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EFFECTIVE SYNTHETIC ROUTES TO 4*H*- AND 10b*H*-PYRIDO[2,1-*a*]ISOINDOL-6-ONES‡

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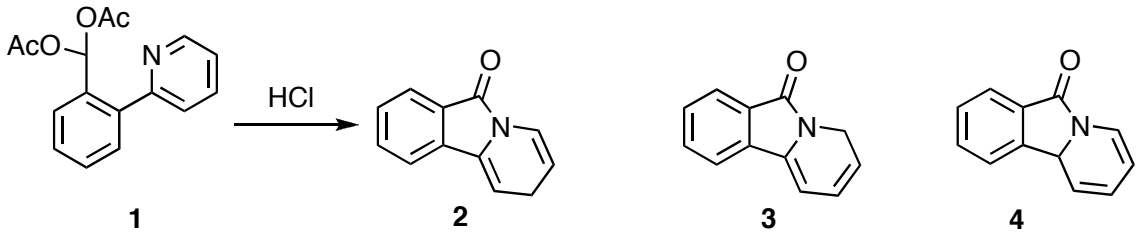
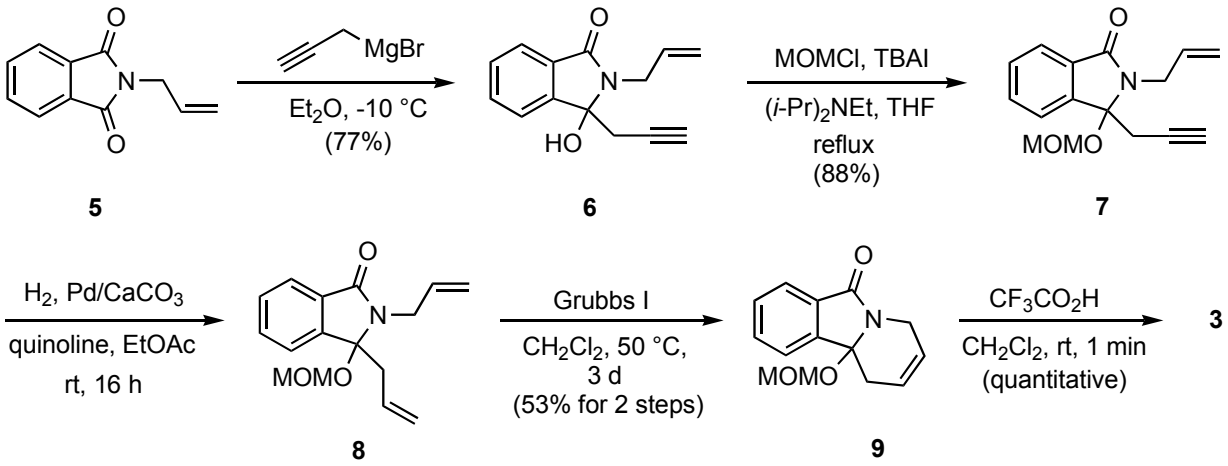
Abstract - Two previously unknown pyridoisoindolones have been synthesized from *N*-allylphthalimide as the common precursor. The methodologies allowing these constructions include a novel twofold dehydrobromination involving an *N*-acyliminium ion that experiences regiocontrolled hydration. The synthetic routes are completed by indirect introduction of the diene unit.

Despite the considerable attention that has been accorded to bridgehead nitrogen compounds, significant gaps in our knowledge of this area persist. The pyridoisoindolones constitute a representative compound class that has been virtually unstudied. While Kanaoka, Igeta and others have demonstrated that treatment of the pyridylbenzal diacetate (**1**) with HCl gives rise to the cross-conjugated cyclized product (**2**),[1] no further chemistry of **2** has been detailed. Nor have synthetic routes to the two possible, more conjugatively extended isomers **3** and **4** yet been devised. Herein we explore preparative pathways that afford a member from each diene class, thereby setting the stage for the further probing of their chemical reactivity.



