Polymer supported naphthalene-catalysed sodium reactions

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Arene-catalysed sodium reactions have been utilised in the generation of organosodium complexes, from a variety of organochloride complexes, in high yield. Phenyltrimethylsilane, benzene and 2-methyl-1-phenyl-1-propanol were prepared in yields >80%, using polymer supported naphthalene-catalysed sodium reactions, whereby phenylsodium, prepared from the reaction of chlorobenzene, sodium powder and polymer-supported naphthalene (5–100%), was quenched with chlorotrimethylsilane, water or Pr^iCHO respectively.

Introduction

The use of alkali metal–arene radical anion complexes, $ArH^{-\bullet} M^+$, as soluble sources of metal in the formation of organoalkali metal species from organic halides, is well established, with early work focusing on the use of lithium naphthalenide.[1] Many radical anion derivatives of lithium have been prepared in recent years, the 4,4-di-*tert*-butylbiphenyl (DBB) complex being particularly noteworthy, in that while it acts as a source of lithium, removal of DBB by-product is facilitated by its low volatility.[2] Other approaches to overcoming the objection of having solutions of the target organolithium species loaded with the arene by-product have been developed by Yus *et al.*[3] and van den Ancker *et al.*[4,5] These have included the use of a catalytic amount of arene, whereby the arene undergoes electron transfer with the bulk metal affording a radical anion complex, which then reacts with a variety of organic compounds (including halides, phosphates, nitriles and alcohols) to generate the corresponding lithium complex, which can be successfully treated with a desired electrophile.[3] In these reactions, only small amounts of the by-product arene are present in the product mixture. Purification, however, is still essential when pure compounds are required.

Macromolecule-supported lithium naphthalenide complexes, prepared from the treatment of the corresponding functionalised macromolecule with lithium biphenylide, developed by van den Ancker *et al.*, have also proven successful in the generation of lithium complexes from a variety of organic compounds including organochlorides, nitriles and phosphates.[4,5] The use of these macromolecule-supported species led to a methodology for producing lithium complexes that could be readily removed from the supported arene. Polymer supported arene-catalysed reactions developed by Yus *et al.*[6] utilised lithium powder in the generation of the active lithium polymer, rather than the biphenylide species. An investigation into the polymer's ability to generate lithium complexes proved viable.[6] Each of these approaches (catalysed, macromolecule- and polymer-catalysed) proved quite successful in the generation of lithium complexes from a range of organic compounds.

Sodium–arene radical anion complexes have received much less attention than their lithium counterparts and do afford organosodium complexes in relatively high yields.[7] As with their lithium counterparts, the solutions of these reagents are loaded with the arene by-product. We previously developed methods for the preparation of sodium reagents using polymer-supported sodium naphthalenide,[4,5] and preparation of sodium complexes *via* arene-catalysed reactions.[8] The polymer-supported sodium naphthalenide, based on a silylnaphthalene-supported polystyrene, generated high yields of the desired sodium complexes, and was furthermore recyclable. The silylnaphthalene polymer, however, was not suitable as a reagent due to the instability of the sodium radical anion complex of the polymer.[5] Arene-catalysed reactions with naphthalene and sodium powder generated high yields of phenylsodium; however, the products still contain the by-product arene, albeit in catalytic amounts.[8]

Following on from the successes of the arene-catalysed sodium reactions of van den Ancker *et al.*[8] and that of the polymer supported arene-catalysed lithium reactions of Yus *et al.*,[6] we have developed a new methodology that enables the generation of sodium reagents, utilising a polymer supported arene-catalysed approach.

Results and discussion

Organosodium generation: Reaction with naphthalene

We had previously determined the optimum condition for the generation of phenylsodium as −78 °C, THF and naphthalene (5%).[8] We have continued with this research and now report on the generation of sodium complexes of a range of organochloride compounds (Scheme 1, Table 1).

