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Preparation and Reactions of Stable 2-Lithio-6-nitrophenol derivatives

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Abstract: *2-Bromo-6-nitrophenyl MOM and SEM ethers form stable lithio compounds on treatment with phenyllithium. Reaction of the lithio species with a variety of electrophiles allows the preparation of 2-substituted-6-nitrophenols. The intramolecular trapping of (2',3'-epoxypropyloxy)-2-lithio-4-methyl-6-nitrobenzene gives the substituted benzofuran (5).*

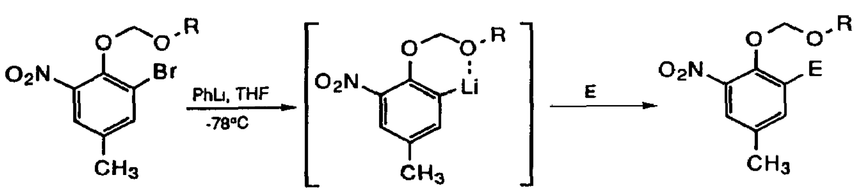
Nitroarenes usually react with organolithium reagents *via* reduction of the nitro group or addition of the base to the aromatic ring[1]. However, in the case where lithium is *ortho* to the nitro group synthetically useful lithio species have been generated at low temperatures[2]. The comparative stability of these species has been attributed to a chelation effect between the lithium and the nitro group aided by an inductive effect[2a]. We believed that if a suitable chelating group could be placed adjacent to the lithium then other stable nitroaryl lithium species could be formed. In this *Letter* we report the generation of stable 3-lithio nitro aromatic species and their reactions.

The use of the OMOM group[3] and more recently the OSEM[4] group to direct *ortho* metallation of aromatic compounds is well established[5a]. We considered that such groups would allow the formation of a stable lithium chelate[5b]. Thus the MOM protected bromonitrophenol (**1a**)[6] and the SEM ether (**1b**)[7] were prepared. Treatment of the MOM ether (**1a**) with phenyllithium (1.1 eq., THF, -78°C) produced the stable orange lithio species (**2a**). The lithio species was trapped with electrophiles to give adducts in good yield (**Table 1**). The reactions of the lithio species with benzaldehyde and benzophenone resulted in the formation of complex mixtures. Similarly, treatment of the SEM ether (**1b**) with phenyl lithium (1.1 eq., THF, -78°C) produced the orange lithio species (**2b**) which was quenched with water to give the proteo compound in 70% yield.

The trapping of such lithio species in an intramolecular sense was demonstrated by treatment of the epoxide (3)[8] with phenyl lithium (THF, -78°C, 2 hrs.) resulting in an exclusively 5-exo-trig "Parham" type cyclisation giving the benzofuran (5) along with the proteo compound (**6**), isolated in 30% and 27% yields respectively. The isolation of the proteo compound (6) demonstrates the stability of the intermediate lithio species (4), **Scheme 1**.

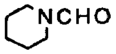
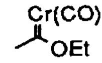
In summary, we have shown that halogen-metal exchange of the MOM and SEM ethers of 2-bromo-4-methyl-6-nitrophenol afford stable aryllithium species which may be trapped with a wide variety of electrophiles, generating a range of organometallic and organic intermediates. These results suggest that lithio-functionalised nitroaromatics may be generally more accessible and synthetically more useful than first anticipated, and could provide new approaches to the synthesis of nitrogen-substituted arenes[9,10].

Table 1: Reactions of Stable 2-Lithio-6-Nitrophenol Derivatives



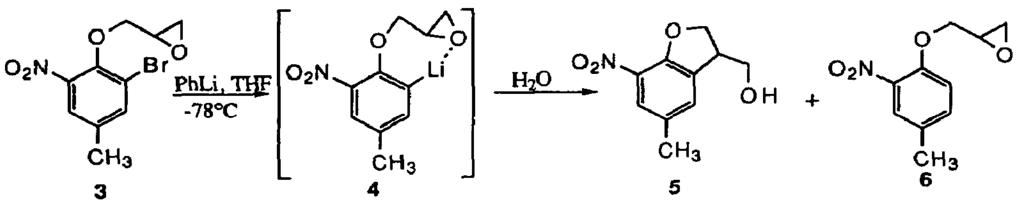
1a R=CH
b R=$CH_2CH_2Si(CH_3)_3$

2a R=CH
b R=$CH_2CH_2Si(CH_3)_3$

R	Electrophile	E	Yield (%)[a]
CH_3	H^+	H	77
		CHO	84
	Bu_3SnCl	$SnBu_3$	54
	i) $Cr(CO)_6$ ii) Et_3OBF_4		87
$CH_2CH_2Si(CH_3)_3$	H^+	H	70

a: Isolated yields

Scheme 1



References and Notes

1. a) Köbrich, G., Buck, P. *Chem. Ber.*, 1970, **103**, 1412; b) Buck, P., Köbrich, G., *ibid*, 1420-1430.
2. a) Voss, G., Gerlach, H., *Chem. Ber.*, 1989, **122**, 1201; b) Fukuhara, K., Miyita, N., Kamiya, S., *Tetrahedron Letters*, 1990, **31**, 3743.
3. Townsend, C. A., Bloom, L. M., *Tetrahedron Letters*, 1981, **22**, 3923.
4. Snieckus, V., Sengupta, S., *Tetrhedron Letters* , 1990, **31**, 4627.
5. a) For a detailed review see V. Snieckus, *Chem. Rev.*, 1990, **90**, 879; b) utilisation of methyl or benzyl ethers afforded highly unstable lithio species upon halogen-metal exchange (PhLi, THF, -78°C).
6. Prepared from 2-bromo-4-methyl-6-nitrophenol: i) NaH, THF; ii) MOMCl (90%)
7. Prepared from 2-bromo-4-methyl-6-nitrophenol: ii) NaH, THF; ii) SEMCl (53%)
8. Prepared from 2-bromo-4-methyl-6-nitrophenol: i) K_2CO_3, C_3H_5Br, acetone (53%); ii) mCPBA, $CHCl_3$ (42%).
9. All new compounds show analytical and spectral data (^1H nmr, ir, ms) consistent with the indicated structures.
10. IRH thanks The Victoria University of Manchester for provision of a Samuel Gratrix Postgraduate Studentship; ELMW thanks the SERC and ICI Paints Division for the provision of a CASE award.

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