

1-1-2002

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KAYHAN, TUBA; NUGAY, NİHAN; and NUGAY, TURGUT (2002) "Metallation of Mesitylene by Organolithium Compounds in the Presence of Lithium Polyether Alkoxides," *Turkish Journal of Chemistry*. Vol. 26: No. 6, Article 18. Available at: <https://journals.tubitak.gov.tr/chem/vol26/iss6/18>

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Metallation of Mesitylene by Organolithium Compounds in the Presence of Lithium Polyether Alkoxides

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Received 20.05.2002

The catalytic effect of polyether alkoxides (PEAs) on the activity of organolithium compounds as a metallating agent studied. The sites of metallation as mono, di, tri, and gem metallation at three different benzylic positions were investigated in terms of relative yield by using gas chromatography-mass spectroscopy (GC-MS couple) techniques. The yield of the trimetallated (1,3,5-metallated) mesitylene was optimized by improving the metallation conditions. Special attention was paid to the effect of metal type, alkoxide structure, solvent polarity, temperature and also relative mole ratios of was reactants such as alkoxide to mesitylene and n-butyllithium to mesitylene on metallation reactions. It was found that when the amount of n-butyllithium increases, and the amount of polyetheralkoxide decreases, the extent of metallation increases. Moreover, the yield of the metallation of mesitylene can be increased if the reaction is carried out at higher temperatures by using n-butyllithium (n-BuLi) and sodium 2-methoxyethoxide (NaOEM) in tetrahydrofuran with a mole ratio NaOEM:n-BuLi:Mesitylene= 3:6.33:1.

Key Words: Metallation of mesitylene, Polyether alkoxide, Organolithium compounds, Regioselectivity

Introduction

The metallation reactions of hydrocarbons have been receiving considerable attention in the chemical literature since the resulting organometallic compounds are very useful in organic chemistry and polymer chemistry. The metal attached to the carbanion can be replaced by an electrophile in order to produce a low molecular weight compound^{1,2} by forming a new carbon-carbon bond³. The carbanion produced by metallation reactions can be used as an initiator for the production of a linear or star polymer via anionic polymerization^{4,5}.

The carbanion could be generated from an organic halide by a halogen/metal exchange⁶. In this case, however, disproportionations as in the case of a Wurtz-type coupling reaction, which begins with the action of the halogen of the alkyl halide rather than with the action of the anion, as a hydrocarbon base, on a

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proton, were observed⁷⁻¹⁰. The organometallic intermediate can be generated by hydrogen/metal exchange rather than by halogen/metal exchange. However, most hydrocarbons are only weakly acidic, and therefore the capability of transforming such substrate to the corresponding carbonions under mild conditions and reasonably short reaction times is highly desired^{3,6}. High C-H acidity is required in order to bring about a hydrogen metal exchange reaction between a hydrocarbon substrate and the classical reagents, phenyllithium or butyllithium⁶. In order to abstract the weakly acidic benzylic or allylic hydrogens n-butyllithium (n-BuLi) was first activated by N,N,N', N'- tetramethylethylenediamine (TMEDA), which makes it powerful in the metallation and multimetallation of benzylic or allylic stabilized hydrocarbons^{11,12}. Such carbanions can be synthesized in high yields by using this complex base. However, using TMEDA requires longer reaction times^{12,6} as well as the metallation of itself⁶.

Later, it was found that mixtures of organolithiums with alkoxides of heavier alkali metals (diversely known as LICKOR reagent, Lochmann's base or Schlosser's base) are very reactive agents for the metallation of hydrocarbons with low acidities¹³⁻¹⁶, even more reactive than the classical reagents butyl lithium or phenyllithium¹⁷. These superbases exhibit unprecedented reactivity and at the same time interesting selectivity profiles, especially when they are applied to the metallation of straight chain and branched olefins^{10,18,19}. Moreover, higher yields and higher reaction rates as well as a more selective metallation in the side chain of alkyl benzenes were achieved by Lochmann and co-workers¹⁰, using superbases containing an enhanced amount of an alkoxide with more bulky groups than t- butoxide, and are second generation superbases.

In this study, it has been tried to increase the activity of the superbase as a metallating agent by using polyether alkoxides, already used in nucleophilic polymerization²⁰, in place of TMEDA or t-BuOK for the metallation of mesitylene. Polyether lithium alkoxides with organolithium compounds were first used by our group for the metallation of toluene and they gave excellent reactivity and selectivity²¹. Special attention has been paid to the effect of the molar ratio of reaction components, reaction time, reaction temperature, basicity and bulkiness of polyether alkoxides on the metallation of mesitylene.