Examples of quenched organosodium reagents, prepared using sodium powder and 5% naphthalene, are presented in Table 1. In all cases, target concentrations of the sodium reagent were 0.1 M. In a typical experiment, THF was added to the sodium powder, then a catalytic amount of naphthalene (5%) was added to the solution. The resulting green suspension was cooled and treated with a solution of the relevant organochloride in THF. During

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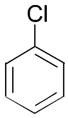
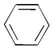
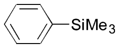
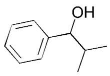
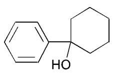
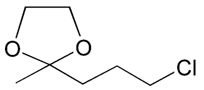
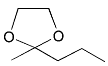
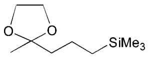
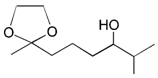
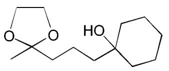
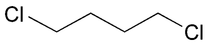
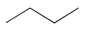
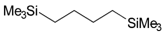
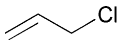
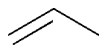
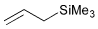
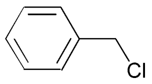
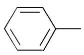
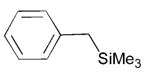
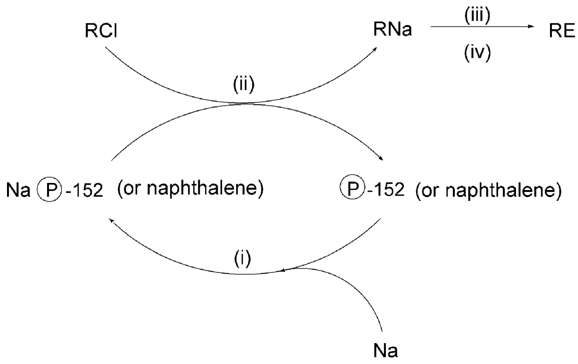
Table 1 Yields of organosodium reagent and quenched products from mixtures of sodium powder and naphthalene (5%)[a]

Reagent (RCl)	Electrophile (E^+)	Activity[b]	Product (RE)	Yield[c]	Ref[d]
	H_2O	>95%		90%	
	$ClSiMe_3$			85%	
	Pr^iCHO			85%	9
	$(CH_2)_5CO$			75%	9
	H_2O	90%		85%	
	$ClSiMe_3$			80%	10
	Pr^iCHO			60%	11
	$(CH_2)_5CO$			60%	11
	H_2O	90%		85%	
	$ClSiMe_3$			85%	
	H_2O	90%		85%	
	$ClSiMe_3$			90%	
	H_2O	95%		90%	
	$ClSiMe_3$			95%	

[a] Average of three runs. [b] Yield of organosodium reagent, established by back-titration. [c] Isolated yield of the quenched product (not optimised). [d] References given for sources of ^1H NMR comparison where pure sample comparison not available.

the addition of the organochloride, the green suspension of the reaction mixture gradually changed colour, depending on the organochloride used. If a colour change was not observed, at −78 °C, the mixture was warmed (−55 °C or −30 °C), to ensure the formation of the organosodium reagent. Reactions involving chlorobenzene and 2-(3′-chloropropyl)-2-methyl-1,3-dioxalane afforded deep red solutions of the corresponding organosodium reagent; allyl chloride generated purple allylsodium, whilst reactions with benzyl chloride and 1,4-dichlorobutane turned yellow–green with the formation of their corresponding organosodium reagents. The activities (Table 1) of the organosodium reagents was determined by triplicate back-titrations, in which aliquots of the solutions were quenched with 0.100 M HCl and back-titrated with 0.100 M NaOH.

The resulting organosodium reagents were then treated with the corresponding electrophile, resulting in the formation of pale



Scheme 1 *Reagents and conditions*: (i) −78 °C (−55 °C or −30 °C), THF, 20 min, (ii) −78 °C, 1 h, (iii) $E^+ = H_2O$, Pr^iCHO, $(CH_2)_5CO$ or $ClSiMe_3$, −78 to 25 °C, 1–24 h, (iv) H_2O.

yellow solutions. Work-up (purification and/or distillation) of these solutions afforded high yields of the desired compound (Table 1). The purities of the products were confirmed utilising ^{1}H NMR, by comparison with the spectra of pure compounds or literature values.[9–11]

