

## A Novel Observation on the Lithiation of 2-Iodo-3-hydroxymethylquinoline

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In the metallation of 2-iodo-3-hydroxymethylquinoline (**3**) with Bu<sup>n</sup>Li (−78 °C), the halogen–metal exchange is shown to be faster than the hydrogen (of the OH group)–metal exchange.

2-Lithioquinolines are readily obtained by halogen–metal exchange reactions. The 2-lithioquinoline (**2**), for example, was obtained recently in this way from 2-iodo-3-(1,3-dioxolan-2-yl)quinoline (**1**).<sup>1</sup> The halogen–metal exchange reaction is carried out at low temperatures (−60 to −78 °C) to avoid or decrease the extent of the competing nucleophilic substitution reaction leading to 2-butylquinolines.

In connection with another study we required 2-substituted 3-hydroxymethylquinolines. It was planned to obtain these compounds from 2-iodo-3-hydroxymethylquinoline (**3**) by a halogen–metal exchange reaction with Bu<sup>n</sup>Li via the 2-lithio compounds. It was hoped that the latter, on treatment with appropriate electrophiles, would furnish the target compounds.

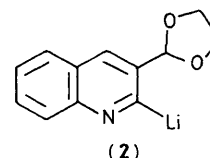
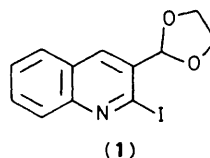
With the above purpose in mind, (**3**) was treated [−78 °C, tetrahydrofuran (THF)] with Bu<sup>n</sup>Li (diethyl ether). Two mole equivalents of Bu<sup>n</sup>Li were used, one for reaction with the OH group and the other for the exchange reaction. In order to detect the formation of the 2-lithio compound, the metallation mixture was first stirred with D<sub>2</sub>O (10 min) and then with H<sub>2</sub>O. Surprisingly, however, the expected 2-deuterioquinoline (**12**) was not obtained but only the simple quinoline (**6**) (yield 92%). In this reaction, presumably, the 2-lithioquinoline (**8**) had formed; otherwise, the replacement of iodine by hydrogen would not have occurred.

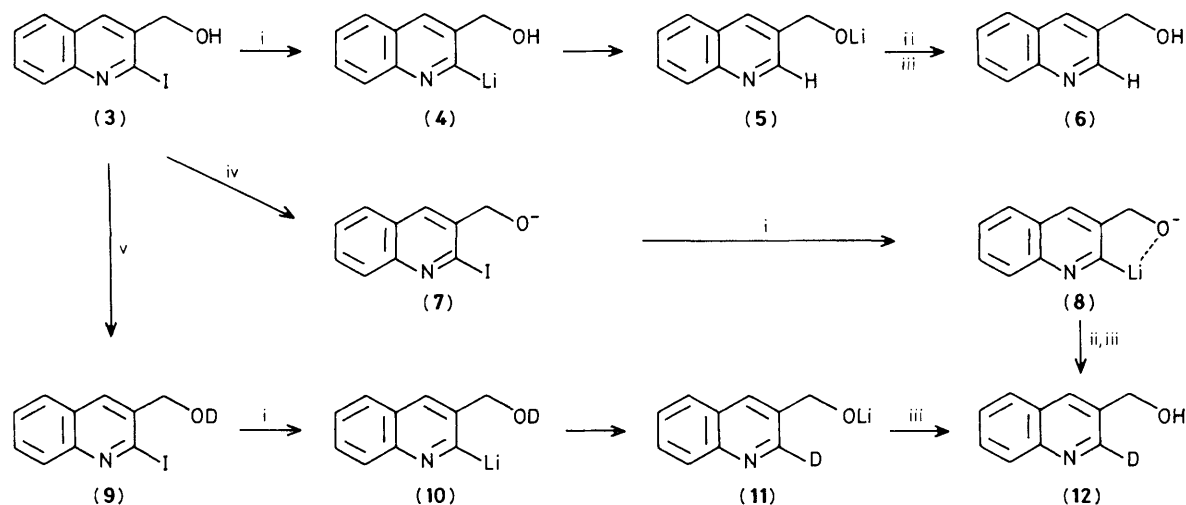
The failure to obtain (**12**) in the above reaction may be due to the reaction of (**8**) with the solvent. Aromatic lithio compounds are known to react with solvents such as THF.<sup>2</sup> Alternatively, it is possible that the first reaction of Bu<sup>n</sup>Li with the substrate is not with the OH group, as normally expected, but with the halogen in a halogen–metal interconversion reaction. Indeed, it is reported that cross-metallation reactions (ArX + BuLi → ArLi + BuBr) are at least as fast and probably faster than the reaction of Bu<sup>n</sup>Li with water or ClSiMe<sub>3</sub>.<sup>3</sup>

The results obtained can be rationalised by the following sequence: in the metallation reaction the 2-lithio compound (**4**) is formed first. This then undergoes an intramolecular hydrogen transfer reaction (from the OH group) to give (**5**). At −78 °C the latter does not react further with Bu<sup>n</sup>Li, which would then be present only in one mole excess. The last point was checked by an independent experiment. In this, when compound (**6**) was first converted into the alkoxide (**5**) by treatment with NaH (THF, −40 °C, 2 h), and then reacted with one mole of Bu<sup>n</sup>Li (−78 °C), workup with water gave only the starting compound (**6**) (recovery 93%).

The above sequence was further established by two experiments. In the first experiment, when compound (**3**) was first converted into the alkoxide (**7**) by treatment with NaH (THF, −40 °C, 2 h) and then reacted with Bu<sup>n</sup>Li, further reaction with D<sub>2</sub>O first and then with H<sub>2</sub>O gave the expected 2-deuterioquinoline (**12**) (83%, 85% D by <sup>1</sup>H n.m.r.). The reaction succeeds because there is no OH group for the intramolecular hydrogen transfer reaction. In the second experiment, when the alcohol (**3**) was first converted into the *O*-deuteriated compound (**9**) and then reacted with Bu<sup>n</sup>Li, further reaction even with H<sub>2</sub>O alone gave (**12**) (91%, 83% D by <sup>1</sup>H n.m.r.). In this case the 2-lithio intermediate (**10**) itself would give the 2-deuterio compound (**12**) by a deuterium transfer reaction (from the OD group).

The study clearly establishes that, in the reaction of 2-iodo-3-hydroxymethylquinoline (**3**) with Bu<sup>n</sup>Li, the halo-





Reagents: *i*, Bu<sup>n</sup>Li, THF, -78 °C; *ii*, D<sub>2</sub>O, 10 min; *iii*, H<sub>2</sub>O; *iv*, NaH, -40 °C, 2 h; *v*, D<sub>2</sub>O.

gen-metal exchange reaction is faster than hydrogen (of the OH group)-metal exchange.

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## References

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