Organo-lithiation and halogen metal exchange reactions in organic synthesis–an anomolous aromatic substitution via halogen-metal exchange

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Abstract. Synthesis via organo-lithium compounds is reviewed. An anomalous aromatic substitution via halogen-metal exchange is described. Here, the substitution does not occur at the position where the halogen was present; but at an alternate position. A mechanism is advanced, in which the halogen-metal exchange is proposed as being faster than the hydrogen(acidic)-metal exchange.

Keywords. Organolithiation; metal-halogen exchange; anomalous substitution and mechanism.

Heteroatom-directed aromatic lithiation (hydrogen-metal exchange) reaction has emerged as a valuable method for regiospecific introduction of substituents in an aromatic ring (Narasimhan and Mali 1987; Gschwend and Rodriguez 1979). Here, the metallation directing heteroatom, which carries an unshared electron pair, may be part of a group, which is an electron donor (i.e. OCH_3) or an electron acceptor (i.e. $CONHCH_3$) in the usual acid catalysed aromatic substitution reactions; but lithiation always occurs at the ortho position provided the heteroatom is directly attached to the aromatic ring or is only one or two atoms away.
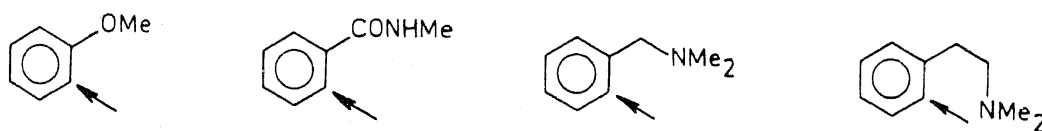
The mechanism of the heteroatom-directed aromatic lithiation is as yet unclear. The consensus, however, is in favour of the Roberts-Curtin mechanism (Roberts and Curtin 1946) where, in the first instance, the alkyllithium reagent complexes with the heteroatom present in the lithiation-directing group and then the *complexed reagent* abstracts an ortho proton.
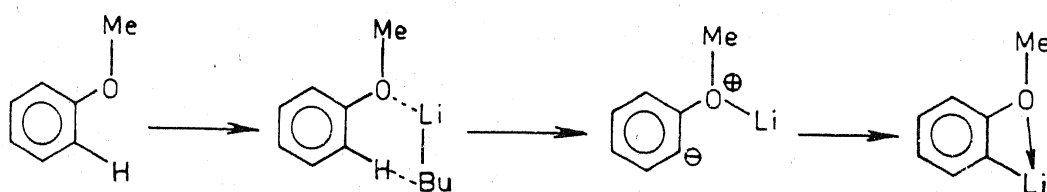
The mechanism is in agreement with several trends in the aromatic lithiation reactions. Thus

(i) when two or more complexing groups are present in an aromatic ring, the group which complexes better with the alkyllithium reagent directs lithiation,

(ii) when two non-equivalent ortho protons are present, with respect to the lithiation directing group, the proton which is more acidic is abstracted, and

(iii) lithiation can also occur at a more distant position, provided the position is accessible to the complexed lithiating agent and the proton at that position is more acidic than the ortho proton.


There are, however, some anomalous observations. Thus, when N, N-dimethyl-*p*-anisidine is lithiated with *n*-BuLi, it was expected that the alkyllithium reagent would complex better with the NMe_2 group and lithiation would occur ortho to this group. Actually, lithiation occurs ortho to the OCH_3 group (Gschwend and Rodriguez 1979).

The reaction, however, can be accommodated in the Roberts-Curtin mechanism. Here, it is necessary to distinguish between the two steps in the mechanism— (i) formation of the complex and (ii) formation of the transition state for the proton abstraction. Both these are equilibrium processes.

In the lithiation of N,N-dimethyl-*p*-anisidine, complexation of the alkyllithium reagent with the amino group will be more favoured. However, as regards the formation of the transition state for the proton abstraction, the one corresponding to abstraction of proton ortho to the amino group, i.e. 1, in which considerable crowding exists between this proton and the two methyl groups on the nitrogen, is less favoured than the alternative transition state, i.e. 2, in which the steric crowding is only between the proton ortho to the methoxyl group and the lone

