

A Facile Method for the Titration of Organolithium Reagents using Naphtylamine or Naphtylmethylamine as Indicators

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Abstract

A simple method for the titration of alkyllithiums with *sec*-butanol, using naphtylamine or naphtylmethylamine as color indicator, is reported. Both amines gave sharp-end points, easily determined by color changes from brown to yellow (naphtylamine) and from green to colorless (naphtylmethylamine). The accuracy of the determination was in accordance with the values obtained by a standard method.

Keywords: Organolithium titration, naphtylamine, naphtylmethylamine.

1. Introduction

Organolithium reagents (RLi), such as *n*-butyllithium, are very useful reagents in organic synthesis. Their use is vital in acid-base reactions and in the preparation of other organometallic compounds. For example, they play a key role in the formation of organo cuprate reagents (i.e. R_2CuLi , $RCu(CN)Li$, $R_2Cu(CN)Li_2$). The knowledge of the quality and quantity of the alkyllithium reagents (RLi) is fundamental in the formation of these copper species. It is not a good practice to assume that a concentration given on a commercially alkyllithium is correct, this concentration might be off-specification (i.e low or high titre) for a number of reasons. Depending on this variation, insufficient or excessive amounts of the alkyllithium reagent can be added into a reaction flask and, in both cases, it can lead to detrimental consequences. For this reason, a rapid and accurate determination of the concentration of these organometallic reagents is desirable.

A wide variety of methods and indicators, for the determination of the concentration of several group IA and group IIA organometallic reagents, have been developed. Typically, these methodologies can be classified [1, 2] into four categories: 1) Titration of the organometallic species with a standard alcohol (e.g. *sec*-BuOH), in the presence of a polycyclic aromatic amine, such as 1,10-phenatroline, 2,2'-biquinoline or 2,2'-bipyridine, which serve as an indicator forming a colored

charge-transfer complex with the alkyllithium [3]. 2) Deprotonation of an indicator compound such as triphenylmethane [4], *N*-benzylidenebenzylamine [5], *N*-phenyl-1-naphtylamine [6] or 9-methylfluorene [7] by the organometallic reagent to generate a colored anion and titration with *sec*-butanol or a standard solution of benzoic acid. 3) Titration of the organometallic species with stoichiometric amounts of compounds such as 2,5-dimethoxybenzyl alcohol [8], 1,3-diphenyl-2-propanone tosylhydrazone [9], biphenylmethanol [10], diphenylacetic acid [11], *N*-pivaloyl-*o*-toluidine [12], 1-pyreneacetic acid [13], salicylaldehyde phenylhydrazone [14], or *N*-benzylbenzamide [2], which form a highly colored dianion after the formation of a colorless monoanion. Diphenyl ditelluride has been reported to react stoichiometrically with alkyllithiums, undergoing a color change in the final point [1]. 4) A double titration: hydrolysis of an aliquot of the organolithium species with water, and titration of the total base with a standard acid solution using phenolphthalein as indicator [15].

The double titration method [15] is a very reliable method, however it can be time-consuming. In some of the methods using stoichiometric amounts of the titrant, relatively large amounts of these indicators may be needed and some of them tend to be expensive [1, 13] or highly toxic [7]. Probably, one of the most accurate and widely used procedures for the titration of alkyllithiums is the Watson and Eastham method using 1,10-phenatroline as indicator [3].

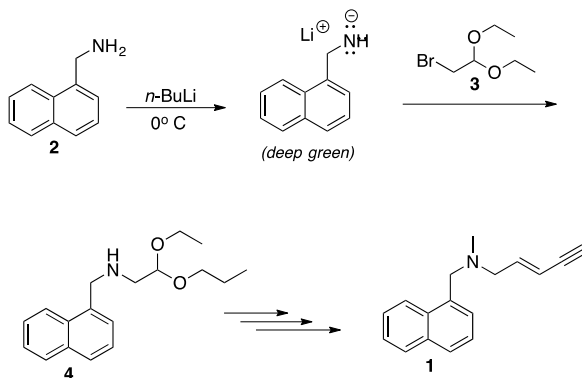
In this paper a simple and direct titration of alkyllithiums with *sec*-butanol, using 1-

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naphtylmethylamine, **2**, or 1-naphtylamine, **5**, as indicators is reported.

