

Solvent and electronic effects on kinetics of cyclization of thermolabile aryllithium reagents. A comparison between 1-bromo-2-(2-bromoethyl)benzene and 4,5-dimethoxy-1-bromo-2-(2-bromoethyl)benzene

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Abstract: A dramatic solvent effect on the stability and kinetics of intramolecular cyclization is described for the aryllithium species generated from 2-bromo-4,5-dimethoxy-(2-bromoethyl)benzene. The aryllithium generated by the halogen-metal exchange reaction with *n*-butyllithium, is stable for > 1h when generated at -95 to -100 °C in diethyl ether/hexane and can be trapped with electrophiles. However, when the reaction is conducted in a THF/hexane mixture, the intermediate undergoes instantaneous intramolecular cyclization to afford 4,5-dimethoxybenzocyclobutene. By comparison, the corresponding 1-lithio-2-(2-bromoethyl)-benzene intermediate is stable for >1h in either THF/hexane or diethyl ether/hexane at -95 to -100 °C. These results indicate that substituent effects as well as the nature of aggregation of these intermediates play key roles in determining the reaction pathway of functionalized aryllithium intermediates when quenched with electrophiles.

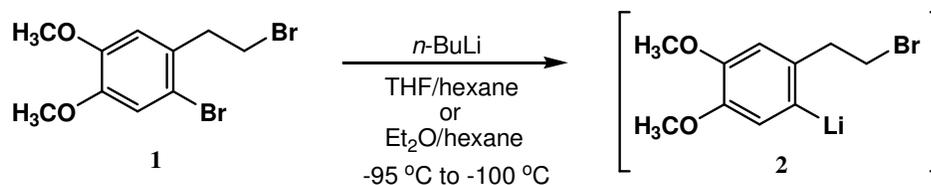
Keywords: Functionalized aryllithium; lithium-halogen exchange; kinetics; solvent effects

1. Introduction

The halogen-lithium exchange reaction has been widely accepted for decades as a powerful tool for organic synthesis.¹⁻⁴ While the reaction has been thoroughly studied, questions remain pertaining to the role of solvent effects on reaction kinetics and pathway. While solvent effects in halogen-lithium exchange reactions are relatively common,^{3, 5-6} there have been varying explanations for the effect.⁷⁻¹³ A quantum chemical study by Jedlicka, *et al.*¹⁴ indicates that the causative factor of the acceleration effect is tight binding of the solvent to the transition state and concomitant destabilization of the reactant adduct without a change in aggregation, while others have argued that lower degrees of solvent-organometallic species aggregation account for the observed rate accelerations and enhanced reactivities akin to those observed through the use of nitrogen bases such as TMEDA and DABCO and other additives, such as HMPA, to alter reaction pathways.^{3, 15-20} The use of functionalized aryllithium reagents

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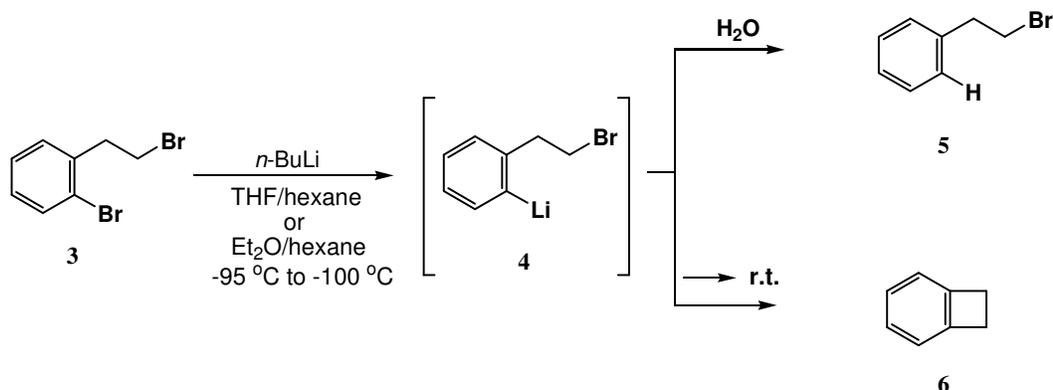
applied to the construction of both heterocyclic and carbocyclic ring systems has likewise proven a valuable synthesis technique, most notably through the use of Parham cyclization chemistry.^{4, 21-24} During the course of studies on the generation and subsequent reactivity of the aryllithium **2** derived from 1-bromo-2-(2-bromoethyl)-4,5-dimethoxybenzene **1**,²⁵ a dramatic solvent effect pertaining to stability and reaction kinetics was observed between diethyl ether and THF as the reaction medium.