Experimental

Materials

n-BuLi was purchased from Janssen as a ca. 1.6 M solution in hexane. Mesitylene was supplied by the Eastman Kodak Company and was purified by distilling over CaH₂ and finally over oligo (styryl lithium) just prior to use. The solvents, cyclohexane and THF were Merck products and were purified via refluxing over sodium benzophenone under a nitrogen atmosphere. Lithium and sodium polyether alkoxides, which are tabulated in Table 1, were prepared according to the procedure given in a previous work²¹.

Table 1. Polyether alkoxides used.

Lithium 2-(2-methoxyethoxy)ethoxide	LiOCH ₂ CH ₂ OCH ₂ CH ₂ OCH ₃	LiOEEM
Lithium 2- methoxy ethoxide	LiOCH ₂ CH ₂ OCH ₃	LiOEM
Sodium 2- methoxy ethoxide	NaOCH ₂ CH ₂ OCH ₃	NaOEM
Sodium 2-(2-methoxyethoxy) ethoxide	NaOCH ₂ CH ₂ OCH ₂ CH ₂ OCH ₃	NaOEEM

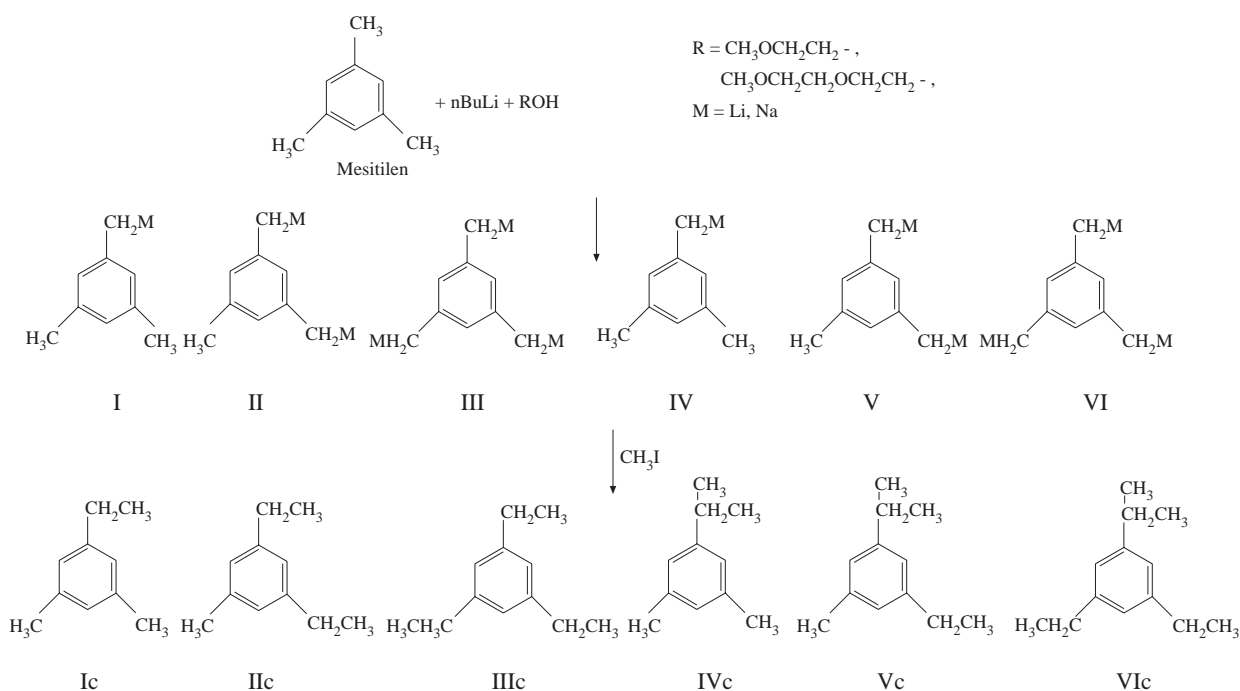
Metallation reactions

All metallation reactions were conducted in a flamed glass reactor under a nitrogen atmosphere. Reagents were transferred through syringe or stainless steel capillaries. Reactions were carried out at different temperatures. Gas chromatographic separations and characterizations of the products were performed on a Hewlett Packard GC-MS 5890 using a fused silica capillary column 30 m in length packed with PDMS (5% phenyl).

