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Effect of solvent and temperature on the lithium–iodine exchange of primary alkyl iodides: reaction of *t*-butyllithium with 1-iodooctane in heptane–ether mixtures

William F. Bailey *, Jason D. Brubaker, Kevin P. Jordan

Department of Chemistry, University of Connecticut, 55 North Eagleville Rd., Storrs, CT 06269-3060, USA

Abstract

The reaction of 1-iodooctane, a representative primary alkyl iodide, with *t*-BuLi at 0 °C in solvent systems composed of heptane and four dialkyl ethers in various proportions has been investigated. Coupling and elimination are unavoidable side reactions that accompany lithium–iodine exchange when the reactions are conducted at 0 °C. The exchange reaction, which is slow in pure hydrocarbon solvent, is significantly facilitated by the presence of essentially catalytic quantities of an ether co-solvent. An optimal ether–heptane ratio for each of the ethers surveyed maximizes the extent of lithium–iodine exchange between 1-iodooctane and *t*-BuLi but in no case does the yield of octyllithium, assayed as octane, exceed ∼90% when reactions were conduced at 0 °C. At lower temperatures, in a solvent system composed of heptane–MTBE (19:1 by volume), side reactions are suppressed and the yield of octyllithium approaches quantitative.
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1. Introduction

Since its discovery in the late 1930s by Wittig [1] and Gilman [2], the remarkably rapid, reversible metathesis reaction known as the lithium–halogen exchange has been widely employed for replacement of a bromine or iodine atom in a substrate with lithium and the vast primary literature detailing the synthetic utility of this process for the preparation of aryllithiums, vinyllithiums, cyclopropyllithiums and other relatively stable organolithiums has been extensively reviewed [3–5]. However, the preparation of simple alkyllithiums by lithium–halogen exchange has historically been viewed as more problematic due to the unfavorable position of the exchange equilibrium [6] and competing reactions such as β-elimination and Wurtz-type coupling [3–5]. Indeed, it is only within the past decade or so that it has proved possible to reliably prepare primary alkyl-

lithiums by the low-temperature lithium–iodine exchange reaction between a primary alkyl iodide and *tert*-butyllithium (*t*-BuLi) [7,8].

The success of the lithium–halogen exchange for the preparation of primary alkyllithiums (Scheme 1) is crucially dependent on the choice of halide, alkyllithium, and solvent. As noted elsewhere [9], alkyl iodides, rather than bromides, must be used to ensure that the reaction proceeds cleanly, most likely via a 10-I-2 ate-complex intermediate or transition state [10]: addition of *t*-BuLi to a primary alkyl bromide often initiates radical-mediated processes [9]. The use of *t*-BuLi establishes a favorable exchange equilibrium [6] and, when 2 M equivalent of the reagent are employed, the exchange is rendered essentially irreversible since, as illustrated in Scheme 1, the second equivalent of the reagent rapidly consumes the *t*-BuI co-product [11]. Because the lithium–iodine exchange appears to involve a dimeric *t*-BuLi solvate [7], the best medium for the preparation of primary alkyllithiums by lithium–iodine exchange is a hydrocarbon solvent system that contains a quantity of a simple alkyl ether, such as Et$_2$O or the like, in which

* Corresponding author. Tel.: +1-860-486-2163; fax: +1-860-486-2981.

E-mail address: bailey@uconn.edu (W.F. Bailey).
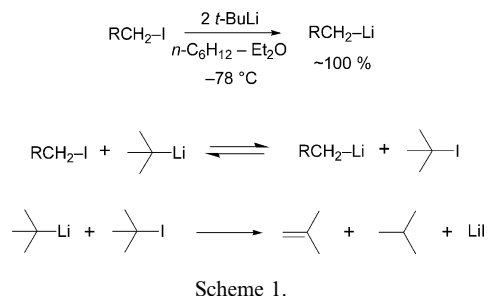
Scheme 1.

the t-BuLi is predominantly dimeric [12]. The overall process depicted in Scheme 1 is quite exothermic; for this reason, the exchange is typically conducted at low temperature to avoid side reactions [7,8].