Scheme 1 - Halogen-metal exchange of 1-bromo-2-(2-bromoethyl)-4,5-dimethoxybenzene

2. Results and Discussion

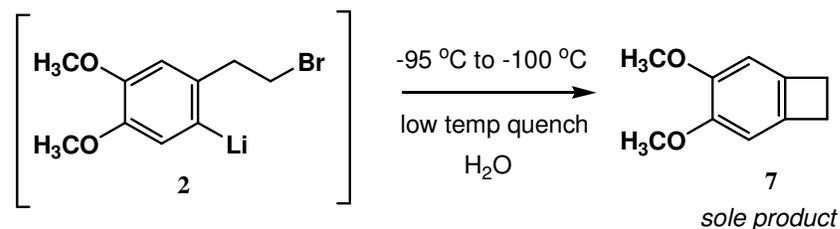
The halogen-lithium exchange reaction between *n*-butyllithium and 1-bromo-2-(2-bromoethyl)-benzene **3** has been well studied.²⁶ The resulting aryllithium derivative **4**, when generated in a THF/hexane or Et₂O/hexane²⁷ mixture at -95 °C to -100 °C, is stable for >1 h based on aliquotting experiments (< 5% benzocyclobutene formation after 30 min). The aryllithium **4** can then be quenched with a variety of electrophiles at low temperature followed by warming to afford product **5** (using water as the quenching agent) or **4** can simply be permitted to warm to ambient temperature to afford benzocyclobutene **6** after an intramolecular nucleophilic displacement reaction.



Scheme 2 - Elaboration of stabilized aryllithium **4**

However, when conducting the same reaction with the dimethoxy analog **1** in a THF/hexane mixture as previously described, only the benzocyclobutene derivative **7** could be detected upon drawing the first aliquot, immediately after completion of the addition of *n*-butyllithium at -95 °C to -100 °C.

cyclization of thermolabile aryllithium reagents based on 1-bromo-2-(2-bromoethyl)benzenes

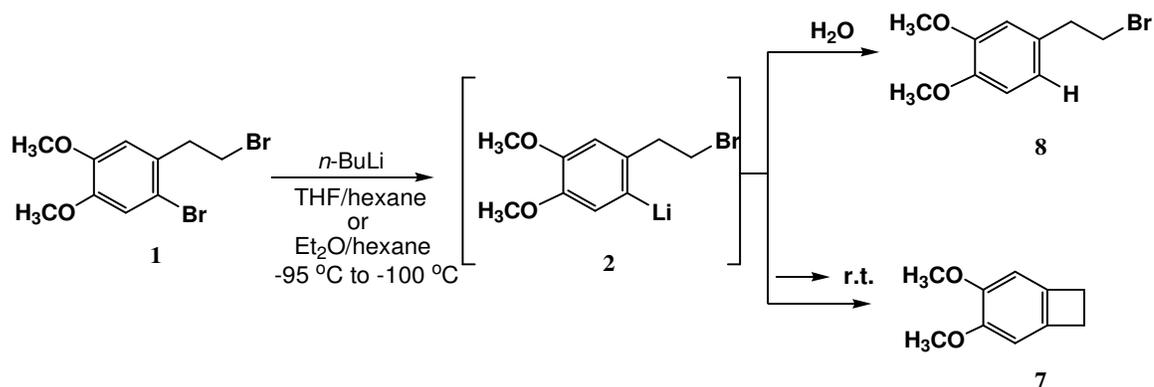


Scheme 3 - Cyclization of dimethoxyaryllithium **2**

When the halogen-lithium exchange reaction between *n*-butyllithium and **1** was conducted in the same fashion with the exception of substituting diethyl ether for THF as the primary solvent, aliquotting experiments indicated that the aryllithium **2** was stable at $-100\text{ }^{\circ}\text{C}$ with little ($<10\%$) benzocyclobutene formation after 1h and could be trapped with electrophiles. This observation was noted by Hergueter, *et. al.* in their description of the preparation of 3,4-dihydroisoquinolines via the halogen-lithium exchange reaction of **1** and subsequent reaction with nitriles using diethyl ether as the reaction medium.²⁸

