Preparation of Isoindolones by a Lithium–Iodide Exchange-Induced Intramolecular Wurtz–Fittig Reaction of *o*-Iodobenzoyl Chloride/Imine Adducts

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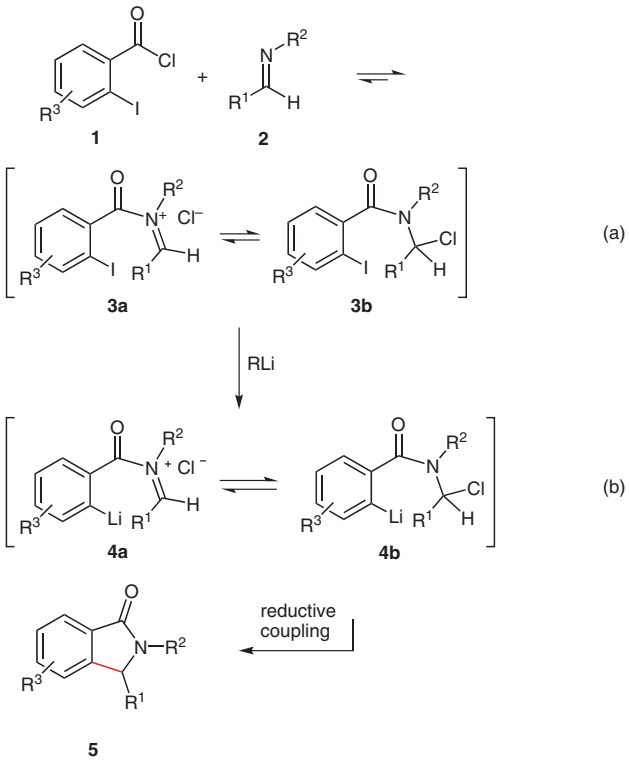
Abstract: Addition of *o*-iodobenzoyl chlorides to imines affords *N*-acyliminium ions, perhaps in equilibrium with α-chlorobenzamides, as adducts. Reaction of the adducts with 1.1 equivalents of phenyllithium at –78 °C followed by warming to ambient temperature induces an intramolecular Wurtz–Fittig coupling to afford 2,3-dihydroisoindolones in excellent yields.

Key words: metal-halogen exchange, Wurtz–Fittig, isoindolone, imines, acid chloride

The reaction of acid chlorides with imines affords adducts **3** which may be represented formally as the *N*-acyliminium ions **3a** or the corresponding α-chloroamides **3b** derived from 1,2-addition across the imine C–N bond.[1] Such adducts of imines and a variety of acylating agents, which include acid chlorides and anhydrides, have been proposed as intermediates in the synthesis of a number of different heterocycles.[2] This has included several complex natural products containing heterocycles as substructures.[3] Reaction of acid chlorides with simple imines has also been used in a method to protect a secondary amide.[4] Our interest in preparing isoindolones prompted speculation that adducts **3** derived from the addition of *o*-iodobenzoyl chlorides to imines might be readily cyclized under reductive coupling conditions to afford 2,3-dihydroisoindolon-1-ones (Scheme 1). Thus, generation of an anion or anion equivalent *ortho* to the benzoyl carbonyl group in the benzoyl chloride/imine adduct **3** should provide an intermediate poised to cyclize to an isoindolone.[5]

We proposed that the desired cyclization might be induced by forming the *ortho*-lithio derivative **4** from the *o*-iodobenzoyl chloride/imine adduct **3**, by lithium–iodide exchange.[6] Such a reaction would be similar in principle, to the Wurtz–Fittig-type cyclization of α,ω-dihaloalkanes induced by *tert*-butyllithium, which was described by Bailey and co-workers.[7] We were also encouraged by our previous work utilizing lithium–iodide exchange to generate internally functionalized aryllithium reagents, in the presence of imines, as method to prepare isoindolones.[8] Direct nucleophilic couplings to form a bond between the carbon α to nitrogen and the *ortho*-C-aryl carbon to form an isoindolone ring are rare (**5**, formation of red bond).[9]



Scheme 1 (a) Addition of acid chlorides to imines to form *N*-acyliminium salts **3a** and/or chloroamides **3b**; (b) lithium–iodide exchange-induced cyclization to form isoindolone **5**

