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THE GENERATION AND REACTIONS OF C,N-DIANIONS OF AROMATIC TOSYLHYDRAZONES: *ortho-N*-DILITHIATED BENZOPHENONE TOSYLHYDRAZONE

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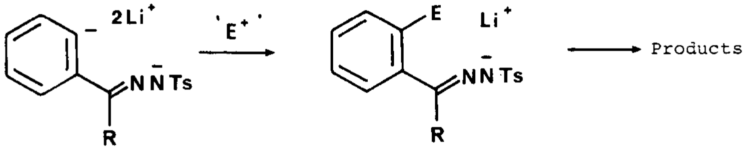
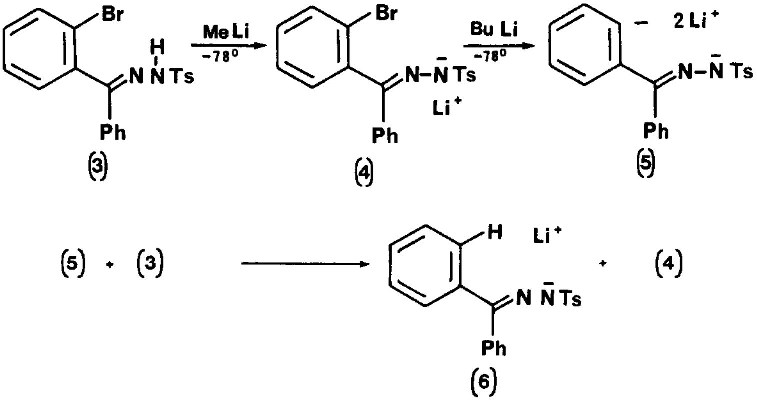
The *ortho, N*-dilithiated derivative of the tosylhydrazone of benzophenone (5) has been generated by metal-halogen exchange at low temperature. A range of alkylation, silylation and acylation reactions are described together with further reactions leading to 1,2-diacylbenzenes, phthalazines, 1,3-diphenylisobenzofuran, and a 1,2,3-diazaborine.

A wide range of *ortho*-substituted aryl lithium reagents has been utilised in organic synthesis in recent years[1-4]. This letter is concerned with the generation and reactions of a new species, the *ortho, N*-dilithiated derivatives of the tosylhydrazones of aromatic ketones (1). Our objectives were to find a route to these intermediates, then to make use of the differentiated nucleophilic reactivity of the C and N centres to functionalise the dianion at C giving (2), and then to utilise the highly versatile reactivity of the tosylhydrazone function to achieve further reactions involving the inserted group E. In principle such reactions could involve the direct reaction of the tosylhydrazone or its salt as a weak N nucleophile, or its ready conversion into a diazo-group[5], carbene[5,6], carbocation[5], vinyl anion[7] or carbonyl group[8], and would provide convenient routes to benzo-annelated carbocyclic and heterocyclic systems *via* known and new cyclisation reactions.

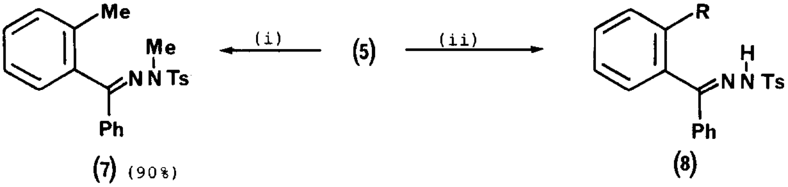


(1) (2)

The work described here deals with the generation of one example of (1), the *ortho, N*-dilithiated derivative of benzophenone tosylhydrazone (5), and with a brief exploration of its reactions with a range of electrophilic reagents. The dianion (5) was generated from *o*-bromobenzophenone tosylhydrazone (3)[9] by sequential proton abstraction and lithium-halogen exchange. In this procedure the essential requirement that proton abstraction from N is complete before metal-halogen exchange takes place was achieved by using methyl-lithium and then n-butyl-lithium in sequence[10]. When n-butyl-lithium alone was used the two processes occurred at comparable rates leading to the formation of mixtures of (4), (5) and (6).



The results of the initial study on the alkylation and silylation of the dianion are shown in Scheme 1. Methyl iodide was reactive enough to alkylate readily at C and N to give (7)[11], while the other iodides and trimethylsilyl chloride proved to be more discriminating and gave the C-substituted products (8a, b, c) in high yield[12] with no detectable reaction at N under the conditions described[10]. The possible extensions of this alkylation reaction by the further reactions of alkyl, alkenyl or alkynyl groups introduced in this way with the diazo, carbene or carbocation potential of the tosylhydrazone group are obvious[13,14].