2. Results and discussion

As part of a program on the synthesis and biological activity of antifungal compounds, the synthesis of enyne, **1**, was needed [16]. The synthesis started with the reaction of 1-naphtylmethylamine, **2**, with *n*-BuLi at 0° C, followed by treatment with bromoacetaldehyde diethyl acetal, **3**, to obtain the corresponding amino ketal **4**, which was later transformed into enyne **1** (Scheme 1).



Scheme 1. Synthesis of antifungal compound 1

It was noticed that when a colorless to slightly yellow THF solution of 1-naphtylmethylamine, **2**, was treated with *n*-BuLi, a deep green color was developed and it faded away as the alkylation reaction with bromide, **3**, proceeded (Scheme 1). Because of such a dramatic color change, the use of 1-naphtylmethylamine, **2**, was investigated as a possible indicator to titrate *n*-BuLi. The possibility to use the less expensive 1-naphtylamine, **5**, was also investigated.

It was found that addition of aliquots of *n*-BuLi to cold (0° C) THF solutions of 1-naphtylmethylamine, **2**, consistently produced a dark green color. These samples were titrated with dry *sec*-butanol, which was added, to the *n*-BuLi solution, dropwise via a 1.00 mL syringe (graduated by 0.01 mL). In all the cases a color change from deep green to colorless was observed at the final point.

To test the accuracy of these determinations, samples were also titrated with *sec*-butanol but using 1,10-phenatroline, **6**, as indicator, according to the method of Watson and Eastham [3]. In all the cases a concordance between both determinations was obtained (Table 1).

Several titrations of *n*-BuLi were performed using 1-naphtylamine, **5**, as indicator. In these cases a color change from brown to yellow was observed at the final

point. These determinations were also corroborated against the Watson and Eastham method [3]. In all the cases similar values were found between the two methods (Table 1).

Table 1. Comparative titrations of *n*-BuLi with *sec*- BuOH. Titre (mmol/mL \pm 0.05)

Batch ^b	Indicator ^a		
	2	5	6
1	2.40	2.40	2.40
2	2.35	2.40	2.40
3	2.30	2.30	2.35

^a Indicators: **2**=1-naphtylmethylamine, **5**=1-naphtylamine, **6**=1,10-phenatroline.

^b In each batch at least three determinations were performed.

These two indicators were also used to titrate samples of *tert*-BuLi and the results were in agreement with the Watson and Eastham method [3].

3. Conclusions

Two aromatic amines, 1-naphtylamine, **5**, and 1-naphtylmethylamine, **2**, were tested as indicators for the determination of the concentration of alkylolithiums. Both of these indicators gave sharp end-points, and the results obtained were in agreement with the ones obtained by a standard method [3]. Although both indicators gave similar results, probably the use of the less expensive 1-naphtylamine, **5**, is preferred over 1-naphtylmethylamine, **2**.

4. Experimental section

General: All glassware and syringes were dried in an oven overnight at 140° C and flushed with nitrogen immediately prior to use. Transfers of reagents were performed with syringes equipped with stainless-steel needles. All titration reactions were carried out under a positive pressure of nitrogen. Nitrogen was passed through a Drierite gas-drying unit prior to use. Tetrahydrofuran was refluxed and freshly distilled from potassium/benzophenone ketyl, under nitrogen atmosphere. *Sec*-butanol was dried and kept under molecular sieves.

Analysis of organolithiums: To a oven-dried, 10 mL round-bottomed flask, cooled under a nitrogen stream, and equipped with a magnetic stirring bar and a septum, was added a small amount (ca 5-10 mgs) of 1-naphtylmethylamine (or 1-naphtylamine). THF (4-5 mL) was added and the resulting solution was cooled to 0° C. An aliquot (1.00 mL) of a solution of *n*-BuLi in hexanes was added and the resulting solution turned green (in the case of 1-naphtylamine the solution turned brown). Anhydrous *sec*-butanol was added dropwise, to the mixture, via a 1.00 mL syringe (graduated by 0.01 mL)

until a colorless solution was obtained at the end-point (in the case of 1-naphtylamine, the end-point was yellow). The concentration of *n*-BuLi was calculated from the amount of *sec*-butanol consumed (1.0 equivalent).

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Conflicts of interest

The author declares that there is no conflict of interest.

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