A representative adduct **3** was prepared by adding *o*-iodobenzoyl chloride to a THF solution of butylidenebutylamine **2**, (R^1 = Pr, R^2 = Bu, R^3 = H) at –25 °C. After stirring for 10 minutes at –25 °C, the resulting solution was cooled to –78 °C and phenyllithium (1.1 equivalent) was added dropwise. The cooling bath was removed immediately, and the mixture was warmed to ambient temperature. Isoindolone **5** (R^1 = Pr, R^2 = Bu, R^3 = H) was isolated in a 90% yield. The reaction was very clean, with only a minor amount of a single by-product being detected. The by-product was identified as *N*-[(1*E*)-1-butenyl]-*N*-butylbenzamide, presumably arising from some minor competing β-elimination from the acid chloride/imine adduct **3** (R^1 = Pr, R^2 = Bu, R^3 = H). Preparation of the acid chloride/imine adduct above –25 °C (e.g., 0 °C), followed by cooling to –78 °C, treating with phenyllithium and warming to ambient temperature gave poorer yields of the isoindolone.[10] Also, warming of the reaction mixture from –78 °C to room temperature before the aqueous quench

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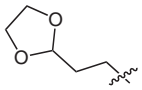
appeared to be critical to the success of the reaction. Thus, quenching reaction mixtures at 0 °C instead of bringing to ambient temperature decreased the yield of isoindolone **5** (R^1 = Pr, R^2 = Bu, R^3 = H) to 66% (Table 1, entry 2). In this particular case, a small amount of *N*-butylbenzamide was also recovered from the reaction mixture, which suggested that the lithium–iodide exchange had proceeded, but the cyclization to form the isoindolone was incomplete. Hydrolysis of the intermediate organolithium reagent **4a** formed from **3** after lithium–iodide exchange would afford *N*-butylbenzamide. From consideration of Baldwin's rules, the expected poor nucleophilic trajectory (5-*endo*-trig), and the probable higher barrier required for ring closure via the *N*-acyliminium are consistent with a higher temperature needed for the cyclization. However, the intermediacy of the α-chloroamide adduct **4b** as opposed to the *N*-acyliminium ion **4a** undergoing the cyclization remains as a possibility through the more favorable 5-*exo*-tet ring closure.[11]

The isoindolone annulation protocol was applied to the synthesis of several other isoindolones (Table 1). The reaction appears relatively general for the synthesis of 2,3-dihydroisoindol-1-ones derived from *o*-iodobenzoyl chlorides and simple imines. Interestingly, the presence of a pendant aryl bromide did not interfere with the purported lithium–iodide exchange[6] and afforded the 5-bromo-substituted 2,3-dihydroisoindol-1-one in excellent yield (Table 1, entry 3). There were some limitations identified. Thus, only a trace of the desired product was detected from the attempted reductive cyclization of the adduct derived from reaction of furylidenepropylamine with *o*-iodobenzoyl chloride (Table 1, entry 9). The relatively carbon-acidic furan ring may undergo competing metallation by reactive organolithium intermediates and interfere with the desired course of reaction. Likewise, the benzylidenallylamine adduct (Table 1, entry 10) afforded only 12% of the isoindolone. In this latter case, a symmetrical stilbene was isolated as a by-product.[12]

We briefly investigated several other approaches to promote the intramolecular reductive coupling on the acid chloride/imine adduct **3** by analogy with the Wurtz–Fittig reaction.[7,13] Thus, treatment of **3** (R^1 = Pr, R^2 = Bu, R^3 = H) with lithium metal with, or without, exposure to ultrasound, afforded only traces of the desired 2,3-dihydroisoindol-1-one **5**. Reaction of **3** (R^1 = Pr, R^2 = Bu, R^3 = H) with ytterbium metal, in the presence or absence of copper(I) salts, again gave only traces of the desired product.[14] Reaction of **3** with freshly prepared SmI_2 did not give any of the isoindolone.[15] Finally, the use of low valent nickel salts[16] and complexes,[17] and indium powder,[18] all of which have been reported to be effective in reductive biaryl and aryl-alkyl couplings, also failed to cyclize the adducts **3**. We did not explore Group VIII mediated cyclizations, involving palladium or platinum, for example.

