

Titration of alkyllithiums with a simple reagent to a blue endpoint

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Abstract

Reaction of readily available *N*-benzylbenzamide (**1**) with a slight excess of BuLi produces a deep blue dianion. Under suitable conditions (THF, -40°C), **1** may be used as a stoichiometric reagent to titrate *n*-BuLi, *s*-BuLi, and *t*-BuLi with good precision. Less reactive alkyllithiums (MeLi and MeLi · LiBr), aryllithiums, and LDA may be titrated at higher temperatures (-20 to 0°C). Titres are comparable to those obtained using the Gilman double titration method, and there appears to be no interference from alkoxides. © 1997 Elsevier Science S.A.

1. Introduction

Over the past few decades, organolithiums have become standard reagents in organic synthesis (see for example Refs. [1,2]). Since these reagents are usually not isolated but used in solution, it is important to be able to determine their concentration. For this purpose, a variety of methods have been developed (for reviews see Ref. [3]). These methods typically involve (a) titration of the alkyllithium with a standard alcohol (e.g. *s*-BuOH) solution in the presence of an indicator (e.g. 1,10-phenanthroline [4], 4-phenylbenzylidene benzylamine [5]), (b) titration using a stoichiometric quantity of a reagent (e.g. 2,5-dimethoxybenzyl alcohol [6], diphenylacetone tosylhydrazone [7], biphenylmethanol [8], *N*-pivaloyl-*o*-toluidine [9], 1-pyrenylacetic acid [10]) which shows a color change as a dianion is formed or which undergoes some other color change (e.g. diphenyl ditelluride [11]), or (c) a 'double titration' which allows calculation of the alkyllithium concentration as the difference between the total base concentration and the 'free base' (hydroxide and alkoxide) concentration [12].

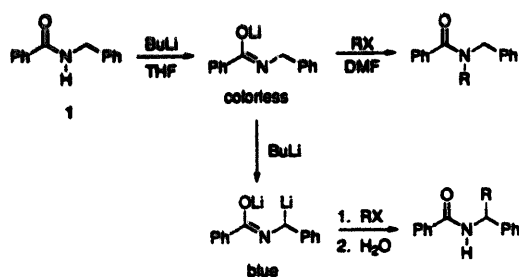
While there are a wide selection of methods to titrate alkyllithiums, there still seems to be some reluctance by researchers to use them on a routine basis. There are various reasons for the lack of widespread acceptance of any one particular method. In our laboratory, the Gilman double titration [12] is the method of choice since it provides information about both the alkyllithium titre

and the alkoxide/hydroxide titre. However, it can be time-consuming. Titration against an alcohol is a good expedient alternative but comes with the inherent limitations of preparing and keeping an alcohol solution of known exact concentration. Titrations with stoichiometric reagents are most convenient but are often unsatisfactory because the yellow–orange–red endpoints may not be very distinct, particularly when the alkyllithium solution is itself yellow–orange. Availability of the reagent may also be an issue. We now report a method with the convenience of a readily available stoichiometric reagent and an endpoint which is easily detected.

2. Results and discussion

As part of a project on the reduction of amides [13], we needed to prepare some 3° amides by *N*-alkylation of *N*-benzylbenzamide (**1**, Scheme 1). When these reactions were carried out, it was noticed that when one equivalent of BuLi was added to benzamide **1**, the solution was colorless but when a slight excess of BuLi was used, the solution became a deep blue reminiscent of Na/benzophenone ketyl or M/NH₃ reactions. A search of the literature revealed that the dianion of **1** had been used in 1978 to prepare alkylated benzylamines and was reported as being deep blue [14]. Furthermore, the researchers involved had advocated (in an advertisement in *Aldrichimica Acta* [15]) using **1** as an indicator for titrating alkyllithiums against a 1.00 M solution of *s*-BuOH in benzene; the endpoint was sig-

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Scheme 1.

naled by a change in color from blue to red to colorless. However, since this method seems to have been overlooked by chemists (this reagent is not mentioned in any of the recent reports on alkyllithium titrations [3,5–11]; possibly because 1,10-phenanthroline had already been established as a good indicator in such titrations) and, since **1** is a crystalline, non-hygroscopic, readily available material (Aldrich #20,101-4; Lancaster #0800), the possibility of using it as a stoichiometric titrant seemed worthy of further investigation.

After some experimentation, it was found that a solution of **1** in THF (it is only sparingly soluble in ether) could be titrated to a blue endpoint using BuLi with good precision. The main variable considered was temperature: at 0°C or room temperature, the endpoint was very distinct but faded after a few seconds to minutes; at –78°C, the blue color persisted well but was slow to develop. At –40°C, the endpoint was distinct and the blue color persisted (30–40 min).

We titrated a number of alkyllithiums using **1** under these conditions and compared the results to titres obtained using the Gilman [12] double titration (Table 1). It is apparent from these results that there is generally excellent agreement between the Gilman double titration results and the results using **1**. It is noteworthy that different samples of BuLi containing widely varying amounts of ‘free base’ all gave good results, suggesting that there is little or no interference from such impurities. Samples of *s*-BuLi and *t*-BuLi also gave good results when titrations were carried out at –40°C. For MeLi and MeLi · LiBr, the blue color was very slow to develop at –40°C; satisfactory results were obtained at –20°C and 0°C, respectively. Similarly, PhLi and 4-MeOC₆H₄Li were best titrated at 0°C. The higher temperatures required for these alkyllithiums and aryl-lithiums is understandable given their lower basicity/reactivity.