Macromolecule-supported lithium reagents,[4,5] arene-catalysed lithiations,[3] polymer supported arene-catalysed lithiations[6] and arene-catalysed naphthalene reactions have all been successful in the generation of the corresponding phenylalkali in high yields. Generation of the other sodium reagents has not been previously well covered. Grignard synthesis of allylic and benzylic halides has been achieved, utilising macromolecule-supported magnesium anthracene.[10,12] Lithiation of benzylic halides and the dioxalane have previously been reported,[3–6] however the lithiation of allylic (mono-chlorinated) compounds utilising macromolecule- or arene-catalysed reactions has not been investigated. Yus *et al.* has recently reported the generation of dilithium reagents from dihalogenated alkanes utilising arene-catalysed lithiations.[13]

In investigating the viability of arene-catalysed sodium reactions in the generation of organosodium reagents, we have further studied a range of halogenated and non-halogentated species including alcohols, nitriles, phosphates and sulfates. These reactions have proven viable, but have required the use of Barbier-type reaction conditions, in which the electrophile is added to the reaction mixture, resulting in lower yields (typically <50%) of the desired quenched product. For Barbier-type reactions the activity of the organosodium complexes is undetermined.[14]

Organosodium generation: Reaction with polymer-supported naphthalene

Sodium powder with varying amounts of polymer-supported naphthalene (P-152) was tested for the ability to form phenylsodium, and the corresponding quenched products (Scheme 1, Table 2), under the same conditions as described for naphthalene-catalysed reactions. The generation of phenylsodium and subsequent formation of the quenched compounds can be followed by a simple colour change.

Initially, the reaction mixture shows the dark green colour of the polymer-supported sodium naphthalene (Na–P152). After addition of chlorobenzene, the colour gradually changes to that of phenylsodium (dark red). The quenching of phenylsodium causes the disappearance of the red colour, usually affording a clear/pale yellow solution with the formation of the desired products. Thus it is not necessary to follow the reaction through spectroscopic or chromatographic means.

Table 2 Yields of phenylsodium and quenched products from mixtures of sodium powder with varying amounts of polymer-supported naphthalene (P152), and spent polymer[a]

		Activity[b]			
P152 (%)	E^+	Cycle 1	Cycle 2	Cycle 3	Yield[c]
100	H_2O	95%	>90%	85%	95%
100	$ClSiMe_3$				80%
100	Pr^iCHO				73%
50	H_2O	95%	90%	85%	95%
50	$ClSiMe_3$				80%
25	H_2O	95%			95%
25	$ClSiMe_3$				85%
10	H_2O	95%	>90%	90%	95%
10	$ClSiMe_3$				85%
10	Pr^iCHO				80%
10	$(CH_2)_5CO$				70%
5	H_2O	90%	75%	75%	85%
5	$ClSiMe_3$				75%

[a] Average of three runs. [b] Yield of phenylsodium, established by back-titration. [c] Isolated yield of the quenched product from cycle 1 (not optimised).

Optimal reaction conditions were determined to be −78 °C, THF and P152 (10%). The spent polymer was tested for recycling potential. After quenching the sodium polymer with chlorobenzene, the resulting phenylsodium was filtered from the spent polymer (Cycle 1, Table 2). The polymer was then isolated and retreated with sodium powder and chlorobenzene to generate phenylsodium (Cycle 2, Table 2). This process was repeated a further time (Cycle 3, Table 2). The polymer changed from white to pale yellow on recycling three times, with limited effect on the activity. The ability of the spent P152 to regenerate Na–P152 is valuable, as previous work on polymer-supported sodium silylnaphthalene had reduced success on subsequent recycling of the spent polymer, due to the formation of dihydronaphthalene species.[4,5] Similar recycling ability of P152 was also noted in corresponding lithiation reactions.[6]

We have generated a variety of sodium reagents based on several organochlorides utilising P152. As yet, reaction conditions, activities and isolated yields have not been optimised.[14]

Conclusions

We have developed a more practical method for generating organosodium complexes. The preparation of the sodium radical anion complex is avoided, the reaction is clean, and easy to follow through colour changes, and the work-up is simplified, with reduced quantities of arene by-products. We have also developed a procedure in which insoluble polymers are utilised, and as such, are readily removed by filtration from the desired reaction products, resulting in products free of arene by-product.