A solution of *n*-BuLi was added dropwise to a solution of polyether alkoxide and a given amount of mesitylene as a substrate through a rubber septum by means of a syringe. Soon after adding the organolithium, the mixture became heterogeneous and remained so throughout the metallation time. The reaction was completed by stirring the mixture for 24 h. After cooling to -50°C , a 2 mol excess of CH_3I was rapidly added to the solution. The mixture was left overnight then LiI was removed by filtration. The structure of soluble reaction products was determined by gas chromatography-mass spectroscopy (GC-MS) analysis.

Results and Discussion

The metallation of mesitylene with *n*-BuLi in the presence of different polyether alkoxides resulted in six different products: 1-mono metallated mesitylene (I), 1,3-dimetallated mesitylene (II), 1,3,5-trimetallated mesitylene (III), 1,1 metallated mesitylene (IV), tris- (1,1-gemmetallated-3-monometallated) mesitylene (V), and tetra (1,1-gemmetallated-3, 5-dimetallated) mesitylene (VI) (Scheme)



Scheme. Metallation of mesitylene with *n*-BuLi/polyetheralkoxide and the termination of its products with CH_3I .

The qualitative and quantitative detection of these products was achieved by using GC-MS techniques after quenching the metallated products with CH₃I, which resulted in the formation of compounds such as 1-ethyl-3, 5-dimethylbenzene (1c), 1-3-diethyl-5-methylbenzene (IIc), 1,3,5- triethylbenzene (IIIc), 3,5-dimethyl isopropyl benzene (IVc), and 3-ethyl-5-methylisopropylbenzene (Vc), 3,5-diethyl-isopropylbenzene (VIc).

A set of reactions was conducted to see the effect of solvent polarity on the metallation process of mesitylene in the presence of two different lithium-based polyether alkoxides and n-BuLi (Table 2).

Table 2. Effect of PEA:n-BuLi:mesitylene molar ratio, bulkiness of lithium based polyether alkoxides and polarity of solvents on the metallation^a of mesitylene.

PEA	Solvent	PEA:nBuLi:Mes	Yield (%)		
			I(a)	II(a)	Unreacted Substrate
LiOEM	Cyclohexane	1:1:1	-	-	100
		3:1:1	-	-	100
		3:4:1	-	-	100
	THF	3:1.5:1	-	2.9	97.1
		3:3:1	-	5.7	94.3
		3:6:1	-	19.5	80.5
		1:3:1	1.0	11.6	87.4
		5:3:1	-	-	100
LiOEEM	Cyclohexane	1:1:1	-	-	100
		3:1:1	-	-	100
		8:1:1	-	-	100
	THF	3:1.5:1	60.8	-	39.2
		3:3:1	20.3	-	79.7
		5:1.5:1	35.3	-	64.7

It is clear that, regardless of the type of lithium-based polyether alkoxide, LiOEM or LiOEEM, neither an increase in the LiOEM concentration nor an increase in n-BuLi concentration resulted in the metallation of mesitylene in cyclohexane at 26°C for 24 h. On the other hand, when the reaction was carried out with a more polar solvent than cyclohexane such as THF, it is possible to observe a small amount of metallated product at all concentrations. Within this series, while n-BuLi concentration increases as the mole ratio of LiOEM to mesitylene is kept constant, the amount of dimetallation product increases to a certain extent. However, III (c), IV (c), V (c), and VI (c) metallated products could not be obtained. The existence of a positive effect of THF on the metallation reaction can be attributed to the prevention of the aggregation of n-BuLi in cyclohexane via this solvent. It is well known that by using polar solvents with a strong solvation effect it is possible to avoid aggregations via dissociation into the more reactive tetramer and dimer, which in turn maintain the necessary contact between mesitylene and superbase causing higher reactivity of the reaction²². Furthermore, an increase in the concentration of n-BuLi in the reaction mixture resulted in increase in both reactivity and yields via decreasing the possible aggregate size.

An increase in polyether alkoxide concentrations in the reactions involving both LiOEM and LiOEEM in THF, on the other hand, caused a decrease in the extent of mesitylene metallation. The role of polyether alkoxide in metallation reactions is to increase the solvation of metal cation by acting as a chelating agent. This causes increased polarization of the carbon metal bonds, which increases the basic activity of n-BuLi. However, when an excess amount of polyether alkoxide is used they may solvate the metal cation to a high

extent so that the metal may not approach the substrate, which in turn results in the decrease in both reactivity and metallation yield.