2. Results and discussion

It occurred to us that it might be possible to prepare primary alkyllithiums at temperatures significantly higher than −78 °C by attenuation of the reactivity of t-BuLi through the simple expedient of employing a predominantly hydrocarbon medium, in which the reagent is tetrameric [13] and essentially unreactive toward an alkyl iodide at low temperature [9], containing a small quantity of an ether co-solvent that would serve to provide the reactive dimeric t-BuLi solvate. As demonstrated by the results presented below, the efficiency of the lithium–iodine exchange between t-BuLi and a primary alkyl iodide is strongly dependent on the quantity of ether in the reaction medium and the temperature at which the reaction is conducted.

Exploratory experiments were conducted at 0 °C in solvent systems composed of heptane–dialkyl ether in various proportions using 1-iodooctane (**1**) as a representative primary alkyl iodide. Diisopropyl ether, methyl t-butyl ether (MTBE), THF, and tetrahydropyran (THP) were surveyed as representative ether co-solvents. As detailed in Section 4, solutions of **1** in heptane–ether solvent were added at 0 °C under an atmosphere of argon to a slight excess (i.e. 2.2 M equivalent) of t-BuLi in heptane and the resulting 0.1 M reaction mixtures were allowed to stand at 0 °C for an additional 20 min, which ensured complete reaction, before quench with water. Crude product mixtures were analyzed by capillary GC and by GC–MS affording base-line

separation of the four products (**2–5**), illustrated in Scheme 2, that accounted for the total material balance. Octane (**2**), 1-octene (**3**), and hexadecane (**5**) were identified by comparison of their retention times and mass spectra to those of authentic samples; 2,2-dimethyldecane (**4**) was identified on the basis of its reported mass spectrum [14]. The results of these experiments are summarized in Table 1.

Cursory inspection of the data (Table 1) reveals that in no case was octane (**2**) the exclusive reaction product. Thus, under the conditions surveyed in these experiments, it is not possible to effect clean, quantitative exchange; elimination and coupling reactions accompany the conversion of **1** to octyllithium. While this result might have been anticipated on the basis of prior art [5], what was not expected was the profound effect of very small quantities of ether on the course of the reaction of t-BuLi with **1**. Comparison of the result of the reaction of t-BuLi with **1** in pure heptane (Table 1, entry 1) with that of the reaction conducted in a predominantly heptane medium containing only 0.5% of (i-Pr)$_2$O (Table 1, entry 5) reveals that the yield of octane (**2**) is improved from 52 to 75%. It might be noted that this small quantity of (i-Pr)$_2$O is equivalent to 0.16 mmol of ether per 1 mmol of t-BuLi. Since the dimeric t-BuLi solvate requires a ratio of two molecules of ether per molecule of t-BuLi [12], the exchange reaction is essentially catalytic in ether. Moreover, while a significant quantity of starting iodide (ca. 18%) remains after treatment of **1** with t-BuLi in pure heptane for 20 min at 0 °C (Table 1, entry 1), the presence of even small amounts of ether co-solvent leads to complete consumption of the iodide.

For each of the ethers surveyed, the yield of octane (**2**) produced in the reaction of t-BuLi with **1** fluctuates in a surprisingly consistent fashion as the proportion of ether in the reaction medium is varied. These trends are perhaps best appreciated by reference to Fig. 1: a qualitatively similar curve is observed for each ether when the yield of octane is plotted versus the ether–heptane solvent ratio. The shape of the plots can be understood by consideration of two extreme conditions: (a) conducting the reaction in pure heptane, and; (b) conducting the reaction in the presence of a high proportion of ether. When no ether is present in the reaction medium, the t-BuLi is predominantly tetra-
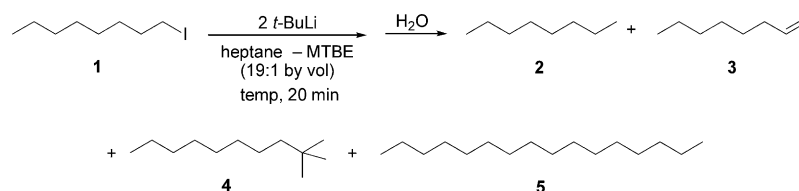
Scheme 2.