We also investigated the use of **1** to titrate lithium amide bases and Grignard reagents. LDA could be titrated with good precision but LiHMDS and NaHMDS did not produce a blue color even when added in large excess. This difference in behavior between LDA and bis(trimethylsilyl)amides is likely due to the very large difference in base strengths (*pK_a* of 35.7 for *i*-Pr₂NH vs. 29.5 for HMDS [2]). Grignard reagents (e.g. *n*-BuMgBr, *i*-PrMgCl) also did not produce a blue color with **1**, reflecting their much poorer metalating ability in comparison with alkyllithiums.

It is interesting to note that the λ_{max} for a number of

Table 1
Titration of alkyllithiums with *N*-benzylbenzamide (**1**)

Sample ^a	Nominal concentration (M)	Titre using Gilman double titration ^b			Titre using 1 (M) ^c
		Total (M)	Free (M)	RLi (M) ^d	
BuLi A ^e	1.6	1.66	0.14	1.52 ± 0.02	1.48 ± 0.03
BuLi B ^f	1.6	1.58	0.88	0.70 ± 0.06	0.73 ± 0.01
BuLi C ^g	1.6	1.68	0.45	1.23 ± 0.02	1.20 ± 0.04
BuLi	2.5	2.77	0.23	2.54 ± 0.03	2.49 ± 0.03
<i>s</i> -BuLi	1.3	1.01	0.45	0.56 ± 0.04	0.57 ± 0.02
<i>t</i> -BuLi	1.7	1.84	0.07	1.77 ± 0.03	1.75 ± 0.03
MeLi · LiBr ^h	1.5	0.90	0.52	0.38 ± 0.04	0.37 ± 0.02
MeLi ⁱ	1.4	1.68	0.15	1.53 ± 0.06	1.52 ± 0.01
PhLi ^{h,i}	1.2	1.25	0.03	1.22 ± 0.05	1.20 ± 0.01
4-MeOC ₆ H ₄ Li ^{h,i}	1.2	0.68	0.05	0.63 ± 0.02	0.62 ± 0.01
LDA ^{i,k}	0.8	—	—	—	0.81 ± 0.01

^a All alkyllithium solutions were commercial samples in Sureseal[®] bottles obtained from Aldrich Chemical Company.

^b Titrations were carried out according to Ref. [12] using 1,2-dibromoethane.

^c The titre is reported as $\bar{x} \pm \sigma_{n-1}$ for triplicate determinations.

^d Concentrations reported are the average triplicate determinations. Errors are reported as the sum of σ_{n-1} for each of the two titrations involved.

^e A freshly opened bottle.

^f A 2 year-old bottle containing considerable amounts of sediment.

^g A 6 month-old bottle.

^h Titration with **1** was carried out at 0°C.

ⁱ Titration with **1** was carried out at –20°C.

^j Prepared according to Ref. [1], p. 24.

^k Prepared by addition of *n*-BuLi to *i*-Pr₂NH in THF at –20°C.

other indicator dianions have been reported, and are in the range 440 (*N*-pivaloyl-*o*-benzylaniline) [9] to 483 nm (4-biphenylmethanol) [8]; these numbers are consistent for yellow–orange solutions. Indicators with red end-points presumably would have $\lambda_{\max} \approx 490\text{--}500\text{ nm}$ [16]. By comparison, the blue dianion from **1** exhibits $\lambda_{\max} = 573\text{ nm}$ (THF, 0°C).

In summary, *N*-benzylbenzamide (**1**) may be used as a stoichiometric reagent to titrate alkylolithiums, aryllithiums and LDA in a simple straightforward manner with good precision and accuracy with minimal interference from alkoxides. The ready availability of **1** (or the inexpensive synthetic precursors to it), the ease with which it is handled, and the distinct blue endpoint which arises from it make it a very attractive reagent.

3. Experimental section

3.1. *N*-benzylbenzamide (**1**)

Benzylamine (10.4 ml, 95 mmol) was added to a solution of benzoyl chloride (11 ml, 95 mmol) and Et₃N (20 ml, 143 mmol) in CH₂Cl₂ (200 ml). After stirring at room temperature for 2 h, the mixture was washed with 1 M HCl (2 × 50 ml) and brine (50 ml). Drying and concentration of the organic layer afforded **1** as a yellow solid; recrystallization from hexane/EtOH gave white needles (17.6 g, 88%). M.p. 105–106°C; lit. [17] m.p. 105–106°C.

3.2. General procedure for titration of alkylolithiums using **1**

A dry 25 ml two-necked flask fitted with a magnetic stirring bar, an Ar inlet and septum is charged with **1** (100–300 mg) and dry (Na/Ph₃CO) THF (10 ml). The solution is cooled to –40°C (dry ice/ethylene glycol:H₂O, 1:1) and the alkylolithium solution is added dropwise via syringe. The colorless solution turns blue as each drop of RLi solution hits it but the color quickly (< 1 s) dissipates; the endpoint is indicated by a persistent light blue color. At this point, the addition of a

single drop of RLi solution gives an intense ink-blue color.

Acknowledgements

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