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# Metalation–cyclisation sequence on *N*-(*o*-halobenzyl)pyrroles. Synthesis of pyrrolo[1,2-*b*]isoquinolones

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**Abstract**

Parham-type cyclisation of *N*-(*o*-halobenzyl)pyrroles has been investigated. Aryllithiums generated from metalation of *N*-(*o*-iodobenzyl)pyrroles undergo intramolecular cyclisation to give pyrrolo[1,2-*b*]isoquinolinones in moderate to good yields, if the *N*,*N*-diethylcarbamoyl group is used as internal electrophile and the aromatic ring is activated. 

*Keywords:* lithiation; cyclisation; pyrroles; pyrroloisoquinolines.

The aromatic metalation–cyclisation sequence is a valuable protocol for the regiospecific construction of carbocyclic and heterocyclic systems.[1] The intramolecular cyclisations that employ aryllithiums generated by lithium–halogen exchange are known as Parham cyclisations and they have allowed the preparation of many carbocycles and heterocycles.[2] In fact, lithium–halogen exchange,[3] though mechanistically controversial, is a particularly useful tactic for the metalation of aromatic substrates, because metal–halogen exchange can effectively compete with the organolithium reaction with internal electrophiles.[4] However, to our knowledge, this kind of strategy has not been applied to the synthesis of pyrrolo[1,2-*b*]isoquinolones. The presence of this structural framework in some natural products such as the lycorine class of *Amaryllidaceae* alkaloids[5] and the phenanthroindolizidine alkaloids[6] were among the considerations that prompted the design of a strategy for its construction, as an extension of our earlier work[7] involving the synthesis of isoquinoline alkaloids from *N*-phenethylimides. In this context, we envisioned that a *N*-(*o*-halobenzyl)pyrrole would be metalated to form an intermediate aryllithium, which could then cyclise onto the carbonyl substituent of the pyrrole ring to give the isoquinolone nucleus of the desired tricyclic system. A related, though intermolecular, approach has been reported[8] that relied on the addition of *ortho*-lithiated benzamides to the carbonyl group of the *N*-benzylpyrrole-2-carbaldehyde. Other approaches to this skeleton imply a tandem cyclisation of amidyl

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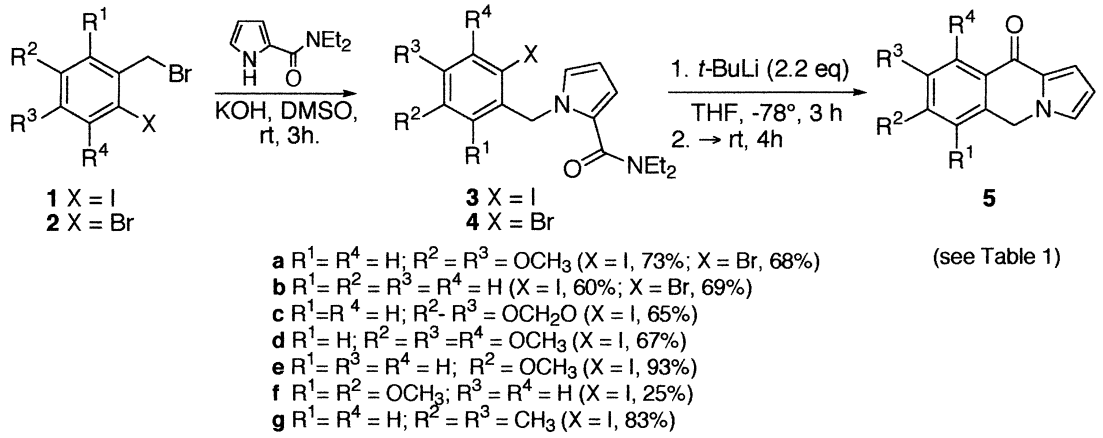
radicals derived from *O*-acyl hydroxamic acid derivatives,[9] or photocyclisation reactions of 1-benzyl-1-pyrrolinium salts.[10]

Herein, we describe our investigations on the Parham-type cyclisation of functionalised *N*-(*o*-halobenzyl)pyrroles.

To initiate our investigations we first evaluated the Parham cyclisation of iodinated *N*-benzylpyrroles with acetyl or methoxycarbonyl groups at the C-2 position of the pyrrole ring as internal electrophiles. However, the use of halogenated ketones in Parham-type cyclisations, while successfully exploited by Aidhen and by Kihara,[4b] or esters did not lead to the pyrroloisoquinolones. In our case, lithium–iodine exchange was not fast enough to compete with addition of the inducing organolithium and/or enolisation, precluding cyclisation.

In view of these results, we decided to test the *N,N*-diethylcarbamoyl group as an internal electrophile. The *N*-(*o*-iodobenzyl)pyrrole **3a** was prepared by alkylation of *N,N*-diethylpyrrole-2-carboxamide with benzyl bromide **1a** under standard conditions (Scheme 1). We next carried out the metalation–cyclisation sequence under several conditions (Scheme 1, Table 1). After some experimentation, we found that lithium–iodine exchange took place very efficiently when the reaction mixture was treated with *t*-BuLi (2.2 equiv.) at –78°C for 3 h, and allowed to reach rt, affording pyrroloisoquinolone **5a** in good yield (79%)[11] (entry 1).




Scheme 1.