Table 1
Reaction of 1-iodooctane (**1**) with *t*-BuLi at 0 °C in heptane–ether solvent
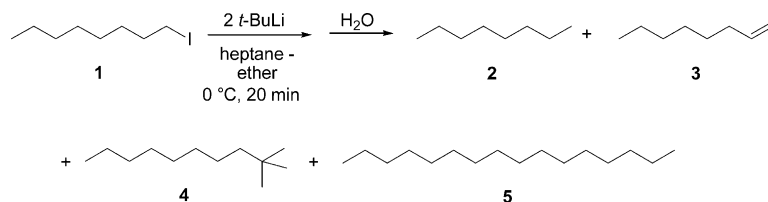
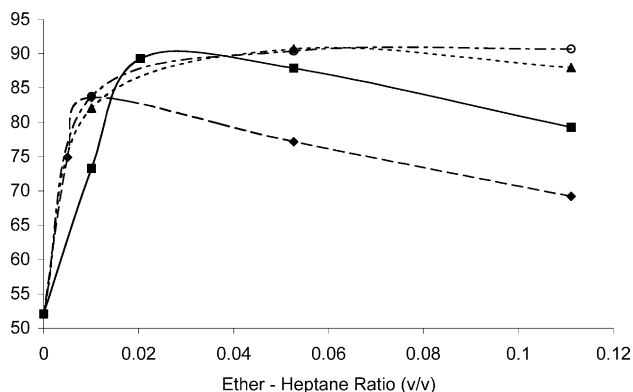| Entry	Ether	Heptane–ether ratio (by volume)	Products				
			2	**3**	**4**	**5**	Recovered **1**
1	None		52.1	3.5	20.0	3.8	17.6
2	(*i*-Pr)$_2$O	9:1	69.2	4.3	14.2	12.3	
3		19:1	77.2	3.7	16.3	2.9	
4		99:1	83.6	5.0	8.8	2.6	
5		199:1	74.9	4.5	16.4	2.9	
6	MTBE	9:1	88.0	2.4	7.7		1.9
7		19:1	90.7	2.2	7.1		
8		99:1	82.1	3.3	12.9		1.7
9	THF	9:1	79.3	2.5	4.2	14.0	
10		19:1	87.9	5.2	5.5	1.4	
11		49:1	89.3	3.0	7.7		
12		99:1	73.3	3.4	7.9	0.9	14.5
13	THP	9:1	90.7	3.2	6.0	0.7	
14		19:1	90.4	2.7	6.9		
15		99:1	83.8	3.7	12.5		

Fig. 1. Plot of yield of octane (**2**) vs. ether–heptane ratio in reaction of 1-iodooctane (**1**) with *t*-BuLi (Scheme 1). Legend: ◆, (*i*-Pr)$_2$O; ▲, MTBE; ■, THF; ○, THP.

meric [13]; consequently, side reactions such as coupling to give **4** and elimination to give **3** are favored over the exchange process. Conversely, when the concentration of ether is high, *t*-BuLi is likely dimeric, favoring the exchange process, but the reagent is also more likely to be consumed by abstraction of a proton from the ether solvent; consequently, consumption of octyllithium by coupling with excess 1-iodooctane to give **5** becomes problematic. Thus, for each of the ethers that were

studied, there is an optimal ether–heptane ratio that maximizes the extent of lithium–iodine exchange to give octyllithium. However, in no case does the yield of octyllithium, assayed as octane, exceed ∼90% when reactions were conduced at 0 °C (Fig. 1 and Table 1).

The large variation in the yield of octane at high ether concentration for the four heptane–ether solvent systems surveyed is striking (Fig. 1). The fairly rapid consumption of *t*-BuLi by reaction with various ethers at elevated temperatures is well known [4] and the half-life of the reagent in a number of ether solvents has been measured by Stanetty and coworkers [15]. The particularly rapid consumption of *t*-BuLi at 0 °C by reaction with THF [15,16] is apparent from the data summarized in Fig. 1 and (*i*-Pr)$_2$O, although not investigated by Stanetty, appears to react even more quickly with *t*-BuLi than does THF. In this connection, it might be noted, as suggested some time ago by Meyers [17], that THP is superior to THF as a solvent for reactions involving organolithium reagents in general and *t*-BuLi in particular since it does not react as rapidly as does THF with these reagents. In the course of the present study, we observed that the concentration of solutions of *t*-BuLi in heptane–MTBE (19:1 by volume) remain fairly stable for considerable periods of time at 0 °C: the concentration of such a solution decreases less than 13% over a period of 70 min and this is consistent with the

relatively high yield of octane observed in experiments employing heptane–MTBE solvent.