Table 1 % Benzocyclobutene at $-100\text{ }^{\circ}\text{C}$

Intermediate	t = 0min	t = 20min	t = 40min	t = 60 min
2				
Et ₂ O	0	3	4	9
THF	>99	-	-	-
4				
Et ₂ O	0	<1	3	4
THF	0	<1	3	8



Scheme 4 - Elaboration of stabilized dimethoxyaryllithium **2**

3. Conclusion

These findings indicate that solvent acceleration effects can be dependent on the electronic nature of aromatic ring substitution within a chemical series in addition to any aggregation effect. Furthermore, the nature of aromatic substituents and substitution patterns which contribute to the electron density at the site of the aromatic C-Li bond dictate reactivity. Future efforts to ascertain a Hammett relationship within this series will be reported in due course.

4. Experimental

THF was dried over benzophenone ketyl prior to use. Diethyl ether and hexane were dried over activated molecular sieves for 24h prior to use. ^1H NMR (300 MHz) and ^{13}C spectra (75 MHz) were recorded on a Varian Gemini 300 MHz spectrometer in CDCl_3 using tetramethylsilane (TMS) as internal reference. All chemical shifts (δ) were reported in ppm from internal TMS.

4.1. Procedure for aliquotting experiments and analysis of products.

To a solution of the requisite 1-bromo-2-bromoethylarene (**1** or **3**; 20 mmol) in dry THF (125 mL) and hexane (25 mL) or dry Et_2O (125 mL) and hexane (25 mL) under N_2 at -100°C ($\text{N}_{2(1)}/\text{Et}_2\text{O}$) in a 3-necked 250 mL round-bottom flask equipped with a pressure-equalizing addition funnel, overhead stirrer with Teflon paddle, and a low temperature thermometer /gas inlet adapter, 1.1 equivalent of *n*-butyllithium (3.92 mL; 1.4 M in hexane; 5.49 mmol) was added at such a rate that a strong exotherm was not produced. Immediately after the addition was completed (< 5 min), 1 mL aliquots were drawn every 20 minutes over a 1h period. Each aliquot was quenched in water (5 mL) and extracted with Et_2O (10 mL). The organics were separated, dried (MgSO_4), filtered, and concentrated *in vacuo*, and analyzed by comparing ^1H NMR (300 MHz) integration ratios for the methylene resonances of the cyclized versus non-cyclized product.

Phenylethylbromide (5): ^1H NMR (300 MHz, in CDCl_3) δ : 3.15 (2H, t, CH_2 , $J=7.0$ Hz); 3.53 (2H, t, CH_2 , $J=7.0$ Hz), 7.15-7.34 (5H, m, ArH).

Benzocyclobutene (6): ^1H NMR (300 MHz, in CDCl_3) δ : 3.18 (s, 4H, CH_2), 7.04 (2H, BB' part of AA'BB' system, quasi d, ArH, $J=2.9$ Hz), 7.17 (2H, AA' part of AA'BB' system, quasi d, ArH; $J=2.9$ Hz).

4,5-dimethoxybenzocyclobutene (7): ^1H NMR (300 MHz, in CDCl_3): δ : 3.14 (4H, s, CH_2); 3.89 (6H, s, OCH_3), 6.63 (2H, s, ArH).

4-(2-bromoethyl)-1,2-dimethoxybenzene (8): ^1H NMR (300 MHz, in CDCl_3): δ : 3.08 (2H, t, CH_2 , $J=7.3$ Hz), 3.52 (2H, t, CH_2 , $J=7.3$ Hz), 3.85 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 6.70-6.98 (m, 3H, ArH).

cyclization of thermolabile aryllithium reagents based on 1-bromo-2-(2-bromoethyl)benzenes

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