Journal of Organometallic Chemistry, 393 (1990) 307–314
Elsevier Sequoia S.A., Lausanne
JOM 20976

Interaction of alkoxides

XVIII *. Utilitization of the complex base from alkyllithium and potassium alkoxides in the dimetallation of phenol, thiophenol, *o*-, *m*- and *p*-cresol

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(Received March 27th, 1990)

Abstract

Successful O- and *ortho*-ring metallation of phenol and side chain metallation in *o*-cresol has been achieved by use of a mixture of two molar equivalents of n-butyllithium, one molar equivalent of potassium t-butoxide, and two molar equivalents of N,N,N',N'-tetramethylethylene diamine in hexane. Poor results were obtained with *m*-cresol, thiophenol and *p*-cresol. *m*-Cresol was effectively dimetallated with a mixture of two molar equivalents of ^{t}BuOK and two molar equivalents of ^{n}BuLi · TMEDA. The effectiveness of another type of complex base based on 2-ethylhexyllithium (EhexLi) and potassium alkoxides has been also investigated, especially in respect of the influence of the concentration and the structure of the alkoxide used. With a complex base from EhexLi and 3 equivalents of potassium 3-methyl-3-pentoxide phenol was successfully dimetallated even in the absence of TMEDA. Thus, the enhanced reactivity of a complex base containing a higher concentration of a more branched potasium alkoxide over that of previously used complex bases has been confirmed.

Introduction

A few years ago Posner [1] described the successful dimetallation of phenol with t-butyllithium in tetrahydropyran to give lithium *o*-lithiophenoxide. Other bases, such as the complex base (CB) from BuLi and ^{t}BuOK, were found to be less

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* Part XVII see ref. 13.

0022-328X/90/$03.50

effective. One year later Bates [2] reported the dimetallation of the isomeric cresols at O and CH_3 with a large excess of this basic reagent under heterogeneous conditions. Three research groups [3–5] very recently showed that thiophenol can be dimetallated at sulfur and the *ortho*-ring carbon atom, with the n-butyllithium/ *N*,*N*,*N*′,*N*′-tetramethylethylene diamine (^{n}BuLi · TMEDA) reagent in hexane. The usefulness of CBs, in particular the BuLi + ^{t}BuOK reagent [6,7], in metallations of compounds with a low acidity, has been amply shown [8,9]. This reagent appears to be generally more reactive than BuLi · TMEDA, and it can be used as a substitute for t-butyllithium [9]. Recently the effectiveness of the combination of BuLi, ^{t}BuOK and TMEDA in hexane was demonstrated for metallation of ethene [10] and hydrogen [11]. Another improvement of the properties of a CB was achieved by increasing the concentration or modifying the structure of the alkoxide [12,13].

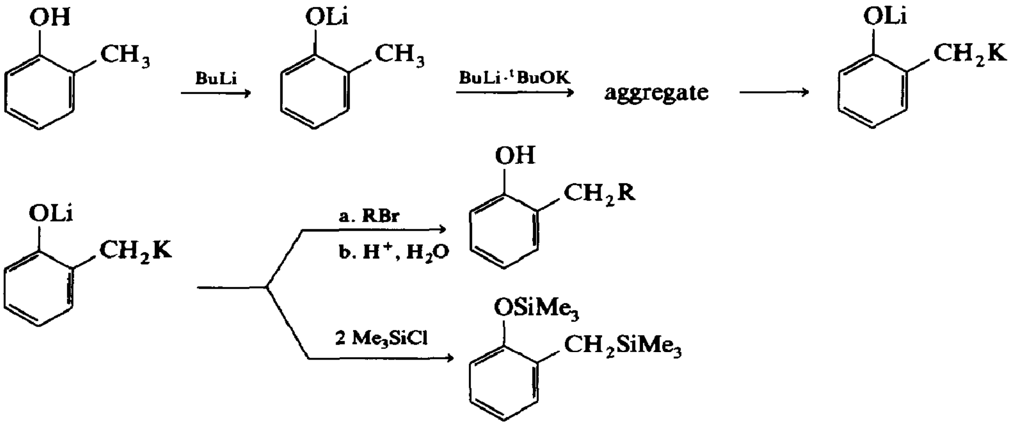
The aim of the present investigation was the use of such a system in the metallation of phenol, thiophenol, *o*-, *m*-, and *p*-cresol.

