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A convenient preparation of 4-iodoindoles from indoles: application to the chemical synthesis of hapalindole alkaloids

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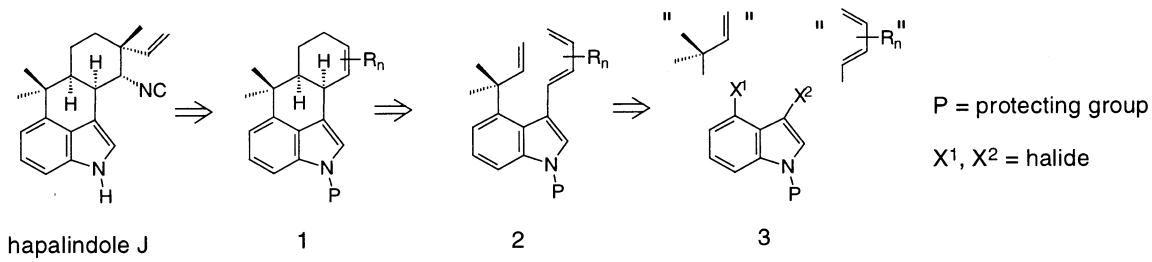
Abstract—4-Iodoindoles were synthesized via regioselective chloromercuration and subsequent iodination of a series of *N*-*p*-toluenesulfonyl indoles bearing a variety of substituents at the 3-position This procedure allows rapid access to 3,4-dihaloindoles which may be used as synthetic precursors to indole alkaloids.

The regioselective functionalization of aromatic systems is an ongoing challenge in organic synthesis.[1] Advances in directed metallation[2] and the use of cross-coupling methodology[3] has allowed the organic chemist access to a wide variety of multi-functionalized benzenoid and heteroaromatic compounds. The functionalization of polyaromatic (both carbocyclic and heteroaromatic) molecules is more complex.

Recently we have undertaken a chemical synthesis of a series of alkaloids of the hapalindole class.[4] Scheme 1 illustrates our retrosynthetic analysis using hapalindole J as an example. The penultimate target would be a suitably functionalized tetracyclic compound such as **1**, which is an intramolecular Diels–Alder cyclization product of **2**. The formation of **2** would arise from sequential cross-coupling reactions which would install the dienophilic and diene moieties (necessary for the cycloaddition onto the 3,4-dihaloindole **3**).

3,4-Disubstitued indoles are well known compounds[5] but their formation usually relies on the formation of the pyrrole ring from a suitably adorned benzenoid precursor. It is rare that a direct fuctionalization of the 4-position can be achieved. A thallation reaction has been used to generate an organometallic species which was subsequently iodinated.[6] Semmelhack has employed a chromium carbonyl adduct of indoles in order to nucleophilicity functionalize the benzopyrrole system.[7] Herein we report a simple and direct halogenation protocol which allows for the preparation of a variety of 3-substituted-4-iodoindoles.

During a synthesis of a 3-iodoindole using the mercuration protocol of Hegedus,[8] we were intrigued by the fact that when a tosylated substrate which already bore a substituent in the 3-position was subjected to these conditions ($Hg(OAc)_2/CH_3CO_2H$/catalytic $HClO_4$), a precipitate formed which was the 4-(acetoxymercurio) derivative (see Table 1). Stirring in aqueous NaCl effected an exchange reaction to the chloromercurioindole which could be isolated in good yield. Titration of the organomercurio species with a solution of iodine in CH_2Cl_2 resulted in the smooth conversion to the 4-



Scheme 1. Retrosynthesis of hapalindole J.

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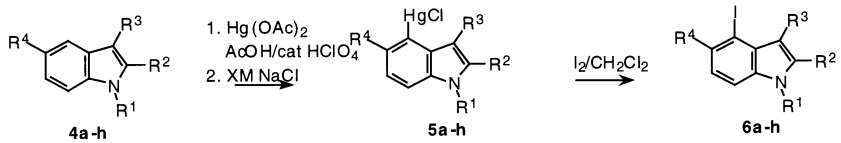
Table 1. The preparation of 4-iodoindoles by mercuration/iodination

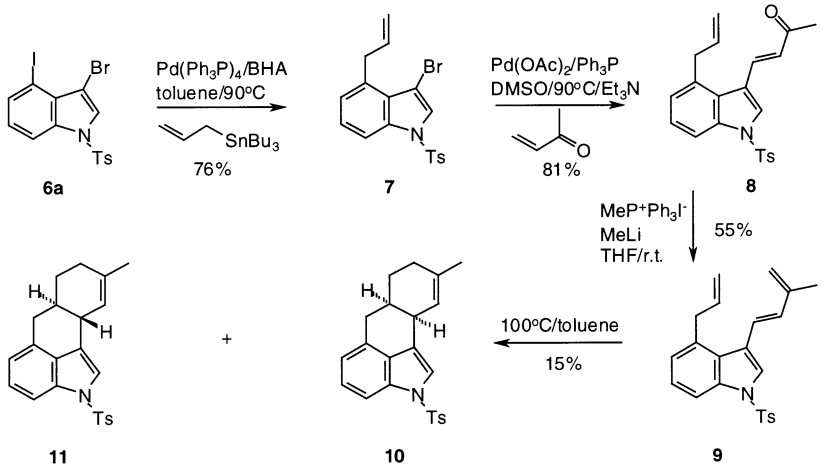


Entry	R^1	R^2	R^3	R^4	Yield of **5**	Yield of **6**
a	Ts	H	Br	H	83	75
b	Ts	H	CHO	H	85	67
c	Ts	H	CH=CH-C(O)Me	H	0	–
d	Ts	H	CO_2Me	H	71	75
e	Ts	H	Me	H	76	70
f	Ts	Me	Me	H	74	69
g	Ts	Me	Br	OMe	49	17
h	Me	Me	Me	H	0	–

iodoindole. We were pleasantly surprised by the efficacy of the procedure and sought to probe its generality. To this end, a series of 3-substitued indoles was subjected to the above conditions; the results are presented in Table 1.[9]