1 **2** **3** **4**

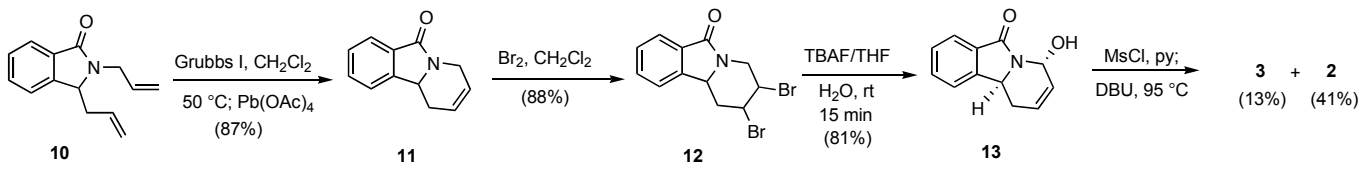
‡Submitted in celebration of the 75th birthday of Ekkehard Winterfeldt whose research accomplishments have been a long time inspiration to us.



Scheme 1

Our initial approach to **3** is based on the realization that 1,2-addition of propargylmagnesium bromide to the well known *N*-allylphthalimide (**5**)[2] delivers tertiary carbinol (**6**) that is amenable to MOM protection as in **7** without competitive rupture of the lactam ring[3] (Scheme 1). Chemoselective reduction of the acetylenic functionality in **7** under Lindlar conditions ensued. The targeted framework was next revealed by ring-closing metathesis involving use of the first-generation Grubbs reagent[4] in CH_2Cl_2 at 50 °C. A salient feature of this approach is the regiocontrolled introduction of the conjugated diene component, which was realized quantitatively upon treatment of **9** with a catalytic quantity of trifluoroacetic acid in CH_2Cl_2 at room temperature for 1 min. The $^1H/^{13}C$ NMR spectral features of the resulting diene (**3**) and its UV absorption profile[5a] are fully consistent with the bonding arrangement shown.

An alternate route to this pyridoisoindolone takes advantage of an unusual aspect of *N*-acyliminium ion chemistry.[6] The initial availability of **10** was realized by exposure of **5** in turn to lithium triethylborohydride, acetic anhydride, and allyltrimethylsilane/bismuth triflate as first described by Pin and coworkers[7] (Scheme 2). As in earlier example **8**, the latent tricyclic substructure defined in **11** was generated by ring-closing metathesis. At this junction, the dibromination of **11** with ensuing twofold dehydrobromination was projected to be a viable means for diene elaboration. A single isomer of **13** was



Scheme 2

indeed formed efficiently. This intermediate proved to be remarkably reactive toward $Bu_4N^+F^-$ in THF at 25 °C for 15 min,[8] conditions that led rapidly to the crystalline carbinol **13**. Proof of the global structure and stereochemistry of **13** was amply furnished by X-ray analysis (Figure 1).

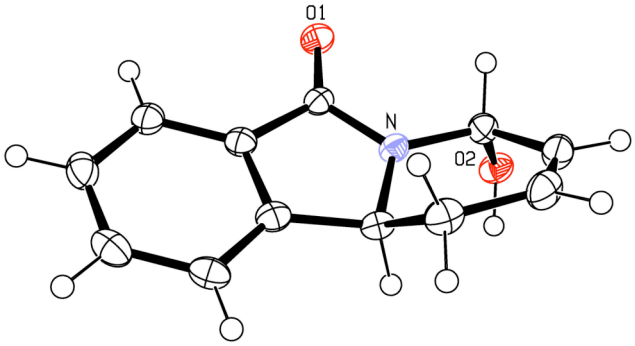
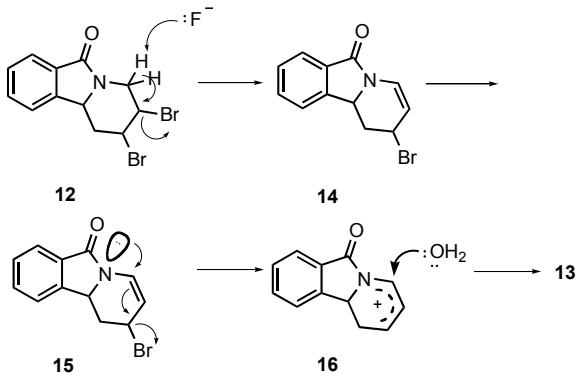