methyl group on the oxygen. It is possible then that, although complexation would occur better with the amino group, lithiation itself would occur only according to the less strained transition state, i.e. 2. The final step in the lithiation reaction, i.e. proton abstraction, being irreversible, lithiation would occur ortho to the methoxyl group. These points are summarised in scheme 1.
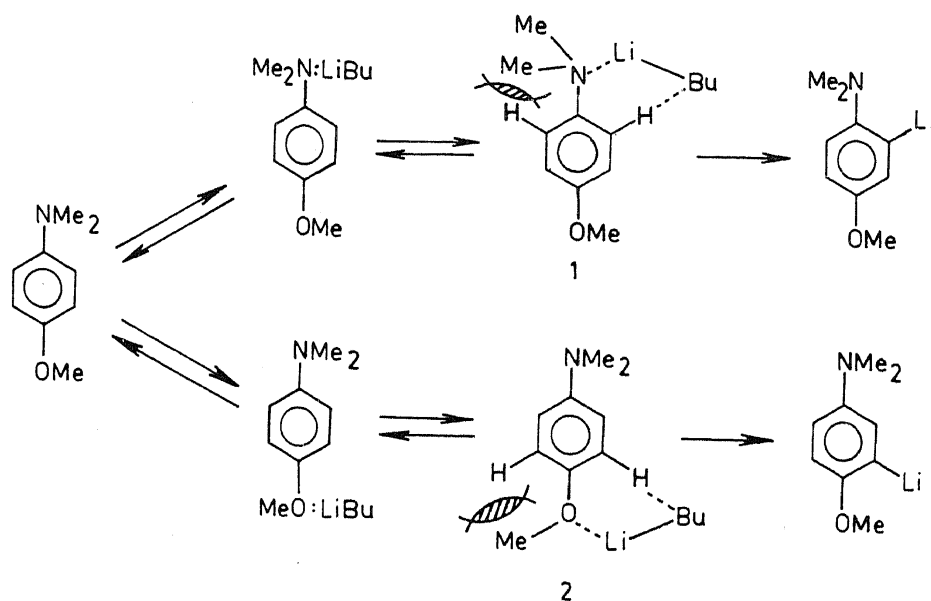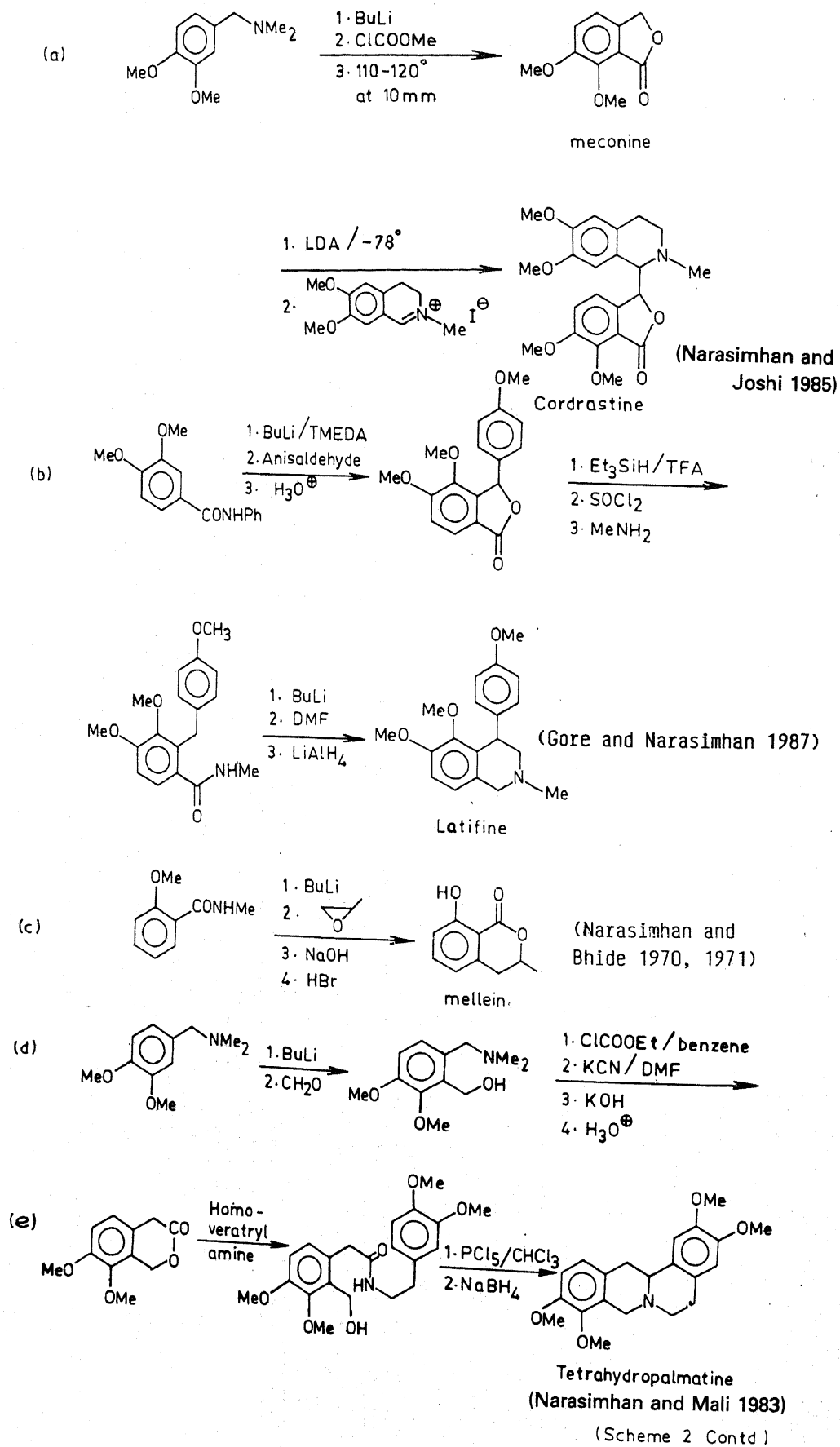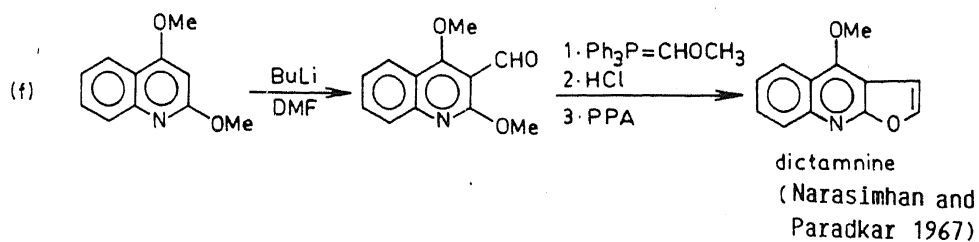