Results and discussion

(a) Dimetallation of o-, m- and p-cresol in the presence of TMEDA

In the general procedure, the substrate was added below −20 °C to a solution of two mol equivalents of BuLi · TMEDA in hexane, and then one molar equivalent of ^{t}BuOK was introduced. After the mixtures had been stirred for 1 h at −20 °C, the temperature was allowed to rise to ~ +5 °C, then a specific amount of THF was added, and the derivatization reactions were then carried out. The outcomes of the reactions with *o*-, *m*- and *p*-cresol showed marked differences. The excellent yield of the bis-trimethylsilyl derivative obtained from *o*-cresol may reflect its relatively easy dimetallation, which may be due to the formation of a mixed aggregate of lithium *o*-cresylate and the CB in which the base is close to the hydrogen atoms of the methyl group.

In the case of *m*-cresol the characteristic yellow to orange suspension of the dimetallation product was formed at a much later stage, indicating a slower side chain metallation. Yields of the silylation and alkylation products were at best ca. 35%, and could not be significantly improved by lengthening of the time of metallation. There was marked improvement when 2 equivalents of ^{t}BuOK were used. Reaction of *m*-cresol for 2 h at −20 °C with the mixture of 2 equivalents BuLi · TMEDA and 2 equivalents of ^{t}BuOK, followed by addition of n-butyl bromide, gave *m*-pentylphenol in 72% yield. This result reflects again the enhanced reactivity of a modified CB [12,13].



Under similar conditions *p*-cresol gave the alkylation product in poor (~ 15%) yield. (When one equivalent of ᵗBuOK was used, practically all the *p*-cresol was recovered.) A mechanism such as suggested for the dimetallation of *o*-cresol, in which the CH_3-group is deprotonated within a mixed aggregate, seems unlikely in the case of *m*- and *p*-cresol. Bates and Siahaan [2] carried out dimetallations of the cresols under heterogeneous conditions using a 100% molar excess of the BuLi + ᵗBuOK reagent in refluxing hexane or heptane, and also obtained relatively poor results with *p*-cresol.

(b) Dimetallation of phenol and thiophenol in the presence of TMEDA

The failure to detect ring-functionalized compounds in our metallation-functionalization experiments with *o*-, *m*- and *p*-cresol contrasts with the relatively smooth (1 h at −20 °C, then 30 min at +10 °C) dimetallation of phenol under similar mild conditions. The electron releasing effect of a methyl group renders the ring less susceptible to deprotonation. Treatment of phenol with two molar equivalents of BuLi · TMEDA and one molar equivalent of ᵗBuOK in hexane under the conditions used for the cresols gave a turbid solution, which upon quenching with chlorotrimethylsilane afforded *o*-trimethylsilylphenyl trimethylsilyl ether in ~ 65% yield.

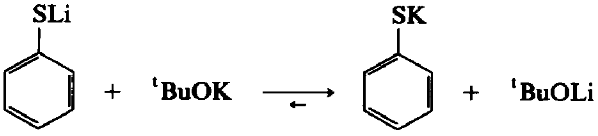
The presence of appreciable amounts of $PhOSiMe_3$ in the forerun of the distillation indicates that not all phenol has been metallated in the ring. Longer reaction times for the metallation or the use of an excess of BuLi + ᵗBuOK did not give better results. Presumably part of the CB is consumed by reaction with TMEDA (compare ref. 14).

The *ortho*-regiospecificity of this metallation (confirmed by comparing the product from Me_3SiCl quenching with an authentic sample prepared from *o*-bromophenol, two equivalents of BuLi in ethyl ether, and Me_3SiCl, see ref. 15) may be attributed to initial formation of a mixed aggregate from PhOLi and BuLi + ᵗBuOK in which the metallation is directed towards the *ortho*-positions.