We have shown that adducts of imine and *o*-iodobenzoyl chlorides serve as convenient precursors to the isoindolone ring system by a direct annulative approach.[19,20] The in situ generation of an aryllithium intermediate is proposed, which promotes the cyclization to form the 2,3-dihydroisoindol-1-ones. The accommodation of certain functional groups indicates that a wider array of functionalized organolithium reagents may be more generally accessible for use in synthesis through transient generation.[21]

Table 1 2,3-Dihydroisoindol-1-one **5** from the Cyclization of Adducts **3** Induced by Phenyllithium

Entry	R^1	R^2	R^3	Product **5**	Yield (%)[a]
1	Pr	Bu	H	**5a**	88
2	Pr	Bu	H	**5a**	66[b]
3	Pr	Bu	5-Br	**5b**	81
4	Pr	Bu	5-Me	**5c**	90
5	Pr	Bu	4-Cl	**5d**	65
6	*c*-hexyl	Bn	H	**5e**	65[c]
7	2-phenethyl	allyl	H	**5f**	70
8	Pr		H	**5g**	79[d]
9	2-furyl	Pr	H	**5h**	ca 10[d]
10	Ph	allyl	H	**5i**	12

[a] Reactions were conducted at –78 °C (±3 °C) using 1.1 equiv of PhLi and 1.0 equiv each of the *o*-iodobenzoyl chlorides and imine followed by warming to ambient temperature, stirring 1 h before quenching with H_2O. Yields are for isolated products by flash chromatography and short-path distillation.
[b] Reaction warmed from –78 °C to 0 °C, stirred 1 h before quenching with H_2O.
[c] Isolated and purified by recrystallization.
[d] Isolated by flash chromatography.