Scheme 1

The observed regioselectivity in aromatic lithiation reactions is valuable in organic synthesis. Indeed, this has been used by us in the development of new syntheses of several heterocyclic ring systems, and further applied to the syntheses, in simple steps, of several natural products, which have not been synthesised or synthesised only through lengthy routes by other methods. Some of our typical syntheses, involving aromatic lithiation reactions, are illustrated in scheme 2.

Lithiation reactions are also amenable to modifications leading to improvement in reactivity and hence yield. Thus, use of TMEDA, as an adjunct, in the reaction, improves the reactivity of the alkyl-lithium reagent. On the other hand, use of $Cr(CO)_6$ to complex with the aromatic substrate, increases the acidity of the aromatic protons and hence favours the proton abstraction process (Semmelhack *et al* 1979). The latter is illustrated by the example shown in scheme 3.

Another modification which is possible with the organolithium compounds, obtained by the lithiation reaction, is their conversion to other organometallic compounds which can exhibit greater reactivity and/or greater functional group selectivity and even chiral selectivity. Illustrative examples of these are shown in scheme 4.

It may be mentioned here that direct ortho-metallation, with other metal reagents, such as of Mg, Pd, Rh, Tl are also known. These are also valuable in organic synthesis. Some examples are given in scheme 5.

(a)

1·BuLi
2·ClCOOMe
3·110–120° at 10mm

meconine

1. LDA / –78°

2.

Cordrastine

(Narasimhan and Joshi 1985)

(b)

1·BuLi/TMEDA
2·Anisaldehyde
3· H₃O⊕

1·Et₃SiH/TFA
2·SOCl₂
3·MeNH₂

1· BuLi
2· DMF
3· LiAlH₄

(Gore and Narasimhan 1987)

Latifine

(c)

1· BuLi
2·
3· NaOH
4· HBr

mellein

(Narasimhan and Bhide 1970, 1971)

(d)

1·BuLi
2·CH₂O

1·ClCOOEt/benzene
2·KCN/DMF
3·KOH
4·H₃O⊕

(e)

Homo-veratryl amine

1·PCl₅/CHCl₃
2·NaBH₄

Tetrahydropalmatine
(Narasimhan and Mali 1983)

(Scheme 2 Contd)

(f)

1·Ph₃P=CHOCH₃
2·HCl
3·PPA

dictamnine
(Narasimhan and
Paradkar 1967)

(Narasimhan and Mali 1973)

Scheme 2

1. BuLi
2. CH₃CO(CH₂)₃ CN
3. CH₃I

1. LiNR₂
2. I₂

(Semmelhack *et al* 1979)
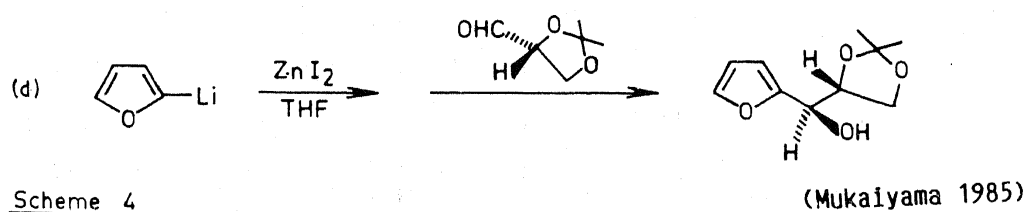
Scheme 3

(a)