As shown previously [3–5], thiophenol can be dimetallated at S and at the *ortho*-carbon atom with excellent results, when two molar equivalents of BuLi · TMEDA in cyclohexane are used. The fact that the presence of ᵗBuOK caused a large acceleration of the ring-metallation of phenol (practically no deprotonation of the ring occurred with BuLi · TMEDA at temperatures between −20 to +20 °C) prompted us to investigate the influence of ᵗBuOK upon the metallation of thiophenol. Thus, in two parallel experiments thiophenol and a mixture of 2 equivalents of BuLi · TMEDA or 2 equivalents of BuLi · TMEDA and one equivalent of ᵗBuOK, respectively, were allowed to interact for 2 hours at −20 °C. Subsequently THF and a large excess of methyl bromide were added below −30 °C. From the first experiment methyl phenyl sulfide was isolated, along with to a few percent of *p*-tolyl methyl sulfide, and in the other only methyl phenyl sulfide was formed. A similar result was obtained when 2 equivalents instead of one equivalent of ᵗBuOK were added or when the reaction was carried out at −10 to

0 °C (attack on TMEDA by the CB presumably predominates [14]). The CB specified under (c) below also proved to be ineffective.

The failure of ^{t}BuOK to promote the ring-metallation of thiophenol may be attributed to preferential initial formation of potassium thiophenolate, which cannot effectively coordinate with the CB.



(c) Dimetallation of phenol with other types of complex bases

Dimetallation of phenol with other types of CB has been investigated for comparison. The CB prepared from 2-ethylhexyllithium (EhexLi) and heavier alkali metal alkoxides are very soluble in heptane, even in the absence of TMEDA, and exhibit a strong metallating ability [16]. The reactivity of CB may be enhanced by increasing the concentration of the heavier alkali metal alkoxide [12] and by changing its structure [13]. We thus thought it likely that more satisfactory conditions for dimetallation of phenol could be found. Moreover, the isolation and analysis of the organometallic reaction product is possible in this case, i.e. before its derivatization by an electrophile, providing additional information about the organometallic intermediate.

Reactions of phenol with CB prepared from EhexLi and various potassium alkoxides at two concentration levels resulted in dimetallation (ring metallation) to various different extents, as shown in Table 1. These reactions were performed in heptane (without TMEDA) at room temperature. The CB from ^{t}BuOK at both concentrations or from an equimolar amount of potassium 3-methyl-3-pentoxide (^{t}MpenOK) and EhexLi formed in the reaction with phenol immediately gave precipitates consisting predominantly of alkali phenoxides or of an adduct of the potassium phenoxide with the excess of ^{t}BuOK. Similar adducts of organopotassium compounds have been described recently [16,17]. The Li content of the precipitate formed in the reactions of the CB formed with an equimolar proportion of potassium alkoxides was much higher than formed with an excess of ^{t}BuOK demonstrating the complex nature of such reactions. However, the reaction of phenol with the CB made from EhexLi and three equivalents of ^{t}MpenOK gave a different result, the precipitate of the phenoxide initially formed, as described above, dissolved almost completely in the 5 h during which the reaction was carried on.

The extent of ring metallation in all these products was roughly estimated by NMR spectroscopy after derivatization of the organometallic product with trimethylchlorosilane. The data in Table 1 reveal a low extent of benzene ring metallation by the first mentioned CB contrast with that observed with the CB made from three equivalents of ^{t}MpenOK, in the latter case the yield of ring metallation was > 70 mol%. This means that the second CB has an extraordinary metallating power equals to that of the CB made from BuLi, ^{t}BuOK and TMEDA, and investigated as described under (a) and (b) above. The starting materials for making a CB from EhexLi or ^{t}MpenOK are not yet commercially available, but their use gives effective and equally reactive CBs for use where a non-solvatating medium is needed, e.g. for

Table 1

Dimetallation of phenol with complex bases from 2-ethylhexyllithium and potassium alkoxides in pure heptane at 20 °C and analysis of the organometallic products [a]