When the effect of types of lithium-based polyether alkoxide is considered, it is clear that the metallation of mesitylene with n-BuLi/LiOEEM in THF gives much higher yields than metallation with n-BuLi/LiOEM. In addition, n-BuLi/LiOEEM gives only the monometallated product, I (c), whereas LiOEM gives only a dimetallated one, II (c). The polyether alkoxide LiOEEM has three oxygens to coordinate with the metal cation whereas LiOEM has only two. The oxygen present in LiOEEM increases its chelating ability with the metal cation giving rise to an increase in the basicity of n-BuLi together with its reactivity, as pointed out by Broaddus¹¹.

The results obtained in the metallation of mesitylene using different types of sodium-based polyether alkoxides are also tabulated in Table 3.

Table 3. Effect of PEA:n-BuLi:Mesitylene molar ratio, bulkiness of sodium based polyether alkoxides and polarity of solvents on the metallation^a of mesitylene in THF.

EA	EA:nBuLi:Mes	Yield (%)				Unreacted Substrate
		I(a)	II(a)	III(a)	VI(a)	
NaOEM	3:3.7:1	5.1	17.6	-	2.4	74.8
	3:4.7:1	7.6	18.2	-	2.8	71.4
	3:6.3:1	17.1	27.7	9.7	8.0	37.4
	6:6.3:1	-	24.3	-	-	75.7
	12:6.3:1	-	-	-	-	100
NaOEEM	5:1.5:1	63.1	-	-	-	36.9

Here, since sodium, as a more reactive metal than lithium, has at the same time a more ionic character than lithium, the metallation reaction was carried out in a more polar solvent, THF, than cyclohexane. It is clear that the same n-BuLi concentration effect, an increase in reactivity and yield resulting from a decrease in aggregate size, which was observed for the reactions conducted in the presence of lithium based alkoxide in the same solvent, exists also for this reaction. It is possible to observe the same decrease in metallation yield with an increase in polyether alkoxide that is the result of the existence of an excessive barrier between the metal and substrate, as stated above.

These results also show that the metallation of mesitylene in the presence of n-BuLi/sodium-based polyether alkoxide resulted in much higher yields in common products than metallation with n-BuLi/lithium-based polyether alkoxides. This was probably due to the more electropositive and ionic character of sodium than lithium that caused increased charge separation and higher carbanionic reactivity.^{18,19}

The effect of reaction temperature on the metallation process of mesitylene in the presence of the nBuLi/ NaOEM with a mole ratio NaEOM:n-BuLi:Mesitylene = 3:6.33:1 in THF for 24 h was finally investigated. The conditions and results upon quenching the product with methyl iodide are given in Table 4.

Upon an increase in reaction temperature from 0°C to 45°C, metallation yield increases drastically. It has also been previously reported that^{21,24} increasing the reaction temperature from room temperature to that of the refluxing solvent has a remarkable effect on the metallating power of the base (from an average charge of 1.3 at room temperature to 2.7 at reflux).

Table 4 Effect of reaction temperature on metallation^a of mesitylene with n-BuLi activated by NaOEM.

Temperature (°C)	Yield (%)				
	I(a)	II(a)	III(a)	VI(a)	Unreacted Substrate
0	17.1	27.7	9.7	8.0	37
26	11.3	34.1	16.4	14.5	23
45	17.8	29.7	38.2	13.8	-

^aReaction time: 24 h; NaOEM:n-BuLi:Mesitylene = 3:6.33:1.

Conclusion

It appears that the metallation of mesitylene in the presence of a mixture of n-BuLi and a polyetheralkoxide can only be possible when the reaction is conducted in a polar solvent such as THF.

It was observed that an increase in the amount of n-BuLi with respect to the amounts of mesitylene and polyetheralkoxide causes an increase in the yield of metallation products. The yield of the metallation can be increased if the reaction is carried out at higher temperatures.

The metallation reaction gives better yields if a maximum one to one mole ratio of alkoxide to mesitylene is employed. A further increase in the moles of alkoxide causes a decrease in metallation yield. Moreover, the structure of the alkoxide also has an impact on metallation; the longer the polyether alkoxide and the higher the chelating ability then the shorter the polyether alkoxide, the higher the solvation power of the metal, and the more basicity. In addition, sodium being more electropositive metal than lithium shows higher reactivity resulting in higher metallation yields for NaOEEM. However, it was observed that with NaOEEM only the monometallated product formed but with NaOEM the formation of the trimetallated product could also be achieved.

Acknowledgment

The authors are deeply indebted to the Boğaziçi University for the support given by Research Foundation project no 01B504.

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