1·s‑BuLi
2·MgBr₂
3. ⟍⟍Br

LDA

(Sibi *et al* 1986)

(b)

1·RLi
2. B(OMe)₃
3. H₃O⊕

1·ArBr
2·Pd(PPh₃)₄

(Sharp and Snieckus 1985)

(c)

1·BuLi
2·CuBr
3. ⟍⟍Br

(Ellefson 1979)

(d)

ZnI₂
THF

(Mukaiyama 1985)

Scheme 4

(a)

(Larock *et al* 1984)

(b)

(Tremont and Rahman 1984)

Z = Ph, CN, CHO, COOMe

(Hiroshi and Naoto 1979)

(c)

(Diamond *et al* 1979)
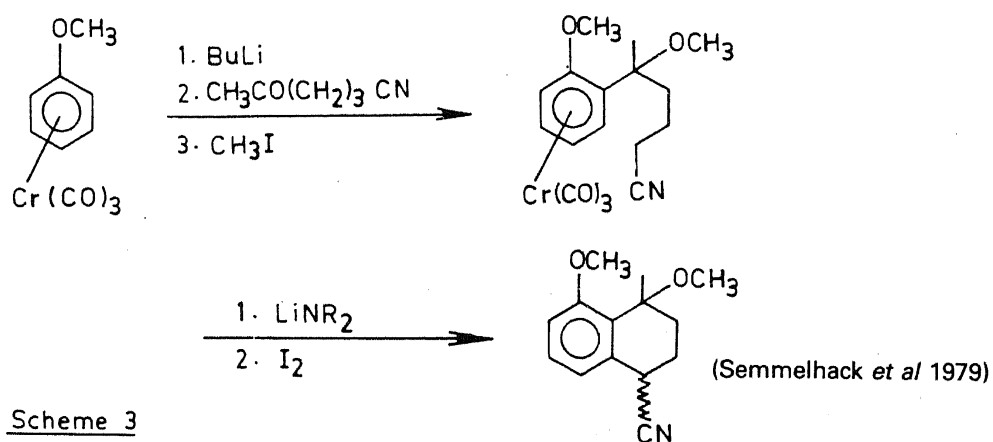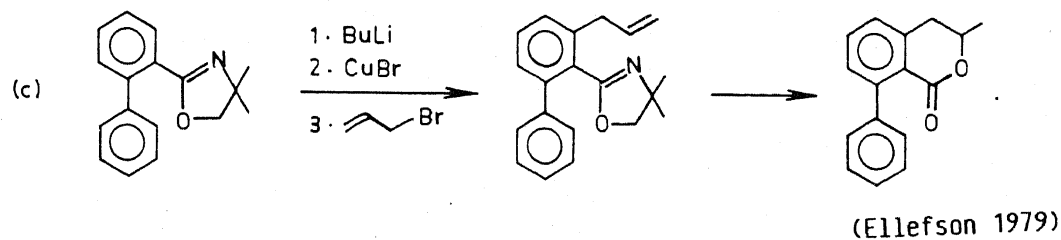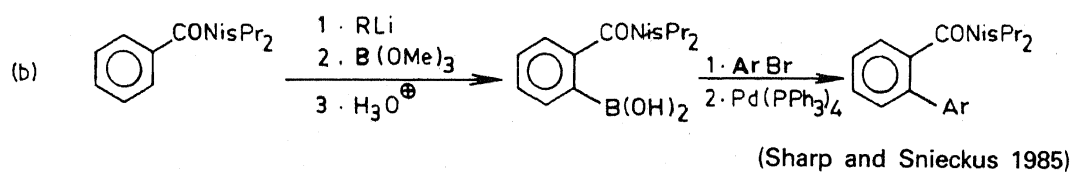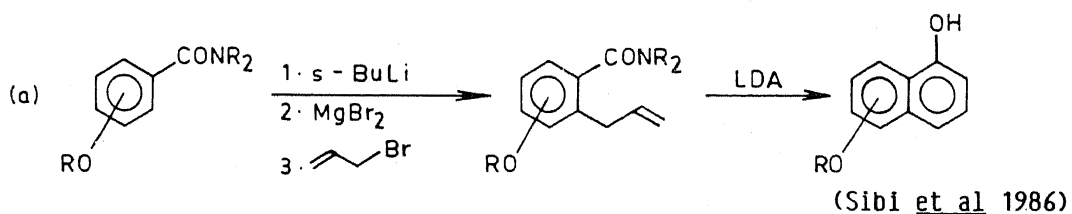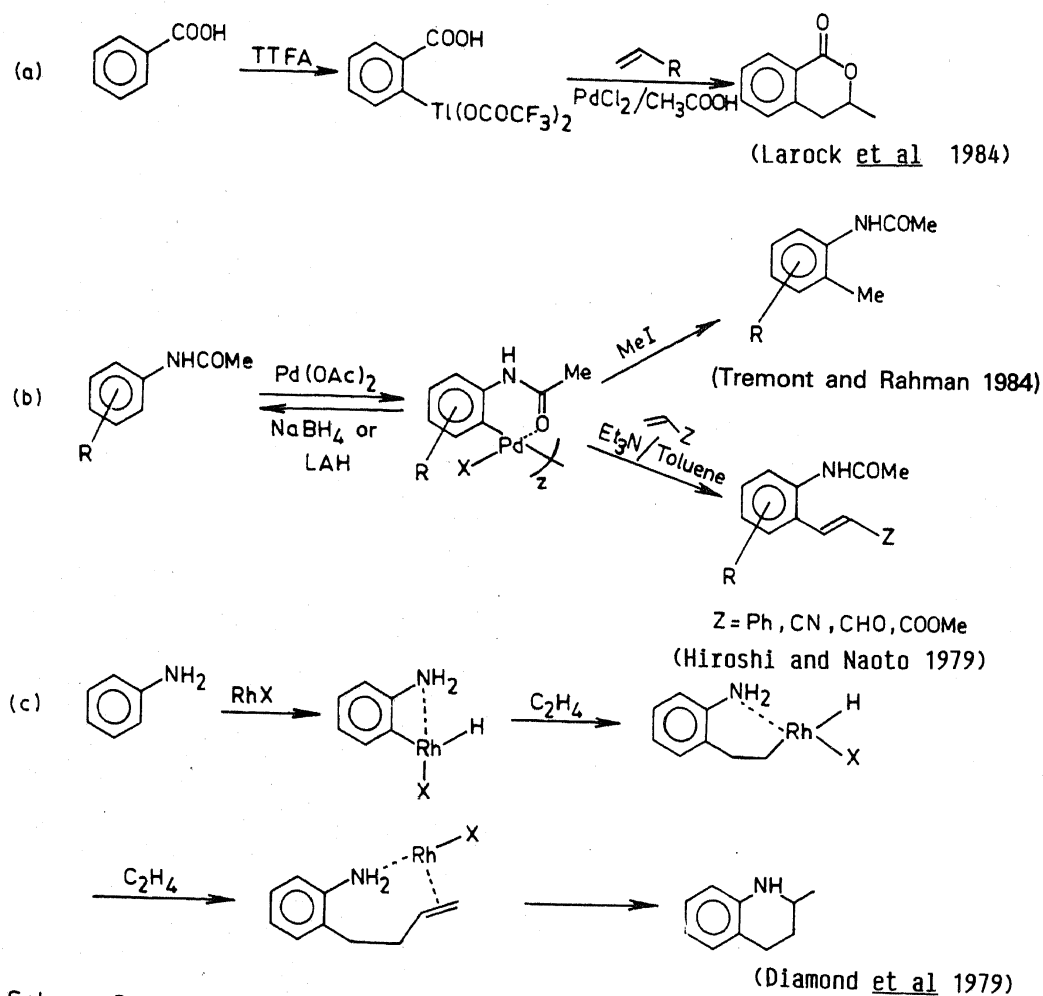
<u>Scheme-5</u>