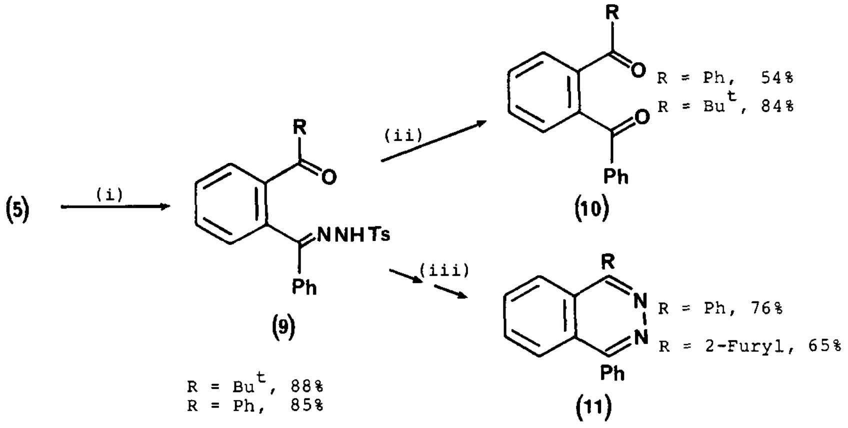


(i) MeI (2.2 mol.equiv.),
(ii) EtI, PrI, or Me_3SiCl (1.2 mol.eqiv) and work-up[10].

(a) R = Et (81%)
(b) R = Pr (82%)
(c) R = Me_3Si (81%)

Scheme 1

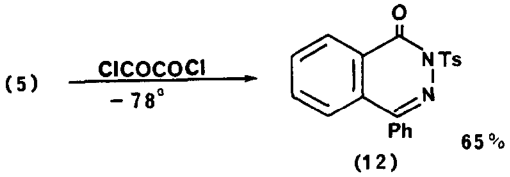
The results of acylation with some acyl halides, followed by nucleophilic cyclisation are shown in Scheme 2. This reaction thus provides a useful route to unsymmetrical 1,2-diacylbenzenes and phthalazines[15]. The primary products (9) were not generally stable enough to be purified but the crude products showed the expected CO and NH i.r. bands. The conditions required for cyclisation of (9) and elimination of the tosyl group to give (11) varied with the nature of R thus (9; R = Ph and R = 2-furyl) required only brief reflux in ethanol, while (9, R = Bu^t) recrystallised unchanged after prolonged boiling in the same solvent.



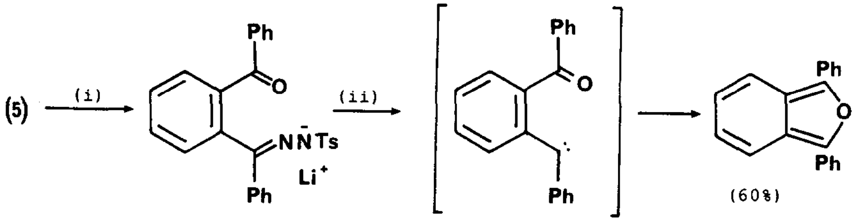
(i) RCOCl at -78°C + work-up[10]
(ii) aq. NaOCl[8]
(iii) see text

Scheme 2

Reaction of (5) with oxalyl chloride gave the phthalazone (12).



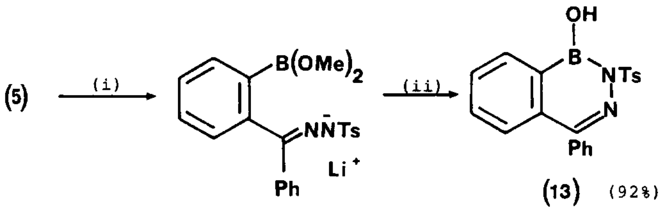
One example of acylation followed by carbenoid cyclisation is shown in Scheme 3. Further work is needed to establish whether this process can be developed into a general route to the synthetically useful isobenzofuran system.



(i) PhCOCl (1.2 mol.equiv.) at -78°C
(ii) warm to R.T., add LiBr (5 mol.equiv.) in THF and reflux overnight.

Scheme 3

The reaction of the dianion (**5**) with methyl borate provided an easy and high yielding route to the diazaborine system (**13**).



(i) $B(OMe)_3$ at -78°C

(ii) usual aqueous work-up[10]

This selection of reactions therefore demonstrates some of the range of possible synthetic uses of dianions of the type (**2**)

Notes and References

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9. Prepared by reaction of *o*-bromobenzophenone with tosylhydrazine, m.p. 164-165°C (from n-propanol).
10. The usual procedure was to add methyl-lithium (10% excess of the Aldrich reagent as complex with lithium bromide) to a cooled (-78°C) solution of the tosylhydrazone (*ca* 1 mmol) in T.H.F. (15-25 ml), stir for 20 min and then add the butyl-lithium (10% excess of the Aldrich reagent in hexane), stir for a further 20 min and then add the electrophilic reagent and allow the mixture to warm up slowly to R.T. Work-up was usually by neutralisation with dilute aqueous acetic acid followed by addition of aqueous sodium hydrogen carbonate solution and extraction into methylene chloride.
11. Identical with an 'authentic' sample prepared from *o*-tolyl phenyl ketone and tosylhydrazine followed by phase-transfer N-methylation.
12. All products had the expected spectral characteristaics (i.r. and n.m.r.) and correct elemental analysis.
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14. "1,3-Dipolar Cycloaddition Chemistry", A. Padwa (Ed), Wiley, New York, 1984, Ch. 12.
15. The yields of compounds (**10**) and (**11**) are based on (**3**) *via* reactions in which (**9**) was not isolated.
16. Structure confirmed by comparison with an 'authentic' sample (m.p. 213°C) prepared by reaction of *o*-benzoylbenzoic acid with *p*-tosylhydrazine.

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