_2 (30 wt %), 1-butanol (1 M), 90 °C, O_2 atmosphere, 48 h. [b] Isolated yields. Mean value from duplicate experiments (±3%). [c] SiO_2 (19 wt %). [d] SiO_2 (35 wt %). [e] Ratio of diastereomeric comformations = 2:1.

the transient axial chirality of the hindered C–N junction. Control of the stereochemical configuration at the newly formed chiral center is currently under investigation in our laboratories.

Synthetic Utility of *N*-Alkenyl Pyridones. *N*-Alkyl pyridones represent a motif of interest for pharmaceutical targets due to their unique semiaromaticity[20] and H-bonding ability. To demonstrate the utility of these species, conversion of the synthetic handles present in alkene **7a** to another functionality was pursued (Scheme 4). Upon treatment with MeI and NaH, the allylic alcohol could be converted into methyl ether **11** in 92% yield.[21] Functionalization of the vinyl iodide in the presence of the free alcohol, however, proved to be more challenging. To avoid this issue, compound **11** was treated with CO, NEt_3, and $PdCl_2(Ph_3P)_2$ in methanol to give methyl ester **13** cleanly in 84% yield.[22] Alternatively, treatment of alcohol **7a** with tosyl chloride and NaH in DMF readily provided access to allylic chloride **14** in 71% yield.[23]

Scheme 4. Elaboration of Pyridone **7a**



A new method for the synthesis of β-iodo *N*-alkenyl pyridones has been developed and applied to a range of substituted 2-propargyloxypyridine precursors **5** in moderate to good yields (41–72%). These pyridones have been shown to adopt different conformations depending on the presence or absence of solvent. The dense core of orthogonal functionality present in these compounds is unprecedented and can be transformed into a variety of other functional groups. Efforts to transform β-iodo *N*-alkenyl pyridones **7** into other complex *N*-alkyl pyridone-containing targets are currently underway in our laboratories.

Acknowledgment. This work was supported by the National Science Foundation under CHE-0911264, awards from Research Corporation for Science Advancement, Arnold and Mabel Beckman Foundation Scholars Program, Donors of the American Chemical Society Petroleum Research Fund, and Calvin College. The CCD based X-ray diffractometer at Michigan State University was upgraded and/or replaced by departmental funds. We thank B. Ooms and L. Schipper (Calvin College) for initial observations and Dr. J. Greaves (UC-Irvine) for work in support of this project.

Supporting Information Available. Representative experimental procedures, ^1H and ^{13}C NMR spectra for all new compounds, further optimization, computational details, and CIF file and solid state packing diagrams for **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) 2-Pyridone possesses 36% of the aromaticity of benzene; see: Elvidge, J. A.; Jackman, L. M. *J. Chem. Soc.* **1961**, 859–866.

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(23) Sureshan, K. M.; Shashidhar, M. S.; Praveen, T.; Gonnade, R. G.; Bhadbhade, M. M. *Carbohydr. Res.* **2002**, *337*, 2399–2410.