Starting system	Precipitate yield (mol%) [b]	Metal content (%) [c]		Molar ratio [K]/[Li]	Molar ratio [d] [^{t}BuOH]/[PhOH]	Extent of ring metallation [e]
		K	Li			
PhOH + 2 [EhexLi + ^{t}BuOK]	120	24.3	2.69	1.60	0.13	0
PhOH + 2 [EhexLi + 3^{t}BuOK]	133	40.0	0.20	35.7	2.58	10:90
PhOH + 2 [EhexLi + ^{t}MpenOK]	150	34.4	2.10	2.90	-	[f]
PhOH + 2 [EhexLi + 3^{t}MpenOK]	precipitate initially formed dissolved during further reaction				-	70:30
[PhOH + 2 EhexLi] + ^{t}BuOK	200	24.2	5.28	0.81	0.46	35:65
[PhOH + 2 EhexLi] + 3^{t}BuOK	140	30.3	2.51	2.57	0.45	60:40

[a] Abbrevations: EhexLi = 2-ethylhexyllithium (n-$C_4H_9CH(C_2H_5)CH_2Li$), ^{t}BuOK = potassium t-butoxide, ^{t}MpenOK = potassium 3-methyl-3-pentoxide ($CH_3(C_2H_5)_2COK$), PhOH = phenol. [b] Calculated as potassium phenoxide. [c] Determined by atomic absorption spectrometry. [d] Determined by GLC after hydrolysis. [e] *Ratio of trimethylsilylphenyl trimethylsilylether to phenyl trimethylsilyl ether. Roughly estimated by NMR spectroscopy after reaction of the metallation product with* trimethylsilylchlorosilane. [f] Ratio could not be determined because many signals were present in the Me_3Si region.

the subsequent derivatization. Moreover, reactions of such CBs, free from TMEDA, may be performed at room temperatures. Rather similar yields of dimetallated phenol can be obtained by use of ^{t}BuOK in another type of procedure, in which the phenol was treated initially with two equivalents of EhexLi then either one or three equivalents of ^{t}BuOK were added; in the first case a low and in the second case a medium yield of *o*-trimethylsilylphenyl trimethylsilylether were observed by NMR spectroscopy after treatment of the metallation mixture with trimethylchlorosilane (Table 1). Thus, a CB prepared in situ seems to be more reactive than the corresponding preformed CB, evidently because of aggregation effects.

In summary, the ring metallation (i.e. overall dimetallation) of phenol can be successfully carried out even in pure heptane when the new, more reactive, CB made from EhexLi and an excess of potassium alkoxides is used.

Experimental

All reactions were carried under an inert gas.

Dimetallation of o-cresol and subsequent reaction with chlorotrimethylsilane or butyl bromide

To a solution of 0.21 mol of BuLi in 140 ml of hexane was added 0.21 mol of TMEDA (dried over machine-powdered potassium hydroxide and subsequently filtered). The solution was cooled to below $-40\,^\circ$C, and a mixture of 0.10 mol of *o*-cresol and 60 ml of hexane was added during a few minutes, the temperature being kept below $-50\,^\circ$C. Finely powdered ^{t}BuOK (0.21 mol) was then quickly introduced through a powder funnel, and the temperature was then allowed to rise to $-20\,^\circ$C. The suspension initially dissolved but after a short time (at -20 to $-25\,^\circ$C) a yellow to orange suspension appeared. The mixture was kept for 1 h at $-20\,^\circ$C, after which the temperature was allowed to rise (by removal of the cooling bath) to $+10\,^\circ$C. After an additional 30 min dry THF (100 ml) was added, and the suspension cooled to $-60\,^\circ$C. Freshly distilled chlorotrimethylsilane (0.35 mol) or n-butyl bromide (0.13 mol) was added in one portion with vigorous stirring and the cooling bath was removed. The reaction with trimethylchlorosilane was completed by stirring the mixture (a white suspension) for 30 min at 30–35 °C. Ice-water (200 ml) was added with vigorous stirring. The aqueous layer was extracted twice with pentane, the organic solutions combined, dried over magnesium sulfate and concentrated in vacuo. Fractional distillation gave the bis(trimethylsilyl) derivative, (b.p. 115 °C/12 mmHg, n_D^{22} 1.4800) in 92% yield.