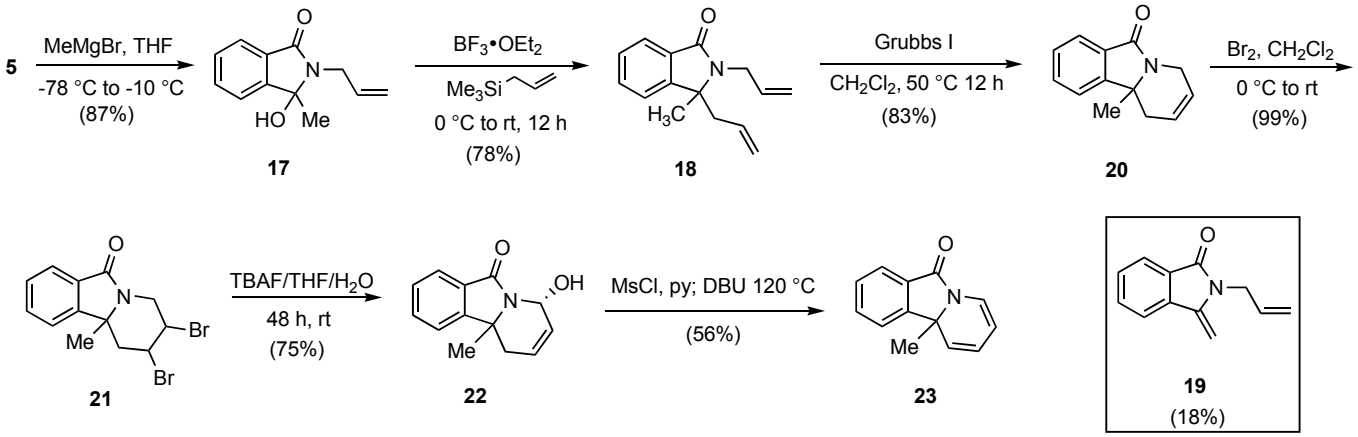
Figure 1



Scheme 3

A mechanistic pathway capable of rationalizing this unusual transformation is offered in Scheme 3. It will be recognized that the initial dehydrobromination step is regiocontrolled by virtue of the activation provided by the proximal amide functionality. Following arrival at **14**, it is rationalized that iminium ion (**16**) is generated via electron donation from the amide nitrogen as in **15**. Ultimately the trapping of water ensues. The dehydration of **13**, best achieved by treatment with methanesulfonyl chloride in neat pyridine followed by DBU and reflux for several hours produced a mixture of **2** and **3**, presumably via initially formed **4**. A factor contributing to operation of the [1,5] hydrogen shift may well be the more extended level of conjugation resident in **3**.

In light of these findings, we considered it advisable to install a methyl group as in **23** that would impede operation of the sigmatropic migration. To this end, CH_3MgBr was added to **5** in advance of a series of steps that mirrored those utilized in the conversion of **10** to **13** as outlined in Scheme 4. With the exception of modest levels of dehydration leading to **19**, the reactivity levels evidenced during the acquisition of **22** proved to be a close parallel as expected. The relative configuration for **22** was assigned by analogy, closely comparable NMR spectra, and response to dehydration.[5b] Unlike diene (**4**), compound (**23**) did not experience any further transformations under the conditions listed for its dehydration.[9]



Scheme 4

ACKNOWLEDGMENT

We would like to thank Dr. Judith C. Gallucci for performing the crystallographic analysis.

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3. This untoward behavior is encountered when the pendant side chain is an allyl group, leading to migration of the olefinic π-bond and rupture of the ring.
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5. (a) For **3**: λ max (isooctane) 379 (ε 5,185), 272 (ε 3,300). (b) For **23**: λ max (isooctane) 333 (ε 5,865), 233 (ε 21,975).
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8. L. A. Paquette, R. D. Dura, N. Fosnaugh, and M. Stepanian, *J. Org. Chem.*, 2006, **71**, 8438.
9. For **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.62 (2H, m), 5.96 (2H, m), 6.20 (1H, m), 7.54 (2H, m), 7.68 (1H, d, *J*=7.6 Hz), 7.89 (1H, d, *J*=7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 42.1, 100.0, 120.1, 121.5, 122.9, 123.0, 128.5, 129.2, 131.1, 134.3, 166.6. For **23**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53 (3H, s), 5.62-5.66 (1H, m), 5.97 (1H, dd, *J*=2.8, 1.2 Hz), 7.02 (1H, dt, *J*=7.2, 1.2 Hz), 7.43-7.47 (2H, m), 7.58 (1H, td, *J*=7.6, 1.2 Hz), 7.86-7.88 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.7, 62.5, 110.0, 120.9, 122.6, 122.6, 124.7, 128.1, 130.4, 132.7, 150.2, 167.0.