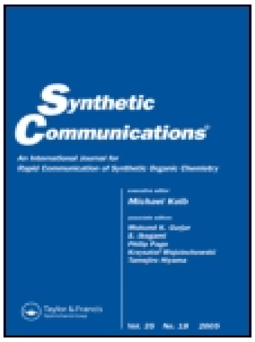

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USE OF METHYLLITHIUM IN METAL/HALOGEN EXCHANGE; A MILD AND EFFICIENT METHOD FOR THE SYNTHESIS OF *ORTHO* SUBSTITUTED TOLUENES

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ABSTRACT

Methyllithium, in the presence of excess methyl iodide, can be used to convert suitably substituted aromatic bromides to the corresponding toluenes under mild conditions and in high yield.

The metal/halogen exchange reaction between an alkyllithium and an aryl bromide or iodide has been used extensively since it was first reported by Gilman and Wittig over 50 years ago.[1,2] The reagent most commonly used for this interconversion is *n*-butyllithium, presumably because it is readily available and is also usually highly effective.[3] However, the formation of *n*-butyl bromide or iodide as a by-product when this reagent is used can give rise to impurities either through alkylation or proton quench

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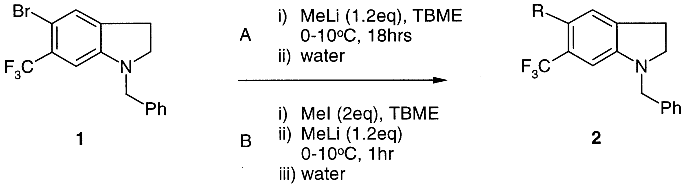
(*via* dehydrohalogenation) of the newly formed aryllithium.[4,5] In large scale reactions where addition times are often longer these side reactions can cause significant problems by lowering the yield or compromising the purity of the product. These undesirable side reactions can be avoided by, for example, using two equivalents of ***tert***-butyllithium as the exchange reagent.[6]

In the early reports of the metal/halogen exchange reaction methyllithium was described as the least effective of all the alkyllithiums investigated and it was therefore believed to have little synthetic utility in this reaction.[7,8] Consequently there are very few literature examples of the use of methyllithium for this interconversion.[9,10] Included in the small number that are known are examples where the methyl bromide by-product reacted with the newly formed aryllithium to produce the corresponding methyl compound.[11,12]

We have found that if methyllithium is reacted with aryl bromides bearing a suitable ortho substituent it is very effective in the metal/halogen exchange reaction (Scheme 1).[13] If the desired product is the corresponding methyl compound excellent yields can be obtained if additional methyl iodide is used. Furthermore, by having the methyl iodide present "*in-situ*" with the aryl bromide before the methyllithium is added, the impurity formed by proton quench of the aryllithium intermediate can be reduced to an almost negligible level. This methodology has been used for the synthesis of multi-kilo quantities of the methylindoline **2** (R = Me).



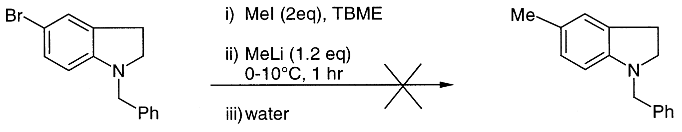
A; 95% yield of **2**, R = Me:H; 4:1

B; 98% yield of **2**, R = Me:H; 99:1

Scheme 1.

In contrast, it was found that 1-benzyl-5-bromoindoline **3** failed to undergo metal/halogen exchange under the same reaction conditions (Scheme 2).

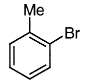
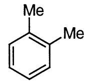
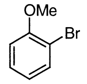
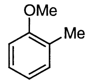
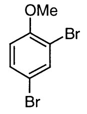
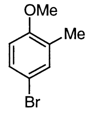
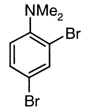
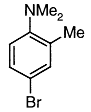
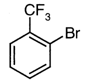
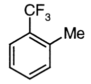
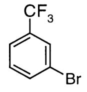
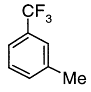
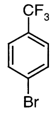
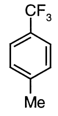
To gain a further understanding of these results we investigated this reaction with a series of aryl bromides. The results shown in Table 1 confirm that a suitable ortho substituent is required to enable metal/halogen exchange to occur when methyllithium is used. Presumably the same factors that facilitate the complementary technique of *ortho* directed lithiation (also first reported by Gilman and Wittig) are in operation here.[14,15] Thus



3 4

Scheme 2.

Table 1. The Reaction of Aryl Bromides with Methyllithium in the Presence of Methyl Iodide

Starting Material[16]	Product	Yield[17]
		0%
		93%
		94%
		92%
		100% by GC
		45% by GC
		20% by GC

heteroatoms that can co-ordinate with the attacking allkyllithium species are particularly effective.

The results shown with the trifluoromethyl substituent indicate that inductively electron withdrawing substituents will facilitate the metal halogen exchange and can also have an albeit diminished influence on the meta and even para positions.

In summary, we have developed a mild and efficient process for the preparation of toluenes bearing a suitable ortho substituent from the corresponding bromo compound.

TYPICAL EXPERIMENTAL PROCEDURE

Methyllithium (3 M solution in diethoxymethane, 1.2 eq)[18] was added dropwise to a stirred mixture of aryl bromide (1 g) and methyl iodide (2 eq) in ***tert***-butyl methyl ether (10 ml) at 5–10°C under nitrogen. The reaction mixture was stirred at ambient over 18 hours before aqueous quench. The aqueous mixture was extracted into TBME (10 ml), the organics were dried over sodium sulphate and the volatiles were removed under vacuum to leave product.[19]

1-Benzyl-5-methyl-6-trifluoromethylindoline 2

To a solution of 1-benzyl-5-bromo-6-trifluoromethylindoline **1** (10 g, 28 mmol) and methyl iodide (7.95 g, 56 mmol) in TMBE (100 ml) stirred at 0–10°C under N_2 was added dropwise methyllithium (3 M solution in diethoxymethane, 11.2 ml, 33.6 mmol). The reaction mixture was stirred at 0–10°C for 1 hour before addition of water (50 ml). The aqueous phase was discarded and the TBME solution of crude product washed with water (50 ml) before drying over sodium sulphate. Solvent was removed under vacuum to leave an oil that crystallised on standing to give **2**, (7.9 g, 97% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.30 (m,5H); 6.99 (s,1H); 6.70 (s,1H) 4.24 (s,2H); 3.32 (m,2H); 2.95 (m,2H); 2.35 (m,3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ :151.2; 138.6; 134.5; 129.3; 128.8; 128.3; 128.2; 127; 126.5; 124.1; 103.0; 53.7; 31.2; 28.3; 21.9; MS (APCI) m/z: 292 ($[M+H]^+$); 200 ($[C_{10}H_9F_3N]^+$).

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16. All starting materials were commercially available with the exception of the N,N-dimethyl compound, prepared according to the method of Giumanini *et al.* from the corresponding dibromoaniline.[20]
17. Refers to isolated yields in which the balance is made up of starting material, unless otherwise stated.
18. A *non-pyrophoric* solution supplied by Chemetall GMBH, Langelsheim, Germany.
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