THE GENERATION OF C,O,O-TRILITHIATED DERIVATIVES OF DIHYDRIC PHENOLS[#]

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Abstract.-Halogenated dihydric phenols (hydroquinones and resorcinols) undergo halogen metal exchange with nBuLi/TMEDA/THF or ether (inverse addition) under sonication, thereby generating a C,O,O-trilithiated species which can be trapped with electrophiles.

The nowadays widely employed aromatic organolithium compounds are usually made via heteroatom directed metalation $(DoM)^1$ or halogen metal exchange.² In preparing them, chemical common sense tells us to temporarily protect any sensitive functional groups present in the molecule, either because these are Brönsted acids readily converted to the often insoluble (again, common sense) lithium salts or simply because they are attacked (and destroyed) by the organolithium reagent.³ Accordingly, till quite recently acidic functional groups such as carboxylic acids, phenols, thiols, etc were, in general, considered unsuitable for lithiation.⁴ A variety of suitable protecting groups concomitantly having a powerful metalation directing capacity have thus been developed over the years for the purpose of facilitating the lithiation of those aromatics having labile functional groups.⁵

In the past few years we have contended that protection of functional groups is, in many cases, futile synthetic work. Accordingly, we and others have dedicated some effort to demonstrate the synthetic potential of lithiated phenols and related compounds. 5

This preliminary report documents our recent experience in generating some Clithiated derivatives of the dilithio salts of dihydric phenols by halogen metal exchange carried out on the corresponding unprotected halogenated dihydric phenols (Fig. 1). To the best of our knowledge this is the first successful attempt at generating such a C,O,O-trilithiated species. A brief preliminary study of their reactivity with a limited number of common electrophiles is also presented herein.

#Dedicated with great admiration to Prof. M.P. Cava on the ocasion of his 65th birthday



Fig. 1

After several unsuccessful attempts at reaching the above organolithium species through direct lithiation of diphenols⁶ (precipitation occurred in most cases, thereby effectively inhibiting the subsequent lithiation), we turned our attention to the halogen metal exchange methodology² as applied to several simple halogenated resorcinols and hydroquinones.⁷ After considerable experimentation with <u>1</u> we found that metalation could be achieved (Scheme 1) though only by working under carefully controlled conditions (*vide infra*). The data shown (Scheme 1) for the remaining substrates were also obtained by working under these controlled conditions, unless otherwise noted.

As shown below best results were obtained by working with n-BuLi-TMEDA under sonication.⁸ A 14:1 ratio of n-BuLi to substrate was found to give high conversion rates (lower ratios gave back variable amounts of unreacted starting material). Also worthy of note is that inverse addition is of fundamental importance to reduce the amount of protonated material.^{9a}

The following salient features of the present methodology need to be emphasized, namely: 1) Protonation of the organometallic intermediate (presumably a C-lithio derivative of a O,O-dilithium salt) appears to be an unavoidable side reaction.¹⁰ Whether the hydrogen source is a phenolic hydrogen (internal protonation) or it comes from some other source is presently unknown.^{9,11} 2) Dibrominated resorcinol **10** undergoes clean monolithiation when submitted to our standard conditions of lithiation (ether was found to be superior than tetrahydrofuran for the lithiation of resorcinols), thus suggesting a powerful method for the preparation of highly substituted polyphenols from symmetric starting materials. 3) Although the limited number of examples examined up to date does not allow a general rule to be drawn, iodinated dihydric phenols seem to undergo halogen metal exchange much more efficiently than the corresponding bromo compounds but, contrary to initial expectations, these educts yielded increasing amounts of the undesired dehalogenated product (Scheme 1).

In spite of the fact that the above C,O,O-trilithiated species function as expected for common aryl lithium compounds, we refrain at the moment to propose a particular (solution) structure for the organolithium species thereby generated. Actually, recent literature reports by Reich and coworkers show that halogen-to-metal exchange on iodobenzene takes place rapidly and gives rise to observable (NMR) "ate" complexes (lithium diaryliodinanide species) which behaved as typical organolithium compounds, therefore casting doubts on the actual structure of the product derived from halogen-to-metal exchange.¹² Work is underway on this interesting issue.



iii.-Isolated as the corresponding naphthoquinone

Scheme 1

The following is the **general experimental procedure** employed throughout: an oven dried cylinder flask (cooled under argon) provided with rubber septum, was charged with 5 ml of commercial 1.4M n-BuLi (7 mmol), under argon. The flask was cooled to 0°C and TMEDA (1 ml) dissolved in THF added with magnetic stirring. The initially turbid suspension turned clear after a few minutes. A THF solution (10 ml) of the halogenated diphenol (0.5 mmol) was then added dropwise via syringe. The flask was subsequently immersed on a commercial ultrasonic (cleaning) bath and irradiated during 2 hours, taking care to keep the bath temperature in the 5-15°C range. Treatment of the resulting very faintly colored (yellowish) heterogeneous mixture with the appropriate electrophile (room temperature, several hours) was followed by the standard extractive workup. The resulting crude mixture thus obtained was first examined by GLC and GLC/MS. Column chromatography of the crude eventually led to the isolation of the functionalized diphenol.

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