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(10) At –78 °C formation of the acid chloride/imine adduct was considerably slower with the yields of isoindolone **4** dropping significantly.
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(19) (a) **General Procedure for the Synthesis of Isoindolones 5 from *o*-Iodobenzoyl Chlorides 1 and Imines 2**: Neat 2-iodobenzoyl chloride (1 mmol) was added dropwise to a solution of the corresponding imine (1 mmol) as a solution in THF at –25 °C. After stirring for 10 min, the reaction was cooled to –78 °C and stirred for an additional 30 min. Phenyllithium (1.1 mmol, typically about 1.8 M in Et_2O–hexanes) was added dropwise to the solution over 5 min followed by stirring the reaction for 1 h at –78 °C. The cooling bath was removed, the reaction warmed to ambient temperature, then stirred for 1 h. The reaction was quenched slowly at ambient temperature by the addition of H_2O. The mixture was stirred for about 30 min, followed by extraction of the mixture with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), concentrated and chromatographed by flash chromatography. The isolated products were typically obtained as viscous oils. Several of the products (designated in Table 1) were distilled in a bulb-to-bulb short path (Kugelrohr) distillation apparatus. [Note: Imines were prepared by one of two procedures. For volatile imines, a procedure using K_2CO_3 reported by Stork et al.[19b] was followed. Imines were distilled and then stored under a nitrogen atmosphere at 0 °C prior to use. For non-volatile imines, the procedure using dibutyltin dichoride and Na_2SO_4 as described by Stetin et al.[19c] was followed. The imines were isolated and used immediately without further purification] (b) Stork, G.; Dowd, S. R. *Org. Synth.* **1974**, *54*, 46. (c) Stetin, C.; de Jeso, B.; Pommier, J. C. *Synth. Commun.* **1982**, *12*, 495.
(20) Spectroscopic and characterization data for selected products: 2-Butyl-3-propyl-2,3-dihydroisoindol-1-one (**5a**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (m, 4 H), 0.95 (t, 3 H, *J* = 7.3 Hz), 1.08 (m, 1 H), 1.37 (m, 2 H), 1.60 (m, 2 H), 1.93 (m, 2 H), 3.08 (m, 1 H), 4.02 (dt, 1 H, *J* = 8.0, 13.9 Hz), 4.59 (t, 1 H, *J* = 3.8 Hz), 7.46 (m, 3 H), 7.83 (d, 1 H, *J* = 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.72, 13.96, 15.76, 20.09, 30.38, 32.60, 39.36, 58.87, 121.90, 123.41, 127.41, 127.85, 131.03, 132.76, 145.16, 168.36. MS: *m*/*z* = 232 [M + H]. Anal. Calcd for $C_{15}H_{21}NO{\cdot}0.25\ H_2O$: C, 76.39; H, 9.19; N, 5.93. Found: C, 76.20; H, 8.82; N, 5.95. 2-Butyl-3-propyl-6-bromo-2,3-dihydroisoindol-1-one (**5b**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (m, 4 H), 0.94 (t, 3 H, *J* = 7.4 Hz), 1.08 (m, 1 H), 1.36 (m, 2 H), 1.61 (m, 2 H), 1.92 (m, 2 H), 3.08 (m, 1 H), 4.00 (dt, 1 H, *J* = 8.0, 13.9 Hz), 4.56 (t, 1 H, *J* = 3.7 Hz), 7.29 (d, 1 H, *J* = 8.1 Hz), 7.63 (d, 1 H, *J* = 8.1 Hz), 7.96 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.76, 13.97, 15.70, 20.13, 30.35, 32.45, 39.57, 58.75, 122.00, 123.61, 126.69, 134.04, 134.91, 143.84, 166.90. MS: *m*/*z* = 310, 312 [M + H]. Anal. Calcd for $C_{15}H_{20}NOBr$: C, 58.07; H, 6.50; N, 4.51. Found: C, 57.76; H, 6.47; N, 4.60. 2-Benzyl-3-cyclohexyl-2,3-dihydroisoindol-1-one (**5e**): mp 163–164.5 °C (methyl *tert*-butyl ether–hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.42 (m, 1 H), 1.06 (m, 2 H), 1.26 (m, 2 H), 1.43 (m, 2 H), 1.68 (m, 2 H), 2.03 (m, 1 H), 3.10 (m, 1 H), 4.20 (d, 1 H, *J* = 15.2, 13.9 Hz), 4,26 (d, 1 H, *J* = 3.1 Hz), 5.40 (d, 1 H, *J* = 15.2 Hz), 7.35 (m, 5 H), 7.45 (m, 3 H), 7.90 (d, 1 H, *J* = 6.45 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.76, 25.95, 26.35, 26.90, 29.69, 39.38, 43.98, 63.57, 123.27, 123.77, 127.46, 127.93, 128.06, 128.66, 128.90, 130.92, 132.82, 137.17, 144.09, 168.68. MS: *m*/*z* = 306 [M + H]. Anal. Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.85. Found: C, 82.11; H, 7.53; N, 5.14. 2-[2-(1,3-Dioxolan-2-yl)ethyl]-3-propylisoindolin-1-one (**5g**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (m, 4 H), 1.07 (m, 1 H), 1.98 (m, 4 H), 3.25 (m, 1 H), 3.85 (m, 2 H), 3.99 (m, 2 H), 4.12 (m, 1 H), 4.64 (m, 1 H), 4.93 (m, 1 H), 7.42 (m, 3 H), 7.81 (d, 1 H, *J* = 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.95, 15.67, 32.41, 32.57, 35.09, 59.17, 64.89, 102.57, 121.96, 123.39, 127.84, 131.12, 132.64, 145.26, 168.38. MS: *m*/*z* = 276 [M+]. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.52; H, 7.57; N, 5.30. 2-Propyl-3-(2-furyl)-2,3-dihydroisoindol-1-one (**5h**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, 3 H, *J* = 7.4 Hz), 1.57 (m, 2 H), 3.08 (m, 1 H), 3.80 (dt, 1 H, *J* = 7.4, 12.2 Hz), 5.60 (s, 1 H), 6.31 (d, 1 H, *J* = 3.2 Hz), 6.37 (dd, 1 H, *J* = 3.2, 1.6 Hz), 7.35 (m, 1 H), 7.47 (d, 1 H, *J* = 1.6 Hz), 7.50 (m, 2 H), 7.88 (m, 1 H). MS: *m*/*z* = 242 [M + H].
(21) By comparison the procedure described in this manuscript provides isoindolones in comparable yields and purity to our previously described work.[8] For larger scale reactions, the present work is more practical to conduct requiring temperatures no lower than –78 °C.