Iodohexahydropyridoindolones. Formation and Reactivity

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This manuscript is dedicated to the memory of Professor Harry H. Wasserman.

Abstract: Described herein is the generation and use of iodohexahydropyridoindolones and their free radical atom transfer reactions with aryl acetylenes to generate quaternary substituted pyridoindolones.

Key words: Indole, hexahydropyridoindolone, free radical reaction, atom transfer, natural products, kapakahine

In an effort to efficiently generate the hexahydropyrido-[2,3,*b*]-indolone ring system, we recently described the efficient synthesis of tetracyclic bromide **2** from a sequential Suzuki cross coupling and oxidative cyclization protocol.^{1,2} We envisioned that **2** would serve as a precursor to a wide range of potentially important small molecules having quaternary substitution through substitution of the bromide.³ However, and in contrast to the corresponding bromopyrroloindolones,⁴ **2** has proven to be immune to reactions with nucleophiles.

Scheme 1. NBS Cyclization to Hexahydropyridoindolone **2**

Because of the difficulties alluded to above, we decided to explore an alternate approach to quaternary substituted pyridoindolones and decided to examine Baran's oxidative coupling technology using **1**.⁵ While this methodology has been employed by the Baran group to build hetero-dimeric pyrroloindoline substrates and members of the kaphakahine family, to the best of our knowledge it has not been used to generate the corresponding hexahydropyridoindolones. With this in mind, we subjected **2** to iodoaniline and NIS and were pleased to generate hexahydropyridoindolone **5** in 90% yield. Because the corresponding unprotected iodopyrroloindolones had been reported to be unstable,⁶ it was interesting that the use of wet CH_3CN in the reaction resulted in the formation of iodohexahydropyridoindolone **3** as the major product.⁷ Optimization of the conditions, namely excluding **4** from the reaction and carrying the reaction out in CH_2Cl_2 resulted in the isolation of **3** in 80% yield.

Scheme 2. Oxidative Generation of Hexahydropyridoindolones

With a continued focus on quaternary substituted substrates, we became interested in the properties of iodide **3**. In contrast to bromide **2**, **3** served as a precursor to aniline and iodoaniline derivatives **5** (Table 1, entries 1-3). Surprisingly, even when care was taken to exclude H₂O, a significant by-product in these transformations was 3° alcohol **6** (entry 3); it was the only product isolated when **3** was exposed to a mixture of CH₃CN and H₂O (entry 5).⁸ Because it would appear to be a likely olefin isomerization candidate, it was surprising to us that the elimination product **7** was stable (entry 3) and that it was the exclusive product when **3** was exposed to 3 Å MS (entry 4). Pyridone **8** was generated as a by-product when **3** was exposed to iodoaniline (entry 1) or as the exclusive product when **3** was exposed to piperidine (entry 6).

Table 1. Iodo-hexahydropyridoindoline Reactions

Entry	Nucleophile	Conditions	R	5:6:7:8	Yield
1	2-iodoaniline	CH ₃ CN, 40 °C	2-iodoaniline	3:3:3:0:1	75%
2	2-iodoaniline	CH ₂ Cl ₂ , reflux	2-iodoaniline	2:2:1:0:0	69%
3	aniline	3 Å MS, CH ₃ CN, 40 °C	aniline	2:2:1:1.3:0	81%
4	-----	3 Å MS, CH ₃ CN, 40 °C	-----	0:0:1:0	79%
5	H ₂ O	H ₂ O, CH ₃ CN (1:1), 40 °C	-----	0:1:0:0	80%
6	piperidine	3 Å MS, CH ₃ CN, 40 °C	piperidine	0:0:0:1	81%
7	-----	O ₂ , BEt ₃ , PhH, 60 °C	-----	0:1:0:0	72%

That 3° alcohol **6** was formed even when water was excluded from the reaction implied that oxygen might be responsible for its formation.^{9,10} To explore this notion further we exposed **3** to oxygen in the presence of BEt₃ as a radical initiator. These conditions resulted in the generation of alcohol **6** in 72% yield even though normally employed reducing agents were absent from the reaction mixture (Table 1, entry 7).¹¹

Cognizant of the free-radical chemistry of the corresponding bromopyrroloindolines and intrigued by the radical chemistry of **3**,¹² we decided to determine whether halogen-substituted hexahydropyridoindolones were susceptible to free-radical induced C–C and C–H bond forming reactions. If these efforts were successful we felt that they would represent a rapid entry into quaternary substituted hexahydropyridoindolones. We initially examined the reaction of bromide **2** using allylstannane and were pleased to isolate

quaternary substituted pyridoindoline **10** in 80% yield (Scheme 3). In a similar fashion, when **2** was exposed to Bu_3SnH we isolated reduced pyridone **9** in 69% yield. While we have not examined all of the possibilities, the reaction of bromide **2** using free radical conditions appears to be limited to stannanes. Subjecting **2** to acrylate or activated alkynes and either Bu_3SnH , AIBN or atom transfer conditions using BEt_3 as an initiator did not result in coupled products.¹³

Scheme 3. Free radical reduction and allyl addition using **2**

In contrast to **2**, when **3** was exposed to atom transfer free radical conditions using phenyl acetylene and BEt_3 at 60 °C we isolated quaternary substituted hexahydropyridoindolone **12** in 67% yield as a single stereoisomer (Table 2, entry 1).^{13,14} Interestingly and in spite of our attempts to exclude oxygen using freeze-pump-thaw techniques, we still isolated **6** as a by-product. We presume that this was due to the exothermic nature of the reaction of oxygen with the free radical from **3** and our inability to completely exclude O_2 from the reaction mixture.¹⁵ By running the reaction at a higher substrate concentration (0.2 mM) we completely avoided the generation of alcohol **6** but began to observe phenyl acetylene derived diene **13** (entry 2). Interestingly, when the reaction was carried out at 0.1 mM vinyl iodide **12** was the only product isolated but its yield was still 70% (entry 3).

Table 2. Optimization of the Atom Transfer Reaction of **3** with Phenyl Acetylene

entry	[3]	yield 12	yield 13	yield 6
1	0.02 mM	67%	-----	10%
2	0.2 mM	70%	15%	-----
3	0.1 mM	70%	trace	-----

We explored the scope of the atom transfer reaction of **3** using the conditions that were optimized for phenyl acetylene by examining the effect of substitution at the *para*-position of the aryl acetylene on the reaction. As illustrated in Table 3, the electronic environment about the acetylene did not significantly impact the yield for the reaction. Both electron rich and electron deficient aryl acetylenes underwent free radical coupling to give the corresponding quaternary substituted hexahydropyridoindolone in yields that ranged from 69% to 84%.

Table 3. Scope of the Free-Radical Atom Transfer Reaction of **3**

^aTrace quantities of a substance that we have tentatively identified as the acetylene dimer (see **13**, Table 2) were also observed in these reactions.

In conclusion, in this manuscript we have described the synthesis of iodo-hexahydropyridoindolone **3** and aniline substituted hexahydropyridoindolone **5** from dihydropyridone **1**. We have also demonstrated that both bromo- and iodo-hexahydropyridoindolone successfully undergo free radical reactions to give quaternary substituted hexahydropyridoindolone substrates.

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