The butylation product was liberated by adding of a mixture of 90 gram of 30% aqueous hydrochloric acid and 300 ml of ice water to the almost colourless suspension. The aqueous layer was extracted three times with diethyl ether. The combined organic solutions were washed once with concentrated aqueous sodium chloride, and the alkylation product (b.p. 126 °C/12 mmHg, n_D^{22} 1.5148) was isolated in 67% yield by careful distillation. The small residue (~ 4 g) which solidified upon cooling consisted mainly of the "dimer" *o*-$OHC_6H_4CH_2CH_2C_6H_4OH$-*o* (compare ref. 2). *o*-Pentylphenol is a known compound [2].

Dimetallation of m-cresol and subsequent butylation

To a solution of 0.12 mol of BuLi in 80 ml of hexane containing 0.12 mol of TMEDA, a mixture of 0.05 mol of *m*-cresol and 30 ml of hexane was added at

< −50 °C. ^{t}BuOK (0.12 mol) was also added at −50 °C, and the mixture was stirred at −20 °C. It initially became homogeneous, but at −20 °C a yellow suspension was soon formed. After stirring of the mixture for 2.5 h the cooling bath was removed and the temperature allowed to rise to +10 °C. THF (50 ml) was then added, and the reaction with n-butyl bromide (0.08 mol) was carried out as described in the preceding experiment. *m*-Pentylphenol, b.p. 125 °C/12 mmHg, was obtained in 72% yield. (For the work-up and isolation procedure see the preceding experiment) A small forerun (~ 1.5 g) consisting of *m*-cresol and its alkylation product, was collected. *m*-Pentylphenol is a known compound [2].

Dimetallation of phenol and subsequent trimethylsilylation

A mixture of 0.10 mol of pure phenol (which had been distilled and then recrystallised from a mixture of ether and hexane) and 60 ml of hexane (warmed at 30 °C) was added (by syringe) during a few minutes to a solution of 0.21 mol of BuLi · TMEDA in 138 ml of hexane, the temperature being kept < −20 °C. Subsequently 0.21 mol of freshly powdered ^{t}BuOK was adding during a few seconds at −35 °C. The resulting, almost clear solution was stirred for 1 h at −20 °C, and the cooling bath was then removed and the temperature allowed to rise to +10 °C. The solution became turbid above 0 °C. THF (100 ml) was then added, and then freshly distilled chlorotrimethylsilane (40 g, excess), added in one portion at −30 °C. The cooling bath was removed and the temperature allowed to rise to > 0 °C. The reaction was completed by stirring the white suspension for an additional 1 h at 40 °C. The excess of chlorotrimethylsilane and most of the solvent were then removed under reduced pressure (rotary evaporator). After addition of ice water to the remaining viscous residue, the product was isolated by extraction with pentane, drying of the extract over $MgSO_4$, evaporation of the solvent in vacuo, and careful distillation of the remaining liquid through a 30-cm Widmer column. *o*-$Me_3SiC_6H_4OSiMe_3$, b.p. 108 °C/12 mmHg, n_D^{24} 1.4854, was isolated in 60–65% yields. The forerun consisted mainly of $PhOSiMe_3$ (b.p. 70 °C/12 mmHg).

General procedure for the investigation of other types of complex bases

Phenol (0.015 mol) was mixed with either the CB made from EhexLi and ^{t}BuOK or with the components of the CB successively in such a manner that the resulting concentration of phenol was 0.35 mol/l; otherwise the conditions were as shown in Table 1. The heterogeneous mixture was shaken with 3 stainless steel balls for 5 h. The precipitate formed was isolated by centrifugation, washing 5 times with hexane, and dried in vacuo for 8 h at room temperature.

For estimation of the extent of dimetallation of phenol, the reaction mixture after metallation was treated with trimethylchlorosilane (2 molar equivalents based on all the alkali metal compounds present) at −50 °C, and the mixture kept for at least 2 h at room temperature. The clear solution obtained by centrifugation was concentrated under reduced pressure and NMR spectrum (60 MHz) of the residue was recorded.

Acknowledgement

This investigation was supported financially by the Netherlands Technology Foundation (STW). The authors are indebted to Mrs. Hana Jakubuv for technical assistance.

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