Tetrahedron Letters, Vol. 33, No. 31, pp. 4433-4434, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Metallation of 2-Phenylindolizine

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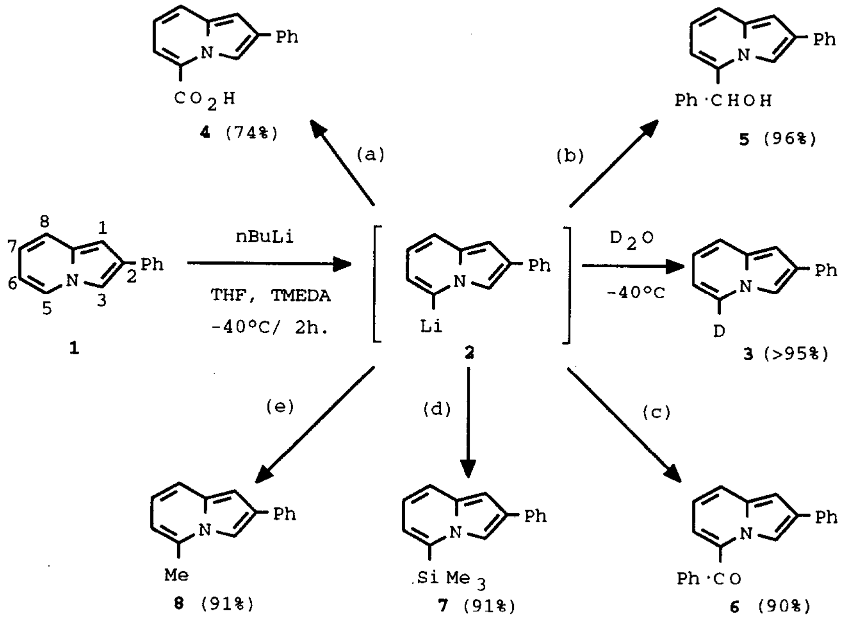
Abstract : Regioselective metallation of 2-phenylindolizine at C(5) and subsequent reaction with an electrophile has afforded the corresponding C(5) functionalised indolizine in high yields.

The electrophilic substitution of the indolizine nucleus has been widely investigated and it was well established that the most reactive positions on the ring are C(3) and C(1), in that order [1,2]. This report presents the first regioselective metallation [3] at position 5 of 2-phenylindolizine **1** [4] and the high reactivity of the resulting organometallic species **2**. It opens therefore a new and easy way to introduce a substituent in this position [5].



(a) CO_2, -78°C; : 74% of **4** (Mp : 236°C) ; (b) C_6H_5CHO, -78°C : 96% of **5** (instable product) ; (c) 1) C_6H_5CN, -40°C to r.t. 2) HCl : 90% of **6** (Mp : 286°C) ; (d) $(CH_3)_3SiCl$, -40°C to r.t : 91% of **7** (Mp : 65°C) ; (e) CH_3I, -40°C to r.t : 91% of **8** (Mp : 81°C).

Although the treatment of 2-phenylindolizine **1** with nBuLi in THF at -78°C, followed by quenching with D_2O, has led to a low deuterium incorporation (6%), the same reaction carried out at -40°C has furnished **3** with 71% regioselective deuterium insertion at C(5)[6]. The use of TMEDA (5 equiv.) as co-solvent, has led after treatment of **1** with nBuLi (1.1 equiv.) at -40°C for 2 h. and after quenching with D_2O, to a clean and quantitative recovery of **3** with > 95% deuterium incorporation at C(5)[6]. The exclusive metallation at C(5) on the ring is probably due to the proximity of the nitrogen atom and to the lower electron density of this position on the indolizine [7-9]. Moreover, quenching of the ortho-lithiated species **2**, by this method, with some electrophiles (CO_2, PhCHO, PhCN, Me_3SiCl, MeI) has given the corresponding new products in excellent yields (74-96%) [10].

References and Notes

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6. The deuterium insertion in **1** was determined by ^1H NMR (200 MHz, $CDCl_3$) on the H(5) signal: **δ 7.9 (dq, J= 1, 1.2 Hz, H(5))**, 7.6-7.7 (m, 2H), 7.57 (dd, J= 0.5, 1.2 Hz, H(3)), 7.2-7.45 (m, 5H), 7.25 (d, J= 8.9 Hz, H(8)), 6.7 (dd, J= 1, 1.2 Hz, H(1)), 6.65 (ddd, J= 1, 6.4, 8.9 Hz, H(7)), 6.4-6.5 (td, J= 1, 6.4 Hz, H(6)).
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10. A typical experimental procedure is as follows: A solution of 2-phenylindolizine **1** (0.959 g, 5 mmol) and TMEDA (3.75 ml, 25 mmol) in 50 ml of dry THF was stirred at -40°C ($CO_{2sol.}$ + CH_3CN) under argon. Normal butyl-lithium (3.41 ml of 1.6 N in hexane, 5.5 mmol) was then added via a syringe. This solution was stirred for two hours at -40°C and iodomethane (0.34 ml, 5.5 mmol) was then added via a syringe. The reaction mixture was allowed slowly to warm to room temperature for 12 hours. The reaction mixture was poured into a rapidly stirred mixture of 500 ml of dichloroethane and 100 ml of saturated aqueous ammonium chloride. The mixture was placed in a separatory funnel and the phases were allowed to separate; further work up gave a mixture of 91% of 5-methyl-2-phenyl indolizine **8** and 9% of residual 2-phenylindolizine **1** (determined by HPLC and ^1H NMR). Purification by silica gel chromatography (80% heptane, 20% triethylamine, Rf **8** = 0.53) gave 91% of pure 5-methyl-2-phenylindolizine (Mp = 81°C).

(Received in France 20 December 1991)