Experimental

General

Sodium powder was obtained, from ACROS chemicals, as a slurry in toluene (30 wt%, <0.1 mm particle size). The sodium powder was filtered and dried *in vacuo* and stored under argon, prior to use. All other chemicals were obtained from Aldrich or Fluka and used without purification. Reagent-grade THF was dried (Na wire), distilled (Na/K benzophenone) and freeze-degassed prior to use. 2-(3′-Chloropropyl)-2-methyl-1,3-dioxalane was prepared from 5-chloro-2-pentanone following literature procedures.[15] Polymer-supported naphthalene (P152) was prepared from vinylnaphthalene (1 mol equiv.), styrene (5 mol equiv.), divinylbenzene (2 mol equiv.) and polyvinyl alcohol in water, following the Itsuno methodology to give crosslinked polymers.[6,16] All reactions utilising sodium powder were carried out in flame-dried, evacuated glassware under an inert atmosphere of high purity argon. ^{1}H NMR spectra were recorded on a Varian Gemini 200 spectrophotometer operating at 200 MHz with $CDCl_3$ as solvent.

General procedure for the synthesis of sodium reagents using naphthalene

In a typical experiment: To a cooled (−78 °C) dark green suspension of sodium powder (0.27 g, 11.7 mmol) and naphthalene (0.005 g, 0.22 mmol) in THF (60 mL), was slowly added a solution of organochloride (4.0 mmol) in THF (40 mL), and the resulting coloured mixture was stirred at −78 °C for 1 h. (The excess of sodium powder was filtered, at −78 °C, affording the coloured organosodium reagent. The activity of the solution was determined by titration.) The sodium reagent was then quenched by the slow addition, over 5 min, of the desired electrophile (H_2O, $ClSiMe_3$, Pr^iCHO or $(CH_2)_5CO$; see Table 1), and the mixture stirred overnight, gradually warming the solution to room temperature. The resulting solutions were subsequently hydrolysed (MeOH, HCl), extracted into diethyl ether and/or hexane, filtered, dried over anhydrous Na_2SO_4 and the solvent removed *in vacuo*, affording the desired product. Alternatively the desired product was distilled from the solvent. Purification, if required, of the desired product was achieved by column chromatography (silica gel, hexane–ethyl acetate 9 : 1). The purity of the isolated products were determined by ^{1}H NMR and compared to literature values.

General procedure for the synthesis of sodium reagents using polymer-supported naphthalene

In a typical experiment: A yellow–green suspension of sodium powder (0.44 g, 19.0 mmol) and polymer-supported naphthalene (0.4–8.0 mmol) in THF (60 mL) was stirred for 20 min at −78 °C. Chlorobenzene (8.0 mmol) in THF (40 mL) was then added slowly, and the resulting red mixture was stirred at −78 °C for 1 h. The mixture was quenched with the corresponding electrophile (Table 2). Work-up followed the procedure as detailed above (chromatographic purification was not required).

General procedure for the testing of the activity of spent polymer

A yellow–green suspension of sodium powder (0.44 g, 19.0 mmol) and polymer-supported naphthalene (0.4–8.0 mmol) in THF (60 mL) was stirred for 20 min at −78 °C. Chlorobenzene (8.0 mmol) in THF (40 mL) was then added slowly, and the resulting red mixture was stirred at −78 °C for 1 h. The excess of sodium powder and polymer-supported naphthalene was filtered, at −78 °C, affording a red solution of phenylsodium. The activity of the solution was determined by titration. The isolated spent polymer was washed with water (to remove any remaining sodium powder), hexane, THF, and dried *in vacuo*. The polymer was then re-treated with sodium powder, THF and chlorobenzene, to regenerate phenylsodium. This process was subsequently repeated once again with the clean, dried, spent polymer.

Acknowledgements

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