To study the influence of the aromatic ring substitution, we prepared a series of *N*-(*o*-iodobenzyl)pyrroles **3b–g** from the corresponding benzyl bromides **1** (Scheme 1).[12] These iodinated pyrroles were submitted to Parham cyclisation under the previously tested conditions affording the desired pyrroloisoquinolones **5** in variable yields. For some of them (Table 1, entries 2–5), reaction conditions were optimised.[13] As shown in Table 1, moderate to good yields of pyrroloisoquinolines **5** were obtained when the aromatic ring is activated with donor groups (entries 1, 5, 7 and 8). An exception was trimethoxy substituted benzylpyrrole **3d**, which only afforded the corresponding deiodinated product in high yield (81%, entry 6). In this case, lithium–iodine exchange took place efficiently, but further cyclisation was precluded, presumably, by steric hindrance of the *ortho*-methoxy group. Significantly lower yields were obtained when no such activation of the ring was present (entries 3 and 9). We also tested the feasibility of using *N*-(*o*-bromobenzyl)pyrroles **4**

Table 1
Parham cyclisation of benzylpyrroles **3** and **4**

| Entry | Substrate | Product | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | **3a** | **5a** | H | $OCH_3$ | $OCH_3$ | H | 79 |
| 2 | **4a** | **5a** | H | $OCH_3$ | $OCH_3$ | H | 21[a] |
| 3 | **3b** | **5b** | H | H | H | H | 28[b] |
| 4 | **4b** | **5b** | H | H | H | H | 29[a] |
| 5 | **3c** | **5c** | H | O-$CH_2$-O | | H | 34[c] |
| 6 | **3d** | - | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | -[d] |
| 7 | **3e** | **5e** | H | $OCH_3$ | H | H | 53 |
| 8 | **3f** | **5f** | $OCH_3$ | $OCH_3$ | H | H | 40 |
| 9 | **3g** | **5g** | H | $CH_3$ | $CH_3$ | H | 10[e] |

[a] Conditions: -78 °C, 3h; → rt, 16h. [b] Conditions: -78 °C, 6h; → rt, 4h. [c] Conditions: -78 °C, 8h; → rt, 16h. [d] No cyclisation product was obtained. 81% of deiodinated benzylpyrrole was isolated. [e] Reaction was carried out with *n*-BuLi.

as substrates. Bromine–lithium exchange took place less efficiently than lithium–iodine exchange, affording lower yields of pyrroloisoquinoline **5a** (entry 2 versus 1), though this effect is not apparent with **5b** (entry 4).

Although in related Parham-type cyclisations no influence of aromatic substitution pattern has been observed,[4d] the different behaviour of iodinated *N*-(*o*-iodobenzyl)pyrroles could be understood in the light of the reaction mechanism. Although few different mechanisms have been suggested for the lithium–halogen exchange reaction,[3] the intermediacy of an ate complex or a $S_N2$ mechanism are nowadays the most generally accepted proposal for those cases that involve aryl halides and alkyllithiums.[14] In our case, iodine–lithium exchange seems to show a leaving group effect, which could be rationalised by both mechanistic possibilities.

In summary, it has been shown that *N*-(*o*-iodobenzyl)pyrrole-2-carboxamides tolerate lithium–halogen exchange reaction conditions, allowing the efficient construction of the isoquinoline nucleus. Though the metalation–cyclisation sequence is limited to aromatic rings activated with donor groups (methoxy, methylenedioxy), two features make it synthetically useful. First, the fact that it allows access to pyrrolo[1,2-*b*]isoquinolinones with the aromatic substitution pattern present in natural lycorine-type alkaloids. Second, this anionic equivalent of a Friedel–Crafts reaction could compete with previously reported strategies.[8–10]

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11. All new compounds gave satisfactory spectroscopic and analytical data. Typical procedure for **5a**: To a solution of the iodinated benzylpyrrole **3a** (169 mg, 0.4 mmol) in dry THF (20 mL), *t*-BuLi (0.9 mL of a 0.92 M solution in pentane, 0.83 mmol) was added at –78°C. The resulting mixture was stirred at this temperature for 3 h, allowed to warm to 20°C, and further stirred for 4 h. The reaction was quenched by the addition of $H_2O$ (5 mL). After standard work-up, flash column chromatography (silica gel, 70% hexane:AcOEt) afforded 7,8-dimethoxypyrrolo-[1,2-*b*]tetrahydroisoquinolin-10-one (**5a**) as a yellowish solid (74 mg, 79%): mp ($Et_2O$) 139–140°C (dec.); IR (neat) 1650 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 3.90 (s, 3H), 3.92 (s, 3H), 5.17 (s, 2H), 6.35 (dd, $J=4.0$, 2.4 Hz, 1H), 6.64 (s, 1H), 6.94–6.98 (m, 1H), 7.08 (dd, $J=4.0$, 1.5 Hz, 1H), 7.63 (s, 1H); $^{13}C$ NMR ($CDCl_3$) 46.4, 56.0, 56.0, 107.1, 107.9, 111.1, 112.7, 123.7, 125.2, 129.2, 129.7, 148.7, 152.8, 174.1; MS (EI) *m*/*z* (rel. intensity) 243 ($M^+$, 100), 242 (22), 228 (21), 212 (28), 200 (13), 199 (13). Anal. calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.24; H, 5.41; N, 5.84.
12. Bromides **1** and **2** were prepared from benzylic alcohols. All aromatic iodination reactions were completely regioselective, except case **f**, which afforded a 2:1 mixture of 6-iodo and 5-iodo alcohols, resulting in a low yield of the desired **3f**, after separation of isomers.
13. In all cases, variable amounts (7–13%) of the corresponding deiodinated benzylpyrroles were isolated together with pyrrolisoquinolones **5**.
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