A typical procedure is as follows. Preparation of **5a**: 3-Bromo-*N*-*p*-toluenesulfonylindole **4a** (0.35 g, 1 mmol) was stirred in glacial acetic acid (20 mL) at ambient temperature. Mercury(II) acetate (0.35 g, 1.1 mmol) was added along with one drop of 70% perchloric acid. The reaction was stirred for 48 h after which time a precipitate formed. The reaction mixture was poured into a saturated NaCl solution (30 mL) with stirring. Stirring was continued for 15 min and the solid material (**6a**) was isolated by filtration, washed liberally with water and dried under vacuum to a constant mass (0.58 g, 92%). Preparation of **6a**: The organomercury compound **5a** (0.58 g, 0.99 mmol) was added at ambient temperature to dry methylene chloride (30 mL) and iodine (0.26 g, 1.01 mmol) was added with strirring. The reaction was stirred form 16 h after which time the mixture was filtered to remove the inorganic material. The filtrate was washed with 5 M sodium thiosulfate solution, water, stirred with decolorizing charcoal, and dried over anhydrous $MgSO_4$. Filtration of the drying agent and removal of the solvent yielded a pale yellow oil which was crystallized from hexanes. The yield of 3-bromo-4-*N*-*p*-toluenesulfonylindole **6a** was 0.35 g (75%).

Several items from Table 1 are worthy of note. In the absence of a tosyl group on the indolic nitrogen, the reaction failed to give a clean product. It is suspected that the tosyl group serves to deactivate the benzopyrrole double bond and remove it from competition for the electrophilic mercury reagent. Even with an electron withdrawing group in the 3-position, the presence of a tosyl group is required. For example, indole 3-carboxaldehyde failed to produce reasonable yields of the 4-mercurioindole. Note that an alkenyl substituent (even a relatively electron poor one as in **4c**) serves to complicate the reaction. In cases where the indole nitrogen was not protected with an electron-withdrawing group, reaction occurred but the exact nature of the reaction mixture was not determined.



Scheme 2. Synthesis of a hapalindole model via a cross-coupling/Diels–Alder strategy.

To demonstrate the feasibility of our cross-coupling/Diels–Alder approach to the synthesis of the tetracyclic hapalindoles, we prepared a simple model system (Scheme 2). Using dihaloindole **6a**, the allyl (dienophilic) moiety was installed using a Stille coupling to produce **7** in 76% yield. A subsequent Heck reaction employing methyl vinyl ketone gave enone **8** in 81% yield. Methylenation in 55% yield produced the Diels–Alder substrate **9** which when heated at 100°C for 12 h in toluene and produced an inseparable mixture of *cis* and *trans* adducts **10** and **11** in a combined yield of 15%.[10]

In summary we have developed a convenient method for the direct mercuration and subsequent iodination of 3-substitued indoles having an *N*-tosyl protecting group. The method appears to be very general and promises to be extremely useful for the preparation of synthetic precursors to a wide range of indole alkaloids and other non-natural indole containing molecules. It is our intention to utilize this method in combination with cross-coupling methodology in our efforts to prepare hapalindoles and other indole alkaloids. Details of the cross-coupling/Diels–Alder methodology presented in Scheme 2 will be reported in due course.

Acknowledgements

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9. Physical data for **5a**: ^{1}H NMR ($CDCl_3$) $d=7.97$ (d, $J=7.1$ Hz, 1H), 7.71 ($d=8.9$ Hz, 2H), 7.41–7.22 (m, 5H), 2.37 (s, 3H). ^{13}C NMR (CDCl3) $\delta=146.1$, 136.9, 134.9, 130.5, 129.9, 127.0, 126.8, 126.4, 120.4, 114.0, 99.3, 21.9. IR (thin film) $v=3110$–3020, 1595, 1372, 1173. HRMS (70 ev) for $C_{15}H_{11}O_2SNHgBr$ (M^+–Cl) calcd:584.5088, found: 584.5098. Physical data for **6a**: ^{1}H NMR ($CDCl_3$) $\delta=8.35$ (d, $J=7.9$ Hz, 1H), 7.75 (d, $J=8.4$ Hz, 2 H), 7.43 (d, $J=9.0$ Hz, 1 H), 7.35–7.22 (m, 2H), 7.20 (d, $J=8.3$ Hz, 2H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$) $\delta=146.3$, 138.2, 134.1, 133.8, 130.0, 127.8, 126.1, 125.1, 124.2, 116.2, 91.0, 89.1, 21.9. IR (thin film): $v=3115$–3050, 1594, 1370, 1175. HRMS (70 ev) for $C_{15}H_{11}O_2SNBrI$ (M^+) calcd: 474.8733, found: 474.8739.
10. Work is in progress to improve this unacceptably low yield using Lewis acids both alone and in concert with high pressures ($\sim$13 kbar).