Halogen-metal exchange reactions

An alternative synthesis of the key aryllithium compounds is by halogen-metal exchange. In this reaction, an arylhalide (usually a bromide) is treated with an alkyllithium reagent, when the exchange reaction occurs. The reaction is valuable for obtaining aryllithium compounds, which are not available by direct lithiation reaction, i.e. by hydrogen-metal exhange. The availability of the arylhalide, however, is a limitation on the usefulness of this method.

Since, in the halogen-metal exchange reaction, lithium is introduced in the aromatic ring at the position where the halogen was present, the method is used to obtain the aryllithium compounds regiospecifically. However, we have observed a case, where lithium is *not* introduced at the position where the halogen was present; but at an alternate position. Thus, when N-phenyl-2-bromo-4, 5-methylenedioxy benzamide 3 was reacted with an *excess* of *n*-BuLi and then with veratraldehyde, further aqueous work-up gave not 4, as anticipated, but only 5. Similarly N-phenyl-2-bromo-4,5-dimethoxy benzamide 3a gave only 5a. The compounds 5 and 5a were identical with those obtained by direct lithiation of N-phenylpiperona-mide and N-phenylveratramide, followed by reaction with veratraldehyde (see experimental).

3   RR = CH$_2$
3a R = CH$_3$

4   RR = CH$_2$
4a R = CH$_3$

5   RR = CH$_2$
5a R = CH$_3$

Compound 5 has no bromine, but only hydrogen in its place. This is possible only if compound 3 had undergone halogen-lithium exchange reaction and the aryllithium compound had *not* reacted with veratraldehyde, but only with a relatively acidic hydrogen *either* during the reaction or during work-up.

Compound 5 has a veratryl group incorporated at the *ortho* position to the methylenedioxy group. This is possible only if a hydrogen-lithium exchange reaction (i.e. aromatic lithiation reaction) had occurred at that position and the aryllithium compound had reacted with veratraldehyde.

A possible intermediate, to account for the above observations, could be the trilithio derivative, 6, which can then react as shown in scheme 6.

Scheme-6

The formation of 6 was unlikely under the experimental conditions used. Further, even if it had formed, it would react with veratraldehyde, first at C–2, rather than at C–6, since the carbanion at the latter position is more stabilised by

the inductive effect of the oxygen at C–5. The amide, i.e. –CONLiPh, of course, would be also less reactive. Since the lithioderivative at C–2 should have been necessarily formed (to account for the absence of bromine) and since no veratryl group has been introduced at C–2, the conclusion is inescapable that the lithioderivative at C–2, which formed had reacted with an acidic hydrogen *during* the reaction, even before veratraldehyde was added to the metallation mixture.

A possible mechanism for the reaction is shown in scheme 7. Here, it is proposed that the halogen-lithium exchange reaction occurs first, before the hydrogen (at N)-lithium exchange, to give 7. This is followed by a hydrogen (at N)-lithium (at the aryl-position) exchange, which may be intermolecular or more likely
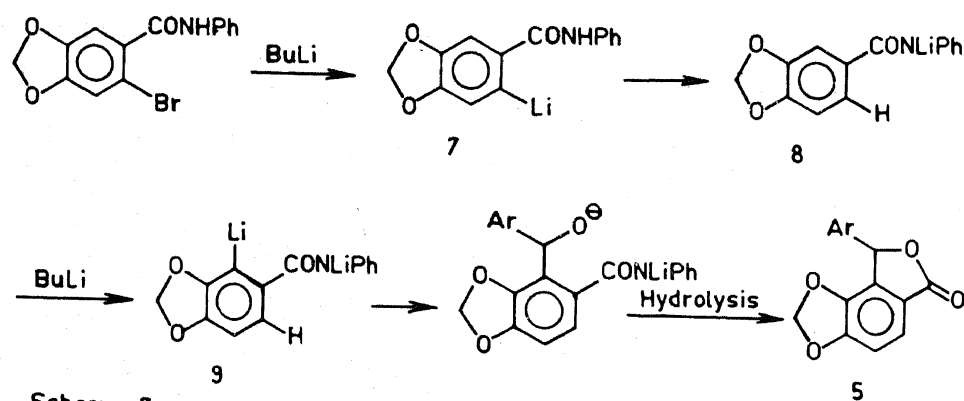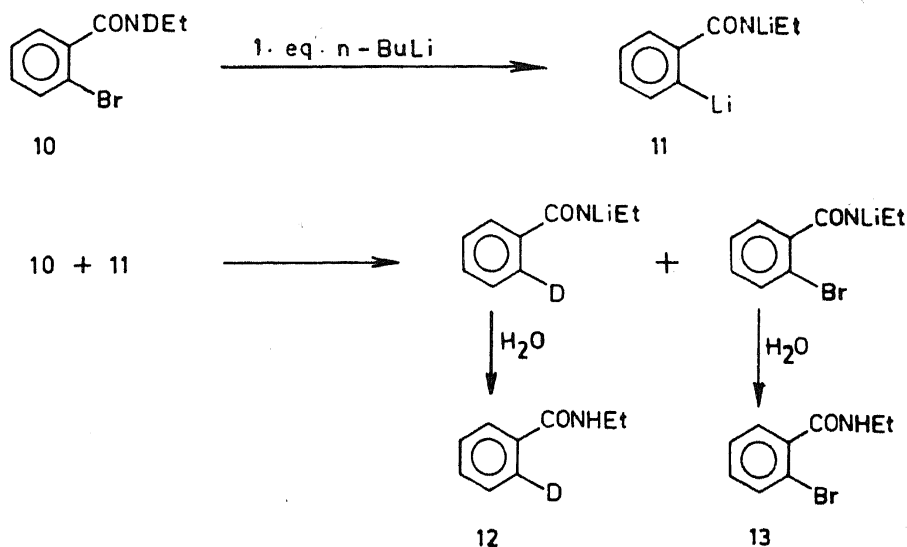

Scheme-7

intra-molecular, to give 8. Compound 8, then undergoes a heteroatom-directed aromatic lithiation, which, on the basis of the orientation rules governing such reactions, can be only at C–6 to give 9. The aryllithium compound then reacts with veratraldehyde and on further hydrolysis gives 5.