It appears that side reactions such as coupling and elimination are unavoidable when the lithium–iodine exchange reaction between a primary alkyl iodide such as **1** and *t*-BuLi is run at 0 °C. In order to study the effect of temperature on the lithium–iodine exchange, the reaction of 1-iodooctane with *t*-BuLi in heptane–MTBE (19:1 by volume) was investigated at several temperatures ranging from +10 to −78 °C. The results of these experiments, which are summarized in Table 2, demonstrate that the yield octyllithium, assayed as octane, increases monotonically as the temperature of the reaction is lowered.

3. Conclusions

Coupling and elimination are unavoidable side reactions when the lithium–iodine exchange reaction between 1-iodooctane (and presumably other primary alkyl iodides) and *t*-BuLi is conducted at 0 °C. The exchange reaction is slow in pure hydrocarbon solvent but even small quantities of an ether co-solvent leads to an improvement in the yield. There is an optimal ether–heptane ratio for each of the four ethers surveyed that maximizes the extent of lithium–iodine exchange between 1-iodooctane and *t*-BuLi but in no case does the yield of octyllithium, assayed as octane, exceed ~ 90% when reactions were conduced at 0 °C. At temperatures lower than 0 °C, in a solvent system composed of heptane–MTBE (19:1 by volume), side reactions are suppressed and the yield of octyllithium approaches quantitative.

4. Experimental

4.1. General

Heptane was distilled from a dark blue solution of sodium–benzophenone–tetraglyme; ethers were freshly distilled from dark blue solutions of sodium–benzophenone. The concentration *t*-BuLi in heptane was determined prior to use by titration with *sec*-butanol using 1,10-phenanthroline as an indicator according to the method of Watson and Eastham [18].

4.2. Reaction of 1-iodooctane with t-BuLi at 0 °C

A flame-dried, septum-capped, 10 ml pear-shaped flask was kept under a positive pressure of argon and charged with ca. 1 mmol of 1-iodooctane. A separate flame-dried, septum-capped, 25 ml round-bottomed flask was kept under a positive pressure of argon and charged with 2.2 mmol equivalents of *t*-BuLi in heptane. The total amount of solvent used for each reaction was determined by calculating the total amount of heptane and dialkyl ether needed to make a 0.1 M solution of 1-iodooctane in the desired solvent ratio. The 1-iodooctane was dissolved in half of the solvent volume including all of the ether and the appropriate amount of heptane. The *t*-BuLi solution was diluted with the remaining heptane, then cooled to 0 °C in an ice-water bath, and the 1-iodooctane solution was added dropwise via a Teflon cannula over a period of 10 min. Upon completion of the addition, the mixture was allowed to stir at 0 °C for an additional 20 min, then quenched with water. The organic layer was washed with water, dried (MgSO$_4$), and filtered. The crude reaction product was analyzed by GC on a 25-m × 0.2-mm × 0.33-μm DB-5 crosslinked 5%-phenyl methyl silicone capillary column

Table 2
Reaction of 1-iodooctane (**1**) with *t*-BuLi in heptane–MTBE (19:1 by volume)
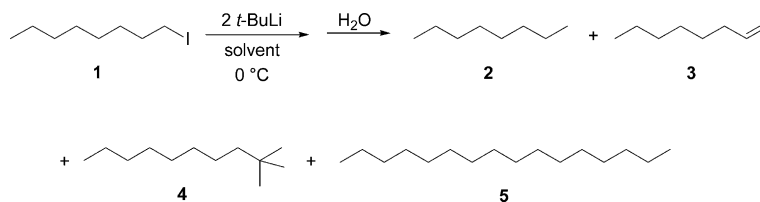
Entry	Temperature (°C)	Products					
		2	**3**	**4**	**5**	Recovered **1**	
1	10	86.4	4.2	7.1	0.5	1.8	
2	0	90.7	2.2	7.1			
3	−10	91.7	2.3	5.3			
4	−20	94.1	2.0	3.9			
5	−40	96.6	1.3	2.1			
6	−78	98.5	~ 0	1.5			

(50 °C for 5 min and 1 °C min^{-1} to 58 °C followed by 10 °C min^{-1} to 250 °C for 5 min) and by GC–MS on a 25-m × 0.2-mm × 0.25-μm HP-5 crosslinked 5% phenyl methyl silicone capillary column (100 °C for 5 min and 10 °C min^{-1} to 250 °C for 5 min). Octane (**2**), 1-octene (**3**), and hexadecane(**5**) were identified by comparison of their retention times and mass spectra to those of authentic samples; 2,2-dimethyldecane (**4**) was identified on the basis of it reported mass spectrum [14].

Acknowledgements

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