The important proposal here is that the halogen-lithium exchange is faster than the hydrogen(acidic)-lithium exchange.
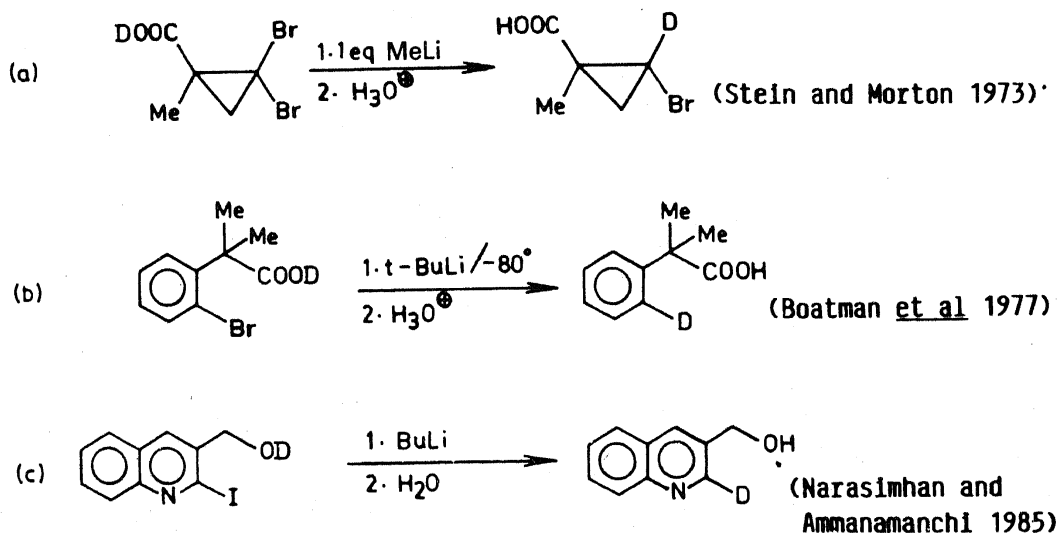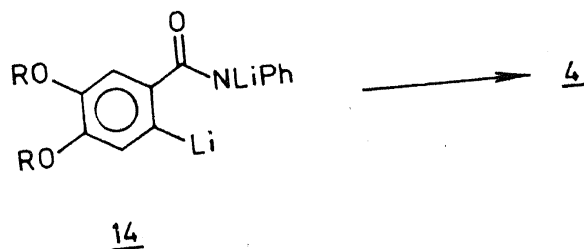
Recently, Beak and Chen (1985) have reported a similar lithiation reaction, in which they have specifically stated that the results obtained by them "does not require that halogen-metal exchange to be faster than deuterium (hydrogen)-metal exhange". Thus it was observed by them that when the N-deuteroorthobromoamide 10 was lithiated with 1 equivalent of *n*-BuLi, after aqueous work-up, a mixture of the ortho deuteroamide 12 and the ortho bromoamide 13 was obtained in 1:1 ratio. It was proposed that here dedeuteration at nitrogen occurred first which was then followed by formation of the dilithio derivative 11. The latter then obtained a deuterium from the starting compound 10. Their mechanism is shown in the scheme 8.

On the basis of the Beak and Chen mechanism, use of excess alkyllithim reagent in their reaction, would have furnished only the dilithio derivative 11. In our reaction it would have been the species 14. The latter would react with veratraldehyed and after aqueous work-up give only 4 and not 5. The Beak and Chen mechanism, obviously does not explain our observations.

There are indeed several reports in literature, where it is proposed that halogen-metal exchange is faster than hydrogen(acidic)-metal exchange. These are shown in scheme 9.

Scheme – 8

14

(a)   (Stein and Morton 1973)·

(b)   (Boatman et al 1977)

(c)   (Narasimhan and Ammanamanchi 1985)

Scheme – 9

The observation that the halogen-metal exchange is faster than the hydrogen (acidic)-metal exchange, is an interesting one. It is difficult to reconcile this with the role of *n*-BuLi as a base. We believe that the above result is due to the possibility of the lithiating agent, i.e. *n*-BuLi, having a dual character– one as a base

towards acidic hydrogen and the other as a single electron transfer agent towards the C–Br bond (Negishi 1980).

Experiments are underway to understand these aspects. In the meantime, our experiments do disclose the important fact that aromatic substitution via halogen-metal exchange is *not* always regioselective and caution needs to be exercised in formulating synthesis using the methodology.

Experimental

The melting points are uncorrected; the NMR chemical shifts are in the δ scale. *n*-BuLi in hexane was prepared according to standard procedures.

Halogen-metal exchange reaction of N-phenyl-2-bromo-4,5-methylenedioxybenzamide 3: To a cooled [−78°C] solution of 3 [300 mg, 1 mmol] in dry tetrahydrofuran [THF, 20 ml], a solution of *n*-BuLi in hexane [5 ml of 0·8 M 4 mmol] was added in two minutes by a syringe. The solution was slowly brought to 0°C [about 30 min]. The red coloured mixture was stirred for 15 min. Veratraldehyde [500 mg, 3·5 mmol] in THF [5 ml] was then added to the above mixture at 0°C in 5 min. The red colour changed to pale yellow. After 30 min, the reaction mixture was decomposed with HCl/water [1:1, 20 ml]. THF was removed under reduced pressure and the aqueous layer extracted with dichloromethane [3 × 20 ml]. The dichloromethane extract was washed with aqueous saturated bicarbonate [2 × 20 ml] and then dried. Removal of solvent and HPLC separation [silica gel; 20% ethylacetate in hexane] of the residue gave two compounds.

The first compound was N-phenylpiperonamide, m.p. 134°–135°C [dichloromethane-hexane]; 60 mg; 25% yield. This was identical with the authentic sample (prepared from piperonylic acid and aniline).

The second compound was 3-[3′,4′-dimethoxyphenyl]-4,5-methylenedioxyphthalide 5; m.p. 156–158°C [methanol]; 185 mg.; 63% yield; IR, 1770 cm^{-1} [lactone carbonyl]; NMR (CDCl$_3$): 7·55 (1H, *d*, *j* = 8 Hz, H$_7$); 7·00 (1H, *d*, *j* = 8 Hz, H$_6$); 6.55 (3H, *m*, H$_{2'}$, H$_{5'}$, H$_{6'}$); 6·35 (1H, *s*, H$_3$); 6·05 (2H, *s*, Ar–O–CH$_2$–O); 3.85 3·80 (6H, 2*s*, 2 × Ar–OCH$_3$). Found, C–64·66, H–4·22, cald., C–64·95, H–4·45%.

Halogen-metal exchange reaction of N-phenyl-2-bromo-4,5-dimethoxy benzamide 3a: The reaction of 3a [300 mg, 1 mmol] with *n*-BuLi [5 ml, 0·8 M, 4 mmol] and veratraldehyde [500 mg, 3·5 mmol], as mentioned in the experiment 1, gave two compounds.

The first was N-phenylveratramide, m.p. 161–162°C [Suzuki *et al* 1983, 163°C]; 70 mg; 31% yield.

The second compound was 3-[3′,4′-dimethoxyphenyl] 4,5-dimethoxy phthalide 5a; m.p. 114–115°C [methanol]; 170 mg; 58% yield; IR, 1760 cm^{-1} [lactone carbonyl]; NMR(CDCl$_3$): 7·60 (1H, *d*, *j* = 8 Hz, H$_7$), 7·10 (1H, *d*, *j* = 8 Hz, H$_6$), 6.75 (3H, *m*, H$_{2'}$, H$_{5'}$, H$_{6'}$), 6·30 (1H, *s*, H$_3$), 3·90, 3·85, 3·80 [9H, 3*s*, 3 × ArOCH$_3$], 3.40 (3H, *s*, Ar–OCH$_3$). Found, C–65·12, H–5·60, cald., C–65·45, H–5·45%.

Lithiation of N-phenyl-3,4-methylenedioxybenzamide: To a cooled solution [0°C] of N-phenyl-3,4-methylenedioxy benzamide [250 mg, 1 mmol] in dry THF [20 ml], a solution of *n*-BuLi in hexane [5 ml, 0·8 M, 4 mmol] was added in 2 min by a

syringe. The solution was stirred for 30 min. The red coloured solution was then treated with veratraldehyde [500 mg, 3·5 mmol] in THF [5 ml]. Further work up as mentioned for compound 3 gave the phthalide 5, m.p. 154°C, 200 mg, 66% yield. This was identical in all respects with the earlier sample.

Lithiation of N-phenyl-3,4-dimethoxybenzamide: Lithiation of N-phenyl-3,4-dimethoxybenzamide [250 mg, 1 mmol] with *n*-BuLi [5 ml, 0·8 M, 4 mmol] and further reaction with veratraldehyde [500 mg, 3·5 mmol], as mentioned above for 5, gave the phthalide 5a, m.p. 115°C, 180 mg, 60% yield. This was identical in all respects with the earlier sample.

Acknowledgement

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